1 Pharmaceutical Calculations

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I. FUNDAMENTALS OF MEASUREMENT AND CALCULATION.

The pharmacist is often required to perform or evaluate a variety of calculations. Many of these calculations involve the use of direct or inverse proportions. **Dimensional** (or **unit**) **analysis** and **approximation** can be useful in solving these problems. In dimensional analysis, dimensions (or units) are included with each number used in the calculation. Units common to the numerator and denominator may be canceled and the remaining units provide the units for the final answer. In approximation, each number used in the calculation is rounded to a single significant digit. Factors common to the numerator and denominator may be canceled, and the answer to this approximation should be reasonably close to the final exact answer.

A. Ratio and proportion

1. **Ratio**. The relative magnitude of two like quantities is a ratio, which is expressed as a fraction. Certain basic principles apply to the ratio, as they do to all fractions.
   a. When the two terms of a ratio are multiplied or divided by the same number, the value of the ratio is unchanged.

$$\frac{1}{3} \times \frac{2}{2} = \frac{2}{6} = \frac{1}{3}$$

   b. Two ratios with the same value are equivalent. Equivalent ratios have equal cross products and equal reciprocals. For example:

$$\frac{1}{3} = \frac{2}{6}$$

   and

$$1 \times 6 = 3 \times 2 = 6$$

   If two ratios are equal, then their reciprocals are equal:

$$\text{if } \frac{1}{3} = \frac{2}{6}, \text{ then } \frac{3}{1} = \frac{6}{2}$$

2. **Proportion**. The expression of the equality of two ratios is a proportion. The product of the extremes is equal to the product of the means for any proportion. The way to express this, from the example cited, would be 1:3 = 2:6, where the means are 3 and 2, and the extremes are 1 and 6. Furthermore, the numerator of the one fraction equals the product of its denominator and the other fraction (i.e., one missing term can always be found given the other three terms). Most pharmaceutical calculations can be performed by use of proportion.
   a. **Proper ratios**. Some pharmacists use proper ratios (in which similar units are used in the numerator and denominator of each ratio) in their proportion calculations. Several examples follow:
      (1) If 240 mL of a cough syrup contains 480 mg of dextromethorphan hydrobromide, then what mass of drug is contained in a child's dose, 1 teaspoon (5 mL) of syrup?

$$\frac{240 \text{ mL}}{5 \text{ mL}} = \frac{480 \text{ mg}}{x \text{ mg}}$$

$$x = \frac{480 \times 5}{240} = 10 \text{ mg}$$

(2) If a child's dose (5 mL) of a cough syrup contains 10 mg of dextromethorphan hydrobromide, what mass of drug is contained in 240 mL?

$$\frac{240\ \text{mL}}{5\ \text{mL}} = \frac{x\ \text{mg}}{10\ \text{mg}}$$

$$x = \frac{240 \times 10}{5} = 480\ \text{mg}$$

(3) If the amount of dextromethorphan hydrobromide in 240 mL of cough syrup is 480 mg, what would be the volume required for a child's dose of 10 mg?

$$\frac{x\ \text{mL}}{240\ \text{mL}} = \frac{10\ \text{mg}}{480\ \text{mg}}$$

$$x = \frac{10 \times 240}{480} = 5\text{mL}$$

(4) How many milligrams of dextromethorphan base (molecular weight = 271.4) are equivalent to 10 mg of dextromethorphan hydrobromide (molecular weight = 352.3)?

$$\frac{x\ \text{mg}}{10\ \text{mg}} = \frac{271.4}{352.3}$$

$$x = 10 \times \frac{271.4}{352.3} = 7.7\ \text{mg}$$

b. Mixed ratios. Some pharmacists use mixed ratios (in which dissimilar units are used in the numerator and denominator of each ratio) in their proportion calculations. Such computations generally give correct answers, providing the conditions in which mixed ratios cannot be used are known. A later example shows mixed ratios leading to failure in the case of dilution, when inverse proportions are required. For **inverse proportions**, similar units must be used in the numerator and denominator of each ratio. Following is an example of a mixed ratio calculation using the previous problem.

$$\frac{480\ \text{mg}}{10\ \text{mL}} = \frac{240\ \text{mg}}{x\ \text{mL}}$$

$$x = 240 \times \frac{10}{480} = 5\ \text{mL}$$

The **same answer** is obtained in this example whether we use proper ratios, with similar units in numerator and denominator, or mixed ratios. This is not the case when dealing with inverse proportions.

3. Inverse proportion. The most common example of the need for inverse proportion for the pharmacist is the case of **dilution**. Whereas in the previous examples of proportion the relationships involved direct proportion, the case of dilution calls for an inverse proportion (i.e., as volume increases, concentration decreases). The necessity of using inverse proportions for dilution problems is shown in this example.

If 120 mL of a 10% stock solution is diluted to 240 mL, what is the final concentration? Using inverse proportion,

$$\frac{120\ \text{mL}}{240\ \text{mL}} = \frac{x\%}{10\%}$$

$$120 \times \frac{10}{240} = 5\%$$

As expected, the final concentration is one-half of the original concentration because the volume is doubled. However, if the pharmacist attempts to use direct proportion and neglects to estimate an appropriate answer, the resulting calculation would provide an answer of 20%, which is twice the actual concentration.

$$\frac{120\ \text{mL}}{240\ \text{mL}} = \frac{10\%}{x\%}$$

$$240 \times \frac{10}{120} = 20\%\ \text{(incorrect answer)}$$

Likewise, the pharmacist using mixed ratios fails in this case

$$\frac{120\text{ mL}}{10\%} = \frac{240\text{ mL}}{x\%}$$

and

$$10 \times \frac{240}{120} = 20\% \text{ (again, incorrect answer)}$$

B. Aliquot. A pharmacist requires the aliquot method of measurement when the **sensitivity** (the smallest quantity that can be measured with the required accuracy and precision) of the measuring device is not great enough for the required measurement. Aliquot calculations can be used for measurement of solids or liquids, allowing the pharmacist to realize the required precision through a process of measuring a multiple of the desired amount, followed by dilution, and finally selection and measurement of an aliquot part that contains the desired amount of material. This example problem involves weighing by the aliquot method, using a prescription balance.

A prescription balance has a sensitivity requirement of 6 mg. How would you weigh 10 mg of drug with an accuracy of ± 5% using a suitable diluent?

1. First, calculate the least weighable quantity for the balance with a sensitivity requirement of 6 mg, assuming ± 5% accuracy is required.

$$\frac{6\text{ mg}}{x\text{ mg}} = \frac{5\%}{100\%};\ x = 120\text{ mg (least weighable quantity for our balance)}$$

2. Now it is obvious that an aliquot calculation is required because 10 mg of drug is required, whereas the least weighable quantity is 120 mg to achieve the required percentage of error. Using the least weighable quantity method of aliquot measurement, use the smallest quantity weighable on the balance at each step to preserve materials.

a. Weigh 12 × 10 mg = 120 mg of drug.

b. Dilute the 120 mg of drug (from step **a**) with a suitable diluent by geometrical dilution to achieve a mixture that will provide 10 mg of drug in each 120-mg aliquot. The amount of diluent to be used can be determined through **proportion**.

$$\frac{120\text{ mg drug}}{10\text{ mg drug}} = \frac{x\text{ mg total mixture}}{120\text{ mg aliquot mixture}}$$

$$x = 1440\text{ mg total mixture}$$

$$1440\text{ mg total} - 120\text{ mg drug} = 1320\text{ mg diluent}$$

c. Weigh 120 mg (1/12) of the total mixture of 1440 mg that will contain the required 10 mg of drug, which is 1/12 of the 120 mg.

II. SYSTEMS OF MEASURE.

The pharmacist must be familiar with **three systems** of measure: the **metric system** and two common systems of measure (the **avoirdupois** and **apothecaries'** systems). The primary system of measure in pharmacy and medicine is the metric system. Most students find it easiest to convert measurements in the common systems to metric units. A table of conversion equivalents is provided and should be memorized by the pharmacist (see Appendix B). The metric system, because of its universal acceptance and broad use, will not be reviewed here.

A. Apothecaries' system of fluid measure. The apothecaries' system of fluid measure is summarized in Appendix B.

B. Apothecaries' system for measuring weight. The apothecaries' system for measuring weight includes units of grains, scruples, drams, ounces, and pounds (see Appendix B).

C. Avoirdupois system of measuring weight. The avoirdupois (AV) system of measuring weight includes the grain, ounce, and pound. The grain is a unit common with the apothecaries' system and allows for easy conversion between the systems. The avoirdupois pound, however, is 16 AV ounces in contrast to the apothecaries' pound that is 12 apothecaries' ounces (see Appendix B).

D. Conversion equivalents. See Appendix B.

III. REDUCING AND ENLARGING FORMULAS.

The pharmacist is often required to reduce or enlarge a recipe. Problems of this type are solved through proportion or by multiplication or division by the appropriate factor to obtain the required amount of each ingredient that will give the desired total mass or volume of the formula. Formulas can be provided in amounts or in parts.

A. Formulas that indicate parts. When dealing with formulas that specify parts, parts by weight will require the determination of weights of ingredients, whereas parts by volume warrant the calculation of volumes of ingredients. Always find the total number of parts indicated in the formula and equate that total with the total mass or volume of the desired formula in order to set up a proportion. Such a proportion will allow calculation of the mass or volume of each ingredient in units common to the total mass or volume.

What quantities should be used to prepare 100 g of "Diaper paste" from the following formula?

R_x	mineral oil	6 parts
	nystatin powder	1 part
	hydrocortisone powder	2 parts
	zinc oxide ointment	200 parts

Label: diaper paste, maximum 1 year expiration

Total number of parts = 200 + 2 + 1 + 6 = 209 parts

For each of the ingredients, the ratio is then set up, such as

$$\frac{6 \text{ parts}}{209 \text{ parts}} = \frac{x \text{ g}}{100 \text{ g}}, \text{ with } x = 2.87 \text{ g for mineral oil or}$$

$$\frac{1 \text{ part}}{209 \text{ parts}} = \frac{y \text{ g}}{100 \text{ g}}, \text{ with } y = 0.48 \text{ g for nystatin powder}$$

B. Formulas that indicate quantities. The following prescription for cold cream provides a 100-g quantity.

What mass of each ingredient is required to provide 1 lb (AV) of cream?

R_x	white wax	12.5 g
	mineral oil	60.0 g
	lanolin	2.5 g
	sodium borate	1.0 g
	rose water	24.0 g

1 lb = 454 g

$\frac{454}{100} = 4.54$ (multiplication factor to use in calculating the quantities of each ingredient)

12.5 g × 4.54 = 56.8 g of white wax
60.0 g × 4.54 = 272 g of mineral oil
2.5 g × 4.54 = 11.4 g of lanolin
1.0 g × 4.54 = 4.54 g of sodium borate
24.0 g × 4.54 = 109 g of rose water

IV. CALCULATING DOSES.

Calculation of doses generally can be performed with dimensional analysis. **Problems** encountered in the pharmacy include calculation of the number of doses, quantities in a dose or total mass/volume, amount of active or inactive ingredients, and size of dose. Calculation of **children's doses** is commonly performed by the pharmacist. Dosage is optimally calculated by using the child's body weight or mass and the appropriate dose in milligrams per kilogram (mg/kg). Without these data, the following formulas based on an adult dose can be used.

A. Fried's rule for infants

$$\frac{\text{age (in months)} \times \text{adult dose}}{150} = \text{dose for infant}$$

B. Clark's rule

$$\frac{\text{weight (lb)} \times \text{adult dose}}{\text{150 lb (avg wt of adult)}} = \text{dose for child}$$

C. Child's dosage based on body surface area (BSA)

$$\frac{\text{BSA of child } (m^2) \times \text{adult dose}}{1.73\ m^2 \text{ (avg adult BSA)}} = \text{approximate dose for child}$$

D. Young's rule for children 2 years old or older

$$\frac{\text{age (in years)}}{\text{age (in years)} + 12} \times \text{adult dose} = \text{dose for child}$$

E. Constant rate intravenous infusions. Some drugs are administered intravenously at a constant (zero-order) rate by using a continuous-drip infusion set or a constant-rate infusion pump. The flow rate (volume per unit time) required can be calculated from the volume to be administered and the duration of the infusion. The rate of drug administration can be calculated from the concentration of drug in the infused solution and the flow rate of the infusion set or pump. Conversion factors may be required to obtain the final answer in the correct units (drops per minute or milliliters per hour).

A vancomycin solution containing 1000 mg of vancomycin hydrochloride diluted to 250 mL with D_5W is to be infused at a constant rate with a continuous-drip intravenous infusion set that delivers 25 drops/mL. **What flow rate (drops per minute) should be used to infuse all 250 mL of the vancomycin hydrochloride solution in 2 hrs?**

$$\frac{250\text{ mL}}{2\text{ hrs}} \times \frac{1\text{ hr}}{60\text{ mins}} \times \frac{25\text{ drops}}{1\text{ mL}} = 52\text{ drops/min}$$

V. PERCENTAGE, RATIO STRENGTH, AND OTHER CONCENTRATION EXPRESSIONS

A. Percentage weight in volume (w/v)

1. **Definition.** Percentage, indicating parts per hundred, is an important means of expressing concentration in pharmacy practice. Percentage w/v indicates the number of grams of a constituent per 100 mL of solution or liquid formulation. The pharmacist may be required to perform **three types** of calculations: determine the **weight** of active ingredient in a certain volume when given the percentage strength, determine the **percentage w/v** when the weight of substance and volume of liquid formulation are known, and determine the **volume** of liquid mixture when the percentage strength and amount of substance are known.
2. **Tolu balsam syrup (from the National Formulary).** Tolu balsam tincture contains 20% w/v tolu balsam.

   What is the percentage concentration of tolu balsam in the syrup from the formula shown in the following?

tolu balsam tincture	50 mL
magnesium carbonate	10 g
sucrose	820 g
purified water, q.s. a.d.	1000 mL

   a. First, determine what the amount of tolu balsam is contained in the 50 mL quantity of tincture used for the syrup. Then, by proportion, calculate the concentration of tolu balsam in the syrup.

$$\text{tolu balsam tincture} = 50\text{ mL} \times \frac{20\text{ g}}{100\text{ mL}} = 10\text{ g tolu balsam}$$

$$\frac{10\text{ g}}{1000\text{ mL}} = \frac{x\text{ g}}{100\text{ mL}};\ x = \frac{1\text{ g}}{100\text{ mL}} = 1\%\text{ tolu balsam in the syrup}$$

In answering this one question, the first two types of problems listed beforehand have been solved, while exhibiting two methods of solving percentage problems—namely, by **dimensional analysis** and **proportion**.

b. For an example of the **third type** of percentage w/v problem, determine what volume of syrup could be prepared if we had only 8 g of magnesium carbonate. Use proportion to find the total volume of syrup that can be made using only 8 g of magnesium carbonate. If we have 10 g of magnesium carbonate in 1000 mL of solution, then, according to the recipe, 800 mL of solution can be prepared using all 8 g of the drug.

$$\frac{10\text{ g}}{1000\text{ mL}} = \frac{8\text{ g}}{x\text{ mL}};\ x = 800\text{ mL}$$

B. Percentage volume in volume (v/v). Percentage v/v indicates the number of milliliters of a constituent in 100 mL of liquid formulation. The percentage strength of mixtures of liquids in liquids is indicated by percentage v/v, which indicates the parts by volume of a substance in 100 parts of the liquid preparation. The **three types** of problems that are encountered involve calculating **percentage strength**, calculating **volume of ingredient**, and calculating **volume of the liquid preparation**. Using the same tolu balsam syrup formula from earlier, we'll now work a percentage v/v problem.

What is the percentage strength v/v of the tolu balsam tincture in the syrup preparation? By proportion, we can solve the problem in one step.

$$\frac{50\text{ mL tolu balsam tincture}}{x\text{ mL tolu balsam tincture}} = \frac{1000\text{ mL syrup}}{100\text{ mL syrup}};\ x = 5\%$$

C. Percentage weight in weight (w/w). Percentage w/w indicates the number of grams of a constituent per 100 g of formulation (solid or liquid). Solution of problems involving percentage w/w is straightforward when the total mass of the mixture is available or when the total mass can be determined from the available data. In calculations similar to those for percentage w/v and v/v, the pharmacist might need to solve several types of problems, including determination of the weight of a constituent, the total weight of a mixture, or the percentage w/w.

1. How many grams of drug substance should be used to prepare 240 g of a 5% w/w solution in water?

a. The first step in any percentage w/w problem is to attempt identification of the total mass of the mixture. In this problem, the total mass is, obviously, provided (240 g).

b. The problem can be easily solved through **dimensional analysis**.

$$240\text{ g mixture} \times \frac{5.0\text{ g drug}}{100\text{ g drug}} = 12\text{ g}$$

2. When the total mass of the mixture is unavailable or cannot be determined, an **extra step** is required in the calculations. Because it is usually impossible to know how much volume is displaced by a solid material, the pharmacist is unable to prepare a specified volume of a solution given the percentage w/w.

How much drug should be added to 30 mL of water to make a 10% w/w solution? The volume of water that is displaced by the drug is unknown, so the final volume is unknown. Likewise, even though the mass of solvent is known (30 mL × 1 g/mL = 30 g), it is not known how much drug is needed, so the total mass is unknown. The water represents 100% − 10% = 90% of the total mixture. Then, by proportion, the mass of drug to be used can be identified.

$$\frac{30\text{ g of mixture (water)}}{x\text{ g of mixture (drug)}} = \frac{90\%}{10\%};\ x = 3.33\text{ g of drug required to make a solution}$$

The **common error** that many students make in solving problems of this type is to assume that 30 g is the total mass of the mixture. Solving the problem with that assumption gives the following incorrect answer.

$$\frac{x\text{ g drug}}{10\text{ g drug}} = \frac{30\text{ g mixture}}{100\text{ g mixture}};\ x = 3\text{ g of drug (incorrect answer)}$$

D. Ratio strength. Solid or liquid formulations that contain low concentrations of active ingredients will often have concentration expressed in **ratio strength**. Ratio strength, as the name implies, is the

expression of concentration by means of a ratio. The numerator and denominator of the ratio indicate grams (g) or milliliters (mL) of a solid or liquid constituent in the total mass (g) or volume (mL) of a solid or liquid preparation. Because **percentage strength** is essentially a ratio of parts per hundred, conversion between ratio strength and percentage strength is easily accomplished by proportion.

1. **Express 0.1% w/v as a ratio strength.**
   a. Ratio strengths are by convention expressed in reduced form, so in setting up our proportion to solve for ratio strength, use the numeral 1 in the numerator of the right-hand ratio as shown:

$$\frac{0.1\text{ g}}{100\text{ mL}} = \frac{1\text{ part}}{x\text{ parts}};\ = 1000\text{ parts, for ratio strength of 1:1000}$$

   b. Likewise, conversion from ratio strength to percentage strength by proportion is easy, as seen in the following example. Keep in mind the definition of percentage strength (parts per hundred) when setting up the proportion.
2. **Express 1:2500 as a percentage strength.**

$$\frac{1\text{ part}}{2500\text{ parts}} = \frac{x\text{ parts}}{100\text{ parts}};\ x = 0.04\text{, indicating } 0.04\%$$

E. Other concentration expressions

1. **Molarity** (M) is the expression of the number of moles of solute dissolved per liter of solution. It is calculated by dividing the moles of solute by the volume of solution in liters.

$$\mathrm{M_A} = \frac{n_\mathrm{A}}{\text{solution (L)}}$$

2. **Normality.** A convenient way of dealing with acids, bases, and electrolytes involves the use of equivalents. One equivalent of an acid is the quantity of that acid that supplies or donates 1 mole of H^+ ions. One equivalent of a base is the quantity that furnishes 1 mole of OH^- ions. One equivalent of acid reacts with one equivalent of base. Equivalent weight can be calculated for atoms or molecules.

$$\text{Equivalent weight} = \frac{\text{atomic weight or molecular weight}}{\text{valence}}$$

   The **normality** (N) of a solution is the number of gram-equivalent weights (equivalents) of solute per liter of solution. Normality is analogous to molarity; however, it is defined in terms of equivalents rather than moles.

$$\text{Normality} = \frac{\#\text{ equivalents of solute}}{\#\text{ liters of solution}}$$

3. **Molality** (m) is the moles of solute dissolved per kilogram of solvent. Molality is calculated by dividing the number of moles of solute by the number of kilograms of solvent. Molality offers an advantage over molarity because it is based on solvent weight and avoids problems associated with volume expansion or contraction owing to the addition of solutes or from a change in temperature.

$$\mathrm{m_A} = \frac{n_\mathrm{A}}{\text{mass}_{\text{ solvent (kg)}}}$$

4. **Mole fraction** (X) is the ratio of the number of moles of one component to the total moles of a mixture or solution.

$$\mathrm{X_A} = \frac{n_\mathrm{A}}{n_\mathrm{A}, n_\mathrm{B}, n_\mathrm{C}\ldots}\text{, where } \mathrm{X_A} + \mathrm{X_B} + \mathrm{X_C} + \ldots = 1$$

VI. DILUTION AND CONCENTRATION.

If the amount of drug remains constant in a dilution or concentration, then any change in the mass or volume of a mixture is inversely proportional to the concentration.

A. Dilution and concentration problems can be solved by the following:

1. Inverse proportion (as mentioned earlier)
2. The equation $\text{quantity}_1 \times \text{concentration}_1 = \text{quantity}_2 \times \text{concentration}_2$

3. Determining the amount of active ingredient present in the initial mixture and, with the assumption that the initial quantity does not change, calculating the final concentration of the new total mass or volume
4. **Alligation medial.** A method for calculating the average concentration of a mixture of two or more substances
5. **Alligation alternate.** A method for calculating the number of parts of two or more components of known concentration to be mixed when the final desired concentration is known

B. Dilution of alcohols and acids

1. **Dilution of alcohols.** When alcohol and water are mixed, a contraction of volume occurs. As a result, the final volume of solution cannot be determined accurately, nor can the volume of water needed to dilute to a certain percentage v/v be identified. Accordingly, percentage w/w is often used for solutions of alcohol.
2. The **percentage strength** of concentrated acids is expressed as percentage w/w. The concentration of diluted acids is expressed as percentage w/v. Determining the volume of concentrated acid to be used in preparing a diluted acid requires the specific gravity of the concentrated acid.

C. Dilution and concentration of liquids and solids. Dilution and concentration problems are solved by identifying the amount of drug involved followed by use of an appropriate proportion.

1. **How many milliliters of a 1:50 stock solution of ephedrine sulfate should be used in compounding the following prescription?**

Rx	ephedrine sulfate	0.25%
	rose water, a.d.	30 mL

$$\frac{0.25\text{ g}}{100\text{ mL}} \times 30\text{ mL} = 0.075\text{ g drug required}$$

$$\frac{50\text{ mL}}{1\text{ g}} = \frac{x\text{ mL}}{0.075\text{ g}};$$

$x = 3.75$ mL of stock solution required for prescription

2. **How many milliliters of a 15% w/v concentrate of benzalkonium chloride should be used in preparing 300 mL of a stock solution such that 15 mL diluted to 1 L will yield a 1:5000 solution?**
   a. First, determine the amount of drug in 1 L of a 1:5000 solution.

$$\frac{5000\text{ mL}}{1000\text{ mL}} = \frac{1\text{ g}}{x\text{ g}}; = 0.2\text{ g of benzalkonium chloride in the final solution}$$

   b. Now, because 15 mL of the stock solution is being diluted to 1 L, a stock solution is needed in which 15 mL contain 0.2 g of drug. The amount of drug required to make 300 mL of the stock solution is found by proportion.

$$\frac{0.2\text{ g}}{x\text{ g}} = \frac{15\text{ mL}}{300\text{ mL}}; x = 4\text{ g of drug required to make 300 mL of solution}$$

   c. Finally, to determine the amount of 15% concentrate required.

$$\frac{15\text{ g}}{4\text{ g}} \times \frac{100\text{ mL}}{x\text{ mL}}; x = 26.7\text{ mL of 15\% solution required to obtain necessary drug}$$

3. When the relative amount of components must be determined for preparation of a mixture of a desired concentration, the problem can be solved using alligation alternate.

   How many grams of 2.5% hydrocortisone cream should be mixed with 360 g of 0.25% cream to make a 1% hydrocortisone cream?

2.5%		0.75 parts of 2.5% cream	= 1 part	0.75/2.25 = 1/3
	1%			
0.25%		1.5 parts of 0.25% cream	= 2 parts	1.5/2.25 = 2/3
		2.25 parts total	= 3 parts	

The relative amounts of the 2.5% and 1% creams are 1 to 2, respectively. By proportion, the mass of 2.5% cream to use can be determined. **If 2 parts of 0.25% cream is represented by 360 g, then the total mass (3 parts) is represented by what mass?**

$$\frac{2 \text{ parts}}{3 \text{ parts}} = \frac{360 \text{ g}}{x \text{ g}}; x = 540 \text{ g total}$$

With the total mass known, the amount of 2.5% cream can be identified. If 3 parts represent the total mass of 540 g, then 1 part represents the mass of 2.5% cream (x g = 180 g).

$$\frac{1 \text{ part}}{3 \text{ parts}} = \frac{x \text{ g}}{540 \text{ g}}; x = 180 \text{ g of 2.5\% cream}$$

VII. ELECTROLYTE SOLUTIONS.

Electrolyte solutions contain species (electrolytes) that dissociate into ions. The **milliequivalent** (mEq) is the unit most frequently used to express the concentration of electrolytes in solution. *Table 1-1* exhibits some physiologically important ions and their properties.

A. Milliequivalents. The milliequivalent is the amount, in milligrams, of a solute equal to 1/1000 of its gram-equivalent weight. Conversion of concentrations in the form of milliequivalent to concentrations in percentage strength, milligrams per milliliter (mg/mL) or any other terms, begins with calculation of the number of milliequivalents of drug. The following examples demonstrate the computation of milliequivalents and manipulation of data from *Table 1-1* to perform the required calculations for preparing electrolyte solutions.

What is the concentration, in percent w/v, of a solution containing 2 mEq of potassium chloride per milliliter?

Calculations involving milliequivalents are easily solved if the practitioner follows a predefined procedure to determine the milliequivalent weight. This involves three steps.

1. Find the molecular weight (mol wt).

Atomic wt K = 39

Atomic wt Cl = 35.5

39 + 35.5 = 74.5 g = mol wt of KCl

Table 1-1 VALENCES, ATOMIC WEIGHTS, AND MILLIEQUIVALENT WEIGHTS OF SELECTED IONS

Ion	Formula	Valence	Atomic/Formula Weight	Milliequivalent Weight (mg)
Aluminum	A^{+++}	3	27	9
Ammonium	NH_4^+	1	18	18
Calcium	Ca^{++}	2	40	20
Ferric	Fe^{+++}	3	56	18.7
Ferrous	Fe^{++}	2	56	28
Lithium	Li^+	1	7	7
Magnesium	Mg^{++}	2	24	12
Bicarbonate	HCO_3^-	1	61	61
Carbonate	CO_3^-	1	60	30
Chloride	Cl^-	1	35.5	35.5
Citrate	$C_6H_5O_7^{---}$	3	189	63
Gluconate	$C_6H_{11}O_7^-$	1	195	195
Lactate	$C_3H_5O_3^-$	1	89	89
Phosphate	$H_2PO_4^-$	1	97	97
Sulfate	SO_4^{--}	2	96	48
Potassium	K^+	1	29	39
Sodium	Na^+	1	23	23
Acetate	$C_2H_3O_2^-$	1	59	59

2. Calculate the equivalent weight (Eq wt) of KCl.

$$\text{Eq wt} = \frac{\text{mol wt}}{\text{valence}} = \frac{74.5}{1} = 74.5 \text{ g}$$

3. Determine the milliequivalent weight, which is 1/1000 of the equivalent weight.

$$\text{mEq wt} = 74.5 \text{ g}/1000 = 0.745 \text{ g or } 74.5 \text{ mg}$$

Now that we know the milliequivalent weight, we can calculate by dimensional analysis and proportion the concentration in percentage in a fourth step.

4. 0.0745 g/mEq × 2 mEq = 0.149 g of drug

$$\frac{0.149 \text{ g drug}}{1 \text{ mL}} = \frac{x \text{ g drug}}{100 \text{ mL}}; \; x = 14.9 \text{ g}/100 \text{ mL} = 14.9\%$$

How many milliequivalents of Na^+ would be contained in a 15-mL volume of the following buffer?

$Na_2HPO_4 \cdot 7H_2O$		180 g
$NaH_2PO_4 \cdot H_2O$		480 g
Purified water	a.d.	1000 mL

For each salt, the mass (and milliequivalents) must be found in a 15-mL dose.

$$\text{mol wt } Na_2HPO_4 \cdot 7H_2O \text{ (disodium hydrogen phosphate)} = 268 \text{ g}$$
$$\text{Eq wt} = 268/2 = 134 \text{ g}$$
$$1 \text{ mEq} = 0.134 \text{ g or } 134 \text{ mg}$$

$$\frac{180 \text{ g}}{x \text{ g}} = \frac{1000 \text{ mL}}{15 \text{ mL}}; \; x = 2.7 \text{ g of disodium hydrogen phosphate in each 15 mL}$$

$$2.7 \text{ g} \times \frac{1 \text{ mEq}}{0.134 \text{ g}} = 20.1 \text{ mEq of disodium hydrogen phosphate}$$

$$\text{mol wt } NaH_2PO_4 \cdot H_2O \text{ (sodium biphosphate)} = 138 \text{ g}$$
$$\text{Eq wt} = 138 \text{ g}$$
$$1 \text{ mEq} = 0.138 \text{ g}$$

$$\frac{480 \text{ g}}{x \text{ g}} = \frac{1000 \text{ mL}}{15 \text{ mL}}; \; x = 7.2 \text{ g of sodium biphosphate in each 15 mL}$$

$$7.2 \text{ g} \times \frac{1 \text{ mEq}}{0.138 \text{ g}} = 52.2 \text{ mEq of sodium biphosphate}$$

$$20.1 \text{ mEq} + 52.2 \text{ mEq} = 72.3 \text{ mEq of sodium in each 15 mL of solution}$$

B. Milliosmoles (mOsmol). Osmotic pressure is directly proportional to the total number of particles in solution. The milliosmole is the unit of measure for osmotic concentration. For nonelectrolytes, 1 millimole represents 1 mOsmol. However, for electrolytes, the total number of particles in a solution is determined by the number of particles produced in a solution and influenced by the degree of dissociation. Assuming complete dissociation, 1 millimole of KCl represents 2 mOsmol of total particles, 1 millimole of $CaCl_2$ represents 3 mOsmol of total particles, etc. The ideal osmolar concentration can be calculated with the following equation.

$$\text{mOsmol/L} = \frac{\text{wt of substance in g/L}}{\text{mol wt in g}} \times \text{number of species} \times 1000$$

The pharmacist should recognize the difference between **ideal** osmolar concentration and **actual** osmolarity. As the concentration of solute increases, interaction between dissolved particles increases, resulting in a reduction of the actual osmolar values.

C. Isotonic solutions. An **isotonic** solution is one that has the same osmotic pressure as body fluids. **Isosmotic** fluids are fluids with the same osmotic pressure. Solutions to be administered to

patients should be isosmotic with body fluids. A **hypotonic** solution is one with a lower osmotic pressure than body fluids, whereas a **hypertonic** solution has an osmotic pressure that is greater than body fluids.

1. **Preparation of isotonic solutions.** Colligative properties, including freezing point depression, are representative of the number of particles in a solution and are considered in preparation of isotonic solutions.
   - **a.** When 1 g mol wt of any nonelectrolyte is dissolved in 1000 g of water, the freezing point of the solution is depressed by 1.86°C. By proportion, the weight of any nonelectrolyte needed to make the solution isotonic with body fluid can be calculated.
   - **b.** Boric acid (H_3BO_3) has a mol wt of 61.8 g. Thus, 61.8 g of H_3BO_3 in 1000 g of water should produce a freezing point of 1.86°C. Therefore, knowing that the freezing point depression of body fluids is −0.52°C,

$$\frac{-1.86°C}{-0.52°C} = \frac{61.8\text{ g}}{x\text{ g}}; x = 17.3\text{ g}$$

     and 17.3 g of H_3BO_3 in 1000 g of water provides a solution that is **isotonic**.
   - **c.** The degree of dissociation of electrolytes must be taken into account in such calculations. For example, NaCl is approximately 80% dissociated in weak solutions, yielding 180 particles in a solution for each 100 molecules of NaCl. Therefore,

$$\frac{-1.86°C \times 1.8}{-0.52°C} = \frac{58\text{ g}}{x\text{ g}}; x = 9.09\text{ g}$$

     indicating that 9.09 g of NaCl in 1000 g of water (0.9% w/v) should make a solution isotonic. Lacking any information on the degree of dissociation of an electrolyte, the following **dissociation values** (*i*) may be used:
     - **(1)** Substances that dissociate into two ions: 1.8
     - **(2)** Substances that dissociate into three ions: 2.6
     - **(3)** Substances that dissociate into four ions: 3.4
     - **(4)** Substances that dissociate into five ions: 4.2
2. **Sodium chloride equivalents.** The pharmacist will often be required to prepare an isotonic solution by adding an appropriate amount of another substance (drug or inert electrolyte or nonelectrolyte). Considering that isotonic fluids contain the equivalent of 0.9% NaCl, the question arises, how much of the added ingredient is required to make the solution isotonic? A **common method** for computing the amount of added ingredient to use for reaching isotonicity involves the use of **sodium chloride equivalents**.
   - **a. Definition.** The sodium chloride equivalent represents the amount of NaCl that is equivalent to the amount of particular drug in question. For every substance, there is one quantity that should have a constant tonic effect when dissolved in 1000 g of water. This is 1 g mol wt of the substance divided by its dissociation value (*i*).
   - **b. Examples**
     - **(1)** Considering H_3BO_3, from the last section, 17.3 g of H_3BO_3 is equivalent to 0.52 g of NaCl in tonicity. Therefore, the relative quantity of NaCl that is equivalent to H_3BO_3 in tonicity effects is determined as follows:

$$\frac{\text{mol wt of NaCl}/i\text{ value}}{\text{mol wt of } H_3BO_3/i\text{ value}} = \frac{58.5/1.8}{61.8/1.0}$$

       Applying this method to atropine sulfate, recall that the molecular weight of NaCl and the molecular weight of atropine sulfate are 58.5 and 695 g, respectively, and their *i* values are 1.8 and 2.6, respectively. Calculate the mass of NaCl represented by 1 g of atropine sulfate (*Table 1-2*).

$$\frac{695 \times 1.8}{58.5 \times 2.6} = \frac{1\text{ g}}{x\text{ g}}; x = 0.12\text{ g NaCl represented by 1 g of atropine sulfate}$$

Table 1-2 SODIUM CHLORIDE (NaCl) EQUIVALENTS

Substance	NaCl Equivalent
Atropine sulfate (H_2O)	0.12
Boric acid	0.52
Chlorobutanol	0.24
Dextrose (anhydrous)	0.18
Ephedrine hydrochloride	0.29
Phenacaine hydrochloride	0.20
Potassium chloride	0.78

(2) An example of the practical use of sodium chloride equivalents is seen in the following problem:

How many grams of boric acid should be used in compounding the following prescription?

Rx	phenacaine hydrochloride	1%
	chlorobutanol	0.5%
	boric acid	q.s.
	purified water, a.d.	60.0 mL
	make isotonic solution	

The prescription calls for 0.3 g of chlorobutanol and 0.6 g of phenacaine. How much boric acid is required to prepare this prescription? The question is best answered in four steps:

(a) Find the mass of sodium chloride represented by all ingredients.

$0.20 \times 0.6 = 0.120$ g of sodium choloride represented by phenacaine hydrochloride

$0.24 \times 0.3 = \underline{0.072 \text{ g}}$ of sodium chloride represented by chlorobutanol

0.192 g of sodium chloride represented by the two active ingredients

(b) Find the mass of sodium chloride required to prepare an equal volume of isotonic solution.

$$\frac{0.9 \text{ g NaCl}}{100 \text{ mL}} = \frac{x \text{ g NaCL}}{60 \text{ mL}}; \; x = 0.540 \text{ g of sodium chloride}$$

in 60 mL of an isotonic sodium chloride solution

(c) Calculate, by subtraction, the amount of NaCl required to make the solution isotonic.

0.540 g NaCl required for isotonicity
$\underline{0.192 \text{ g}}$ NaCl represented by ingredients
0.348 g NaCl required to make isotonic solution

(d) Because the prescription calls for boric acid to be used, one last step is required

$$\frac{0.348 \text{ g}}{0.52} \text{ (sodium chloride equivalent for boric acid)} = 0.669 \text{ g of boric acid to be used}$$

Study Questions

Directions for questions 1–30: Each question, statement, or incomplete statement in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. If a vitamin solution contains 0.5 mg of fluoride ion in each milliliter, then how many milligrams of fluoride ion would be provided by a dropper that delivers 0.6 mL?

(A) 0.30 mg
(B) 0.10 mg
(C) 1.00 mg
(D) 0.83 mg

2. How many chloramphenicol capsules, each containing 250 mg, are needed to provide 25 mg/kg/d for 7 days for a person weighing 200 lb?

(A) 90 capsules
(B) 64 capsules
(C) 13 capsules
(D) 25 capsules

3. If 3.17 kg of a drug is used to make 50000 tablets, how many milligrams will 30 tablets contain?

(A) 1.9 mg
(B) 1900 mg
(C) 0.0019 mg
(D) 3.2 mg

4. A capsule contains ⅛ gr of ephedrine sulfate, ¼ gr of theophylline, and 1/16 gr of phenobarbital. What is the total mass of the active ingredients in milligrams?

(A) 20 mg
(B) 8 mg
(C) 28 mg
(D) 4 mg

5. If 1 fluid ounce of a cough syrup contains 10 gr of sodium citrate, how many milligrams are contained in 10 mL?

(A) 650 mg
(B) 65 mg
(C) 217 mg
(D) 20 mg

6. How many capsules, each containing ¼ gr of phenobarbital, can be manufactured if a bottle containing 2 avoirdupois ounces of phenobarbital is available?

(A) 771 capsules
(B) 350 capsules
(C) 3500 capsules
(D) 1250 capsules

7. Using the formula for calamine lotion, determine the amount of calamine (in grams) necessary to prepare 240 mL of lotion.

calamine	80 g
zinc oxide	80 g
glycerin	20 mL
bentonite magma	250 mL
calcium hydroxide topical solution	sufficient quantity to make 1000 mL

(A) 19.2 g
(B) 140.0 g
(C) 100.0 g
(D) 24.0 g

8. From the following formula, calculate the amount of white wax required to make 1 lb of cold cream. Determine the mass in grams.

cetyl esters wax	12.5 parts
white wax	12.0 parts
mineral oil	56.0 parts
sodium borate	0.5 parts
purified water	19.0 parts

(A) 56.75 g
(B) 254.24 g
(C) 54.48 g
(D) 86.26 g

9. How many grams of aspirin should be used to prepare 1.255 kg of the powder?

Aspirin	6 parts
phenacetin	3 parts
caffeine	1 part

(A) 125 g
(B) 750 g
(C) 175 g
(D) 360 g

10. A solution contains 1.25 mg of a drug per milliliter. At what rate should the solution be infused (drops per minute) if the drug is to be administered at a rate of 80 mg/hr? (1 mL = 30 drops)

(A) 64.00 drops/min
(B) 1.06 drops/min
(C) 32.00 drops/min
(D) 20.00 drops/min

11. The recommended maintenance dose of aminophylline for children is 1.0 mg/kg/hr by injection. If 10 mL of a 25-mg/mL solution of aminophylline is added to a 100-mL bottle of 5% dextrose, what should be the rate of delivery in mL/hr for a 40-lb child?

(A) 2.30 mL/hr
(B) 8.00 mL/hr
(C) 18.90 mL/hr
(D) 18.20 mL/hr

12. For children, streptomycin is to be administered at a dose of 30 mg/kg of body weight daily in divided doses every 6 to 12 hrs. The dry powder is dissolved by adding water for injection, in an amount to yield the desired concentration as indicated in the following table (for a 1-g vial).

Approximate Concentration (mg/mL)	Volume (mL)
200	4.2
250	3.2
400	1.8

Reconstituting at the lowest possible concentration, what volume (in mL) would be withdrawn to obtain a day's dose for a 50-lb child?

(A) 3.40 mL
(B) 22.73 mL
(C) 2.50 mL
(D) 2.27 mL

13. The atropine sulfate is available only in the form of 1/150 gr tablets. How many atropine sulfate tablets would you use to compound the following prescription?

atropine sulfate	1/200 gr
codeine phosphate	¼ gr
aspirin	5 gr
d.t.d.	#24 capsules
Sig:	1 capsule p.r.n.

(A) 3 tablets
(B) 6 tablets
(C) 12 tablets
(D) 18 tablets

14. In 25.0 mL of a solution for injection, there are 4.00 mg of the drug. If the dose to be administered to a patient is 200 μg, what quantity (in mL) of this solution should be used?

(A) 1.25 mL
(B) 125.00 mL
(C) 12.00 mL
(D) None of the above

15. How many milligrams of papaverine will the patient receive each day?

R_x	papaverine hcl	1.0 g
	aqua	30.0 mL
	syrup tolu, q.s. a.d.	90.0 mL
	Sig:	1 teaspoon t.i.d.

(A) 56.0 mg
(B) 5.6 mg
(C) 166.0 mg
(D) 2.5 mg

16. Considering the following formula, how many grams of sodium bromide should be used in filling this prescription?

R_x	sodium bromide	1.2 g
	syrup tolu	2.0 mL
	syrup wild cherry, q.s. a.d.	5.0 mL
	d.t.d.	#24

(A) 1.2 g
(B) 1200.0 g
(C) 28.8 g
(D) 220.0 g

17. How many milliliters of a 7.5% stock solution of $KMnO_4$ should be used to obtain the KMnO needed?

$KMnO_4$, q.s.
Distilled water, a.d. 1000 mL
Sig: 2 teaspoons diluted to 500 mL yield a 1:5000 solution

(A) 267.0 mL
(B) 133.0 mL
(C) 26.7 mL
(D) 13.3 mL

18. The formula for Ringer's solution follows. How much sodium chloride is needed to make 120 mL?

R_x	sodium chloride	8.60 g
	potassium chloride	0.30 g
	calcium chloride	0.33 g
	water for injection, q.s. a.d.	1000 mL

(A) 120.00 g
(B) 1.03 g
(C) 0.12 g
(D) 103.00 g

19. How many grams of talc should be added to 1 lb of a powder containing 20 g of zinc undecylenate per 100 g to reduce the concentration of zinc undecylenate to 3%?

(A) 3026.7 g
(B) 2572.7 g
(C) 17.0 g
(D) 257.0 g

20. How many milliliters of a 0.9% aqueous solution can be made from 20.0 g of sodium chloride?

(A) 2222 mL
(B) 100 mL
(C) 222 mL
(D) 122 mL

21. The blood of a reckless driver contains 0.1% alcohol. Express the concentration of alcohol in parts per million.

(A) 100 ppm
(B) 1000 ppm
(C) 1 ppm
(D) 250 ppm

22. Syrup is an 85% w/v solution of sucrose in water. It has a density of 1.313 g/mL. How many milliliters of water should be used to make 125 mL of syrup?

(A) 106.25 mL
(B) 164.10 mL
(C) 57.90 mL
(D) 25.00 mL

23. How many grams of benzethonium chloride should be used in preparing 5 gal of a 0.025% w/v solution?

(A) 189.25 g
(B) 18.90 g
(C) 4.73 g
(D) 35.00 g

24. How many grams of menthol should be used to prepare this prescription?

R_x	menthol	0.8%
	alcohol, q.s. a.d.	60.0 mL

(A) 0.48 g
(B) 0.80 g
(C) 4.80 g
(D) 1.48 g

25. How many milliliters of a 1:1500 solution can be made by dissolving 4.8 g of cetylpyridinium chloride in water?

(A) 7200.0 mL
(B) 7.2 mL
(C) 48.0 mL
(D) 4.8 mL

26. The manufacturer specifies that one Domeboro tablet dissolved in 1 pint of water makes a modified Burow's solution approximately equivalent to a 1:40 dilution. How many tablets should be used in preparing ½ gal of a 1:10 dilution?

(A) 16 tablets
(B) 189 tablets
(C) 12 tablets
(D) 45 tablets

27. How many milliosmoles of calcium chloride ($CaCl_2 \cdot 2H_2O$ − mol wt = 147) are represented in 147 mL of a 10% w/v calcium chloride solution?

(A) 100 mOsmol
(B) 200 mOsmol
(C) 300 mOsmol
(D) 3 mOsmol

28. How many grams of boric acid should be used in compounding the following prescription?

Phenacaine HCl 1.0% (NaCl eq = 0.17)
Chlorobutanol 0.5% (NaCl eq = 0.18)
Boric acid, q.s. (NaCl eq = 0.52)
Purified H_2O, a.d. 30 mL
Make isotonic solution
Sig: 1 drop in each eye

(A) 0.37 g
(B) 0.74 g
(C) 0.27 g
(D) 0.47 g

29. A pharmacist prepares 1 gal of KCl solution by mixing 565 g of KCl (valence = 1) in an appropriate vehicle. How many milliequivalents of K^+ are in 15 mL of this solution? (atomic weights: K = 39; Cl = 35.5)

(A) 7.5 mEq
(B) 10.0 mEq
(C) 20.0 mEq
(D) 30.0 mEq
(E) 40.0 mEq

30. A vancomycin solution containing 1000 mg of vancomycin hydrochloride diluted to 250 mL with D_5W is to be infused at a constant rate with an infusion pump in 2 hrs. What is the rate of drug administration?

(A) 2.08 mg/min
(B) 8.33 mg/min
(C) 4.17 mg/min
(D) 16.70 mg/min
(E) 5.21 mg/min

Answers and Explanations

1. **The answer is A** *[see I.A.2]*.

2. **The answer is B** *[see II]*.

3. **The answer is B** *[see II]*.

4. **The answer is C** *[see II]*.

5. **The answer is C** *[see I.A.2]*.

6. **The answer is C** *[see II]*.

7. **The answer is A** *[see III]*.

8. **The answer is C** *[see II; III.A]*.
The formula tells the pharmacist that white wax (W.W.) represents 12 parts out of the total 100 parts in the prescription. What we wish to determine is the mass of white wax required to prepare 454 g (1 lb) of the recipe. This can be easily solved by proportion:

$$\frac{12 \text{ parts W.W.}}{100 \text{ parts total}} = \frac{x}{454 \text{ parts (grams)}}; x = 54.48 \text{ g}$$

9. **The answer is B** *[see III.A]*.

10. **The answer is C** *[see IV.E]*.

11. **The answer is B** *[see II; IV]*.

12. **The answer is A** *[see IV]*.

13. **The answer is D** *[see II; III.B]*.

14. **The answer is A** *[see I.A.2; II]*.
Dimensional analysis is often useful for calculating doses. Considering that 4 mg of the drug is present in each 25 mL of solution, we can easily calculate the number of milliliters to be used to give a dose of 0.200 mg (200 μg). Always include units in your calculations.

$$\frac{25 \text{ mL}}{4 \text{ mg}} \times 0.200 \text{ mg} = 1.25 \text{ mL}$$

15. **The answer is C** *[see III.B]*.

16. **The answer is C** *[see III.B]*.

17. **The answer is B** *[see V.A; VI]*.
First, determine the mass of drug in the final diluted solution.

$$\frac{1 \text{ part}}{5000 \text{ parts}} = \frac{x \text{ g}}{500 \text{ g}}; x = 0.1 \text{ g}$$

Now, if 0.1 g of drug is present in 500 mL of 1:5000 solution, 2 teaspoons (10 mL) of the prescription contains the same amount of drug (0.1 g) before dilution. From this, the amount of drug in 1000 mL (the total volume) of the prescription can be determined:

$$\frac{0.1 \text{ g}}{10 \text{ mL}} = \frac{x \text{ g}}{1000 \text{ mL}}; x = 10 \text{ g}$$

Finally, to obtain the correct amount of drug to formulate the prescription (10 g), we are to use a 7.5% stock solution. Recalling the definition of percentage strength w/v

$$\frac{100 \text{ mL}}{7.5 \text{ g}} \times 10 \text{ g} = 133.3 \text{ mL or } 133 \text{ mL}$$

18. **The answer is B** *[see III.B]*.

19. **The answer is B** *[see V.C; VI.C]*.

20. **The answer is A** *[see I.A.2; V.A]*.
Using dimensional analysis

$$\frac{20 \text{ g} \times 100 \text{ mL}}{0.9 \text{ g}} = 2222 \text{ mL}$$

21. **The answer is B** *[see V.D.1]*.

22. **The answer is C** *[see I.A; V.A.1]*.
Using the density, the weight of 125 mL of syrup can be calculated:

$$125 \text{ mL} \times 1.313 \text{ g/mL} = 164.125 \text{ g}$$

Using proportion and the sucrose concentration in w/v, the weight of sucrose in 125 mL of syrup can be calculated:

$$\frac{100 \text{ mL}}{125 \text{ mL}} = \frac{85 \text{ g}}{x \text{ g}}; x = 106.25 \text{ g}$$

Finally, the weight of water in 125 mL of syrup can be calculated:

$$164.125 \text{ g} - 106.25 \text{ g} = 57.875 \text{ g}$$

which has a volume of 57.90 mL.

23. **The answer is C** *[see I; II; V]*.

24. **The answer is A** *[see I; V]*.

25. **The answer is A** *[see I; V]*.
The problem is easily solved by proportion. The question to be answered is if 1 g of drug is present in 1500 mL of a solution, what volume can be made with 4.8 g of drug?

$$\frac{1 \text{ g}}{4.8 \text{ g}} = \frac{1500 \text{ mL}}{x \text{ mL}}; x = 7200.0 \text{ mL}$$

(the volume of 1 to 1500 solution that can be prepared from 4.8 g of drug)

26. **The answer is A** *[see I; V]*.

27. The answer is C *[see VII.B]*.
Recalling the expression for ideal osmolar concentration:

$$\text{mOsmol/L} = \frac{100\ \text{g/L}}{147\ \text{g/mol}} \times 3 \times 1000$$
$$= \text{mOsmol/L} \times 0.147\ \text{L}$$
$$= 300\ \text{mOsmol}$$

28. The answer is A *[see VII.C]*.

29. The answer is D *[see VII.A]*.

30. The answer is B *[see IV.E]*.
Using dimensional analysis:

$$\frac{1000\ \text{mg}}{250\ \text{mL}} \times \frac{250\ \text{mL}}{2\ \text{hr}} \times \frac{1\ \text{hr}}{60\ \text{min}} = 8.33\ \text{mg/min}$$

2 Pharmaceutical Principles and Drug Dosage Forms

LAWRENCE H. BLOCK

I. INTRODUCTION.

Pharmaceutical principles are the underlying physicochemical principles that allow a drug to be incorporated into a pharmaceutical **dosage form** (e.g., solution, capsule). These principles apply whether the drug is extemporaneously compounded by the pharmacist or manufactured for commercial distribution as a **drug product**.

A. The finished **dosage form** contains the active drug ingredient in association with nondrug (usually inert) ingredients (**excipients**) that make up the **vehicle**, or **formulation matrix**.

B. The **drug delivery system** concept, which has evolved since the 1960s, is a more holistic concept. It embraces not only the drug (or prodrug) and its formulation matrix, but also the dynamic interactions among the drug, its formulation matrix, its container, and the physiologic milieux of the patient. These dynamic interactions are the subject of **biopharmaceutics** (see Chapter 3).

II. INTERMOLECULAR FORCES OF ATTRACTION

A. Introduction. The application of pharmaceutical principles to drug dosage forms is illustrated when drug dosage forms are **categorized** according to their **physical state**, **degree of heterogeneity**, and **chemical composition**. The usual relevant states of matter are **gases**, **liquids**, and **solids**. Intermolecular forces of attraction are weakest in gases and strongest in solids. Conversions from one physical state to another can involve simply overcoming intermolecular forces of attraction by adding energy (heat). Chemical composition can have a dramatic effect on physicochemical properties and behavior. For this reason, it is necessary to distinguish between **polymers**, or **macromolecules**, and more conventional (i.e., smaller) molecules, or **micromolecules**.

B. Intermolecular forces of attraction. Because atoms vary in their electronegativity, electron sharing between different atoms is likely to be unequal. This asymmetric electron distribution causes a shift in the overall electron cloud in the molecule. As a result, the molecule tends to behave as a **dipole** (i.e., as if it had a positive and a negative pole). The dipole associated with each covalent bond has a corresponding **dipole moment** (μ) defined as the product of the distance of charge separation (d) and the charge (q):

$$\mu = q \times d$$

The molecular dipole moment may be viewed as the vector sum of the individual bond moments.

1. **Nonpolar** molecules that have **perfect symmetry** (e.g., carbon tetrachloride) have dipole moments of zero (*Figure 2-1*).

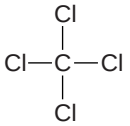


Figure 2-1. The carbon tetrachloride molecule.

2. **Polar** molecules are **asymmetric** and have nonzero dipole moments.
3. When **dipolar** molecules approach one another close enough—"positive to positive" or "negative to negative"—so that their electron clouds interpenetrate, **intermolecular repulsive forces** arise. When these dipolar molecules approach one another so that the positive pole of one is close to the negative pole of the other, molecular **attraction** occurs (**dipole–dipole interaction**). When the identically charged poles of the two molecules are closer, **repulsion** occurs.

C. **Types of intermolecular forces of attraction** include the following:
1. Nonpolar molecules do not have permanent dipoles. However, the instantaneous electron distribution in a molecule can be asymmetric. The resultant transient dipole moment can induce a dipole in an adjacent molecule. This **induced dipole-induced dipole interaction** (**London dispersion force**), with a force of 0.5 to 1 kcal/mol, is sufficient to facilitate order in a molecular array. These relatively weak electrostatic forces are responsible for the liquefaction of nonpolar gases.
2. The transient dipole induced by a permanent dipole, or **dipole-induced dipole interaction** (**Debye induction force**), is a stronger interaction, with a force of 1 to 3 kcal/mol.
3. **Permanent dipole interactions** (**Keesom orientation forces**), with a force of 1 to 7 kcal/mol, together with Debye and London forces, constitute **van der Waals forces**. Collectively, they are responsible for the more substantive structure and molecular ordering found in liquids.
4. **Hydrogen bonds**. Because they are small and have a large electrostatic field, hydrogen atoms can approach highly electronegative atoms (e.g., fluorine, oxygen, nitrogen, chlorine, sulfur) and interact electrostatically to form a hydrogen bond. Depending on the electronegativity of the second atom and the molecular environment in which hydrogen bonding occurs, hydrogen bond energy varies from approximately 1 to 8 kcal/mol.
5. **Ion–ion**, **ion–dipole**, **and ion-induced dipole forces**. **Positive–negative ion interactions** in the solid state involve forces of 100 to 200 kcal/mol. Ionic interactions are reduced considerably in liquid systems in the presence of other electrolytes. **Ion–dipole** interaction, or **dipole induction by an ion**, can also affect molecular aggregation, or ordering, in a system.

III. STATES OF MATTER

A. **Gases**. Molecules in the gaseous state can be pictured as moving along straight paths, in all directions and at high velocities (e.g., mean velocity for H_2O vapor: 587 m/sec; for O_2: 440 m/sec), until they collide with other molecules. As a result of these random collisions, molecular velocities and paths change, and the molecules continue to collide with other molecules and with the boundaries of the system (e.g., the walls of a container holding the gas). This process, repeated incessantly, is responsible for the **pressure** exhibited within the confines of the system.
1. The interrelation among **volume** (**V**), **pressure** (**P**), and the **absolute temperature** (**T**) is given by the **ideal gas law**, which is the equation of state for an ideal gas:

$$PV = nRT$$
$$PV = (g/M)RT$$

where n is the number of moles of gas—equivalent to the number of grams (g) of gas divided by the molecular weight of the gas (M)—and R is the **molar gas constant** (0.08205 L atm/mole deg).
2. Pharmaceutical gases include the **anesthetic gases** (e.g., nitrous oxide, halothane). **Compressed gases** include oxygen (for therapy), nitrogen, and carbon dioxide. **Liquefiable gases**, including certain **halohydrocarbons** and **hydrocarbons**, are used as propellants in **aerosol products** (**pressurized packaging**), as are compressed gases, such as nitrous oxide, nitrogen, and carbon dioxide. Ethylene oxide is a gas used to sterilize or disinfect heat-labile objects.
3. In general, as the temperature of a substance increases, its **heat content**, or **enthalpy**, increases as well.
   a. Substances can undergo a change of state, or phase change, from the solid to the liquid state (**melting**) or from the liquid to the gaseous state (**vaporization**).
   b. **Volatile liquids** (e.g., ether, halothane, methoxyflurane) are used as inhalation anesthetics. Amyl nitrite is a volatile liquid that is inhaled for its vasodilating effect in acute angina.
   c. **Sublimation** occurs when a solid is heated directly to the gaseous, or vapor, state without passing through the liquid state (e.g., camphor, iodine). Ice sublimes at pressures below 3 torr. The process of **freeze-drying**, or **lyophilization**, is a form of vacuum drying in which water is

removed by sublimation from the frozen product. It is an especially useful process for drying aqueous solutions or dispersions of heat- or oxygen-sensitive drugs and biologicals (e.g., proteins, peptides).

d. The reverse process (i.e., direct transition from the vapor state to the solid state) is also referred to as sublimation, but the preferred term is **deposition**. Some forms of sulfur and colloidal silicon dioxide are prepared in this way.

4. The intermolecular forces of attraction in gases are virtually nonexistent at room temperature. Gases display little or no ordering.

B. Liquids. The intermolecular forces of attraction in liquids (**van der Waals forces**) are sufficient to impose some ordering, or regular arrangement, among the molecules. **Hydrogen bonding** increases the likelihood of cohesion in liquids and further affects their physicochemical behavior. However, these forces are much weaker than **covalent** or **ionic** forces. Therefore, liquids tend to display short-range rather than long-range order. Hypothetically, although molecules of a liquid would tend to aggregate in localized clusters, no defined structuring would be evident.

1. Surface and interfacial tension

a. Molecules in the bulk phase of a liquid are surrounded by other molecules of the same kind (*Figure 2-2A*). Molecules at the surface of a liquid are not completely surrounded by like molecules (*Figure 2-2B*). As a result, molecules at or near the surface of a liquid experience a net inward pull from molecules in the interior of the liquid. Because of this net inward intermolecular attraction, the liquid surface tends to spontaneously contract. Thus, liquids tend to assume a spherical shape (i.e., a volume with the minimum surface area). This configuration has the least free energy.

b. Any expansion of the surface increases the free energy of the system. Thus, **surface free energy** can be defined by the work required to increase the surface area A of the liquid by 1 area unit. This value is expressed as the number of millinewtons (mN) needed to expand a 1-m^2 surface by 1 unit:

$$\text{work} = \gamma \times \Delta A$$

where ΔA is the increase in surface area and γ is the **surface tension**, or **surface free energy**, in mN m^{-1}—equivalent to centimeter-gram-second (CGS) units of dynes cm^{-1}. At 20°C, water has a surface tension of 72 mN m^{-1}, whereas *n*-octanol has a surface tension of 27 mN m^{-1}. Thus more work must be expended to expand the surface of water than to expand the surface of *n*-octanol (i.e., to proceed from a given volume of bulk liquid to the corresponding volume of small droplets).

c. At the **boundary**, or **interface**, between two immiscible liquids that are in contact with one another, the corresponding **interfacial tension** (i.e., free energy or work required to expand the interfacial area) reflects the extent of the intermolecular forces of attraction and repulsion at the interface. When the interface is between two liquids, substantial molecular interaction occurs across the interface between the two phases. This interaction reduces the imbalance in forces of attraction within each phase. The interfacial tension between *n*-octanol and water is reduced to 8.5 mN m^{-1} from 72 mN m^{-1} (γ air/water). This reduction indicates, in part, the interfacial interaction between *n*-octanol and water.

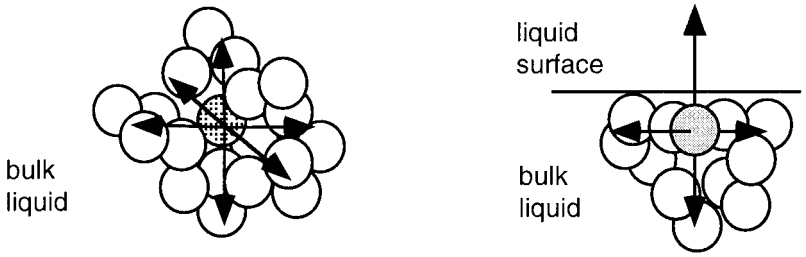


Figure 2-2. A. Molecules in the bulk phase. **B.** Molecules at the surface of a liquid.

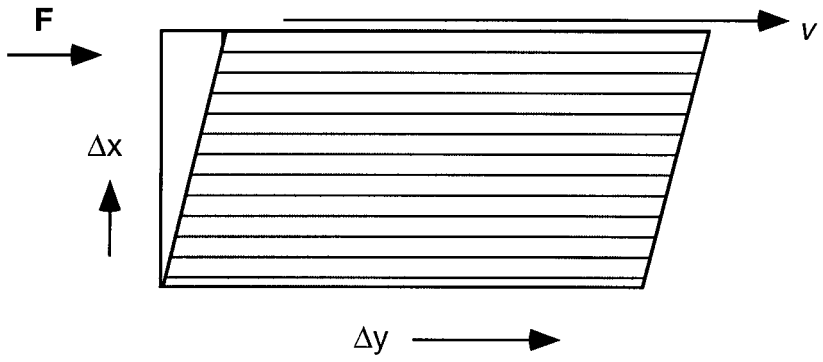


Figure 2-3. Liquid flow.

2. The flow of a liquid across a solid surface can be examined in terms of the **velocity**, or rate of movement, of the liquid relative to the surface across which it flows. More insight can be gained by visualizing the flow of liquid as involving the movement of numerous parallel layers of liquid between an upper, movable plate and a lower, fixed plate (*Figure 2-3*). The application of a constant force (F) to the upper plate causes both this plate and the uppermost layer of liquid in contact with it to move with a velocity $\Delta y/\Delta x$. The interaction between the fixed bottom plate and the liquid layer closest to it prevents the movement of the bottom layer of liquid. The **velocity** (v) of the remaining layers of liquid between the two plates is proportional to their distance from the immovable plate (i.e., $\Delta y/\Delta x$). The **velocity gradient** leads to deformation of the liquid with time. This deformation is the **rate of shear**, dv/dx, or D. **Newton** defined flow in terms of the ratio of the force F applied to a plate of area A—**shear stress** (τ)—divided by the velocity gradient (D) induced by τ:

$$\frac{F}{A} = \eta \frac{dv}{dx}$$

or

$$\frac{\tau}{D} = \eta$$

The proportionality constant η is the coefficient of **viscosity**. It indicates the resistance to flow of adjacent layers of fluid. The reciprocal of η is **fluidity**. Units of viscosity in the CGS system are dynes $cm^{-2}s^{-1}$, or poise. In the SI system, the units are Newtons $m^{-2}s^{-1}$, which corresponds to 10 poise. The viscosity of water at 20°C is approximately 0.01 poise, or 1 centipoise (cps), which corresponds to 1 mN $m^{-2}s^{-1}$ or 1 mPa · s (milliPascal second).

   a. Substances that flow in accordance with the equation in III.B.2 (Newton's law) are known as **Newtonian substances**. Liquids that consist of simple molecules and dilute dispersions tend to be **Newtonian**. For a Newtonian fluid, a plot of shear stress as a function of shear rate (a **flow curve** or **rheogram**) yields a straight line with a slope of η (*Figure 2-4*, *Curve 1*).

   b. **Non-Newtonian substances** do not obey Newton's equation of flow. These substances tend to exhibit **shear-dependent** or **time-dependent viscosity**. In either case, viscosity is more aptly termed **apparent viscosity** because Newton's law is not strictly obeyed. Heterogeneous liquids and solids are most likely non-Newtonian.

      (1) **Shear-dependent viscosity** involves either an *increase* in apparent viscosity (i.e., **shear thickening** or **dilatancy**) (*Figure 2-4*, *Curve 3*) or a *decrease* in apparent viscosity (i.e., **shear thinning** or **pseudoplasticity**) (*Figure 2-4*, *Curve 2*) with an increase in the rate of shear. Shear thickening is displayed by suspensions that have a high solid content of small, deflocculated particles. Shear thinning is displayed by polymer or macromolecule solutions. **Plastic**, or **Bingham body**, behavior (*Figure 2-4*, *Curve 4*) is exemplified by flocculated particles in concentrated suspensions that show no apparent response to low-level stress. Flow begins only after a limiting yield stress (**yield value**) is exceeded.

      (2) **Time-dependent viscosity**

         (a) The yield value of **plastic** systems may be time dependent (i.e., may depend on the time scale involved in the application of force). **Thixotropic** systems display shear-thinning behavior but do not immediately recover their higher apparent viscosity

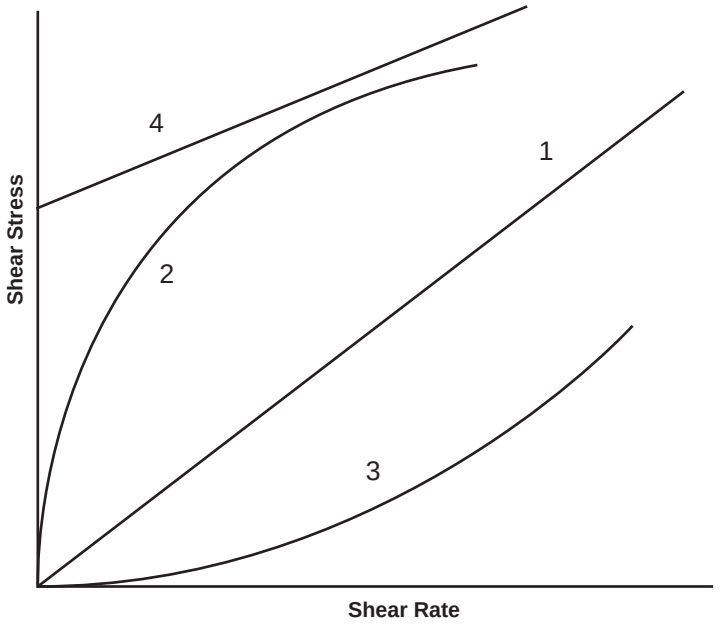


Figure 2-4. Non-Newtonian flow curves.

when the rate of shear is lowered. In a thixotropic system, structural recovery is relatively slow compared with structural breakdown.

(b) **Thixotropy** occurs with heterogeneous systems that involve a three-dimensional structure or network. When such a system is at rest, it appears to have a relatively rigid consistency. Under shear, the structure breaks down and fluidity increases (i.e., **gel–sol** transformation).

(c) **Rheopexy** (**negative thixotropy**, **or antithixotropy**) occurs when the apparent viscosity of the system continues to increase with continued application of shear up to some equilibrium value at a given shear rate. These systems display a **sol–gel** transformation. One explanation for antithixotropic behavior is that continued shear increases the frequency of particle or macromolecule interactions and leads to increased structure in the system.

C. Solids. Intermolecular forces of attraction are stronger in solids than in liquids or gases. Molecular arrangements in solids may be characterized as either crystalline or amorphous.

1. **Crystalline solids** have the following attributes:
   - **a.** Fixed **molecular order** (i.e., molecules occupy set positions in a specific array)
   - **b.** A distinct melting point
   - **c.** **Anisotropicity** (i.e., their properties are not the same in all directions), with the exception of cubic crystals
2. **Amorphous solids** have the following attributes:
   - **a.** Randomly arranged molecules with the short-range order typical of liquids
   - **b.** No melting points
   - **c.** **Isotropicity** (i.e., properties are the same in all directions)
   - **d.** Less thermodynamic stability than the corresponding crystalline solid and therefore more apt to exhibit chemical and physical instability, increased dissolution rate, etc.
3. **Polymorphism** is the condition wherein substances can exist in more than one crystalline form. These **polymorphs** have different molecular arrangements or crystal lattice structures. As a result, the different polymorphs of a drug solid can have different properties. For example, the melting point, solubility, dissolution rate, density, and stability can differ considerably among the polymorphic forms of a drug. Many drugs exhibit polymorphic behavior. Fatty (triglyceride) excipients (e.g., theobroma oil, cocoa butter) are recognized for their polymorphic behavior.
4. The incorporation of solvent molecules into the crystal lattice of a solid results in a molecular adduct known as a **solvate** or **hydrate** (the latter term is used when water is the solvent). In general, solvates or hydrates exhibit different solubilities and dissolution rates than their unsolvated/anhydrous counterparts.

5. **Melting point and heat of fusion**. The melting point of a solid is the temperature at which the solid is transformed to a liquid. When 1 g of a solid is heated and melts, the heat absorbed in the process is referred to as the **latent heat of fusion**.

D. Phase diagrams and phase equilibria. A **phase diagram** represents the states of matter (i.e., solid, liquid, and gas) that exist as temperature and pressure are varied (*Figure 2-5*). The data arrays separating the phases in *Figure 2-5* delineate the temperatures and pressures at which the phases can coexist. Thus, gas (or vapor) and liquid coexist along "curve" *BC*, solid and liquid coexist along "curve" *AB*, and solid and gas (or vapor) coexist along "curve" *DB*. Depending on the change in temperature and pressure, **evaporation** or **condensation** occur along curve *BC*, **fusion** or **melting** along curve *AB*, and **sublimation** or **deposition** along curve *DB*. The three "curves" intersect at point *B*. Only at this unique temperature and pressure, known as the **triple point**, do all three phases exist in equilibrium. (The triple point for water is 0.01°C and 6.04×10^{-3} atm) Continuing along curve *BC*, to higher temperatures and pressures, one ultimately reaches point *C*, known as the **critical point**, above which there is no distinction between the liquid and the gas phases. Substances that exist above this critical point are known as **supercritical fluids**. Supercritical fluids such as carbon dioxide (critical point, 30.98°C and 73.8 atm) often exhibit markedly altered physicochemical properties (e.g., density, diffusivity, or solubility characteristics) that render them useful as solvents and processing aids in the production of pharmaceuticals and drug delivery systems.

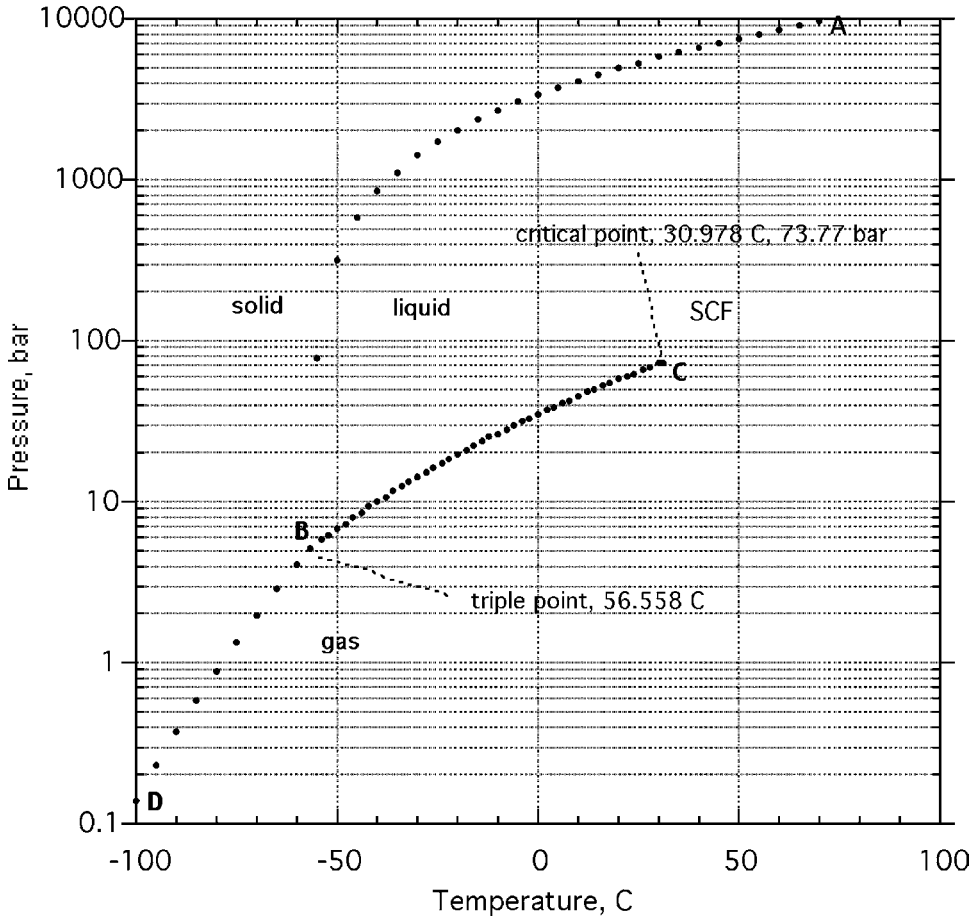


Figure 2-5. Phase diagram for CO_2 showing the variation of the state of matter as pressure and temperature are varied. The solid state exists in the region *ABD*; the liquid state, in the region *ABC*; and the gas state, in the region to the right of curve *CD*. *B* corresponds to the triple point, the pressure and temperature at which all three phases coexist. *C* corresponds to the critical point, the pressure and temperature above which the liquid and gas phases are indistinguishable.

IV. PHYSICOCHEMICAL BEHAVIOR

A. Homogeneous systems

1. A **solution** is a homogeneous system in which a **solute** is molecularly dispersed, or dissolved, in a **solvent**. The solvent is the predominant species. **Saturated solutions** are solutions that, at a given temperature and pressure, contain the maximum amount of solute that can be accommodated by the solvent. If the saturation, or solubility, limit is exceeded, a fraction of the solute can separate from the solution and exist in equilibrium with it.
   a. **Solutes** can be gases, liquids, or solids, and nonelectrolytes or electrolytes.
      (1) **Nonelectrolytes** are substances that **do not form ions** when dissolved in water. Examples are estradiol, glycerin, urea, and sucrose. Their aqueous solutions do not conduct electric current.
      (2) **Electrolytes** are substances that **do form ions** in solution. Examples are sodium chloride, hydrochloric acid, and atropine. As a result, their aqueous solutions conduct electric current. Electrolytes are characterized as **strong** or **weak**. Strong electrolytes (e.g., sodium chloride, hydrochloric acid) are **completely ionized** in water at all concentrations. Weak electrolytes (e.g., aspirin, atropine) are **partially ionized** in water.
   b. The **colligative properties of a solution** depend on the total **number of ionic and nonionic solute molecules in the solution**. These properties depend on ionization but are **independent of other chemical properties of the solute**.
2. **Colligative properties** include the following:
   a. **Lowering of vapor pressure**. The **partial vapor pressure** of each volatile component in a solution is equal to the product of the mole fraction of the component in the solution and the vapor pressure of the pure component. This is **Raoult's law**:

$$P_A = P_A^0 \times x_A$$

   where P_A is the partial vapor pressure above a solution in which the mole fraction of the solute A is x_A and P_A^0 is the **vapor pressure** of the pure component A. The vapor pressure is the pressure at which equilibrium is established between the molecules of A in the liquid state and the molecules of A in the gaseous (vapor) state in a closed, evacuated container. The vapor pressure is temperature dependent, but independent of the amount of liquid and vapor. Raoult's law holds for ideal solutions of nonelectrolytes. For a **binary solution** (i.e., a solution of component B in component A)

$$\frac{P_A^0 - P_A}{P_A^0} = (1 - x_A) = x_B$$

   The lowering of the vapor pressure of the solution relative to the vapor pressure of the pure solvent is proportional to the number of molecules of solute in the solution. The actual lowering of the vapor pressure by the solute, Δp_A, is given by

$$\Delta p_A = (P_A^0 - p_A) = x_B P_A^0$$

   b. **Elevation of the boiling point**. The **boiling point** is the temperature at which the vapor pressure of a liquid equals an external pressure of 760 mm Hg. A solution of a nonvolatile solute has a higher boiling point than a pure solvent because the solute lowers the vapor pressure of the solvent. The amount of elevation of the boiling point (ΔT_b) depends on the concentration of the solute:

$$\Delta T_b = \frac{RT_0^2 M_1 m}{1000 \times \Delta H_{vap}} = K_b m$$

   where K_b is the molal boiling point elevation constant, R is the molar gas constant, T is absolute temperature (degrees K), M_1 is the molecular weight of the solute, m is the molality of the solution, and ΔH_{vap} is the molal enthalpy of vaporization of the solvent.
   c. **Depression of the freezing point**. The **freezing point**, or melting point, of a pure compound is the temperature at which the solid and the liquid phases are in equilibrium under a pressure of 1 atmosphere (atm). The freezing point of a solution is the temperature at which the solid

phase of the pure solvent and the liquid phase of the solution are in equilibrium under a pressure of 1 atm. The amount of depression of the freezing point (ΔT_f) depends on the molality of the solution:

$$\Delta T_f = \frac{RT_0^2 M_1 m}{1000 \times \Delta H_{fusion}} = K_f m$$

where K_f is the molal freezing point constant and ΔH_{fusion} is the molal heat of fusion.

d. Osmotic pressure. **Osmosis** is the process by which solvent molecules pass through a semipermeable membrane (a barrier through which only solvent molecules may pass) from a region of dilute solution to one of more concentrated solution. Solvent molecules transfer because of the inequality in chemical potential on the two sides of the membrane. Solvent molecules in a concentrated solution have a lower chemical potential than solvent molecules in a more dilute solution.

(1) **Osmotic pressure** is the **pressure** that must be applied to the solution to prevent the flow of pure solvent into the concentrated solution.

(2) Solvent molecules move from a region where their **escaping tendency is high** to one where their **escaping tendency is low**. The presence of dissolved solute lowers the escaping tendency of the solvent in proportion to the solute concentration.

(3) The **van't Hoff equation** defines the osmotic pressure π as a function of the number of moles of solute n_2 in the solution of volume V:

$$\pi V = n_2 RT$$

3. Electrolyte solutions and ionic equilibria

a. Acid–base equilibria

(1) According to the **Arrhenius dissociation theory**, an **acid** is a substance that liberates H^+ in aqueous solution. A **base** is a substance that liberates hydroxyl ions (OH^-) in aqueous solution. This definition applies only under aqueous conditions.

(2) The **Lowry–Brønsted theory** is a more powerful concept that applies to aqueous and nonaqueous systems. It is most commonly used for pharmaceutical and biologic systems because these systems are primarily aqueous.

(a) According to this definition, an **acid** is a substance (charged or uncharged) that is capable of donating a proton. A **base** is a substance (charged or uncharged) that is capable of accepting a proton from an acid. The dissociation of an acid (HA) always produces a base (A^-) according to the following formula:

$$HA \leftrightarrow H^+ + A^-$$

(b) HA and A^- are a **conjugate acid–base pair** (an acid and a base that exist in equilibrium and differ in structure by a proton). The proton of an acid does not exist free in solution, but combines with the solvent. In water, this **hydrated proton** is a **hydronium ion** (H_3O^+).

(c) The relative **strengths** of acids and bases are determined by their ability to donate or accept protons. For example, in water, HCl donates a proton more readily than does acetic acid. Thus HCl is a stronger acid. Acid strength is also determined by the affinity of the solvent for protons. For example, HCl may dissociate completely in liquid ammonia, but only very slightly in glacial acetic acid. Thus, HCl is a strong acid in liquid ammonia and a weak acid in glacial acetic acid.

(3) The **Lewis theory** extends the acid–base concept to reactions that do not involve protons. It defines an **acid** as a molecule or ion that accepts an electron pair from another atom and a **base** as a substance that donates an electron pair to be shared with another atom.

b. H^+ concentration values are very small. Therefore, they are expressed in **exponential notation as pH**. The pH is the logarithm of the reciprocal of the H^+ concentration

$$pH = \log\left(\frac{1}{[H^+]}\right)$$

where $[H^+]$ is the molar concentration of H^+. Because the logarithm of a reciprocal equals the **negative logarithm** of the number, this equation may be rewritten as

$$pH = -\log [H^+]$$

or

$$[H^+] = 10^{-pH}$$

Thus, the pH value may be defined as the negative logarithm of the $[H^+]$ value. For example, if the H^+ concentration of a solution is 5×10^{-6}, the pH value may be calculated as follows:

$$\begin{aligned} pH &= -\log (5 \times 10^{-6}) \\ \log 5 &= 0.699 \\ \log 10^{-6} &= -6.0 \\ pH &= -(-6 + 0.699) \\ &= -(-5.301) \\ &= 5.301 \end{aligned}$$

c. As pH decreases, **H^+ concentration increases exponentially**. When the pH decreases from 6 to 5, the H^+ concentration increases from 10^{-6} to 10^{-5}, or 10 times its original value. When the pH falls from 5 to 4.7, the H^+ concentration increases from 1×10^{-5} to 2×10^{-5}, or double its initial value.

d. **Dissociation constants**. **Ionization** is the complete separation of the ions in a crystal lattice when the salt is dissolved. **Dissociation** is the separation of ions in solution when the ions are associated by interionic attraction.

(1) For **weak electrolytes**, dissociation is a reversible process. The equilibrium of this process can be expressed by the law of mass action. This law states that the rate of the chemical reaction is proportional to the product of the concentration of the reacting substances, each raised to a power of the number of moles of the substance in solution.

(2) For **weak acids**, dissociation in water is expressed as

$$HA \leftrightarrow H^+ + A^-$$

The dynamic equilibrium between the simultaneous forward and reverse reactions is indicated by the arrows. By the law of mass action,

$$\text{rate of forward reaction} = K_1[HA]$$
$$\text{rate of reverse reaction} = K_2[H^+][A^-]$$

At equilibrium, the forward and reverse rates are equal. Therefore,

$$K_1[HA] = K_2[H^+][A^-]$$

Thus, **the equilibrium expression for the dissociation of a weak acid** is written as

$$K_a = \frac{K_1}{K_2} = \frac{[H^+][A^-]}{[HA]}$$

where K_a represents the acid dissociation constant. For a weak acid, the **acid dissociation constant** is conventionally expressed as **pK_a**, which is $-\log K_a$. For example, the K_a of acetic acid at 25°C is 1.75×10^{-5}. The pK_a is calculated as follows:

$$\begin{aligned} pK_a &= -\log (1.75 \times 10^{-5}) \\ \log 1.75 &= 0.243 \\ \log 10^{-5} &= -5 \\ pH &= -(-5 + 0.243) \\ &= -(-4.757) \\ &= 4.76 \end{aligned}$$

(3) For **weak bases**, dissociation may also be expressed with the K_a expression for the **conjugate acid of the base**. This acid is formed when a proton reacts with the base. For a base that does not contain a hydroxyl group,

$$BH^+ \leftrightarrow H^+ + B$$

The **dissociation constant** for this reaction is expressed as

$$K_a = \frac{[H^+][B]}{[BH^+]}$$

However, a **base dissociation constant** is traditionally defined for a weak base with this expression:

$$B + H_2O \leftrightarrow OH^- + BH^+$$

$$K_b = \frac{[OH^-][BH^+]}{[B]}$$

where K_b represents the dissociation constant of a weak base. This **dissociation constant** can be expressed as $\mathbf{pK_b}$ as follows:

$$pK_b = -\log K_b$$

(4) **Certain compounds** (acids or bases) can accept or donate more than one proton. Consequently, they have **more than one dissociation constant**.

e. **Henderson–Hasselbalch equations** describe the relation between the ionized and the un-ionized species of a weak electrolyte.

(1) For **weak acids**, the Henderson–Hasselbalch equation is obtained from the equilibrium relation described in IV.A.3d.(2).

$$pH = pK_a + \log \frac{[salt]}{[acid]}$$

(2) Similarly, the Henderson–Hasselbalch equation for **weak bases** is as follows:

$$pH = pK_a + \log \frac{[B]}{[BH^+]}$$

where B is the un-ionized weak base and BH^+ is the protonated base.

f. The **degree of ionization (α)**, the fraction of a weak electrolyte that is ionized in solution, is calculated from the following equation:

$$\alpha = \frac{[I]}{[I] + [U]}$$

where [I] and [U] represent the concentrations of the ionized and un-ionized species, respectively. The degree of ionization depends solely on the pH of the solution and the pK_a of the weak electrolyte. **When $\mathbf{pH = pK_a}$**, the Henderson–Hasselbalch equations are for a weak acid and a weak base, respectively:

$$pH - pK_a = 0 = \log \frac{[A^-]}{[HA]}$$

thus

$$\frac{[A^-]}{[HA]} = 1$$

$$pH - pK_a = 0 = \log \frac{[B]}{[BH^+]}$$

thus

$$\frac{[B]}{[BH^+]} = 1$$

In effect, when the pH of the solution is numerically equivalent to the pK_a of the weak electrolyte, whether a weak base or a weak acid, [I] = [U] and the degree of ionization $\alpha = 0.5$ (i.e., 50% of the solute is ionized).

g. Solubility of a weak electrolyte varies as a function of pH.

(1) For a **weak acid**, the total solubility C_s is given by the expression

$$C_s = [HA] + [A^-]$$

where [HA] is the intrinsic solubility of the un-ionized weak acid and is denoted as C_0, whereas $[A^-]$ is the concentration of its anion. Because $[A^-]$ can be expressed in terms of C_0 and the dissociation constant K_a,

$$C_s = C_0 + \frac{K_a C_0}{[H^+]}$$

Thus, the **solubility of a weak acid increases with increasing pH** (i.e., with an increasing degree of ionization, as the anion is more polar and therefore more water soluble than the un-ionized weak acid).

(2) Similarly, for **weak bases**,

$$C_s = C_0 + \frac{C_0[H^+]}{K_a}$$

Thus, the **solubility decreases with increasing pH** because more of the weak base is in the unprotonated form. This form is less polar and therefore less water soluble.

h. Buffers and buffer capacity

(1) A **buffer** is a mixture of salt with acid or base that resists changes in pH when small quantities of acid or base are added. A buffer can be a **combination** of a weak acid and its conjugate base (salt) or a combination of a weak base and its conjugate acid (salt). However, buffer solutions are more **commonly prepared** from weak acids and their salts. They are not ordinarily prepared from weak bases and their salts because weak bases are often unstable and volatile.

(a) For a **weak acid and its salt**, the following buffer equation is satisfactory for calculations with a pH of 4 to 10. It is important in the preparation of buffered pharmaceutical solutions:

$$pH = pK_a + \log \frac{[salt]}{[acid]}$$

(b) For a **weak base and its salt**, the buffer equation is similar but also depends on the dissociation constant of water (pK_w). The equation becomes

$$pH = pK_w - pK_b \log \frac{[base]}{[salt]}$$

(2) **Buffer action** is the resistance to a change in pH.

(3) **Buffer capacity** is the ability of a buffer solution to resist changes in pH. The **smaller the pH change** caused by addition of a given amount of acid or base, the **greater the buffer capacity** of the solution.

(a) Buffer capacity is the number of gram equivalents of an acid or base that changes the pH of 1 L of buffer solution by 1 U.

(b) Buffer capacity is affected by the concentration of the buffer constituents. A higher concentration provides a greater acid or base reserve. Buffer capacity (β) is related to total concentration (C) as follows:

$$\beta = \frac{2.3\, C K_a [H^+]}{(K_a + [H^+])^2}$$

where C represents the molar concentrations of the acid and the salt.

(c) Thus, buffer capacity depends on the value of the ratio of the salt to the acid form. It increases as the ratio approaches unity. Maximum buffer capacity occurs when $pH = pK_a$ and is represented by $\beta = 0.576C$.

B. Heterogeneous (disperse) systems

1. Introduction

a. A **suspension** is a two-phase system that is composed of a solid material dispersed in an oily or aqueous liquid. The particle size of the dispersed solid is usually > 0.5 μm.

b. An **emulsion** is a heterogeneous system that consists of at least one immiscible liquid that is intimately dispersed in another in the form of droplets. The droplet diameter usually exceeds 0.1 μm. Emulsions are **inherently unstable** because the droplets of the dispersed liquid tend to coalesce to form large droplets until all of the dispersed droplets have coalesced. The third component of the system is an **emulsifying agent**. This agent prevents coalescence and maintains the integrity of the individual droplets.

2. Dispersion stability. In an **ideal dispersion**, the dispersed particles do not interact. The particles are uniform in size and undergo no change in position other than the random movement that results from Brownian motion. In contrast, in a **real dispersion**, the particles are not uniformly sized (i.e., they are not **monodisperse**). The particles are subject to particulate aggregation, or clumping, and the dispersion becomes more heterogeneous with time. The **rate of settling** (**separating or creaming**) of the dispersed phase in the dispersion medium is a function of the particle size, dispersion phase viscosity, and difference in density between the dispersed phase and the dispersion medium, in accordance with **Stokes's law**:

$$\text{sedimentation rate} = \frac{d^2 g(\rho_1 - \rho_2)}{18\,\eta}$$

where d is the particle diameter, g is the acceleration owing to gravity, η is the viscosity of the dispersion medium, and $(\rho_1 - \rho_2)$ is the difference between the density of the particles (ρ_1) and the density of the dispersion medium (ρ_2). Although Stokes's law was derived to determine the settling, or sedimentation, of noninteracting spherical particles, it also provides guidance for determining the stabilization of dispersion:

a. **Particle size** should be as **small** as possible. Smaller particles yield slower sedimentation, or flotation, rates.

b. **High particulate (dispersed phase) concentrations** increase the rate of particle–particle collisions and interaction. As a result, particle aggregation occurs, and instability increases as the aggregates behave as larger particles. In the case of liquid–liquid dispersions, particle–particle collisions can lead to coalescence (i.e., larger particles) and decrease dispersion stability.

c. **Avoidance of particle–particle interactions**

(1) Aggregation can be prevented if the particles have a similar electrical charge. Particles in an aqueous system always have some electrical charge because of **ionization** of chemical groups on the particle surface or **adsorption** of charged molecules or ions at the interface. If the adsorbed species is an **ionic surfactant** (e.g., sodium lauryl sulfate), the charge associated with the surfactant ion (e.g., lauryl sulfate anion) will accumulate at the interface. However, if a relatively non–surface-active electrolyte is adsorbed, the sign of the charge of the adsorbed ion is less readily predicted.

(2) The **magnitude of the charge** is the difference in electrical potential between the charged surface of the particle and the bulk of the dispersion medium. This magnitude is approximated by the **electrokinetic**, or **zeta**, **potential (ζ)**. The zeta potential is measured from the fixed, avidly bound layers of ions and solvent molecules on the particle surface. When ζ is high (e.g., ≥ 25 mV), interparticulate **repulsive forces** exceed the attractive forces. As a result, the dispersion is **deflocculated** and relatively stable to collision and subsequent aggregation (**flocculation**). When ζ is so low that interparticulate **attractive forces** predominate, loose particle aggregates, or **flocs**, form (i.e., **flocculation** occurs).

d. **Density** can be manipulated to decrease the rate of dispersion instability. The settling rate decreases as $(\rho_1 - \rho_2)$ approaches zero. However, the density of the dispersion medium usually cannot be altered sufficiently to halt the settling (or flotation) process. In the dispersed phase, the density of solid particles is not readily altered; altering the density of liquid particles would require the addition of a miscible liquid of higher (or lower) density. Altering the composition of suspensions is also problematic because most solid particles are denser than the dispersion medium. Additives of higher (or lower) density might alter the biopharmaceutical

characteristics of the formulation (e.g., rate of drug release, residence time at the site of administration, or absorption).

e. The **sedimentation**, or **flotation**, **rate** is inversely proportional to the **viscosity**. An **increase** in the **viscosity of the dispersion medium** decreases the rate of settling, or flotation. However, although the rate of destabilization can be slowed by an increase in viscosity, it cannot be halted.

3. Emulsion stability. **Coalescence** occurs in emulsion systems when the liquid particles of the dispersed phase merge to form larger particles. Coalescence is largely prevented by the **interfacial film** of surfactant around the droplets. This film prevents direct contact of the liquid phase of the droplets. Coalescence of droplets in oil in water (o/w) emulsions is also inhibited by the **electrostatic repulsion** of similarly charged particles. **Creaming** is the **reversible** separation of a layer of emulsified particles. Because mixing or shaking may be sufficient to reconstitute the emulsion system, creaming is not necessarily unacceptable. However, **cracking**, or **irreversible phase separation**, is never acceptable. **Phase inversion**, or emulsion-type reversal, involves the reversion of an emulsion from an o/w to water in oil (w/o) form, or vice versa. Phase inversion can change the consistency or texture of the emulsion or cause further deterioration in its stability.

V. CHEMICAL KINETICS AND DRUG STABILITY

A. Introduction. The **stability** of the **active component** of a drug is a major criterion in the rational design and evaluation of drug dosage forms. Problems with **stability** can determine whether a given formulation is accepted or rejected.

1. Extensive chemical degradation of the active ingredient can cause **substantial loss** of active ingredient from the dosage form.

2. Chemical degradation can produce a **toxic product** that has undesirable side effects.

3. Instability of the drug product can cause **decreased bioavailability**. As a result, the therapeutic efficacy of the dosage form may be substantially reduced.

B. Rates and orders of reactions

1. The **rate of a reaction**, or degradation rate, is the velocity with which the reaction occurs. This rate is expressed as dC/dt (the change in concentration, or C, within a given time interval, or dt).

a. Reaction rates depend on certain conditions (e.g., **reactant concentration**, **temperature**, **pH**, **presence of solvents or additives**). Radiation and catalytic agents (e.g., polyvalent cations) also have an effect.

b. The effective study of reaction rates in the body requires application of **pharmacokinetic principles** (see Chapter 5).

2. The **order of a reaction** is the way in which the concentration of the drug or reactant in a chemical reaction affects the rate. The rate of a reaction, dC/dt, is proportional to the concentration to the nth power, where n is the order of the reaction—that is,

$$\frac{dC}{dt} \propto C^n$$

The study of reaction orders is a crucial aspect of pharmacokinetics (see Chapter 5). Usually, **pharmaceutical degradation** can be treated as a **zero-order**, **first-order**, or **higher order reaction**. The first two are summarized as follows:

a. In a **zero-order reaction**, the **rate is independent of the concentration of the reactants** (i.e., $dC/dt \propto C^0$) (see Chapter 5). Other factors, such as absorption of light in certain photochemical reactions, determine the rate.

(1) A **zero-order reaction** can be expressed as

$$C = -k_0 t + C_0$$

where C is the drug concentration, k_0 is the zero-order rate constant in units of concentration/time, t is the time, and C_0 is the initial concentration.

(2) When this equation is plotted with C on the vertical axis (ordinate) against t on the horizontal axis (abscissa), the **slope of the line is equal to $-k_0$** (*Figure 2-6*). The negative sign indicates that the slope is decreasing.

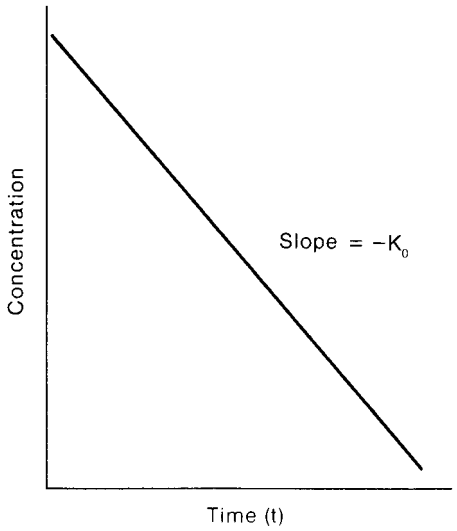


Figure 2-6. Concentration *(C)* versus time *(t)* for a zero-order reaction. The slope of the line equals $-k_0$. The slope of the line is not equal to the rate constant because it includes the minus sign.

b. In a **first-order reaction**, the **rate depends on the first power of the concentration of a single reactant** (i.e., $dC/dt \propto C^1$).

(1) In a first-order reaction, **drug concentration decreases exponentially with time**, in accordance with the equation

$$C = C_0 e^{-k_1 t}$$

where C is the concentration of the reacting material, C_0 is the initial concentration, k_1 is the first-order rate constant in units of reciprocal time, and t is time. A plot of the logarithm of concentration against time produces a straight line with a slope of $-k/2.303$ (*Figure 2-7*).

(2) The **half-life** ($t_{½}$) of a reaction is the time required for the concentration of a drug to decrease by one-half. For a first-order reaction, half-life is expressed by

$$t_{½} = \frac{0.693}{k_1}$$

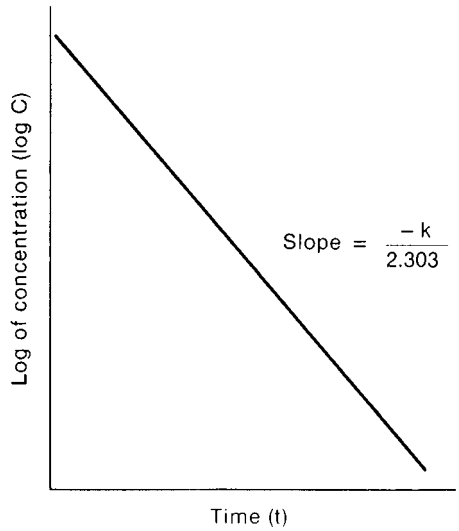


Figure 2-7. Logarithm of concentration (log *C*) versus time (*t*) for a first-order reaction. The slope of the line equals $-k/2.303$.

(3) The **time required for a drug to degrade** to 90% of its original concentration ($t_{90\%}$) is also important. This time represents a reasonable limit of degradation for the active ingredients. The $t_{90\%}$ can be calculated as

$$t_{90\%} = \frac{2.303}{k_1} \log \frac{100}{90} = \frac{0.105}{k_1}$$

(a) because

$$k_1 = 0.693 / t_{½}$$

(b) then

$$t_{90\%} = \frac{0.105}{0.693 / t_{½}} = 0.152 \times t_{½}$$

(4) Both $t_{½}$ and $t_{90\%}$ are **concentration independent**. Thus, for $t_{½}$, it takes the same amount of time to reduce the concentration of the drug from 100 to 50 mM as it does from 50 to 25 mM.

C. Factors that affect reaction rates. Factors other than concentration can affect the reaction rate and stability of a drug. These factors include temperature, the presence of a solvent, pH, and the presence of additives.

1. Temperature. An **increase in temperature** causes an increase in reaction rate, as expressed in the equation first suggested by Arrhenius:

$$k = A \cdot e^{-Ea/RT}$$

or

$$\log k = \log A - \left(\frac{Ea}{2.303} \times \frac{1}{RT}\right)$$

where k is the specific reaction rate constant, A is a constant known as the frequency factor, Ea is the energy of activation, R is the molar gas constant (1.987 cal/degree × mole), and T is the absolute temperature.

a. The **constants *A* and *Ea*** are obtained by determining k at several temperatures and then plotting $\log k$ against $1/T$. The slope of the resulting line equals $-Ea/(2.303 \times R)$. The intercept on the vertical axis equals $\log A$.

b. The activation energy (Ea) is the amount of energy required to put the molecules in an **activated state**. Molecules must be activated to react. As **temperature increases**, more molecules are activated, and the **reaction rate increases**.

2. Presence of solvent. Many dosage forms require the incorporation of a water-miscible solvent—for example, low-molecular-weight alcohols, such as the polyethylene glycols (PEGs)—to stabilize the drug.

a. A change in the solvent system **alters** the transition state and the **activity coefficients** of the reactant molecules. It can also cause simultaneous changes in physicochemical parameters, such as pK_a, surface tension, and viscosity. These changes **indirectly affect the reaction rate**.

b. In some cases, **additional reaction pathways** are generated. For example, with an increasing concentration of ethanol in an aqueous solution, aspirin degrades by an extra route and forms the ethyl ester of acetylsalicylic acid. However, a **change in solvent can also stabilize the drug**.

3. Change in pH. The magnitude of the rate of a hydrolytic reaction catalyzed by H^+ and OH^- can vary considerably with pH.

a. **H^+ catalysis** predominates at **lower pH**, whereas **OH^- catalysis** operates at **higher pH**. At **intermediate pH**, the rate may be **pH independent** or may be catalyzed by **both H^+ and OH^-**. Rate constants in the intermediate pH range are typically less than those at higher or lower pH.

b. To determine the **effect of pH on degradation kinetics**, decomposition is measured at several H^+ concentrations. The **pH of optimum stability** can be determined by plotting the logarithm of the rate constant (k) as a function of pH (*Figure 2-8*). The **point of inflection** of the plot is the pH of optimum stability. This value is useful in the development of a stable drug formulation.

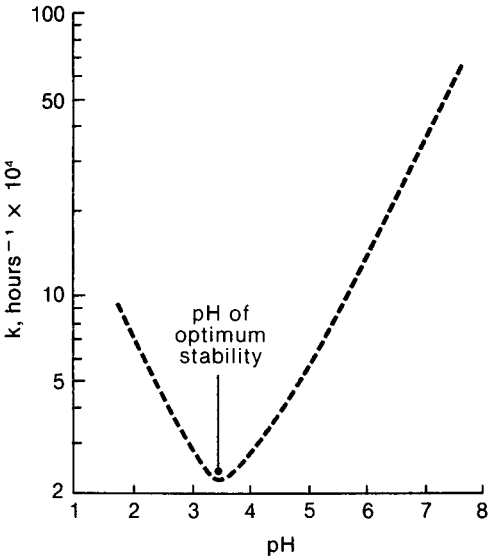


Figure 2-8. Semilogarithmic plot of the rate constant (*k*) versus pH. This plot is used to determine the pH of optimum stability.

4. **Presence of additives**
   a. **Buffer salts** must be added to many drug solutions to maintain the formulation at optimum pH. These salts **can affect the rate of degradation**, primarily as a result of salt increasing the ionic strength.
      (1) Increasing salt concentrations, particularly from polyelectrolytes (e.g., citrate, phosphate), can **substantially affect the magnitude of pK_a.** In this way, they change the rate constant.
      (2) Buffer salts can also **promote drug degradation** through general acid or base catalysis.
   b. The **addition of surfactants** may accelerate or decelerate drug degradation.
      (1) **Acceleration of degradation** is common and is caused by micellar catalysis.
      (2) **Stabilization of a drug** through the addition of a surfactant is less common.
   c. **Complexing agents** can improve drug stability. Aromatic esters (e.g., benzocaine, procaine, tetracaine) **increase in half-life** in the presence of caffeine. This increased stability appears to result from the formation of a less reactive complex between the aromatic ester and the caffeine.

D. **Modes of pharmaceutical degradation**. The decomposition of active ingredients in a dosage form occurs through several pathways (e.g., hydrolysis, oxidation, photolysis; see Chapter 8, II.A).
   1. **Hydrolysis** is the most common type of degradation because many medicinal compounds are esters, amides, or lactams.
      a. **H^+ and OH^-** are the most common catalysts of hydrolytic degradation in solution.
      b. **Esters** usually undergo hydrolytic reactions that cause drug instability. Because esters are rapidly degraded in aqueous solution, formulators are reluctant to incorporate drugs that have ester functional groups into liquid dosage forms.
   2. **Oxidation** is usually mediated through reaction with atmospheric oxygen under ambient conditions (auto-oxidation).
      a. Medicinal compounds that undergo auto-oxidation at room temperature are affected by **oxygen dissolved in the solvent** and in the head space of their packages. These compounds should be packed in an **inert atmosphere** (e.g., nitrogen) to exclude air from their containers.
      b. Most oxidation reactions involve a **free radical mechanism** and a **chain reaction**. Free radicals tend to take electrons from other compounds.
         (1) **Antioxidants** in the formulation react with the free radicals by providing electrons and easily available hydrogen atoms. In this way, they prevent the propagation of chain reactions.
         (2) **Commonly used antioxidants** include ascorbic acid, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate, sodium bisulfite, sodium sulfite, and the tocopherols.
   3. **Photolysis** is the degradation of drug molecules by normal sunlight or room light.
      a. Molecules may absorb the proper wavelength of light and **acquire sufficient energy to undergo reaction**. Usually, photolytic degradation occurs on exposure to light of wavelengths < 400 nm.

b. An **amber glass bottle** or an **opaque container** acts as a barrier to this light, thereby preventing or retarding photolysis. For example, sodium nitroprusside in aqueous solution has a shelf life of only 4 hrs if exposed to normal room light. When protected from light, the solution is stable for at least 1 year.

E. Determination of shelf life. The shelf life of a drug preparation is the amount of time that the product can be stored before it becomes unfit for use, through either chemical decomposition or physical deterioration.

1. **Storage temperature** affects shelf life. It is generally understood to be ambient temperature unless special storage conditions are specified.
2. **In general, a preparation is considered fit for use if it varies from the nominal concentration or dose by no more than 10%**, provided that the decomposition products are not more toxic or harmful than the original material.
3. **Shelf life testing** aids in determining the standard shelf life of a formulation.
   a. Samples are stored at 3° to 5°C and at room temperature (20° to 25°C). The samples are then analyzed at various intervals to determine the **rate of decomposition**. Shelf life is calculated from this rate.
   b. Because storage time at these temperatures can result in an extended testing time, **accelerated testing** is conducted as well, with a range of higher temperatures. The **rate constants** obtained from these samples are used to predict shelf life at ambient or refrigeration temperatures. **Temperature-accelerated stability testing** is not useful if temperature changes are accompanied by changes in the reaction mechanism or by physical changes in the system (e.g., change from the solid to the liquid phase).
   c. **Stability at room temperature** can be predicted from accelerated testing data by the Arrhenius equation:

$$\log\left(\frac{k_{T_2}}{k_{T_1}}\right) = \frac{Ea(T_2 - T_1)}{2.303 \times R \times T_2 \times T_1}$$

   where k_{T_2} and k_{T_1} are the rate constants at the absolute temperatures T_2 and T_1, respectively; R is the molar gas constant; and Ea is the energy of activation.
   d. Alternatively, an expression of concentration can be plotted as a linear function of time. Rate constants (k) for degradation at several temperatures are obtained. The logarithm of the rate constant ($\log k$) is plotted against the reciprocal of absolute temperature ($1/T$) to obtain, by extrapolation, the rate constant for degradation at room temperature (*Figure 2-9*).

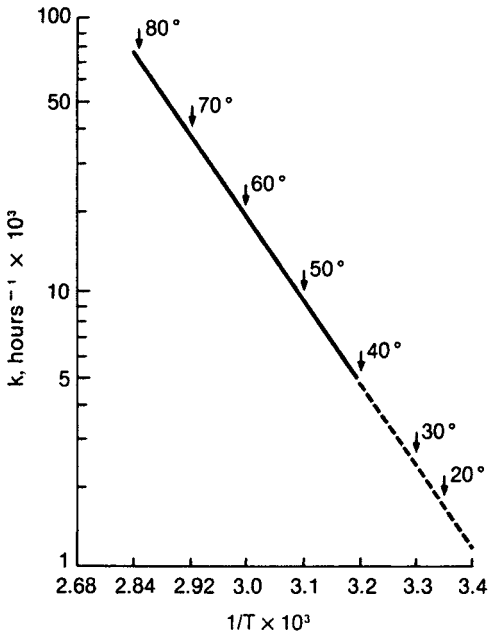


Figure 2-9. Semilogarithmic plot of the rate constant (k) versus the reciprocal of absolute temperature ($1/T$), showing the temperature dependency of degradation rates.

e. The **length of time that the drug will maintain its required potency** can also be predicted by calculation of the $t_{90\%}$ (see V.B.2.b.(3)). This method applies to chemical reactions with activation energies of 10 to 30 kcal/mol—the magnitude of the activation energy for many pharmaceutical degradations that occur in a solution.

VI. DRUG DOSAGE FORMS AND DELIVERY SYSTEMS

A. Oral solutions. The ***United States Pharmacopeia*** (***USP***) **34/*National Formulary*** (***NF***) **29** categorizes **oral solutions** as "liquid preparations, intended for oral administration, that contain one or more substances with or without flavoring, sweetening, or coloring agents dissolved in water or cosolvent-water mixtures." Oral solutions can contain certain polyols (e.g., sorbitol, glycerin) to inhibit crystallization and to modify solubility, taste, mouth feel, and other vehicle properties. They can be "formulated for direct oral administration to the patient or they may be dispensed in a more concentrated form that must be diluted prior to administration." **Drugs in solution** are more homogeneous and easier to swallow than drugs in solid form. For drugs that have a slow dissolution rate, onset of action and bioavailability are also improved. However, drugs in solution are bulkier dosage forms, degrade more rapidly, and are more likely to interact with constituents than those in solid form.

1. Water is the **most commonly used vehicle** for drug solutions. The ***USP*** recognizes seven types of water for the preparation of dosage forms:

a. Purified water *USP* is water obtained by distillation, ion exchange, reverse osmosis, or other suitable treatment. It cannot contain more than 10 parts per million (ppm) of total solid and should have a pH between 5 and 7. Purified water is used in prescriptions and finished manufactured products except parenteral and ophthalmic products.

b. Water for injection *USP* is water obtained by distillation or by reverse osmosis. It conforms to the standards of purified water but is also free of pyrogen. Water for injection is used as a solvent for the preparation of parenteral solutions.

c. Sterile water for injection *USP* is water for injection that is sterilized and packaged in single-dose containers of type I and II glass. These containers do not exceed a capacity of 1 L. The limitations for total solids depend on the size of the container.

d. Bacteriostatic water for injection *USP* is sterile water for injection that contains one or more suitable antimicrobial agents. It is also packaged in single- or multiple-dose containers of type I or II glass. These containers do not exceed the capacity of 30 mL.

e. Sterile water for inhalation *USP* is water that is purified by distillation or by reverse osmosis (i.e., water for injection) and rendered sterile. It contains no antimicrobial agents, except when used in humidifiers or similar devices. This type of water should not be used for parenteral administration or for other sterile dosage forms.

f. Sterile water for irrigation *USP* is water for injection that is sterilized and suitably packaged. It contains no antimicrobial agents or other added substance.

g. Sterile purified water *USP* is purified water sterilized and suitably packaged. It contains no antimicrobial agent. It is not intended for use in parenterals.

2. Oral drug solutions include **syrups** and **elixirs** as well as other less widely prescribed classic (**galenical**) formulations, such as **aromatic waters**, **tinctures**, **fluid extracts**, and **spirits**.

a. Syrups are traditionally per oral solutions that contain high concentrations of sucrose or other sugars. Through common usage, the term *syrup* has also come to include any other liquid dosage form prepared in a sweet, viscous vehicle, including per oral suspensions.

(1) Syrup *NF* (**simple syrup**) is a concentrated or nearly saturated aqueous solution of sugar (85%; 65% w/w).

(2) Syrups have a **low solvent capacity for water-soluble drugs** because the hydrogen bonding between sucrose and water is very strong. For this reason, it can be difficult or impossible to dissolve a drug in syrup. Often, the drug is best dissolved in a small quantity of water, and the flavoring syrup is added.

(3) The **sucrose concentration** of syrup plays a crucial role in the control of microbial growth. Dilute sucrose solutions are excellent media for microorganisms. As the concentration of sucrose approaches saturation, the syrup becomes self-preserving (i.e., requires no additional preservative). However, a saturated solution is undesirable because temperature

fluctuations may cause crystallization. **Syrup *NF*** is a self-preserved solution with a minimal tendency to undergo crystallization.

b. Elixirs are traditionally per oral solutions that contain alcohol as a cosolvent. Many per oral solutions are not described as elixirs but contain alcohol.

(1) To be considered an elixir, the solution **must contain alcohol**. Traditionally, the alcohol content of elixirs has varied from 5% to 40%. Most elixirs become turbid when moderately diluted by aqueous liquids. Elixirs are not the preferred vehicle for salts because alcohol accentuates saline taste. Salts also have limited solubility in alcohol. Therefore, the alcoholic content of salt-containing elixirs must be low.

(2) **Aromatic elixir *NF***, prepared in part from syrup, contains approximately 22% alcohol. The limited usefulness of this elixir as a solvent for drugs was offset by the development of **iso-alcoholic elixir**. It is a combination of **low-alcoholic elixir**, an elixir with low alcoholic content (8% to 10% alcohol), and **high-alcoholic elixir**, an elixir with high alcoholic content (73% to 78% alcohol). Mixing appropriate volumes of the two elixirs provides an alcoholic content sufficient to dissolve the drugs.

B. Miscellaneous solutions

1. Aromatic waters are clear, **saturated aqueous solutions of volatile oils** or other aromatic or volatile substances. Aromatic waters may be used as pleasantly flavored vehicles for a water-soluble drug or as an aqueous phase in an emulsion or suspension. If a large amount of water-soluble drug is added to aromatic water, then an insoluble layer may form at the top. This **"salting out"** is a competitive process. The molecules of water-soluble drugs have more attraction for the solvent molecules of water than the "oil" molecules. The associated water molecules are pulled away from the oil molecules, which are no longer held in solution. Aromatic waters should be stored in tight, light-resistant bottles to reduce volatilization and degradation from sunlight. Aromatic waters are usually prepared by one of the following methods:

a. Distillation is a universal method but is not practical or economical for most products. It is the only method, however, for preparing strong rose water and orange flower water.

b. With the **solution method**, the volatile or aromatic substance is admixed with water, with or without the use of a dispersant (e.g., talc).

2. Spirits, or **essences**, are alcoholic or hydroalcoholic solutions of volatile substances that contain 50% to 90% alcohol. This **high alcoholic content** maintains the water-insoluble volatile oils in solution. If water is added to a spirit, the oils separate. Some spirits are **medicinal** (e.g., aromatic ammonia spirit). Many spirits (e.g., compound orange spirit, compound cardamom spirit) are used as flavoring agents. Spirits should be stored in tight containers to reduce loss by evaporation.

3. Tinctures are alcoholic or hydroalcoholic solutions of chemicals or soluble constituents of vegetable drugs. Although tinctures vary in drug concentration ($\leq$ 50%), those prepared from potent drugs are usually 10% in strength (i.e., 100 mL of the tincture has the activity of 10 g of the drug). Tinctures are usually considered stable. The alcohol content of the official tinctures varies from 17% to 21% for opium tincture *USP* and from 74% to 80% for compound benzoin tincture *USP*. Most tinctures are prepared by an **extraction process** of maceration or percolation. The selection of a **solvent**, or menstruum, is based on the solubility of the active and inert constituents of the crude drugs. Aging can cause precipitation of the inactive constituents of tinctures. Glycerin may be added to the hydroalcoholic solvent to increase the solubility of the active constituent and reduce precipitation on storage. Tinctures must be tightly stoppered and kept from excessive temperatures. Because many of their constituents undergo a photochemical change when exposed to light, tinctures must be stored in light-resistant containers.

4. Fluid extracts are liquid extracts of vegetable drugs that contain alcohol as a solvent, preservative, or both. Fluid extracts are prepared by percolation so that each milliliter contains the therapeutic constituents of 1 g of the standard drug. Because of their high drug content, fluid extracts are sometimes referred to as "100% tinctures." Fluid extracts of potent drugs are usually 10 times as concentrated, or potent, as the corresponding tincture. For example, the usual dose of tincture belladonna is 0.6 mL; the equivalent dose of the more potent fluid extract is 0.06 mL. Many fluid extracts are considered too potent for self-administration by patients, so they are almost never prescribed. In addition, many fluid extracts are simply too bitter. Today, most fluid extracts are modified by either flavoring or sweetening agents.

5. **Nasal**, **ophthalmic**, **otic**, and **parenteral solutions** are classified separately because of their specific use and method of preparation.
6. **Mouthwashes** are solutions that are used to cleanse the mouth or treat diseases of the oral mucous membrane. They often contain alcohol or glycerin to aid in dissolving the volatile ingredients. Mouthwashes are more often used cosmetically than therapeutically.
7. **Astringents** are locally applied solutions that precipitate protein. They reduce cell permeability without causing injury. Astringents cause **constriction**, with wrinkling and blanching of the skin. Because astringents **reduce secretions**, they can be used as antiperspirants.
   a. **Aluminum acetate** and **aluminum subacetate solutions** are used as wet dressings in contact dermatitis. The precipitation is minimized by the addition of boric acid.
   b. **Calcium hydroxide solution** is a mild stringent that is used in lotions as a reactant and an alkalizer.
8. **Antibacterial topical solutions** (e.g., benzalkonium chloride, strong iodine, povidone–iodine) kill bacteria when applied to the skin or mucous membrane in the proper strength and under appropriate conditions.

C. Suspensions

1. **Lotions**, **magmas** (i.e., suspensions of finely divided material in a small amount of water), and **mixtures** are all suspensions that have had official formulas for some time (e.g., calamine lotion *USP*, kaolin mixture with pectin *NF*). Official formulas are given in the *USP*/*NF*.
   a. A **complete formula** and a **detailed method of preparation** are available for some official suspensions. For others, only the **concentration** of the active ingredients is given, and the manufacturer has considerable latitude in the formulation.
   b. Some drugs are packaged in a **dry form** to circumvent the instability of aqueous dispersions. Water is added at the time of dispensing to reconstitute the suspension.
2. **Purposes of suspension**
   a. **Sustaining effect**. For a sustained-release preparation, a suspension necessitates drug dissolution before absorption.
   b. **Stability**. Drug degradation in suspension or solid dosage forms occurs much more slowly than degradation in solution form.
   c. **Taste**. A drug with an unpleasant taste can be converted into an insoluble form and then prepared as a suspension.
   d. **Basic solubility**. When suitable solvents are not available, the suspension provides an alternative. For example, only water can be used as a solvent for ophthalmic preparations because of the possibility of corneal damage. Ophthalmic suspensions provide an alternative to ophthalmic solutions.
3. **Suspending agents** include hydrophilic colloids, clays, and a few other agents. Some are also used as **emulsifying agents** (see VI.D.3).
   a. **Hydrophilic colloids** (i.e., **hydrocolloids**) increase the viscosity of water by binding water molecules, thus limiting their mobility, or fluidity. Viscosity is proportional to the concentration of the hydrocolloid. These agents **support the growth of microorganisms** and require a preservative. They are mostly **anionic**, with the exception of methyl cellulose (neutral) and chitosan (cationic). Thus, the anionic hydrocolloids are incompatible with quaternary antibacterial agents and other positively charged drugs. Chitosan is incompatible with negatively charged drugs and excipients. Most hydrocolloids are **insoluble in alcoholic solutions**.
      (1) **Acacia** is usually used as 35% dispersion in water (mucilage). Its viscosity is greatest between pH 5 and pH 9. Acacia is susceptible to microbial decomposition.
      (2) **Tragacanth** is usually used as 6% dispersion in water (mucilage). One advantage of tragacanth over acacia is that less is needed. Also, tragacanth does not contain the oxidase that is present in acacia. This oxidase catalyzes the decomposition of organic chemicals. The viscosity of tragacanth is greatest at pH 5.
      (3) **Methyl cellulose** is a polymer that is nonionic and stable to heat and light. It is available in several viscosity grades. Because it is soluble in cold water, but not in hot water, dispersions are prepared by adding methyl cellulose to boiling water and then cooling the preparation until the material dissolves.
      (4) **Carboxymethylcellulose** is an anionic material that is soluble in water. Prolonged exposure to heat causes loss of viscosity.

b. Clays (e.g., bentonite, Veegum) are silicates that are anionic in aqueous dispersions. They are strongly hydrated and exhibit **thixotropy** (the property of forming a gel-like structure on standing and becoming fluid on agitation).

(1) The official form of **bentonite** is the 5% magma.

(2) Veegum is hydrated to a greater degree than bentonite. Thus, it is more viscous at the same concentration.

c. Other agents include agar, chondrus (carrageenan), gelatin, pectin, and gelatinized starch. Their use is limited by their susceptibility to bacterial attack, their incompatibilities, and their cost. Xanthan gum is used in many modern suspension formulations because of its cosolvent compatibility, its stability, and its solution's high viscosity relative to concentration.

4. Preparation

a. Solids are wetted initially to separate individual particles and coat them with a layer of dispersion medium. Wetting is accomplished by **levigation** (i.e., addition of a suitable nonsolvent, or **levigating agent**, to the solid material, followed by blending to form a paste), using a glass mortar and pestle or an ointment slab. A **surfactant** can also be used.

b. Suspending agents are then added as dry powder along with the active ingredient. For best results, the suspending agent is added in the form of its **aqueous dispersion**.

(1) The aqueous dispersion is added to the solid (or the levigated solid) by **geometric dilution**.

(2) The preparation is brought to the desired volume by stirring in the appropriate vehicle.

D. Emulsions

1. Purposes of emulsions

a. Increased drug solubility. Many drugs have limited aqueous solubility but have maximum solubility in the oil phase of an emulsion. Drug partitioning from the oil phase to the water phase can maintain or enhance activity.

b. Increased drug stability. Many drugs are more stable when incorporated into an emulsion rather than an aqueous solution.

c. Prolonged drug action. Incorporation of a drug into an emulsion can prolong bioavailability, as with certain intramuscular injection preparations.

d. Improved taste. Drugs with an unpleasant taste are more palatable and thus more conveniently administered in emulsion form.

e. Improved appearance. Oily materials intended for topical application are more appealing in an emulsified form.

2. Phases of emulsions. Most emulsions are considered **two-phase systems**.

a. The **liquid droplet** is known as the **dispersed**, **internal**, or **discontinuous phase**. The other liquid is known as the **dispersion medium**, **external phase**, or **continuous phase**.

b. In pharmaceutical applications, one phase is usually an **aqueous solution**. The other phase is usually **lipid** or **oily**. The lipids range from vegetable or hydrocarbon oils to semisolid hydrocarbons and waxes. Emulsions are usually described in terms of water and oil. Oil is the lipid, or nonaqueous, phase regardless of its composition.

(1) If water is the **internal phase**, the emulsion is classified as **w/o**.

(2) If water is the **external phase**, the emulsion is classified as **o/w**.

c. The **type of emulsion** formed is primarily determined by the **relative phase volumes** and the **emulsifying agent** used.

(1) For an ideal emulsion, the maximum concentration of internal phase is 74% (i.e., theoretically, an o/w emulsion can be prepared containing $\leq$ 74% oil).

(2) The choice of an emulsifying agent is more important than the relative phase volumes in determining the final emulsion type. Most agents preferentially form one type of emulsion or the other if the phase volume permits.

3. Emulsifying agents. Any compound that lowers the interfacial tension and forms a film at the interface can potentially function as an emulsifying agent. The effectiveness of the emulsifying agent depends on its chemical structure, concentration, solubility, pH, physical properties, and electrostatic effect. **True emulsifying agents** (primary agents) can form and stabilize emulsions by themselves. **Stabilizers** (auxiliary agents) do not form acceptable emulsions when used alone,

but assist primary agents in stabilizing the product (e.g., increase viscosity). Emulsifying agents are either **natural** or **synthetic**.

a. Natural emulsifying agents

(1) **Acacia** forms a good, stable emulsion of low viscosity. It tends to cream easily, is acidic, and is stable at a pH range of 2 to 10. Like other gums, it is negatively charged, dehydrates easily, and usually requires a preservative. It is incompatible with Peruvian balsam, bismuth salts, and carbonates.

(2) **Tragacanth** forms a stable emulsion that is coarser than acacia emulsion. It is anionic, is difficult to hydrate, and is used mainly for its effects on viscosity. Less than 1/10 of the amount used for acacia is needed.

(3) **Agar** is an anionic gum that is primarily used to increase viscosity. Its stability is affected by heating, dehydration, and destruction of charge. It is also susceptible to microbial degradation.

(4) **Pectin** is a quasi-emulsifier that is used in the same proportion as tragacanth.

(5) **Gelatin** provides good emulsion stabilization in a concentration of 0.5% to 1.0%. It may be anionic or cationic, depending on its isoelectric point. Type A gelatin (+), prepared from an acid-treated precursor, is used in acidic media. Type B gelatin (−), prepared from an alkali-treated precursor, is used in basic media.

(6) **Methyl cellulose** is nonionic and induces viscosity. It is used as a primary emulsifier with mineral oil and cod liver oil, and yields an o/w emulsion. It is usually used in 2% concentration.

(7) **Carboxymethylcellulose** is anionic and is usually used to increase viscosity. It tolerates alcohol up to 40%, forms a basic solution, and precipitates in the presence of free acids.

b. Synthetic emulsifying agents are anionic, cationic, or nonionic. Although these surfactants are amphiphilic molecules, their lipophilic and hydrophilic regions are seldom inverse equals of each other: Some surfactant molecules tend to be predominantly lipophilic, whereas others are predominantly hydrophilic. This imbalance is reflected in the hydrophilic–lipophilic balance (HLB) scale: The larger the HLB value, the more hydrophilic the molecule. *Table 2-1* lists HLB values for surfactants and their corresponding uses.

(1) **Anionic** synthetic agents include **sulfuric acid esters** (e.g., sodium lauryl sulfate), **sulfonic acid derivatives** (e.g., dioctyl sodium sulfosuccinate), and **soaps**. Soaps are for external use. They have a high pH and are, therefore, sensitive to the addition of acids and electrolytes.

(a) **Alkali soaps** are hydrophilic and form an o/w emulsion.

(b) **Metallic soaps** are water insoluble and form a w/o emulsion.

(c) **Monovalent soaps** form an o/w emulsion.

(d) **Polyvalent soaps** form a w/o emulsion.

(2) **Cationic** synthetic agents (e.g., benzalkonium chloride) are used as surface-active agents in 1% concentration. They are incompatible with soaps.

(3) **Nonionic** synthetic agents are resistant to the addition of acids and electrolytes.

(a) The **sorbitan esters** known as **Spans** are hydrophobic in nature and form w/o emulsions. They have low hydrophilic–lipophilic balance values (1–9) (*Table 2-2*).

Table 2-1 HYDROPHILIC–LIPOPHILIC BALANCE (HLB)

HLB Value Range	Surfactant Application
0–3	Antifoaming agents
4–6	Water-in-oil emulsifying agents
7–9	Wetting agents
8–18	Oil-in-water emulsifying agents
13–15	Detergents
10–18	Solubilizing agents

Table 2-2 COMMONLY USED SURFACTANTS AND THEIR HYDROPHILIC–LIPOPHILIC BALANCE (HLB) VALUES

Agent	HLB Value
Sorbitan trioleate (Span 85, Arlacel 85)	1.8
Sorbitan tristearate (Span 65)	2.1
Propylene glycol monostearate (pure)	3.4
Sorbitan sesquioleate (Arlacel C)	3.7
Sorbitan monooleate (Span 80y)	4.3
Sorbitan monostearate (Arlacel 60)	4.7
Sorbitan monopalmitate (Span 40, Arlacel 40)	6.7
Sorbitan monolaurate (Span 20, Arlacel 20)	8.6
Glyceryl monostearate (Aldo 28, Tegin)	5.5
Gelatin	9.8
Triethanolamine oleate (Trolamine)	12.0
Polyoxyethylene alkyl phenol (Igepal CA-630)	12.8
Tragacanth	13.2
Polyoxyethylene sorbitan monolaurate (Tween 21)	13.3
Polyoxyethylene castor oil (Atlas G-1794)	13.3
Polyoxyethylene sorbitan monooleate (Tween 80)	15.0
Polyoxyethylene sorbitan monopalmitate (Tween 40)	15.6
Polyoxyethylene sorbitan monolaurate (Tween 20)	16.7
Polyoxyethylene lauryl ether (Brij 35)	16.9
Sodium oleate	18.0
Sodium lauryl sulfate	40.0

(b) The **polysorbates** known as **Tweens** are hydrophilic and tend to form o/w emulsions. They may form complexes with phenolic compounds. They have high hydrophilic–lipophilic balance values (11–20).

4. Preparation. Various methods are used to prepare emulsions, depending on the type of emulsifying agent.

a. Classical, acacia-stabilized emulsions are prepared by one of the following four methods:

(1) Wet gum (English) method. A primary emulsion of fixed oil, water, and acacia (in a 4:2:1 ratio) is prepared as follows:

(a) Two parts of water are added all at once to one part of acacia. The mixture is triturated until a smooth mucilage is formed.

(b) Oil is added in small increments (1 to 5 mL), with continuous trituration, until the primary emulsion is formed.

(c) The mixture (an o/w emulsion) is triturated for another 5 mins.

(d) The o/w mixture can then be brought to volume with water and mixed to achieve homogeneity.

(2) Dry gum (continental) method. A primary emulsion of the fixed oil, water, and acacia (in a 4:2:1 ratio) is prepared as follows:

(a) Oil is added to the acacia, and the mixture is triturated until the powder is distributed uniformly throughout the oil. Water is added all at once, followed by rapid trituration to form the primary emulsion.

(b) Any remaining water and other ingredients are added to finish the product.

(i) Electrolytes in high concentration tend to crack an emulsion. They should be added last and in as dilute a form as possible.

(ii) Alcoholic solutions tend to dehydrate and precipitate hydrocolloids. They should be added in as dilute a concentration as possible.

(3) **Bottle method** (a variation of the dry gum method used for volatile oils). Oil is added to the acacia in a bottle. The ratio of oil, water, and acacia should be 3:2:1 or 2:1:1. The low viscosity of the volatile oil requires a higher proportion of acacia.

(4) **Nascent soap method**. A soap is formed by mixing relatively equal volumes of an oil and an aqueous solution that contains a sufficient amount of alkali. The soap acts as an emulsifying agent.

(a) This method is used to form an o/w or a w/o emulsion, depending on the soap formed. For example, olive oil, which contains oleic acid, is mixed with lime water during the preparation of calamine lotion to calcium oleate, an emulsifying agent.

(b) A 50:50 ratio of oil to water ensures sufficient emulsion, provided that the oil contains an adequate amount of free fatty acid. Olive oil usually does. Cottonseed oil, peanut oil, and some other vegetable oils do not.

(c) The addition of an acid destroys the emulsifying soap and causes the emulsion to separate.

b. Emulsions stabilized by synthetic emulsifying agents are readily prepared by a two-phase procedure.

(1) Oil-miscible ingredients and water-miscible ingredients are separately admixed, using heat if necessary to ensure liquefaction and ease of mixing of each phase.

(a) High melting point oil-miscible ingredients (e.g., waxes) are melted before lower melting point ingredients (e.g., oils) are added.

(2) The two phases are heated to 70° to 80°C and then combined with stirring until the resultant emulsion has cooled.

(a) In general, heat-labile or volatile ingredients should not be incorporated in the separate phases but in the resultant emulsion after it has cooled to about 40°C or less.

(3) Further mechanical processing of the emulsion by a hand homogenizer, immersion blender, or other equipment may be warranted to improve the homogeneity and stability of the product.

5. Incorporation of medicinal agents. Medicinal agents can be incorporated into an emulsion either during or after its formation.

a. Addition of a drug during emulsion formation. It is best to incorporate a drug into a vehicle during emulsion formation, when it can be incorporated in molecular form. Soluble drugs should be dissolved in the appropriate phase (e.g., drugs that are soluble in the external phase of the emulsion should be added as a solution to the primary emulsion).

b. Addition of a drug to a preformed emulsion can present some difficulty, depending on the type of emulsion and the nature of the emulsifier (*Table 2-3*).

(1) **Addition of oleaginous materials to a w/o emulsion** presents no problem because of the miscibility of the additive with the external phase. However, **addition of oleaginous materials to an o/w emulsion** can be difficult after emulsion formation.

(a) Occasionally, a small amount of oily material is added if excess emulsifier was used in the original formation.

(b) A small amount of an oil-soluble drug can be added if it is dissolved in a very small quantity of oil with geometric dilution techniques.

(2) **Addition of water or an aqueous material to a w/o emulsion** is extremely difficult, unless enough emulsifier has been incorporated into the emulsion. However, **addition of aqueous materials to an o/w emulsion** usually presents no problems if the added material does not interact with the emulsifying agent. Potential interactions should be expected with cationic compounds and salts of weak bases.

(3) **Addition of small quantities of alcoholic solutions to an o/w emulsion** is possible if the solute is compatible or dispersible in the aqueous phase of the emulsion. If acacia or another gum is used as the emulsifying agent, the alcoholic solution should be diluted with water before it is added. *Table 2-3* lists some commercial emulsion bases and their general composition.

(4) **Addition of crystalline drugs to a w/o emulsion** occurs more easily if the drugs are dissolved or dispersed in a small quantity of oil before they are added.

Table 2-3 SELECTED COMMERCIAL EMULSION BASES: EMULSION TYPE AND EMULSIFIER USED

Commercial Base	Emulsion Type	Emulsifier Type
Allercreme skin lotion	o/w	Triethanolamine stearate
Almay emulsion base	o/w	Fatty acid glycol esters
Cetaphil	o/w	Sodium lauryl sulfate
Dermovan	o/w	Fatty acid amides
Eucerin	w/o	Wool wax alcohol
HEB base	o/w	Sodium lauryl sulfate
Keri lotion	o/w	Nonionic emulsifiers
Lubriderm	o/w	Triethanolamine stearate
Neobase	o/w	Polyhydric alcohol esters
Neutrogena lotion	o/w	Triethanolamine lactate
Nivea cream	w/o	Wool wax alcohols
pHorsix	o/w	Polyoxyethylene emulsifiers
Polysorb hydrate	w/o	Sodium sesquioleate
Velvachol	o/w	Sodium lauryl sulfate

o/w, oil in water; w/o, water in oil.

E. Ointments

1. **Introduction**. **Ointments** are **semisolid preparations intended for external use**. They are easily spread. Modifying the formulation controls their plastic viscosity. Ointments are typically used as
   a. **emollients** to make the skin more pliable,
   b. **protective barriers** to prevent harmful substances from coming in contact with the skin, and
   c. **vehicles** in which to incorporate medication.
2. **Ointment bases**
   a. **Oleaginous bases** are anhydrous and insoluble in water. They cannot absorb or contain water and are not washable in water.
      (1) **Petrolatum** is a good base for oil-insoluble ingredients. It forms an occlusive film on the skin, absorbs $< 5\%$ water under normal conditions, and does not become rancid. Wax can be incorporated to stiffen the base.
      (2) **Synthetic esters** are used as constituents of oleaginous bases. These esters include glyceryl monostearate, isopropyl myristate, isopropyl palmitate, butyl stearate, and butyl palmitate. Long-chain alcohols (e.g., cetyl alcohol, stearyl alcohol, PEG) can also be used.
      (3) **Lanolin derivatives** are often used in topical and cosmetic preparations. Examples are lanolin oil and hydrogenated lanolin.
   b. **Absorption bases** are anhydrous and water insoluble. Therefore, they are not washable in water, although they can absorb water. These bases permit water-soluble medicaments to be included through prior solution and uptake as the internal phase.
      (1) **Wool fat** (anhydrous lanolin) contains a high percentage of cholesterol as well as esters and alcohol that contain fatty acids. It absorbs twice its weight in water and melts between 36°C and 42°C.
      (2) **Hydrophilic petrolatum** is a white petrolatum combined with 8% beeswax, 3% stearyl alcohol, and 3% cholesterol. These components are added to a w/o emulsifier. Prepared forms include Aquaphor, which uses wool alcohol to render white petrolatum emulsifiable. Aquaphor is superior in its ability to absorb water.
   c. **Emulsion bases** may be w/o emulsions, which are water insoluble and are not washable in water. These emulsions can absorb water because of their aqueous internal phase. Emulsion bases may also be o/w emulsions, which are water insoluble but washable in water. They can absorb water in their aqueous external phase.
      (1) **Hydrous wool fat** (lanolin) is a w/o emulsion that contains approximately 25% water. It acts as an emollient and occlusive film on the skin, effectively preventing epidermal water loss.

(2) **Cold cream** is a w/o emulsion that is prepared by melting white wax, spermaceti, and expressed almond oil together; adding a hot aqueous solution of sodium borate; and stirring until the mixture is cool.
   (a) The use of mineral oil rather than almond oil makes a more stable cold cream. However, cold cream prepared with almond oil makes a better emollient base.
   (b) This ointment should be freshly prepared.

(3) **Hydrophilic ointment** is an o/w emulsion that uses sodium lauryl sulfate as an emulsifying agent. It absorbs 30% to 50% w/w without losing its consistency. It is readily miscible with water and is removed from the skin easily.

(4) **Vanishing cream** is an o/w emulsion that contains a large percentage of water as well as humectant (e.g., glycerin, propylene glycol) that retards moisture loss. An excess of stearic acid in the formula helps form a thin film when the water evaporates.

(5) **Other emulsion bases** include Dermovan, a hypoallergenic, greaseless emulsion base, and Unibase, a nongreasy emulsion base that absorbs approximately 30% of its weight in water and has a pH close to that of the skin.

d. **Water-soluble bases** may be anhydrous or may contain some water. They are washable in water and absorb water to the point of solubility.

(1) **PEG ointment** is a blend of water-soluble polyethylene glycols that form a semisolid base. This base can solubilize water-soluble drugs and some water-insoluble drugs. It is compatible with a wide range of drugs.
   (a) This base contains 40% PEG 3350 and 60% PEG 400. It is prepared by the fusion method (see VI.E.3.b).
   (b) Only a small amount of liquid (< 5%) can be incorporated without loss of viscosity. This base can be made stiffer by increasing the amount of PEG 3350 to 60%.
   (c) If 6% to 25% of an aqueous solution is to be incorporated, 5 g of the 40 g of PEG 3350 can be replaced with an equal amount of stearyl alcohol.

(2) **Propylene glycol** and **propylene glycol–ethanol** form a clear gel when mixed with 2% hydroxypropyl cellulose. This base is a popular dermatologic vehicle.

3. **Incorporation of medicinal agents**. Medicinal substances may be incorporated into an ointment base by **levigation** or by the **fusion method**. Insoluble substances should be reduced to the finest possible form and levigated before incorporation with a small amount of compatible levigating agent or with the base itself.

a. **Levigation**. The substance is incorporated into the ointment by levigation on an ointment slab.

(1) A stainless-steel spatula with a long, broad, flexible blade should be used. If the substance may interact with a metal spatula (e.g., when incorporating iodine and mercuric salts), then a hard rubber spatula can be used.

(2) Insoluble substances should be powdered finely in a mortar and mixed with an equal quantity of base until a smooth, grit-free mixture is obtained. The rest of the base is added in increments.

(3) Levigation of powders into a small portion of base is facilitated by the use of a melted base or a small quantity of compatible levigation aid (e.g., mineral oil, glycerin).

(4) Water-soluble salts are incorporated by dissolving them in the smallest possible amount of water and incorporating the aqueous solution directly into a compatible base.
   (a) Usually, organic solvents (e.g., ether, chloroform, alcohol) are not used to dissolve the drug because the drug may crystallize as the solvent evaporates.
   (b) Solvents are used as levigating aids only if the solid will become a fine powder after the solvent evaporates.

b. **Fusion method**. This method is used when the base contains solids that have higher melting points (e.g., waxes, cetyl alcohol, glyceryl monostearate). This method is also useful for solid medicaments, which are readily soluble in the melted base.

(1) The oil phase should be melted separately, starting with materials that have the highest melting point. All other oil-soluble ingredients are added in decreasing order of melting point.

(2) The ingredients in the water phase are combined and heated separately to a temperature that is equal to or several degrees above that of the melted oil phase.

(3) The two phases are combined. If a w/o system is desired, then the hot aqueous phase is incorporated into the hot oil phase with agitation. If an o/w system is preferred, then the hot oil phase is incorporated into the hot aqueous phase.

(4) Volatile materials (e.g., menthol, camphor, iodine, alcohol, perfumes) are added after the melted mixture cools to 40°C or less.

F. Suppositories

1. **Introduction**. A suppository is a **solid or semisolid mass intended to be inserted into a body orifice** (i.e., rectum, vagina, urethra). After it is inserted, a suppository either melts at body temperature or dissolves (or disperses) into the aqueous secretions of the body cavity.
   a. Suppositories are often used for local effects (e.g., relief of hemorrhoids or infection).
   b. When used rectally, suppositories can provide systemic medication. The absorption of a drug from a suppository through the rectal mucosa into the circulation involves two steps:
      (1) The drug is released from a vehicle and partitions/diffuses through the mucosa.
      (2) The drug is transported through the veins or lymph vessels into systemic fluids or tissues. The first-pass effect is avoided because the rectal veins "bypass" the liver.
   c. Rectal suppositories are useful when oral administration is inappropriate, as with infants, debilitated or comatose patients, and patients who have nausea, vomiting, or gastrointestinal disturbances. Some drugs can cause disturbances of the gastrointestinal tract.
2. **Types of suppositories**
   a. **Rectal suppositories** are usually cylindrical and tapered to a point, forming a bullet-like shape. As the rectum contracts, a suppository of this shape moves inward rather than outward. Suppositories for adults weigh approximately 2 g. Suppositories for infants and children are smaller.
   b. **Vaginal suppositories** are oval and typically weigh approximately 5 g. Drugs administered by this route are intended to have a local effect, but systemic absorption can occur. Antiseptics, contraceptive agents, and drugs used to treat trichomonal, monilial, or bacterial infections are often formulated as vaginal suppositories.
   c. **Urethral suppositories** are typically long and tapered. They are approximately 60 mm long and 4 to 5 mm in diameter. They are administered for a local effect and are most often used for anti-infective agents. Alprostadil, or prostaglandin E_1 (PGE_1), when used to treat erectile dysfunction, is available for urethral insertion in the form of a micropellet, or microsuppository, that is only 3 to 6 mm long and 1.4 mm in diameter.
3. **Suppository bases**
   a. **Criteria for satisfactory suppository bases**. Suppository bases should
      (1) Remain firm at room temperature to allow insertion. The suppository should not soften < 30°C to avoid melting during storage.
      (2) Have a narrow, or sharp, melting range
      (3) Yield a clear melt just below body temperature or dissolve rapidly in the cavity fluid
      (4) Be inert and compatible with a variety of drugs
      (5) Be nonirritating and nonsensitizing
      (6) Have wetting and emulsifying properties
      (7) Have an acid value of < 0.2, a saponification value of 200 to 245, and an iodine value of < 7 if the base is fatty
   b. **Selecting a suppository base**. Lipid–water solubility must be considered because of its relation to the drug-release rate.
      (1) If an oil-soluble drug is incorporated into an oily base, then the rate of absorption is somewhat less than that achieved with a water-soluble base. The lipid-soluble drug tends to remain dissolved in the oily pool from the suppository. It is less likely to escape into the mucous secretions from which it is ultimately absorbed.
      (2) Conversely, a water-soluble drug tends to pass more rapidly from the oil phase to the aqueous phase. Therefore, if rapid onset of action is desired, the water-soluble drug should be incorporated into the oily base.
   c. **Bases that melt** include **cocoa butter**, other **combinations of fats and waxes**, **Witepsol bases**, and **Wecobee bases** (*Table 2-4*).
      (1) **Cocoa butter** (theobroma oil) is the most widely used suppository base. It is firm and solid up to a temperature of 32°C, at which point it begins to soften. At 34° to 35°C, it melts to produce a thin, bland, oily liquid.
         (a) Cocoa butter is a good base for a **rectal suppository**, but it is less than ideal for a vaginal or urethral suppository.

Table 2-4 COMPOSITION, MELTING RANGE, AND CONGEALING RANGE OF SELECTED BASES THAT MELT

Base	Composition	Melting Range (°C)	Congealing Range (°C)
Cocoa butter	Mixed triglycerides of oleic, palmitic, and stearic acids	34–35	28 or less
Cotmar	Partially hydrogenated cottonseed oil	34–75	—
Dehydag	Hydrogenated fatty alcohols		
Base I	and esters	33–36	32–33
Base II		37–39	36–37
Base III		9 ranges	9 ranges
Wecobee R	Glycerides of saturated fatty acids C_{12}–C_{18}	33–35	31–32
Wecobee SS	Triglycerides derived from coconut oil	40–43	33–35
Witepsol	Triglycerides of saturated fatty		
H12	acids C_{12}–C_{18}, with varied	32–33	29–32
H15	portions of the corresponding	33–35	32–34
H85	partial glycerides	42–44	36–38

(b) A mixture of triglycerides, cocoa butter exhibits polymorphism. Depending on the fusion temperature, it can crystallize into any one of four crystal forms.

(c) **Major limitations of cocoa butter**. Because of the following limitations, many combinations of fats and waxes are used as substitutes (*Table 2-4*):

(i) **An inability to absorb aqueous solutions**. The addition of nonionic surfactants to the base ameliorates this problem to some extent. However, the resultant suppositories have poor stability and may turn rancid rapidly.

(ii) **The lowering of the melting point produced by certain drugs** (e.g., chloral hydrate).

(2) **Witepsol** bases contain natural saturated fatty acid chains between C_{12} and C_{18}. Lauric acid is the major component. All 12 bases of this series are colorless and almost odorless. The drug-release characteristics of Witepsol H15 are similar to those of cocoa butter.

(a) Unlike cocoa butter, Witepsol bases do not exhibit polymorphism when heated and cooled.

(b) The interval between softening and melting temperatures is very small. Because Witepsol bases solidify rapidly in the mold, lubrication of the mold is not necessary.

(3) **Wecobee** bases are derived from coconut oil. Their action is similar to that of Witepsol bases. Incorporation of glyceryl monostearate and propylene glycol monostearate makes these bases emulsifiable.

d. **Bases that dissolve** include **PEG** polymers with a molecular weight of 400 to 6000.

(1) At room temperature, PEG 400 is a liquid, PEG 1000 is a semisolid, PEG 1500 and 1600 are fairly firm semisolids, and PEG 3350 and 6000 are firm waxlike solids.

(2) These bases are water soluble, but the dissolution process is very slow. In the rectum and vagina, where the amount of fluid is very small, they dissolve very slowly, but they soften and spread.

(3) PEGs complex with several drugs and affect drug release and absorption.

(4) Mixtures of PEG polymers in varying proportions provide a base of different properties (*Table 2-5*).

4. **Preparation**. Suppositories are prepared by the following three methods:

a. **Hand-rolling** involves molding the suppository with the fingers after a plastic mass is formed.

(1) A finely powdered drug is mixed with the grated base in a mortar and pestle, using levigation and geometric dilution techniques. A small quantity of fixed oil may be added to facilitate preparation.

Table 2-5 MIXTURES OF POLYETHYLENE GLYCOL (PEG) BASES PROVIDING SATISFACTORY ROOM TEMPERATURE STABILITY AND DISSOLUTION CHARACTERISTICS

Base	Comments	Components	Proportion (%)
1	Provides a good general-purpose, water-soluble suppository	PEG 6000	50
		PEG 1540	30
		PEG 400	20
2	Provides a good general-purpose base that is slightly softer than base 1 and dissolves more rapidly	PEG 4000	60
		PEG 1500	30
		PEG 400	10
3	Has a higher melting point than the other bases, which is usually sufficient to compensate for the melting point lowering effect of such drugs as chloral hydrate and camphor	PEG 6000	30
		PEG 1540	70

(2) The uniformly mixed semiplastic mass is kneaded further, rolled into a cylinder, and divided into the requisite number of suppositories. Each small cylinder is rolled by hand until a suppository shape is fashioned.

b. Compression is generally used when cocoa butter is used as a base.

(1) A uniform mixture of drug and base is prepared as for the hand-rolling method.

(2) The mixture is placed into a suppository compression device. Pressure is applied, and the mixture is forced into lubricated compression mold cavities. The mold is then cooled and the suppositories ejected.

(3) This procedure generally produces a 2-g suppository. However, a large volume of the active ingredients can affect the amount of cocoa butter required for an individual formula.

(a) The amount of cocoa butter needed is determined by calculating the total amount of active ingredient to be used, dividing this number by the cocoa butter density factor (*Table 2-6*), and subtracting the resulting number from the total amount of cocoa butter required for the desired number of suppositories.

(b) For example, suppose 12 suppositories, each containing 300 mg aspirin, are required. Each mold cavity has a 2-g capacity. For 13 suppositories (calculated to provide one

Table 2-6 COCOA BUTTER DENSITY FACTORS OF DRUGS COMMONLY USED IN SUPPOSITORIES

Drug	Cocoa Butter Density Factor	Drug	Cocoa Butter Density Factor
Aloin	1.3	Dimenhydrinate	1.3
Aminophylline	1.1	Diphenhydramine hydrochloride	1.3
Aminopyrine	1.3	Gallic acid	2.0
Aspirin	1.1	Morphine hydrochloride	1.6
Barbital sodium	1.2	Pentobarbital	1.2
Belladonna extract	1.3	Phenobarbital sodium	1.2
Bismuth subgallate	2.7	Salicylic acid	1.3
Chloral hydrate	1.3	Secobarbital sodium	1.2
Codeine phosphate	1.1	Tannic acid	1.6
Digitalis leaf	1.6		

extra), 3.9 g aspirin (13 × 0.3 g = 3.9 g) is required. This number is divided by the density factor of aspirin (1.1) (*Table 2-6*). Thus, 3.9 g of aspirin replaces 3.55 g of cocoa butter. The total amount of cocoa butter needed for 13 suppositories of 2 g each equals 26 g. The amount of cocoa butter required is 26 g − 3.55 g, or 22.45 g.

c. The **fusion method** is the principal way that suppositories are made commercially. This method is used primarily for suppositories that contain cocoa butter, PEG, and glycerin–gelatin bases. Molds made of aluminum, brass, or nickel–copper alloys are used and can make 6 to 50 suppositories at one time.

(1) The **capacity of the molds** is determined by melting a sufficient quantity of base over a steam bath, pouring it into the molds, and allowing it to congeal. The "blank" suppositories are trimmed, removed, and weighed. Once the weight is known, the drug-containing suppositories are prepared.

(a) To prepare suppositories, the drug is reduced to a fine powder. A small amount of grated cocoa butter is liquefied in a suitable container placed in a water bath at 33°C or less.

(b) The finely powdered drug is mixed with melted cocoa butter with continuous stirring.

(c) The remainder of the grated cocoa butter is added with stirring. The temperature is maintained at or below 33°C. The liquid should appear creamy rather than clear.

(d) The mold is very lightly lubricated with mineral oil, and the creamy melt is poured into the mold at room temperature. The melt is poured continuously to avoid layering.

(e) After the suppositories congeal, they are placed in a refrigerator to harden. After 30 mins, they are removed from the refrigerator, trimmed, and unmolded.

(2) The fusion process should be used carefully with **thermolabile drugs** and **insoluble powders**.

(a) Insoluble powders in the melt may settle or float during pouring, depending on their density. They may also collect at one end of the suppository before the melt congeals, and cause a nonuniform drug distribution.

(b) Hard crystalline materials (e.g., iodine, merbromin) can be incorporated by dissolving the crystals in a minimum volume of suitable solvent before they are incorporated into the base.

(c) Vegetable extracts can be incorporated by moistening with a few drops of alcohol and levigating with a small amount of melted cocoa butter.

G. Powders

1. Introduction. A pharmaceutical powder is a mixture of finely divided drugs or chemicals in dry form. The powder may be used internally or externally.

a. Advantages of powders

(1) Flexibility of compounding

(2) Good chemical stability

(3) Rapid dispersion of ingredients because of the small particle size

b. Disadvantages of powders

(1) Time-consuming preparation

(2) Inaccuracy of dose

(3) Unsuitability for many unpleasant-tasting, hygroscopic, and deliquescent drugs

c. Milling is the mechanical process of reducing the particle size of solids (**comminution**) before mixing with other components, further processing, or incorporation into a final product (*Tables 2-7 and 2-8*). The particle size of a powder is related to the proportion of the powder that can pass through the opening of standard sieves of various dimensions in a specified amount of time. **Micromeritics** is the study of particles.

(1) Advantages of milling

(a) Increases the surface area, which may increase the dissolution rate as well as bioavailability (e.g., griseofulvin)

(b) Increases extraction, or leaching, from animal glands (e.g., liver, pancreas) and from crude vegetable extracts

(c) Facilitates drying of wet masses by increasing the surface area and reducing the distance that moisture must travel to reach the outer surface. Micronization and subsequent drying, in turn, increase stability as occluded solvent is removed.

Table 2-7 *UNITED STATES PHARMACOPEIA* STANDARDS FOR POWDERS OF ANIMAL AND VEGETABLE DRUGS

Type of Powder	Sieve Size All Particles Pass Through	Sieve Size Percentage of Particles Pass Through
Very coarse (#8)	#20 sieve	20% through a #60 sieve
Coarse (#20)	#20 sieve	40% through a #60 sieve
Moderately coarse (#40)	#40 sieve	40% through a #80 sieve
Fine (#60)	#60 sieve	40% through a #100 sieve
Very fine (#80)	#80 sieve	No limit

(d) Improves mixing, or blending, of several solid ingredients if they are reduced to approximately the same size; also minimizes segregation and provides greater dose uniformity

(e) Permits uniform distribution of coloring agents in artificially colored solid pharmaceuticals

(f) Improves the function of lubricants used to coat the surface of the granulation or powder in compressed tablets and capsules

(g) Improves the texture, appearance, and physical stability of ointments, creams, and pastes

(2) **Disadvantages** of milling

(a) Can change the polymorphic form of the active ingredient, rendering it less active

(b) Can degrade the drug as a result of heat buildup, oxidation, or adsorption of unwanted moisture because of increased surface area

(c) Decreases the bulk density of the active compound and excipients, causing flow problems and segregation.

(d) Decreases the particle size of the raw materials and may create problems with static charge, which may cause particle aggregation and decrease the dissolution rate

(e) Increases surface area, which may promote air adsorption and inhibit wettability

(3) **Comminution techniques**. On a large scale, various mills and pulverizers (e.g., rotary cutter, hammer, roller, fluid energy mill) are used during manufacturing. On a small scale, the pharmacist usually uses one of the following comminution techniques:

(a) **Trituration**. The substance is reduced to small particles by rubbing it in a mortar with a pestle. Trituration also describes the process by which fine powders are intimately mixed in a mortar.

(b) **Pulverization by intervention**. Substances are reduced and subdivided with an additional material (i.e., solvent) that is easily removed after pulverization. This technique is often used with gummy substances that reagglomerate or resist grinding. For example, camphor is readily reduced after a small amount of alcohol or other volatile solvent is added. The solvent is then permitted to evaporate.

Table 2-8 *UNITED STATES PHARMACOPEIA* STANDARDS FOR POWDERS OF CHEMICALS

Type of Powder	Sieve Size All Particles Pass Through	Sieve Size Percentage of Particles Pass Through
Coarse (#20)	#20 sieve	60% through a #40 sieve
Moderately coarse (#40)	#40 sieve	60% through a #60 sieve
Fine (#80)	#80 sieve	No limit
Very fine (#120)	#120 sieve	No limit

(c) **Levigation**. The particle size of the substance is reduced by adding a suitable nonsolvent (levigating agent) to form a paste. The paste is then rubbed in a mortar and pestle or using an ointment slab and spatula. This method is often used to prevent a gritty feel when solids are incorporated into dermatologic or ophthalmic ointments and suspensions. Mineral oil is a common levigating agent.

2. **Mixing powders**. Powders are mixed, or blended, by the following five methods:
   a. **Spatulation**. A spatula is used to blend small amounts of powders on a sheet of paper or a pill tile.
      (1) This method is not suitable for large quantities of powders or for powders that contain potent substances because homogeneous blending may not occur.
      (2) This method is particularly useful for solid substances that liquefy or form **eutectic mixtures** (i.e., mixtures that melt at a lower temperature than any of their ingredients) when in close, prolonged contact with one another because little compression or compaction results.
         (a) These substances include phenol, camphor, menthol, thymol, aspirin, phenylsalicylate, and phenacetin.
         (b) To diminish contact, powders prepared from these substances are commonly mixed with an inert diluent (e.g., light magnesium oxide or magnesium carbonate, kaolin, starch, bentonite).
         (c) Silicic acid (approximately 20%) prevents eutexia with aspirin, phenylsalicylate, and other troublesome compounds.
   b. **Trituration** is used both to comminute and to mix powders.
      (1) If comminution is desired, a porcelain or ceramic mortar with a rough inner surface is preferred to a glass mortar with a smooth working surface.
      (2) A glass mortar is preferable for chemicals that stain a porcelain or ceramic surface as well as for simple admixture of substances without special need for comminution. A glass mortar cleans more readily after use.
   c. **Geometric dilution** is used when potent substances must be mixed with a large amount of diluent.
      (1) The potent drug and an approximately equal volume of diluent are placed in a mortar and thoroughly mixed by trituration.
      (2) A second portion of diluent, equal in volume to the powder mixture in the mortar, is added, and trituration is repeated. The process is continued; equal volumes of diluent are added to the powder mixture in the mortar until all of the diluent is incorporated.
   d. **Sifting**. Powders are mixed by passing them through sifters similar to those used to sift flour. This process results in a light, fluffy product. Usually, it is not acceptable for incorporating potent drugs into a diluent base.
   e. **Tumbling** is the process of mixing powders in a large container rotated by a motorized process. These blenders are widely used in industry, as are large-volume powder mixers that use motorized blades to blend the powder in a large mixing vessel.
3. **Use and packaging of powders**. Depending on their intended use, powders are packaged and dispensed by pharmacists as bulk powders or divided powders.
   a. Bulk powders are dispensed by the pharmacist in bulk containers. A **perforated**, or **sifter**, **can** is used for external dusting, and an **aerosol container** is used for spraying on skin. A **wide-mouthed glass jar** permits easy removal of a spoonful of powder.
      (1) Powders commonly dispensed in bulk form
         (a) **Antacid and laxative powders** are used by mixing the directed amount of powder (usually approximately 1 teaspoon) in a portion of liquid, which the patient then drinks.
         (b) **Douche powders** are dissolved in warm water and applied vaginally.
         (c) **Medicated and nonmedicated powders for external use** are usually dispensed in a sifter for convenient application to the skin.
         (d) **Dentifrices**, or **dental cleansing powders**, are used for oral hygiene.
         (e) Powders for the **ear**, **nose**, **throat**, **tooth sockets**, or **vagina** are administered with an insufflator or powder blower.
      (2) **Nonpotent substances** are usually dispensed in bulk powder form. Those intended for external use should be clearly labeled.

(3) **Hygroscopic**, **deliquescent**, or **volatile** powders should be packed in glass jars rather than pasteboard containers. Amber or green glass should be used if needed to prevent decomposition of light-sensitive components. All powders should be stored in tightly closed containers.

b. **Divided powders** are dispensed in individual doses, usually in folded **papers** (i.e., chartulae). They may also be dispensed in metal foil, small heat-sealed or resealable **plastic bags**, or other containers.

(1) After the ingredients are weighed, comminuted, and mixed, the powders must be accurately **divided** into the prescribed number of doses.

(2) Depending on the potency of the drug substance, the pharmacist decides whether to **weigh** each portion separately before packaging or to approximate portions by the **block-and-divide method**.

(3) **Powder papers** can be of any convenient size that fits the required dose. Four basic types are used:

(a) **Vegetable parchment** is a thin, semiopaque, moisture-resistant paper.

(b) **White bond** is an opaque paper that has no moisture-resistant properties.

(c) **Glassine** is a glazed, transparent, moisture-resistant paper.

(d) **Waxed paper** is a transparent waterproof paper.

(4) Hygroscopic and volatile drugs are best protected with waxed paper that is double wrapped and covered with a bond paper to improve the appearance. Parchment and glassine papers are of limited use for these drugs.

4. **Special problems**. Volatile substances, eutectic mixtures, liquids, and hygroscopic or deliquescent substances present problems when they are mixed into powders that require special treatment.

a. **Volatile substances** (e.g., camphor, menthol, essential oils) can be lost by volatilization after they are incorporated into powders. This process is prevented or retarded by the use of heat-sealed plastic bags or by double wrapping with waxed or glassine paper inside white bond paper.

b. **Liquids** are incorporated into divided powders in small amounts.

(1) Magnesium carbonate, starch, or lactose can be added to increase the absorbability of the powders by increasing the surface area.

(2) When the liquid is a solvent for a nonvolatile heat-stable compound, it is evaporated gently in a water bath. Some fluid extracts and tinctures are treated in this way.

c. **Hygroscopic and deliquescent substances** that become moist because of an affinity for moisture in the air can be prepared as divided powders by adding inert diluents. Double wrapping is desirable for further protection.

d. **Eutectic mixtures**

H. **Capsules**

1. **Introduction**. Capsules are solid dosage forms in which one or more medicinal or inert substances (as powder, compact, beads, or granulation) are enclosed within a small gelatin shell. Gelatin capsules may be hard or soft. Most capsules are intended to be swallowed whole, but occasionally, the contents are removed from the gelatin shell and used as a premeasured dose.

2. **Hard gelatin capsules**

a. **Preparation of filled hard capsules** includes preparing the formulation, selecting the appropriate capsule, filling the capsule shells, and cleaning and polishing the filled capsules.

(1) Empty hard capsule shells are manufactured from a mixture of gelatin, colorants, and sometimes an opacifying agent (e.g., titanium dioxide). The *USP* also permits the addition of 0.15% sulfur dioxide to prevent decomposition of gelatin during manufacture.

(2) Gelatin *USP* is obtained by partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals. Types A and B are obtained by acid and alkali processing, respectively.

(3) Capsule shells are cast by dipping cold metallic molds or pins into gelatin solutions that are maintained at a uniform temperature and an exact degree of fluidity.

(a) Variation in the viscosity of the gelatin solution increases or decreases the thickness of the capsule wall.

(b) After the pins are withdrawn from the gelatin solution, they are rotated while being dried in kilns. A strong blast of filtered air with controlled humidity is forced through the kilns. Each capsule is then mechanically stripped, trimmed, and joined.

b. Storage. Hard capsules should be stored in tightly closed glass containers and protected from dust and extremes of humidity and temperature.

(1) These capsules contain 12% to 16% water, varying with storage conditions. When humidity is low, the capsules become brittle. When humidity is high, the capsules become flaccid and shapeless.

(2) Storage at high temperatures also affects the quality of hard gelatin capsules.

c. Sizes. Hard capsules are available in various sizes.

(1) Empty capsules are **numbered** from 000, which is the largest size that can be swallowed, to 5, the smallest size. The approximate capacity of capsules ranges from 600 to 30 mg for capsules from 000 to 5, respectively. The capacity varies because of varying densities of powdered drug materials and the degree of pressure used to fill the capsules.

(2) Large capsules are available for **veterinary medicine**.

(3) Selecting capsules. Capsule size should be chosen carefully. A properly filled capsule should have its body filled with the drug mixture and its cap fully extended down the body. The cap is meant to enclose the powder, not to retain additional powder. Typically, hard gelatin capsules are used to encapsulate between 65 mg and 1 g of powdered material, including the drug and any diluents needed.

(a) If the drug dose is inadequate to fill the capsule, a diluent (e.g., lactose) is added.

(b) If the amount of drug needed for a usual dose is too large to place in a single capsule, two or more capsules may be required.

(c) Lubricants such as magnesium stearate (frequently, 1%) are added to facilitate the flow of the powder when an automatic capsule-filling machine is used.

(d) Wetting agents (e.g., sodium lauryl sulfate) may be added to capsule formulations to enhance drug dissolution.

d. Filling capsules. Whether on a large- or a small-production scale, the cap is first separated from the body of the capsule before filling the capsule body with the formulation and then reattaching the cap. Automated and semiautomated capsule-filling equipment fill the capsule bodies with the formulation by gravity fill, tamping, or a screw-feed (i.e., auger) mechanism. Extemporaneously compounded capsules are usually filled by the punch method.

(1) The powder is placed on paper and flattened with a spatula so that the layer of powder is no more than approximately one-third the length of the capsule. The paper is held in the left hand. The body of the capsule is held in the right hand and repeatedly pressed into the powder until the capsule is filled. The cap is replaced and the capsule weighed.

(2) Granular material that does not lend itself well to the punch method can be poured into each capsule from the powder paper on which it was weighed.

(3) Crystalline materials, especially those that consist of a mass of filament-like crystals (e.g., quinine salts), will not fit into a capsule easily unless they are powdered.

(4) After they are filled, capsules must be cleaned and polished.

(a) On a **small scale**, capsules are cleaned individually or in small numbers by rubbing them on a clean gauze or cloth.

(b) On a **large scale**, many capsule-filling machines have a cleaning vacuum that removes any extraneous material as the capsules leave the machine.

3. Soft gelatin capsules

a. Preparation

(1) Soft gelatin capsules are prepared from gelatin shells. Glycerin or a polyhydric alcohol (e.g., sorbitol) is added to these shells to make them elastic or plastic-like.

(2) These shells contain preservatives (e.g., methyl and propyl parabens, sorbic acid) to prevent the growth of fungi.

b. Uses. Soft gelatin shells are oblong, elliptical, or spherical. They are used to contain liquids, suspensions, pastes, dry powders, or pellets.

(1) Drugs that are commercially prepared in soft capsules include demeclocycline hydrochloride (Declomycin, Lederle), chloral hydrate, digoxin (Lanoxicaps, GlaxoSmithKline), vitamin A, and vitamin E.

(2) Soft gelatin capsules are usually prepared by the plate process or by the rotary or reciprocating die process.

4. **Uniformity and disintegration**
   a. The **uniformity** of dosage forms can be demonstrated by either weight variation or content uniformity methods. The official compendia should be consulted for details of these procedures.
   b. **Disintegration** tests are not usually required for capsules unless they have been treated to resist solution in gastric fluid (enteric coated). In this case, they must meet the requirements for disintegration of enteric-coated tablets.

I. Tablets

1. **Introduction**
   a. The **oral route** is the most important method for administering drugs for systemic effect. Oral drugs can be given as solids or liquids.
      (1) **Advantages of solid dosage forms**
         (a) Accurate dosage
         (b) Easy shipping and handling
         (c) Less shelf space needed per dose than for liquid
         (d) No preservation requirements
         (e) No taste-masking problem
         (f) Generally more stable than liquids, with longer expiration dates
      (2) **Advantages of liquid dosage forms**
         (a) For some drugs (e.g., adsorbents, antacids), greater effectiveness than solid form
         (b) Useful for patients who have trouble swallowing solid dosage forms
   b. **Tablets** are the **most commonly used solid dosage form**.
      (1) **Advantages**
         (a) Precision and low content variability of the unit dose
         (b) Low manufacturing cost
         (c) Easy to package and ship
         (d) Simple to identify
         (e) Easy to swallow
         (f) Appropriate for special-release forms
         (g) Best suited to large-scale production
         (h) Most stable of all oral dosage forms
         (i) Essentially tamperproof
      (2) **Disadvantages**
         (a) Some drugs resist compression into tablets.
         (b) Some drugs (i.e., those with poor wetting, slow dissolution properties, intermediate to large doses, optimum absorption high in the gastrointestinal tract, or any combination of these features) may be difficult to formulate to provide adequate bioavailability.
         (c) Some drugs (e.g., those with an objectionable taste or odor, those sensitive to oxygen or atmospheric moisture) require encapsulation or entrapment before compression. These drugs are more appropriate in capsule form.

2. **Tablet design and formulation**
   a. **Characteristics of ideal tablets**
      (1) Free of defects (e.g., chips, cracks, discoloration, contamination)
      (2) Strong enough to withstand the mechanical stresses of production
      (3) Chemically and physically stable over time
      (4) Capable of releasing medicinal agents in a predictable and reproducible manner
   b. **Tablet excipients**. Tablets are manufactured by **wet granulation**, **dry granulation**, or **direct compression**. Regardless of the method of manufacture, tablets for oral ingestion usually contain excipients, which are components added to the active ingredients that have special functions (*Table 2-9*).
      (1) **Diluents** are fillers designed to make up the required bulk of the tablet when the drug dosage amount is inadequate. Diluents may also improve cohesion, permit direct compression, or promote flow.
         (a) **Common diluents** include kaolin, lactose, mannitol, starch, microcrystalline cellulose, powdered sugar, and calcium phosphate.
         (b) **Selection of the diluent** is based on the experience of the manufacturer as well as on the cost of the diluent and its compatibility with the other tablet ingredients.

Table 2-9 SOME COMMON TABLET EXCIPIENTS

Diluents
Calcium phosphate dihydrate *NF* (dibasic)
Calcium sulfate dihydrate *NF*
Cellulose *NF* (microcrystalline)
Cellulose derivatives
Dextrose
Lactose *USP*
Lactose *USP* (anhydrous)
Lactose *USP* (spray dried)
Mannitol *USP*
Starches (directly compressible)
Starches (hydrolyzed)
Sorbitol
Sucrose *USP* (powder)
Sucrose-based materials

Binders and adhesives
Acacia
Cellulose derivatives
Gelatin
Glucose
Povidone (PVP)
Sodium alginate and alginate derivatives
Sorbitol
Starch (paste)
Starch (pregelatinized)
Tragacanth

Disintegrants
Alginates
Cellulose
Cellulose derivatives
Clays
Crospovidone (cross-linked PVP)
Starch
Starch derivatives

Lubricants
PEGs
Stearic acid
Stearic acid salts
Stearic acid derivatives
Surfactants
Talc
Waxes

Glidants
Cornstarch
Silica derivatives
Talc

Colors, flavors, and sweeteners
FD&C and D&C dyes and lakes
Flavors available in two forms (spray dried, oil)
Artificial sweeteners
Natural sweetener

D&C, drugs and cosmetics; *FD&C,* food, drugs, and cosmetics; *NF, National Formulary; PEG,* polyethylene glycol; *PVP,* polyvinylpyrrolidone (more commonly, povidone); *USP, United States Pharmacopeia.*

For example, calcium salts cannot be used as fillers for tetracycline products because calcium interferes with the absorption of tetracycline from the gastrointestinal tract.

(2) **Binders and adhesives** are added in either dry or liquid form to promote granulation or to promote cohesive compacts during direct compression.
- **(a)** **Common binding agents** include a 10% to 20% aqueous preparation of cornstarch, a 25% to 50% solution of glucose, molasses, various natural gums (e.g., acacia), cellulose derivatives (e.g., methylcellulose, carboxymethylcellulose, microcrystalline cellulose), gelatins, and povidone. The natural gums are variable in composition and are usually contaminated with bacteria.
- **(b)** If the drug substance is adversely affected by an aqueous binder, a **nonaqueous binder** can be used or the binder can be added dry. The binding action is usually more effective when the binder is mixed in liquid form.
- **(c)** The **amount** of binder or adhesive used depends on the experience of the manufacturer as well as on the other tablet ingredients. Overwetting usually produces granules that are too hard to allow proper tableting. Underwetting usually produces tablets that are too soft and tend to crumble.

(3) **Disintegrants** are added to tablet formulations to facilitate disintegration when the tablet contacts water in the gastrointestinal tract. Disintegrants function by drawing water into the tablet, swelling, and causing the tablet to burst.
- **(a)** Tablet disintegration may be critical to the subsequent dissolution of the drug and to satisfactory drug bioavailability.

(b) **Common disintegrants** include cornstarch and potato starch, starch derivatives (e.g., sodium starch glycolate), cellulose derivatives (e.g., sodium carboxymethylcellulose, croscarmellose sodium), clays (e.g., Veegum, bentonite), and cation exchange resins.

(c) The total **amount of disintegrant** is not always added to the drug–diluent mixture. A portion can be added, with the lubricant, to the prepared granulation of the drug. This approach causes double disintegration of the tablet. The portion of disintegrant that is added last causes the tablet to break into small pieces or chunks. The portion that is added first breaks the pieces of tablet into fine particles.

(4) **Lubricants**, **antiadherents**, and **glidants** have overlapping function.

(a) **Lubricants** reduce the friction that occurs between the walls of the tablet and the walls of the die cavity when the tablet is ejected. Talc, magnesium stearate, and calcium stearate are commonly used.

(b) **Antiadherents** reduce sticking, or adhesion, of the tablet granulation or powder to the faces of the punches or the die walls.

(c) **Glidants** promote the flow of the tablet granulation or powder by reducing friction among particles.

(5) **Colors and dyes** disguise off-color drugs, provide product identification, and produce a more aesthetically appealing product. **Food**, **drug**, and **cosmetic dyes** are applied as solutions. **Lakes** are dyes that have been absorbed on a hydrous oxide. Lakes are typically used as dry powders.

(6) **Flavoring agents** are usually limited to chewable tablets or tablets that are intended to dissolve in the mouth.

(a) Water-soluble flavors usually have poor stability. For this reason, flavor oils or dry powders are typically used.

(b) Flavor oils may be added to tablet granulations in solvents, dispersed on clays and other adsorbents, or emulsified in aqueous granulating agents. Usually, the maximum amount of oil that can be added to a granulation without affecting its tablet characteristics is 0.5% to 0.75%.

(7) **Artificial sweeteners**, like flavors, are typically used only with chewable tablets or tablets that are intended to dissolve in the mouth.

(a) Some **sweetness** may come from the diluent (e.g., mannitol, lactose). Other agents (e.g., saccharin, aspartame) may also be added.

(b) **Saccharin** has an unpleasant aftertaste.

(c) **Aspartame** is not stable in the presence of moisture and heat.

(8) **Adsorbents** (e.g., magnesium oxide, magnesium carbonate, bentonite, silicon dioxide) hold quantities of fluid in an apparently dry state.

3. **Tablet types and classes**. Tablets are classified according to their route of administration, drug delivery system, and form and method of manufacture (*Table 2-10*).

a. **Tablets for oral ingestion** are designed to be swallowed intact, with the exception of chewable tablets. Tablets may be coated for a number of reasons: to mask the taste, color, or odor of the drug; to control drug release; to protect the drug from the acid environment of the stomach; to incorporate another drug and provide sequential release or avoid incompatibility; or to improve appearance.

(1) **Compressed tablets** are formed by compression and have no special coating. They are made from powdered, crystalline, or granular materials, alone or in combination with excipients such as binders, disintegrants, diluents, and colorants.

(2) **Multiple compressed tablets** are layered or compression coated.

(a) **Layered tablets** are prepared by compressing a tablet granulation around a previously compressed granulation. The operation is repeated to produce multiple layers.

(b) **Compression-coated**, **or dry-coated**, **tablets** are prepared by feeding previously compressed tablets into a special tableting machine. This machine compresses an outer shell around the tablets. This process applies a thinner, more uniform coating than sugar coating, and it can be used safely with drugs that are sensitive to moisture.

Table 2-10 TABLET TYPES AND CLASSES

Tablets for oral ingestion	Tablets used in the oral cavity
Compressed	Buccal
Multiple compressed	Sublingual
Layered	Troches, lozenges, and dental cones
Compression coated	**Tablets used to prove solutions**
Repeat-action	Effervescent
Delayed action and enteric coated	Dispensing
Sugar coated and chocolate coated	Hypodermic
Film coated	Triturates
Air suspension coated	
Chewable	

This process can be used to separate incompatible materials, to produce repeat-action or prolonged-action products, or to produce tablets with a multilayered appearance.

(3) **Repeat-action tablets** are layered or compression-coated tablets in which the outer layer or shell rapidly disintegrates in the stomach (e.g., Repetabs, Schering, Extentabs, Wyeth). The components of the inner layer or inner tablet are insoluble in gastric media but soluble in intestinal media.

(4) **Delayed-action** and **enteric-coated tablets** delay the release of a drug from a dosage form. This delay is intended to prevent destruction of the drug by gastric juices, to prevent irritation of the stomach lining by the drug, or to promote absorption, which is better in the intestine than in the stomach.

- **(a)** **Enteric-coated** tablets are coated and remain intact in the stomach, but yield their ingredients in the intestines (e.g., Ecotrin, GlaxoSmithKline). Enteric-coated tablets are a form of delayed-action tablet. However, not all delayed-action tablets are enteric or are intended to produce an enteric effect.
- **(b)** Agents used to coat these tablets include fats, fatty acids, waxes, shellac, and cellulose acetate phthalate.

(5) **Sugar-coated** and **chocolate-coated tablets** are compressed tablets that are coated for various reasons. The coating may be added to protect the drug from air and humidity, to provide a barrier to a drug's objectionable taste or smell, or to improve the appearance of the tablet.

- **(a)** Tablets may be coated with a colored or an uncolored sugar. The process includes **seal coating** (waterproofing), **subcoating**, **syrup coating** (for smoothing and coloring), and **polishing**. These steps take place in a series of mechanically operated coating pans.
- **(b)** **Disadvantages** of sugar-coated tablets include the time and expertise required for the process and the increase in tablet size and weight. Sugar-coated tablets may be 50% larger and heavier than the original tablets.
- **(c)** Chocolate-coated tablets are rare today.

(6) **Film-coated tablets** are compressed tablets that are coated with a thin layer of a water-insoluble or water-soluble polymer (e.g., hydroxypropyl methylcellulose [hypromellose], ethylcellulose, povidone, PEG).

- **(a)** The film is usually colored. It is more durable, less bulky, and less time consuming to apply than sugar coating. Although the film typically increases tablet weight by only 2% to 3%, it increases formulation efficiency, resistance to chipping, and output.
- **(b)** Film-coating solutions usually contain a film former, an alloying substance, a plasticizer, a surfactant, opacifiers, sweeteners, flavors, colors, glossants, and a volatile solvent.
- **(c)** The volatile solvents used in these solutions are expensive and potentially toxic when released into the atmosphere. Specifically formulated **aqueous dispersions** of

polymers (e.g., ethylcellulose) are now available as alternatives to organic solvent-based coating solutions.

(7) **Air suspension–coated tablets** are fed into a vertical cylinder and supported by a column of air that enters from the bottom of the cylinder. As the coating solution enters the system, it is rapidly applied to the suspended, rotating solids (**Wurster process**). Rounding coats can be applied in < 1 hr when blasts of warm air are released in the chamber.

(8) **Chewable tablets** disintegrate smoothly and rapidly when chewed or allowed to dissolve in the mouth. These tablets contain specially colored and flavored mannitol and yield a creamy base.

(a) Chewable tablets are especially useful in formulations for children.

(b) They are commonly used for multivitamin tablets and are used for some antacids and antibiotics.

b. Tablets used in the oral cavity are allowed to dissolve in the mouth.

(1) **Buccal** and **sublingual** tablets allow absorption through the oral mucosa after they dissolve in the buccal pouch (buccal tablets) or below the tongue (sublingual tablets). These forms are useful for drugs that are destroyed by gastric juice or poorly absorbed from the intestinal tract. Examples include sublingual nitroglycerin tablets, which dissolve promptly to give rapid drug effects, and buccal progesterone tablets, which dissolve slowly.

(2) **Troches**, **lozenges**, and **dental cones** dissolve slowly in the mouth and provide primarily local effects.

c. Tablets used to prepare solutions are dissolved in water before administration.

(1) **Effervescent tablets** are prepared by compressing granular effervescent salts or other materials (e.g., citric acid, tartaric acid, sodium bicarbonate) that release carbon dioxide gas when they come into contact with water. Commercial alkalinizing analgesic tablets are often made to effervesce to encourage rapid dissolution and absorption (e.g., Alka-Seltzer, Bayer).

(2) Other tablets used to prepare solutions include **dispensing tablets**, **hypodermic tablets**, and **tablet triturates**.

4. Processing problems

a. Capping is the partial or complete separation of the top or bottom crown from the main body of the tablet. **Lamination** is separation of a tablet into two or more distinct layers. These problems are usually caused by entrapment of air during processing.

b. Picking is removal of the surface material of a tablet by a punch. Sticking is adhesion of tablet material to a die wall. These problems are caused by excessive moisture or the inclusion of substances with low melting temperatures in the formulation.

c. Mottling is unequal color distribution, with light or dark areas standing out on an otherwise uniform surface. This problem occurs when a drug has a different color than the tablet excipients or when a drug has colored degradation products. Colorants solve the problem but can create other problems.

5. Tablet evaluation and control

a. The general appearance of tablets is an important factor in consumer acceptance. It also allows monitoring of lot-to-lot uniformity, tablet-to-tablet uniformity, and elements of the manufacturing process. The appearance of the tablet includes visual identity and overall appearance. The appearance of the tablet is controlled by measurement of attributes such as size, shape, color, odor, taste, surface, texture, physical flaws, consistency, and legibility of markings.

b. Hardness and resistance to friability are necessary for tablets to withstand the mechanical shocks of manufacture, packaging, and shipping, and to ensure consumer acceptance. Hardness involves both tablet disintegration and drug dissolution. Certain tablets that are intended to dissolve slowly are made hard. Other tablets that are intended to dissolve rapidly are made soft. Friability is the tendency of the tablet to crumble.

(1) Tablet hardness testers measure the degree of force required to break a tablet.

(2) **Friabilators** determine **friability** by allowing the tablet to roll and fall within a rotating tumbling apparatus. The tablets are weighed before and after a specified number of rotations, and the weight loss is determined.

(a) Resistance to weight loss indicates the ability of the tablet to withstand abrasion during handling, packaging, and shipping. Compressed tablets that lose < 0.5% to 1% of their weight are usually considered acceptable.

(b) Some chewable tablets and most effervescent tablets are highly friable and require special unit packaging.

c. Tablets are routinely weighed to ensure that they contain the proper amount of drug.

(1) The *USP* defines a **weight variation standard** to which tablets must conform.

(2) These standards apply to tablets that contain 50 mg or more of drug substance when the drug substance is 50% or more (by weight) of the dosage form unit.

d. Content uniformity is evaluated to ensure that each tablet contains the desired amount of drug substance, with little variation among contents within a batch. The *USP* defines content uniformity tests for tablets that contain 50 mg or less of drug substance.

e. Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract.

(1) All *USP* tablets must pass an official **disintegration test** that is conducted in vitro with special equipment.

(a) Disintegration times for uncoated *USP* tablets are as low as 2 mins (nitroglycerin) to 5 mins (aspirin). Most have a maximum disintegration time of less than 30 mins.

(b) Buccal tablets must disintegrate within 4 hrs.

(c) Enteric-coated tablets must show no evidence of disintegration after 1 hr in simulated gastric fluid. In simulated intestinal fluid, they should disintegrate in 2 hrs plus the time specified.

(2) Dissolution requirements in the *USP* have replaced earlier disintegration requirements for many drugs.

f. Dissolution characteristics are tested to determine drug absorption and physiologic availability.

(1) The *USP* gives standards for tablet dissolution.

(2) An increased emphasis on testing tablet dissolution and determining drug bioavailability has increased the use of sophisticated testing systems.

J. Aerosol products

1. Introduction. Aerosol products, or **aerosols**, are **pressurized dosage forms**. They are designed to deliver drug systemically or topically with the aid of a liquefied or propelled gas (propellant). Aerosol products consist of a pressurizable container (tin-plated steel, aluminum, glass, or plastic), a valve that allows the pressurized product to be expelled from the container (either continuously or intermittently) when the actuator is pressed, and a dip tube that conveys the formulation from the bottom of the container to the valve assembly. Aerosols are prepared by special methods (cold filling, pressure filling) because of the gaseous components.

2. Systemic or pulmonary drug delivery is provided by aerosol drug delivery systems, or **metered dose inhalers (MDIs)**. These devices allow a drug to be inhaled as a fine mist of drug or drug-containing particles. MDIs use special metering valves to regulate the amount of formulation and drug that is dispensed with each dose (i.e., each actuation of the container). Aerosol products are used for topical drug delivery. The formulations range from solutions to dispersions. Metering valves may also be used with topical aerosol products to regulate the amount of drug applied per application.

3. Propellants used in aerosol products

a. Compressed gases include carbon dioxide, nitrogen, and nitrous oxide. Aerosol products that contain compressed gas tend to lose pressure over time as the product is dispensed. The drop in pressure reflects the expansion of the head space in the container (i.e., increase in the volume that the gas can occupy) as formulation is withdrawn for use. For this reason, higher initial pressures are typically used with compressed gas-based systems than with liquefiable gas-based formulations.

b. Liquefiable gases include saturated hydrocarbons (n-butane, isobutane, propane); chlorofluorocarbons (CFCs), including tetrafluorodichloroethane (propellant 114), dichlorodifluoromethane (propellant 12), and trichlorofluoromethane (propellant 11); dimethyl ether; and hydrofluorocarbons, such as 1,1,1,2-fluoroethane (propellant 134a) and 1,1-difluoroethane (propellant 152a). The negative effect of older CFCs on atmospheric ozone and the potential for global warming led to the worldwide reduction in CFC production under the Montreal Protocol. This plan called for a general ban on CFC production in industrialized countries by January 1996. As a result, the use of CFCs in pharmaceutical products is being phased out. Temporary exemptions for CFCs in MDIs will eventually lapse (in 2008) as stable, safe,

and effective alternative formulations are developed with more acceptable propellants (e.g., hydrofluorocarbons).

4. Advantages of aerosol products include the convenience of push-button dispensing of medication and the stability afforded by a closed, pressurized container that minimizes the likelihood of tampering and protects the contents from light, moisture, air (oxygen), and microbial contamination. Aerosol formulations and packaging components (valves, actuators) permit a wide range of products to be dispensed as sprays, foams, or semisolids.
5. The principal disadvantage of aerosol products is environmental (e.g., disposal of pressurized packages, venting of propellants to the atmosphere).

K. Controlled-release dosage forms

1. Introduction. Controlled-release dosage forms are also known as delayed-release, sustained-action, prolonged-action, sustained-release, prolonged-release, timed-release, slow-release, extended-action, and extended-release forms. They are designed to release drug substance slowly to provide prolonged action in the body.
2. Advantages of controlled-release forms:
   - **a.** Fewer problems with patient compliance
   - **b.** Use of less total drug
   - **c.** Fewer local or systemic side effects
   - **d.** Minimal drug accumulation with long-term dosage
   - **e.** Fewer problems with potentiation or loss of drug activity with long-term use
   - **f.** Improved treatment efficiency
   - **g.** More rapid control of the patient's condition
   - **h.** Less fluctuation in drug level
   - **i.** Improved bioavailability for some drugs
   - **j.** Improved ability to provide special effects (e.g., morning relief of arthritis by bedtime dose)
   - **k.** Reduced cost
3. Sustained-release forms can be grouped according to their pharmaceutical mechanism.
   - **a. Coated beads** or **granules** (e.g., Spansules, GlaxoSmithKline, Sequels, Wyeth) produce a blood level profile similar to that obtained with multiple dosing.
     - **(1)** A solution of the drug substance in a nonaqueous solvent (e.g., alcohol) is coated on small, inert beads, or granules, made of a combination of sugar and starch. When the drug dose is large, the starting granules may be composed of the drug itself.
     - **(2)** Some of the granules are left uncoated to provide immediate release of the drug.
     - **(3)** Coats of a lipid material (e.g., beeswax) or a cellulosic material (e.g., ethylcellulose) are applied to the remaining granules. Some granules receive few coats, and some receive many. The various coating thicknesses produce a sustained-release effect.
   - **b. Microencapsulation** is a process by which solids, liquids, or gases are encased in microscopic capsules. Thin coatings of a "wall" material are formed around the substance to be encapsulated.
     - **(1) Coacervation** is the most common method of microencapsulation. It occurs when a hydrophilic substance is added to colloidal drug dispersion and causes layering and the formation of microcapsules.
     - **(2)** Film-forming substances that are used as the coating material include a variety of natural and synthetic polymers. These materials include shellacs, waxes, gelatin, starches, cellulose acetate phthalate, and ethylcellulose. After the coating material dissolves, all of the drug inside the microcapsule is immediately available for dissolution and absorption. The thickness of the wall can vary from 1 to 200 mm, depending on the amount of coating material used (3% to 30% of total weight).
   - **c. Matrix tablets** use insoluble plastics (e.g., polyethylene, polyvinyl acetate, polymethacrylate), hydrophilic polymers (e.g., methylcellulose, hydroxypropyl methylcellulose), or fatty compounds (e.g., various waxes, glyceryl tristearate). Examples include Gradumet (Abbott) and Dospan (Aventis).
     - **(1)** The most common method of preparation is mixing of the drug with the matrix material followed by compression of the material into tablets.
     - **(2)** The primary dose, or the portion of the drug to be released immediately, is placed on the tablet as a layer, or coat. The rest of the dose is released slowly from the matrix.

d. Osmotic systems include the Oros system (Alza), which is an oral osmotic pump composed of a core tablet and a semipermeable coating that has a small hole (0.4 mm in diameter) for drug exit. The hole is produced by a laser beam. Examples include Glucotrol XL (glipizide extended-release tablets, Pfizer) and Procardia XL (nifedipine extended-release tablets, Pfizer).

(1) This system requires only osmotic pressure to be effective. It is essentially independent of pH changes in the environment.

(2) The drug-release rate can be changed by changing the tablet surface area, the nature of the membrane, or the diameter of the drug-release aperture.

e. Ion-exchange resins can be complexed with drugs by passage of a cationic drug solution through a column that contains the resin. The drug is complexed to the resin by replacement of hydrogen atoms. Examples include Ionamin capsules (Celltech; resin complexes of phentermine) and the Pennkinetic system (Celltech), which incorporates a polymer barrier coating and bead technology in addition to the ion-exchange mechanism.

(1) After the components are complexed, the resin–drug complex is washed and tableted, encapsulated, or suspended in an aqueous vehicle.

(2) Release of drug from the complex depends on the ionic environment within the gastrointestinal tract and on the properties of the resin. Usually, release is greater in the highly acidic stomach than in the less acidic small intestine.

f. Complex formation is used for certain drug substances that combine chemically with other agents. For example, hydroxypropyl-β-cyclodextrin forms a chemical complex that can be only slowly soluble from body fluids, depending on the pH of the environment. Tannic acid (i.e., tannates) complexes with the amino groups of weak bases dissolve at a slow rate in the gastrointestinal tract, thereby providing for a prolonged release of drug. Examples of the latter include brompheniramine tannate (Brovex, Athlon) and chlorpheniramine/phenylephrine tannates (Rynatan, Wallace).

Study Questions

Directions for questions 1–28: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by one of the suggested answers or phrases. Choose the best answer.

1. Which substance is classified as a weak electrolyte?

(A) glucose
(B) urea
(C) ephedrine
(D) sodium chloride
(E) sucrose

2. The pH value is calculated mathematically as the

(A) log of the hydroxyl ion (OH^-) concentration.
(B) negative log of the OH^- concentration.
(C) log of the hydrogen ion (H^+) concentration.
(D) negative log of the H^+ concentration.
(E) ratio of H^+/OH^- concentration.

3. Which property is classified as colligative?

(A) solubility of a solute
(B) osmotic pressure
(C) hydrogen ion (H^+) concentration
(D) dissociation of a solute
(E) miscibility of the liquids

4. The colligative properties of a solution are related to the

(A) pH of the solution.
(B) number of ions in the solution.
(C) total number of solute particles in the solution.
(D) number of un-ionized molecules in the solution.
(E) pK_a of the solution.

5. The pH of a buffer system can be calculated with the

(A) Noyes–Whitney equation.
(B) Henderson–Hasselbalch equation.
(C) Michaelis–Menten equation.
(D) Young equation.
(E) Stokes equation.

6. Which mechanism is most often responsible for chemical degradation?

(A) racemization
(B) photolysis
(C) hydrolysis
(D) decarboxylation
(E) oxidation

7. Which equation is used to predict the stability of a drug product at room temperature from experiments at accelerated temperatures?

(A) Stokes equation
(B) Young equation
(C) Arrhenius equation
(D) Michaelis–Menten equation
(E) Hixson–Crowell equation

8. Based on the relation between the degree of ionization and the solubility of a weak acid, the drug aspirin ($pK_a = 3.49$) will be most soluble at

(A) pH 1.0.
(B) pH 2.0.
(C) pH 3.0.
(D) pH 4.0.
(E) pH 6.0.

9. Which solution is used as an astringent?

(A) strong iodine solution *USP*
(B) aluminum acetate topical solution *USP*
(C) acetic acid *NF*
(D) aromatic ammonia spirit *USP*
(E) benzalkonium chloride solution *NF*

10. The particle size of the dispersed solid in a suspension is usually greater than

(A) 0.5 μm.
(B) 0.4 μm.
(C) 0.3 μm.
(D) 0.2 μm.
(E) 0.1 μm.

11. In the extemporaneous preparation of a suspension, levigation is used to

(A) reduce the zeta potential.
(B) avoid bacterial growth.
(C) reduce particle size.
(D) enhance viscosity.
(E) reduce viscosity.

12. Which compound is a natural emulsifying agent?

(A) acacia
(B) lactose
(C) polysorbate 20
(D) polysorbate 80
(E) sorbitan monopalmitate

13. Vanishing cream is an ointment that may be classified as

(A) a water-soluble base.
(B) an oleaginous base.
(C) an absorption base.
(D) an emulsion base.
(E) an oleic base.

14. Rectal suppositories intended for adult use usually weigh approximately

(A) 1 g.
(B) 2 g.
(C) 3 g.
(D) 4 g.
(E) 5 g.

15. In the fusion method of making cocoa butter suppositories, which substance is most likely to be used to lubricate the mold?

(A) mineral oil
(B) propylene glycol
(C) cetyl alcohol
(D) stearic acid
(E) magnesium silicate

16. A very fine powdered chemical is defined as one that

(A) completely passes through a #80 sieve.
(B) completely passes through a #120 sieve.
(C) completely passes through a #20 sieve.
(D) passes through a #60 sieve and not more than 40% through a #100 sieve.
(E) passes through a #40 sieve and not more than 60% through a #60 sieve.

17. Which technique is typically used to mill camphor?

(A) trituration
(B) levigation
(C) pulverization by intervention
(D) geometric dilution
(E) attrition

18. The dispensing pharmacist usually blends potent powders with a large amount of diluent by

(A) spatulation.
(B) sifting.
(C) trituration.
(D) geometric dilution.
(E) levigation.

19. Which type of paper best protects a divided hygroscopic powder?

(A) waxed paper
(B) glassine
(C) white bond
(D) blue bond
(E) vegetable parchment

20. Which capsule size has the smallest capacity?

(A) 5
(B) 4
(C) 1
(D) 0
(E) 000

21. The shells of soft gelatin capsules may be made elastic or plastic-like by the addition of

(A) sorbitol.
(B) povidone.
(C) polyethylene glycol (PEG).
(D) lactose.
(E) hydroxypropyl methylcellulose.

22. The *United States Pharmacopeia* (*USP*) content uniformity test for tablets is used to ensure which quality?

(A) bioequivalency
(B) dissolution
(C) potency
(D) purity
(E) toxicity

23. All of the following statements about chemical degradation are true *except*

(A) as temperature increases, degradation decreases.
(B) most drugs degrade by a first-order process.
(C) chemical degradation may produce a toxic product.
(D) chemical degradation may result in a loss of active ingredients.
(E) chemical degradation may affect the therapeutic activity of a drug.

24. All of the following statements concerning zero-order degradation are true *except*

(A) its rate is independent of the concentration.
(B) a plot of concentration versus time yields a straight line on rectilinear paper.
(C) its half-life is a changing parameter.
(D) its concentration remains unchanged with respect to time.
(E) the slope of a plot of concentration versus time yields a rate constant.

25. All of the following statements about first-order degradation are true *except*

(A) its rate is dependent on the concentration.
(B) its half-life is a changing parameter.
(C) a plot of the logarithm of concentration versus time yields a straight line.
(D) its $t_{90\%}$ is independent of the concentration.
(E) a plot of the logarithm of concentration versus time allows the rate constant to be determined.

26. A satisfactory suppository base must meet all of the following criteria *except*

(A) it should have a narrow melting range.
(B) it should be nonirritating and nonsensitizing.
(C) it should dissolve or disintegrate rapidly in the body cavity.
(D) it should melt $< 30°C$.
(E) it should be inert.

27. Cocoa butter (theobroma oil) exhibits all of the following properties *except*

(A) it melts at temperatures between 33°C and 35°C.
(B) it is a mixture of glycerides.
(C) it is a polymorph.
(D) it is useful in formulating rectal suppositories.
(E) it is soluble in water.

28. *United States Pharmacopeia* (*USP*) tests to ensure the quality of drug products in tablet form include all of the following *except*

(A) disintegration.
(B) dissolution.
(C) hardness and friability.
(D) content uniformity.
(E) weight variation.

Directions for questions 29–42: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E.**

A if **I only** is correct
B if **III only** is correct
C if **I** and **II** are correct
D if **II** and **III** are correct
E if **I**, **II**, and **III** are correct

29. Forms of water that are suitable for use in parenteral preparations include

I. purified water *USP*.
II. water for injection *USP*.
III. sterile water for injection *USP*.

30. The particles in an ideal suspension should satisfy which of the following criteria?

I. Their size should be uniform.
II. They should be stationary or move randomly.
III. They should remain discrete.

31. The sedimentation of particles in a suspension can be minimized by

I. adding sodium benzoate.
II. increasing the viscosity of the suspension.
III. reducing the particle size of the active ingredient.

32. Ingredients that may be used as suspending agents include

I. methylcellulose.
II. acacia.
III. talc.

33. Mechanisms that are thought to provide stable emulsifications include the

I. formation of interfacial film.
II. lowering of interfacial tension.
III. presence of charge on the ions.

34. Nonionic surface-active agents used as synthetic emulsifiers include

I. tragacanth.
II. sodium lauryl sulfate.
III. sorbitan esters (Spans).

35. Advantages of systemic drug administration by rectal suppositories include

I. avoidance of first-pass effects.
II. suitability when the oral route is not feasible.
III. predictable drug release and absorption.

36. True statements about the milling of powders include

I. a fine particle size is essential if the lubricant is to function properly.
II. an increased surface area may enhance the dissolution rate.
III. milling may cause degradation of thermolabile drugs.

37. Substances used to insulate powder components that liquefy when mixed include

I. talc.
II. kaolin.
III. light magnesium oxide.

38. A ceramic mortar may be preferable to a glass mortar when

I. a volatile oil is added to a powder mixture.
II. colored substances (dyes) are mixed into a powder.
III. comminution is desired in addition to mixing.

39. Divided powders may be dispensed in

I. individual-dose packets.
II. a bulk container.
III. a perforated, sifter-type container.

40. True statements about the function of excipients used in tablet formulations include

I. binders promote granulation during the wet granulation process.
II. glidants help promote the flow of the tablet granulation during manufacture.
III. lubricants help the patient swallow the tablets.

41. Which manufacturing variables would be likely to affect the dissolution of a prednisone tablet in the body?

I. the amount and type of binder added
II. the amount and type of disintegrant added
III. the force of compression used during tableting

42. Agents that may be used to coat enteric-coated tablets include

I. hydroxypropyl methylcellulose.
II. carboxymethylcellulose.
III. cellulose acetate phthalate.

Directions for questions 43–46: Each of the following tablet-processing problems can be the result of one of the following reasons. The processing problems may be used more than once or not at all. Choose the **best** answer, **A–E**.

A excessive moisture in the granulation
B entrapment of air
C tablet friability
D degraded drug
E tablet hardness

43. Picking

44. Mottling

45. Capping

46. Sticking

Directions for questions 47–49: Each of the following processes can be described by one of the following comminution procedures. The processes may be used more than once or not at all. Choose the **best** answer, **A–E**.

A trituration
B spatulation
C levigation
D pulverization by intervention
E tumbling

47. Rubbing or grinding a substance in a mortar that has a rough inner surface

48. Reducing and subdividing a substance by adding an easily removed solvent

49. Adding a suitable agent to form a paste and then rubbing or grinding the paste in a mortar

Directions for questions 50–53: Each of the following controlled-release dosage forms is represented by one of the following drug products. The dosage forms may be used more than once or not at all. Choose the **best** answer, **A–E**.

A matrix formulations
B ion-exchange resin complex
C drug complexes
D osmotic system
E coated beads or granules

50. Ionamin capsules

51. Thorazine Spansule capsules

52. Rynatan pediatric suspension

53. Procardia XL

Answers and Explanations

1. **The answer is C** *[see IV.A.1.a; IV.A.3.d].*
Glucose, urea, and sucrose are nonelectrolytes. Sodium chloride is a strong electrolyte. Electrolytes are substances that form ions when dissolved in water. Thus, they can conduct an electric current through the solution. Ions are particles that bear electrical charges: Cations are positively charged, and anions are negatively charged. Strong electrolytes are completely ionized in water at all concentrations. Weak electrolytes (e.g., ephedrine) are only partially ionized at most concentrations. Because nonelectrolytes do not form ions when in solution, they are nonconductors.

2. **The answer is D** *[see IV.A.3.b].*
The pH is a measure of the acidity, or hydrogen ion concentration, of an aqueous solution. The pH is the logarithm of the reciprocal of the hydrogen ion (H^+) concentration expressed in moles per liter. Because the logarithm of a reciprocal equals the negative logarithm of the number, the pH is the negative logarithm of the H^+ concentration. A pH of 7.0 indicates neutrality. As the pH decreases, the acidity increases. The pH of arterial blood is 7.35 to 7.45; of urine, 4.8 to 7.5; of gastric juice, approximately 1.4; and of cerebrospinal fluid, 7.35 to 7.40. The concept of pH was introduced by Sörensen in the early 1900s. Alkalinity is the negative logarithm of $[OH^-]$ and is inversely related to acidity.

3. **The answer is B** *[see IV.A.2.d].*
Osmotic pressure is an example of a colligative property. The osmotic pressure is the magnitude of pressure needed to stop osmosis across a semipermeable membrane between a solution and a pure solvent. The colligative properties of a solution depend on the total number of dissociated and undissociated solute particles. These properties are independent of the size of the solute. Other colligative properties of solutes are reduction in the vapor pressure of the solution, elevation of its boiling point, and depression of its freezing point.

4. **The answer is C** *[see IV.A.1.b].*
The colligative properties of a solution are related to the total number of solute particles that it contains. Examples of colligative properties are the osmotic pressure, lowering of the vapor pressure, elevation of the boiling point, and depression of the freezing or melting point.

5. **The answer is B** *[see IV.A.3.e].*
The Henderson–Hasselbalch equation for a weak acid and its salt is as follows:

$$pH = pK_a + \log \frac{[salt]}{[acid]}$$

where pK_a is the negative log of the dissociation constant of a weak acid and [salt]/[acid] is the ratio of the molar concentration of salt and acid used to prepare a buffer.

6. **The answer is C** *[see V.D.1].*
Although all of the mechanisms listed can be responsible, the chemical degradation of medicinal compounds, particularly esters in liquid formulations, is usually caused by hydrolysis. For this reason, drugs that have ester functional groups are formulated in dry form whenever possible. Oxidation is another common mode of degradation and is minimized by including antioxidants (e.g., ascorbic acid) in drug formulations. Photolysis is reduced by packaging susceptible products in amber or opaque containers. Decarboxylation, which is the removal of COOH groups, affects compounds that include carboxylic acid. Racemization neutralizes the effects of an optically active compound by converting half of its molecules into their mirror-image configuration. As a result, the dextrorotatory and levorotatory forms cancel each other out. This type of degradation affects only drugs that are characterized by optical isomerism.

7. **The answer is C** *[see V.E.3.d].*
Testing of a drug formulation to determine its shelf life can be accelerated by applying the Arrhenius equation to data obtained at higher temperatures. The method involves determining the rate constant (k) values for the degradation of a drug at various elevated temperatures. The log of k is plotted against the reciprocal of the absolute temperature, and the k value for degradation at room temperature is obtained by extrapolation.

8. **The answer is E** *[see IV.A.3.g].*
The solubility of a weak acid varies as a function of pH. Because pH and pK_a (the dissociation constant) are related, solubility is also related to the degree of ionization. Aspirin is a weak acid that is completely ionized at a pH that is two units greater than its pK_a. Therefore, it is most soluble at pH 6.0.

9. **The answer is B** *[see VI.B.7].*
Aluminum acetate and aluminum subacetate solutions are astringents that are used as antiperspirants and as wet dressings for contact dermatitis. Strong iodine solution and benzalkonium chloride are topical antibacterial solutions. Acetic acid is added to products as an acidifier. Aromatic ammonia spirit is a respiratory stimulant.

10. **The answer is A** *[see IV.B.1.a].*
A suspension is a two-phase system that consists of a finely powdered solid dispersed in a liquid vehicle. The particle size of the suspended solid should be as small as possible to minimize sedimentation, but it is usually > 0.5 μm.

11. **The answer is C** *[see VI.E.3.a].*
Levigation is the process of blending and grinding a substance to separate the particles, reduce their size, and form a paste. Levigation is performed by adding a small amount of suitable levigating agent (e.g., glycerin) to the solid and blending the mixture with a mortar and pestle.

12. **The answer is A** *[see VI.D.3].*
Acacia, or gum arabic, is the exudate obtained from the stems and branches of various species of *Acacia*, a woody plant native to Africa. Acacia is a natural emulsifying agent that provides a stable emulsion of low viscosity. Emulsions are droplets of one or more immiscible liquids dispersed in another liquid. Emulsions are inherently unstable: The droplets tend to coalesce into larger and larger drops. The purpose of an emulsifying agent is to keep the droplets dispersed and prevent them from coalescing. Polysorbate 20, polysorbate 80, and sorbitan monopalmitate are also emulsifiers, but are synthetic, not natural, substances.

13. **The answer is D** *[see VI.E.2].*
Ointments are typically used as emollients to soften the skin, as protective barriers, or as vehicles for medication. A variety of ointment bases are available. Vanishing cream, an emulsion type of ointment base, is an oil-in-water emulsion that contains a high percentage of water. Stearic acid is used to create a thin film on the skin when the water evaporates.

14. **The answer is B** *[see VI.F.2.a].*
By convention, a rectal suppository for an adult weighs approximately 2 g. Suppositories for infants and children are smaller. Vaginal suppositories typically weigh approximately 5 g. Rectal suppositories are usually shaped like an elongated bullet (cylindrical and tapered at one end). Vaginal suppositories are usually ovoid.

15. **The answer is A** *[see VI.F.4.c].*
In the fusion method of making suppositories, molds made of aluminum, brass, or nickel–copper alloys are used. Finely powdered drug mixed with melted cocoa butter is poured into a mold that is lubricated very lightly with mineral oil.

16. **The answer is B** *[see VI.G; Table 2-8].*
The *USP* defines a very fine chemical powder as one that completely passes through a standard #120 sieve, which has 125-μm openings. The *USP* classification for powdered vegetable and animal drugs differs from that for powdered chemicals. To be classified as very fine, powdered vegetable and animal drugs must pass completely through a #80 sieve, which has 180-μm openings.

17. **The answer is C** *[see VI.G.1.c.(3.(b)].*
Pulverization by intervention is the milling technique that is used for drug substances that are gummy and tend to reagglomerate or resist grinding (e.g., camphor, iodine). In this sense, intervention is the addition of a small amount of material that aids milling and can be removed easily after pulverization is complete. For example, camphor can be reduced readily if a small amount of volatile solvent (e.g., alcohol) is added. The solvent is then allowed to evaporate.

18. **The answer is D** *[see VI.G.2.c].*
The pharmacist uses geometric dilution to mix potent substances with a large amount of diluent. The potent drug and an equal amount of diluent are first mixed in a mortar by trituration. A volume of diluent equal to the mixture in the mortar is added, and the mix is again triturated. The procedure is repeated, and each time, diluent equal in volume to the mixture then in the mortar is added, until all of the diluent is incorporated.

19. The answer is A *[see VI.G.3.b.(4)].*
Hygroscopic and volatile drugs are best protected by waxed paper, which is waterproof. The packet may be double-wrapped with a bond paper to improve the appearance of the completed powder.

20. The answer is A *[see VI.H.2.c.(1)].*
Hard capsules are numbered from 000 (largest) to 5 (smallest). Their approximate capacity ranges from 600 to 30 mg; however, the capacity of the capsule depends on the density of the contents.

21. The answer is A *[see VI.H.3.a–b].*
The shells of soft gelatin capsules are plasticized by the addition of a polyhydric alcohol (polyol), such as glycerin or sorbitol. An antifungal preservative can also be added. Both hard and soft gelatin capsules can be filled with a powder or another dry substance. Soft gelatin capsules are also useful dosage forms for fluids or semisolids.

22. The answer is C *[see VI.H.4.a].*
A content uniformity test is a test of potency. To ensure that each tablet or capsule contains the intended amount of drug substance, the *USP* provides two tests: weight variation and content uniformity. The content uniformity test can be used for any dosage unit but is required for coated tablets, for tablets in which the active ingredient makes up $<$ 50% of the tablet, for suspensions in single-unit containers or in soft capsules, and for many solids that contain added substances. The weight variation test can be used for liquid-filled soft capsules, for any dosage form unit that contains at least 50 mg of a single drug if the drug makes up at least 50% of the bulk, for solids that do not contain added substances, and for freeze-dried solutions.

23. The answer is A *[see V.A and V.B].*
The reaction velocity, or degradation rate, of a pharmaceutical product is affected by several factors, including temperature, solvents, and light. The degradation rate increases two to three times with each 10°C increase in temperature. The effect of temperature on reaction rate is given by the Arrhenius equation:

$$k = Ae^{-Ea/RT}$$

where k is the reaction rate constant, A is the frequency factor, Ea is the energy of activation, R is the gas constant, and T is the absolute temperature.

24. The answer is D *[see V.B.2.a].*
In zero-order degradation, the concentration of a drug decreases over time. However, the change of concentration with respect to time is unchanged. In the equation

$$-\frac{dC}{dt} = k$$

the fact that dC/dt is negative signifies that the concentration is decreasing. However, the velocity of the concentration change is constant.

25. The answer is B *[see V.B.2.b.(2)].*
The half-life ($t_{½}$) is the time required for the concentration of a drug to decrease by one-half. For a first-order degradation:

$$t_{½} = \frac{0.693}{k}$$

Because both k and 0.693 are constants, $t_{½}$ is a constant.

26. The answer is D *[see VI.F.3].*
A satisfactory suppository base should remain firm at room temperature. Preferably, it should not melt $<$ 30°C to avoid premature softening during storage and insertion. It should also be inert, nonsensitizing, nonirritating, and compatible with a variety of drugs. Moreover, it should melt just below body temperature and should dissolve or disintegrate rapidly in the fluid of the body cavity into which it is inserted.

27. The answer is E *[see VI.F.3.c.(1)].*
Cocoa butter is a fat that is obtained from the seed of *Theobroma cacao*. Chemically, it is a mixture of stearin, palmitin, and other glycerides that are insoluble in water and freely soluble in ether and chloroform. Depending on the fusion temperature, cocoa butter can crystallize into any one of four crystal forms. Cocoa butter is a good base for rectal suppositories, although it is less than ideal for vaginal or urethral suppositories.

28. The answer is C *[see VI.I.5].*
To satisfy the *USP* standards, tablets are required to pass one of two tests. A weight variation test is used if the active ingredient makes up the bulk of the tablet. A content uniformity test is used if the tablet is coated or if the active ingredient makes up $<$ 50% of the bulk of the tablet. Many tablets for oral administration are required to meet a disintegration test. Disintegration times are specified in the individual monographs. A dissolution test may be required instead if the active component of the tablet has limited water solubility. Hardness and friability would affect the disintegration and dissolution rates, but hardness and friability tests are in-house quality control tests, not official *USP* tests.

29. The answer is D (II, III) *[see VI.A.1].*
Water for injection *USP* is water that has been purified by distillation or by reverse osmosis. This water is used to prepare parenteral solutions that are subject to final sterilization. For parenteral solutions that are prepared aseptically and not subsequently sterilized, sterile water for injection *USP* is used. Sterile water for injection *USP* is water for injection *USP* that has been sterilized and suitably packaged. This water meets the *USP* requirements for sterility. Bacteriostatic water for injection *USP* is sterile water for injection *USP* that contains one or more antimicrobial agents. It can be used in parenteral solutions if the antimicrobial additives are compatible with the other ingredients in the solution, but it cannot be used in newborns. Purified water *USP* is not used in parenteral preparations.

30. The answer is E (I, II, III) *[see IV.B.2].*
An ideal suspension would have particles of uniform size, minimal sedimentation, and no interaction between particles. Although these ideal criteria are rarely met, they can be approximated by keeping the particle size as small as possible, the densities of the solid and the dispersion medium as similar as possible, and the dispersion medium as viscous as possible.

31. The answer is D (II, III) *[see IV.B.2].*
As Stokes's law indicates, the sedimentation rate of a suspension is slowed by reducing its density, reducing the size of the suspended particles, or increasing its viscosity by incorporating a thickening agent. Sodium benzoate is an antifungal agent and would not reduce the sedimentation rate of a suspension.

32. The answer is C (I, II) *[see VI.C.3].*
Acacia and methylcellulose are common suspending agents. Acacia is a natural product, and methylcellulose is a synthetic polymer. By increasing the viscosity of the liquid, these agents enable particles to remain suspended for a longer period.

33. The answer is E (I, II, III) *[see VI.D.3].*
Emulsifying agents provide a mechanical barrier to coalescence. They also reduce the natural tendency of the droplets in the internal phase (oil or water) of the emulsion to coalesce. Three mechanisms appear to be involved. Some emulsifiers promote stability by forming strong, pliable interfacial films around the droplets. Emulsifying agents also reduce interfacial tension. Finally, ions (from the emulsifier) in the interfacial film can lead to charge repulsion that causes droplets to repel one another, thereby preventing coalescence.

34. The answer is B (III) *[see VI.D.3].*
All of the substances listed are emulsifying agents, but only sorbitan esters are nonionic synthetic agents. Tragacanth, like acacia, is a natural emulsifying agent. Sodium lauryl sulfate is an anionic surfactant. Sorbitan esters (known colloquially as Spans because of their trade names) are hydrophobic and form water-in-oil emulsions. The polysorbates (known colloquially as Tweens) are also nonionic, synthetic sorbitan derivatives. However, they are hydrophilic and therefore form oil-in-water emulsions. Sodium lauryl sulfate, as alkali soap, is also hydrophilic and thus forms oil-in-water emulsions.

35. The answer is C (I, II) *[see VI.F.1–2].*
Rectal suppositories are useful for delivering systemic medication under certain circumstances. Absorption of a drug from a rectal suppository involves release of the drug from the suppository vehicle, diffusion through the rectal mucosa, and transport to the circulation through the rectal veins. The rectal veins bypass the liver, so this route avoids rapid hepatic degradation of certain drugs (first-pass effect). The rectal route is also useful when a drug cannot be given orally (e.g., because of vomiting). However, the extent of drug release and absorption is variable. It depends on the properties of the drug, the suppository base, and the environment in the rectum.

36. The answer is E (I, II, III) *[see VI.G.1.c].*
Milling is the process of mechanically reducing the particle size of solids before they are formulated into a final product. To work effectively, a lubricant must coat the surface of the granulation or powder. Hence, fine particle size is essential. Decreasing the particle size increases the surface area and can enhance the dissolution rate. Thermolabile drugs may undergo degradation because of the buildup of heat during milling.

37. The answer is D (II, III) *[see VI.G.2.a.(2)].*
Some solid substances (e.g., aspirin, phenylsalicylate, phenacetin, thymol, camphor) liquefy or form eutectic mixtures when in close, prolonged contact with one another. These substances are best insulated by the addition of light magnesium oxide or magnesium carbonate. Other inert diluents that can be used are kaolin, starch, and bentonite.

38. The answer is B (III) *[see VI.G.2.b].*
When powders are mixed, if comminution is especially important, a porcelain or ceramic mortar that has a rough inner surface is preferred over the smooth working surface of a glass mortar. Because a glass mortar cleans more easily after use, it is preferred for chemicals that may stain a porcelain or ceramic mortar as well as for simple mixing of substances that do not require comminution.

39. The answer is A (I) *[see VI.G.3.a–b].*
Powders for oral use can be dispensed by the pharmacist in bulk form or divided into premeasured doses (divided powders). Divided powders are traditionally dispensed in folded paper packets (chartulae) made of parchment, bond paper, glassine, or waxed paper. However, individual doses can be packaged in metal foil or small plastic bags if the powder needs greater protection from humidity or evaporation.

40. The answer is C (I, II) *[see VI.I.2.b].*
Tablets for oral ingestion usually contain excipients that are added to the formulation for their special functions. Binders and adhesives are added to promote granulation or compaction. Diluents are fillers that are added to make up the required tablet bulk. They can also aid in the manufacturing process. Disintegrants aid in tablet disintegration in gastrointestinal fluids. Lubricants, antiadherents, and glidants aid in reducing friction or adhesion between particles or between tablet and die. For example, lubricants are used in the manufacture of tablets to reduce friction when the tablet is ejected from the die cavity. Lubricants are usually hydrophobic substances that can affect the dissolution rate of the active ingredient.

41. The answer is E (I, II, III) *[see VI.2.b.(3)].*
Disintegrants are added to tablet formulations to facilitate disintegration in gastrointestinal fluids. Disintegration of the tablet in the body is critical to its dissolution and subsequent absorption and bioavailability. The binder and the compression force used during tablet manufacturing affect the hardness of the tablet as well as tablet disintegration and drug dissolution.

42. The answer is B (III) *[see VI.I.3.a.(4)].*
An enteric-coated tablet has a coating that remains intact in the stomach, but dissolves in the intestines to yield the tablet ingredients there. Enteric coatings include various fats, fatty acids, waxes, and shellacs. Cellulose acetate phthalate remains intact in the stomach because it dissolves only when the pH $>$ 6. Other enteric-coating materials include povidone (polyvinylpyrrolidone), polyvinyl acetate phthalate, and hydroxypropyl methylcellulose phthalate.

43. The answer is A *[see VI.I.4].*

44. The answer is D *[see VI.I.4].*

45. The answer is B *[see VI.I.4].*

46. The answer is A *[see VI.I.4].*
Sticking is adhesion of tablet material to a die wall. It may be caused by excessive moisture or by the use of ingredients that have low melting temperatures. Mottling is uneven color distribution. It is most often caused by poor mixing of the tablet granulation but may also occur when a degraded drug produces a colored metabolite. Capping is separation of the top or bottom crown of a tablet from the main body. Capping implies that compressed powder is not cohesive. Reasons for capping include excessive force of compression, use of insufficient binder, worn tablet tooling equipment, and entrapment of air during processing. Picking is adherence of tablet surface material to a punch. It can be caused by a granulation that is too damp, by a scratched punch, by static charges on the powder, and particularly by the use of a punch tip that is engraved or embossed.

47. The answer is A *[see VI.G.1.c; VI.G.2].*

48. The answer is D *[see VI.G.1.c; VI.G.2].*

49. The answer is C *[see VI.G.1.c; VI.G.2].*
Comminution is the process of reducing the particle size of a powder to increase its fineness. Several comminution techniques are suitable for small-scale use in a pharmacy. Trituration is used both to comminute and to mix dry powders. If comminution is desired, the substance is rubbed in a mortar that has a rough inner surface. Pulverization by intervention is often used for substances that tend to agglomerate or resist grinding. A small amount of easily removed (e.g., volatile) solvent is added. After the substance is pulverized, the solvent is allowed to evaporate or is otherwise removed. Levigation is often used to prepare pastes or ointments. The powder is reduced by adding a suitable nonsolvent (levigating agent) to form a paste and then either rubbing the paste in a mortar with a pestle or rubbing it on an ointment slab with a spatula. Spatulation and tumbling are techniques that are used to mix or blend powders, not to reduce them. Spatulation is blending small amounts of powders by stirring them with a spatula on a sheet of paper or a pill tile. Tumbling is blending large amounts of powder in a large rotating container.

50. The answer is B *[see VI.K.3.e].*

51. The answer is E *[see VI.K.3.a].*

52. The answer is C *[see VI.K.3.f].*

53. The answer is D *[see VI.K.3.d].*

Controlled-release dosage forms are designed to release a drug slowly for prolonged action in the body. A variety of pharmaceutical mechanisms are used to provide the controlled release. Ion-exchange resins may be complexed to drugs by passing a cationic drug solution through a column that contains the resin. The drug is complexed to the resin by replacement of hydrogen atoms. Release of drug from the complex depends on the ionic environment within the gastrointestinal tract and on the properties of the resin. Coated beads (e.g., Thorazine Spansule capsules) or granules produce blood levels similar to those obtained with multiple dosing. The various coating thicknesses produce a sustained-release effect.

Matrix devices may use insoluble plastics, hydrophilic polymers, or fatty compounds. These components are mixed with the drug and compressed into a tablet. The primary dose, or the portion of the drug to be released immediately, is placed on the tablet as a layer or coat. The remainder of the dose is released slowly from the matrix. Relatively insoluble tannate–amine complexes provide for a prolonged gastrointestinal absorption phase and sustained systemic concentrations of the weak bases. Osmotic systems employ osmotic pressure to control the release of the active ingredient from the formulation. Osmotic tablet formulations provide a semipermeable membrane as a coating that surrounds the osmotically active core. The coating allows water to diffuse into the core but does not allow drug to diffuse out. As water flows into the tablet, the drug dissolves. The laser-drilled hole in the coating allows the drug solution within the tablet to flow to the outside at a rate that is equivalent to the rate of water flow into the tablet. The osmotic pressure gradient and a zero-order drug-release rate will be maintained as long as excess osmotically active solute (e.g., electrolyte) remains in the tablet core.

3 Biopharmaceutics and Drug Delivery Systems

LAWRENCE H. BLOCK

I. INTRODUCTION

A. Biopharmaceutics is the study of the relation of the physical and chemical properties of a drug to its bioavailability, pharmacokinetics, and pharmacodynamic and toxicologic effects.

1. A **drug product** is the finished dosage form (e.g., tablet, capsule, solution) that contains the active drug ingredient in association with nondrug (usually inactive) ingredients (**excipients**) that make up the **vehicle** or **formulation matrix**.
2. The phrase *drug delivery system* is often used interchangeably with the terms *drug product* or *dosage form*. However, a **drug delivery system** is a more comprehensive concept, which includes the drug formulation and the dynamic interactions among the drug, its formulation matrix, its container, and the patient.
3. **Bioavailability** is a measurement of the rate and extent (amount) of systemic absorption of the therapeutically active drug.

B. Pharmacokinetics is the study of the time course of drug movement in the body during absorption, distribution, and elimination (excretion and biotransformation).

C. Pharmacodynamics is the study of the relation of the drug concentration or amount at the site of action (receptor) and its pharmacologic response as a function of time.

II. DRUG TRANSPORT AND ABSORPTION

A. Transport of drug molecules *across* cell membranes. Drug absorption requires the drug to be transported across various cell membranes. Drug molecules may enter the bloodstream and be transported to the tissues and organs of the body. Drug molecules may cross additional membranes to enter cells. Drug molecules may also cross an intracellular membrane, such as the nuclear membrane or endoplasmic reticulum, to reach the site of action. *Figure 3-1* demonstrates some of the key transport processes involved in drug absorption.

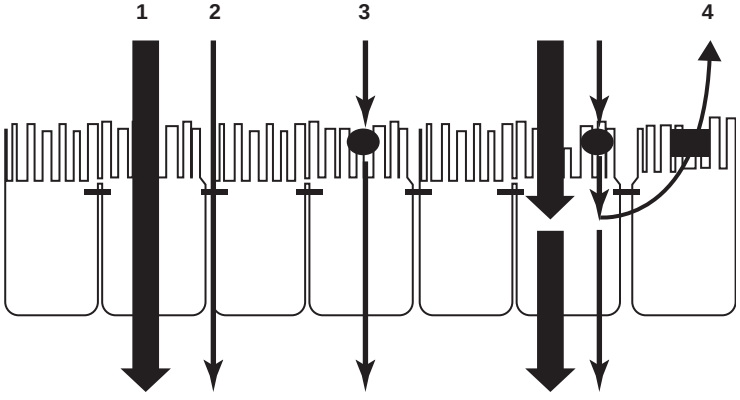


Figure 3-1. The key drug transport processes in intestinal epithelial cells. *1*, Transcellular passive (diffusion and partitioning); *2*, paracellular transport (diffusion and convection); *3*, carrier-mediated transport; *4*, P-glycoprotein–mediated efflux. Modified from Brayden DJ. Human intestinal epithelial cell monolayers as prescreens for oral drug delivery. *Pharm News*. 1997;4(1):11–15.

1. **General principles**
   a. A **cell membrane** is a semipermeable structure composed primarily of lipids and proteins.
   b. Drugs may be transported by **passive diffusion**, **partitioning**, **carrier-mediated transport**, **paracellular transport**, or **vesicular transport**.
   c. Usually, **proteins**, **drugs bound to proteins**, and **macromolecules** do not easily cross cell membranes.
   d. **Nonpolar lipid-soluble drugs** traverse cell membranes more easily than do **ionic** or **polar water-soluble drugs**.
   e. **Low-molecular-weight drugs** diffuse across a cell membrane more easily than do **high-molecular-weight drugs**.
2. **Passive diffusion and partitioning**
   a. ***Within* the cytoplasm** or in **interstitial fluid**, most drugs undergo transport by simple diffusion.
   b. **Fick's law of diffusion. Simple passive diffusion** involves the transfer of drugs from an area of high concentration (C_1) to an area of lower concentration (C_2) according to Fick's law of diffusion:

$$\frac{dQ}{dt} = \frac{DA}{h}(C_1 - C_2)$$

   where dQ/dt is the rate of drug diffusion, D is the diffusion coefficient for the drug, A is the surface area of the plane across which transfer occurs, h is the thickness of the region through which diffusion occurs, and $(C_1 - C_2)$ is the difference between the drug concentration in area 1 and area 2, respectively.
   c. Passive drug transport *across* cell membranes involves the successive **partitioning** of a solute between aqueous and lipid phases as well as **diffusion** within the respective phases. Modifying Fick's law of diffusion to accommodate the partitioning of drug gives the following:

$$\frac{dQ}{dt} = \frac{DAK}{h}(C_1 - C_2)$$

   The rate of drug diffusion, dQ/dt, now reflects its direct dependence on K, the oil to water partition coefficient of the drug, as well as on A and $(C_1 - C_2)$.
   d. **Ionization of a weak electrolyte** is affected by the pH of the medium in which the drug is dissolved as well as by the pK_a of the drug. The nonionized species is more lipid soluble than the ionized species, and it partitions more readily across cell membranes.
3. **Carrier-mediated transport**
   a. **Active transport** of the drug across a membrane is a carrier-mediated process that has the following characteristics:
      (1) The drug moves against a concentration gradient.
      (2) The process requires energy.
      (3) The carrier may be selective for certain types of drugs that resemble natural substrates or metabolites that are normally actively transported.
      (4) The carrier system may be saturated at a high drug concentration.
      (5) The process may be competitive (i.e., drugs with similar structures may compete for the same carrier).
   b. **Facilitated diffusion** is also a carrier-mediated transport system. However, facilitated diffusion occurs with (i.e., in the direction of) a concentration gradient and does not require energy.
4. **Paracellular transport.** Drug transport across tight (narrow) junctions between cells or transendothelial channels of cells is known as **paracellular transport**. It involves both diffusion and the **convective** (bulk) flow of water and accompanying water-soluble drug molecules through the paracellular channels.
5. **Vesicular transport** is the process of engulfing particles or dissolved materials by a cell. Vesicular transport is the only transport mechanism that does not require a drug to be in an aqueous solution to be absorbed. **Pinocytosis** and **phagocytosis** are forms of vesicular transport.
   a. **Pinocytosis** is the engulfment of small solute or fluid volumes.
   b. **Phagocytosis** is the engulfment of larger particles, or macromolecules, generally by macrophages.
   c. **Endocytosis** and **exocytosis** are the movement of macromolecules into and out of the cell, respectively.

6. **Other transport mechanisms: transporter proteins.** Various **transporter proteins** (e.g., **P-glycoprotein**) are embedded in the lipid bilayer of cell membranes in tandem in α-helical transmembrane regions or domains. These proteins are adenosine triphosphate (ATP; energy) dependent "pumps," which can facilitate the efflux of drug molecules from the cell. Because these transmembrane efflux pumps are often found in conjunction with metabolizing enzymes such as **cytochrome P450 3A4**, their net effect is to substantially reduce intracellular drug concentrations. Thus they determine, to a large extent, the pharmacokinetic disposition and circulating plasma concentrations of drugs (e.g., cyclosporine, nifedipine, digoxin) that are substrates for these proteins.

B. Routes of drug administration

1. **Parenteral administration**
   a. **Intravenous bolus injection.** The drug is injected directly into the bloodstream, distributes throughout the body, and acts rapidly. Any side effects, including an intense pharmacologic response, anaphylaxis, or overt toxicity, also occur rapidly.
   b. **Intra-arterial injection.** The drug is injected into a specific artery to achieve a high drug concentration in a specific tissue before drug distribution occurs throughout the body. Intra-arterial injection is used for diagnostic agents and occasionally for chemotherapy.
   c. **Intravenous infusion.** The drug is given intravenously at a constant input rate. Constant-rate intravenous infusion maintains a relatively constant plasma drug concentration once the infusion rate is approximately equal to the drug's elimination rate from the body (i.e., once steady state is reached).
   d. **Intramuscular injection.** The drug is injected deep into a skeletal muscle. The rate of absorption depends on the vascularity of the muscle site, the lipid solubility of the drug, and the formulation matrix.
   e. **Subcutaneous injection.** The drug is injected beneath the skin. Because the subcutaneous region is less vascular than muscle tissues, drug absorption is less rapid. The factors that affect absorption from intramuscular depots also affect subcutaneous absorption.
   f. **Miscellaneous parenteral routes**
      (1) **Intra-articular injection.** The drug is injected into a joint.
      (2) **Intradermal (intracutaneous) injection.** The drug is injected into the dermis (i.e., the vascular region of the skin below the epidermis).
      (3) **Intrathecal injection.** The drug is injected into the spinal fluid.
2. **Enteral administration**
   a. **Buccal and sublingual administration.** A tablet or lozenge is placed under the tongue (**sublingual**) or in contact with the mucosal (**buccal**) surface of the cheek. This type of administration allows a nonpolar, lipid-soluble drug to be absorbed across the epithelial lining of the mouth. After buccal or sublingual administration, the drug is absorbed directly into the systemic circulation, bypassing the liver and any first-pass effects.
   b. **Peroral (oral) drug administration.** The drug is administered orally, is swallowed, and undergoes absorption from the gastrointestinal tract through the mesenteric circulation to the hepatic portal vein into the liver and then to the systemic circulation. The peroral route is the most common route of administration.
      (1) The peroral route is the most convenient and the safest route.
      (2) Disadvantages of this route include the following:
         (a) The drug may not be absorbed from the gastrointestinal tract consistently or completely.
         (b) The drug may be digested by gastrointestinal enzymes or decomposed by the acid pH of the stomach.
         (c) The drug may irritate mucosal epithelial cells or complex with the contents of the gastrointestinal tract.
         (d) Some drugs may be incompletely absorbed because of first-pass effects or presystemic elimination (e.g., the drug is metabolized by the liver before systemic absorption occurs).
         (e) The absorption rate may be erratic because of delayed gastric emptying or changes in intestinal motility.
      (3) Most drugs are **xenobiotics** or **exogenous** molecules and, consequently, are absorbed from the gastrointestinal tract by **passive diffusion** and **partitioning**. **Carrier-mediated transport**, **paracellular transport**, and **vesicular transport** play smaller—but critical—roles, particularly for endogenous molecules.

(4) Drug molecules are absorbed throughout the gastrointestinal tract; but the **duodenal region**, which has a large surface area because of the villi and microvilli, is the primary absorption site. The large blood supply provided by the mesenteric vessels allows the drug to be absorbed more efficiently (see II.A.2).

(5) **Altered gastric emptying** affects arrival of the drug in the duodenum for systemic absorption. **Gastric emptying time** is affected by food content, food composition (fats, acids delay gastric emptying), emotional state, circadian effects (gastric emptying tends to be more rapid in the morning than in the evening), and drugs that alter gastrointestinal tract motility (e.g., anticholinergics, narcotic analgesics, prokinetic agents). In general, the T_{max} (**time** of peak systemic drug concentration) occurs earlier, when gastric emptying is faster than normal, and later, when gastric emptying is slower than normal. The effect of gastric emptying on C_{max} (**peak** systemic drug concentration) varies, depending on the absorption mechanism, pH dependence of dissolution, extent of presystemic elimination, etc.

(6) Normal intestinal motility from **peristalsis** brings the drug in contact with the intestinal epithelial cells. A sufficient period of contact (residence time) is needed to permit drug absorption across the cell membranes from the mucosal to the serosal surface.

(7) Some drugs, such as **cimetidine** and **acetaminophen**, when given in an immediate-release peroral dosage form to fasted subjects produce a systemic drug concentration time with two peaks. This **double-peak phenomenon** is attributed to variability in stomach emptying, variable intestinal motility, and enterohepatic cycling.

c. Rectal administration. The drug in solution (enema) or suppository form is placed in the rectum. Drug diffusion from the solution or release from the suppository leads to absorption across the mucosal surface of the rectum. Drug absorbed in the lower two-thirds of the rectum enters the systemic circulation directly, bypassing the liver and any first-pass effects.

3. Respiratory tract administration

a. Intranasal administration. The drug contained in a solution or suspension is administered to the nasal mucosa, either as a spray or as drops. The medication may be used for local (e.g., nasal decongestants, intranasal steroids) or systemic effects.

b. Pulmonary inhalation. The drug, as liquid or solid particles, is inhaled perorally (with a nebulizer or a metered-dose aerosol) into the pulmonary tree. In general, **particles > 60 μm** are primarily deposited in the **trachea**. **Particles > 20 μm** do not reach the bronchioles, and **particles < 0.6 μm** are not deposited and are **exhaled**. Particles between **2 and 6 μm** can reach the **alveolar ducts**, although only particles of **1 to 2 μm are retained in the alveoli**.

4. Transdermal and topical administration

a. Transdermal (**percutaneous**) drug absorption is the placement of the drug (in a lotion, ointment, cream, paste, or patch) on the skin surface for systemic absorption. An occlusive dressing or film improves systemic drug absorption from the skin. Small lipid-soluble molecules, such as nitroglycerin, nicotine, scopolamine, clonidine, fentanyl, and steroids (e.g., 17-β-estradiol, testosterone), are readily absorbed from the skin.

b. Drugs (e.g., antibacterials, local anesthetic agents) are applied **topically** to the skin for a local effect.

5. Miscellaneous routes of drug administration include **ophthalmic**, **otic**, **urethral**, and **vaginal** administration. These routes of administration are generally used for local therapeutic activity. However, some systemic drug absorption may occur.

C. Local drug activity versus **systemic drug absorption.** The route of administration, absorption site, and bioavailability of the drug from the dosage form are major factors in the design of a drug product.

1. Drugs intended for **local activity** such as topical antibiotics, anti-infectives, antifungal agents, and local anesthetics are formulated in dosage forms that minimize systemic absorption. The concentration of these drugs at the application site affects their activity.

2. When **systemic absorption** is desired, the bioavailability of the drug from the dosage form at the absorption site must be considered (e.g., a drug given intravenously is 100% bioavailable because all of the drug is placed directly into the systemic circulation). The amount, or dose, of drug in the dosage form is based on the extent of drug absorption and the desired systemic drug concentration. The type of dosage form (e.g., immediate release, controlled release) affects the rate of drug absorption.

III. BIOPHARMACEUTIC PRINCIPLES

A. Physicochemical properties

1. **Drug dissolution.** For most drugs with limited water solubility, the rate at which the solid drug enters into solution (i.e., the rate of dissolution) is often the rate-limiting step in bioavailability. The **Noyes–Whitney** equation describes the diffusion-controlled rate of drug dissolution (dm/dt; i.e., the change in the amount of drug in solution with respect to time):

$$\frac{dm}{dt} = \frac{DA}{\delta}(C_s - C_b)$$

where D is the diffusion coefficient of the solute, A is the surface area of the solid undergoing dissolution, δ is the thickness of the diffusion layer, C_s is the concentration of the solvate at saturation, and C_b is the concentration of the drug in the bulk solution phase at time t.

2. **Drug solubility** in a saturated solution (see Chapter 2, IV) is a static (equilibrium) property. The dissolution rate of a drug is a dynamic property related to the rate of absorption.
3. **Particle size** and **surface area** are inversely related. As solid drug particle size decreases, particle surface area increases.
   - **a.** As described by the Noyes–Whitney equation, the dissolution rate is directly proportional to the surface area. An increase in surface area allows for more contact between the solid drug particles and the solvent, resulting in a faster dissolution rate (see III.A.1).
   - **b.** With certain **hydrophobic drugs**, excessive particle size reduction does not always increase the dissolution rate. Small particles tend to reaggregate into larger particles to reduce the high surface free energy produced by particle size reduction.
   - **c.** To prevent the formation of aggregates, small drug particles are molecularly dispersed in polyethylene glycol (PEG), polyvinylpyrrolidone (PVP; povidone), dextrose, or other agents. For example, a molecular dispersion of griseofulvin in a water-soluble carrier such as PEG 4000 (e.g., Gris–PEG) enhances its dissolution and bioavailability.
4. **Partition coefficient and extent of ionization**
   - **a.** The **partition coefficient** of a drug is the ratio of the solubility of the drug, at equilibrium, in a nonaqueous solvent (e.g., *n*-octanol) to that in an aqueous solvent (e.g., water; pH 7.4 buffer solution). Hydrophilic drugs with higher water solubility have a faster dissolution rate than do hydrophobic or lipophilic drugs, which have poor water solubility.
   - **b. Extent of ionization.** Drugs that are weak electrolytes (acids or bases) exist in both an ionized form and a nonionized form in solution. The extent of ionization depends on the pK_a of the weak electrolyte and the pH of the solution. The ionized form is more polar, and therefore more water soluble, than the nonionized form. The **Henderson–Hasselbalch equation** describes the relation between the ionized and the nonionized forms of a drug as a function of pH and pK_a. When the pH of the medium equals the pK_a of the drug, 50% of the drug in solution is nonionized and 50% is ionized, as can be shown from the following equations:
     - **(1) For weak acids:**

$$pH = pK_a + \log\left(\frac{\text{salt}}{\text{nonionized acid}}\right)$$

     - **(2) For weak bases:**

$$pH = pK_a + \log\left(\frac{\text{nonionized base}}{\text{salt}}\right)$$

5. **Salt formation**
   - **a.** The choice of salt form for a drug depends on the desired physical, chemical, or pharmacologic properties. Certain salts are designed to provide slower dissolution, slower bioavailability, and longer duration of action. Other salts are selected for greater stability, less local irritation at the absorption site, or less systemic toxicity.
     - **(1)** Some soluble salt forms are less stable than the nonionized form. For example, sodium aspirin is less stable than aspirin in the acid form.
     - **(2)** A solid dosage form containing buffering agents may be formulated with the free acid form of the drug (e.g., buffered aspirin).

(a) The buffering agent forms an alkaline medium in the gastrointestinal tract, and the drug dissolves in situ.

(b) The dissolved salt form of the drug diffuses into the bulk fluid of the gastrointestinal tract, forms a fine precipitate that redissolves rapidly, and becomes available for absorption.

b. Effervescent granules or **tablets** containing the acid drug in addition to sodium bicarbonate, tartaric acid, citric acid, or other ingredients are added to water just before oral administration. The excess sodium bicarbonate forms an alkaline solution in which the drug dissolves. Carbon dioxide is also formed by the decomposition of carbonic acid.

c. For weakly acidic drugs, potassium and sodium salts are more soluble than divalent cation salts (e.g., calcium, magnesium) or trivalent cation salts (e.g., aluminum).

d. For weak bases, common water-soluble salts include the hydrochloride, sulfate, citrate, and gluconate salts. The estolate, napsylate, and stearate salts are less water soluble.

6. Polymorphism is the ability of a drug to exist in more than one crystalline form.

a. Different polymorphs have different physical properties, including melting point and dissolution rate.

b. Amorphous, or **noncrystalline**, **forms** of a drug have faster dissolution rates than do crystalline forms.

7. Chirality is the ability of a drug to exist as **optically active stereoisomers** or **enantiomers**. Individual enantiomers may not have the same pharmacokinetic and pharmacodynamic activity. Because most chiral drugs are used as racemic mixtures, the results of studies with such mixtures may be misleading because the drug is assumed to behave as a single entity. For example, ibuprofen exists as the *R*- and *S*-enantiomers; only the *S*-enantiomer is pharmacologically active. When the racemic mixture of ibuprofen is taken orally, the *R*-enantiomer undergoes presystemic inversion in the gut to the *S*-enantiomer. Because the rate and extent of inversion are site specific and formulation dependent, ibuprofen activity may vary considerably.

8. Hydrates. Drugs may exist in a **hydrated**, or **solvated**, **form** or as an **anhydrous molecule**. Dissolution rates differ for hydrated and anhydrous forms. For example, the anhydrous form of ampicillin dissolves faster and is more rapidly absorbed than the hydrated form.

9. Complex formation. A **complex** is a species formed by the reversible or irreversible association of two or more interacting molecules or ions. **Chelates** are complexes that typically involve a ringlike structure formed by the interaction between a partial ring of atoms and a metal. Many biologically important molecules (e.g., hemoglobin, insulin, cyanocobalamin) are chelates. Drugs such as tetracycline form chelates with divalent (e.g., Ca^{++}, Mg^{++}) and trivalent (e.g., Al^{+++}, Bi^{+++}) metal ions. Many drugs adsorb strongly on charcoal or clay (e.g., kaolin, bentonite) particles by forming complexes. Drug complexes with proteins, such as albumin or α_1-acid glycoprotein, often occur.

a. Complex formation usually alters the physical and chemical characteristics of the drug. For example:

(1) The chelate of tetracycline with calcium is less water soluble and is poorly absorbed.

(2) Theophylline complexed with ethylenediamine to form aminophylline is more water soluble and is used for parenteral and rectal administration.

(3) Cyclodextrins are used to form complexes with many drugs to increase their water solubility.

b. Large drug complexes, such as drug–protein complexes, do not cross cell membranes easily. These complexes must dissociate to free the drug for absorption at the absorption site or to permit transport across cell membranes or glomerular filtration before the drug is excreted into the urine.

B. Drug product and delivery system formulation

1. General considerations

a. Design of the appropriate dosage form or **delivery system** depends on the

(1) physical and chemical properties of the drug,

(2) dose of the drug,

(3) route of administration,

(4) type of drug delivery system desired,

(5) desired therapeutic effect,

(6) physiologic release of the drug from the delivery system,

(7) bioavailability of the drug at the absorption site, and
(8) pharmacokinetics and pharmacodynamics of the drug.

b. Bioavailability. The more complicated the formulation of the finished drug product (e.g., controlled-release tablet, enteric-coated tablet, transdermal patch), the greater the potential for a bioavailability problem. For example, the **release** of a drug from a peroral dosage form and its subsequent bioavailability depend on a succession of rate processes (*Figure 3-2*). These processes may include the following:
(1) **Attrition**, **disintegration**, or **disaggregation** of the drug product
(2) **Dissolution** of the drug in an aqueous environment
(3) **Convection** and **diffusion** of the drug molecules to the absorbing surface
(4) **Absorption** of the drug across cell membranes into the systemic circulation

c. The **rate-limiting step** in the bioavailability of a drug from a drug product is the slowest step in a series of kinetic processes.
(1) For most conventional solid drug products (e.g., capsules, tablets), the dissolution rate is the slowest, or rate-limiting, step for bioavailability.
(2) For a controlled- or sustained-release drug product, the release of the drug from the delivery system is the rate-limiting step.

2. Solutions are homogeneous mixtures of one or more solutes dispersed molecularly in a dissolving medium (solvent).

a. Compared with other oral and peroral drug formulations, a drug dissolved in an aqueous solution is in the most bioavailable and consistent form. Because the drug is already in solution,

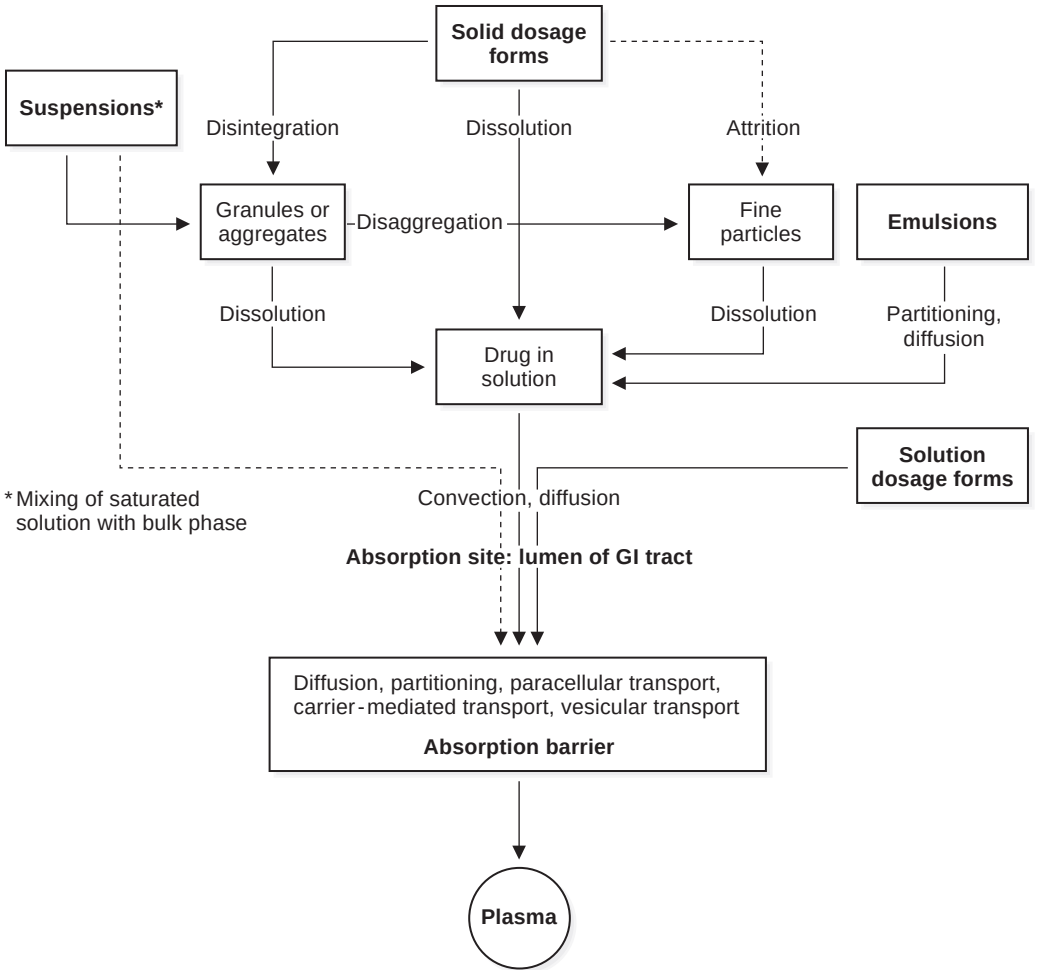


Figure 3-2. The processes involved in drug release from peroral dosage forms. *GI*, gastrointestinal.

no dissolution step is necessary before systemic absorption occurs. Peroral drug solutions are often used as the reference preparation for solid peroral formulations.

b. A drug dissolved in a hydroalcoholic solution (e.g., elixir) also has good bioavailability. Alcohol aids drug solubility. However, when the drug is diluted by gastrointestinal tract fluid and other gut contents (e.g., food), it may form a finely divided precipitate in the lumen of the gastrointestinal tract. Because of the extensive dispersion and large surface area of such finely divided precipitates, redissolution and subsequent absorption occur rapidly.

c. A viscous drug solution (e.g., syrup) may interfere with dilution and mixing with gastrointestinal tract contents. The solution decreases the gastric emptying rate and the rate of transfer of drug solution to the duodenal region, where absorption is most efficient.

3. **Suspensions** are dispersions of finely divided solid particles of a drug in a liquid medium in which the drug is not readily soluble. The liquid medium of a suspension comprises a saturated solution of the drug in equilibrium with the solid drug.

   a. The bioavailability of the drug from suspensions may be similar to that of a solution because the finely divided particles are dispersed and provide a large surface area for rapid dissolution. On the other hand, a slow dissolution rate decreases the absorption rate.

   b. **Suspending agents** are often hydrophilic colloids (e.g., cellulose derivatives, acacia, xanthan gum) added to suspensions to increase viscosity, inhibit agglomeration, and decrease the rate at which particles settle. Highly viscous suspensions may prolong gastric emptying time, slow drug dissolution, and decrease the absorption rate.

4. **Capsules** are solid dosage forms with hard or soft gelatin shells that contain drugs, usually admixed with excipients. **Coating** the capsule shell or the drug particles within the capsule can affect bioavailability.

   a. **Hard gelatin capsules** are usually filled with a powder blend that contains the drug. Typically, the powder blend is simpler and less compacted than the blend in a compressed tablet. After ingestion, the gelatin softens, swells, and begins to dissolve in the gastrointestinal tract. Encapsulated drugs are released rapidly and dispersed easily, and bioavailability is good. Hard gelatin capsules are the preferred dosage form for early clinical trials of new drugs.

   b. **Soft gelatin capsules** may contain a nonaqueous solution, a powder, or a drug suspension. The vehicle may be water miscible (e.g., PEG). The cardiac glycoside digoxin, dispersed in a water-miscible vehicle (Lanoxicaps), has better bioavailability than a compressed tablet formulation (Lanoxin). However, a soft gelatin capsule that contains the drug dissolved in a **hydrophobic** vehicle (e.g., vegetable oil) may have poorer bioavailability than a compressed tablet formulation of the drug.

   c. **Aging** and **storage conditions** can affect the moisture content of the gelatin component of the capsule shell and the bioavailability of the drug.

      (1) At low moisture levels, the capsule shell becomes brittle and is easily ruptured.

      (2) At high moisture levels, the capsule shell becomes moist, soft, and distorted. Moisture may be transferred to the capsule contents, particularly if the contents are hygroscopic.

5. **Compressed tablets** are solid dosage forms in which high pressure is used to compress a powder blend or granulation that contains the drug and other ingredients, or excipients, into a solid mass.

   a. **Excipients**, including diluents (fillers), binders, disintegrants, lubricants, glidants, surfactants, dye, and flavoring agents, have the following properties:

      (1) They permit the efficient manufacture of compressed tablets.

      (2) They affect the physical and chemical characteristics of the drug.

      (3) They affect bioavailability. The higher the ratio of excipient to active drug, the greater the likelihood that the excipients affect bioavailability.

   b. **Examples**

      (1) **Disintegrants** (e.g., starch, croscarmellose, sodium starch glycolate) vary in action, depending on their concentration; the method by which they are mixed with the powder formulation or granulation; and the degree of tablet compaction. Although tablet disintegration is usually not a problem because it often occurs more rapidly than drug dissolution, it is necessary for dissolution in immediate-release formulations. Inability to disintegrate may interfere with bioavailability.

(2) **Lubricants** are usually hydrophobic, water-insoluble substances such as stearic acid, magnesium stearate, hydrogenated vegetable oil, and talc. They may reduce wetting of the surface of the solid drug particles, slowing the dissolution and bioavailability rates of the drug. Water-soluble lubricants, such as L-leucine, do not interfere with dissolution or bioavailability.

(3) **Glidants** (e.g., colloidal silicon dioxide) improve the flow properties of a dry powder blend before it is compressed. Rather than posing a potential problem with bioavailability, glidants may reduce tablet-to-tablet variability and improve product efficacy.

(4) **Surfactants** enhance drug dissolution rates and bioavailability by reducing interfacial tension at the boundary between solid drug and liquid and by improving the wettability (contact) of solid drug particles by the solvent.

c. **Coated compressed tablets** have a sugar coat, a film coat, or an enteric coat with the following properties:

(1) It protects the drug from moisture, light, and air.

(2) It masks the taste or odor of the drug.

(3) It improves the appearance of the tablet.

(4) It may affect the release rate of the drug.

d. In addition, **enteric coatings** minimize contact between the drug and the gastric region by resisting dissolution or attrition and preventing contact between the underlying drug and the gastric contents or gastric mucosa. Some enteric coatings minimize gastric contact because they are insoluble at acidic pHs. Other coatings resist attrition and remain whole long enough for the tablet to leave the gastric area. By resisting dissolution or attrition, enteric coatings may decrease bioavailability. Enteric coatings are used to

(1) minimize irritation of the gastric mucosa by the drug;

(2) prevent inactivation or degradation of the drug in the stomach; and

(3) delay the release of drug until the tablet reaches the small intestine, where conditions for absorption may be optimal.

6. **Modified-release dosage forms** are drug products that alter the rate or timing of drug release. Because modified-release dosage forms are more complex than conventional immediate-release dosage forms, more stringent quality control and bioavailability tests are required. **Dose dumping** or the abrupt, uncontrolled release of a large amount of drug is a problem.

a. **Extended-release dosage forms** include **controlled-release**, **sustained-action**, and **long-acting drug delivery systems.** These delivery systems allow at least a twofold reduction in dosing frequency compared with conventional immediate-release formulations.

(1) The extended, slow release of controlled-release drug products produces a relatively flat, sustained plasma drug concentration that avoids toxicity (from high drug concentrations) or lack of efficacy (from low drug concentrations).

(2) Extended-release dosage forms provide an immediate (initial) release of the drug, followed by a slower sustained release.

b. **Delayed-release dosage forms** release active drug at a time other than immediately after administration at a desired site in the gastrointestinal tract. For example, an enteric-coated drug product does not allow for dissolution in the acid environment of the stomach but, rather, in the less acidic environment of the small intestine.

7. **Transdermal drug delivery systems**, or **patches**, are controlled-release devices that contain the drug for systemic absorption after topical application to the skin surface. Transdermal drug delivery systems are available for a number of drugs (nitroglycerin, nicotine, scopolamine, clonidine, fentanyl, 17-β-estradiol, and testosterone). Although the formulation matrices of these delivery systems differ somewhat, they all differ from conventional topical formulations in the following ways:

a. They have an impermeable **occlusive backing film** that prevents insensible water loss from the skin beneath the patch. This film causes increased hydration and skin temperature under the patch and enhanced permeation of the skin by the drug.

b. The formulation matrix of the patch maintains the drug concentration gradient within the device after application so that drug delivery to the interface between the patch and the skin is sustained. As a result, drug partitioning and diffusion into the skin persist, and systemic absorption is maintained throughout the dosing interval.

c. Transdermal drug delivery systems are kept in place on the skin surface by an **adhesive layer**, ensuring drug contact with the skin and continued drug delivery.

8. **Targeted (site-specific) drug delivery systems** are drug carrier systems that place the drug at or near the receptor site. Examples include macromolecular drug carriers (protein drug carriers), particulate drug delivery systems (e.g., liposomes, nanoparticles), and monoclonal antibodies. With targeted drug delivery, the drug may be delivered to
   a. the capillary bed of the active site,
   b. a special type of cell (e.g., tumor cells) but not to normal cells, and
   c. a specific organ or tissue by complexing with a carrier that recognizes the target.
9. **Inserts**, **implants**, and **devices** are used to control drug delivery for localized or systemic drug effects. The drug is impregnated into a biodegradable or nonbiodegradable material and is released slowly. The inserts, implants, and devices are inserted into a variety of cavities (e.g., vagina, buccal cavity) or tissues (e.g., skin). For example, the leuprolide acetate implant, Viadur, is inserted beneath the skin of the upper arm. It provides palliative treatment of advanced prostate cancer for 1 year.

Study Questions

Directions: Each question, statement, or incomplete statement in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which statement best describes bioavailability?
   (A) relation between the physical and the chemical properties of a drug and its systemic absorption
   (B) measurement of the rate and amount of therapeutically active drug that reaches the systemic circulation
   (C) movement of the drug into body tissues over time
   (D) dissolution of the drug in the gastrointestinal tract
   (E) amount of drug destroyed by the liver before systemic absorption from the gastrointestinal tract occurs

2. The route of drug administration that gives the most rapid onset of the pharmacologic effect is
   (A) intramuscular injection.
   (B) intravenous injection.
   (C) intradermal injection.
   (D) peroral administration.
   (E) subcutaneous injection.

3. The route of drug administration that provides complete (100%) bioavailability is
   (A) intramuscular injection.
   (B) intravenous injection.
   (C) intradermal injection.
   (D) peroral administration.
   (E) subcutaneous injection.

4. After peroral administration, drugs generally are absorbed best from the
   (A) buccal cavity.
   (B) stomach.
   (C) duodenum.
   (D) ileum.
   (E) rectum.

5. The characteristics of an active transport process include all of the following *except* for which one?
   (A) Active transport moves drug molecules against a concentration gradient.
   (B) Active transport follows Fick's law of diffusion.
   (C) Active transport is a carrier-mediated transport system.
   (D) Active transport requires energy.
   (E) Active transport of drug molecules may be saturated at high drug concentrations.

6. The passage of drug molecules from a region of high drug concentration to a region of low drug concentration is known as
   (A) active transport.
   (B) bioavailability.
   (C) biopharmaceutics.
   (D) simple diffusion.
   (E) pinocytosis.

7. Which equation describes the rate of drug dissolution from a tablet?
   (A) Fick's law
   (B) Henderson–Hasselbalch equation
   (C) Law of mass action
   (D) Michaelis–Menten equation
   (E) Noyes–Whitney equation

8. Which condition usually increases the rate of drug dissolution from a tablet?

(A) increase in the particle size of the drug
(B) decrease in the surface area of the drug
(C) use of the free acid or free base form of the drug
(D) use of the ionized, or salt, form of the drug
(E) use of sugar coating around the tablet

9. Dose dumping is a problem in the formulation of

(A) compressed tablets.
(B) modified-release drug products.
(C) hard gelatin capsules.
(D) soft gelatin capsules.
(E) suppositories.

10. The rate-limiting step in the bioavailability of a lipid-soluble drug formulated as an immediate-release compressed tablet is the rate of

(A) disintegration of the tablet and release of the drug.
(B) dissolution of the drug.
(C) transport of the drug molecules across the intestinal mucosal cells.
(D) blood flow to the gastrointestinal tract.
(E) biotransformation, or metabolism, of the drug by the liver before systemic absorption occurs.

11. The extent of ionization of a weak electrolyte drug depends on the

(A) pH of the media and pK_a of the drug.
(B) oil to water partition coefficient of the drug.
(C) particle size and surface area of the drug.
(D) Noyes–Whitney equation for the drug.
(E) polymorphic form of the drug.

12. The rate of drug bioavailability is most rapid when the drug is formulated as a

(A) controlled-release product.
(B) hard gelatin capsule.
(C) compressed tablet.
(D) solution.
(E) suspension.

13. The amount of drug that a transdermal patch (i.e., transdermal drug delivery system) delivers within a 24-hrs period depends on the

(A) patch composition, which includes an occlusive backing and an adhesive film in contact with the skin.
(B) affinity of the drug for the formulation matrix relative to its affinity for the stratum corneum.
(C) rate of drug partitioning and/or diffusion through the patch to the skin surface.
(D) surface area of the patch.
(E) All of the above

Answers and Explanations

1. The answer is B *[see I.A.3]***.**
Bioavailability is the measurement of the rate and extent (amount) of therapeutically active drug that reaches the systemic circulation. The relation of the physical and the chemical properties of a drug to its systemic absorption (i.e., bioavailability) is known as its biopharmaceutics. The movement of a drug into body tissues is an aspect of pharmacokinetics, which is the study of drug movement in the body over time. The dissolution of a drug in the gastrointestinal tract is a physicochemical process that affects bioavailability. Significant destruction of a drug by the liver before it is systemically absorbed (known as the first-pass effect because it occurs during the first passage of the drug through the liver) decreases bioavailability.

2. The answer is B *[see II.B.1.a]***.**
When the active form of the drug is given intravenously, it enters the systemic circulation directly. The drug is delivered rapidly to all tissues, including the drug receptor sites. For all other routes of drug administration, except intra-arterial injection, the drug must be systemically absorbed before it is distributed to the drug receptor sites. For this reason, the onset of pharmacologic effects is slower. If the drug is a prodrug that must be converted to an active drug, oral administration, not intravenous injection, may not provide the most rapid onset of activity if conversion to the active form takes place in the gastrointestinal tract or liver.

3. The answer is B *[see II.C.2]***.**
When a drug is given by intravenous injection, the entire dose enters the systemic circulation. With other routes of administration, the drug may be lost before it reaches the systemic circulation. For example, with first-pass effects, a portion of an orally administered drug is eliminated, usually through degradation by liver enzymes, before the drug reaches its receptor sites.

4. The answer is C *[see II.B.2.b.(4)]***.**
Drugs given orally are well absorbed from the duodenum. The duodenum has a large surface area because of the presence of villi and microvilli. In addition, because the duodenum is well perfused by the mesenteric blood vessels, a concentration gradient is maintained between the lumen of the duodenum and the blood.

5. **The answer is B** *[see II.A.2–3]***.**
Fick's law of diffusion describes passive diffusion of drug molecules moving from a high concentration to a low concentration. This process is not saturable and does not require energy.

6. **The answer is D** *[see II.A.2]***.**
The transport of a drug across a cell membrane by passive diffusion follows Fick's law of diffusion: The drug moves with a concentration gradient (i.e., from an area of high concentration to an area of low concentration). In contrast, drugs that are actively transported move against a concentration gradient.

7. **The answer is E** *[see III.A.1]***.**
The Noyes–Whitney equation describes the rate at which a solid drug dissolves. Fick's law is similar to the Noyes–Whitney equation in that both equations describe drug movement caused by a concentration gradient. Fick's law generally refers to passive diffusion, or passive transport, of drugs. The law of mass action describes the rate of a chemical reaction, the Michaelis–Menten equation involves enzyme kinetics, and the Henderson–Hasselbalch equation gives the pH of a buffer solution.

8. **The answer is D** *[see III.A.1–3]***.**
The ionized, or salt, form of a drug has a charge and is generally more water soluble and therefore dissolves more rapidly than the nonionized (free acid or free base) form of the drug. The dissolution rate is directly proportional to the surface area and inversely proportional to the particle size. An increase in the particle size or a decrease in the surface area slows the dissolution rate.

9. **The answer is B** *[see III.B.6]***.**
A modified-release, or controlled-release, drug product contains two or more conventional doses of the drug. An abrupt release of the drug, known as dose dumping, may cause intoxication.

10. **The answer is B** *[see III.B.1.c]***.**
For lipid-soluble drugs, the rate of dissolution is the slowest (i.e., rate-limiting) step in drug absorption and thus in bioavailability. The disintegration rate of an immediate-release or conventional compressed tablet is usually more rapid than the rate of drug dissolution. Because the cell membrane is a lipoprotein structure, transport of a lipid-soluble drug across the cell membrane is usually rapid.

11. **The answer is A** *[see III.A.4.b]***.**
The extent of ionization of a weak electrolyte is described by the Henderson–Hasselbalch equation, which relates the pH of the solution to the pK_a of the drug.

12. **The answer is D** *[see III.B.2.a]***.**
Because a drug in solution is already dissolved, no dissolution is needed before absorption. Consequently, compared with other drug formulations, a drug in solution has a high rate of bioavailability. A drug in aqueous solution has the highest bioavailability rate and is often used as the reference preparation for other formulations. Drugs in hydroalcoholic solution (e.g., elixirs) also have good bioavailability. The rate of drug bioavailability from a hard gelatin capsule, compressed tablet, or suspension may be equal to that of a solution if an optimal formulation is manufactured and the drug is inherently rapidly absorbed.

13. **The answer is E** *[see III.B.7]***.**
Drug delivery from a transdermal drug delivery system depends on all of the factors cited—that is, on the presence of an occlusive backing (to maintain skin hydration and elevate skin temperature slightly) and an adhesive film to maintain contact of the formulation matrix with the skin to enable drug transfer from the patch into the skin. If the drug's affinity for the formulation matrix is greater than its affinity for the stratum corneum, the drug's escaping tendency from the patch will be reduced, minimizing the gradient for drug transfer into the skin. The microviscosity of the formulation matrix, the presence of a membrane between the drug reservoir in the patch and the skin surface, and the interaction of the drug with the formulation matrix affect the rate and extent of diffusion and/or partitioning of the drug through the patch to the skin surface. Finally, the extent of drug delivery from the patch is directly proportional to the surface area of the patch in contact with the skin surface.

4 Extemporaneous Prescription Compounding

LOYD V. ALLEN JR.

I. INTRODUCTION

A. Definitions

1. **Compounding versus manufacturing**
2. It is important, but oftentimes difficult, to distinguish between compounding and manufacturing.
3. **Compounding** is defined by the *United States Pharmacopeia* (*USP*) as the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice. Compounding includes the following:
   - Preparation of drug dosage forms for both human and animal patients
   - Preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns
   - Reconstitution or manipulation of commercial products that may require the addition of one or more ingredients
   - Preparation of drugs or devices for the purposes of, or as an incident to, research (clinical or academic), teaching, or chemical analysis
   - Preparation of drugs and devices for prescriber's office use where permitted by federal and state law
4. **Manufacturing** has been defined as the production, preparation, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction of the drug from substances of natural origin or by means of chemical or biological synthesis. Manufacturing may also include any packaging or repackaging of the substance(s) or labeling or relabeling of container for resale by pharmacies, practitioners, or other persons.
5. The purpose of pharmaceutical compounding is to prepare an individualized drug treatment for a patient based on an order from a duly licensed prescriber. The fundamental difference between compounding and manufacturing is the existence of a pharmacist/prescriber/patient relationship that controls the compounding of the drug preparation. Compounded drugs are not for resale but rather are personal and responsive to the patient's immediate needs. They are prepared and administered by the patient, caregiver, or patient's health care professionals, which allows for the monitoring of patient outcomes. On the other hand, drug manufacturers produce batches consisting of tens or hundreds of thousands of dosage units, such as tablets or capsules, for resale, using many personnel and large-scale manufacturing equipment. These products are distributed through the normal channels of interstate commerce to individuals unknown to the company. Manufacturers are not required to, and do not, provide oversight of individual patients. It is also acceptable and routine practice for pharmacists to compound for "office use" those preparations that are not commercially available. These preparations are "for office use only" and are not for resale or to be given to the patients to take home; they are to be administered at the office.

6. The *USP* uses the term *preparation* to refer to compounded prescriptions and the term *products* to refer to manufactured pharmaceuticals. Also, for stability purposes, compounded preparations are assigned a "beyond-use" date, and manufactured products are assigned an "expiration date."

B. Regulation

1. **Current good manufacturing practices (cGMPs)** are the standards of practice used in the pharmaceutical industry and are regulated by the U.S. Food and Drug Administration (FDA).
2. **Good compounding practices (GCPs)** are the standards of practice detailed in the *USP*, Chapter [795]. Community pharmacists must comply with state board of pharmacy laws, regulations, and guidelines to ensure a quality preparation, which includes using proper materials, weighing equipment, documented techniques, and dispensing and storage instructions.
3. **Legal considerations**
   a. Extemporaneous compounding by the pharmacist or a prescription order from a licensed practitioner, as with the dispensing of any other prescription, is controlled by the state boards of pharmacy.
   b. The legal risk (liability) of compounding is no greater than the risk of filling a prescription for a manufactured product because the pharmacist must ensure that the correct drug, dose, and directions are provided. The pharmacist is also responsible for preparing a quality pharmaceutical preparation, providing proper instructions regarding its storage, and advising the patient of any adverse effects.
4. **U.S. Food and Drug Administration.** The FDA has developed a list of preparations that should not be extemporaneously compounded. This list was developed primarily from commercial products that have been removed from the market owing to safety and/or efficacy concerns. This is a lengthy list and must be read carefully because, in some cases, only certain dosage forms of a specific drug are included on the list and others are not. The list is too extensive to include here but can be accessed at http://www.gpo.gov/fdsys/pkg/FR-1999-03-08/html/99-5517.htm.

C. Stability and quality control of compounded preparations

1. **Beyond-use dates.** The assignment of a beyond-use date is one of the most difficult tasks required of a compounding pharmacist. Chapters [795] and [797] of the *USP* provide guidelines for this task. Chapter [795] involves nonsterile preparations, and Chapter [797] involves sterile preparations. For nonsterile preparations, the current *USP* criteria are applicable in the absence of stability information to a specific drug and preparation. For nonaqueous liquids and solid formulations (for which a manufactured drug product is the source of active ingredients), include a beyond-use date not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier. When a *USP* or *National Formulary* (*NF*) substance is the source of active ingredient, the beyond-use date is not later than 6 months. For water-containing oral formulations, the beyond-use date is not later than 14 days when stored at cold temperatures; for water-containing topical/dermal and mucosal liquid and semisolid formulations, the beyond-use date is not later than the intended duration of therapy or 30 days. These beyond-use dates may be exceeded when there is supporting valid scientific stability information that is directly applicable to the specific preparation.

   For sterile preparations and if not sterility tested, the following can be used provided that the preparation is properly packaged and stored. If the preparation is sterility tested, the beyond-use dates for nonsterile preparations apply.

   Low-risk level compounded sterile preparations: Not more than 48 hrs at controlled room temperature, not more than 14 days at a cold temperature (refrigerator), and for 45 days frozen at −20°C or colder.

   Medium-risk level compounded sterile preparations: Not more than 30 hrs at controlled room temperature, not more than 9 days at cold temperature (refrigerator), and for 45 days frozen at −20°C or colder.

   High-risk level compounded sterile preparations: Not more than 24 hrs at controlled room temperature, not more than 3 days at cold temperature (refrigerator), and for 45 days frozen at −20°C or colder.

   As in nonsterile compounding, these beyond-use dates for sterile compounding may be exceeded when there is supporting valid scientific stability information that is directly applicable to the specific preparation.

2. **Quality control.** Quality control is becoming one of the fastest growing aspects of pharmacy compounding. Guidelines for establishing a quality control program are detailed in *USP* [1163] Quality Assurance in Pharmaceutical Compounding. Pharmacists are becoming more involved in the final testing of compounded preparations or are sending them to contract laboratories for testing. For example, the following quality control tests can be considered for the respective compounded dosage forms:
   a. **Ointments, creams, and gels.** Theoretical weight compared to actual weight, pH, specific gravity, active drug assay, physical observations (color, clarity, texture–surface, texture–spatula spread, appearance, feel), and rheological properties
   b. **Hard gelatin capsules.** Weight overall, average weight, individual weight variation, dissolution of capsule shell, disintegration of capsule contents, active drug assay, physical appearance (color, uniformity, extent of fill, locked), and physical stability (discoloration, changes in appearance)
   c. **Special hard gelatin capsules.** Weight overall, average weight, individual weight variation, dissolution of capsule shell, disintegration of capsule contents, active drug assay, physical appearance (color, uniformity of appearance, uniformity of extent of fill, closures), and physical stability (discoloration or other changes)
   d. **Suppositories, troches, lollipops, and sticks.** Weight, specific gravity, active drug assay, physical observations (color, clarity, texture of surface, appearance, feel), melting test, dissolution test, and physical stability
   e. **Oral and topical liquids.** Weight to volume, pH, specific gravity, active drug assay, globule size range, rheological properties/pourability, physical observations (color, clarity), and physical stability (discoloration, foreign materials, gas formation, mold growth)
   f. **Parenteral preparations.** Weight or volume, pH, specific gravity, osmolality, assay, physical observations (color, clarity), particulate matter, sterility, and pyrogenicity
3. **Quality control testing.** Pharmacists have the option of doing testing in-house or outsourcing it to laboratories.
   a. **In-house testing** can include measurements such as weight, volume, pH, specific gravity, osmolality, physical observations, sterility, and endotoxins.
   b. **Out-sourced testing** can include sterility, endotoxins, potency, and dissolution.
   c. **Test results** should be kept on file with the compounding records for the individual compounded preparations.

II. REQUIREMENTS FOR COMPOUNDING

A. Sources for chemicals and drugs. Pharmacists can obtain small quantities of the appropriate chemicals or drugs from wholesalers or chemical supply houses. These suppliers then may also serve as compounding consultants to the pharmacists to aid in ensuring their product's purity and quality.

B. Equipment. The correct equipment is important in a compounding pharmacy. Many state boards of pharmacy have a required minimum list of equipment for compounding prescriptions. Equipment appropriate for the type and extent of compounding being conducted is vital. Appropriate standard operating procedures must be in place and followed for the maintenance, operation, and calibration of the equipment.

C. Location of compounding area. Many pharmacies actively involved in compounding have dedicated a separate area in the pharmacy to this process. The ideal location is away from heavy foot traffic and is near a sink where there is sufficient space to work and store all chemicals and equipment. For compounding of sterile preparations, a laminar airflow hood and a clean room are current practice, or isolation barrier technology equipment appropriately positioned.

D. Sources of information

1. Library at a college of pharmacy
2. **References**
   a. Allen LV Jr. *The Art, Science and Technology of Pharmaceutical Compounding*. 4th ed. Washington, DC: American Pharmaceutical Association; 2012.
   b. Allen LV Jr, ed. *Remington: The Science and Practice of Pharmacy*. 22nd ed. Baltimore, MD: Pharmaceutical Press; 2012.
   c. O'Neil MJ, ed. *Merck Index*. 14th ed. Whitehouse Station, NJ: Merck & Co; 2006.

d. *The USP Pharmacists' Pharmacopeia*. 2nd ed. Rockville, MD: U.S. Pharmacopeial Convention, Inc.; 2008.
e. Allen LV Jr, Popovich NG, Ansel HC. *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

3. **Journals**
   a. *International Journal of Pharmaceutical Compounding*
   b. *U.S. Pharmacist*
   c. *Pharmacy Times*
   d. *Lippincott's Hospital Pharmacy*
4. Manufacturers' drug product information inserts; compounding specialty suppliers
5. **Web sites**
   a. Compounding Today: http://www.CompoundingToday.com
   b. *International Journal of Pharmaceutical Compounding*: http://www.ijpc.com
   c. Paddock Laboratories, Inc.: http://www.paddocklabs.com

III. COMPOUNDING OF SOLUTIONS

A. Definition. *USP* 34 defines **solutions** as liquid preparations that contain one or more chemical substances dissolved (i.e., molecularly dispersed) in a suitable solvent or mixture of mutually miscible solvents. Although the uniformity of the dosage in a solution can be assumed, the stability, pH, solubility of the drug or chemicals, taste (for oral solutions), and packaging need to be considered.

B. Types of solutions
1. **Sterile parenteral and ophthalmic solutions** require special consideration for their preparation (see XI).
2. **Nonsterile solutions** include oral, topical, and otic solutions.

C. Preparation of solutions. Solutions are the easiest of the dosage forms to compound extemporaneously, as long as a few general rules are followed.
1. Each drug or chemical is dissolved in the solvent in which it is most soluble. Thus, the solubility characteristics of each drug or chemical must be known.
2. If an alcoholic solution of a poorly water-soluble drug is used, the aqueous solution is added to the alcoholic solution to maintain as high an alcohol concentration as possible.
3. The salt form of the drug—not the free acid or base form, which both have poor solubility—is used.
4. Flavoring or sweetening agents are prepared ahead of time.
5. When adding a salt to a syrup, dissolve the salt in a few milliliters of water first; then add the syrup to volume.
6. The proper vehicle (e.g., syrup, elixir, aromatic water, purified water) must be selected.

D. Examples
1. **Example 1**
   a. Medication order

Triamcinolone acetonide	100 mg
Menthol	50 mg
Ethanol	10 mL
Propylene glycol	30 mL
Glycerin	20 mL
Sorbitol 70% solution, q.s.	100 mL
Sodium saccharin	100 mg
Sodium metabisulfite	20 mg
Disodium EDTA	100 mg
Purified water	5 mL

   b. Compounding procedure. Triamcinolone acetonide 0.1% mouthwash solution is prepared by dissolving the triamcinolone acetonide and menthol in the ethanol. Add the propylene glycol, glycerin, and about 10 mL of the 70% sorbitol and mix well. Dissolve the sodium saccharin, sodium metabisulfite, and disodium EDTA in the purified water. Add the aqueous

solution to the drug mixture and mix well. Add sufficient 70% sorbitol solution to volume and mix well.

How much of the triamcinolone base is present in this prescription? The molecular weight of triamcinolone is 394.4 and that of triamcinolone acetonide is 434.5.

$$\frac{394.4}{434.5} \times 100 \text{ mg} = 91 \text{ mg of triamcinolone base}$$

2. **Example 2**
   a. **Medication order**

Potassium chloride	1 mEq/mL
Preserved flavored, oral vehicle, q.s.	100 mL

   b. **Calculations.** The molecular weight of potassium chloride is 74.5 (K = 39; Cl = 35.5). One milliequivalent (mEq) weighs 74.5 mg.

$$100 \text{ mL} \times 74.5 \text{ mg/mL} = 7450 \text{ mg or } 7.45 \text{ g of KCl required}$$

   What is the molar concentration of this prescription?
   7.45 g per 100 mL or 74.5 g per 1000 mL
   1 mole of KCl weighs 74.5 g
   It is a 1 molar solution.
   c. **Compounding procedure.** The solubility of potassium chloride is 1 g in 2.8 mL water. Therefore, dissolve the 7.45 g KCl in 21 mL of purified water. Add sufficient preserved flavored oral vehicle to volume and mix well.
3. **Example 3**
   a. **Medication order**

Salicylic acid	2%
Lactic acid	6 mL
Flexible collodion, a.d.	30 mL

   b. **Compounding procedure.** Pharmacists must use caution when preparing this prescription because flexible collodion is extremely flammable. A 1-oz applicator-tip bottle is calibrated, using ethanol, which is poured out and any remaining alcohol is allowed to evaporate, resulting in a dry bottle. Salicylic acid (0.6 g) is added directly into the bottle, to which is added the 6 mL of lactic acid. The bottle is agitated or a glass stirring rod is used to dissolve the salicylic acid. Flexible collodion is added up to the calibrated 30-mL mark on the applicator-tip bottle.
4. **Example 4**
   a. **Medication order**

Iodine	2%
Sodium iodide	2.4%
Alcohol, q.s.	30 mL

   b. **Compounding procedure.** Iodine (0.6 g) and sodium iodide (0.72 g) are dissolved in the alcohol, and the final solution is placed in an amber bottle. A rubber or plastic spatula is used because iodine is corrosive.

IV. COMPOUNDING OF SUSPENSIONS

A. Definition. Suspensions are defined by *USP* 34 as liquid preparations that consist of solid particles dispersed throughout a liquid phase in which the particles are not soluble.

B. General characteristics

1. Some suspensions should contain an antimicrobial agent as a preservative.
2. Particles settle in suspensions even when a suspending agent is added; thus, suspensions must be well shaken before use to ensure the distribution of particles for a uniform dose.
3. Tight containers are necessary to ensure the stability of the final preparation.
4. Principles to keep in mind when compounding include the following:
   a. Insoluble powders should be small and uniform in size to decrease settling.
   b. The suspension should be viscous.
   c. Topical suspensions should have a smooth, impalpable texture.
   d. Oral suspensions should have a pleasant odor and taste.

C. Formation of suspensions. Suspensions are easy to compound; however, physical stability after compounding the final preparation is problematic. The following steps may minimize stability problems.

1. The particle size of all powders used in the formulation should be reduced.
2. A thickening (suspending) agent may be used to increase viscosity. Common thickening agents include alginic acid, bentonite, VEEGUM, methylcellulose, and tragacanth.
3. A levigating agent may aid in the initial dispersion of insoluble particles. Common levigating agents include glycerin, propylene glycol, alcohol, syrups, and water.
4. Flavoring agents and preservatives should be selected and added if the preparation is intended for oral use. Common preservatives include methylparaben, propylparaben, benzoic acid, and sodium benzoate. Flavoring agents may be any flavored syrup or flavored concentrate (*Table 4-1*).
5. The source of the active ingredients (e.g., bulk powders vs. tablets or capsules) must be considered; if commercial dosage forms are used, the inactive ingredients must be considered and only immediate-release tablets or capsules should be used and not modified release, unless necessary and they can be used appropriately.

D. Preparation of suspensions

1. The insoluble powders are triturated to a fine powder.
2. A small portion of liquid is used as a levigating agent, and the powders are triturated until a smooth paste is formed.
3. The vehicle containing the suspending agent is added in divided portions. A high-speed mixer greatly increases the dispersion.
4. The preparation is brought to the required volume using the vehicle.
5. The final mixture is transferred to a "tight" bottle for dispensing to the patient.
6. All suspensions are dispensed with a "shake well" label.
7. Suspensions are not filtered.
8. The water-soluble ingredients, including flavoring agents, are mixed in the vehicle before mixing with the insoluble ingredients.

E. Examples

1. **Example 1**
   a. **Medication order**

Propranolol HCl	4 mg/mL
Disp	30 mL
Sig:	1 mL p.o. t.i.d.

   b. **Calculations.** Propranolol HCl: 4 mg/mL × 30 mL = 120 mg. Propranolol HCl is available as a powder or in immediate-release and extended-release (long-acting) dosage forms. Only the powder or the immediate-release tablets are used for compounding prescriptions; therefore, some combination of propranolol HCl tablets that yields 120-mg active drug (e.g., 3 × 40-mg tablets) may be used.
   c. **Compounding procedure.** The propranolol tablets are reduced to a fine powder in a mortar. The powder or the comminuted tablets are levigated to a smooth paste, using a 2% methylcellulose

Table 4-1 SELECTED FLAVOR APPLICATIONS

Drug Category	Preferred Flavors
Antibiotics	Cherry, maple, pineapple, orange, raspberry, banana-pineapple, banana-vanilla, butterscotch-maple, coconut custard, strawberry, vanilla, lemon custard, cherry custard, fruit-cinnamon
Antihistamines	Apricot, black currant, cherry, cinnamon, custard, grape, honey, lime, loganberry, peach-orange, peach-rum, raspberry, root beer, wild cherry
Barbiturates	Banana-pineapple, banana-vanilla, black currant, cinnamon-peppermint, grenadine-strawberry, lime, orange, peach-orange, root beer
Decongestants and expectorants	Anise, apricot, black currant, butterscotch, cherry, coconut custard, custard mint-strawberry, grenadine-peach, strawberry, lemon, coriander, orange-peach, pineapple, raspberry, strawberry, tangerine
Electrolyte solutions	Cherry, grape, lemon-lime, raspberry, wild cherry, black currant, grenadine-strawberry, lime, Port wine, Sherry wine, root beer, wild strawberry

solution. To this mixture, about 10 mL of a suitable flavoring agent is added. The mixture is transferred to a calibrated container and brought to the final volume with purified water or suitable suspending vehicle. A "shake well" label is attached to the prescription container.

2. **Example 2**
   a. Medication order

Zinc oxide	10 g
Ppt sulfur	10 g
Bentonite	3.6 g
Purified water, a.d.	90 mL
Sig:	Apply t.i.d.

   b. **Compounding procedure.** The powders are reduced to a fine uniform mixture in a mortar. The powders are mixed to form a smooth paste using water and transferred to a calibrated bottle. The final volume is attained with purified water. A "shake well" label is attached to the prescription container.
3. **Example 3**
   a. **Medication order**

Rifampin suspension	20 mg/mL
Disp	120 mL
Sig:	u.d.

   b. **Calculations.** Rifampin: 20 mg/mL × 120 mL = 2400 mg. Rifampin is available in 150-mg and 300-mg capsules. Hence, 8 capsules containing 300 mg of rifampin in each capsule or 16 capsules containing 150 mg of rifampin per capsule are needed.
   c. **Compounding procedure.** The contents of the appropriate number of rifampin capsules are emptied into a mortar and comminuted with a pestle. This powder is levigated with a small amount of 1% methylcellulose solution. Then 20 mL of simple syrup are added and mixed. The mixture is brought to the final volume with simple syrup. "Shake well" and "refrigerate" labels are attached to the prescription container.

V. EMULSIONS

A. Definition. Emulsions are **two-phase systems** in which one liquid is dispersed throughout another liquid in the form of small droplets.

B. General characteristics. Emulsions can be used externally as lotions and creams or internally to mask the taste of medications.

1. The two liquids in an emulsion are immiscible and require the use of an emulsifying agent.
2. Emulsions are classified as either **oil-in-water (o/w)** or **water-in-oil (w/o)**; there can also be multiple emulsions, such as **oil-in-water-in-oil (o/w/o)** and **water-in-oil-in-water (w/o/w)**, as well as emulsion gels, in which the external phase of an oil in water emulsion is thickened with a gelling agent.
3. Emulsions are **unstable** by nature, and the following steps should be taken to prevent the two phases of an emulsion from separating into two layers after preparation.
   a. The correct **proportions** of oil and water should be used during preparation. The internal phase should represent 40% to 60% of the total volume.
   b. An emulsifying **agent** is needed for emulsion formation.
   c. A **hand homogenizer**, which reduces the size of globules of the internal phase, may be used; if small quantities are compounded, two 60-mL syringes attached with a Luer-Lock adapter can be used and the materials pushed back and forth between the two syringes.
   d. **Preservatives** should be added if the preparation is intended to last longer than a few days. Generally, a combination of methylparaben (0.2%) and propylparaben (0.02%) may be used.
   e. A **"shake well"** label should be placed on the final preparation.
   f. The preparation should be **protected** from light and extreme temperature. Both freezing and heat may have an effect on stability.

C. Emulsifying agents

1. **Gums**, such as acacia or tragacanth, are used to form o/w emulsions. These emulsifying agents are for general use, especially for emulsions intended for internal administration (*Table 4-2*).
   a. Use 1 g of acacia powder for every 4 mL of fixed oil or 1 g to 2 mL for a volatile oil.
   b. If using tragacanth in place of acacia, 0.1 g of tragacanth is used for every 1 g of acacia.

Table 4-2 AGENTS USED IN PRESCRIPTION COMPOUNDING

Ointments	
Oleaginous or hydrocarbon bases	Hydrous emulsion bases (w/o)
Anhydrous	Hydrous
Nonhydrophilic	Will absorb water
Insoluble in water	Insoluble in water
Not water removable (occlusive)	Not water removable (occlusive)
Good vehicles for antibiotics	Examples
Example	Cold cream
Petrolatum	Hydrous lanolin
Absorption bases	Emulsion bases (o/w)
Anhydrous	Hydrous
Will absorb water	Hydrophilic
Insoluble in water	Insoluble in water
Not water removable (occlusive)	Water removable
Examples	Can absorb 30%–50% of weight
Hydrophilic petrolatum	Examples
Lanolin *USP* (anhydrous)	Hydrophilic ointment *USP*
	Acid mantle cream
	Water soluble
	Anhydrous or hydrous
	Soluble in water
	Water removable
	Hydrophilic
	Example
	Polyethylene glycol ointment
Suspending Agents	
Acacia 10%	Methylcellulose 1%–7%
Alginic acid 1%–2%	Sodium alginate 1%–2%
Bentonite 6%	Tragacanth 1%–3%
Carboxymethylcellulose 1%–5%	VEEGUM 6%
Preservatives	
Methylparaben 0.02%–0.2%	Propylparaben 0.01%–0.04%
Emulsifying Agents	
Hydrophilic colloids	Surfactants, nonionic
Acacia	Concentrations used (1%–30%)
Tragacanth	Tweens (e.g., polysorbate 80)
Pectin; favor o/w	Spans
Carboxymethylcellulose	
Methylcellulose	
Proteins	Soaps
Gelatin	Triethanolamine
Egg whites; favor o/w	Stearic acid
Inorganic gels and magmas	Others
Milk of magnesia	Sodium lauryl sulfate
Bentonite; favor o/w	Dioctyl sodium sulfosuccinate
	Cetylpyridinium chloride

o/w, oil-in-water; *w/o*, water-in-oil.

2. **Methylcellulose and carboxymethylcellulose** are used for o/w emulsions. The concentrations of these agents vary, depending on the grade that is used. Methylcellulose is available in several viscosity grades, ranging from 15 to 4000 and designated by a centipoise number, which is a unit of viscosity.
3. **Soaps** can be used to prepare o/w or w/o emulsions for external preparations.
4. **Nonionic emulsifying agents** can be used for o/w and w/o emulsions.

D. Formation and preparation of emulsions. The procedure for preparing an emulsion depends on the desired emulsifying agent in the formulation.

1. A **mortar** and **pestle** are frequently all the equipment that is needed.
   a. A mortar with a **rough surface** (e.g., Wedgwood) should be used. This rough surface allows maximal dispersion of globules to produce a fine particle size.
   b. A **rapid motion** is essential when triturating an emulsion using a mortar and pestle.
   c. The mortar should be able to hold at least three times the **quantity** being made. Trituration seldom requires more than 5 mins to create the emulsion.
2. **Electric mixers** and hand homogenizers are useful for producing emulsions after the coarse emulsion is formed in the mortar.
3. The **order** of mixing of ingredients in an emulsion depends on the type of emulsion being prepared (i.e., o/w or w/o) as well as the emulsifying agent chosen. Methods used for compounding include the following:
   a. **Dry gum** (continental) method is used for forming emulsions using natural emulsifying agents and requires a specific order of mixing.
   b. **Wet gum** (English) method is used for forming emulsions using natural emulsifying agents and requires a specific order of mixing.
   c. **Bottle method** is used for forming emulsions using natural emulsifying agents and requires a specific order of mixing.
   d. **Beaker method** is used to prepare emulsions using synthetic emulsifying agents and produces a satisfactory preparation regardless of the order of mixing.
4. **Preservatives.** If the emulsion is kept for an extended period, refrigeration is usually sufficient. The preparation should not be frozen. If a preservative is used, it must be soluble in the water phase to be effective.
5. **Flavoring agents.** If the addition of a flavor is needed to mask the taste of the oil phase, the flavor should be added to the external phase before emulsification (*Table 4-3*).

E. Examples

1. **Example 1**
   a. **Medication order**

Mineral oil	18 mL
Acacia	q.s.
Distilled water, q.s. a.d.	90 mL
Sig:	1 tablespoon q.d.

   b. **Compounding procedure.** With the dry gum method, an initial emulsion (primary emulsion) is formed, using four parts (18 mL) of oil, two parts (9 mL) of water, and one part (4.5 g) of powdered acacia. The mineral oil is triturated with the acacia in a Wedgwood mortar. The 9 mL of water is added all at once and, with rapid trituration, form the primary emulsion, which is triturated for about 5 mins. The remaining water is incorporated in small amounts

Table 4-3 FLAVOR SELECTION GUIDE

Taste	Masking Flavor
Salt	Butterscotch, maple
Bitter	Wild cherry, walnut, chocolate mint, licorice
Sweet	Fruit, berry, vanilla
Acid	Citrus

with trituration. The emulsion is transferred to a 90-mL prescription bottle, and a "shake well" label is attached to the container.

2. **Example 2**
   a. **Medication order**

Olive oil	30 mL
Zinc oxide	8 g
Calamine	8 g
Limewater	30 mL

   b. **Compounding procedure.** The olive oil is placed in a suitably sized beaker. Using an electric mixer, the zinc oxide, the calamine, and the limewater are added in that order. This yields a w/o emulsion. This procedure is known as the *nascent soap method*. The olive oil reacts with the calcium hydroxide solution (limewater) and forms a soap. For this reaction to occur, fresh limewater (calcium hydroxide solution) is required. A small quantity of oleic acid can also be added to further stabilize the emulsion.
3. **Example 3**
   a. **Medication order**

Mineral oil	50 mL
Water, q.s.	100 mL
Sig:	2.5 mL p.o. h.s.

   b. **Compounding procedure.** Using a combination of nonionic emulsifying agents, such as Span 40 and Tween 40, the correct hydrophilic–lipophilic balance (HLB) is obtained. Next, the mineral oil is warmed in a water bath to about 60°C, and the Span 40 is dissolved in the heated mineral oil. The water is warmed to about 65°C, and the Tween 40 is dissolved in the heated water. This mixture is added to the mineral oil and dissolved Span 40 and stirred until cooled. An "external use only" label is added to the container.

VI. POWDERED DOSAGE FORMS

A. Definition. Powders are intimate mixtures of dry, finely divided drugs and/or chemicals that may be intended for internal (oral powders) or external (topical powders) use. The major types are powder papers, bulk powders, and insufflations.

B. General characteristics

1. Powder dosage forms are used when **drug stability** or **solubility** is a concern. These dosage forms may also be used when the powders are too bulky to make into capsules and when the patient has difficulty swallowing a capsule.
2. Some **disadvantages** to powders include unpleasant-tasting medications and, occasionally, the rapid deterioration of powders.
3. **Blending** of powders may be accomplished by using trituration in a mortar, stirring with a spatula, and sifting. Geometric dilution should be used if needed. When heavy powders are mixed with lighter ones, the heavier powder should be placed on top of the lighter one and then blended. When mixing two or more powders, each powder should be pulverized separately to about the same particle size before blending together.
   a. The mortar and pestle method is preferred when **pulverization** and a thorough mixing of ingredients are desired (geometric dilution). A Wedgwood mortar is preferable, but glass or porcelain may also be used.
   b. Light powders are mixed best by using the **sifting method**. The sifting is repeated three to four times to ensure thorough mixing of the powders.

C. Preparation of powder dosage forms

1. **Bulk powders**, which may be used internally or topically, include dusting powders, douche powders, laxatives, antacids, and insufflation powders.
2. After a bulk powder has been pulverized and blended, it should be dispensed in an appropriate container.
   a. **Hygroscopic** or **effervescent** salts should always be placed in a tight, wide-mouth jar.
   b. **Dusting** powders should be placed in a container with a sifter top.
3. **Eutectic mixtures** of powders can cause problems because they may liquefy. One remedy is to add an inert powder, such as magnesium oxide, to separate the eutectic materials.

4. **Powder papers** are also called *divided powders*.
   a. The entire powder is initially blended. Each dose is then individually weighed.
   b. The dosage should be weighed, then transferred onto a powder paper and folded. This technique requires practice. Hygroscopic, deliquescent, and effervescent powders require the use of glassine paper as an inside lining. Plastic bags or envelopes with snap-and-seal closures offer a convenient alternative to powder papers.
   c. The folded papers are dispensed in a powder box or other suitable container; however, these containers are not child resistant.

D. **Examples**
   1. **Example 1**
      a. **Medication order**

Camphor	100 mg
Menthol	200 mg
Zinc oxide	800 mg
Talc	1.9 g
M foot powder	
Sig:	Apply to feet b.i.d.

      b. **Compounding procedure.** The camphor and menthol are triturated together in a glass mortar, where a liquid eutectic is formed. The zinc oxide and talc are blended and mixed with the eutectic, using geometric dilution. This mixing results in a dry powder, which is passed through a wire mesh sieve. The final preparation is dispensed in a container with a sifter top.
   2. **Example 2**
      a. **Medication order**

Citric acid	0.3 g
Sodium bicarbonate	0.25 g
Psyllium mucilloid	2 g
Powdered flavor, q.s.	
M. Ft d.t.d. charts v	
Sig: Empty the contents of one chart into a glass of water and take h.s.	

      b. **Calculations.** Calculate for one extra powder paper:
      Citric acid 0.3 g × 6 doses = 1.8 g
      Sodium bicarbonate 0.25 g × 6 doses = 1.5 g
      Psyllium mucilloid 2 g × 6 doses = 12 g
      Total weight = 15.3 g
      15.3 g/6 doses = 2.55 g/dose
      Note: Also consider the weight of the powdered flavor.
      c. **Compounding procedure.** The ingredients are first pulverized and weighed. The citric acid and sodium bicarbonate are mixed together first; the psyllium mucilloid is then added along with the powdered flavor, using geometric dilution. Each dose (2.55 g) of the resultant mixture is weighed and placed into a powder paper. This preparation is an effervescent powder. When dissolved in water, the citric acid and sodium bicarbonate react to form carbonic acid, which yields carbon dioxide, making the solution more palatable.

VII. CAPSULES

A. **Definition. Capsules** are solid dosage forms in which the drug is enclosed within either a hard or soft soluble container or shell. The shells are usually made from a suitable gelatin. Hard gelatin capsules may be manually filled for extemporaneous compounding.

B. **Capsule sizes**
   1. A list of capsule sizes and the approximate amount of powder that may be contained in the capsule appear on the side of the capsule box (*Table 4-4*).
   2. Capsule sizes for oral administration in humans range from no. 5, the smallest, to no. 000, the largest.
   3. No. 0 is usually the largest oral size suitable for human patients, although larger sizes are occasionally used.

Table 4-4 APPROXIMATE AMOUNT OF POWDER CONTAINED IN CAPSULES

Capsule Size	Range of Powder Capacity (mg)
No. 5	60–130
No. 4	95–260
No. 3	130–390
No. 2	195–520
No. 1	225–650
No. 0	325–910
No. 00	390–1300
No. 000	650–2000

4. Capsules for veterinarians are available in no. 10, no. 11, and no. 12, containing approximately 30, 15, and 7.5 g, respectively.

C. Preparation of hard and soft capsules

1. As with the bulk powders, all ingredients are triturated and blended, using geometric dilution.
2. The correct size capsule must be determined by trying different capsule sizes, weighing them, and then choosing the appropriate size.
3. Before filling capsules with the medication, the body and cap of the capsule are separated. Filling is accomplished by using the "punch" method (Alternatively, small capsule machines are commonly used to prepare up to 300 capsules at a time, extemporaneously).
   a. The powder formulation is compressed with a spatula on a pill tile or paper sheet with a uniform depth of approximately half the length of the capsule body.
   b. The empty capsule body is repeatedly pressed into the powder until full.
   c. The capsule is then weighed to ensure an accurate dose. An empty tare capsule of the same size is placed on the pan containing the weights.
4. For a large number of capsules, capsule-filling machines can be used for small-scale use to save time. Most commonly, capsule machines used are capable of preparing 100 to 300 capsules at a time.
5. The capsule is wiped clean of any powder or oil and dispensed in a suitable prescription vial.

D. Examples

1. **Example 1**
   a. **Medication order**

      Rifampin 100 mg
      dtd #50
      Sig: 1 cap p.o. q.d.

   b. **Calculations.** Compound this prescription using the commercially available 300-mg capsules as the drug source. Calculate for at least one extra capsule.

$$51 \text{ caps} \times 100 \text{ mg/cap} = 5100 \text{ mg rifampin}$$

$$5100 \text{ mg rifampin} \div 300 \text{ mg/cap} = 17 \text{ caps}$$

   c. **Compounding procedure.** Use 17 rifampin capsules, each containing 300 mg rifampin. The content of each capsule is emptied, and the powder is weighed. The powder equivalent to 100 mg rifampin is placed in a capsule (e.g., if the total contents of one capsule weigh 360 mg; then $100/300 = x/360$; $x = 120$ mg of active drug powder required from the capsule contents to provide 100 mg active drug) and sufficient lactose added to fill the capsule. The total filled capsule contents weigh 200 mg. The weight of the active drug powder is subtracted from 200 mg to obtain the amount of lactose required per capsule, which is 200 mg − 120 mg = 80 mg. This is multiplied by 51 capsules. Enough lactose (51 capsules × 80 mg/

cap = 4.08 g) is added to make a total of 10.2 g of powder. The powders are combined, using geometric dilution, and 50 capsules can be punched out. Each capsule should weigh 200 mg (10.2 g/51 caps).

2. **Example 2**
   a. **Medication order.** This order is for veterinary use only.

Castor oil	8 mL
Disp	12 caps
Sig:	2 caps p.o. h.s.

   b. **Calculations.** No calculations are necessary.
   c. **Compounding procedure.** A no. 11 veterinary capsule is used. Using a calibrated dropper or a pipette, 8 mL of the oil is carefully added to the inside of each capsule body. Next, the lower inside portion of the cap is moistened, using a glass rod or brush. The cap and body are joined together, using a twisting motion, to form a tight seal. The capsules are placed on a piece of filter paper and checked for signs of leakage. The capsules are dispensed in the appropriate size and type of prescription vial. They can be stored in a refrigerator if desired.

VIII. MOLDED TABLETS (TABLET TRITURATES)

A. Definition. Tablet triturates are small, usually cylindrical molded or compressed tablets. They are made of powders created by moistening the powder mixture with alcohol and water or by the process of sintering. They can be used for compounding potent drugs in small doses and for preparation of a rapidly disintegrating/dissolving dosage form.

B. Formulation and preparation of tablet triturates using moistened powders

1. Tablet triturates are made in special molds consisting of a pegboard and a corresponding perforated plate.
2. In addition to the mold, a diluent, usually a mixture of lactose and sucrose (80:20), and a moistening agent, usually a mixture of ethyl alcohol and water (60:40), are required.
3. The diluent is triturated with the active ingredients.
4. A paste is then made, using the alcohol and water mixture.
5. This paste is spread into the mold; the tablets are punched out and remain on the pegs until dry.

C. Example

1. **Medication order**

Atropine sulfate	0.4 mg
Disp	#500 TT
Sig:	u.d.

2. **Calculations.** For 500 TT: 500 × 0.4 mg = 200 mg atropine sulfate
3. **Compounding procedure.** The mold prepares 70-mg tablets. The 200 mg of atropine sulfate, 6.8 g of sucrose, and 28 g of lactose are weighed and mixed by geometric dilution. The powder is wet with a mixture of 40% purified water and 60% ethyl alcohol (95%). The paste that is formed is spread onto the tablet triturate mold; the tablets are then punched out of the mold and allowed to dry on the pegs. This procedure is repeated until the required number of tablet triturates has been prepared.

D. Formulation and preparation of tablet triturates using sintering

1. These tablet triturates are made in special molds consisting of materials that can tolerate heat to about 100°C.
2. In addition to the mold, a diluent, usually a mixture of active drug and diluent, which make up approximately 65% of the tablet weight, are blended together. Mannitol is good to use in combination with lactose for particle sizes of 60 to 80 mesh fraction.
3. The mixture is triturated with polyethylene glycol 3350 with a particle size of 80 to 100 mesh fraction.
4. The powder mixture is placed into appropriate molds and lightly tamped.
5. The molds containing the powder are placed in an oven at about 90°C for 10 to 20 mins, removed, and allowed to cool. Depending on the molds used, the tablets can be dispensed in the molds or removed from the molds and packaged and labeled.

E. Example

1. Medication order

Homatropine hydrobromide	300 mg
Mannitol	3.5 g
Lactose	3.47 g
Flavor (dry powder type)	q.s.
Polyethylene glycol 3350	3.5 g

2. Calculations. As presented, this formula is for 100 rapid-dissolving tablet triturates.

3. Compounding procedure. Blend the homatropine hydrobromide, mannitol, lactose, and dry flavor together until fine and uniformly mixed. Separately, reduce the particle size of the polyethylene glycol 3350 to 100 to 200 mesh fraction. Lightly blend in the polyethylene glycol 3350 into the previously blended powders. Place 100 mg of the powder into the cavities of a mold (some blister packs work well; otherwise, obtain a tablet triturate mold or a special mold for preparing these tablets). Place the mold containing the powder in an oven at 80° to 90°C for 15 to 20 mins. The time depends on the mold, formulation, oven, etc. Remove from the oven and place in a refrigerator for approximately 5 mins. Remove from the refrigerator and let set at room temperature. Package and label.

IX. OINTMENTS, CREAMS, PASTES, AND GELS

A. Definitions

1. Ointments, **creams**, and **pastes** are semisolid dosage forms intended for topical application to the skin or mucous membranes. **Ointments** are characterized as being oleaginous in nature; **creams** are generally o/w or w/o emulsions, and **pastes** are characterized by their high content of solids (about 25%).

2. Gels (sometimes called jellies) are semisolid systems consisting of suspensions made up of either small inorganic particles or large organic molecules interpenetrated by a liquid.

B. General characteristics. These dosage forms are semisolid preparations generally applied externally. Semisolid dosage forms may contain active drugs intended to

1. act solely on the surface of the skin to produce a local effect (e.g., antifungal agent, topicals);

2. release the medication, which, in turn, penetrates into the skin (e.g., hydrocortisone cream); and

3. release medication for systemic absorption through the skin (e.g., nitroglycerin, transdermals).

C. Types of ointment bases

1. Hydrophobic bases feel greasy and contain mixtures of fats, oils, and waxes. Hydrophobic bases cannot be washed off using water.

2. Hydrophilic bases are usually emulsion bases. The o/w-type emulsion bases can be easily washed off with water, but the w/o type is slightly more difficult to remove.

D. Preparation of ointments, creams, pastes, and gels

1. Mixing can be done in a mortar or on an ointment slab or tile or using an ointment mill.

2. Liquids are incorporated by gradually adding them to an absorption-type base and mixing.

3. Insoluble powders are reduced to a fine powder and then added to the base, using geometric dilution.

4. Water-soluble substances are dissolved with water and then incorporated into the base.

5. The final preparation should be smooth (impalpable) and free of any abrasive particles.

E. Examples

1. Example 1

a. Medication order

Sulfur	
Salicylic acid, a.a.	600 mg
White petrolatum, a.d.	30 g
Sig:	Apply t.i.d.

b. Compounding procedure. The particle sizes of the sulfur and salicylic acid are reduced separately in a Wedgwood mortar and then blended together. Using a pill tile, the powder mixture is levigated with the base. Using geometric dilution, the base and powders are blended to the final weight. An ointment jar or plastic tube is used for dispensing, and an "external use only" label is placed on the container.

c. Alternate method. Suppose you have sulfur 5% in white petrolatum ointment and a salicylic acid 5% ointment. **How can you prepare the prescription using these and diluting with white petrolatum?**

However, since we are using two different 5% ointments, two parts of each, this leaves one part for the white petrolatum. A total of five parts is to be used to make 30 g (6 g per part): two parts (12 g) of the sulfur 5%, two parts (12 g) of the salicylic acid 5%, and one part (6 g) of the white petrolatum could be used. To check:

$$12\text{ g} \times 0.05 = 600\text{ mg of sulfur}$$
$$12\text{ g} \times 0.05 = 600\text{ mg of salicylic acid}$$
$$12\text{ g} + 12\text{ g} + 6\text{ g} = 30\text{ g}$$

2. Example 2

a. Medication order

Methylparaben	0.25 g
Propylparaben	0.15 g
Sodium lauryl sulfate	10 g
Propylene glycol	120 g
Stearyl alcohol	250 g
White petrolatum	250 g
Purified water	370 g
Disp	60 g
Sig:	Apply u.d.

b. Calculations. The quantity of each ingredient required to prepare 60 g is obtained as follows. The medication order is for 1000 g; therefore, the multiplication factor is 60/1000 = 0.06.

$$0.25\text{ g} \times 0.06 = 0.15\text{ g methylparaben}$$
$$0.15\text{ g} \times 0.06 = 0.009\text{ g propylparaben}$$
$$10\text{ g} \times 0.06 = 0.6\text{ g sodium lauryl sulfate}$$
$$120\text{ g} \times 0.06 = 7.2\text{ g propylene glycol}$$
$$250\text{ g} \times 0.06 = 15\text{ g stearyl alcohol}$$
$$250\text{ g} \times 0.06 = 15\text{ g white petrolatum}$$
$$370\text{ g} \times 0.06 = 22.2\text{ g purified water}$$

Since the 0.009 g of propylparaben is too small to accurately weigh, a dilution can be prepared as follows, assuming a minimum weighable quantity of 120 mg. Weigh 120 mg of propylparaben and add to 40 mL of propylene glycol, resulting in a propylparaben concentration of 3 mg/mL. Take 3 mL of this solution to obtain the propylparaben and subtract the 3 mL from the quantity of propylene glycol required in the formula.

c. Compounding procedure. The stearyl alcohol and the white petrolatum are melted on a steam bath and heated to about 75°C. The other ingredients, previously dissolved in purified water at about 78°C, are added. The mixture is stirred until it congeals. An ointment jar is used for dispensing, and an "external use only" label is placed on the jar.

3. Example 3

a. Medication order

Scopolamine hydrobromide	0.25%
Soy lecithin	12 g
Isopropyl palmitate	12 g
Pluronic F-127 20% gel, q.s.	100 mL
Sig:	Apply 0.1 mL t.i.d.

b. Calculations. The quantity of scopolamine hydrobromide required for the prescription will be

$$0.0025 \times 100\text{ mL} = 0.25\text{ g or }250\text{ mg}$$

c. Compounding procedure. Mix the soy lecithin with the isopropyl palmitate. Dissolve the scopolamine hydrobromide in about 3 mL of purified water and add to about 70 mL of the Pluronic F-127 gel. Add the soy lecithin–isopropyl palmitate mixture, and mix well. Add sufficient Pluronic F-127 gel to volume and mix well using a shearing technique. Package and label.

X. SUPPOSITORIES

A. General characteristics

1. Suppositories are **solid bodies** of various weights and shapes, adapted for introduction into the rectal, vaginal, or urethral orifices of the human body. They are used to deliver drugs for their local or systemic effects.
2. Suppositories differ in **size** and **shape** and include
   - **a.** rectal,
   - **b.** vaginal, and
   - **c.** urethral.

B. Common suppository bases

1. **Cocoa butter** (theobroma oil), which melts at body temperature, is a fat-soluble mixture of triglycerides that is most often used for rectal suppositories. Witepsol is a synthetic triglyceride. Fatty acid bases include Fattibase.
2. **Polyethylene glycol** (PEG, carbowax) derivatives are water-soluble bases suitable for vaginal and rectal suppositories. Polybase is an example.
3. **Glycerinated gelatin** is a water-miscible base often used in vaginal and rectal suppositories.

C. Suppository molds

1. Suppository molds can be made of rubber, plastic, brass, stainless steel, or other suitable material.
2. The formulation and volume of the base depend on the size of the mold used, less the displacement caused by the active ingredient.

D. Methods of preparing and dispensing suppositories

1. **Molded suppositories** are prepared by first melting the base and then incorporating the medications uniformly into the base. This mixture is then poured into the suppository mold (fusion method).
2. **Hand-rolled suppositories** require a special technique. With proper technique, it is possible to make a preparation equal in quality to the molded suppositories.
3. **Containers for the suppositories** are determined by the method and base used in preparation. Hand-rolled and molded suppositories should be dispensed in special boxes that prevent the suppositories from coming in contact with each other. Suppositories made using plastic strip molds are easily dispensed in various types of packages.
4. **Storage conditions.** If appropriate, a "refrigerate" label should appear on the container. Regardless of the base or medication used in the formulation, the patient should be instructed to store the suppositories in a cool, dry place.

E. Examples

1. **Example 1**
   - **a. Medication order**

Naproxen suppository	500 mg
Disp	#12
Sig:	Insert u.d. into rectum

   - **b. Calculations.** Each standard adult suppository should weigh 2 g, but it depends on the mold used and should be calibrated before compounding. Also, the displacement must be determined for the added powder.

     2 g (total weight) − 0.540 g (weight of base displaced by the 500-mg tablet) per suppository

     = 1.46 g cocoa butter per suppository × 13 suppositories
     = 18.98 g cocoa butter

   - **c. Compounding procedure.** The 13 naproxen 500-mg tablets are triturated to a fine powder, using a Wedgwood or porcelain mortar. The 18.98 g cocoa butter base is melted in a beaker, using a water bath. The temperature of the water bath should not exceed 36°C. The powder is then added and stirred until mixed. The mixture is poured into an appropriate rectal suppository mold (about 2 g per suppository) and placed into a refrigerator until the suppositories congeal. Any excess is scraped from the top of the mold, and a suppository box is used for dispensing. A "refrigerate" label is placed on the box.

2. **Example 2**
   a. **Medication order**
      Progesterone 50 mg
      Disp #14
      Sig: 1 per vagina once daily on days 14 to 28 of cycle
   b. **Calculations.** Total weight of each vaginal suppository is 1.9 g. Assuming 50 mg progesterone displaces 50 mg PEG base:
      50 mg progesterone/suppository × 15 = 750 mg progesterone
      1.9 g (total weight) − 0.050 g progesterone
      = 1.85 g PEG × 15 suppositories
      = 27.75 g PEG total
   c. **Compounding procedure.** The PEG is melted to 55° to 57°C, and 750 mg progesterone is added. This mixture is poured into a vaginal suppository mold, allowed to cool, cleaned, and dispensed.

XI. STERILE PREPARATIONS

A. General requirements. The extemporaneous compounding of sterile preparations occurs in many pharmacy environments, including community, home health care, hospital, and nuclear. Minimum requirements include

1. proper equipment and supplies;
2. proper facilities, including a laminar-flow clean bench and a clean room or isolation barrier technology equipment;
3. proper documentation of all preparations made;
4. quality control, including batch sterility testing;
5. proper storage both at the facility and in transport to the patient's home;
6. proper labeling of the prescription preparation;
7. knowledge of product's/preparation's stability and incompatibilities; and
8. knowledge of all ancillary equipment involved in compounding or delivery of the medications.

B. Compounding of parenteral preparations

1. Compounding of sterile preparations, including intravenous admixtures, requires special skills and training. Compounding parenteral preparations or providing this service without proper training should not be attempted.
2. These preparations must be compounded in a clean environment, using aseptic technique (i.e., working under controlled conditions to minimize contamination).
3. Dry powders of parenteral drugs for reconstitution are used for drug products or preparations that are unstable as solutions. It is important to know the correct diluents that can be used to yield a solution.
4. Solutions of drugs for parenteral administration may also be further diluted before administration. If further dilution is required, then the pharmacist must know the stability and compatibility of the drug in the diluent.

C. Reconstitution of a dry powder from a vial

1. Work takes place in a clean-air environment, observing aseptic technique.
2. The manufacturer's instructions should be checked to determine the required volume of diluent.
3. The appropriate needle size and syringe are chosen, keeping in mind that the capacity of the syringe should be slightly larger than the volume required for reconstitution.
4. Using the correct diluent, the surface of the container is cleaned, using an alcohol prep pad, after which the alcohol is permitted to evaporate.
5. The syringe is filled with the diluent to the proper volume.
6. The surface of the vial containing the sterile powder is cleaned, using an alcohol prep pad, after which it is permitted to dry. The diluent is injected into the vial containing the dry powder.
7. The vial is gently shaken or rolled, and the powder is allowed to dissolve.
8. After the powder has dissolved, the vial is inverted, and the desired volume is withdrawn.

9. The vehicle is prepared by swabbing the medication port of the bag or bottle with an alcohol prep pad.
10. The solution in the syringe is injected into the vehicle. If a plastic container is used, care must be taken not to puncture the sidewalls of the container with the tip of the needle.
11. The container should be shaken or kneaded or rotated to ensure thorough mixing of the contents.
12. The contents of the container should be checked for particulate matter.
13. A sterile seal or cap is applied over the port of the container.
14. All needles and syringes should be properly discarded.
15. The bag is labeled.

D. Removing the fluid contents from an ampule

1. The ampule is held upright to open it, and the top is tapped to remove any solution trapped in this area.
2. The neck of the ampule is swabbed with an alcohol swab.
3. The ampule is grasped on each side of the neck with the thumb and index finger of each hand and quickly snapped open.
4. A 5-μm filter needle is attached to a syringe of the appropriate size.
5. The ampule is tilted, and the needle is inserted.
6. The needle is positioned near the neck of the ampule, and the solution is withdrawn from the ampule.
7. If the solution is for an intravenous push (bolus injection), the filter needle is removed from the syringe and replaced with a cap.
8. If the solution is for an intravenous infusion, then the filter needle is removed and replaced with a new needle of the appropriate size. The drug is injected into the appropriate vehicle.
9. All materials should be discarded properly, and the final product or preparation should be labeled.

E. Removing drug solution from a vial

1. The tab around the rubber closure on the vial is removed, and this surface is swabbed with an alcohol prep pad.
2. An equivalent amount of sterile air is injected into the vial to prevent a negative vacuum from being created and to allow the drug to be removed.
3. Using the appropriate needle size and syringe, the needle is inserted into the rubber closure.
4. The plunger is pushed down, and air is released into the vial; when the plunger is pulled back, the solution is withdrawn.
5. The solution is then injected into the appropriate vehicle.

F. Examples

1. **Example 1**
   a. **Medication order**

Progesterone	5 g
Benzyl alcohol	10 mL
Sesame oil, q.s.	100 mL

   b. **Compounding procedure.** Dissolve the progesterone in the benzyl alcohol. Add sufficient sesame oil to make 100 mL. Sterilize by filtration through a sterile 0.2-μm filter or by dry heat (170°C for 1.5 hrs). Package in sterile vials and label.
2. **Example 2**
   a. **Medication order**

Fentanyl (as the citrate)	2 mg
Bupivacaine hydrochloride	125 mg
0.9% sodium chloride injection, q.s.	100 mL

   b. **Calculations.** Since 157 μg fentanyl citrate is equivalent to 100 μg fentanyl, the quantity of fentanyl citrate required is (157/100) × 2 mg = 3.14 mg fentanyl citrate. This is the quantity of fentanyl citrate that would be required if compounding as a high-risk preparation from bulk powders. It would also require 125 mg bupivacaine, and the remainder is the 0.9% sodium chloride injection. However, commercial products are available so we can calculate how much of each might be required using fentanyl 50 μg/mL injection and bupivacaine hydrochloride 0.5% injection.

$$2 \text{ mg fentanyl} = 2000 \text{ μg}$$

$$\frac{2000\ \mu g}{50\ \mu g/mL} = 40\ mL \text{ of fentanyl injection}$$

Bupivacaine hydrochloride 0.5% injection contains 500 mg/100 mL; therefore,

$$\frac{500}{100} = 125/x \qquad x = 25\ mL$$

If 40 mL of fentanyl injection is used, and 25 mL of bupivacaine hydrochloride injection is used, then 40 + 25 = 65 mL; the quantity of 0.9% sodium chloride injection required is 100 mL − 65 mL = 35 mL. Note: **If the order is to be filled in a 20-mL pump with delivery for 30 days, what is the delivery rate in microliter per hour?**

$$\frac{20\ mL}{30\ d} = 0.667\ mL/d$$

$$\frac{0.667\ mL}{day/24\ hrs} = 0.0277\ mL/hr$$

$$0.0277\ mL \times 1000\ \mu L/mL = 27.7\ \mu L/hr$$

c. Compounding procedure. Using commercially available injections, accurately measure the volume of each and fill into a sterile ambulatory pump reservoir. An air bubble can be injected and used to thoroughly mix the solution. Remove the air from the reservoir, and tightly seal/close the outlet. Label.

3. Example 3

a. Medication order

Morphine sulfate	5 g
Citric acid	100 mg
Sodium chloride, q.s. to isotonic	
Methylparaben	150 mg
Sterile water for injection, q.s.	100 mL

b. Calculations. Using a sodium chloride equivalent of 0.09 for a 5% morphine sulfate solution, 0.18 for citric acid, 1 for sodium chloride, and ignoring the methylparaben, the calculations can be made as follows:
5 g morphine sulfate is equivalent to 450 mg sodium chloride (5 g × 0.09 = 450 mg).
100 mg citric acid is equivalent to 18 mg sodium chloride (100 mg × 0.18 = 18 mg)

$$450\ mg + 18\ mg = 468\ mg$$

To be isotonic, the solution needs the equivalent of 900 mg of sodium chloride in the 100 mL: 900 mg − 468 mg = 432 mg sodium chloride needs to be added.

c. Compounding procedure. Dissolve the methylparaben in about 90 mL of sterile water for injection. A small amount of heat may be required. Cool the solution to room temperature, then add the morphine sulfate, citric acid, and sodium chloride. Add sufficient sterile water for injection to volume and mix well. Sterilize by filtration through a sterile 0.2-μm filter into a sterile vial or reservoir. Package and label.

4. Example 4

a. Medication order

Mefoxitin	1 g
Diluent to final concentration of 125 mg/mL	

b. Calculations. A 1-g vial of Mefoxin (cefoxitin for injection) is reconstituted with 10 mL of diluent to provide for approximate withdrawal of 10.5 mL and an approximate average concentration of 95 mg/mL. **What quantity of diluent should be added to provide an approximate average concentration of 125 mg/mL?**

$$10.5\ mL - 10\ mL = 0.5\ mL \text{ occupied by the powder}$$

$$\frac{1000\ mg}{125\ mg/mL} = 8\ mL \text{ total volume}$$

$$8\ mL - 0.5\ mL = 7.5\ mL \text{ diluent to be added}$$

c. Compounding procedure. Aseptically, withdraw 7.5 mL of diluent and inject into the vial to be reconstituted, using an appropriate vented needle. Gently swirl until dissolved.

Study Questions

Directions for questions 1–3: Each question or incomplete statement in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

The following medication order is given to the pharmacist by the physician.

Olive oil	60 mL
Vitamin A	60,000 U
Water	120 mL
Sig:	15 mL t.i.d.

1. The final dosage form of this prescription will be

(A) a solution.
(B) an elixir.
(C) an emulsion.
(D) a suspension.
(E) a lotion.

2. When preparing this prescription, the pharmacist needs to add

(A) Tween 80.
(B) acacia.
(C) glycerin.
(D) alcohol.
(E) propylene glycol.

3. Which of the following caution labels should the pharmacist affix to the container when dispensing this preparation?

(A) Do not refrigerate.
(B) Shake well.
(C) For external use only.
(D) No preservatives added.

Directions for questions 4–9: Each question or statement in this section can be correctly answered or completed by one or more of the suggested answers or phrases. Choose the correct answer, A–E:

A if **I** only is correct
B if **III** only is correct
C if **I** and **II** are correct
D if **II** and **III** are correct
E if **I**, **II**, and **III** are correct

4. Which statements about the following prescription are correct?

Morphine	1 mg/mL
Flavored vehicle, q.s. a.d.	120 mL
Sig:	5 to 20 mg p.o. q 3 to 4 hrs p.r.n. pain

I. The amount of morphine needed is 240 mg.
II. Powdered morphine alkaloid should be used when compounding this prescription.
III. The final dosage form of this prescription is a solution.

5. When preparing the following prescription, the pharmacist should

Podophyllum	5%
Salicylic acid	10%
Acetone	20%
Flexible collodion, a.d.	30 mL
Sig:	Apply q h.s.

I. triturate 1.5 g of podophyllum with the 8 mL of acetone.
II. add 3 g of salicylic acid to the collodion with trituration.
III. affix an "external use only" label to the container.

6. Which statements about the following prescription are correct?

Sulfur	6 g
Purified water	
Camphor water, a.a. q.s. a.d.	60

I. Precipitated sulfur can be used to prepare this prescription.
II. The sulfur can be triturated with glycerin before mixing with other ingredients.
III. A "shake well" label should be affixed to the bottle.

7. Which statements about the following prescription are correct?

Starch	10%
Menthol	1%
Camphor	2%
Calamine, q.s. a.d.	120

I. The powders should be blended together in a mortar, using geometric dilution.
II. The prescription should be prepared by dissolving the camphor in a sufficient amount of 90% alcohol.
III. A eutectic mixture should be avoided.

8. When preparing the following prescription, the pharmacist should

Salicylic acid	3 g
Sulfur ppt	7 g
Lanolin	10 g
White petrolatum	10 g

I. reduce the particle size of the powders, using a mortar and pestle or using the pill tile with a spatula.

II. place on an ointment tile and levigate the ingredients, using geometric dilution.

III. package the ointment in an ointment jar or tube.

9. An equal volume of air is injected when removing drug solutions from

I. vials.

II. ampules.

III. syringes.

Answers and Explanations

1. The answer is C *[see V.B.1.]***.**

2. The answer is B *[see V.B.2; V.C.1]***.**

3. The answer is B *[see V.B.3]***.**
For 1–3: Because olive oil and water are two immiscible liquids, their incorporation requires a two-phase system in which one liquid is dispersed throughout another liquid in the form of small droplets. To accomplish this, an emulsifying agent is necessary. Acacia is the most suitable emulsifying agent when forming an oil-in-water emulsion that is intended for internal use. Emulsions are physically unstable, and they must be protected against the effects of microbial contamination and physical separation. Shaking before use redistributes the two layers of emulsion. Because light, air, and microorganisms also affect the stability of an emulsion, preservatives can be added.

4. The answer is B (III) *[see III.C.3]***.**
The concentration of morphine needed for the prescription described in the question is 1 mg/mL, and because 120 mL is the final volume, 120 mg of morphine is needed to compound this prescription. Morphine alkaloid has poor solubility; therefore, one of the salt forms should be used. Because morphine is dissolved in the vehicle, resulting in a liquid preparation, the final dosage form is a solution.

5. The answer is B (III) *[see III.C.1; III.C.5; III.D.3]***.**
Calculating for the amount of each ingredient of the prescription in the question requires 1.5 g of podophyllum, 3 g of salicylic acid, and 6 mL of acetone. The correct procedure would be to triturate the podophyllum with the acetone, then add the triturated salicylic acid to a calibrated bottle containing the podophyllum and acetone. Flexible collodion is then added up to the 30-mL calibration. An "external use only" label should be affixed to the container.

6. The answer is E (I, II, and III) *[see IV.B.2; IV.C.5; IV.D.1–2]***.**
Although precipitated sulfur can be used to prepare the prescription described in the question, it is difficult to triturate; therefore, it must first be levigated with a suitable levigating agent (e.g., glycerin). All suspensions, owing to their instability, require shaking before use to redistribute the insoluble ingredients.

7. The answer is A (I) *[see VI.C.3; VI.D.1]***.**
The proper procedure for compounding the prescription described in the question is to first form a liquid eutectic. This is done by triturating the menthol and camphor together in a mortar. This eutectic is then blended with the powdered starch and calamine, using geometric dilution.

8. The answer is E (I, II, and III) *[see IX.D.1–3; IX.E.1]***.**
The proper procedure for preparing the prescription given in the question is to reduce the particle size of each powder and mix them together, using geometric dilution. This ensures the proper blending of the powders. Next, this powdered mixture is incorporated, geometrically, with the petrolatum. Then, the lanolin is added geometrically.

9. The answer is A (I) *[see XI.E.2]***.**
An equal volume of air must be injected when removing a drug solution from a vial. This is done to prevent the formation of a vacuum within the vial. This problem does not occur with ampules and syringes containing drug solutions; therefore, it is unnecessary to inject any air when removing them.

5 Basic Pharmacokinetics

ELISE DUNZO, LEON SHARGEL

I. PHARMACOKINETICS

A. Introduction

1. **Pharmacokinetics** is the quantitative measurement of drug absorption, distribution, and elimination (i.e., excretion and metabolism) and includes the rate processes for drug movement into the body, within the body, and out of the body.
2. Commonly used units in pharmacokinetics are tabulated in *Table 5-1*.
3. **Rates and orders of reactions.** The **rate** of a chemical reaction or pharmacokinetic process is the velocity with which it occurs. **The order** of a reaction is the way in which the concentration of a drug or reactant in a chemical reaction affects the rate.
   a. **Zero-order reaction.** The drug concentration changes with respect to time at a constant rate, according to the following equation:

$$\frac{dC}{dt} = -k_0$$

Table 5-1 COMMON UNITS IN PHARMACOKINETICS

Pharmacokinetic Parameter	Abbreviation	Fundamental Units	Units Example
Area under the curve	AUC	Concentration × time	μg × hr/mL
Total body clearance	Cl_T	Volume/time	L/hr
Renal clearance	Cl_R	Volume/time	L/hr
Hepatic clearance	Cl_H	Volume/time	L/hr
Apparent volume of distribution	V_D	Volume	L
Volume of distribution at steady state	V_{ss}	Volume	L
Peak plasma drug concentration	C_{max}	Concentration	mg/L
Plasma drug concentration	C_p	Concentration	mg/L
Steady-state drug concentration	C_{ss} or C_{av}	Concentration	mg/L
Time for peak drug concentration	T_{max}	Time	hr
Dose	D_0	Mass	mg
Loading dose	D_L	Mass	mg
Maintenance dose	D_M	Mass	mg
Amount of drug in the body	D_B	Mass	mg
Rate of drug infusion	R	Mass/time	mg/hr
First-order rate constant for drug absorption	k_A	1/time	1/hr or hr^{-1}
Zero-order rate constant for drug absorption	k_0	Mass/time	mg/hr
First-order rate constant for drug elimination	k (sometimes referred to as kel)	1/time	1/hr or hr^{-1}
Elimination half-life	$t_{½}$	Time	hr
Fraction of drug absorbed	F	(no units)	Ranges from 0 to 1 (0%–100%)

where C is the drug concentration and k_0 is the **zero-order rate constant** expressed in units of concentration per time (e.g., milligrams per milliliter per hour). Integration of this equation yields the linear (straight-line) equation:

$$C = -k_0 t + C_0$$

where k_0 is the slope of the line (see *Figure 2-6*) and C_0 is the y intercept, or drug concentration, when time (t) equals zero. The negative sign indicates that the slope is decreasing.

b. First-order reaction. The change in drug concentration with respect to time equals the product of the rate constant and the concentration of drug remaining, according to the following equation:

$$\frac{dC}{dt} = -kC$$

where k is the first-order rate constant, expressed in units of reciprocal time, or time^{-1} (e.g., 1/hr or hr^{-1}).

(1) Integration and subsequent transformation of this equation yields the following mathematically equivalent equations:

$$C = C_0 e^{-kt}$$
$$\ln C = -kt + \ln C_0$$
$$\log C = \frac{-kt}{2.3} + \log C_0$$

(2) A graph of the equation in *Figure 5-1* shows the linear relation of the log of the concentration versus time. In *Figure 5-1*, the slope of the line is equal to $-k/2.3$, and the y intercept is C_0. The values for C are plotted on logarithmic coordinates, and the values for t are shown on linear coordinates.

(3) The **half-life** ($t_{½}$) of a reaction or process is the time required for the concentration of a drug to decrease by one-half. For a first-order reaction or process, the half-life is a constant and is related to the first-order rate constant, according to the following equation:

$$t_{½} = \frac{0.693}{k}$$

4. Models and compartments

a. A **model** is a mathematic description of a biologic system and is used to express quantitative relationships.

b. A **compartment** is a group of tissues with similar blood flow and drug affinity. A compartment is not a real physiologic or anatomic region.

5. Drug distribution

a. Drugs distribute rapidly to tissues with high blood flow (e.g., liver) and more slowly to tissues with low blood flow (e.g., adipose).

b. Drugs rapidly cross capillary membranes into tissues because of **passive diffusion** and **hydrostatic pressure. Drug permeability** across capillary membranes varies.

(1) Drugs easily cross the capillaries of the glomerulus of the kidney and the sinusoids of the liver.

(2) The capillaries of the brain are surrounded by glial cells that create a **blood–brain barrier**, which acts as a thick lipid membrane. Polar and ionic hydrophilic drugs cross this barrier slowly.

(3) In disease states, membranes may become more permeable to drugs. For example, in meningitis, the blood–brain barrier becomes more permeable to the penetration of drugs into the brain.

c. Drugs may accumulate in tissues as a result of their physicochemical characteristics or special affinity of the tissue for the drug.

(1) Lipid-soluble drugs may accumulate in adipose (fat) tissue because of partitioning of the drug.

(2) Tetracycline may accumulate in bone because complexes are formed with calcium.

d. Plasma protein binding of drugs affects drug distribution.

(1) A drug bound to a protein forms a complex that is too large to cross cell membranes.

(2) **Albumin** is the major plasma protein involved in drug protein binding. **α_1-Glycoprotein**, also found in plasma, is important for the binding of such basic drugs as propranolol.

(3) Potent drugs, such as phenytoin, that are highly bound (> 95%) to plasma proteins may be displaced by other highly bound drugs. The displacement of the bound drug results in more free (nonbound) drug, which rapidly reaches the drug receptors and may cause a more intense pharmacologic response.

(4) A few hormonal drugs bind to specific plasma proteins. For example, prednisone binding to transcortin (and albumin) results in dose-dependent pharmacokinetics of prednisone. This nonlinear pharmacokinetics is due to saturable protein binding. Transcortin has high affinity and low capacity, whereas albumin has low affinity and high capacity.

B. One-compartment model

1. Intravenous bolus injection. The entire drug dose enters the body instantaneously, and the rate of absorption is therefore assumed to be negligible in calculations (*Figure 5-1*). The entire body acts as a single compartment, and the drug rapidly equilibrates with all of the tissues in the body.

a. Drug elimination is generally a first-order kinetic process according to the equations in I.A.3.b.

(1) The first-order elimination rate constant (k or k_{el}) is the sum of the rate constants for removal of drug from the body, including the rate constants for renal excretion and metabolism (**biotransformation**) as described by the following equation:

$$k = k_e + k_m$$

where k_e is the rate constant for renal excretion and k_m is the rate constant for metabolism. This equation assumes that all rates are first-order processes.

(2) The **elimination half-life ($t_{½}$)** is given by the following equation:

$$t_{½} = \frac{0.693}{k}$$

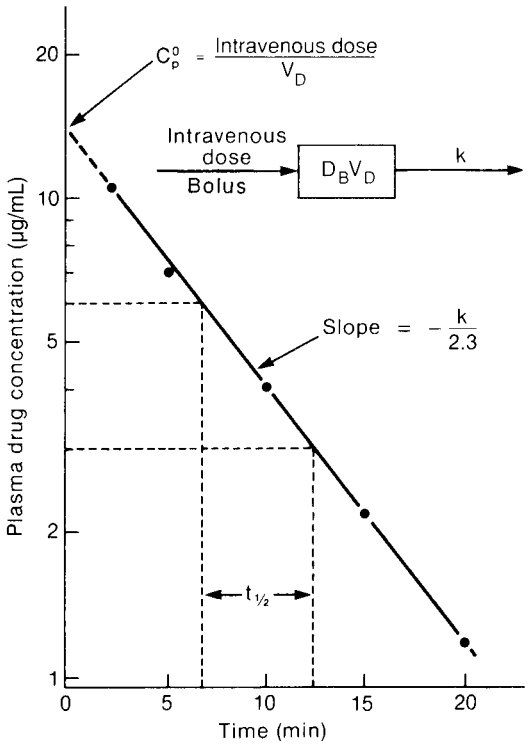


Figure 5-1. Generalized pharmacokinetic model for a drug administered by rapid intravenous bolus injection. C_P^0, extrapolated drug concentration; V_D, apparent volume of distribution; D_B, amount of drug in the body; k, elimination rate constant; $t_{½}$, elimination half-life. Adapted with permission from Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd ed. New York, NY: Marcel Dekker, Inc.; 1982. Copyright © 1982 Routledge/Taylor & Francis Group, LLC.

b. Apparent volume of distribution (V_D) is the hypothetical volume of body fluid in which the drug is dissolved. This value is not a true anatomic or physical volume.

(1) V_D is needed to estimate the amount of drug in the body relative to the concentration of drug in the plasma, as shown in the following:

$$V_D \times C_p = D_B$$

where V_D (liters) is the apparent volume of distribution, C_p (milligrams per liter) is the plasma drug concentration, and D_B (milligram) is the amount of drug in the body.

(2) To calculate the V_D after an intravenous bolus injection, the equation is rearranged to give:

$$V_D = \frac{D_B^0}{C_P^0}$$

where D_B^0 is the dose (D_B) of drug given by intravenous bolus and C_p^0 is the extrapolated drug concentration at zero time on the *y* axis, after the drug equilibrates (*Figure 5-1*).

(3) According to the equation, V_D is increased and C_p^0 is decreased when the drug is distributed more extravascularly into the tissues. When more drug is contained in the vascular space or plasma, C_p^0 is increased and V_D is decreased.

2. Single oral dose. If the drug is given in an oral dosage form (e.g., tablet, capsule), the drug is generally absorbed by first-order kinetics. Elimination of the drug also follows the principles of first-order kinetics (*Figure 5-2*).

a. The following equation describes the pharmacokinetics of **first-order absorption and elimination**:

$$C_P = \frac{FD_0k_A}{V_D(k_A - k)}(e^{-kt} - e^{-K_At})$$

where k_A is the first-order absorption rate constant and F is the fraction of drug bioavailable. Changes in F, D_0, V_D, k_A, and k affect the plasma drug concentration.

b. The time for maximum, or **peak**, **drug absorption** is given by the following equations:

$$t_{max} = \frac{2.3 \log (k_A/k)}{k_A - k}$$

where t_{max} depends only on the rate constants k_A and k, not on F, D_0, or V_D.

c. After t_{max} is obtained, the peak drug concentration (C_{max}) is calculated, using the equation in I.B.2.a and substituting t_{max} for t.

d. The area under the curve (AUC) may be determined by integration of $\int_0^t C_P\,dt$ using the trapezoidal rule or by the following equation:

$$[AUC]_0^\infty = \int_0^\infty C_P\,dt = \frac{FD_0}{V_Dk}$$

changes in F, D_0, k, and V_D affect the AUC. Minor changes in k_A do not affect the AUC.

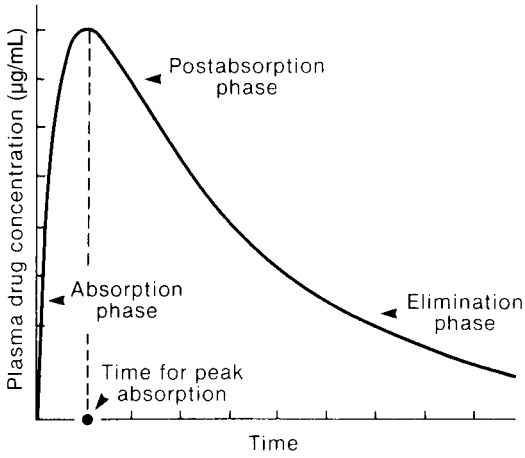


Figure 5-2. Generalized plot for a one-compartment model showing first-order drug absorption and first-order drug elimination. Adapted with permission from Shargel L, Wu-Pong S, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. 5th ed. New York, NY: McGraw-Hill; 2005.

e. To obtain $[AUC]_0^\infty$, obtain the [AUC] from 0 to t by the trapezoidal rule and add on the extrapolated section of AUC, which is the last measurable drug concentration at time, t, divided by the slope of the terminal elimination curve, as shown in the following equation:

$$[AUC]_0^\infty = [AUC]_0^t + \frac{C_{P,t}}{k}$$

f. **Lag time** occurs at the beginning of systemic drug absorption. For some individuals, systemic drug absorption is delayed after oral drug administration because of delayed stomach emptying or other factors.

3. Intravenous infusion

a. Intravenous infusion is an example of zero-order absorption and first-order elimination (*Figure 5-3*).

b. A few oral controlled-release drug products release the drug by zero-order kinetics and have **zero-order systemic absorption.**

c. The plasma drug concentration at any time after the start of an intravenous infusion is given by the following equation:

$$C_p = \frac{R}{V_D k}(1 - e^{-kt})$$

where R is the zero-order rate of infusion given in units as milligrams per hour or milligrams per minute.

d. If the intravenous infusion is discontinued, the plasma drug concentration declines by a first-order process. The elimination half-life or elimination rate constant, k, may be obtained from the declining plasma drug concentration versus time curve.

e. As the drug is infused, the plasma drug concentration increases to a plateau, or **steady-state concentration** ($\mathbf{C_{SS}}$).

(1) Under steady-state conditions, the fraction of drug absorbed equals the fraction of drug eliminated from the body.

(2) The plasma concentration at steady state (C_{ss}) is given by the following equation:

$$C_{ss} = \frac{R}{V_D k} = \frac{R}{Cl_T}$$

where Cl_T is total body clearance (see section I.E.).

(3) The rate of drug infusion (R) may be calculated from a rearrangement of the equation if the desired C_{ss}, the V_D, and the k are known. These values can often be obtained from the drug literature. To calculate the rate of infusion, the following equation is used:

$$R = C_{ss}\, V_D k = C_{ss}\, Cl_T$$

where C_{ss} is the desired (target) plasma drug concentration and Cl_T is total body clearance.

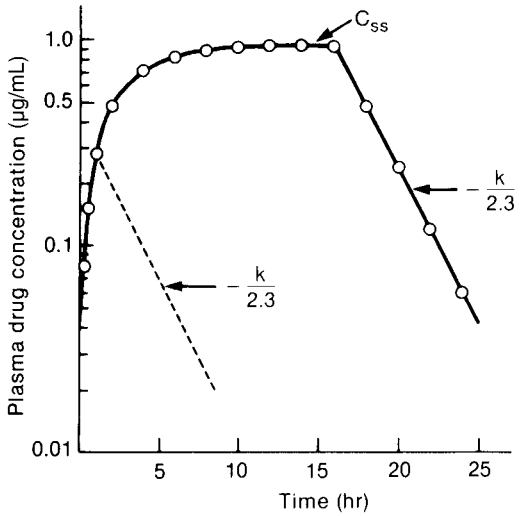


Figure 5-3. Generalized semilogarithmic plot for a drug showing zero-order absorption and first-order elimination. C_{ss}, steady-state concentration; k, elimination rate constant. Adapted with permission from Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd ed. New York, NY: Marcel Dekker, Inc.; 1982.

f. A **loading dose** ($\boldsymbol{D_L}$) is given as an initial intravenous bolus dose to produce the C_{ss} as rapidly as possible. The intravenous infusion is started at the same time as the D_L.

(1) The time to reach C_{ss} depends on the elimination half-life of the drug. Reaching 90%, 95%, or 99% of the C_{ss} without a D_L takes 3.32, 4.32, or 6.65 half-lives, respectively. Thus, for a drug with an elimination $t_{½}$ of 8 hrs, it will take 3.32 × 8 hrs, or 26.56 hrs, to reach 90% of C_{ss} if no loading dose is given.

(2) The D_L is the amount of drug that, when dissolved in the apparent V_D, produces the desired C_{ss}. Thus, D_L is calculated by the following equation:

$$D_L = C_{ss}V_D \text{ and } D_L = \frac{R}{k}$$

g. An intravenous infusion provides a relatively constant plasma drug concentration and is particularly useful for drugs that have a narrow therapeutic range. The IV infusion keeps the plasma drug concentration between the *minimum toxic concentration* (MTC) and the *minimum effective concentration* (MEC).

4. Intermittent intravenous infusions

a. Intermittent intravenous infusions are infusions in which the drug is infused for short periods to prevent accumulation and toxicity.

b. Intermittent intravenous infusions are used for a few drugs, such as the aminoglycosides. For example, gentamicin may be given as a 1-hr infusion every 12 hrs. In this case, steady-state drug concentrations are not achieved.

c. The peak drug concentration in the plasma for a drug given by intermittent intravenous infusion may be calculated by the following equation:

$$C_{p,\,n} = \frac{R(1 - e^{-kt})(1 - e^{-nk\tau})}{Cl(1 - e^{-k\tau})}$$

where $C_{p,n}$ is the peak drug concentration, R is the rate of drug infusion, Cl is total body clearance, k is the dosage interval, n is the number of infusions, t is the time for the infusion, and τ is the dosage interval.

5. Multiple doses. Many drugs are given intermittently in a multiple-dose regimen for continuous or prolonged therapeutic activity. This regimen is often used to treat chronic disease.

a. If drug doses are given frequently before the previous dose is completely eliminated, then plasma drug concentrations accumulate and increase to a steady-state level.

b. At **steady state**, plasma drug concentration fluctuates between a maximum $\left(C^{\infty}_{\max}\right)$ and a minimum $\left(C^{\infty}_{\min}\right)$ value (*Figure 5-4*).

c. When a multiple-dose regimen is calculated, the **superposition principle** assumes that previous drug doses have no effect on subsequent doses. Thus, the predicted plasma drug

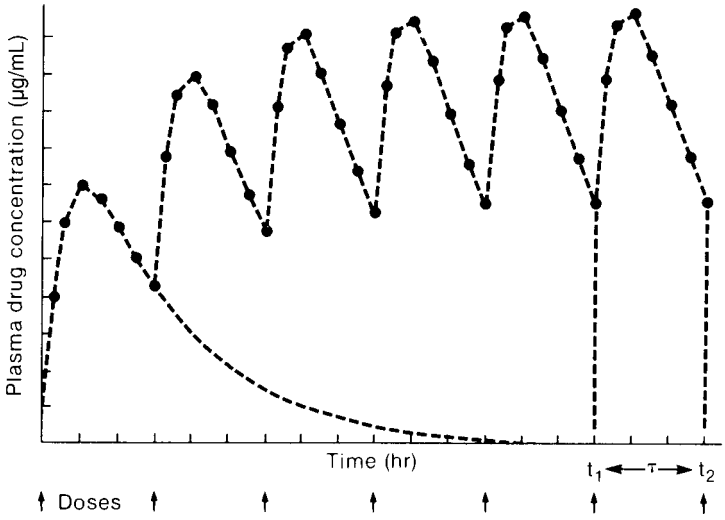


Figure 5-4. Generalized plot showing plasma drug concentration levels after administration of multiple doses and levels of accumulation when equal doses are given at equal time intervals. τ, time interval between doses (*t*), or the frequency of dosing. Adapted with permission from Shargel L, Wu-Pong S, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. 5th ed. New York, NY: McGraw-Hill; 2005.

concentration is the total plasma drug concentration obtained by adding the residual drug concentrations found after each previous dose.

d. When a multiple-dose regimen is designed, only the **dosing rate** (D_0/τ) can be adjusted easily.

(1) The dosing rate is based on the **size of the dose** (D_0) and the **interval** (τ) **between doses**, or the **frequency of dosing**.

(2) The dosing rate is given by the following equation:

$$\text{Dosing rate} = \frac{D_0}{\tau}$$

(3) As long as the dosing rate is the same, the expected **average drug concentration at steady state** $\left(C^{\infty}_{\text{min}}\right)$ is the same (*Figure 5-4*).

(a) For example, if a 600-mg dose is given every 12 hrs, the dosing rate is 600 mg/12 hrs, or 50 mg/hr.

(b) A dose of 300 mg every 6 hrs or 200 mg every 4 hrs also gives the same dosing rate (50 mg/hr), with the same expected C^{∞}_{Av}. However, the C^{∞}_{max} and C^{∞}_{min} values will be different.

(c) For a larger dose given over a longer interval (e.g., 600 mg every 12 hrs), the C^{∞}_{max} is higher and the C^{∞}_{min} is lower compared with a smaller dose given more frequently (e.g., 200 mg every 4 hrs).

e. Certain antibiotics are given by **multiple rapid intravenous bolus injections.**

(1) The peak, or **maximum**, **serum drug concentration** at steady state may be estimated by the following equation:

$$C^{\infty}_{\text{max}} = \frac{\frac{D_0}{V_{\text{D}}}}{1 - e^{-k\tau}}$$

(2) The **minimum serum drug concentration** $\left(C^{\infty}_{\text{min}}\right)$ at steady state is the drug concentration after the drug declines one dosage interval. Thus, C^{∞}_{min} is determined by the following equation:

$$C^{\infty}_{\text{min}} = C^{\infty}_{\text{min}}\, e^{-k\tau}$$

(3) The **average drug concentration** $\left(C^{\infty}_{\text{Av}}\right)$ at steady state is estimated with the equation used for multiple oral doses:

$$C^{\infty}_{\text{Av}} = \frac{FD_0}{kV_{\text{D}}\tau}$$

For intravenous bolus injections, $F = 1$.

f. Orally administered drugs given in **immediate-release dosage forms** (e.g., solutions, conventional tablets, capsules) by multiple oral doses are usually rapidly absorbed ($k_{\text{A}} \geq k$) and slowly eliminated. C^{∞}_{max} and C^{∞}_{min} for these drugs are approximated by the equations shown in I.B.5.e.(1)–(2).

(1) For more exact calculations of C^{∞}_{min} and C^{∞}_{max} after multiple oral doses, the following equations are used:

$$C^{\infty}_{\text{max}} = \frac{FD_0k_{\text{A}}}{V_{\text{D}}(k_{\text{A}} - k)}\left(\frac{1}{1 - e^{-}k\tau}\right) \text{ and}$$

$$C^{\infty}_{\text{min}} = \frac{FD_0k_{\text{A}}}{V_{\text{D}}(k_{\text{A}} - k)}\left(\frac{1}{1 - e^{-}k\tau}\right) e^{-}k\tau$$

(2) The calculation of C^{∞}_{Av} is the same as for multiple intravenous bolus injections, using the equation shown in I.B.5.e.(3).

(3) The term $1/(1 - e^{-k\tau})$ is known as the **accumulation rate.**

(4) The fraction of drug remaining in the body (f) after a dosage interval is given by the following equation:

$$f = e^{-k\tau}$$

g. Loading dose. An initial loading dose (D_L) is given to obtain a therapeutic steady-state drug level quickly.

(1) For multiple oral doses, D_L is calculated by:

$$D_L = D_M \frac{1}{1 - e^{-k\tau}}$$

where D_M is the maintenance dose.

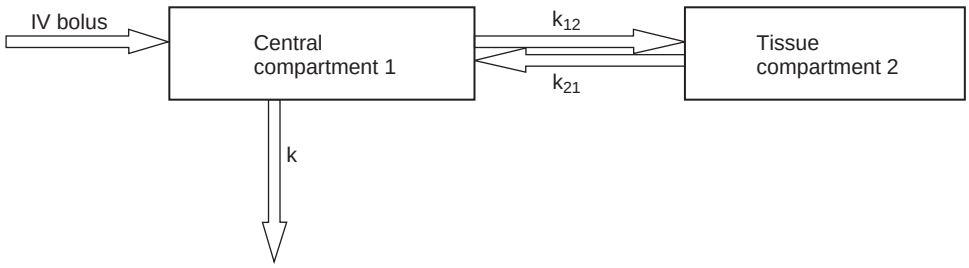
(2) If D_M is given at a dosage interval equal to the elimination half-life of the drug, then D_L equals twice the maintenance dose.

C. Multicompartment models

1. Drugs that exhibit multicompartment pharmacokinetics distribute into different tissue groups at different rates. Tissues with high blood flow equilibrate with a drug more rapidly than tissues with low blood flow. Drug concentration in various tissues depends on the physical and chemical characteristics of the drug and the nature of the tissue. For example, highly lipid-soluble drugs accumulate slowly in fat (lipid) tissue.

2. Two-compartment model (intravenous bolus injection)

a. After an intravenous bolus injection, the drug distributes and equilibrates rapidly into highly perfused tissues (**central compartment**) and more slowly into peripheral tissues (**tissue compartment**).



b. The initial rapid decline in plasma drug concentration is known as the **distribution phase**. The slower rate of decline in drug concentration after complete equilibration is achieved is known as the **elimination phase** (*Figure 5-5*).

c. The **plasma drug concentration** at any time is the sum of two first-order processes, as given in the following equation:

$$C_p = Ae^{-at} + Be^{-bt}$$

where a and b are hybrid first-order rate constants and A and B are y intercepts.

(1) The **hybrid first-order rate constant *b*** is obtained from the slope of the elimination phase of the curve (*Figure 5-5*) and represents the first-order elimination of drug from the body after the drug equilibrates with all tissues.

(2) The **hybrid first-order rate constant *a*** is obtained from the slope of the residual line of the distribution phase after the elimination phase is subtracted.

d. The **apparent volume of distribution** depends on the type of pharmacokinetic calculation. Volumes of distribution include the volume of the central compartment (V_p), the volume of distribution at steady state (V_{ss}), and the volume of the tissue compartment (V_t).

3. Two-compartment model (oral drug administration)

a. A drug with a rapid distribution phase may not show two-compartment characteristics after oral administration. As the drug is absorbed, it equilibrates with the tissues so that the elimination half-life of the elimination portion of the curve equals $0.693/b$.

b. Two-compartment characteristics are seen if the drug is absorbed rapidly and the distribution phase is slower.

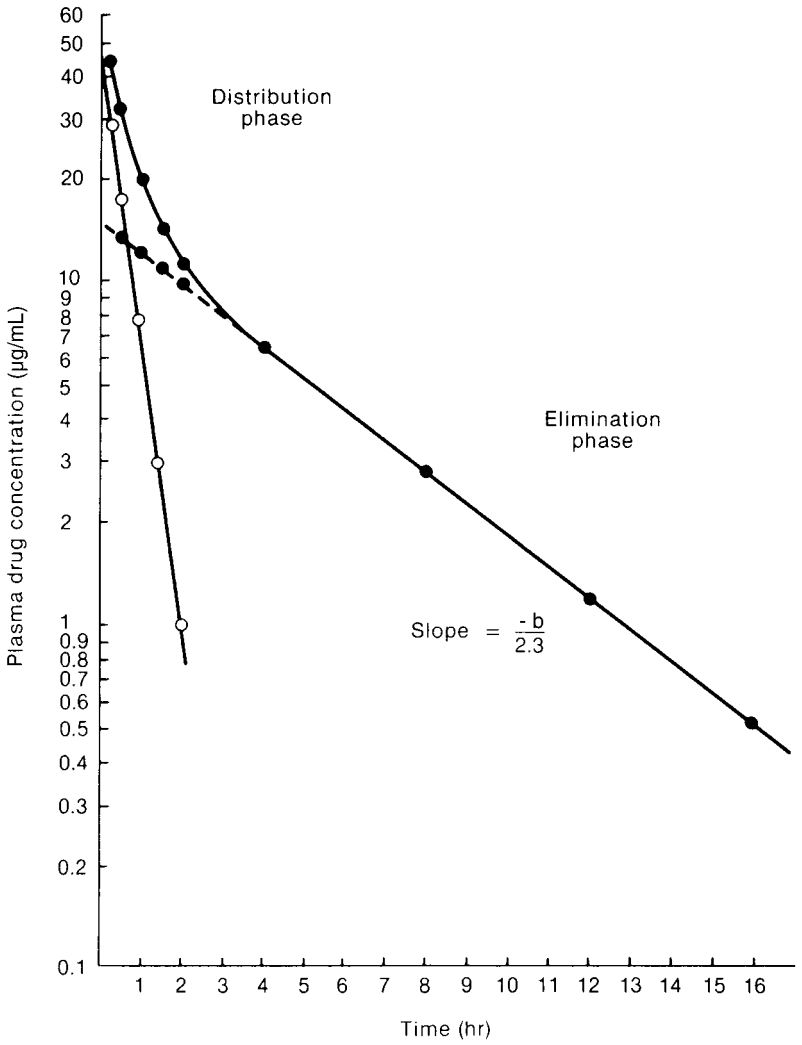


Figure 5-5. Generalized plot showing drug distribution and equilibration for a two-compartment model (intravenous bolus injection). The distribution phase is the initial rapid decline in plasma drug concentration. The elimination phase is the slower rate of decline after complete equilibration of the drug is achieved. Adapted with permission from Shargel L, Wu-Pong S, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. 5th ed. New York, NY: McGraw-Hill; 2005.

4. **Models with additional compartments**
   - **a.** The addition of each new compartment to the model requires an additional first-order plot.
   - **b.** The addition of a third compartment suggests that the drug slowly equilibrates into a deep tissue space. If the drug is given at frequent intervals, the drug begins to accumulate into the third compartment.
   - **c.** The terminal linear phase generally represents the elimination of the drug from the body after equilibration occurs. The rate constant from the elimination phase is used to calculate dosage regimens.
   - **d.** Adequate pharmacokinetic description of multicompartment models is often difficult and depends on proper plasma sampling and determination of drug concentrations.
5. **Elimination rate constants**
   - **a.** The elimination rate constant, *k*, represents drug elimination from the central compartment.
   - **b.** The terminal elimination rate constant (λ or *b* in the two-compartment model) represents drug elimination after drug distribution is mostly completed.

D. **Nonlinear pharmacokinetics** is also known as capacity-limited, dose-dependent, or saturation pharmacokinetics. Nonlinear pharmacokinetics do not follow first-order kinetics as the dose increases (*Figure 5-6*). Nonlinear pharmacokinetics may result from the saturation of an enzyme- or carrier-mediated system.

1. **Characteristics of nonlinear pharmacokinetics** include the following:
   - **a.** The AUC is not proportional to the dose.
   - **b.** The amount of drug excreted in the urine is not proportional to the dose.
   - **c.** The elimination half-life may increase at high doses.
   - **d.** The ratio of metabolites formed changes with increased dose.

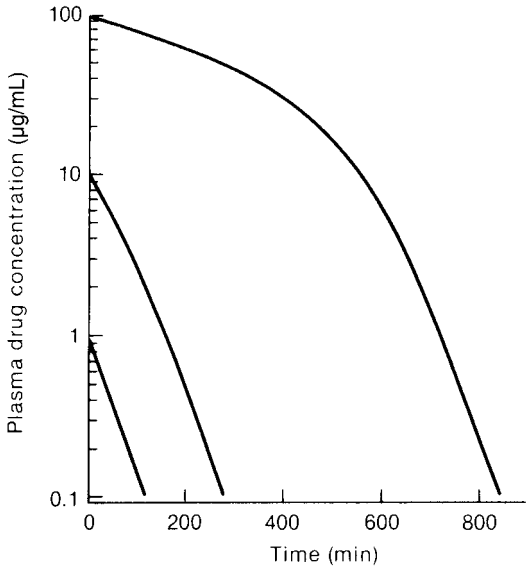


Figure 5-6. Generalized plot showing plasma drug concentration versus time for a drug with Michaelis–Menten (nonlinear) elimination kinetics. For this one-compartment model (intravenous injection), the doses are 1 mg, 10 mg, and 100 mg, and the apparent in vivo rate constant (k_M) is 10 mg. The maximum velocity of the reaction (V_{max}) is 0.2 mg/min. Adapted with permission from Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd ed. New York, NY: Marcel Dekker, Inc.; 1982. Copyright © 1982 Routledge/Taylor & Francis Group, LLC.

2. **Michaelis–Menten kinetics** describes the velocity of enzyme reactions. Michaelis–Menten kinetics is used to describe nonlinear pharmacokinetics.
   a. The **Michaelis–Menten equation** describes the rate of change (velocity) of plasma drug concentration after an intravenous bolus injection as follows:

$$\frac{dC_p}{dt} = \frac{-V_{max}C_p}{k_M + Cp}$$

   where V_{max} is the maximum velocity of the reaction, C_p is the substrate or plasma drug concentration, and k_M is the Michaelis constant equal to the C_p at 0.5 V_{max}.
   b. At low C_p values, where $C_p << k_M$, this equation reduces to a first-order rate equation because both k_M and V_{max} are constants.

$$\frac{dC_p}{dt} = \frac{-V_{max}C_p}{k_M} = -k'C_p$$

   c. At high C_p values, where $C_p >> k_M$, the Michaelis–Menten equation is a zero-order rate equation as follows:

$$\frac{dC_p}{dt} = -V_{max}$$

3. Drugs that follow nonlinear pharmacokinetics may show zero-order elimination rates at high drug concentrations, fractional-order elimination rates at intermediate drug concentrations, and first-order elimination rates at low drug concentrations (*Figure 5-6*).

E. **Clearance** is a measurement of drug elimination from the body. Units for clearance are volume per time (e.g., liters per hour).
1. **Total body clearance (Cl_T)** is the drug elimination rate divided by the plasma drug concentration. According to the concept of clearance, the body contains an apparent volume of distribution in which the drug is dissolved. A constant portion of this volume is cleared, or removed, from the body per unit time.
   a. The following equations express the measurement of total body clearance:

$$Cl_T = \frac{\text{drug elimination}}{\text{plasma drug concentration}} = \frac{(dDe/dt)}{Cp}$$

$$Cl_T = V_D k$$

$$Cl_T = \frac{FD_0}{AUC}$$

b. For drugs that follow first-order (linear) pharmacokinetics, total body clearance is the sum of all the clearances in the body, as shown in the following equation:

$$Cl_T = Cl_R + Cl_{NR}$$

where Cl_R is renal clearance and Cl_{NR} is nonrenal clearance. Nonrenal clearance, Cl_{NR}, is often equated with hepatic clearance, Cl_H.

c. The relation between Cl_T and $t_{½}$ is obtained by substituting $0.693/t_{½}$ for k in the equation in I.E.1 a to obtain the following expression:

$$t_{½} = \frac{0.693 V_D}{Cl_T}$$

where V_D and Cl_T are considered independent variables, and $t_{½}$ is considered a dependent variable.

d. As clearance decreases (e.g., in renal disease), $t_{½}$ increases. Changes in V_D also cause proportional changes in $t_{½}$.

2. Renal drug excretion is the major route of drug elimination for polar drugs, water-soluble drugs, drugs with low molecular weight (< 500 g/mol), and drugs that are biotransformed slowly. The relation between the drug excretion rate and the plasma drug concentration is shown in *Figure 5-7*. Drugs are excreted through the kidney into the urine by glomerular filtration, tubular reabsorption, and active tubular secretion.

a. Glomerular filtration is a passive process by which small molecules and drugs are filtered through the glomerulus of the nephron.

(1) Drugs bound to plasma proteins are too large to be filtered at the glomerulus.

(2) Drugs such as **creatinine and inulin** are not actively secreted or reabsorbed. They are used to measure the **glomerular filtration rate** (**GFR**).

b. Tubular reabsorption is a passive process that follows Fick's law of diffusion.

(1) Lipid-soluble drugs are reabsorbed from the lumen of the nephron back into the systemic circulation.

(2) For weak electrolyte drugs, urine pH affects the ratio of nonionized and ionized drug.

(a) If the drug exists primarily in the nonionized or lipid-soluble form, then it is reabsorbed more easily from the lumen of the nephron.

(b) If the drug exists primarily in the ionized or water-soluble form, then it is excreted more easily in the urine.

(c) Depending on the pK_a of the drug, alteration of urine pH alters the ratio of ionized to nonionized drug and affects the rate of drug excretion. For example, alkalinization of the urine by the administration of sodium bicarbonate increases the excretion of salicylates (weak acids) into the urine.

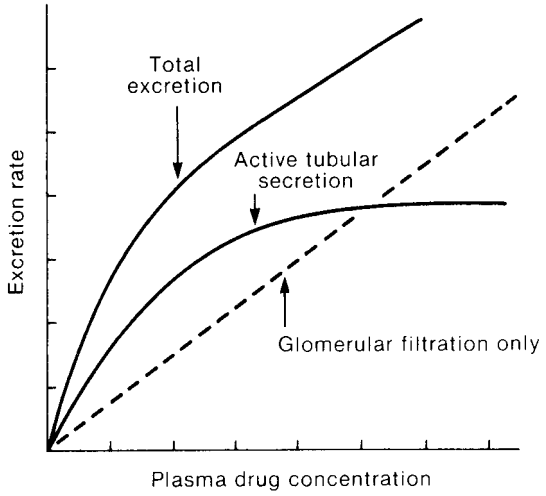


Figure 5-7. Generalized plot showing the excretion rate versus plasma drug concentration for a drug with active tubular secretion and for a drug secreted by glomerular filtration only. Adapted with permission from Shargel L, Wu-Pong S, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. 5th ed. New York, NY: McGraw-Hill; 2005.

(3) An increase in urine flow caused by simultaneous administration of a diuretic decreases the time for drug reabsorption. Consequently, more drug is excreted if given with a diuretic.

c. **Active tubular secretion** is a carrier-mediated active transport system that requires energy.
(1) Two active tubular secretion pathways exist in the kidney: one system for weak acids and one system for weak bases.
(2) The active tubular secretion system shows competition effects. For example, **probenecid** (a weak acid) competes for the same system as penicillin, decreasing the rate of penicillin excretion, resulting in a longer penicillin $t_{½}$.
(3) The renal clearance of drugs that are actively secreted, such as ***p*-aminohippurate (PAH)**, is used to measure **effective renal blood flow (ERBF).**

3. **Renal clearance** is the volume of drug contained in the plasma that is removed by the kidney per unit time. **Units for renal clearance** are expressed in volume per time (e.g., milliliters per minute or liters per hour).
a. Renal clearance may be measured by dividing the rate of drug excretion by the plasma drug concentration, as shown in the following equation:

$$Cl_R = \frac{\text{rate of drug excretion}}{C_p} = \frac{\frac{dD_u}{dt}}{C_p}$$

b. Measurement of renal clearance may also be expressed by the following equation:

$$Cl_R = k_e V_D$$

where k_e is the first-order renal excretion rate constant, and

$$Cl_R = \frac{D_u^\infty}{AUC}$$

where D_u^∞ is the total amount of parent (unchanged) drug excreted in the urine.
c. Renal clearance is measured without regard to the physiologic mechanism of renal drug excretion. The probable mechanism for renal clearance is obtained with a **clearance ratio**, which relates drug clearance to inulin clearance (a measure of GFR).
(1) If the clearance ratio is < 1.0, the mechanism for drug clearance may result from filtration plus reabsorption.
(2) If the ratio is 1.0, the mechanism may be filtration only.
(3) If the ratio is > 1.0, the mechanism may be filtration plus active tubular secretion.

4. **Hepatic clearance** is the volume of plasma-containing drug that is cleared by the liver per unit time.
a. **Measurement of hepatic clearance**. Hepatic clearance is usually measured indirectly, as the difference between total body clearance and renal clearance, as shown in the following equation:

$$Cl_H = Cl_T - Cl_R$$

where Cl_H is the hepatic clearance. Hepatic clearance is generally considered to be equivalent to Cl_{NR}, or nonrenal drug clearance. Hepatic clearance can also be calculated as the **product of the liver blood flow** (**Q**) and the **extraction ratio** (**ER**), as shown in the following equation:

$$Cl_H = Q(ER)$$

(1) The **extraction ratio** is the fraction of drug that is irreversibly removed by an organ or tissue as the plasma-containing drug perfuses that tissue.
(2) The extraction ratio is obtained by measuring the plasma drug concentration entering the liver and the plasma drug concentration exiting the liver:

$$ER = \frac{C_a - C_v}{C_a}$$

where C_a is the arterial plasma drug concentration entering the liver and C_v is the venous plasma drug concentration exiting the liver.
(3) Values for the ER range from 0 to 1. For example, if the ER is 0.9, then 90% of the incoming drug is removed as the plasma perfuses the liver. If the ER is 0, then no drug is removed by the liver.

b. Blood flow, **intrinsic clearance**, and **protein binding** affect hepatic clearance.

(1) Blood flow to the liver is approximately 1.5 L/min and may be altered by exercise, food, disease, or drugs.

(a) Blood enters the liver through the hepatic portal vein and hepatic artery and leaves through the hepatic vein.

(b) After oral drug administration, the drug is absorbed from the gastrointestinal tract into the mesenteric vessels and proceeds to the hepatic portal vein, liver, and systemic circulation.

(2) Intrinsic clearance, Cl_{int}, describes the ability of the liver to remove the drug independently of blood flow.

(a) Intrinsic drug clearance primarily occurs because of the inherent ability of the **biotransformation enzymes** (mixed-function oxidases) to metabolize the drug as it enters the liver.

(b) Normally, basal level mixed-function oxidase enzymes biotransform drugs. Levels of these enzymes may be increased by various drugs (e.g., phenobarbital) and environmental agents (e.g., tobacco smoke). These enzymes may be inhibited by other drugs and environmental agents (e.g., cimetidine, acute lead poisoning).

(3) Protein binding. Drugs that are bound to protein are not easily cleared by the liver or kidney because only the free, or nonplasma protein-bound, drug crosses the cell membrane into the tissue.

(a) The free drug is available to drug-metabolizing enzymes for biotransformation.

(b) A sudden increase in free-drug plasma concentration results in more available drug at pharmacologic receptors, producing a more intense effect in the organs (e.g., kidney, liver) involved in drug removal.

(c) Blood flow (Q), intrinsic clearance (Cl_{int}), and fraction of free drug in plasma (f) are related to hepatic clearance as shown in the following equation:

$$Cl_H = Q\left(\frac{fCl_{int}}{Q + fCl_{int}}\right)$$

(4) The hepatic clearance of drugs that have high extraction ratios and high Cl_{int} values (e.g., propranolol) is most affected by changes in blood flow and inhibitors of the drug metabolism enzymes.

(5) The hepatic clearance of drugs that have low extraction ratios and low Cl_{int} values (e.g., theophylline) is most affected by changes in Cl_{int} and is affected only slightly by changes in hepatic blood flow.

(6) Only drugs that are highly plasma protein bound (i.e., $>$ 95%) and have a low intrinsic clearance (e.g., phenytoin) are affected by a sudden shift in protein binding. This shift causes an increase in free drug plasma concentration.

c. Biliary drug excretion, an active transport process, is also included in hepatic clearance. Separate active secretion systems exist for weak acids and weak bases.

(1) Drugs that are excreted in bile are usually high-molecular-weight compounds (i.e., $>$ 500 g/mol) or polar drugs, such as reserpine, digoxin, and various glucuronide conjugates.

(2) Drugs may be recycled by the **enterohepatic circulation**.

(a) Some drugs are absorbed from the gastrointestinal tract through the mesenteric and hepatic portal veins, proceeding to the liver. The liver may secrete some of the drug (unchanged or as a glucuronide metabolite) into the bile.

(b) The bile and drug are stored in the gallbladder and will empty into the gastrointestinal tract through the bile duct and then may be reabsorbed.

(c) If the drug is a **glucuronide metabolite**, bacteria in the gastrointestinal tract may hydrolyze the glucuronide moiety, allowing the released drug to be reabsorbed.

d. First-pass effects (presystemic elimination) occur with drugs given orally. A portion of the drug is eliminated before systemic absorption occurs.

(1) First-pass effects generally result from rapid drug biotransformation by liver enzymes. Other mechanisms include metabolism of the drug by gastrointestinal mucosal cells, intestinal flora, and biliary secretion.

(2) First-pass effects are usually observed by measuring the **absolute bioavailability** (F) of the drug (see Chapter 6). If $F < 1$, then some of the drug was eliminated before systemic drug absorption occurred.
(3) Drugs that have a **high hepatic extraction ratio**, such as propranolol and morphine, show first-pass effects.
(4) To obtain better systemic absorption of a drug that demonstrates high first-pass effects, then either
(a) the drug dose could be increased (e.g., propranolol, penicillin);
(b) the drug could be given by an alternate route of administration (e.g., nitroglycerin sublingual, insulin subcutaneous, estradiol transdermal); or
(c) the dosage form could be modified as a delayed-release drug product (e.g., enteric-coated aspirin, mesalamine), so that the drug may be absorbed more distally in the gastrointestinal (GI) tract.

F. **Noncompartment methods**. Some pharmacokinetic parameters for absorption, distribution, and elimination may be estimated with noncompartment methods. These methods usually require comparison of the areas under the curve.

1. **Mean residence time**
   a. **Mean residence time** (**MRT**) is the average time for the drug molecules to reside in the body. MRT is also known as the *mean transit time* and *mean sojourn time*.
   b. The MRT depends on the route of administration and assumes that the drug is eliminated from the central compartment.
   c. The MRT is the total residence time for all molecules in the body divided by the total number of molecules in the body, as shown in the following equation:

$$\text{MRT} = \frac{\text{total residence time for all drug molecules in the body}}{\text{total number of drug molecules}}$$

   d. **MRT after IV bolus injection**
      (1) The MRT after a bolus intravenous injection is calculated by the following equation:

$$\text{MRT}_{\text{IV}} = \frac{\text{AUMC}}{\text{AUC}_{0-\infty}}$$

      where AUMC is the area under the first moment versus time curve from $t = 0$ to $t =$ infinity and $\text{AUC}_{0-\infty}$ is the area under the plasma drug concentration versus time curve from $t = 0$ to $t =$ infinity. $\text{AUC}_{0-\infty}$ is also known as the *zero-moment curve*.
      (2) The MRT_{IV} is related to the elimination rate constant by the following expression:

$$\text{MRT}_{\text{IV}} = 1/k$$

      (3) During MRT_{IV}, 62.3% of the intravenous bolus dose is eliminated.
      (4) The MRT for a drug given by a noninstantaneous input is longer than the MRT_{IV}.
2. **Mean absorption time** (**MAT**) is the difference between MRT and MRT_{IV} after an extravascular route is used.

$$\text{MAT} = \text{MRT}_{\text{ev}} - \text{MRT}_{\text{IV}}$$

   When first-order absorption occurs, $\text{MAT} = 1/ka$.
3. **Clearance** is the volume of plasma cleared of drug per unit time and may be calculated without consideration of the compartment model.

$$Cl = \frac{FD_0}{\text{AUC}_{0-\infty}}$$

   After an IV dose, $F = 1$.
4. **Steady-state volume of distribution** (V_{ss})
   a. The steady-state volume of distribution is the ratio of the amount of drug in the body at steady state and the average steady-state drug concentration.
   b. After an intravenous bolus injection, V_{ss} is calculated by the following equation:

$$V_{ss} = \frac{\text{dose}_{\text{IV}}\,(\text{AUMC})}{\text{AUC}^2}$$

II. CLINICAL PHARMACOKINETICS

A. Definition

1. Clinical pharmacokinetics is the application of pharmacokinetic principles for the rational design of an individualized dosage regimen. The two main objectives are **maintenance of an optimum drug concentration at the receptor site** to produce the desired therapeutic response for a specific period and **minimization of any adverse or toxic effects** of the drug.

III. TOXICOKINETICS

A. Definitions

1. Toxicokinetics is the application of pharmacokinetic principles to the design, conduct, and interpretation of drug safety evaluation studies.

2. **Toxicokinetics** is also used to validate dose-related exposure in animals. Toxicokinetic studies are performed in animals during preclinical drug development to aid in prediction of human drug toxicity. Toxicokinetic (nonclinical) studies may continue after the drug has been tested in humans.

3. **Clinical toxicology** is the study of adverse effects of drugs and toxic substances (poisons) in the human body. The pharmacokinetics of a drug in an overmedicated (intoxicated) patient may be very different from the pharmacokinetics of the same drug given in therapeutic doses. For example, a very high toxic dose may show nonlinear pharmacokinetics due to saturation kinetics compared to the drug given at lower therapeutic doses in which the drug levels follow linear pharmacokinetics.

IV. POPULATION PHARMACOKINETICS

A. Definition

1. Population pharmacokinetics is the study of sources and correlates of variability in drug concentrations among individuals who are the target patient population. Population pharmacokinetics is most often applied to the clinical patient who is receiving relevant doses of a drug of interest. Both pharmacokinetic and nonpharmacokinetic data may be considered, including gender, age, weight, creatinine clearance, and concomitant disease. Population pharmacokinetics can be used to assist with therapeutic drug monitoring and the principles of dosage adjustments (see Chapter 26).

Study Questions

Directions: Each question, statement, or incomplete statement in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Creatinine clearance is used as a measurement of

(A) renal excretion rate.
(B) glomerular filtration rate (GFR).
(C) active renal secretion.
(D) passive renal absorption.
(E) drug metabolism rate.

For questions 2–5: A new cephalosporin antibiotic was given at a dose of 5 mg/kg by a single intravenous bolus injection to a 58-year-old man who weighed 75 kg. The antibiotic follows the pharmacokinetics of a one-compartment model and has an elimination half-life of 2 hrs. The apparent volume of distribution is 0.28 L/kg, and the drug is 35% bound to plasma proteins.

2. What is the initial plasma drug concentration (C_p^0) in this patient?

(A) 0.24 mg/L
(B) 1.80 mg/L
(C) 17.9 mg/L
(D) 56.0 mg/L
(E) 1339 mg/L

3. What is the predicted plasma drug concentration (C_p) at 8 hr after the dose?
   (A) 0.73 mg/L
   (B) 1.11 mg/L
   (C) 2.64 mg/L
   (D) 4.02 mg/L
   (E) 15.10 mg/L

4. How much drug remains in the patient's body (D_B) 8 hrs after the dose?
   (A) 15.3 mg
   (B) 23.3 mg
   (C) 84.4 mg
   (D) 100.0 mg
   (E) 112.0 mg

5. How long after the dose is exactly 75% of the drug eliminated from the patient's body?
   (A) 2 hrs
   (B) 4 hrs
   (C) 6 hrs
   (D) 8 hrs
   (E) 10 hrs

For questions 6–11: A 35-year-old man who weighs 70 kg and has normal renal function needs an intravenous infusion of the antibiotic carbenicillin. The desired steady-state plasma drug concentration is 15 mg/dL. The physician wants the antibiotic to be infused into the patient for 10 hrs. Carbenicillin has an elimination half-life ($t_{½}$) of 1 hr and an apparent volume distribution (V_D) of 9 L in this patient.

6. Assuming that no loading dose was given, what rate of intravenous infusion is recommended for this patient?
   (A) 93.6 mg/hr
   (B) 135.0 mg/hr
   (C) 468.0 mg/hr
   (D) 936.0 mg/hr
   (E) 1350.0 mg/hr

7. Assuming that no loading intravenous dose was given, how long after the initiation of the intravenous infusion would the plasma drug concentration reach 95% of the theoretic steady-state drug concentration?
   (A) 1.0 hrs
   (B) 3.3 hrs
   (C) 4.3 hrs
   (D) 6.6 hrs
   (E) 10.0 hrs

8. What is the recommended loading dose?
   (A) 93.6 mg
   (B) 135.0 mg
   (C) 468.0 mg
   (D) 936.0 mg
   (E) 1350.0 mg

9. To infuse the antibiotic as a solution containing 10-g drug in 500 mL 5% dextrose, how many milliliters per hour of the solution would be infused into the patient?
   (A) 10.0 mL/hr
   (B) 46.8 mL/hr
   (C) 100.0 mL/hr
   (D) 936.0 mL/hr
   (E) 1141.0 mL/hr

10. What is the total body clearance rate for carbenicillin in this patient?
    (A) 100 mL/hr
    (B) 936 mL/hr
    (C) 4862 mL/hr
    (D) 6237 mL/hr
    (E) 9000 mL/hr

11. If the patient's renal clearance for carbenicillin is 86 mL/min, what is the hepatic clearance for carbenicillin?
    (A) 108 mL/hr
    (B) 1077 mL/hr
    (C) 3840 mL/hr
    (D) 5160 mL/hr
    (E) 6844 mL/hr

12. The earliest evidence that a drug is stored in tissue is
    (A) an increase in plasma protein binding.
    (B) a large apparent volume of distribution (V_D).
    (C) a decrease in the rate of formation of metabolites by the liver.
    (D) an increase in the number of side effects produced by the drug.
    (E) a decrease in the amount of free drug excreted in the urine.

13. The intensity of the pharmacologic action of a drug is most dependent on the
    (A) concentration of the drug at the receptor site.
    (B) elimination half-life ($t_{½}$) of the drug.
    (C) onset time of the drug after oral administration.
    (D) minimum toxic concentration (MTC) of the drug in plasma.
    (E) minimum effective concentration (MEC) of the drug in the body.

14. Drugs that show nonlinear pharmacokinetics have which property?
    (A) A constant ratio of drug metabolites is formed as the administered dose increases.
    (B) The elimination half-life ($t_{½}$) increases as the administered dose increases.
    (C) The area under the plasma drug concentration versus time curve (AUC) increases in direct proportion to an increase in the administered dose.
    (D) Both low and high doses follow first-order elimination kinetics.
    (E) The steady-state drug concentration increases in direct proportion to the dosing rate.

15. The loading dose (D_L) of a drug is usually based on the
- **(A)** total body clearance (Cl_T) of the drug.
- **(B)** percentage of drug bound to plasma proteins.
- **(C)** fraction of drug excreted unchanged in the urine.
- **(D)** apparent volume of distribution (V_D) and desired drug concentration in plasma.
- **(E)** area under the plasma drug concentration versus time curve (AUC).

16. The renal clearance of inulin is used as a measurement of
- **(A)** effective renal blood flow.
- **(B)** rate of renal drug excretion.
- **(C)** intrinsic enzyme activity.
- **(D)** active renal secretion.
- **(E)** GFR.

17. All of the following statements about plasma protein binding of a drug are true *except* which one?
- **(A)** Displacement of a drug from plasma protein binding sites results in a transient increased volume of distribution (V_D).
- **(B)** Displacement of a drug from plasma protein binding sites makes more free drug available for glomerular filtration.
- **(C)** Displacement of a potent drug that is normally $>$ 95% bound may cause toxicity.
- **(D)** Albumin is the major protein involved in protein binding of drugs.
- **(E)** Drugs that are highly bound to plasma proteins generally have a greater V_D compared with drugs that are highly bound to tissue proteins.

18. The onset time for a drug given orally is the time for the drug to
- **(A)** reach the peak plasma drug concentration.
- **(B)** reach the MEC.
- **(C)** reach the MTC.
- **(D)** begin to be eliminated from the body.
- **(E)** begin to be absorbed from the small intestine.

19. The initial distribution of a drug into tissue is determined chiefly by the
- **(A)** rate of blood flow to tissue.
- **(B)** GFR.
- **(C)** stomach emptying time.
- **(D)** affinity of the drug for tissue.
- **(E)** plasma protein binding of the drug.

20. Which tissue has the greatest capacity to biotransform drugs?
- **(A)** brain
- **(B)** kidney
- **(C)** liver
- **(D)** lung
- **(E)** skin

21. The principle of superposition in designing multiple-dose regimens assumes that
- **(A)** each dose affects the next subsequent dose, causing nonlinear elimination.
- **(B)** each dose of drug is eliminated by zero-order elimination.
- **(C)** steady-state plasma drug concentrations are reached at approximately 10 half-lives.
- **(D)** early doses of drug do not affect subsequent doses.
- **(E)** the fraction of drug absorbed is equal to the fraction of drug eliminated.

For questions 22–24: A new cardiac glycoside is developed for oral and intravenous administration. The drug has an elimination half-life ($t_{½}$) of 24 hrs and an apparent volume of distribution (V_D) of 3 L/kg. The effective drug concentration is 1.5 ng/mL. Toxic effects of the drug are observed at drug concentrations $>$ 4 ng/mL. The drug is bound to plasma proteins at approximately 25%. The drug is 75% bioavailable after an oral dose.

22. What is the oral maintenance dose, if given once a day, for a 68-year-old man who weighs 65 kg and has congestive heart failure (CHF) and normal renal function?
- **(A)** 0.125 mg
- **(B)** 0.180 mg
- **(C)** 0.203 mg
- **(D)** 0.270 mg
- **(E)** 0.333 mg

23. What is the loading dose (D_L) for this patient?
- **(A)** 0.270 mg
- **(B)** 0.293 mg
- **(C)** 0.450 mg
- **(D)** 0.498 mg
- **(E)** 0.540 mg

24. If the drug is available in tablets of 0.125 mg and 0.250 mg, what is the patient's plasma drug concentration if he has a dosage regimen of 0.125 mg every 12 hrs?
- **(A)** 1.39 ng/mL
- **(B)** 1.85 ng/mL
- **(C)** 2.78 ng/mL
- **(D)** 3.18 ng/mL
- **(E)** 6.94 ng/mL

25. If digoxin has a half-life of 35 hrs how long will it take for a toxic plasma concentration of 8 ng/mL to decline to a therapeutic plasma concentration of 2 ng/mL?
- **(A)** 17.5 hrs
- **(B)** 35 hrs
- **(C)** 70 hrs
- **(D)** 105 hrs
- **(E)** 140 hrs

Directions for question 26: The question in this section can be correctly answered by **one or more** of the suggested answers. Choose the correct answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I** and **II** are correct
D if **II** and **III** are correct
E if **I**, **II**, and **III** are correct

26. Which equation is true for a zero-order reaction rate of a drug?

I. $\frac{dA}{dt} = -k$
II. $t_{½} = \frac{0.693}{k}$
III. $A = A_0 e^{-kt}$

Answers and Explanations

1. The answer is B *[see I.E.2.a]*.
A substance that is used to measure the GFR must be filtered but not reabsorbed or actively secreted. Although inulin clearance gives an accurate measurement of GFR, creatinine clearance is generally used because no exogenous drug must be given. However, creatinine formation depends on muscle mass and muscle metabolism, which may change with age and various disease conditions.

2. The answer is C *[see I.B.1.b.(2)]*.

3. The answer is B *[see I.A.3.b.(1); I.B.1]*.

4. The answer is B *[see I.B.1.a.(2)]*.

5. The answer is B *[see I.B.1.a.(2)]*.
Substituting the data for this patient in the equation for the initial plasma drug concentration (C_p^0) gives

$$C_p^0 = \frac{D_0}{V_D} = \frac{5 \text{ mg}}{0.28 \text{ L/kg}} = 17.9 \text{ mg/L}$$

To obtain the patient's plasma drug concentration (C_p) 8 hrs after the dose, the following calculation is performed:

$$C_p = C_p^0 \, e^{-kt}$$

$$k = \frac{0.693}{t_{½}} = \frac{0.963}{2} = 0.347 \text{ hr}^{-1}$$

$$C_p = 17.9e^{-(0.347)(8)}$$

$$C_p = (17.9)(0.0623) = 1.11 \text{ mg/L}$$

The amount of drug in the patient's body at 8 hrs is calculated as follows:

$$D_B = C_p V_D = (1.11)(0.28)(75) = 23.3 \text{ mg}$$

For any first-order elimination process, 50% of the initial amount of drug is eliminated at the end of the first half-life, and 50% of the remaining drug (i.e., 75% of the original amount) is eliminated at the end of the second half-life. Because the drug in the current case has an elimination half-life ($t_{½}$) of 2 hrs, 75% of the dose is eliminated in two half-lives or 4 hrs.

6. The answer is D *[see I.B.3.e.(3)]*.

7. The answer is C *[see I.B.3.c]*.

8. The answer is E *[see I.B.3.f.(2)]*.

9. The answer is B *[see I.B.3.e.(3)]*.

10. The answer is D *[see I.B.3.e.(3); I.E.1.a]*.

11. The answer is B *[see I.E.4.a]*.
The equation for the plasma concentration at steady state (C_{ss}) provides the formula for calculating the rate of an intravenous infusion (R). The equation is

$$C_{ss} = \frac{R}{kV_D}$$

where k is the first-order elimination rate constant and V_D is the apparent volume of distribution. Rearranging the equation and substituting the data for this patient give the following calculations:

$$R = C_{ss} k V_D = \frac{15 \text{ mg}}{100 \text{ mL}} \times \frac{0.693}{1 \text{ hr}} \times 9000 \text{ mL}$$

$$R = 936 \text{ mg/hr}$$

The time it takes for an infused drug to reach the C_{ss} depends on the elimination half-life of the drug. The time required to reach 95% of the C_{ss} is equal to 4.3 times the half-life, whereas the time required to reach 99% of the C_{ss} is equal to 6.6 times the half-life. Because the half-life in the current case is 1 hr, the time to reach 95% of the C_{ss} is 4.3 × 1 hr or 4.3 hrs.
The loading dose (D_L) is calculated as follows:

$$D_L = C_{ss} V_D = \frac{15 \text{ mg}}{100 \text{ mL}} \times 9000 \text{ mL} = 1350 \text{ mg}$$

The answer to question 6 shows that the infusion rate should be 936 mg/hr. Therefore, if a drug solution containing 10 g in 500 mL is used, the required infusion rate is

$$\frac{936 \text{ mg}}{1 \text{ hr}} \times \frac{500 \text{ mL}}{10000 \text{ mg}} = 46.8 \text{ mL/hrs}$$

The patient's total body clearance (Cl_T) is calculated as follows:

$$Cl_T = kV_D$$

$$Cl_T = \frac{0.693}{1} \times 9000 \text{ mL} = 6237 \text{ mL/hr}$$

The hepatic clearance (Cl_H) is the difference between total clearance (Cl_T) and renal clearance (Cl_R):

$$Cl_H = Cl_T - Cl_R$$

$$Cl_H = 6237 - (86 \text{ mL/min} \times 60 \text{ min/hr})$$

$$= 1077 \text{ mL/hr}$$

12. The answer is B *[see I.B.1.b.(1)]*.
A large apparent volume of distribution (V_D) is an early sign that a drug is not concentrated in the plasma but is distributed widely in tissue. An increase in plasma protein binding suggests that the drug is located in the plasma rather than in tissue. A decrease in hepatic metabolism, an increase in side effects, or a decrease in urinary excretion of free drug is caused by a decrease in drug elimination.

13. The answer is A *[see I.A.5.d.(3)]*.
As more drug is concentrated at the receptor site, more receptors interact with the drug to produce a pharmacologic effect. The intensity of the response increases until it reaches a maximum. When all of the available receptors are occupied by drug molecules, additional drug does not produce a more intense response.

14. The answer is B *[see I.D]*.
Nonlinear pharmacokinetics is a term used to indicate that first-order elimination of a drug does not occur at all drug concentrations. With some drugs, such as phenytoin, as the plasma drug concentration increases, the elimination pathway for metabolism of the drug becomes saturated and the half-life increases. The area under the plasma drug concentration versus time curve (AUC) of the drug is not proportional to the dose, neither is the rate of metabolite formation. The metabolic rate is related to the effects of the drug.

15. The answer is D *[see I.B.1.b.(2); I.B.5.g.(1)]*.
A loading dose (D_L) of a drug is given to obtain a therapeutic plasma drug level as rapidly as possible. The D_L is calculated based on the apparent volume of distribution (V_D) and the desired plasma level of the drug.

16. The answer is E *[see I.E.3.c]*.
Inulin is neither reabsorbed nor actively secreted. Therefore, it is excreted by glomerular filtration only. The inulin clearance rate is used as a standard measure of the GFR, a test that is useful both in a clinical situation and in the development of new drugs.

17. The answer is E *[see I.A.5.d]*.
Drugs that are highly bound to plasma proteins diffuse poorly into tissue and have a low apparent volume of distribution (V_D).

18. The answer is B *[see I.B.3.g]*.
The onset time is the time from the administration of the drug to the time when absorbed drug reaches the MEC. The MEC is the drug concentration in the plasma that is proportional, but not necessarily equal, to the minimum drug concentration at the receptor site that elicits a pharmacologic response.

19. The answer is A *[see I.A.5.a]*.
The initial distribution of a drug is chiefly determined by blood flow, whereas the affinity of the drug for tissue determines whether the drug concentrates at that site. The GFR affects the renal clearance of a drug, not its initial distribution. The gastric emptying time and degree of plasma protein binding affect drug distribution but are less important than the rate of blood flow to tissue.

20. The answer is C *[see I.E.4.b.(2)]*.
The kidney, lung, skin, and intestine all have some capacity to biotransform, or metabolize, drugs; but the brain has little capacity for drug metabolism. The liver has the highest capacity for drug metabolism.

21. The answer is D *[see I.B.5.c]*.
The superposition principle, which underlies the design of multiple-dose regimens, assumes that earlier drug doses do not affect subsequent doses. If the elimination rate constant or total body clearance of the drug changes during multiple dosing, then the superposition principle is no longer valid. Changes in the total body clearance (Cl_T) may be caused by enzyme induction, enzyme inhibition, or saturation of an elimination pathway. Any of these changes would cause nonlinear pharmacokinetics.

22. The answer is D *[see I.B.5.e.(3)]*.

23. The answer is E *[see I.B.5.g.(1)]*.

24. The answer is A *[see I.B.5.d.(2); I.B.5.e.(3)]*.
The oral maintenance dose (D_0) should maintain the patient's average drug concentration at the effective drug concentration. The bioavailability of the drug (F), the apparent volume of distribution (V_D), the dosage interval (τ), and the excretion rate constant (k) must be considered in calculating the dose. The equation used is

$$C_{Av}^{\infty} = FD_0 / kV_D\tau$$

For this drug, $F = 0.75$, $k = 0.693/24$ hrs, $V_D = 3$ L/kg $\times$ 65 kg, $\tau = 24$ hrs, and $C^{\infty}_{Av} = 1.5$ ng/mL, or 1.5 μg/L. Therefore, by substitution, $D_0 = 270$ μg, or 0.270 mg. When the maintenance dose is given at a dosage frequency equal to the half-life, then the loading dose is equal to twice the maintenance dose, in this case 540 μg, or 0.540 mg. To determine the plasma drug concentration for a dosage regimen of 0.125 mg every 12 hrs, the C^{∞}_{Av} formula is used. This time, $F = 0.75$, $D_0 = 0.125$ mg, $k = 0.693/24$ hrs, $V_D = 3$ L/kg $\times$ 65 kg, and $\tau = 12$ hrs. Therefore, $C^{\infty}_{Av} = 1.39$ ng/mL. For cardiac glycosides, the peak (C_{max}) and trough (C_{min}) concentrations are calculated, and plasma drug concentrations are monitored after dosing. The loading dose (D_L) may be given in small increments over a specified period, according to the dosage regimen suggested by the manufacturer.

25. The answer is C *[see I.A.3.b]*.
For first-order elimination, it takes two half-lives for plasma drug concentration of 8 ng/mL to decline to 2 ng/mL. The first half-life, the plasma drug concentration declines to 4 ng/mL, and the next half-life, the plasma drug concentration declines to 2 ng/mL.

26. The answer is A (I) *[see I.A.3.a]*.
The first equation in the question describes a zero-order reaction (dA/dt) in which the reaction rate increases or decreases at a constant rate (k). A zero-order reaction produces a graph of a straight line with the equation of $A = -kt + A_o$ when A is plotted against time (t). The other equations in the question represent first-order reactions.

6 Bioavailability and Bioequivalence

MANISH ISSAR, LEON SHARGEL

I. DEFINITIONS[1]

A. **Bioavailability** is a measurement of the rate and extent (amount) to which the active ingredient or active moiety becomes available at the site of action. Bioavailability is also considered a measure of the rate and extent of therapeutically active drug that is systemically absorbed. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

B. **Bioequivalent drug products**. A generic drug product is considered bioequivalent to the **reference listed drug** (**RLD**) **product** if both products are pharmaceutical equivalents and the generic drug product's rate and extent of systemic drug absorption (bioavailability) do not show a statistically significant difference when administered in the same molar dose of the active ingredient, in the same chemical form, in a similar dosage form, by the same route of administration, and under the same experimental conditions. The RLD is generally the brand product.

C. **Generic drug product**

1. The generic drug product requires an **abbreviated new drug application** (ANDA) for approval by the U.S. Food and Drug Administration (FDA) and may be marketed after patent expiration of the reference drug product.

2. The generic drug product must be a **therapeutic equivalent** to the reference drug product but may differ in certain characteristics, including shape, scoring configuration, packaging, and excipients (such as colors, flavors, preservatives, expiration date, and minor aspects of labeling).

3. FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

D. **Pharmaceutical equivalents** are drug products that contain the same therapeutically active drug ingredient(s); contain the same salt, ester, or chemical form; are of the same dosage form; and are identical in strength, concentration, and route of administration. Pharmaceutical equivalents may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, and excipients (including colors, flavoring, and preservatives).

E. **The reference listed drug product** is usually the currently marketed, brand-name product with a full **new drug application** (**NDA**) approved by the FDA. The RLD is the reference drug product identified by FDA (see *Electronic Orange Book* at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm).

[1]The U.S. Food and Drug Administration (FDA) annually publishes the book *Approved Drug Products with Therapeutic Equivalence Evaluation* also known as the *Electronic Orange Book* (available online at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm). This source should be consulted for the latest definitions of therapeutic equivalence–related terms.

F. **Therapeutic equivalent drug products** are pharmaceutical equivalents that can be expected to have the same clinical effect and safety profile when administered to patients under the same conditions specified in the labeling. Therapeutic equivalent drug products have the following criteria:
   1. The products are safe and effective.
   2. The products are pharmaceutical equivalents that contain the same active drug ingredient in the same dosage form, given by the same route of administration; meet compendial or other applicable standards of strength, quality, purity, and identity; and meet an acceptable in vitro standard.
   3. The drug products are bioequivalent in that they do not present a known potential problem and are shown to meet an appropriate bioequivalence standard.
   4. The drug products are adequately labeled.
   5. The drug products are manufactured in compliance with current good manufacturing practice regulations.

G. **Pharmaceutical alternatives** are drug products that contain the same therapeutic moiety but are different salts, esters, or complexes of that moiety (e.g., tetracycline hydrochloride vs. tetracycline phosphate) or are different dosage forms (e.g., tablet versus capsule; immediate-release dosage form versus controlled-release dosage form) or strengths.

II. DRUG PRODUCT PERFORMANCE

A. **Drug product performance**, in vivo, may be defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance. Performance tests relate the quality of the drug product to its clinical safety and efficacy.

B. **Bioavailability studies** are used for establishing dosage regimens of new drug products. Bioavailability is one attribute to product quality that links in vivo performance of the drug product used to original formulation that was used in the clinical safety and efficacy studies.

C. **Bioequivalence studies** can be useful during the investigational new drug (IND) development or NDA development period to establish links between
   1. early and late clinical trial formulations;
   2. formulations used in clinical trial and stability studies, if different; and
   3. clinical trial formulations and to-be-marketed drug product.

D. **Bioequivalence studies** are a critical component of ANDA submissions.
   1. The purpose of these studies is to demonstrate bioequivalence between a pharmaceutically equivalent generic drug product and the corresponding reference listed drug (usually the brand drug product).
   2. Together with the determination of pharmaceutical equivalence, establishing bioequivalence allows a regulatory conclusion of therapeutic equivalence.

E. **Scale-up and post-approval changes (SUPACs)**. After market approval, a drug product may undergo a manufacturing change. A bioequivalence study may be needed to show that the new formulation or the new method of manufacture (test product) and the prior formulation or method of manufacture (reference product) are equivalent.

III. BIOAVAILABILITY AND BIOEQUIVALENCE.

These may be determined directly using pharmacokinetic studies (e.g., plasma drug concentration versus time profiles, urinary drug excretion studies), measurements of an acute pharmacodynamic effect, comparative clinical studies, or in vitro studies. The choice of study used is based on the site of action of the drug and the ability of the study design to compare drug delivered to that site by the two products.

A. **Acute pharmacodynamic effects**, such as changes in heart rate, blood pressure, electrocardiogram (ECG), clotting time, or forced expiratory volume in 1 sec (FEV_1) can be used to measure bioavailability when no assay for plasma drug concentration is available or when the plasma drug concentration does not relate to the pharmacological response (e.g., a bronchodilator such as albuterol given by inhalation). Quantitation of the pharmacological effect versus time profile can be used as a measure of bioavailability and/or bioequivalence (*Figure 6-1*).
   1. **Onset time**. As the drug is systemically absorbed, the drug concentration at the receptor rises to a **minimum effective concentration** (MEC), and a pharmacological response is initiated. The time from drug administration to the MEC is known as the onset time.

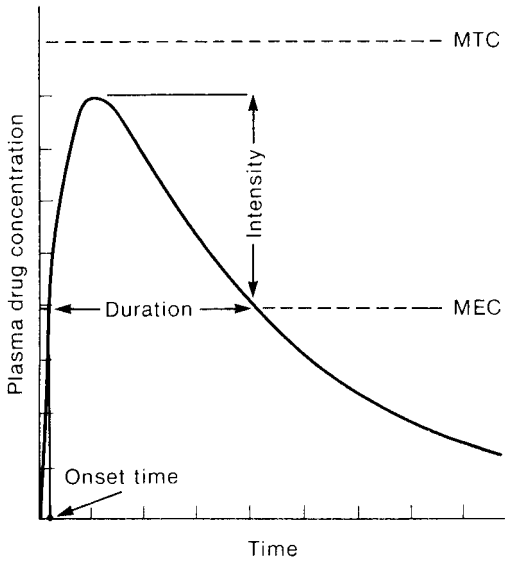


Figure 6-1. Generalized plasma drug concentration versus time curve after oral drug administration. *MEC*, minimum effective concentration; *MTC*, minimum toxic concentration. Adapted with permission from Shargel L, Wu-Pong S, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics.* 5th ed. New York, NY: McGraw-Hill; 2005:6.

2. **Intensity**. The intensity of the pharmacological effect is proportional to the number of receptors occupied by the drug up to a *maximum* pharmacological effect. The maximum pharmacological effect may occur before, after, or at peak drug absorption.
3. **Duration of action**. As long as the drug concentration remains above the MEC, pharmacological activity is observed. The duration of action is the time for which the drug concentration remains above the MEC.
4. **Therapeutic window**. As the drug concentration increases, other receptors may combine with the drug to exert a toxic or adverse response. This drug concentration is the **minimum toxic concentration** (MTC). The drug concentration range between the MEC and the MTC is known as the *therapeutic window*.

B. Plasma drug concentration. The plasma drug concentration versus time curve is most often used to measure the systemic bioavailability of a drug from a drug product (*Figure 6-2*).

1. **Time for peak plasma drug concentration** (T_{max}) relates to the rate constants for systemic drug absorption and elimination. If two oral drug products contain the same amount of active drug but different excipients, the dosage form that yields the faster rate of drug absorption has the shorter T_{max}.

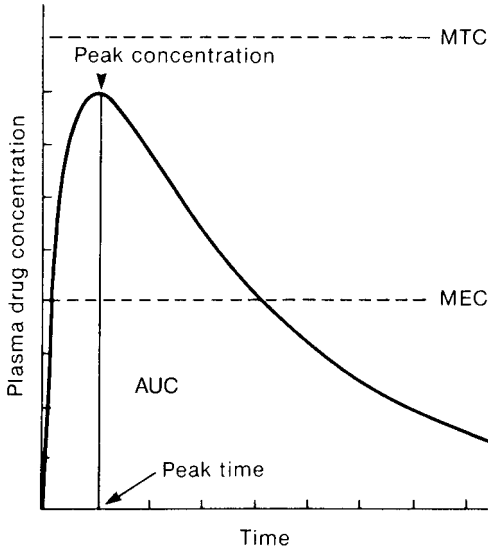


Figure 6-2. Generalized plasma drug concentration versus time curve, showing peak time and peak concentration. *AUC*, area under the curve; *MEC*, minimum effective concentration; *MTC*, minimum toxic concentration. Adapted with permission from Shargel L, Wu-Pong S, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics.* 5th ed. New York, NY: McGraw-Hill; 2005:7.

2. **Peak plasma drug concentration** (C_{max}). The plasma drug concentration at T_{max} relates to the intensity of the pharmacological response. Ideally, C_{max} should be within the therapeutic window.
3. **Area under the plasma drug concentration versus time curve** (AUC) relates to the amount or extent of drug absorption. The amount of systemic drug absorption is directly related to the AUC. The AUC is usually calculated by the **trapezoidal rule** and is expressed in units of concentration multiplied by time (e.g., μg/mL × hr).

C. Urinary drug excretion. Measurement of urinary drug excretion can determine bioavailability from a drug product. This method is most accurate if the active therapeutic moiety is excreted unchanged in significant quantity in the urine (*Figure 6-3*).

1. **The cumulative amount of active drug excreted in the urine** $\left(D_U^{\infty}\right)$ is directly related to the extent of systemic drug absorption.
2. **The rate of drug excretion in the urine** (dD_U/dt) is directly related to the rate of systemic drug absorption.
3. **The time for the drug to be completely excreted** (t^{∞}) corresponds to the total time for the drug to be systemically absorbed and completely excreted after administration.

D. Comparative clinical trials to a drug can be used to measure bioavailability quantitatively. Clinical studies are highly variable and less precise than other methods because of individual differences in drug pharmacodynamics and subjective measurements.

E. In vitro measurements of bioequivalence. Bioequivalence may sometimes be demonstrated using an in vitro bioequivalence standard, especially when such an in vitro test has been correlated with human in vivo bioavailability data. For example, the rate of drug dissolution in vitro for certain drug products correlates with drug bioavailability in vivo. If the dissolution test in vitro is considered statistically adequate to predict drug bioavailability, then, in some cases, dissolution may be used in place of an in vivo bioavailability study. This relationship between in vitro dissolution and in vivo bioavailability is also known as in vitro–in vivo correlation (IVIVC).

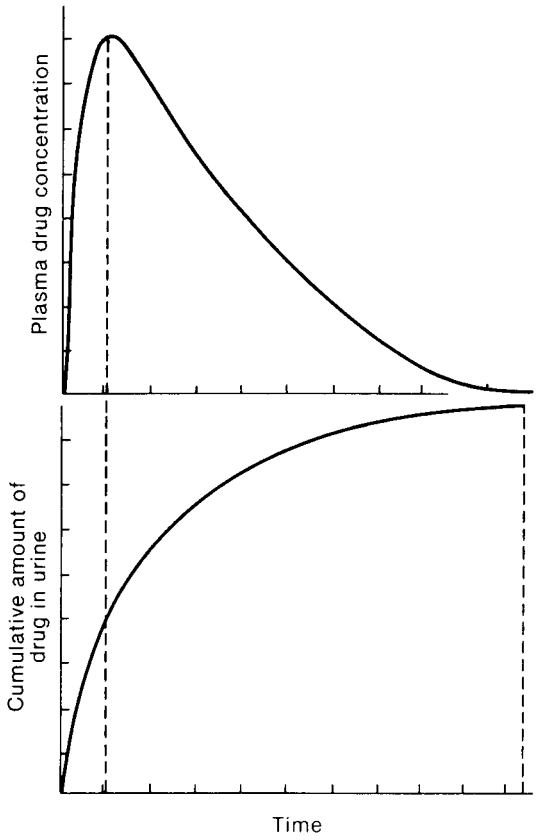


Figure 6-3. These corresponding plots show the relationship of the plasma drug concentration versus time curve to the cumulative amount of drug in the urine versus time curve. Adapted with permission from Shargel L, Wu-Pong S, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics.* 5th ed. New York, NY: McGraw-Hill; 2005:463.

IV. RELATIVE AND ABSOLUTE BIOAVAILABILITY

A. Relative bioavailability (RBA) is the systemic availability of the drug from a dosage form as compared to a reference standard given by the same route of administration. Relative bioavailability is calculated as the ratio of the AUC for the dosage form to the AUC for the reference dosage form given in the same dose. A relative bioavailability of 1 (or 100%) implies that drug bioavailability from both dosage forms is the same but does not indicate the completeness of systemic drug absorption. The determination of relative bioavailability is important in generic drug studies (e.g., bioequivalence studies). Bioequivalence is a relative bioavailability study.

$$RBA = \frac{[AUC]_{0\,oralTEST}^{\infty} / Dose_{oralTEST}}{[AUC]_{0\,REF.}^{\infty} / Dose_{REF.}}$$

B. Absolute bioavailability (F) is the fraction of drug systemically absorbed from the dosage form. F is calculated as the ratio of the AUC for the dosage form given orally to the AUC obtained after intravenous (IV) drug administration (adjusted for dose). A parenteral drug solution given by IV administration is considered to have 100% systemic absorption (i.e., $F = 1$). An F value of 0.80 (or 80%) indicates that only 80% of the drug was systemically available from the oral dosage form.

$$F = \frac{[AUC]_{0\,oral}^{\infty} / Dose_{oral}}{[AUC]_{0\,i.v.}^{\infty} / Dose_{i.v.}}$$

V. BIOEQUIVALENCE STUDIES FOR SOLID ORAL DRUG PRODUCTS

A. Objective of bioequivalence studies. The objective of a bioequivalence study is to measure and compare formulation performance between two or more pharmaceutically equivalent drug products.

B. Design of bioequivalence studies

1. The FDA's Division of Bioequivalence, Office of Generic Drugs provides guidance for the performance of in vitro dissolution and in vivo bioequivalence studies. These guidances are available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
2. **Fasting study**. Bioequivalence studies are usually evaluated by a single-dose, two-period, two-treatment, two-sequence, open-label, randomized crossover design, comparing equal doses of the test (generic) and reference (brand) products in fasted, adult, healthy subjects.
   - **a.** Both men and women may be used in the study.
   - **b.** Blood sampling is performed just before the dose (zero time) and at appropriate intervals after the dose to obtain an adequate description of the plasma drug concentration versus time profile.
3. **Food intervention study**. If the bioavailability of the active drug ingredient is known to be affected by food, the generic drug manufacturer must include a single-dose, randomized, crossover, food effects study comparing equal doses of the test product and reference products given immediately after a standard high-fat–content breakfast.
4. **Other study designs**. Crossover studies may not be practical in drugs with a long half-life in the body, and a parallel study design may be used instead. Alternate study methods, such as in vitro studies or equivalence studies with clinical or pharmacodynamic end points, are used for drug products where plasma concentrations are not useful to determine delivery of the drug substance to the site of activity (such as inhalers, nasal sprays, and topical products applied to the skin).
5. **Waiver of an in vivo bioequivalence study (biowaiver)**
   - **a.** A comparative in vitro dissolution (drug-release) study between the test and the reference products may be used in lieu of an in vivo bioequivalence study for some immediate-release (conventional) oral drug products.
   - **b.** No bioequivalence study is required for certain drug products given as a solution such as oral, parenteral, ophthalmic, or other solutions because bioequivalence is self-evident. In this case, the drug is in a pure aqueous solution, and there is no drug dissolution rate consideration.
   - **c.** Immediate-release (IR) solid oral drug products that meet biopharmaceutics classification system (BCS) class 1 drugs—that is, highly water soluble, rapidly dissolving, and rapid permeation of cellular membranes—may obtain a biowaiver.

d. Drug products containing a lower dose strength (e.g., 200 mg, 100 mg, and 50 mg IR tablets). The drug product must be in the same dosage form, lower strength, and is proportionately similar in its active and inactive ingredients.

C. Pharmacokinetic evaluation of the data. Pharmacokinetic analysis includes calculation for each subject of the AUC to the last quantifiable concentration (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$), T_{max}, and C_{max}. In addition, the elimination rate constant (k), the elimination half-life ($t_{½}$), and other parameters may be estimated.

D. Statistical evaluation of the data

1. The statistical methodology for analyzing bioequivalence studies is called the *two one-sided test procedures*. Two situations are tested with this statistical methodology.

a. The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference), is significantly less bioavailable.

b. The second of the two one-sided tests determines whether a brand-name product (reference), when substituted for a generic product (test), is significantly less bioavailable.

c. Based on the opinions of FDA medical experts, a difference of $>$ 20% for each of the aforementioned tests was determined to be significant and, therefore, undesirable for all drug products.

2. An analysis of variance (ANOVA) should be performed on the log transformed AUC and C_{max} values obtained from each subject. The 90% confidence intervals for both pharmacokinetic parameters, AUC and C_{max}, must be entirely within the 80% to 125% boundaries based on log transformation of the data. The ratio of the means of the study data (test to reference) should lie in the center of the 90% confidence interval, or close to 100% (equivalent to a test to reference ratio of 1) (*Table 6-1*).

3. Different statistical criteria are sometimes used when bioequivalence is demonstrated through comparative clinical trials, pharmacodynamic studies, or comparative in vitro methodology.

4. The bioequivalence methodology and criteria described earlier simultaneously control for both differences in the average response between test and reference products as well as the precision with which the average response in the population is estimated. This precision depends on the within-subject (normal volunteer or patient) variability in the pharmacokinetic parameters (AUC and C_{max}) of the two products and on the number of subjects in the study. The width of the 90% confidence interval is a reflection in part of the within-subject variability of the test and reference products in the bioequivalence study.

VI. BIOEQUIVALENCE ISSUES

A. Problems in determining bioequivalence include lack of an adequate study design; inability to accurately measure the drug analytes, including metabolites and enantiomers (chiral drugs); and lack of systemic drug absorption (*Table 6-2*).

B. Bioequivalence studies for which objective blood drug concentrations cannot be obtained require either a pharmacodynamic study, a clinical trial, or an in vitro study that has been correlated with human in vivo bioavailability data.

1. Pharmacodynamic measurements are more difficult to obtain, and the data tend to be variable, requiring a larger number of subjects compared to the bioequivalence studies for systemically absorbed drugs.

a. A bioequivalence study using pharmacodynamic measurements tries to obtain a pharmacodynamic effect versus time profile for the drug in each subject.

b. The area under the effect versus time profile, peak effect, and time for peak effect are obtained for the test and reference products and are then statistically analyzed.

2. Comparative clinical trials are more difficult to run, do not have easily quantifiable observations, and are quite costly.

3. In vitro studies may require the development of a reliable surrogate marker that may be correlated with human in vivo bioavailability data. Examples include the following:

a. Comparative in vitro drug release/dissolution studies in which the dissolution profile of the test and reference drug products under different conditions of pH and media are performed.

b. Comparison of binding of bile acids to cholestyramine (Questran®) and the test product.

Table 6-1 BIOAVAILABILITY COMPARISON OF A GENERIC (TEST) AND BRAND (REFERENCE) DRUG PRODUCT

LN-Transformed Data								
		Geometric Mean			90% Confidence Interval			
PK Variable	Units	Test	Reference	% Ratio T/R	(Lower Limit, Upper Limit)	*P* Values for Product Effects	Power of ANOVA	ANOVA % CV
C_{max}	ng/mL	344.79	356.81	96.6	(89.5, 112)	.3586	0.8791	17.90%
AUC_{0-t}	ng hr/mL	2659.12	2674.92	99.4	(95.1, 104)	.8172	1.0000	12.60%
AUC_{inf}	ng hr/mL	2708.63	2718.52	99.6	(95.4, 103)	.8865	1.0000	12.20%
T_{max}	hr	4.29	4.24	101				
k_{elim}	1/hr	0.0961	0.0980	98.1				
$t_{½}$	hr	8.47	8.33	101.7				

AUC, area under the curve; C_{max}, peak plasma drug concentration; T_{max}, time for peak plasma drug concentration.
The results were obtained from a two-way crossover, single-dose, fasting study in 36 healthy adult volunteers. Mean values are reported. No statistical differences were observed between AUC and C_{max} values for the test and reference products.

Table 6-2 PROBLEM ISSUES IN THE DETERMINATION OF BIOEQUIVALENCE

Problem Issues	Example
Drugs with highly variable bioavailability[a]	Propranolol, verapamil
Drugs with active metabolites	Selegiline
Chiral drugs	Ibuprofen, albuterol
Drugs with nonlinear pharmacokinetics	Phenytoin
Orally administered drugs that are not systemically absorbed	Cholestyramine resin, sucralfate
Drugs with long elimination half-lives	Probucol
Variable-dosage forms	Dyazide, conjugated estrogens
Nonoral drug delivery	
Topical drugs	Steroids, antifungals
Transdermal delivery systems	Estrogen patch
Drugs given by inhalation aerosols	Bronchodilators, steroids
Intranasal drugs	Intranasal steroids
Biotechnology-derived drugs	Erythropoietin, interferon
Bioavailable drugs that should not reach peak drug levels	Potassium supplements, hormone replacement therapy
Target population used in the bioequivalence studies	Pediatric patients; renal disease

[a]These drugs have high intrasubject variability.

VII. DRUG PRODUCTION SELECTION

A. Generic drug substitution

1. **Generic drug substitution** is the process of dispensing a generic drug product in place of the prescribed drug product (e.g., generic product for brand-name product, generic product for another generic product, brand-name product for generic product). The substituted product must be a therapeutic equivalent to the prescribed product.
2. Generic drug products that are classified as therapeutic equivalents by the FDA are expected to produce the same clinical effect and safety profile as the prescribed drug.

B. Therapeutic substitution

1. Therapeutic substitution is the process of dispensing a therapeutic alternative in place of the prescribed drug product. For example, amoxicillin is dispensed for ampicillin.
2. The substituted drug product is usually in the same therapeutic class (e.g., calcium channel blocker) and is expected to have a similar clinical profile.

C. Formulary issues

1. A **formulary** is a list of drugs. A **positive** formulary lists all the drugs that may be substituted, whereas a **negative** formulary lists drugs for which the pharmacist may not substitute. A **restrictive** formulary lists only those drugs that may be reimbursed without justification by the prescriber; for drugs not listed in the restrictive formulary, the prescriber must justify the need for the nonlisted drug.
2. Many states have legal requirements that address the issue of drug product selection. States may provide information and guidance in drug product selection through positive, negative, or restrictive formularies.
3. The FDA annually publishes *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*). This publication is also reproduced in the *United States Pharmacopeia* (*USP*), DI Vol. III, *Approved Drug Products and Legal Requirements*, published annually by the *USP* Convention. The *Electronic Orange Book* may be found at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
   a. The *Orange Book* provides therapeutic evaluation codes for drug products (*Table 6-3*).
      (1) "A-rated" drug products are drug products that contain active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems or drug quality standards issues. However, all oral dosage forms must meet an appropriate in vitro bioequivalence standard that is acceptable to the FDA to be approved as therapeutically equivalent and may be interchanged.

Table 6-3 THERAPEUTIC EQUIVALENCE EVALUATION CODES

A Codes	Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products
AA	Products in conventional dosage forms not presenting bioequivalence problems
AB	Products meeting bioequivalence requirements
AN	Solutions and powders for aerosolization
AO	Injectable oil solutions
AP	Injectable aqueous solutions
AT	Topical products
B Codes	**Drug products that the FDA does not at this time consider to be therapeutically equivalent to other pharmaceutically equivalent products**
BC	Extended-release tablets, extended-release capsules, and extended-release injectables
BD	Active ingredients and dosage forms with documented bioequivalence problems
BE	Delayed-release oral dosage forms
BN	Products in aerosol-nebulizer drug delivery systems
BP	Active ingredients and dosage forms with potential bioequivalence problems
BR	Suppositories or enemas for systemic use
BS	Products with drug standard deficiencies
BT	Topical products with bioequivalence issues
BX	Insufficient data

FDA, U.S. Food and Drug Administration.

(2) "B-rated" drug products are drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. These products often have specific dosage form problems rather than a problem with the active ingredients (e.g., two different nicotine patches). "B-rated" drug products are not considered therapeutically equivalent to other pharmaceutically equivalent products and are not interchangeable.

(3) Certain products present special situations that deserve a more complete explanation than can be provided by the two codes used in the *Orange Book*. These drugs have particular problems with standards of identity, analytical methodology, or bioequivalence that are considered individually. For these drugs, consult the *Orange Book*.

(4) FDA may approve drug products containing the same active drug from different pharmaceutical manufacturers under a separate NDA for their own product. The two branded drug products such as Adalat® and Procardia® brands of nifedipine are not bioequivalent to each other. In this case, the practitioner/user must decide which products are bioequivalent and therapeutic equivalent (*Table 6-4*).

b. For some drug products, bioequivalence has not been established or no generic product is currently available.

4. Various hospitals, institutions, insurance plans, health maintenance organizations (HMOs), and other third-party plans may have a formulary that provides guidance for drug product substitution.

D. Generic biologics (biosimilar drug products)

1. *Biologics*, or biotechnology-derived drugs, in contrast to drugs that are chemically synthesized, are derived from living sources such as human, animal, or microorganisms.

2. Many biologics are complex mixtures that are not easily identified or characterized and are manufactured using biotechnology or are purified from natural sources.

3. Other biological drugs, such as insulin and growth hormone, are proteins derived by biotechnology and have been well characterized.

4. Due to the Affordable Care Act (2010), FDA has issued guidances on drug product development regarding biotechnology-derived drug products, sometimes referred to as *generic biologics*, *biosimilar* drug products, or "follow-on" proteins.

Table 6-4 THERAPEUTIC EVALUATION CODES FOR NIFEDIPINE EXTENDED RELEASE TABLETS

TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Propietary Name	Applicant
AB1	*Yes*	Nifedipine tablet	Extended release; oral	90 mg	Adalat CC	Bayer HealthCare Pharmaceuticals
AB1	No	Nifedipine tablet	Extended release; oral	90 mg	Nifedipine	Biovail
BX	No	Nifedipine tablet	Extended release; oral	90 mg	Nifedipine	Martec USA LLC
AB2	*Yes*	Nifedipine tablet	Extended release; oral	90 mg	Procardia XL	Pfizer
AB2	No	Nifedipine tablet	Extended release; oral	90 mg	Nifedipine	Osmotica Pharmaceutical

In Table 6-4, AB1 products are bioequivalent to each other and can be substituted. AB2 products are bioequivalent to each other and can be substituted. However, an AB1 product cannot be substituted for an AB2 product. The BX product should not be used.

Study Questions

Directions for questions 1–3: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by one of the suggested answers or phrases. Choose the best answer.

1. The parameters used to describe bioavailability are

(A) C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.
(B) C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and T_{max}.
(C) C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{½}$.
(D) C_{max} and AUC_{0-t}.
(E) C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, and $t_{½}$.

2. To determine the absolute bioavailability of a drug given as an oral extended-release tablet, the bioavailability of the drug must be compared to the bioavailability of the drug from

(A) an immediate-release oral tablet containing the same amount of active ingredient.
(B) an oral solution of the drug in the same dose.
(C) a parenteral solution of the drug given by intravenous (IV) bolus or IV infusion.
(D) a reference (brand) extended-release tablet that is a pharmaceutical equivalent.
(E) an immediate-release hard gelatin capsule containing the same amount of active drug and lactose.

3. A single-dose, two-way crossover, fasting, comparative bioavailability study was performed in 24 healthy, adult male subjects. Plasma drug concentrations were obtained for each subject, and the results shown in *Table 6-Q3* were obtained. The relative bioavailability of the drug from the generic tablet compared to the reference tablet is

(A) 82.3%.
(B) 69.8%.
(C) 91.7%.
(D) 96.2%.
(E) 103.9%.

Table 6-Q3

Drug Product	Dose (mg)	C_{max} (μg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (μghr/mL)
IV bolus injection	100			1714
Oral solution	200	21.3	1.2	3143
Generic tablet	200	17.0	2.1	2822
Reference tablet	200	16.5	1.9	2715

IV, intravenous.

Directions for questions 4–6: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, A–E.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I**, **II**, **and III** are correct

4. For two drug products, generic (test) and brand (reference), to be considered bioequivalent,

I. there should be no statistical difference between the extent of bioavailability of the drug from the test product compared to the reference product.
II. the 90% confidence interval about the ratio of the means of the C_{max} and AUC values for the test product to reference product must be within 80% to 125% of the reference product.
III. there should be no statistical differences between the mean C_{max} and AUC values for the test product compared to the reference product.

5. For which of the following products is measuring plasma drug concentrations not appropriate for estimating bioequivalence?

I. metered-dose inhaler containing a bronchodilator
II. antifungal agent for the treatment of a vaginal infection
III. enteric-coated tablet containing a nonsteroidal anti-inflammatory agent

6. Bioequivalence studies compare the bioavailability

I. of the generic drug product to the brand drug product.
II. of a reformulated brand drug product to the original formulation of the brand product.
III. of a to-be-marketed brand product to the drug product used in the clinical trials.

Answers and Explanations

1. The answer is B *[see III.B]***.**
AUC relates to the extent of drug absorption. C_{max} and T_{max} relate to the rate of drug absorption. The elimination $t_{½}$ of the drug is usually independent of the route of drug administration and is not used as a measure of bioavailability. For the FDA, only the C_{max} and AUC parameters must meet 90% confidence intervals of 80% to 125% of the reference (brand) product (*Table 6-1*).

2. The answer is C *[see IV.B]***.**
After an IV bolus injection or IV infusion, the entire dose is absorbed into the body. The ratio of the AUC of the drug given orally to the AUC of the drug given by IV injection is used to obtain the absolute bioavailability (F) of the drug.

3. The answer is E *[see IV.A]***.**
The relative bioavailability is determined from the ratio of the AUC of the generic (test) product to the AUC of the reference standard. Thus, the relative bioavailability can exceed 100%, whereas the absolute bioavailability cannot exceed 100%. $AUC_{generic}/AUC_{reference} = 2822/2715 = 1.039$ or 103.9%.

4. The answer is E (I, II, III) *[see V.C]***.**
Although T_{max} is an indication of rate of drug absorption, it is a discrete measurement and usually too variable to use for statistical comparisons in bioequivalence studies. Statistical comparisons use AUC and C_{max} values from test and reference drug products as the basis of bioequivalence.

5. The answer is C (I, II) *[see V.A]***.**
Although some systemic absorption may be demonstrated after administering a metered dose inhaler containing a bronchodilator or a vaginal antifungal agent, bioequivalence can be determined only by using a clinical response measurement.

6. The answer is E (I, II, III) *[see I.A–E]***.**
Bioequivalence studies compare the bioavailability of a drug from one drug product to another drug product containing the same active ingredient. Drug products such as capsules that are used in clinical trials should be bioequivalent to the marketed drug product, which may be a tablet. Generic drug products and the corresponding brand drug product must be bioequivalent. For any change in a formulation, the manufacturer (brand or generic) must demonstrate that the formulation change does not affect the bioavailability compared to the original product.

7 Biotechnology Drug Products

SUSANNA WU-PONG

I. INTRODUCTION.

Pharmaceutical biotechnology has enabled the creation, modification, and manufacture of recombinant biological products for therapeutic use. Cell lines, recombinant DNA, and highly sensitive and specific analytical methods are now routinely used to design, discover, and evaluate highly specific new drugs, imaging agents, and diagnostics.

A. Currently available biological drugs primarily fall into two categories: nucleic acid or protein/peptide drugs.

1. **Nucleic acid drugs.** Macromolecular nucleic acid drugs include oligonucleotides and other compounds still in clinical trials, such as gene therapy or microRNAs.
2. **Protein drugs.** Protein and peptide drugs include **monoclonal antibodies** (mAbs) and recombinant proteins. mAbs are also used as imaging and targeting agents.

B. Biological drugs are manufactured usually using engineered cells or recombinant methods in vitro, although smaller molecules may be chemically synthesized. Such cell- and gene-based methods are distinctly different from chemical synthetic techniques used to manufacture most small-molecule drugs; the manufacturing process and materials used for biologic products are intricately linked to the quality and properties of the product, even when identical gene sequences are being expressed. Several examples of differences in adverse reactions have been reported for the same recombinant proteins (erythropoietin, interferon-β1a, and botulism A toxin) made by different manufacturers or using slightly different processes or materials.

C. Recombinant DNA techniques are used to design and produce protein drugs and many of the emerging nucleic acid drugs. Therefore, these biologic products can be engineered to a specific sequence and/or structure.

D. Biologic drugs are biological products, so they have unique challenges in the areas of stability, delivery, formulation, and analysis. Protein drugs and products are dependent on having correct protein structure for activity and are often active in very low concentrations. Thus, formulation, storage, and analysis must be able to differentiate, preserve, and measure the active protein in low concentrations.

E. Most biologic products should be refrigerated at 2° to 8°C and should not be frozen, shaken, or exposed to light. Products must be used within a specified time after dilution. Specific product information should always be consulted before storage or use.

II. BASIC TERMINOLOGY

A. An **antigen** is a substance or molecule that stimulates the production of antibodies by the immune system.

B. An **antibody** is an immunoglobulin molecule that is produced by the immune system after stimulation from an antigen. The plasma contains a mixture of antibodies synthesized to bind many different antigens (**polyclonal** antibodies). **Monoclonal antibodies** are produced in vitro and consist of copies of a single antibody that binds a single epitope. Antibodies are part of the body's immune system, which identifies and neutralizes foreign molecules.

C. **Antisense** refers to synthetic and chemically modified DNA or RNA molecules designed to bind and inhibit complementary, or sense, RNA molecules.
D. **Colony-stimulating factors** (**CSFs**) are glycoproteins that regulate the differentiation and proliferation of hematopoietic stem cells into white cells.
E. **Cytokines** are a group of secreted proteins that cause a signaling response to influence cell function in other cells (also see **hormones** in later discussions).
F. **DNA** (deoxyribonucleic acid) is a double-helix, nucleic acid polymer coding genetic information of a cell. DNA consists of four deoxynucleotide subunits: adenosine, guanosine, cytidine, and thymidine.
G. An **enzyme** is a molecule, usually a protein, that catalyzes the conversion of a substrate to a product.
H. An **epitope** is the portion of an antigen that is recognized by an antibody in immune system.
I. A **gene** is a unit of heredity composed of a segment of DNA that is transcribed into RNA.
J. A **genome** is all of the genetic information in a cell or organism.
K. A **glycoprotein** is a protein molecule conjugated to a carbohydrate group.
L. Similar to cytokines, a **hormone** is an endogenous substance that is secreted by one type of cell and causes a response in another type of cell. The current distinction between a hormone and a cytokine may only be their active concentration ranges (10^{-9} M for hormones, 10^{-12} M for cytokines).
M. To **humanize** refers to genetically engineering a protein to modify the sequences that express nonhuman epitopes to be more similar to human variants.
N. A **hybridoma** is a hybrid cell designed to secrete a single antibody (Ab) that binds only one epitope (i.e., an mAb) and produced by fusing a myeloma cell and an antibody-producing B lymphocyte.
O. **Interferons** (**IFNs**) are glycoproteins produced by animal cells used to stimulate the immune response to viral or bacterial infection.
P. **Interleukins** (**ILs**) are cytokines released by white cells and other cell types in response to antigen and other stimulation whose function is primarily to regulate the immune system.
Q. A **lymphokine** is a cytokine produced by a lymphocyte. ILs 2-6 and TNF-γ are examples of lymphokines.
R. An **oligonucleotide** is a short, usually single-stranded DNA or RNA molecule used to identify or inhibit a protein or mRNA molecule.
S. **Pegylated** refers to containing a conjugate of **polyethylene glycol** (PEG). PEG conjugation reduces glomerular filtration so it is often used to extend the half-life of drugs cleared by renal excretion.
T. **Polymorphism** refers to natural sequence variants of a gene.
U. A **plasmid** is a circular piece of nonchromosomal DNA that can replicate independently. Plasmids are used as vectors for the transfer and expression of rDNA.
V. **RNA** (ribonucleic acid) is a polymeric macromolecule made of ribonucleotide subunits that is used for gene regulation. RNA exists in cells as ribosomal (rRNA), transfer (tRNA), microRNA (miRNA), and messenger (mRNA). RNA also comprises the genetic material of some viruses (known as **retroviruses**).
W. **Recombinant DNA** (**rDNA**) are hybrid DNA molecules formed when DNA fragments from different sequences are joined using restriction endonucleases.
X. A **restriction endonuclease** is an enzyme that cleaves DNA in a sequence-specific manner. Restriction enzymes are used in rDNA technology.
Y. **Reverse transcriptase** is an enzyme used by RNA viruses to transcribe viral RNA into DNA.
Z. **Tumor necrosis factor** (**TNF**) is a lymphokine produced by macrophages to induce cell death.

III. PROTEINS AND PEPTIDES

A. **Native proteins.** Proteins and peptides are essential for cell structure and function. These amino acid polymers generally require maintenance of their primary structure as well as secondary, tertiary, and quarternary structures to retain their function and activity. In addition, posttranslational modifications such as glycosylation may be necessary for activity or in vivo properties.
B. **Protein drugs.** Recombinant proteins have become the fastest growing class of pharmaceuticals and have quickly replaced many animal sources for therapeutic agents, such as bovine insulin. Recombinant proteins such as **recombinant human insulin** are used to supplement or replace proteins that are inactive or expressed in insufficient quantity in the body. Some proteins may be naturally expressed in the body, but also given pharmacologically in therapeutic doses to elicit a desired

therapeutic effect, such as **thrombolysis**. Clinicians should understand recombinant proteins' unique properties and requirements for storage, use, and administration because—as biological molecules—they are large, complex, and unstable compared to traditional small-molecule drugs.

IV. IMMUNOGLOBULIN (Ig) AND mAbs

A. Overview

1. Immunoglobulins are glycoprotein antibodies, an important component of the immune system. Polyclonal serum IgGs have been used for many years to provide passive immunity to patients. In contrast, mAbs have more recently been developed to provide purified antibodies that bind a single epitope on an antigen. These mAbs are usually derived from mouse hybridoma cells and, therefore, are proteins of mouse origin, although human mAbs are now made from hybridomas from transgenic mice.
2. mAbs have primarily been developed to **target** cancer cells and for autoimmune diseases such as **rheumatoid arthritis**. mAbs act as antagonists (such as TNF-α blockers) by binding to antigen and/or by binding to cell surface markers on target cells and inducing cell death by **antibody-dependent**, **cell-mediated cytotoxicity** and **complement-dependent cytotoxicity**. Most of the mAb products may have severe side effects. See *Table 7-1* for a list of black box warnings.
3. Because the original mAbs were of mouse origin and therefore immunogenic, newer generation mAbs are genetically engineered to modify the mouse regions to appear more "**humanized**." mAb nomenclature indicates "-umab" as human (produced using transgenic technology), "-ximab" as chimeric, and "-zumab" as humanized (*Table 7-1*).

B. Examples

1. **Abciximab** (ReoPro®) is a chimeric human-murine monoclonal antibody Fab fragment that inhibits platelet aggregation by binding platelet glycoprotein IIb–IIIa receptors. Abciximab is used for **myocardial infarction**, **ischemia**, and **angina**. The recommended dosage for myocardial infarction is a 0.25 mg/kg IV bolus over 5 mins, then 0.125 mcg/kg/min (maximum of 10 mcg/min) for 12 hrs with fibrinolytic treatment. Platelet aggregation is almost completely inhibited 2 hrs after the initiation of abciximab therapy. The major complication of abciximab infusion is dose-related bleeding.
2. **Adalimumab** (Humira®) is a human mAb that binds TNF-α and in the presence of complement lyses cells that express surface TNF-α. Adalimumab is used to treat **autoimmune disorders**, such as **Crohn's disease**, **psoriatic arthritis**, and moderate-to-severe **rheumatoid arthritis**. The maintenance dose is 40 mg SQ every other week but begins with a 160-mg taper in Crohn's disease. Humira® has a black box warning for increased infections and possibly cancer in children, adolescent, and young adult male patients. Patients should report signs of infection, persistent fevers, night sweats, or weight loss.
3. **Alemtuzumab** (Campath-1®) is used for **immunosuppression** in organ transplant by targeting CD52 on T cells and monocytes. Campath-1® is also used to treat chronic **lymphocytic leukemia** and **T-cell prolymphocytic leukemia** where it is dosed 3 g daily as 2-hrs IV infusions, then increased to 30 mg three times per week when tolerated. Serious, even fatal, cytopenias and infections can result from using this drug.
4. **Muromonab-CD3** (Orthoclone-OKT3®) is an immunosuppressive mAb targeted to the CD3 glycoprotein on human T cells. Lymphocytes containing CD3, CD4, CD8, and CD11 levels fall quickly after administration, and after 2 to 7 days, lymphocytes containing CD4, CD8, and CD11 return to circulation. Muromonab-CD3 is used to reverse **acute renal allograft rejection**. Severe side effects have been reported including anaphylaxis, pulmonary edema, shock, cardiac arrest, seizures, and coma. Patients should be premedicated with methylprednisolone to minimize symptoms of cytokine release syndrome. CD3 positive cells and muromonab-CD3 levels ($\leq$ 800 ng/mL) should be monitored during therapy.
5. **Bevacizumab** (Avastin®) is a humanized mAb that binds **VEGF** (vascular endothelial growth factor), thus inhibiting **angiogenesis** in metastatic tissue. Bevacizumab is used to treat **metastatic colorectal cancer** and **nonsquamous**, **non-small cell lung cancer**; **HER-2 negative breast cancer**; **progressive glioblastoma**; and **metastatic renal cell cancer**. Unlabeled uses include **age-related macular degeneration**, **recurrent ovarian and cervical cancer**, and **soft tissue sarcomas**. Doses range from 5 to 15 mg/kg IV every 2 to 3 weeks.

Table 7-1 THERAPEUTIC mAbs

Antibody	Brand Name	Type	Target	Warnings	Indication
Abciximab	ReoPro®	Chimeric	Glycoprotein IIb/IIIa	—	Cardiovascular disease
Adalimumab	Humira®	Human	TNF-α	Risk for fatal infections, malignancies especially in children, adolescents, and young adult males	Autoimmune disorders
Alefacept	Amevive®		CD2	—	Psoriasis
Alemtuzumab	Campath®	Humanized	CD52	Risk for hematologic toxicity, infection, infusion reactions	Chronic lymphocytic leukemia
Basiliximab	Simulect®	Chimeric	IL-2Rα receptor (CD25)	Should be administered by transplant physician	Transplant rejection
Bevacizumab	Avastin®	Humanized	VEGF	Risk for GI perforation, hemorrhage, wound-healing complications	Colorectal cancer
Cetuximab	Erbitux®	Chimeric	EGF receptor	Risk for cardiopulmonary arrest in patients also receiving radiation therapy, infusion reactions	Colorectal cancer, head and neck cancer
Certolizumab pegol	Cimzia®	Pegylated humanized	TNF-α	Risk for T-cell lymphoma, infection risk, evaluate for tuberculosis	Crohn's disease
Daclizumab	Zenapax®	Chimeric humanized	IL-2Rα receptor (CD25)	Should be administered by transplant physician	Transplant rejection
Eculizumab	Soliris®	Humanized	Complement system protein C5	Risk for meningococcal infection	Paroxysmal nocturnal hemoglobinuria
Gemtuzumab ozogamicin	Mylotarg®	Humanized	CD33	—	Acute myeloid and promyelocytic leukemia
Ibritumomab tiuxetan	Zevalin®	Murine (with ^{90}Y or ^{111}In)	CD20	Risk for cutaneous and mucocutaneous reactions, cytopenia, infusion reaction	Non-Hodgkin lymphoma
Infliximab	Remicade®	Chimeric	TNF-α	Risk for fatal infections, malignancies especially in children, adolescents, and young adult males	Autoimmune disorders
Muromonab-CD3	Orthoclone OKT3®	Murine	T-cell CD3 receptor	Risk for anaphylaxis, should be administered by transplant physician	Transplant rejection
Natalizumab	Tysabri®	Humanized	α4-Integrin	Risk for progressive multifocal leukoencephalopathy (PML)	Multiple sclerosis and Crohn's disease
Omalizumab	Xolair®	Humanized	IgE on mast cells and basophils	Risk for anaphylaxis	Allergic asthma
Palivizumab	Synagis®	Humanized	RSV	—	Respiratory syncytial virus
Panitumumab	Vectibix®	Human	EGF receptor	Risk for dermatologic toxicity (90% of patients), infusion reaction	Refractory metastatic colorectal cancer
Ranibizumab	Lucentis®	Humanized	VEGF-A	—	Macular degeneration
Rituximab	Rituxan® MabThera®	Chimeric	CD20	Risk for infusion reactions, mucocutaneous reactions, PML	Chronic lymphocytic leukemia
Tositumomab and ^{131}I tositumomab	Bexxar®	Murine	CD20	Radioisotope; risk for anaphylaxis, bone marrow suppression, and fetal toxicity	Non-Hodgkin lymphoma
Trastuzumab	Herceptin®	Humanized	Human EGFR	Risk for cardiotoxicity, pulmonary toxicity, infusion reactions, and fetal toxicity	HER-2 positive breast cancer and gastric adenocarcinoma

TNF, tumor necrosis factor; *IL*, interleukin; *GI*, gastrointestinal; *Ig*, immunoglobulin; *VEGF*, vascular endothelial growth factor; *EGF*, epidermal growth factor; *EGFR*, epidermal growth factor receptor; *RSV*, respiratory syncytial virus.

6. **Infliximab** (Remicade®) is a chimeric mAb that binds and inhibits TNF-α. Infliximab is used to treat Crohn's disease and has an onset of action of about 2 weeks and elimination half-life of 7 to 12 days. The drug is infused over 2 or more hrs at 3 to 5 mg/kg starting at 0, 2, and 6 weeks, then every 8 weeks thereafter. The drug is also used to treat other autoimmune diseases such as rheumatoid arthritis.
7. **Rituximab** (Rituxan®) is an mAb targeted to the CD20 major histocompatibility protein on B lymphocytes. It is used to treat cancers such as **CD20-positive non-Hodgkin lymphoma** and also **rheumatoid arthritis**. The elimination half-life is 18 to 78 days depending on the disease and the patient.

V. CYTOKINE IMMUNOMODULATORS

A. Overview

1. Cytokine immunomodulators include **colony-stimulating factors**, **interleukins**, **interferons**, **chemokines**, and **thymic hormones**.
2. CSFs are **glycoprotein** cytokines that regulate the production, differentiation, and activation of hematopoietic cells in the body. These include **macrophages**, **megakaryocytes**, **eosinophils**, **neutrophils**, **basophils**, and **platelets**. **Erythropoietin** stimulates red cell production and is in the CSF class. Natural and modified CSFs are used to treat several **congenital disorders** and several forms of cancer.
3. **Interleukins** are proteins secreted by leukocytes that mediate communication between leukocytes. IL actions are similar to TNF but without the ability to produce septic shock symptoms.
4. **Interferons** are secreted in response to infection. In combination with other cytokines, IFNs participate in the immune response to infection. IFN-α and IFN-β are produced by leukocytes and fibroblasts and act in the antiviral immune response, whereas IFN-γ is secreted by T lymphocytes to stimulate macrophages and innate immunity.
5. **Tumor necrosis factor** is secreted in response to bacterial lipopolysaccharide and then recruits neutrophils and monocytes to the site of infection. TNF also mediates the symptoms of **septic shock**, characterized by intravascular collapse and disseminated intravascular coagulation.

B. Examples

1. **Darbepoetin alfa** (Aranesp®) and **epoetin alfa** (Epogen® and Procrit®) are recombinant human erythropoietin used for the treatment of **anemia** associated with **chronic renal failure** (darbepoetin or epoetin) or HIV (epoetin). Erythropoiesis-stimulating agents should be used as hemoglobin falls below 10 g/dL. Some recombinant human erythropoietin's in vivo properties are product dependent. Darbepoetin's half-life (21 hrs) is approximately three times longer than epoetin (4 to 13 hrs) when administered IV.
2. **Filgrastim** (Neupogen®) is recombinant hG-CSF (human granulocyte colony-stimulating factor) used for severe, chronic **neutropenia,** neutropenia associated with chemotherapy and for **bone marrow transplant**. hG-CSF and filgrastim both promote the proliferation, differentiation, maturation, and activation of neutrophils. Onset of action is within 24 hrs, levels return to baseline within 4 days. **Pegfilgrastim** (Neulasta®) is **pegylated** filgrastim with a half-life of 15 to 80 hrs compared to 3.5 hrs for the unpegylated filgrastim.
3. **Aldesleukin** (Proleukin®), a lymphokine, is a human recombinant IL-2 product that is used to treat **metastatic renal cell carcinoma** and **metastatic melanoma**. The starting dose is 600,000 IU/kg every 8 hrs by a 15-mins intravenous infusion for no more than 14 doses, then repeated after 9 days. Aldesleukin follows two-compartment pharmacokinetics, with an α-half-life of 6 to 13 mins and a β-half-life of 80 to 120 mins, and is excreted renally. The drug has several black box warnings including risk for capillary leak syndrome, severe central nervous system (CNS) effects, and infection, and should not be used in patients with cardiopulmonary disease.
4. **Etanercept** (Enbrel®) is a dimeric soluble form of the TNF receptor that binds both TNF-α and TNF-β. Like Humira®, Enbrel® is used for autoimmune disorders such as Crohn's disease and rheumatoid arthritis, given as 50-mg weekly injections, either as a single or divided dose. Patients taking Enbrel® are at increased risk for infection.
5. **Interferon-β** (Betaseron®, Extavia®) differs from naturally occurring IFN-β in its lack of carbohydrate side chains and a single amino acid substitution. Many of its effects are similar to those of IFN-α. Betaseron® is used to treat **multiple sclerosis** (**MS**), dosed at 0.0625 mg SQ every other day for relapsing MS (0.125 mg for secondary progressive MS), slowly increasing to a target dose of 0.25 mg every other day. Common side effects include lymphopenia (88%), injection site reaction (85%), headache (5%), muscle weakness (61%), and flulike syndrome (60%).

6. **Interferon β-1a** (Avonex®, Rebif®) is human recombinant IFN β-1a and used for relapsing multiple sclerosis. Avonex is dosed 30 mcg IM once weekly; Rebif® is dosed SQ three times weekly titrating up to 44 or 22 mcg/week.
7. **Interferon-γ** (Actimmune®) is human recombinant IFN-γ and plays a role in macrophage-induced killing. Recombinant IFN-γ is used to treat **chronic granulomatous disease**. Actimmune® has a half-life of 38 mins when given IV, 4 hrs when given IM, and 7 hrs when given SQ.
8. **Sargramostim** (Leukine®) is a GM-CSF used for myeloid reconstitution after **bone marrow transplant or chemotherapy**. Nausea (58% to 70%), diarrhea (< 89%), vomiting (46% to 70%), and fever (81%) are the most common side effects. The onset of action is 7 to 14 days before changes in white blood cell (WBC) levels are measurable.

VI. PLASMA PROTEINS, COAGULATION, FIBRINOLYSIS

A. Overview. The human plasma is rich in proteins such as **albumin** that are designed to maintain osmotic balance, acid–base balance, viscosity of the plasma, act as a protein reserve for the body, and transport insoluble molecules such as vitamins and hormones via plasma protein binding. In addition, immune globulins are present in high concentration in the plasma as part of immune surveillance (see antibodies, discussed earlier). Also, **fibrinogen** is an important plasma protein involved in blood clotting. Several key proteins have been made available by recombinant methods for either replacement therapy or given in therapeutic doses for their pharmacologic activity.

B. Proteins providing pharmacologic activity

1. **Alteplase** (Activase®, Cathflo®) is a **thrombolytic** agent also known as **tissue plasminogen activator**. Intravenous alteplase lyses thrombi in coronary arteries after ST-elevation **myocardial infarction**, **acute ischemic stroke** (within 3 hrs of onset of symptoms), or **pulmonary embolism**. An unlabeled use is for **acute ischemic stroke** presenting 3 to 4.5 hrs after onset of symptoms. The drug is given as a bolus dose over 1 to 2 mins or over 2 hrs for pulmonary embolism. Practitioners should avoid agitation during dilution. **Bleeding complications** and **reperfusion arrhythmias** are the primary adverse events associated with this therapy. Other examples of thrombolytics include **reteplase** (Retavase®) and **tenecteplase** (TNKase®).
2. **Desirudin** (Iprivask®) inhibits thrombin and is used as an **anticoagulant**. Specifically, it is used for **DVT** prophylaxis and is dosed 15 mg SQ every 12 hrs. Bleeding is the most common adverse reaction with anticoagulants. Other thrombin inhibitors include **lepirudin** (Refludan®) and **bivalirudin** (Angiomax®).

C. Proteins for replacement therapy. **Protein C** is available in recombinant form as an anticoagulant for congenital protein C deficiency. **Antihemophilic factors VIIA, VIII, and IX** are also available in recombinant forms in the treatment of patients with hemophilia.

VII. MISCELLANEOUS OTHER PROTEIN DRUGS

A. Enzymes. Many congenital disorders result in insufficient or inactive enzyme expression. As a result, recombinant technology is perfectly suited to design drugs for replacement therapy. Examples of these types of drugs include **alglucosidase** for **Pompe disease**, **Pulmozyme** for **cystic fibrosis**, **galsulfase** for **Maroteaux–Lamy syndrome**, **imiglucerase** for **Gaucher disease**, **laronidase** for **Hurler syndrome**, **PEG-ADA** (pegylated adenosine deaminase) for **ADA deficiency**, and **idursulfase** for **Hunter syndrome**. Some enzyme drugs are used for their pharmacologic properties, such as **glucarpidase** for **methotrexate overdose**, **pegloticase** (pegylated uricase; half-life: 10 to 12 days) for **gout**, and **rasburicase** (uricase; half-life: 8 hrs) to manage uric acid levels in some malignancies.

B. Hormones. Congenital defects also can result in insufficient or inactive hormone synthesis or be administered in therapeutic doses to elicit a pharmacologic effect. **Parathyroid hormone** (**teriparatide**), **insulin-like growth factor** (**mecasermin**), and **platelet-derived growth factor** (**becaplermin**) are available in recombinant forms for hormone supplement. **Gonadotropin** (**follitropin-α**, **follitropin-β**, **leutropin**, **urofollitropin**) is also used to stimulate ovulation.

1. **Somatropin** (Genotropin®, Humatrope®, Norditropin®, Nutropin®, Omnitrope®, Saizen®, Serostim®, Tev-Tropin®, Zorbtive®) is recombinant human growth hormone. The most common side effect of somatropin is edema, arthralgias, and myalgias. Many manufacturers produce this protein, and each is dosed differently because of their different SQ bioavailabilities (product dependent, ranging from 70% to 90%) and formulations (*Table 7-2*). A now-discontinued growth hormone

Table 7-2 SOMATROPIN COMPARISONS

Trade (Manufacturer) Cell Line	Adult GH Deficiency	Pediatric GH Deficiency	Other Indications	Formulation
Genotropin® (Pfizer) *Escherichia coli*	0.15–0.3 mg/d SQ; increase by 0.1–0.2 mg/d every 1–2 mo	*GH deficiency:* 0.16–0.24 mg/kg/wk SQ × 6–7 doses/wk	*Turner syndrome*: 0.33 mg/kg divided into equal doses 6–7 d/wk *Decreased body growth*: 0.24 mg/kg/wk SQ × 6–7 d/wk	*Miniquick* (disposable premeasured syringe): no refrigeration Pen (reusable pen): refrigerate Mixer (reusable, automatic mixer): refrigerate
Humatrope® (Lilly) *E. coli*	0.15–0.3 mg/d SQ; increase by 0.1–0.2 mg/d every 1–2 mo	0.18–0.3 mg/kg/wk SQ	*Turner syndrome*: 0.375 mg/kg divided into equal doses 6–7 d/wk *SHOX deficiency*: 0.35 mg/kg divided into equal doses 6–7 d/wk	Injection powder for solution; SQ powder for solution
Norditropin® (Novo Nordisk) *E. coli*	0.15–0.3 mg/d SQ; increase by 0.1–0.2 mg/d every 1–2 mo	0.024–0.34 mg/kg/d SQ × 6–7 d/wk	*Turner syndrome*: up to 0.067 mg/kg/d	*FlexPro*: SQ solution *Nordiflex* (prefilled): no refrigeration after initial use *PenMate* (needle-free): SQ solution
Nutropin®; Nutropin AQ® (Genentech) *E. coli*	0.15–0.3 mg/d SQ; increase by 0.1–0.2 mg/d every 1–2 mo	0.3 mg/kg/wk SQ × 6–7 d/wk up to 0.7 mg/kg/wk for pubertal patients	*Turner* syndrome: ≤ 0.375 mg/kg divided into equal doses 3–7 d/wk	*AQ NuSpin 5* (prefilled automatic): SQ solution *AQ Pen cartridge*: SQ solution Nutropin: powder *Nutropin AQ*: SQ solution
Omnitrope® (Sandoz) *E. coli*	< 0.04 mg/kg/wk SQ in divided dose; may increase to < 0.08 mg/kg/wk	0.16–0.24 mg/kg/wk SQ × 6–7 d	*Decreased body growth*: 0.24 mg/kg/wk SQ × 6–7 d/wk	SQ powder; SQ solution
Serostim® (EMD Serono) mammalian cell			*AIDS-associated cachexia*: body weight < 35 kg, 0.1 mg/kg SQ; otherwise 4–6 mg SQ	SQ powder store at room temperature prior to reconstitution; discard after reconstitution
Saizen® (EMD Serono) mammalian cell	0.005 mg/kg/d SQ or IM; after 4 wks, may adjust to ≤ 0.01 mg/kg/d	0.6 mg/kg SQ or IM 3 × per wk		*Cool Click* (needle-free) *Easypod* (automated device) Store powder at room temperature; refrigerate after reconstitution
Tev-Tropin®		0.1 mg/kg SQ, 3 × per wk		Store powder at room temperature; refrigerate after reconstitution
Zorbtive® (EMD Serono) *E. coli*			*Short bowel syndrome*: 0.1 mg/kg SQ daily for 4 wks; increase to ≤ 8 mg/d	SQ powder

From Page AV, Caplan ES. Immunomodulators. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:611–624.

product contained an extra methionine amino acid at the N-terminus (Protropin®). **Growth hormone** antagonist (**pegvisomant**) is a pegylated growth hormone analog used in the treatment of **acromegaly** where growth hormone is overproduced.

2. **Insulin** (Humulin® R, Humulin® R U-500, Novolin®) is regular, short-acting human recombinant insulin used to treat diabetes mellitus. Insulin is either given as regular insulin SQ boluses (baseline plus bolus dosing) or via dosing two to three times per day using a mixture of regular and intermediate-acting isophane insulin, also known as NPH insulin (Humulin® N, Iletin® I NPH, Iletin® II NPH, Novolin®, Novolin® N Innolet®, ReliOn N, ReliOn N Innolet®). **NPH insulin** is insulin modified with zinc and protamine to promote dimer and hexamer formation, resulting in prolonged absorption and action. The disadvantage of NPH insulin is variable absorption but it does have a long clinical history compared to other types of insulin. Lente insulin is another type of intermediate-acting insulin product. Other insulin forms, such as rapid acting (semilente insulin, insulin aspart, insulin glulisine, and insulin lispro) or long acting (ultralente insulin insulin detemir, insulin glargine, protamine-zinc insulin), are also used in various combinations to individualize glucose control. **Insulin pumps** are also used for continuous infusion of basal insulin and also boluses at meals but must be changed every 3 days. **Inhaled insulin** (Exubera®) is no longer on the market.

VIII. MACROMOLECULAR NUCLEIC ACID DRUGS

A. Background

1. **DNA** (deoxyribonucleic acid) is a polymeric, double-stranded helix that comprises the genetic material of all organisms. DNA is transcribed into **RNA** (ribonucleic acid), which is translated into protein. DNA sequences can be modified with high accuracy using recombinant DNA technology. **Restriction endonucleases** are key tools for sequence-specific modification and recombination of DNA.
2. **Viruses**' genetic material may consist of either RNA or double-stranded or single-stranded DNA. RNA viruses, or retroviruses, use reverse transcriptase to transcribe their genome into DNA.
3. The **Human Genome Project** was designed to sequence the human genome. Other technologies using high-throughput sequencing have also been useful to sequence individual genes and their variants. Knowledge of the role of these genetic variants, or **polymorphisms**, are useful for better understanding disease etiology and for the development of new, more specific drugs.

B. Oligonucleotide drugs

1. **Background**. Oligonucleotide drugs are single-stranded DNA or RNA molecules that are usually chemically modified to improve in vivo stability and cellular uptake. They are used to block gene expression or act as substrate inhibitors. **Antisense** drugs bind to or "hybridize to" mRNA complementary sequences to inhibit translation. The primary applications for antisense therapy are cancer or antiviral therapies, but any disease or disorder where inhibition of a specific gene is desired has a potential application. An **aptamer** is an oligonucleotide with secondary structure that binds with high affinity to a substrate in the same manner that a DNA-binding protein binds DNA.
2. **Examples**. **Pegaptanib** (Macugen®) is a 2′-fluoro, PEG-conjugated, oligoribonucleotide aptamer, which binds to and inhibits VEGF. It is used in the treatment of **age-related macular degeneration**. The drug is administered 0.3 mg intravitreally every 6 weeks and has a plasma half-life of 6 to 14 days. Pegaptanib may cause hypertension or ocular side effects such as conjunctivitis. **Fomivirsen** (Vitravene®) is an antisense phosphorothioate oligonucleotide used to treat HIV patients with **cytomegaloviral** infections in the eye. It is dosed 330 mcg intravitreally every 2 weeks for two doses, then every 4 weeks thereafter. Onset and duration of action is 8 and 10 days, respectively.

C. Gene therapy. Despite decades of research and development, and currently more than 1500 clinical trials worldwide, gene therapy therapeutics have not yet been approved by the U.S. Food and Drug Administration (FDA). Scores of gene therapy formulations are in advanced clinical trials, but the technology continues to be plagued by insufficient expression of the therapeutic gene and safety questions. Should this technology finally resolve its development hurdles, the ability to provide therapeutic genes to somatic cells has incredible potential, especially in the areas of cancer, cardiovascular disease, and genetic disorders.

Study Questions

Directions: Choose the **best** answer to each of the following questions.

1. Most biologic drugs are sensitive to all of the following **except**
   (A) heat.
   (B) shaking.
   (C) stainless steel.
   (D) light.

2. Recombinant protein drugs are designed to replicate which of the following types of molecules?
   (A) Antibodies
   (B) Enzymes
   (C) Proteins in the plasma
   (D) All of the above
   (E) None of the above

3. Nucleic acid drugs or drug candidates include which of the following?
   (A) Gene therapy
   (B) Oligonucleotides
   (C) A and B
   (D) None of the above

4. Glycoprotein is a protein linked to _____.
   (A) a carbohydrate
   (B) a nucleotide
   (C) an amino acid
   (D) a lipid molecule
   (E) None of the above

5. Examples of monoclonal antibody drugs include all of the following **except**
   (A) infliximab.
   (B) Herceptin.
   (C) trypsin.
   (D) rituximab.

6. An example of a recombinant cytokine is _____.
   (A) muromonab
   (B) albumin
   (C) oligonucleotide
   (D) interferon
   (E) growth hormone

7. A recombinant protein will have the same in vivo properties if the genetic sequence is the same. This statement is _____.
   (A) always true
   (B) not necessarily true
   (C) always false

8. Monoclonal antibodies are most often used for what type of clinical indications?
   (A) Cancer
   (B) Correcting congenital deficiencies
   (C) Replacement therapy
   (D) Psychiatric disorders
   (E) None of the above

9. Gene therapy _____.
   (A) is a technology that is widely used in patient care
   (B) involves short nucleic acid sequences to inhibit gene expression
   (C) has not been tested in clinical trials
   (D) All of the above
   (E) None of the above

10. Which of the following statements is true for polyethylene glycol (PEG)?
    (A) It is a carbohydrate used to increase clearance of drugs.
    (B) It is conjugated only to recombinant hormones.
    (C) It blocks the renal filtration of drugs.
    (D) It is naturally occurring on many biologic molecules.

Answers and Explanations

1. **The answer is C** *[see I.E.]***.**
   Biologic drugs are sensitive to high (and very low) temperatures, agitation, and light.

2. **The answer is D** *[see IV; VI; VII.A.]***.**
   Protein drugs are used for protein replacement or for providing pharmacologic activity when used in therapeutic doses. Besides enzymes, plasma proteins, mAbs, and cytokines, hormones are also classes of proteins that have been made into recombinant drugs.

3. **The answer is C** *[see VIII]***.**
   Many macromolecular nucleic acid drugs are in clinical trials and preclinical development, such as miRNA, ribozymes, siRNA, and gene therapy, but only oligonucleotides have become approved drugs at this time. Nucleoside

drugs are small nucleic acid drug molecules and many are in use, especially for antiviral therapy.

4. **The answer is A** *[see II.K]***.**
Glycoproteins are made of a carbohydrate linked to a protein.

5. **The answer is C** *[see IV.B; Table 7-1]***.**
Trypsin is an enzyme that digests proteins. The other drugs listed are examples of mAbs.

6. **The answer is D** *[see V]***.**
Muromonab is an mAb, albumin is a plasma protein, oligonucleotides are nucleic acid drugs, and growth hormone is a hormone. Only interferon is considered a cytokine of this list.

7. **The answer is B** *[see I.B; VII.B.1; Table 7-2]***.**
Because product quality and even structure are dependent on the manufacturing process (including cell line, equipment, chemicals and their impurities, material handling, etc.), each biologic product is unique even if the original gene sequence used is identical. Therefore, generic versions of biologics are not available; rather, similar products that follow the innovator are called **biosimilars**.

8. **The answer is A** *[see IV.B; Table 7-1]***.**
mAbs bind to unique epitopes on specific antigens, which either act as an antagonist to the antigen or employ the immune system to elicit an immune response against the target. Congenital defects in the immune system would result in an overall lack of antibody defense instead of lacking a single antibody type.

9. **The answer is E** *[see VIII.C]***.**
Gene therapies are in clinical trials but have not yet been FDA approved. Gene therapy involves delivery of a gene (usually thousands of double-stranded nucleotides in size) compared to an oligonucleotide (15–30 single-stranded nucleotides).

10. **The answer is C** *[see Table 7-1; II.S; V.B.2; VII.A; VII.B.2; VIII.B.2]***.**
Polyethylene glycol (PEG) is a synthetic polymer that is conjugated to protein and nucleic acid drugs to increase the half-life and decrease the renal clearance of a drug by glomerular filtration. Many different protein drugs have employed this method to improve the pharmacokinetic properties of the compound, including filgrastim, adenosine deamidase, and anti-TNF antibody.

8

Drug Metabolism, Prodrugs, and Pharmacogenetics

MICHAEL L. ADAMS, S. THOMAS ABRAHAM

I. INTRODUCTION TO DRUG METABOLISM.

Xenobiotic metabolism is a general term used to describe the protective biochemical process by which a living organism either enzymatically or nonenzymatically alters a xenobiotic (foreign substance) to a metabolite that is inactive or quickly eliminated from the organism. *Drug metabolism* is a more specific term that applies the concept of xenobiotic metabolism to pharmaceutical agents. In general, drug metabolism begins with a lipophilic drug or substrate and converts it to a more hydrophilic metabolite to facilitate its elimination. There are multiple enzymes and paths that are possible for a single xenobiotic, so it is common for multiple metabolites with varying properties to be observed. An understanding of the drug metabolism process and the potential outcomes is critical for developing safe and useful pharmaceuticals.

II. CONSEQUENCES OF DRUG METABOLISM.

In the process of converting a drug to a metabolite, the pharmacological activity of the drug may be changed. Metabolites can be broadly classified as either inactive or active metabolites.

A. **Inactive metabolites** of drugs are devoid of pharmacological activity that was characteristic of the drug or toxicant. This metabolic change may be considered an **inactivation** or **detoxification**. There may be a disruption in the pharmacophore, the chemical functional groups, and their orientation relative to each other that is required for proper receptor binding or activity, or a change in the distribution of the drug because of the change in the physicochemical properties of the drug that facilitates elimination.

1. The hydrolysis of procaine (Novocain) to *p*-aminobenzoic acid and diethylethanolamine results in a loss of anesthetic activity (*Figure 8-1A*).

2. Acetaminophen is glucuronidated on its phenolic hydroxyl group to an inactive metabolite that is rapidly eliminated (*Figure 8-1B*).

B. **Active metabolites** of drugs have pharmacological activity, which can either be similar to the desired pharmacological activity or a new activity that is absent from the parent drug.

1. Metabolites with similar pharmacological activity retain the desired biological activity that is inherent in the parent compound.

a. Codeine is demethylated to the more active analgesic, morphine (*Figure 8-2A*).

b. Imipramine (Tofranil) is demethylated to the essentially equiactive antidepressant, desipramine (Norpramin) (*Figure 8-2B*).

2. In the case that the metabolite has the **desired pharmacological activity** although the parent is inactive, the metabolism is called **bioactivation**. The parent compound devoid of pharmacological activity before metabolism is called a prodrug.

a. The prodrug enalapril (Vasotec) is hydrolyzed to enalaprilat, a potent antihypertensive (*Figure 8-3A*).

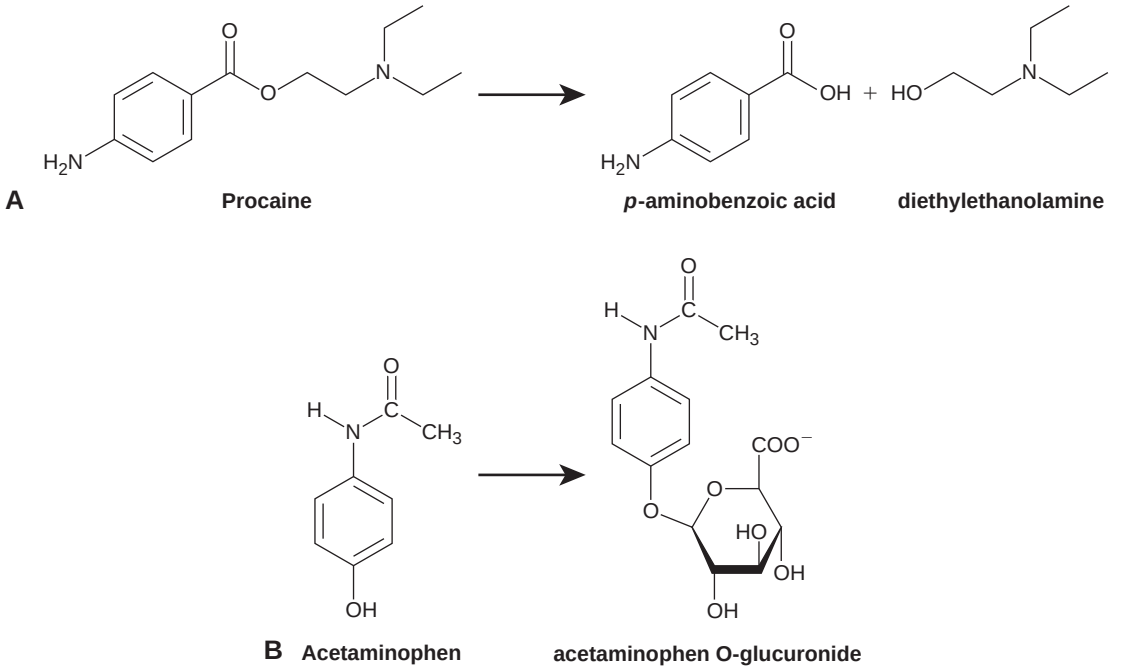


Figure 8-1. Examples of metabolism to inactive metabolites. **A.** Ester hydrolysis of the local anesthetic procaine to produce two inactive metabolites. **B.** Glucuronidation of acetaminophen to an inactive metabolite.

   b. Nabumetone (Relafen) is a prodrug that is oxidized in the body to an active nonsteroidal anti-inflammatory drug (NSAID) (*Figure 8-3B*).

3. **Bioactivation** of a drug can also result in a **toxic metabolite**. The parent activated is called a protoxicant.
   a. Halothane (Fluothane) is a general anesthetic that is oxidized to a reactive metabolite that is associated with hepatotoxicity (*Figure 8-4A*).
   b. Acetaminophen (Tylenol) can be oxidized into a reactive metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI), that can lead to hepatotoxicity (*Figure 8-4B*; Chapter 11, section IV.D.4).

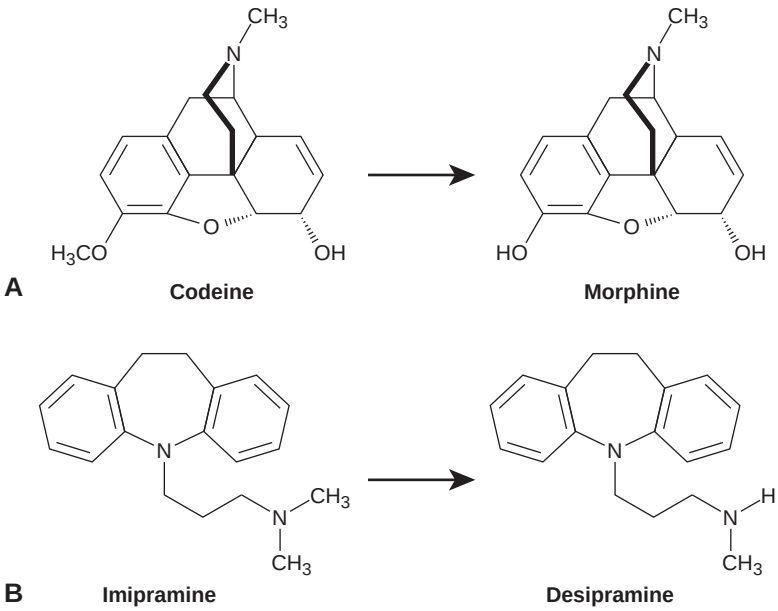


Figure 8-2. Examples of metabolism to metabolites with similar pharmacological activity. **A.** Codeine, a mild analgesic, is metabolized to morphine, a potent analgesic. **B.** Imipramine, a tricyclic antidepressant, is metabolized to the active antidepressant, desipramine.

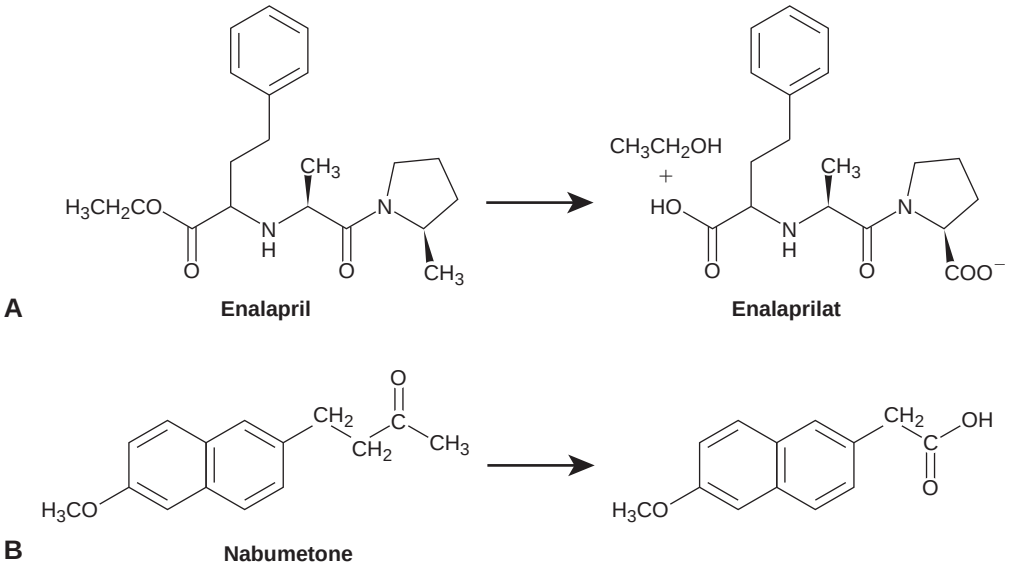


Figure 8-3. Examples of metabolism of an inactive prodrug to the desired pharmacological activity. **A.** Ester hydrolysis of the prodrug enalapril to the active enalaprilat. **B.** Oxidation of the ketone on the prodrug nabumetone to the active nonsteroidal anti-inflammatory carboxylic acid.

III. METABOLIC PATHWAYS.

Drug metabolism is performed by a large number of different enzymes and even by some nonenzymatic processes. The liver is the organ with the highest concentration of drug-metabolizing enzymes because of its localization between the gastrointestinal (GI) tract, where the body has the highest exposure to foreign substances, and the systemic circulation. The enzymes involved in drug metabolism can be classified by several different categories. The enzymes can either be localized in the cytosol (cytosolic) or the endoplasmic reticulum (ER) membrane (microsomal) portion of the cell. A general classification of enzymatic processes based on the type of reactions involved includes **phase I** and **phase II**.

A. Phase I metabolism is characterized as a **functionalization reaction**. Phase I reactions add or reveal a polar functional group on a substrate by oxidation, reduction, or hydrolysis. The addition of the polar group **increases** the overall **polarity** of the metabolites to increase water solubility and facilitate excretion in the urine. Many phase I metabolites are substrates for phase II reactions (see II.B).

1. **Oxidation** is the most common phase I reaction. Several phase I oxidation reactions are further described later and illustrated in *Table 8-1*.

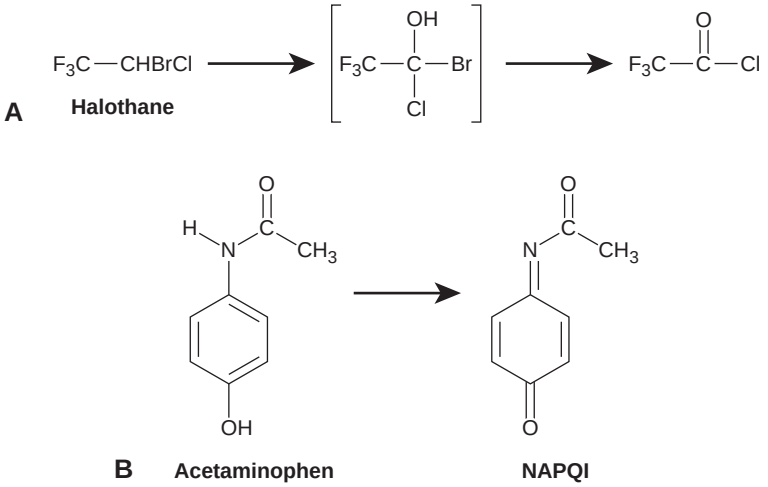
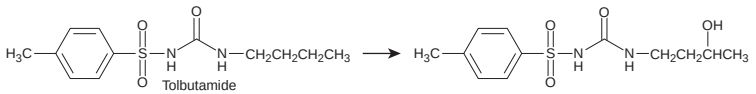
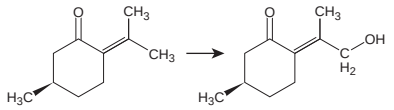
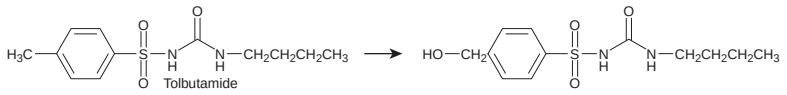
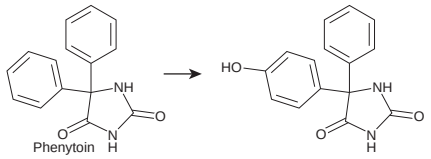
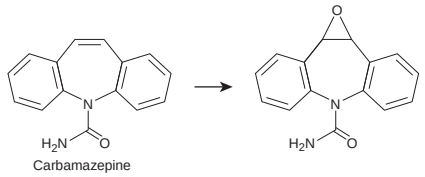
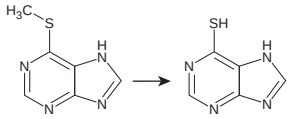
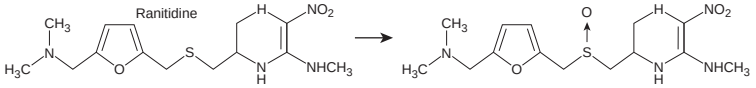
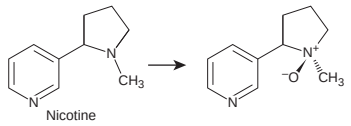
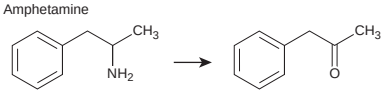
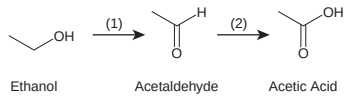
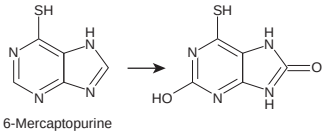


Figure 8-4. Examples of metabolism of active drugs to toxic metabolites. **A.** Halothane, a general anesthetic, is metabolized to a reactive metabolite associated with hepatotoxicity. **B.** Acetaminophen, an antipyretic, is metabolized to the reactive metabolite, NAPQI, associated with hepatotoxicity.

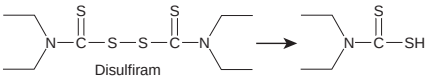
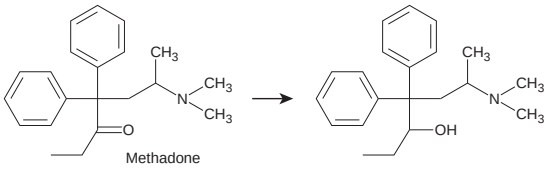
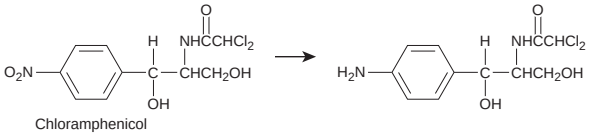
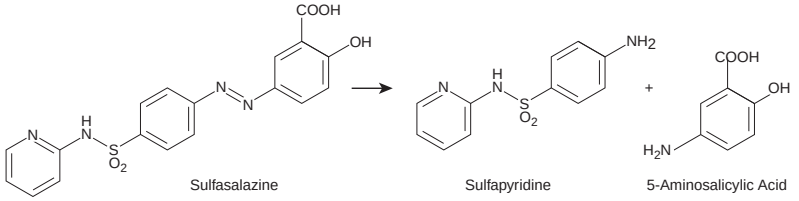
Table 8-1 COMMON OXIDATION REACTIONS

Reaction (Enzyme)	Examples
Aliphatic hydroxylation (CYP450)	 Tolbutamide
Allylic hydroxylation (CYP450)	
Benzylic hydroxylation (CYP450)	 Tolbutamide
Aromatic hydroxylation (CYP450)	 Phenytoin
Epoxidation (CYP450)	 Carbamazepine
O-Dealkylation (CYP450)	Codeine to morphine (see *Figure 8-2A*)
S-Dealkylation (CYP450)	
S-Oxidation (CYP450 or FMO)	 Ranitidine
N-Dealkylation (CYP450)	Imipramine to desipramine (see *Figure 8-2B*)
N-Oxidation (FMO or CYP450)	 Nicotine
Deamination (CYP450 or monoamine oxidase)	 Amphetamine
Dehalogenation (CYP450)	Halothane (see *Figure 8-4A*)
Alcohol oxidation (*1*) (alcohol dehydrogenase) Aldehyde oxidation (*2*) (aldehyde dehydrogenase)	 Ethanol Acetaldehyde Acetic Acid
Oxidation (xanthine oxidase)	 6-Mercaptopurine

FMO, Flavin-containing monooxygenase; *CYP450*, Cytochrome P450s.

2. **Cytochrome P450** (CYP450) is a superfamily of mixed function oxidases that are responsible for the majority of oxidation reactions.
   a. CYP450 is classified as a **microsomal enzyme** and in the cell is bound to the ER. CYP450 is found in very **high concentrations in the liver** and to a lesser extent in the intestinal mucosa, lungs, and kidneys. CYP450 is dependent on the porphyrin prosthetic group, commonly called the heme group, and NADPH to metabolize a wide array of substrates to numerous metabolites. Common CYP450 reactions are illustrated in *Table 8-1*.
   b. There are **several isoforms of CYP450** responsible for drug metabolism, which gives wide substrate specificity to the family of CYP450 enzymes. Each isoform has different substrate specificities based on the size and amino acid composition of the CYP450 active site. The **nomenclature** for the CYP450 enzymes is based on **amino acid homology** and divides the CYP450's into **families** designated by an Arabic number, **subfamilies** designated by a letter, and individual genes designated by an Arabic number preceded by "CYP." For example, CYP3A4 is an example where the family is 3, the subfamily is A, and the individual gene is 4. The CYP450 families most responsible for drug metabolism include CYP1, CYP2, CYP3, and CYP4 with subfamilies CYP2C, CYP2D, and CYP3A metabolizing most drugs. CYP families CYP7, CYP11, CYP17, CYP19, CYP21, and CYP27 contribute to steroid and bile acid synthesis and metabolism required for homeostasis.
3. **Flavin-containing monooxygenase** (FMO) is a family of **microsomal phase I** drug-metabolizing enzymes responsible for the oxidation of N- and S-containing soft nucleophile substrates with metabolites similar to CYP450 metabolites (see *Table 8-1*).
4. **Alcohol dehydrogenase** is a **cytosolic** enzyme that oxidizes alcohols into aldehydes (from primary alcohols) or ketones (from secondary alcohols). This oxidation is reversible and is frequently observed in primary alcohols where the aldehyde can be further oxidized to a carboxylic acid (see Aldehyde Dehydrogenase, III.A.5).
5. **Aldehyde dehydrogenase** is a general name for a group of enzymes expressed both in the mitochondria and the cytosol that is responsible for oxidizing an aldehyde to a carboxylic acid. A common reaction performed by an aldehyde dehydrogenase and aldehyde oxidase is the conversion of acetaldehyde to acetic acid in the metabolism of ethanol.
6. **Xanthine oxidase** and **xanthine dehydrogenase** are the two forms of the same gene product that are responsible for the breakdown of **endogenous purines**. Xanthine oxidase is a cytosolic enzyme that contributes to the metabolism of the purine anticancer drugs (i.e., 6-mercaptopurine) and other xanthines including caffeine and theophylline. Xanthine oxidase is also inhibited by antigout drugs like allopurinol (Zyloprim) to slow the production of uric acid from purines.
7. **Monoamine** and **diamine oxidase** are mitochondrial enzymes that metabolize amines to aldehydes through an **oxidative deamination** process. Monoamine oxidase is responsible for the metabolic inactivation of catecholamines in neurons and the hepatic inactivation of biogenic amines absorbed from the GI tract. Monoamine oxidase is also a target for inhibition in the treatment of depression (i.e., monoamine oxidase inhibitors including phenelzine [Nardil]).
8. **Reduction reactions** are less common than oxidation but are still **phase I** reactions that add or reveal a functional group to increase the water solubility of the molecule to facilitate elimination. There are several reductase enzymes and even CYP450 may have reductase activity. Common reduction reactions include the reduction of disulfide bonds, carbonyls, and nitro or azo functional groups.
   a. A common reduction reaction is the **reduction of disulfide bonds** commonly found between cysteine residues in proteins. Other sulfhydryl-containing molecules can form disulfides that may be reduced back to the free sulfhydryls, or disulfide-containing drugs can be reduced like disulfiram (*Table 8-2*).
   b. **Aldo-keto reductases** reduce a carbonyl-containing compound back to an alcohol in a process opposite the oxidation performed by the alcohol dehydrogenases (*Table 8-2*; see also III.A.4).
   c. **Reduction** of the **aromatic nitro** (NO_2) group and the **azo** (N=N) group is performed by a class of enzymes generically called nitroreductases and azoreductases, respectively, to produce free aromatic amines. Example reactions are included in *Table 8-2*. The liver contains these reductases both in the cytosol and the microsomal cellular fraction. Additionally, gut bacteria have significant reductase activity for both nitro and azo groups.

Table 8-2 COMMON REDUCTION REACTIONS

Reaction (Enzyme)	Examples
Reduction of disulfide bond	 Disulfiram
Aldehyde and/or keto reduction	 Methadone
Nitro (—NO_2) reductions	 Chloramphenicol
Azo reductions (—N=N—)	 Sulfasalazine; Sulfapyridine; 5-Aminosalicylic Acid

9. **Hydrolysis** reactions add water across a bond to produce a more water-soluble metabolite. Common hydrolysis reactions include ester hydrolysis, amide hydrolysis, and epoxide hydrolysis.
   a. **Ester hydrolysis** is commonly performed by the ubiquitous **esterase** enzymes found throughout the body. There is a significant esterase activity in the plasma that is responsible for the hydrolysis of an ester into a more water-soluble alcohol and carboxylic acid. This metabolic process can be an inactivating or activating (see Prodrugs, V) reaction. A **lactone**, like found in erythromycin, is a cyclic ester that can also be metabolized by esterase enzymes.
   b. **Amide hydrolysis** is performed by **amidase** enzymes that are generally expressed in the liver. Analogous to the ester hydrolysis reaction, the products of amide hydrolysis are an amine and a carboxylic acid (*Table 8-3*). A cyclic amide is called a **lactam** and is the key structural feature for the β-lactam antibiotics.
   c. **Epoxide hydrolase** converts epoxides into diols, which can be targets for conjugation reactions to facilitate elimination of xenobiotics (*Table 8-3*). There is both a microsomal and cytosolic form of epoxide hydrolase.

B. **Phase II reactions** are commonly called **conjugation reactions** because they use a functional group on the xenobiotic (either from phase I metabolism or part of the xenobiotic itself) to add or conjugate a biomolecule that usually increases the polarity of the xenobiotic and facilitates elimination from the body. These conjugation reactions require an enzyme generally termed as **transferase** that transfers a high-energy molecule called the **cofactor** or **cosubstrate** to the xenobiotic. The transferred cofactor is usually large and very polar-forming inactive metabolites. There are exceptions like methylation (see later discussion) that do not increase polarity but do generally form inactive metabolites. Common phase II reactions are discussed later and examples are included in *Table 8-4*.
   1. **Glucuronidation** is the most common phase II reaction. **Glucuronosyltransferase** is the microsomal enzyme that uses uridine diphosphate glucuronic acid (UDP-GA) as the cofactor to transfer the glucuronic acid to several different functional groups, including hydroxyl groups, carboxylic acid groups, hydroxylamines, and sulfonamides. The glucuronic acid adds a significant amount of hydrophilicity to the molecule and facilities its elimination in the urine. High-molecular-weight glucuronides (MW $>$ 500 Da) are secreted into the bile, which ends up in the intestines.

Table 8-3 COMMON HYDROLYSIS REACTIONS

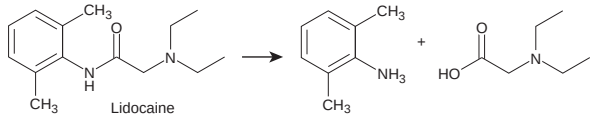
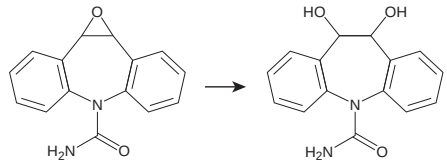
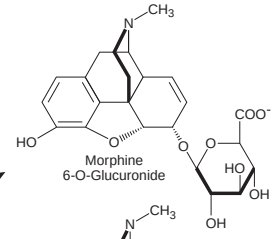
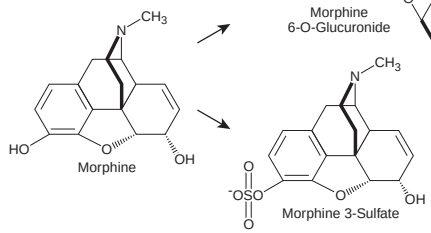
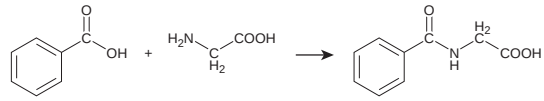
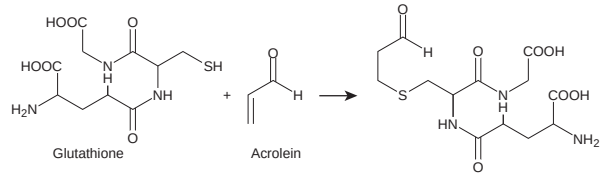
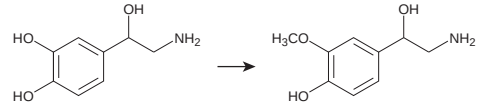
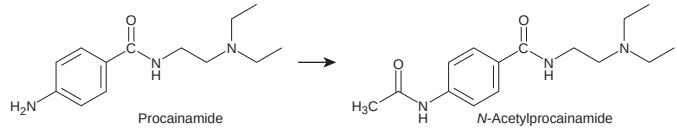
Reaction	Examples
Ester hydrolysis (esterase)	See *Figure 8-3A*
Amide hydrolysis (amidase; peptidase)	 Lidocaine
Epoxide hydrolysis (epoxide hydrolase)	 Carbamazepine epoxide

Table 8-4 COMMON PHASE II REACTIONS

Reaction	Enzyme	Cofactor	Examples
Glucuronidation	Glucuronosyltransferase	UDP-GA	 Morphine 6-O-Glucuronide
Sulfation	Sulfotransferase	PAPS	 Morphine; Morphine 3-Sulfate
Amino acid conjugation	*N*-Acyltransferase	Glycine and/ or glutamine	
Glutathione conjugation	Glutathione-S-transferase	Glutathione	 Glutathione; Acrolein
Methylation	Methyltransferase	SAM	
Acetylation	*N*-Acetyltransferase	Acetyl-CoA	 Procainamide; *N*-Acetylprocainamide

UDP-GA, uridine diphosphate glucuronic acid; *PAPS*, 3′-phosphoadenosine-5′-phosphosulfate; *SAM*, *S*-adenosylmethionine; *Acetyl-CoA*, acetyl coenzyme A.

2. **Sulfation** is less common than glucuronidation but is also a phase II reaction that increases the polarity of the parent drug by conjugating an endogenous molecule to the xenobiotic. **Sulfotransferase** is the enzyme that uses the cofactor 3′-phosphoadenosine-5′-phosphosulfate (PAPS) to add a sulfate to hydroxyl groups, arylamines, and *N*-hydroxyl compounds. The sulfate conjugate is ionized and highly polar to dramatically increase water solubility and excretion of the xenobiotic.
3. The **amino acid conjugation** reaction adds either a glycine or a glutamine to a carboxylic acid of the parent drug to form an amide. Coenzyme A forms an intermediate with the carboxylic acid of the parent drug called the acyl coenzyme A intermediate. ***N*-Acyltransferase** then catalyzes the reaction of the activated xenobiotic (acyl coenzyme A) with the amino acid to form the amide-containing metabolite. In this case, the carboxylic acid target is activated into a high-energy intermediate (acyl coenzyme A) that interacts with the amino acid.
4. **Glutathione conjugation** results from the addition of a glutathione molecule (a tripeptide including glycine, cysteine, and glutamic acid) to an electrophilic substrate. Electrophilic compounds react with nucleophiles and the nucleophile on glutathione (the cysteine sulfhydryl) generally acts to detoxify electrophiles. **Glutathione-S-transferase** is the enzyme responsible for the reaction of glutathione with electrophiles, including epoxides and halides to name a few. After glutathione is conjugated to the electrophile, the tripeptide is further processed by amide hydrolysis and *N*-acetyltransferase to the **mercapturic acid metabolite** (*Table 8-4* and *Figure 8-5*). This is a common metabolite excreted in the urine after glutathione conjugation.
5. **Methylation** depends on the cofactor *S*-adenosylmethionine (SAM) and the enzyme **methyltransferase** to add a methyl group to oxygen-, nitrogen-, or sulfur-containing functional groups. The result of this reaction is generally less polar molecules that can inactivate compounds like the catechol-containing neurotransmitters including norepinephrine (*Table 8-4*). More commonly, methylation is responsible for biosynthesis of endogenous compounds like epinephrine through the *N*-methylation of norepinephrine.
6. **Acetylation** depends on the cofactor acetyl coenzyme A (acetyl-CoA) and the enzyme ***N*-acetyltransferase** to add an acetyl group to primary amines, hydrazines, sulfonamides, and occasionally amides (*Table 8-4*). The *N*-acetyl metabolites are less polar than the parent drug and may retain pharmacological activity, both of which are unusual for a phase II reaction.

C. **Extrahepatic metabolism**, or drug biotransformation outside of the liver, is also an important process in determining the metabolic rate of xenobiotics. Sites with significant metabolic capacity are located at the portals of entry (e.g., GI mucosa, nasal passages, lungs) and the portals of excretion (e.g., kidneys), but other tissues also contain various drug-metabolizing enzymes.
   1. The **intestinal mucosa** is a significant site of metabolism for drugs that are administered orally and contributes to the observed **first-pass effect** or **presystemic metabolism**. Several metabolic processes have been identified in the intestinal mucosa, including microsomal oxidation

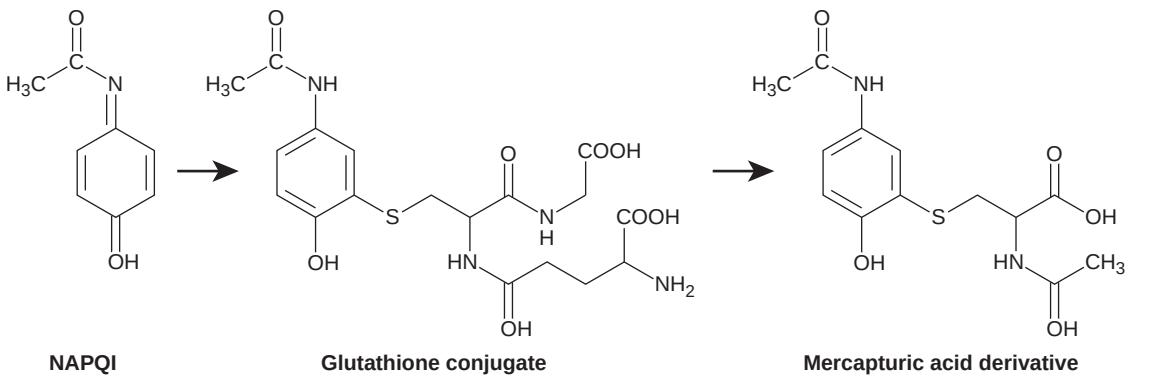


Figure 8-5. Conjugation of NAPQI with glutathione and the processing to the ultimate metabolite, the mercapturic acid derivative.

(e.g., CYP450 and FMO), glucuronidation, sulfation, and ester hydrolysis. Conversion in the intestinal mucosa of a lipophilic xenobiotic into a more hydrophilic and potentially inactivated metabolite prevents the pharmacologically active compound from entering the systemic circulation (i.e., **presystemic metabolism**).

2. The **intestinal flora** is also responsible for producing many **reductase** and **β-glucuronidase enzymes**.
   a. **Reductases**, including nitroreductase and azoreductase, reduce aromatic nitro and azo functional groups into amines (see previous discussion). One example of an azoreductase activity is the reduction of the azo bond in sulfasalazine (Azulfidine) to release the anti-inflammatory aminosalicylic acid and the antibacterial sulfapyridine (*Table 8-2*).
   b. The **β-glucuronidase** enzymes are responsible for the hydrolysis of the polar glucuronide conjugates in the bile to release the free, deglucuronidated drug, which is free for reabsorption. This process of glucuronide conjugates secretion into the GI tract with the bile, being hydrolyzed by β-glucuronidases, and then being reabsorbed is called **enterohepatic circulation**. Estrogen is an example of a drug that demonstrates enterohepatic circulation.
   c. Changes in the number or population of intestinal flora can influence the activity of a drug. Conditions such as diarrhea, intestinal diseases, or antibiotic treatment all alter the intestinal flora and therefore may result in changes in drug activity.
3. The **nasal mucosa**, like the GI mucosa, is considered a portal of entry and contains a high level of CYP450 activity as well as some FMO, esterase, and conjugation activity. This provides a protective mechanism for the exposure to xenobiotics in the air but may also activate some xenobiotics to toxic metabolites. Many compounds administered nasally also undergo significant nasal metabolism to decrease the systemic effects. Examples include topical decongestants, anesthetics, nicotine, and cocaine.
4. The **lungs** express many CYP450s, FMO, epoxide hydrolase, and conjugation pathways and therefore contribute to the metabolism of many xenobiotics that either enter the body through the lungs or via the circulation. The lungs are the site of first-pass metabolism for drugs administered intravenously, intramuscularly, transdermally, or subcutaneously and the site of second-pass metabolism for xenobiotics that leave the liver.
5. Plasma contains **esterases** that hydrolyze esters to either inactive ester-containing drugs (e.g., procaine [Novocain] and succinylcholine [Anectine]) or activate ester prodrugs (e.g., enalapril [Vasotec]).
6. The **placenta** has very limited drug-metabolizing capacity. Drugs that are easily absorbed are usually capable of crossing the placenta. Placentas of mothers that smoke tobacco have a significant increase in the expression of the CYP1A subfamily. This is of concern because it may result in increased exposure of the fetus to reactive metabolites that may have detrimental effects.
7. The extent of **fetal metabolism** is dependent on the age of the fetus. CYP450 activity is present early in gestation but glucuronidation is deficient until after birth. This lack of glucuronidation results in gray baby syndrome after chloramphenicol administration and neonatal hyperbilirubinemia.
8. The **kidney** expresses CYP450s that are mostly involved in the hydroxylation of steroids, arachidonic acid, and 25-hydroxycholecalciferol.
9. **Nonenzymatic degradation** of drugs can occur in the body, but the acidic environment of the stomach can cause the degradation of a number of drug molecules, including penicillin G, erythromycin, tetracycline, and peptides like insulin.

IV. FACTORS THAT INFLUENCE DRUG METABOLISM

A. The **chemical structure** of a xenobiotic has one of the largest influences on the metabolism of a compound. The presence or absence of certain functional groups will determine the necessity, route, and extent of metabolism.

B. **Genetic difference**, or **polymorphisms**, can influence the activity or the extent of expression of the drug-metabolizing enzymes. Section VII will explore these differences in more detail. The rate of acetylation is one example that depends on the amount of *N*-acetyltransferase that is expressed. Individuals can be divided into fast or slow acetylators based on the expression of *N*-acetyltransferase. Many CYP450s also have genetic polymorphisms that influence their activity. CYP2D6 is a highly

polymorphic enzyme that results in the division of individuals into ultrarapid, intermediate, or poor metabolizers of substrates like debrisoquine and dextromethorphan.

C. Gender. Metabolic differences between the sexes have been observed for a number of compounds, suggesting that androgen, estrogen, and/or adrenocorticoid activity might affect the activity of certain CYP450 enzyme isozymes.

1. Metabolism of diazepam (Valium), prednisolone (Orapred), caffeine, and acetaminophen (Tylenol) is slightly faster in women.
2. Metabolism of propranolol (Inderal), chlordiazepoxide (Librium), lidocaine (Xylocaine), and some steroids is faster in men than in women.

D. Age

1. The **fetus** and the **neonate** do not have fully developed drug-metabolizing enzymes, particularly phase II glucuronidation. As a result, smaller doses are often required to avoid drug accumulation and adverse effects during the first 6 to 8 weeks of life.
2. The **elderly patient** shows a **decrease in the drug-metabolizing capacity** compared to young adults. This may be related to changes in hepatic blood flow, body mass, and/or other disease states. Drug clearance is therefore generally slower and blood concentrations are higher, increasing the potential for toxicity.

E. Circadian rhythms. The nocturnal plasma levels of drugs, such as theophylline (Theochron, Uniphyl) and diazepam (Valium), are lower than the diurnal plasma levels.

F. Various **disease states** that influence the function of the liver, the major site of drug metabolism, can affect a drug's hepatic clearance. Alterations in liver blood flow, loss of functional hepatocytes, and changes in albumin production can influence the extent of drug metabolism and toxicity and therefore require caution when administering a drug that requires hepatic biotransformation for detoxification or elimination.

G. The **nutritional status** of an individual can also influence the activity of drug-metabolizing enzymes by altering the amount of conjugating agents, protein, essential fatty acids, minerals, and/or vitamins available for use. Various alterations in drug-metabolizing activity have been identified for each category listed previously.

H. Interacting substances. Xenobiotics, whether they are drugs or not, can influence the activity of drug-metabolizing enzymes in a variety of ways.

1. **Inducers** are xenobiotics that cause an increase in the drug-metabolizing activity of a target enzyme, usually by increasing the concentration of the enzyme in the liver or other tissue. Several **CYP450 enzymes** and **glucuronosyltransferases** are known to be inducible. In the case of drug–drug interactions, the compound causing the induction is called the **precipitant drug**, whereas the drug that is being affected is called the **object drug**. The consequence of induction is dependent on the extent of induction by the precipitant drug and the pharmacological characteristics of the object drug. For example, if the object drug is metabolized to a toxic metabolite, then induction by the precipitant drug may result in greater toxicity as a result of the increased drug-metabolizing activity.
2. **Inhibitors** are opposite of inducers in that they **decrease** the metabolizing activity of a target enzyme, usually by competing with the object drug for the enzyme and preventing its metabolism. The extent of inhibition is dependent on the affinity of the inhibitor, the availability of **alternate metabolic pathways** of the object, and the **pharmacologic characteristics** of the object drug. For example, if the object drug has a narrow margin of safety and one metabolic route of elimination, the addition of an inhibitor to that pathway could result in accumulation of the object drug and ultimately toxicity.
3. The extent of **protein binding** can be altered by the administration of another compound that is also highly protein bound. Two drugs that compete for similar binding sites on plasma proteins can result in the displacement of (usually) the agent with the lower affinity. As a result, there is an **increase in the free fraction** of one or both drugs that can lead to increased receptor interactions, metabolism, or toxicity of the displaced drug.
4. **Antibiotic therapy** may also influence the metabolic rate of a drug that is dependent on the gut microflora for its metabolism or **enterohepatic circulation** (see III.C.2.b).

I. Route of administration can dramatically influence the metabolic rate of a drug.

1. **Orally administered drugs** are subject to **first-pass metabolism in the liver** through the portal circulation or **presystemic metabolism in the gut**. This first-pass or presystemic metabolism can

significantly reduce the amount of drug that enters the systemic circulation. Often, this problem can be overcome by administering more drug orally so that the systemic concentration is sufficient for pharmacologic activity.

2. **Intravenous administration (IV) bypasses any barriers to GI absorption and first-pass metabolism** and generally requires a smaller dose for the same effect. For example, oral morphine undergoes significant first-pass metabolism so an equivalent IV dose is approximately one-sixth that of an oral dose. **Sublingual** and **buccal administrations** also bypass the first-pass metabolism because they are not part of the portal circulation. **Rectal administration** is more variable but also bypasses first-pass metabolism to a significant extent.

J. The **dose** can also influence the extent of metabolism. There is a finite amount of drug-metabolizing enzymes, so higher doses can result in **saturation** of a particular metabolic pathway. When this occurs, an alternate pathway may contribute to the metabolism of the drug. For example, acetaminophen (Tylenol) given at therapeutic doses is metabolized almost exclusively by glucuronidation and sulfation but toxic doses saturate these processes, leading to increased metabolism by CYP2E1 to the proposed toxic metabolite NAPQI causing hepatotoxicity.

V. PRODRUGS.

These drugs are molecules that are either inactive or very weakly active and require in vivo **biotransformation** to produce the pharmacologically active drug. The phase I metabolic processes discussed previously activate prodrugs. There are a variety of advantages to using a prodrug instead of the active form of the drug.

A. An **increase in water solubility** is useful for the preparation of ophthalmic and parenteral formulations. Sodium succinate esters and sodium phosphate esters have been used to make a number of water-soluble steroid prodrugs.

B. An **increase in lipid solubility** is useful for a variety of reasons.

1. **Increased oral absorption** is obtained by converting carboxylic acid groups to esters. These esters can then be rapidly converted to the active acids by plasma esterases. Enalaprilat is a potent angiotensin-converting enzyme (ACE) inhibitor that is used for parenteral administration, but, due to its high polarity, it is orally inactive. Its monoethyl ester, enalapril (Vasotec), is considerably more lipophilic and, thus, provides good oral absorption. This strategy has been successfully used for a variety of other compounds, including additional ACE inhibitors, fibric acid derivatives, ampicillin, and several cephalosporins.
2. **Increased duration of action**. Lipid-soluble esters of estradiol, such as benzoate, valerate, and cypionate, are used to prolong estrogenic activity. IM injections of these esters in oil result in a deposit of drug that is slowly released and hydrolyzed to free estradiol over a prolonged period (see section VI.A.3).
3. **Increased topical absorption** of steroids is obtained by masking hydroxyl groups with less polar functional groups such as esters or acetonides. This decrease in polarity allows for increased dermal permeability to treat inflammatory, allergic, and pruritic skin conditions. Examples include triamcinolone acetonide (Kenalog), diflorasone diacetate (ApexiCon), and betamethasone valerate (Betaderm).
4. **Increased palatability**. Antibiotics such as sulfisoxazole have a bitter taste and are not suitable for administration to children who are unable to swallow tablets or capsules. Esterification to produce sulfisoxazole acetyl decreases the water solubility of the antibiotic and, thus, decreases its interaction with bitter taste receptors on the tongue. This compound is marketed as a flavored suspension with erythromycin ethylsuccinate. Similar strategies have been used to mask the bitter taste of chloramphenicol and other antibiotics.

C. A **decrease in GI irritation**. NSAIDs produce gastric irritation and ulceration via two mechanisms: a direct irritant effect of the acidic molecule and inhibition of gastroprotective prostaglandin production. The prodrugs sulindac (Clinoril) and nabumetone (Relafen) produce less GI irritation because the gastric and intestinal mucosa are not exposed to high concentrations of active drug during oral administration. Additionally, nabumetone is a ketone, not an acid, and lacks any direct irritant effects.

D. **Site specificity** is useful for increasing the concentration of the drug at the active site and for decreasing side effects.

1. Methyldopa (Aldomet) is a prodrug that is structurally similar to L-dopa. As a result, methyldopa is transported into the central nervous system (CNS) and metabolized to the active

compound, α-methylnorepinephrine, via the same path used for the synthesis of norepinephrine. This allows a significant amount of α-methylnorepinephrine to activate central α_2-adrenergic receptors.

2. Omeprazole (Prilosec) is used to treat gastric ulcers and other hypersecretory disorders. After oral absorption, it is selectively activated at the acidic pH levels (pH less than 1) seen in gastric parietal cells. This allows the active form of the drug to be produced in proximity to the enzyme H^+/K^+-ATPase (proton pump), resulting in irreversible inhibition of the enzyme and a decrease in gastric acid secretion. Activation in the stomach prior to absorption can be prevented by the use of enteric-coated formulations.
3. Formaldehyde is an effective urinary tract antiseptic; however, oral administration results in significant toxicity. To avoid this problem, the prodrug methenamine (Hiprex, Urex) is administered instead. Methenamine is stable and nontoxic at normal physiological pH but is selectively hydrolyzed to formaldehyde and ammonium ions in the acidic urine (pH less than 5.5). As with omeprazole, activation before absorption can be prevented by the use of enteric-coated formulations.
4. Olsalazine (Dipentum) is a highly polar dimer of 5-aminosalicylic acid that is poorly absorbed after oral administration. On reaching the large intestine, colonic bacteria cleave the azo bond and liberate the active anti-inflammatory agent. Olsalazine and a related compound, sulfasalazine, are useful in treating inflammatory bowel disease.

E. Increased shelf life of both solids and parenteral admixtures can be obtained by the use of prodrugs. Cyclophosphamide (Cytoxan) is a prodrug that requires in vivo oxidation, followed by nonenzymatic decomposition, to produce the active phosphoramide mustard. As a result, aqueous solutions of cyclophosphamide are much more stable than those of other nitrogen mustards (i.e., mechlorethamine). Mechlorethamine (Mustargen) is highly reactive, does not require in vivo activation, and can rapidly decompose in aqueous environments before administration.

VI. STRATEGIES TO MANAGE DRUG METABOLISM.

A variety of methods have been used to circumvent the rapid metabolism of certain drugs. These methods seek to improve drug therapy by decreasing the overall extent of metabolism and increasing the duration of action. In some instances, these methods have provided increased site specificity.

A. Pharmaceutical strategies involve the use of different **dosage forms** to either avoid or compensate for rapid metabolism.

1. **Sublingual tablets** are useful for delivering drugs directly into the systemic circulation and avoiding hepatic first-pass metabolism. **Nitroglycerin**, a rapidly acting antianginal agent, is essentially ineffective when administered orally due to an extremely high first-pass effect but is very effective in treating acute attacks of angina if given sublingually.
2. **Transdermal patches** and **ointment formulations** provide a continuous supply of drug over an extended period and are useful for rapidly metabolized compounds such as nitroglycerin. These delivery systems, although not suited to treat acute anginal symptoms, are effective in providing prophylactic concentrations of nitroglycerin.
3. **Intramuscular depot injections** also provide a continuous supply of drug over an extended period. Highly lipid-soluble esters of **estradiol** and **testosterone** (e.g., estradiol benzoate, testosterone enanthate) are slowly absorbed from their administration site. Hydrolysis of these prodrugs (see section V) produces a steady supply of these rapidly metabolized hormones.
4. **Enteric-coated formulations** can protect acid-sensitive drugs as they pass through the acidic environment of the stomach. **Methenamine**, **erythromycin**, and **omeprazole** are examples of acid-sensitive agents that are available as enteric-coated preparations.
5. **Nasal administration** allows for the delivery of peptides such as **calcitonin salmon**, which have very low (if any) oral bioavailability. Characteristics of the mucosa make it ideal for the administration of peptides. Aerosolized drugs only need to penetrate a thin epithelial layer to reach abundant capillary beds.
6. **Inhalation** as a route of administration is most commonly used for local activity but can bypass gastric or hepatic metabolism for systemic administration. This is a viable route of administration for peptides because the lungs contain protease inhibitors that allow for greater stability. Inhaled insulin is effective but was removed from the market because of adverse effects on the lungs.

B. Pharmacological strategies involve the concurrent use of enzyme inhibitors to decrease drug metabolism. In some instances, the concurrent use of an additional agent does not prevent metabolism but rather prevents the toxicity caused by metabolites of the therapeutic agent.

1. **Levodopa** (L-dopa), the amino acid precursor of dopamine, is used in the treatment of parkinsonism. Unlike dopamine, L-dopa can penetrate the blood–brain barrier and reach the CNS. Once in the brain, it is decarboxylated to dopamine. To ensure that adequate concentrations of L-dopa reach the CNS, peripheral metabolism of the drug must be blocked. The concurrent administration of **carbidopa**, a dopa decarboxylase inhibitor that cannot penetrate the blood–brain barrier, prevents peripheral conversion of L-dopa to catecholamines and allows enhanced delivery of L-dopa to the CNS.
2. **β-Lactam antibiotics**. The antibacterial activity of a number of β-lactam antibiotics is reduced by microorganisms capable of secreting the enzyme β-lactamase. This enzyme hydrolyzes the β-lactam ring and inactivates the antibiotic. To counter this resistance mechanism, a β-lactamase inhibitor, such as **clavulanic acid**, is used in conjunction with a penicillin, such as **amoxicillin**, to successfully treat infections caused by β-lactamase–producing bacteria.
3. **Ifosfamide** is an alkylating agent that must undergo in vivo metabolism to produce an active nitrogen mustard. In the process of this metabolic activation, significant concentrations of **acrolein** are produced. These acrolein molecules react with nucleophiles on renal proteins and produce hemorrhagic cystitis. To prevent this toxicity, ifosfamide is always coadministered with **mesna**, a sulfhydryl-containing compound that reacts with and neutralizes any acrolein that is present in the kidney.
4. **HIV protease inhibitors** are extensively metabolized by CYP3A isozymes but they also inhibit these same isozymes in the process. This latter action has been used to optimize therapy. **Ritonavir** is an HIV protease inhibitor with very high affinity for CYP3A isozymes, whereas **lopinavir** is rapidly oxidized and inactivated by the same enzyme. A combination of low dose ritonavir with a therapeutic dose of lopinavir results in an inhibition of CYP3A, the establishment of adequate plasma levels of lopinavir, and therapeutic efficacy without hepatotoxicity.

C. Chemical strategies involve the addition, deletion, or isosteric modification of key functional groups. These molecular modifications hinder or completely eliminate metabolic transformations (*Figure 8-6*).

1. **Testosterone** is not orally active due to rapid oxidation of its 17-hydroxyl group to a ketone. Addition of a 17α-methyl group converts the labile secondary alcohol to a stable tertiary alcohol. The resulting compound, **methyltestosterone**, is only half as potent as testosterone; however, it is

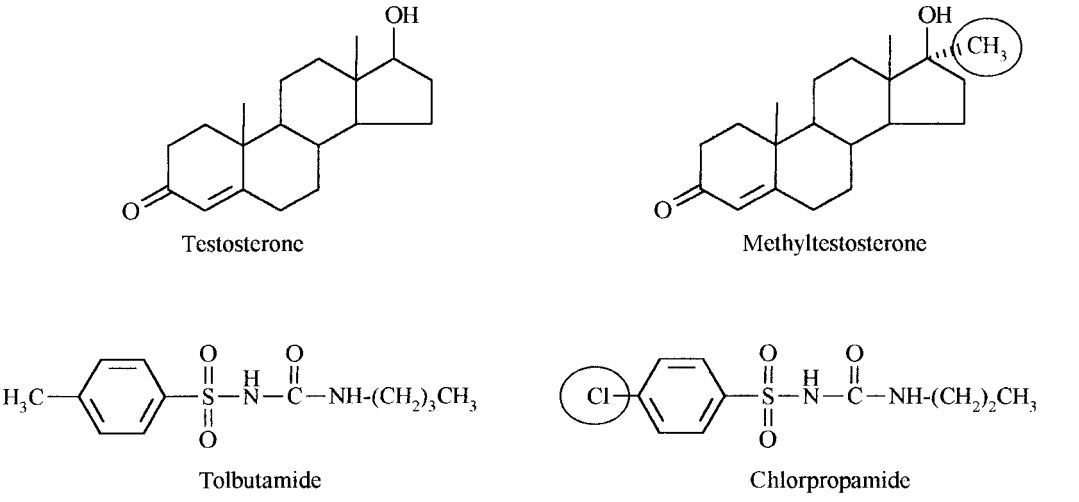


Figure 8-6. Selected examples of chemical modification that eliminate metabolic transformations. Methylation of testosterone blocks the rapid oxidation of the 17-hydroxyl group and allows oral activity, whereas replacement of the metabolically labile *para*-methyl group on tolbutamide with a chloro group allows for a much longer duration of action.

not subject to rapid first-pass metabolism and can be used orally. A similar strategy has been used to make orally active estradiol analogues.

2. **Tolbutamide** is an oral hypoglycemic with a short duration of action. This sulfonylurea rapidly undergoes oxidation of its para-methyl group. A structurally similar compound, **chlorpropamide**, has a nonmetabolizable para-chloro group and, as a result, has a much longer duration of action.
3. **Isoproterenol** is a potent β-adrenergic agonist used for the relief of bronchospasm associated with bronchial asthma. Because it is a catechol (i.e., 3,4-dihydroxy–substituted benzene ring), isoproterenol is subject to rapid metabolism by catechol-*O*-methyltransferase (COMT) and, thus, has poor oral activity. Alteration of the 3,4-dihydroxy substitution to a 3,5-dihydroxy substitution produces **metaproterenol**, a bronchodilator that is not susceptible to COMT, is orally active, and has a longer duration of action than isoproterenol.
4. **Octreotide** is a synthetic octapeptide used to suppress or inhibit severe diarrhea associated with certain tumors. Octreotide mimics the actions of **somatostatin**, a naturally occurring, 14–amino acid peptide. Somatostatin undergoes rapid proteolysis, has a half-life of 1 to 3 mins, and must be administered as a continuous intravenous infusion. Octreotide contains the amino acids essential for clinical efficacy but replaces two of the amino acids with their D-enantiomers. These unnatural D–amino acids are more resistant to hydrolysis. As a result, octreotide has an increased half-life and can be administered as a subcutaneous injection.

VII. PHARMACOGENETICS

PHARMACOGENETICS is the study of the **genetic basis for variation in drug response**. Because genes code for the proteins involved in drug absorption, distribution, metabolism, elimination, and receptors, it is clear that gene changes will alter the response to drugs. In this chapter, we will focus on the genetic basis for variation in drug response with some emphasis on drug metabolism.

A. Phenotypic description of variability. Historically, genetic variation related to drug metabolism has been described in terms of phenotypic observations such as fast or slow metabolizers of a particular compound. Now that the genetics behind the phenotype is often understood, an observed effect or a phenotype can be connected to the gene sequence or **genotype**. With this knowledge, the phenotype can be predicted regardless of the medication in question. The ability to predict drug response as it relates to drug metabolism or other factors is critical in providing truly personalized medicine, the ultimate goal of pharmacogenetics.

B. Genetics review. A review of the vocabulary of genetics will help with the understanding of the genetic basis of variation in drug response and metabolism.

1. **Genes** are defined as a **segment of DNA** that can be replicated for cell division and direct the biosynthesis of specific proteins that include receptors, enzymes, and structural proteins.
2. An **allele** is **one of several variants of a gene**. An individual has two alleles, one allele from each parent, of each gene. In polymorphic genes, the wild-type or most common allele is indicated as the *1 allele and the variant alleles are numbered based on discovery. For example, CYP2D6*1 is the most common allele of cytochrome P450 2D6 but other variants include CYP2D6*3 and CYP2D6*4, both of which lack drug-metabolizing activity.
3. **Promoters** are segments of DNA that aid or direct the transcription of a particular gene.
4. **Transcription** is the process of **copying genes from DNA into complementary RNA called messenger RNA** (**mRNA**). This is the first step in the process of expressing a gene as a protein.
5. **Splicing** is the **processing of mRNA** to remove the **introns** (noncoding RNA) and join together **exons** (coding mRNA) to make mature mRNA that encodes for the desired protein.
6. **Translation** is the process of converting the processed or mature **mRNA into protein**. Translation occurs on the **ribosomes** using transfer RNA (tRNA) to read the mRNA and produce a chain of amino acids. The amino acids are connected by peptide, or amide, bonds to make a protein.
7. **Polymorphism** is defined as the existence of two or more variants of a gene that occur in the population with a population frequency of at least 1% for the less common variant.

C. Genetic variation in the DNA sequence can cause certain populations of individuals to be more likely to develop specific disease states, to be more likely to follow a specific path of disease progression, to

be more likely to respond to specific drug therapy, and/or to be more likely to develop certain adverse drug effects. It is estimated that individuals differ from one another by one nucleotide, or SNP, every 300–1000 nucleotides in the genome.

1. The most common type of genetic variation is the **single nucleotide polymorphism** (SNP). The consequence of a SNP depends on its location and the change itself.
   a. SNP, pronounced "snip," is a single base pair change in the DNA sequence at a particular point compared with the "common" or "wild-type" gene sequence.
   b. A **synonymous SNP** in the coding region does not result in a change in the amino acid sequence compared to the common or wild-type sequence and therefore generally has no discernible effects.
   c. A **nonsynonymous SNP** in the coding region results in a change in the amino acid sequence compared to the common or wild-type gene. This change can have negligible effects if the new amino acid has similar properties as compared to the original amino acid (e.g., aspartic acid replaced with a glutamic acid) or can have significant effects if the properties change sufficiently (e.g., aspartic acid replaced with lysine). As an example of a significant, nonsynonymous SNP, a mutation from A to C at position 3023 of the CYP2D6 gene results in histidine 324 in the native protein being replaced by a proline ($H_{324}P$). This change produces the allele identified as CYP2D6*7, which has no drug-metabolizing activity.
   d. SNPs outside of the coding region may not influence the amino acid composition of the protein but can have significant effects on the expression of a protein. SNPs in a **promoter** can alter the transcription rate of the target protein, resulting in either more or less of the protein being expressed. SNPs in a **splicing control** region may result in alternative splicing, creating either a novel protein or a nonsense codon that terminates that translation of the protein. In each of these examples, expression and activity of the gene is altered. Vitamin K epoxide reductase complex 1 (VKORC1) is an example of a protein where SNPs in the promoter region result in various levels of protein expression. This is important because VKORC1 is the molecular target for the anticoagulant warfarin. The efficacy of warfarin varies widely across the population and about 25% of this dose variation can be explained by variability in the expression of VKORC1.
2. Other common genetic variations, which may be SNPs, are **insertions** and **deletions**. Just as the name sounds, nucleotides are either inserted or deleted from the sequence of the gene. Recall that nucleotides are translated into amino acids using a three-nucleotide codon, so adding or deleting one nucleotide can result in the significant changes to the gene. The CYP2D6*3 allele is the result of a deletion of one nucleotide (A_{2637}), which causes a reading frameshift in translation. This change results in CYP2D6 with no activity.
3. **Copy number variations** are also a possible genetic variation. In this case, large segments of DNA are duplicated, deleted, or inverted. In duplications, the gene of interest is repeated in the genome multiple times. A deletion is a complete absence of the functional gene, and inversions may disrupt gene function by changing the location of the gene and its promoters. CYP2D6 is one drug-metabolizing enzyme identified to have multiple copies (CYP2D6xN where N is between 2 and 12 copies) of the functional CYP2D6 gene. These multiple copies result in a very high expression of functional CYP2D6. These patients are ultrarapid metabolizers of CYP2D6 substrates.

D. Clinical pharmacogenetic assays

1. The goal of a clinical pharmacogenetic assay is to provide the best patient care possible to prevent adverse effects while gaining the best response possible. Ideally, a useful clinical pharmacogenetic assay will place patients into one of four categories.
   a. Individuals who are most likely to respond and are at a low risk for adverse effects.
   b. Individuals who are most likely to respond and are at a high risk for adverse effects.
   c. Individuals who are less likely to respond and are at low risk for adverse effects.
   d. Individuals who are less likely to respond and are at a high risk for adverse effects.
2. There are several known genetic variations that affect specific drug efficacy and safety. These variations are related to alterations in drug-metabolizing enzymes, targets, or side effects.
   a. **Warfarin** (Coumadin). Patients demonstrate significant variation in the effective dose of warfarin, which requires careful monitoring and a personalized dose. Part of this variability can be explained by the variation in the drug-metabolizing enzyme CYP2C9. Polymorphisms in

CYP2C9 result in slower clearance of warfarin that translates into drug accumulation and increased risk for bleeding at average doses. Of particular concern are the patients that carry the CYP2C9*2 or CYP2C9*3 allele, which encode for CYP2C9 protein with greatly reduced enzymatic activity. As a result, the metabolism of warfarin is dramatically diminished and the risk for drug accumulation and bleeding is significant. More of the variation can be explained by the variable expression of vitamin K epoxidase (VKORC1), the molecular target for warfarin. This variation is dependent on a SNP in the promoter region of VKORC1. Genetic tests for both CYP2C9 and VKORC1 are recommended in the warfarin labeling as tests that will provide guidance in induction and final therapeutic dose for individuals with specific CYP2C9 and VKORC1 alleles.

b. **6-Mercaptopurine** (Purinethol) and **azathioprine** (Imuran), which is initially bioactivated to 6-mercaptopurine, are inactivated by the drug-metabolizing enzyme **thiopurine methyltransferase** (TPMT). Genetic variations in TPMT, including the TPMT*2, TPMT*3A, and TPMT*3C alleles, are known to result in decreased metabolizing capacity and increased bone marrow toxicity as 6-mercaptopurine accumulates in the body. Although the genotypes for TPMT are known, phenotyping of red blood cells is more commonly used to evaluate TPMT activity.

c. **Procainamide** (Pronestyl), **hydralazine** (Apresoline), and **isoniazid** (Stanozide) are metabolized by ***N*-acetyltransferase**, a polymorphic drug-metabolizing enzyme. Each of these drugs listed here has a different adverse effect profile based on the ability of variants of *N*-acetyltransferase to metabolize the targets. A slow acetylator taking these drugs is likely to accumulate the drug and develop symptoms of overdose, including hypotension and lupus-like syndrome for procainamide and hydralazine and peripheral neuropathy for isoniazid. Although genetic tests are commercially available, there is currently no recommendation for testing.

d. **Salmeterol** (Serevent Diskus) and **albuterol** (Proventil or Ventolin) are **β_2-adrenergic receptor agonists** used to treat **asthma**. Genetic variations in the β_2-adrenergic receptor yield different responses to these agonists, which results in differences in efficacy in the treatment of asthma. Currently, the labeling for the β_2-agonists does not include a recommendation for genetic testing.

e. **Maraviroc** (Selzentry) is an HIV drug that is only active against HIV infections that require the **CCR5 coreceptor** to penetrate cells. Maraviroc works by antagonizing the CCR5 receptor, but if the HIV does not require CCR5 to penetrate the cell, it will not be effective in the treatment of HIV infections. To determine the HIV-1 tropism, a DNA test of the virus in a patient's blood, called a Trofile DNA, can be performed. A phenotypic assay can also be performed if there is a significant viral load detected called Trofile.

f. **Abacavir** (Ziagen) is an HIV drug that is associated with a serious **hypersensitivity reaction** associated with a particular variation in the major histocompatibility complex, class I, B allele (i.e., HLA-B*5701). Patients with the HLA-B*5701 allele are about 15 times more likely to develop abacavir hypersensitivity when compared to patients without the HLA-B*5701 allele. Genetic screening for the HLA-B*5701 allele is recommended prior to abacavir treatment but does not eliminate the risk for serious abacavir hypersensitivity.

g. **Codeine** is a mild analgesic that is **metabolized by CYP2D6** to morphine, a much more potent analgesic. **CYP2D6 is highly polymorphic**, including a potential for multiple copies of the gene resulting in an ultrametabolizer phenotype. This can lead to increased metabolism to morphine and increases in morphine-related toxicity, including constipation and respiratory depression. CYP2D6 also contributes to the metabolism of several selective serotonin reuptake inhibitors (i.e., fluoxetine [Prozac]), tricyclic antidepressants (i.e., amitriptyline [Elavil]), antipsychotics (i.e., clozapine [Clozaril]), and beta-blockers (i.e., propranolol [Inderal]). In these cases, the CYP2D6 alleles, CYP2D6*3, *4, *5, or *6, that are associated with poor metabolizers result in drug accumulation and toxicity. Genetic testing for CYP2D6 is commercially available, and the consequences of polymorphisms are mentioned in the drug labeling of several agents, but genetic testing is not widely recommended.

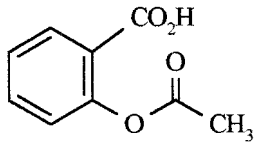
Study Questions

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the one lettered answer or completion that is **best** in each case.

1. Which of the following statements concerning drug metabolism is true?

(A) Generally, a single metabolite is excreted for each drug administered.
(B) Often, a drug may undergo a phase II reaction followed by a phase I reaction.
(C) Drug-metabolizing enzymes are found only in the liver.
(D) All metabolites are less active pharmacologically than their parent drugs.
(E) Phase I metabolites more likely are able to cross cellular membranes than phase II metabolites.

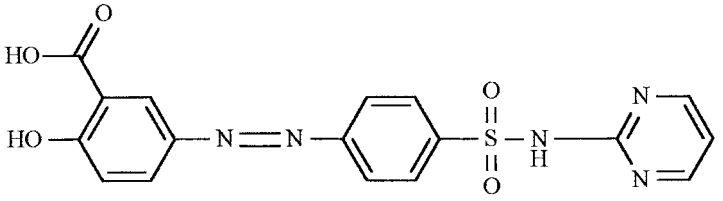
2. Which of the following metabolites would be the least likely excretion product of orally administered aspirin (see structure below)?



(A) Glycine conjugate
(B) Ester glucuronide
(C) Unchanged drug
(D) Ether glucuronide
(E) Hydroxylated metabolite

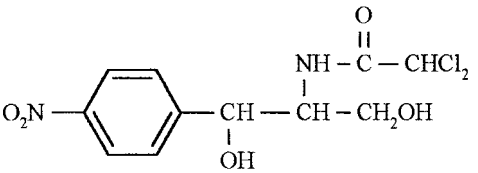
3. Sulfasalazine (see structure below) is a prodrug that is activated in the intestine by bacterial enzymes. The enzyme most likely responsible is

(A) azoreductase.
(B) pseudocholinesterase.
(C) *N*-acetyltransferase.
(D) β-glucuronidase.
(E) methyltransferase.



4. Chloramphenicol (see structure below) is considered to be toxic in infants (gray baby syndrome). This is due to tissue accumulation of unchanged chloramphenicol, resulting from an immature metabolic pathway. Which of the following enzymes would most likely be deficient?

(A) Pseudocholinesterase
(B) Glucuronyltransferase
(C) *N*-Acetyltransferase
(D) Azoreductase
(E) Methyltransferase



5. Which of the following therapeutic advantages cannot be obtained by the use of prodrugs?

(A) oral absorption
(B) water solubility
(C) duration of action
(D) potency
(E) palatability

6. Which of the following routes of administration would be subject to first-pass metabolism in the liver?
   (A) IV (intravenous)
   (B) Inhalation
   (C) Sublingual
   (D) IM (intramuscular)
   (E) Oral

7. A compound that slows the metabolism of a xenobiotic is called a(n)
   (A) inducer.
   (B) epimer.
   (C) reductase.
   (D) inhibitor.
   (E) object.

8. Which family of drug-metabolizing enzymes is characterized as a microsomal enzyme that contains a porphyrin prosthetic group?
   (A) Glucuronosyltransferases
   (B) Cytochrome P450s
   (C) Flavin-containing monooxygenases
   (D) Esterases
   (E) *N*-Acetyltransferases

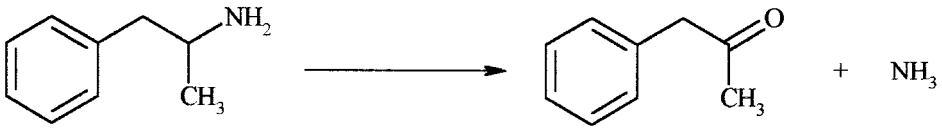
9. The most common type of genetic variation is a(n)
   (A) copy number variation.
   (B) insertion.
   (C) deletion.
   (D) frameshift.
   (E) single nucleotide polymorphism.

10. Which polymorphic enzyme is responsible for the conversion of codeine to morphine?
    (A) TPMT
    (B) *N*-Acetyltransferase
    (C) CYP2D6
    (D) CYP2C9
    (E) CCR5 coreceptor

Directions: Each question in this section contains three suggested answers, of which **one or more** is correct. Choose the answer.

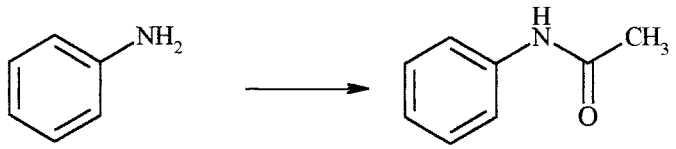
A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I**, **II**, **and III** are correct

11. Terms that may be used to describe the following metabolic reaction include
    I. *N*-oxidation.
    II. oxidative deamination.
    III. phase I metabolism.

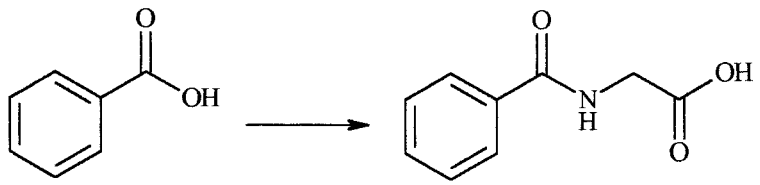


12. Which of the following reactions can be classified as phase II metabolism?

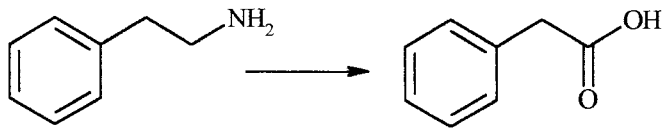
I.



II.



III.



13. Conditions that tend to increase the action of an orally administered drug that undergoes phase II metabolism include

- **I.** enterohepatic circulation.
- **II.** enzyme saturation.
- **III.** first-pass effect.

14. Which of the following statements concerning CYP450 are correct?

- **I.** The CYP7, CYP11, and CYP27 subfamilies are involved in steroid and bile acid synthesis and metabolism.
- **II.** A single drug may be metabolized by multiple isoforms of CYP450.
- **III.** The majority of xenobiotics, or drugs, are metabolized by the CYP4B and CYP1A subfamilies.

15. Which of the following are genetic contributors to variation in the therapeutic dose of warfarin among patients?

- **I.** CYP2C9
- **II.** VKORC1
- **III.** CYP2D6

16. Examples of phase II enzymes include

- **I.** CYP450.
- **II.** *N*-acetyltransferase.
- **III.** sulfotransferase.

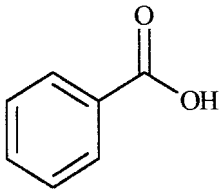
Directions: The group of items in this section consists of lettered options followed by a set of numbered items. For each item, select the **one** lettered option that is most closely associated with it. Each lettered option may be selected once, more than once, or not at all.

Questions 17–20

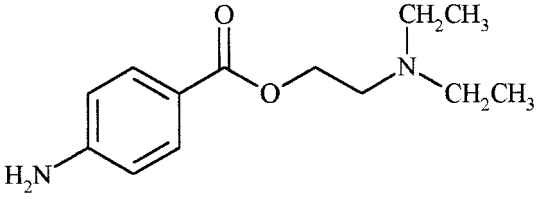
For each drug, select its most likely metabolic pathway.

(A) Ether glucuronidation
(B) Ester glucuronidation
(C) Nitroreduction
(D) Oxidative deamination
(E) Ester hydrolysis

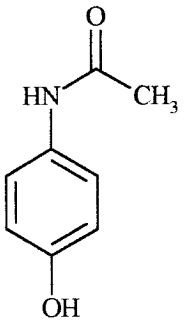
17. Benzoic acid



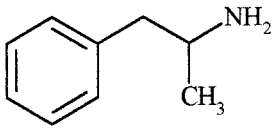
18. Procaine



19. Acetaminophen



20. Amphetamine



Answers and Explanations

1. The answer is E *[see III.A; III.B]*.
Phase I metabolites are often somewhat more polar than their parents. With the exception of acetylated and methylated metabolites, phase II metabolites are much more polar than their parents. Thus, phase I metabolites are more likely to retain some lipid solubility and are more likely to cross cellular membranes.

It is unusual for a single metabolite to be excreted for a given drug. Most drugs yield a mixture of metabolites. Because of the high polarity and subsequent high excretion of phase II metabolites, they are not likely to undergo further metabolism. Phase I metabolites, on the other hand, are less polar and are very likely to undergo further phase II metabolic reactions.

Whereas the major site of metabolism is the liver, there are many extrahepatic sites that secrete drug-metabolizing enzymes. Although many metabolites are less pharmacologically active than their parents, there are many drugs whose metabolites have equal or greater pharmacological activity and sometimes greater toxicity as well. Prodrugs (i.e., drugs inactive in the form administered) always form at least one active metabolite.

2. The answer is C *[see III.B.1; III.B.3; Table 8-1]*.
Because of the types of functional groups present, aspirin may undergo a number of different metabolic reactions. These include hydroxylation of the aromatic nucleus, conjugation of the carboxyl group with glycine,

conjugation of the carboxyl group with glucuronic acid with the formation of an ester glucuronide, hydrolysis of the acetate ester, and conjugation of the phenol group (resulting from hydrolysis of the acetate ester) with glucuronic acid to form an ether glucuronide.

Because the acetate ester is a simple ester, aspirin is susceptible to hydrolysis in the acid media of the stomach before absorption takes place. In addition, any acetylated molecules that are absorbed are subjected to hydrolysis and are catalyzed by the many esterases present in the circulation. Any acetylated molecules not hydrolyzed in the circulation are subject to hydrolysis in the liver. All of these processes occur before the drug reaches the glomerular filtrate; therefore, excretion of the unchanged acetylated drug is highly unlikely.

3. **The answer is A** *[see III.A.8.c; Table 8-2]***.**
Sulfasalazine has both anti-inflammatory and antibacterial activity when converted to aminosalicylic acid and sulfapyridine in the body. This reaction occurs by reductive cleavage of the "azo" linkage contained in the sulfasalazine molecule and is catalyzed in the intestine by bacterial azoreductase. This is a form of site-specific delivery because the intact drug is not absorbed from the stomach or upper intestine and reaches the colon, where it is metabolized. Sulfasalazine is one of a few drugs that are effective for the treatment of ulcerative colitis.

4. **The answer is B** *[see IV.D.1; Table 8-4]***.**
The chloramphenicol molecule contains an aromatic nucleus, which would be subject to hydroxylation; a nitro group that is subject to reduction; an amide group that is subject to liver hydrolysis; and alcohol groups that are subject to glucuronidation. Of all the enzyme systems responsible for these reactions, the system responsible for glucuronidation is developed poorly in premature infants and infants up to approximately 6 to 8 weeks of age.

5. **The answer is D** *[see V]***.**
By definition, prodrugs are inactive or very weakly active molecules that require in vivo activation to the parent molecule. Thus, conversion of a drug molecule to a prodrug does not increase potency because the original molecule, with whatever potency it contains, is produced after administration. A variety of advantages, including increased water solubility, duration of action, oral absorption, and palatability, can be obtained through the use of prodrugs, but none of these advantages results in an increase in potency of the parent molecule.

6. **The answer is E** *[see IV.I.1–2]***.**
First-pass metabolism in the liver refers to biotransformation of a xenobiotic after absorption from the GI tract before it reaches the systemic circulation. Orally administered drugs that are absorbed from the GI tract enter the portal circulation and pass through the liver where they are metabolized. Routes of administration that bypass the first-pass metabolism in the liver include IV, IM, sublingual, buccal, rectal, and inhalation. These routes of administration allow for absorption either outside of the GI tract or in regions of the GI tract that are not part of portal circulation.

7. **The answer is D** *[see IV.H.2]***.**
An inhibitor, also called the precipitant drug, is a substance that blocks the metabolism of another drug called the *object drug*. An inducer is a compound that increases the expression of drug-metabolizing enzymes. Both inhibitors and inducers alter drug metabolism that may cause toxicity or lack of efficacy depending on the metabolic consequence of the object drug.

8. **The answer is B** *[see II.A.2.a]***.**
The family of cytochrome P450 enzymes are microsomal proteins that contain a porphyrin prosthetic group. Glucuronosyltransferases and flavin-containing monooxygenases are both microsomal enzymes, but they do not contain the porphyrin group.

9. **The answer is E** *[see VII.C.1–3]***.**
The most common genetic variation is a single nucleotide polymorphism (SNP), which may be an insertion or deletion that causes a frameshift. These polymorphisms can be called a synonymous SNP if the amino acid expressed is not changed or a nonsynonymous SNP if the amino acid expressed is different. These polymorphisms may also influence the promoter region or the splicing sites for proteins that would not result differences in the amino acids expressed. Multiple copies of a gene, as reported with CYP2D6, are called copy number variations.

10. **The answer is C** *[see VII.D.2.a–c, e, & g]***.**
CYP2D6 is a highly polymorphic drug-metabolizing enzyme that is responsible for the conversion of codeine to morphine. TPMT, *N*-acetyltransferase, and CYP2C9 are polymorphic drug-metabolizing enzymes but are not responsible for the conversion codeine to morphine. The CCR5 coreceptor is not a drug-metabolizing enzyme but is involved in the cellular penetration of HIV.

11. The answer is D (II, III) *[see III.A; Table 8-1]***.**
The reaction shown in the question involves the conversion of one functional group to another (amine to carbonyl); thus, it is classified as a phase I reaction. The introduction of oxygen into the molecule indicates oxidation, and the loss of the amino group signifies deamination; thus, the reaction also can be classified as oxidative deamination. *N*-Oxidation reactions by CYP450 or FMO are observed but result in the addition of an oxygen to the nitrogen. In this case, no oxygen has been added to the nitrogen; therefore, this is not an *N*-oxidation reaction.

12. The answer is C (I, II) *[see III.A–B; Table 8-4]***.**
Phase II metabolic reactions involve masking an existing functional group with a natural endogenous constituent. The formulas shown in choices I and II represent this type of reaction, with choice I being an acetylation reaction and choice II a glycine conjugation reaction. Choice III represents a change in an existing functional group and, thus, represents a phase I reaction. It is an oxidative deamination reaction.

13. The answer is C (I, II) *[see III.C.2.b; IV.I.1; IV.J]***.**
Enterohepatic circulation refers to the process by which glucuronides, which are secreted into the intestine with the bile, are hydrolyzed by intestinal bacterial β-glucuronidase. The hydrolyzed free drug, which is no longer polar, becomes available for intestinal reabsorption into the system and subsequent penetration to its active site.

If an enzyme system becomes saturated, then the active drug cannot be inactivated by that pathway. If the drug cannot undergo an alternative pathway, the increased plasma levels of an unchanged active drug can result in increased activity or toxicity.

The first-pass effect results in metabolism of a drug by the liver before the drug reaches its site of action, resulting in an overall decrease in its activity. Drugs that undergo first-pass metabolism generally are effective in much smaller intravenous doses as compared to oral doses.

14. The answer is C (I, II) *[see I; III.A.2.b]***.**
There are six mammalian families involved in steroid and bile acid metabolism. These are CYP7, CYP11, CYP17, CYP19, CYP21, and CYP27. Because cholesterol is the common intermediate for the biosynthesis of all endogenous steroids, some of these enzymes are directly involved in cholesterol metabolism. The families listed, CYP7, CYP11, and CYP27, all metabolize cholesterol, whereas the other three families catalyze additional oxidations of the initial metabolites.

There are multiple enzymes and paths that are possible for a single xenobiotic, so it is common that multiple metabolites with varying properties are possible and observed. The cytochrome P450 subfamilies responsible for the majority of the biotransformations are CYP2C, CYP2D, and CYP3A.

15. The answer is C (I, II) *[see VII.D.2.a]***.**
Some of the individual variability in dosing is related to the metabolism of warfarin by CYP2C9 and by the level of expression of the warfarin target, VKORC1. With CYP2C9, the variability is related to differences in the metabolic efficiency of the different alleles, whereas differences in the promoter region of VKORC1 result in different levels of expression of the enzyme inhibited by warfarin. CYP2D6, although highly polymorphic, does not contribute to the variability of warfarin dosing.

16. The answer is D (II, III) *[see III.A.2; III.B.2 & 5]***.**
Phase II drug-metabolizing enzymes are commonly called transferase enzymes because they transfer a biomolecule from an activated cofactor to a target functional group. Phase II enzymes include glucuronosyltransferase, sulfotransferase, *N*-acyltransferase, glutathione-S-transferase, *N*-acetyltransferase, and methyltransferase. CYP450 is the most common phase I enzyme.

17–20. The answers are 17-B *[see III.B.1]***, 18-E** *[see III.A.9.a]***, 19-A** *[see III.B.1]***, 20-D** *[see Table 8-1]***.**
Benzoic acid contains a carboxylic acid, a functional group that commonly undergoes conjugation with glucuronic acid. The resulting conjugation produces an ester. Carboxylic acids can also undergo conjugation with the amino acids glycine and glutamine. Additionally, benzoic acid can undergo aromatic hydroxylation, a common phase I pathway for drugs containing unsubstituted aromatic rings. Of these options, ester glucuronidation is the only answer available here.

Procaine is an ester-containing local anesthetic. Due to the wide physiological distribution of esterase enzymes, it is extremely susceptible to in vivo hydrolysis. This susceptibility to hydrolysis is the major reason why ester-containing local anesthetics have shorter durations of action as compared to those in other chemical classes.

One of the principal functional groups in acetaminophen is the phenol group. Similar to the carboxylic acid in benzoic acid, the phenol commonly undergoes glucuronide conjugation. The one difference is that a phenol (or an alcohol) produces an **ether** glucuronide, whereas a carboxylic acid produces an **ester** glucuronide. Phenols also commonly undergo sulfate conjugation reactions and occasionally undergo O-methylation reactions.

The principal functional group in amphetamine is its primary amine. Oxidative deamination is a very common metabolic path for primary amines. Occasionally, primary amines undergo phase II acetylation; however, this is a less common pathway. Aromatic hydroxylation, similar to that discussed previously for benzoic acid, is also possible for amphetamine.