Briefing

C 1160 Pharmaceutical Calculations in Prescription Compounding, USP 37 page 1033. It is proposed to change the title of this general information chapter to Pharmaceutical Calculations in Pharmacy Practice C 1160. This change will provide a better description of the contents of the revised general chapter. The proposed general chapter is revised with new material that includes the deletion of problem types that are no longer relevant, more practical pharmaceutical calculations and problem examples, updated definitions, new sections, and added resources. The new information proposed in this chapter will educate the reader on the advancements in pharmacy practice.

Additionally, minor editorial changes have been made to update the chapter to current USP style.

The proposed chapter is posted online at www.usp.org/usp-nf/notices/GC1160-compounding-notice with line numbers. To ensure that your comments are received and addressed, please provide the line numbers corresponding to your comments when submitting comments to CompoundingSL@usp.org.

(CMP: J. Sun.) Correspondence Number—C135267

Change to read:

1160 PHARMACEUTICAL CALCULATIONS IN PRESCRIPTION COMPOUNDING PHARMACY PRACTICE. 1S (USP38)

Change to read:

INTRODUCTION

The purpose of this chapter is to provide general information to guide and assist pharmacists in performing the necessary calculations when preparing or compounding any pharmaceutical article (see Pharmaceutical Compounding—Nonsterile Preparations C 795), Pharmaceutical Compounding—Sterile Preparations C 797, and Good Compounding Practices C 1075) or when simply dispensing prescriptions (see Stability Considerations in Dispensing Practice C 1191).
Correct pharmaceutical calculations can be accomplished by using, for example, proper conversions from one measurement system to another and properly placed decimal points, by understanding the arithmetical concepts, and by paying close attention to the details of the calculations. Before proceeding with any calculation, pharmacists should do the following: (a) read the entire formula or prescription carefully; (b) determine which materials are needed; and then (c) select the appropriate methods of preparation and the appropriate calculation.

There are often several ways to solve a given problem. Logical methods that require as few steps as possible should be selected in order to ensure that calculations are done correctly. The best approach is the one that yields results that are accurate and free of error. The pharmacist must double-check each calculation before proceeding with the preparation of the article or prescription order. One way of double-checking is by estimation. This involves rounding off the quantities involved in the calculation, and comparing the estimated result with the calculated value.

Finally, the following steps should be taken: the dosage of each active ingredient in the prescription should be checked; all calculations should be doubly checked, preferably by another pharmacist; and where instruments are used in compounding, they should be carefully checked to ascertain that they will function properly. See USP general chapters Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers, Deliverable Volume, Density of Solids, Osmolality and Osmolarity, pH, Pharmaceutical Compounding—Nonsterile Preparations, Pharmaceutical Compounding—Sterile Preparations, Viscosity, Specific Gravity, Cleaning Glass Apparatus, Medicine Dropper, Prescription Balances and Volumetric Apparatus, Teaspoon, Weighing on an Analytical Balance, and Good Compounding Practices for information on specific instruments.

**BASIC MATHEMATICAL CONCEPTS**

**SIGNIFICANT FIGURES**

Expressed values are considered significant to the last digit shown (see Significant Figures and Tolerances in the General Notices). Significant figures are digits with practical meaning. The accuracy of the determination is implied by the number of figures used in its expression. In some calculations zeros may not be significant. For example, for a measured weight of 0.0298 g, the zeros are not significant; they are used merely to locate the decimal point. In the example, 2980 g, the zero may also be used to indicate the decimal point, in which case the zero is not significant. Alternately, however, the zero may indicate that the weight is closer to 2981 g or 2979 g, in which case the zero is significant. In such a case, knowledge of the method of measurement would be required in order to indicate whether the zero is or is not significant. In the case of a volume measurement of 298 mL, all of the digits are significant. In a given result, the last significant figure written is approximate but all preceding figures are accurate. For example, a volume of 29.8 mL implies that 8 is approximate.
volume falls between 29.75 and 29.85. Thus, 29.8 mL is accurate to the nearest 0.1 mL, which means that the measurement has been made within ±0.05 mL. Likewise, a value of 298 mL is accurate to the nearest 1 mL and implies a measurement falling between 297.5 and 298.5, which means that the measurement has been made within ±0.5 mL and is subject to a maximum error calculated as follows:

\[(0.5 \text{ mL} / 298 \text{ mL}) \times 100\% = 0.17\%\]

A zero in a quantity such as 298.0 mL is a significant figure and implies that the measurement has been made within the limits of 297.95 and 298.05 with a possible error calculated as follows:

\[(0.05 \text{ mL} / 298.0 \text{ mL}) \times 100\% = 0.017\%\]

**EXAMPLES—**

1. 29.8 mL = 29.8 ± 0.05 mL (accurate to the nearest 0.1 mL)
2. 29.80 mL = 29.80 ± 0.005 mL (accurate to the nearest 0.01 mL)
3. 29.800 mL = 29.800 ± 0.0005 mL (accurate to the nearest 0.001 mL)

The degree of accuracy in the last example is greatest. Thus, the number of significant figures provides an estimate both of true value and of accuracy.

**EXAMPLES OF SIGNIFICANT FIGURES—**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Number of Significant Figures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.98</td>
<td>3</td>
</tr>
<tr>
<td>2.980</td>
<td>4</td>
</tr>
<tr>
<td>0.0298</td>
<td>3</td>
</tr>
<tr>
<td>0.0029</td>
<td>2</td>
</tr>
</tbody>
</table>

**Calculations—** All figures should be retained until the calculations have been completed. Only the appropriate number of significant figures, however, should be retained in the final result.

**Determining the number of significant figures—**

**Sums and Differences—** When adding or subtracting, the number of decimal places in the result shall be the same as the number of decimal places in the component with the fewest decimal places.

**EXAMPLE—**

\[11.5 + 11.65 + 9.90 = 33.1\]

**Products and Quotients—** When multiplying or dividing, the result shall have no more significant figures than the measurement with the smallest number of significant figures entering into the calculation.
EXAMPLE—

\[ 4.266 \times 21 = 90 \]

Rounding Off—For rules on rounding off measurements or calculated results, see Interpretation of Requirements under Significant Figures and Tolerances in the General Notices. Note, however, that in the example above, if 21 is an absolute number (e.g., the number of doses), then the answer, 89.586, is rounded off to 89.59 which has 4 significant figures.

LOGARITHMS

The logarithm of a number is the exponent or the power to which a given base must be raised in order to equal that number.

Definitions—

\[ \text{pH} = -\log [\text{H}^+] \text{, and} \]
\[ \text{pKa} = -\log \text{Ka} \]

\[ \text{pH} = -\log [\text{H}^+] \text{, and pKa} = -\log \text{Ka} \text{, where [H+] is the hydrogen ion concentration in an aqueous solution and Ka is the ionization constant of the acid in an aqueous solution.} \]

The \([\text{H}^+] = \text{the antilogarithm of (-pH)}\), and the \(\text{Ka} = \text{the antilogarithm of (-pKa)}\).

The pH of an aqueous solution containing a weak acid may be calculated using the Henderson-Hasselbalch equation:

\[ \text{pH} = \text{pKa} + \log \frac{[\text{salt}]}{[\text{acid}]} \]

EXAMPLE—

A solution contains 0.020 moles per L of sodium acetate and 0.010 mole per L of acetic acid, which has a pKa value of 4.76. Calculate the pH and the \([\text{H}^+]\) of the solution.

Substituting into the above equation, \(\text{pH} = 4.76 + \log \frac{0.020}{0.010} = 5.06\), and the \([\text{H}^+] = \text{antilogarithm of (-5.06)} = 8.69 \times 10^{-6}.\)

BASIC PHARMACEUTICAL CALCULATIONS

The remainder of this chapter will focus on basic pharmaceutical calculations. It is important to recognize the rules involved when adding, subtracting, dividing, and multiplying values. The interrelationships between various units within the different weighing and measuring systems are also important and have to be understood.

CALCULATIONS IN COMPOUNDING

The pharmacist must be able to calculate the amount or concentration of drug substances in each unit or dosage portion of a compounded preparation at the time it is dispensed. Pharmacists must perform calculations and measurements to obtain, theoretically, 100% of the amount of each ingredient in compounded formulations. Calculations must account for the active ingredient, or active moiety, and water content of drug substances, which includes that in the chemical formulas of hydrates. Official drug substances and added substances must meet the requirements under Loss on Drying (731), which must be included in the calculations of amounts and concentrations of ingredients. The pharmacist should consider the effect of ambient humidity on the gain or loss of water from drugs and added substances in containers.
subjected to intermittent opening over prolonged storage. Each container should be opened for the shortest duration necessary and then closed tightly immediately after use.

The nature of the drug substance that is to be weighed and used in compounding a prescription must be known exactly. If the substance is a hydrate, its anhydrous equivalent weight may need to be calculated. On the other hand, if there is adsorbed moisture present that is either specified on a certificate of analysis or that is determined in the pharmacy immediately before the drug substance is used by the procedure under Loss on Drying, this information must be used when calculating the amount of drug substance that is to be weighed in order to determine the exact amount of anhydrous drug substance required.

There are cases in which the required amount of a dose is specified in terms of a cation [e.g., Li⁺, netilmicin (n⁺)], an anion [e.g., F⁻], or a molecule (e.g., theophylline in aminophylline). In these instances, the drug substance weighed is a salt or complex, a portion of which represents the pharmacologically active moiety. Thus, the exact amount of such substances weighed must be calculated on the basis of the required quantity of the pharmacological moiety.

The following formula may be used to calculate the exact theoretical weight of an ingredient in a compounded preparation:

$$ W = \frac{ab}{de} $$

in which $W$ is the actual weighed amount; $a$ is the prescribed or pharmacist-determined weight of the active or functional moiety of drug or added substance; $b$ is the chemical formula weight of the ingredient, including waters of hydration for hydrous ingredients; $d$ is the fraction of dry weight when the percent by weight of adsorbed moisture content is known from the loss on drying procedure (see Loss on Drying); and $e$ is the formula weight of the active or functional moiety of a drug or added substance that is provided in the formula weight of the weighed ingredient.

**Example 1:** Triturate Morphine Sulfate USP and Lactose NF to obtain 10 g in which there are 30 mg of Morphine Sulfate USP for each 200 mg of the morphine-lactose mixture. [NOTE—Clinical dosages of morphine mean Morphine Sulfate USP, which is the pentahydrate.]

<table>
<thead>
<tr>
<th>Equation Factor</th>
<th>Numerical Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$W$</td>
<td>weight, in g, of Morphine Sulfate USP</td>
</tr>
<tr>
<td>$a$</td>
<td>1.5 g of morphine sulfate pentahydrate in the prescription</td>
</tr>
<tr>
<td>$b$</td>
<td>759 g/mole</td>
</tr>
<tr>
<td>$d$</td>
<td>1.0</td>
</tr>
<tr>
<td>$e$</td>
<td>759 g/mole</td>
</tr>
</tbody>
</table>

$$ W = \frac{(1.5 \times 759 \text{ g/mole})}{(1.0 \times 759 \text{ g/mole})} = 1.5 \text{ g} $$

**Example 2:** Accurately weigh an amount of Aminophylline USP to obtain 250 mg of anhydrous theophylline. [NOTE—The powdered aminophylline dihydrate weighed contains 0.4% w/w adsorbed moisture as stated in the Certificate of Analysis.]
**Example 3:** Accurately weigh an amount of Lithium Citrate USP (containing 2.5% moisture as stated in the Certificate of Analysis) to obtain 200 mEq of lithium (Li⁺).

[NOTE—One mEq of Li⁺ is equivalent to 0.00694 g of Li⁺.]

<table>
<thead>
<tr>
<th>Equation Factor</th>
<th>Numerical Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>W</strong></td>
<td>weight, in g, of Lithium Citrate USP (tetrahydrate)</td>
</tr>
<tr>
<td><strong>a</strong></td>
<td>200 mEq of Li⁺ or 1.39 g of Li⁺</td>
</tr>
<tr>
<td><strong>b</strong></td>
<td>282 g/mole</td>
</tr>
<tr>
<td><strong>d</strong></td>
<td>0.975</td>
</tr>
<tr>
<td><strong>e</strong></td>
<td>3 × 6.94 g/mole or 20.8 g/mole</td>
</tr>
</tbody>
</table>

\[ W = \frac{(1.39 \text{ g} \times 282 \text{ g/mole})}{(0.975 \times 20.8 \text{ g/mole})} = 19.3 \text{ g} \]

**Example 4:** Accurately weigh an amount of Netilmicin Sulfate USP, equivalent to 2.5 g of netilmicin. [NOTE—Using the procedure under Loss on Drying (731), the Netilmicin Sulfate USP that was weighed lost 12% of its weight.]

<table>
<thead>
<tr>
<th>Equation Factor</th>
<th>Numerical Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>W</strong></td>
<td>weight, in g, of Netilmicin Sulfate USP</td>
</tr>
<tr>
<td><strong>a</strong></td>
<td>2.5 g</td>
</tr>
<tr>
<td><strong>b</strong></td>
<td>1442 g/mole</td>
</tr>
<tr>
<td><strong>d</strong></td>
<td>0.88</td>
</tr>
<tr>
<td><strong>e</strong></td>
<td>951 g/mole</td>
</tr>
</tbody>
</table>

\[ W = \frac{(2.5 \text{ g} \times 1442 \text{ g/mole})}{(0.88 \times 951 \text{ g/mole})} = 4.31 \text{ g} \]

**BUFFER SOLUTIONS**

**Definition**—A buffer solution is an aqueous solution that resists a change in pH when small quantities of acid or base are added, when diluted with the solvent, or when the temperature changes. Most buffer solutions are mixtures of a weak acid and one of its salts or mixtures of a weak base and one of its salts. Water and solutions of a neutral salt such as sodium chloride have very little ability to resist the change of pH and are not capable of effective buffer action.
Preparation, Use, and Storage of Buffer Solutions—Buffer solutions for Pharmacopeial tests should be prepared using freshly boiled and cooled water (see Standard Buffer Solutions under Buffer Solutions in Reagents, Indicators, and Solutions). They should be stored in containers such as Type I glass bottles and used within 3 months of preparation.

Buffers used in physiological systems are carefully chosen so as not to interfere with the pharmacological activity of the medicament or the normal function of the organism. Commonly used buffers in parenteral products, for example, are acetic, citric, glutamic, and phosphoric acids and their salts. Buffer solutions should be freshly prepared.

The Henderson-Hasselbalch equation, noted above, allows the pH of a buffer solution of a weak acid and its salt to be calculated. Appropriately modified, this equation may be applied to buffer solutions composed of a weak base and its salt.

Buffer Capacity—The buffer capacity of a solution is the measurement of the ability of that solution to resist a change in pH upon addition of small quantities of a strong acid or base. An aqueous solution has a buffer capacity of 1 when 1 L of the buffer solution requires 1 gram equivalent of strong acid or base to change the pH by 1 unit. Therefore, the smaller the pH change upon the addition of a specified amount of acid or base, the greater the buffer capacity of the buffer solution. Usually, in analysis, much smaller volumes of buffer are used in order to determine the buffer capacity. An approximate formula for calculating the buffer capacity is gram equivalents of strong acid or base added per L of buffer solution per unit of pH change, i.e., (Eq/L)/(pH change).

EXAMPLE—The addition of 0.01 g equivalents of sodium hydroxide to 0.25 L of a buffer solution produced a pH change of 0.50. The buffer capacity of the buffer solution is calculated as follows:

\[
\frac{0.01}{0.25}/0.50 = 0.08 \text{ (Eq/L)/(pH change)}
\]

DOSAGE CALCULATIONS

Special Dosage Regimens—Geriatric and pediatric patients require special consideration when designing dosage regimens. In geriatric patients, the organs are often not functioning efficiently as a result of age-related pharmacokinetic changes or disease. For these patients, modifications in dosing regimens are available in references such as USP Drug Information.

For pediatric patients, where organs are often not fully developed and functioning, careful consideration must be applied during dosing. Modifications in dosing regimens for pediatric patients are also available in references such as USP Drug Information. General rules for calculating doses for infants and children are available in pharmacy calculation textbooks. These rules are not drug-specific and should be used only in the absence of more complete information.

The usual method for calculating a dose for children is to use the information provided for children for the specific drug. The dose is frequently expressed as mg of drug per kg of body weight for a 24-hour period, and is then usually given in divided portions.

The calculation may be made using the following equation:

\[
\text{mg of drug per kg of body weight } \times \text{ kg of body weight} = \text{dose for an individual for a 24-hour period}
\]
A less frequently used method of calculating the dose is based on the surface area of the individual's body. The dose is expressed as amount of drug per body surface area in m², as shown in the equation below:

\[(\text{amount of drug per m² of body surface area}) \times (\text{body surface area in m²}) = \text{dose for an individual for a 24-hour period}\]

The body surface area (BSA) may be determined from nomograms relating height and weight in dosage handbooks. The BSA for adult and pediatric patients may also be determined using the following equations:

\[\text{BSA (m²)} = \sqrt{\frac{\text{Height (in)} \times \text{Weight (lb)}}{3131}}\]

or

\[\text{BSA (m²)} = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}\]

**EXAMPLE—**

Rx for Spironolactone Suspension 25 mg/tsp. Sig: 9 mg BID for an 18-month-old child who weighs 22 lbs.

The USP DI 2002, 22nd ed., states that the normal pediatric dosing regimen for Spironolactone is 1 to 3 mg per kg per day. In this case, the weight of the child is 22 lbs, which equals 22 lbs/(2.2 lbs/kg) = 10 kg. Therefore the normal dose for this child is 10 to 30 mg per day and the dose ordered is 18 mg per day as a single dose or divided into 2 to 4 doses. The dose is acceptable based on published dosing guidelines.

**PERCENTAGE CONCENTRATIONS**

Percentage concentrations of solutions are usually expressed in one of three common forms:

- **Volume percent (v/v)** = Volume of solute/Volume of solution × 100%

- **Weight percent (w/w)** = (Weight of solute × 100%)/Weight of solution

- **Weight in volume percent (w/v)** = (Weight of solute (in g)/Volume of solution (in mL)) × 100%

See also Percentage Measurements under Concentrations in the General Notices. The above three equations may be used to calculate any one of the three values (i.e., weights, volumes, or percentages) in a given equation if the other two values are known.

Note that weights are always additive, i.e., 50 g plus 25 g = 75 g. Volumes of two different solvents or volumes of solvent plus a solid solute are not strictly additive. Thus 50 mL of water + 50 mL of pure alcohol do not produce a volume of 100 mL.

Nevertheless, it is assumed that in some pharmaceutical calculations, volumes are additive, as discussed below under Reconstitution of Drugs Using Volumes Other than Those on the Label.

**EXAMPLES—**

1. Calculate the percentage concentrations (w/w) of the constituents of the solution prepared by dissolving 2.50 g of phenol in 10.00 g of glycerin. Using the weight percent equation above, the calculation is as follows:
Total weight of the solution = 10.00 g + 2.50 g = 12.50 g

Weight percent of phenol = (2.50 g × 100%) / 12.50 g = 20.0% of phenol

Weight percent of glycerin = (10 g × 100%) / 12.50 g = 80.0% of glycerin

2. A prescription order reads as follows:

Eucalyptus Oil 3% (v/v) in Mineral Oil.
Dispense 30.0 mL.
What quantities should be used for this prescription? Using the volume percent equation above, the calculation is as follows:

Amount of Eucalyptus Oil:

3% = (Volume of oil in mL / 30.0 mL) × 100%

Solving the equation, the volume of oil = 0.90 mL.

Amount of Mineral Oil: To 0.90 mL of Eucalyptus Oil add sufficient Mineral Oil to prepare 30.0 mL.

3. A prescription order reads as follows:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc oxide</td>
<td>7.5 g</td>
</tr>
<tr>
<td>Calamine</td>
<td>7.5 g</td>
</tr>
<tr>
<td>Starch</td>
<td>15 g</td>
</tr>
<tr>
<td>White petrolatum</td>
<td>30 g</td>
</tr>
</tbody>
</table>

4. Calculate the percentage concentration for each of the four components. Using the weight percent equation above, the calculation is as follows.

5. Total weight = 7.5 g + 7.5 g + 15 g + 30 g = 60.0 g

6. Weight percent of zinc oxide = (7.5 g zinc oxide / 60 g ointment) × 100% = 12.5%

7. Weight percent of calamine = (7.5 g calamine / 60 g ointment) × 100% = 12.5%

8. Weight percent of starch = (15 g starch / 60 g ointment) × 100% = 25%

9. Weight percent of white petrolatum = (30 g white petrolatum / 60 g ointment) × 100% = 50%

SPECIFIC GRAVITY

The definition of specific gravity is usually based on the ratio of weight of a substance in air at 25° to that of the weight of an equal volume of water at the same temperature.
The weight of 1 mL of water at 25° is approximately 1 g. The following equation may be used for calculations:

\[ \text{Specific Gravity} = \frac{\text{Weight of the substance}}{\text{Weight of an equal volume of water}} \]

**EXAMPLES—**

1. A liquid weighs 125 g and has a volume of 110 mL. What is the specific gravity?

   The weight of an equal volume of water is 110 g.

   Using the above equation,

   \[ \text{specific gravity} = \frac{125 \text{ g}}{110 \text{ g}} = 1.14 \]

2. Hydrochloric Acid NF is approximately a 37% (w/w) solution of hydrochloric acid (HCl) in water. How many grams of HCl are contained in 75.0 mL of HCl NF?

   (Specific gravity of Hydrochloric Acid NF is 1.18.)

   Calculate the weight of HCl NF using the above equation.

   The weight of an equal volume of water is 75 g.

   \[ \text{Specific Gravity} 1.18 = \frac{\text{weight of the HCl NF g}}{75.0 \text{ g}} \]

   Solving the equation, the weight of HCl NF is 88.5 g.

   Now calculate the weight of HCl using the weight percent equation.

   \[ 37.0 \% \text{ (w/w)} = \left( \frac{\text{weight of solute g}}{88.5 \text{ g}} \right) \times 100 \]

   Solving the equation, the weight of the HCl is 32.7 g.

**DILUTION AND CONCENTRATION**

A concentrated solution can be diluted. Powders and other solid mixtures can be triturated or diluted to yield less concentrated forms. Because the amount of solute in the diluted solution or mixture is the same as the amount in the concentrated solution or mixture, the following relationship applies to dilution problems.

The quantity of Solution 1 \((Q_1)\) \times concentration of Solution 1 \((C_1)\) = the quantity of Solution 2 \((Q_2)\) \times concentration of Solution 2 \((C_2)\), or

\[ (Q_1)(C_1) = (Q_2)(C_2) \]

Almost any quantity and concentration terms may be used. However, the units of the terms must be the same on both sides of the equation.

**EXAMPLES—**
1. Calculate the quantity \( Q_2 \), in g, of diluent that must be added to 60 g of a 10% (w/w) ointment to make a 5% (w/w) ointment. Let
\[
(Q_1) = 60 \text{g}, \quad (C_1) = 10\%, \quad \text{and} \quad (C_2) = 5\%
\]
Using the above equation,

\[60 \text{g} \times 10\% = (Q_2) \times 5\% \text{ (w/w)}\]

Solving the above equation, the quantity of product needed, \( Q_2 \), is 120 g. The initial quantity of product added was 60 g, and therefore an additional 60 g of diluent must be added to the initial quantity to give a total of 120 g.

2. How much diluent should be added to 10 g of a trituration (1 in 100) to make a mixture that contains 1 mg of drug in each 10 g of final mixture?

Determine the final concentration by first converting mg to g. One mg of drug in 10 g of mixture is the same as 0.001 g in 10 g. Let
\[
(Q_1) = 10 \text{g}, \quad (C_1) = (1 \text{ in } 100),
\]
and
\[
(C_2) = (0.001 \text{ in } 10)
\]
Using the equation for dilution,

\[10 \text{g} \times (1/100) = (Q_2) \times (0.001/10)\]

Solving the above equation,

\[(Q_2) = 1000 \text{g}\]

Because 10 g of the final mixture contains all of the drug and some diluent, (1000 g – 10 g) or 990 g of diluent is required to prepare the mixture at a concentration of 0.001 g of drug in 10 g of final mixture.

3. Calculate the percentage strength of a solution obtained by diluting 400 mL of a 5.0% solution to 800 mL. Let
\[
(Q_1) = 400 \text{mL}, \quad (C_1) = 5\%, \quad \text{and} \quad (Q_2) = 800 \text{mL}
\]
Using the equation for dilution,

\[400 \text{mL} \times 5\% = 800 \text{mL} \times (C_2)\%\]
Solving the above equation,

\[(C.) = 2.5\% \ (w/v)\]

**USE OF POTENCY UNITS**

See *Units of Potency* in the *General Notices*.

Because some substances may not be able to be defined by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency.

**EXAMPLES—**

1. One mg of Pancreatin contains not less than 25 USP Units of amylase activity, 2.0 USP Units of lipase activity, and 25 USP Units of protease activity. If the patient takes 0.1 g (100 mg) per day, what is the daily amylase activity ingested?

   1 mg of Pancreatin corresponds to 25 USP Units of amylase activity.

   100 mg of Pancreatin corresponds to

   \[100 \times (25 \text{ USP Units of amylase activity}) = 2500 \text{ Units}\]

2. A dose of penicillin G benzathine for streptococcal infection is 1.2 million units intramuscularly. If a specific product contains 1180 units per mg, how many milligrams would be in the dose?

   1180 units of penicillin G benzathine are contained in 1 mg.

   1 unit is contained in \(\frac{1}{1180}\) mg.

   \[1,200,000 \text{ units are contained in } (1,200,000 \times 1)/1180 \text{ units} = 1017 \text{ mg}\]

**BASE VS SALT OR ESTER FORMS OF DRUGS**

Frequently, for stability or other reasons such as taste or solubility, the base form of a drug is administered in an altered form such as an ester or salt. This altered form of the drug usually has a different molecular weight (MW), and at times it may be useful to determine the amount of the base form of the drug in the altered form.

**EXAMPLES—**

1. Four hundred milligrams of erythromycin ethylsuccinate (molecular weight, 862.1) is administered. Determine the amount of erythromycin (molecular weight, 733.9) in this dose.

   862.1 g of erythromycin ethylsuccinate corresponds to 733.9 g of erythromycin.
1 g of erythromycin ethylsuccinate corresponds to \((\frac{733.9}{862.1})\) g of erythromycin.

0.400 g of erythromycin ethylsuccinate corresponds to \((\frac{733.9}{862.1}) \times 0.400\) g or 0.3405 g of erythromycin.

2. The molecular weight of testosterone cypionate is 412.6 and that of testosterone is 288.4. What is the dose of testosterone cypionate that would be equivalent to 60.0 mg of testosterone?

288.4 g of testosterone corresponds to 412.6 g of testosterone cypionate.

1 g of testosterone corresponds to \(\frac{412.6}{288.4}\) g of testosterone cypionate.

60.0 mg or 0.0600 g of testosterone corresponds to \(\frac{412.6}{288.4} \times 0.0600 = 0.0858\) g or 85.8 mg of testosterone cypionate.

**RECONSTITUTION OF DRUGS USING VOLUMES OTHER THAN THOSE ON THE LABEL**

Occasionally it may be necessary to reconstitute a powder in order to provide a suitable drug concentration in the final product. This may be accomplished by estimating the volume of the powder and liquid medium required.

**EXAMPLES—**

1. If the volume of 250 mg of ceftriaxone sodium is 0.1 mL, how much diluent should be added to 500 mg of ceftriaxone sodium powder to make a suspension having a concentration of 250 mg per mL?

\[
500 \text{ mg} \times \left(\frac{1 \text{ mL}}{250 \text{ mg}}\right) = 2 \text{ mL}
\]

Volume of 500 mg of ceftriaxone sodium = 500 mg \(\times\) (0.1 mL/250 mg) = 0.2 mL

Volume of the diluent required = (2 mL of suspension) \(−\) (0.2 mL of Ceftriaxone Sodium) = 1.8 mL

2. What is the volume of dry powder cefonicid, if 2.50 mL of diluent is added to 1 g of powder to make a solution having a concentration of 325 mg per mL?

\[
\text{Volume of solution containing 1 g of the powder} = 1 \text{ g of cefonicid} \times \left(\frac{1000 \text{ mg}}{1 \text{ g}}\right) \times \left(\frac{1 \text{ mL of solution}}{325 \text{ mg of cefonicid}}\right) = 3.08 \text{ mL}
\]

\[
\text{Volume of dry powder cefonicid} = 3.08 \text{ mL of solution} - 2.50 \text{ mL of diluent} = 0.58 \text{ mL}
\]

**ALLIGATION ALTERNATE AND ALGEBRA**

**Alligation**—Alligation is a rapid method of determining the proportions in which substances of different strengths are mixed to yield a desired strength or concentration.
Once the proportion is found, the calculation may be performed to find the exact amounts of substances required. Set up the problem as follows.

1. Place the desired percentage or concentration in the center.
2. Place the percentage of the substance with the lower strength on the lower left-hand side.
3. Place the percentage of the substance with the higher strength on the upper left-hand side.
4. Subtract the desired percentage from the lower percentage, and place the obtained difference on the upper right-hand side.
5. Subtract the higher percentage from the desired percentage, and place the obtained difference on the lower right-hand side.

The results obtained will determine how many parts of the two different percentage strengths should be mixed to produce the desired percentage strength of a drug mixture.

**EXAMPLES—**

1. How much ointment having a 12% drug concentration and how much ointment having a 16% drug concentration must be used to make 1 kg of a preparation containing a 12.5% drug concentration?

![Diagram showing the calculation process]

In a total of 4.0 parts of 12.5% product, 3.5 parts of 12% ointment and 0.5 parts of 16% ointment are needed.

4 parts correspond to 1 kg or 1000 g.

1 part corresponds to 250 g.

3.5 parts correspond to 3.5 × 250 g or 875 g.

0.5 parts correspond to 0.5 × 250 g or 125 g.
2. How many mL of 20% dextrose in water and 50% dextrose in water are needed to make 750 mL of 35% dextrose in water?

In a total of 30 parts of 35% dextrose in water, 15 parts of 50% dextrose in water and 15 parts of 20% dextrose in water are required.

30 parts correspond to 750 mL.

15 parts correspond to 375 mL.

Thus use 375 mL of the 20% solution and 375 mL of the 50% solution to prepare the product.

**Algebra**—Instead of using alligation to solve the above problems, algebra may be used, following the scheme outlined below.

In order to represent the total quantity (weights, parts, or volumes) of the final mixture or solution, 1 or a specified quantity is used.

Let x be the quantity of one portion and [1 (or the specified amount) – x] be the remaining portion. Set up the equation according to the statement below, and solve.

The amount of drug in one part plus the amount of drug in the other part equals the total amount in the final mixture or solution.

**EXAMPLES**—

1. How much ointment having a 12% drug concentration and how much ointment having a 16% drug concentration must be used to make 1 kg of a preparation containing a 12.5% drug concentration?

Let 1 kg be the total quantity of ointment to be prepared, let x be the quantity, in kg, of the 12% ointment, and let (1 – x) be the quantity in kg of the 16% ointment. The equation is as follows:

\[(12/100)x + (16/100)(1 – x) = (12.5/100)(1)\]
Solving the equation, \( x \) equals 0.875 kg of the 12% ointment and \((1-x)\) equals 0.125 kg of the 16% ointment.

2. How many mL of 20% dextrose in water and 50% dextrose in water are needed to make 750 mL of 35% dextrose in water?

Let \( x \) be the volume, in mL, of the 20% solution, and let \((750-x)\) be the volume in mL of the 50% solution. The equation is as follows:

\[
\frac{20}{100}x + \frac{50}{100}(750-x) = \frac{35}{100}(750)
\]

Solving the equation, \( x \) equals 375 mL of the 20% solution and \((750-375)\) or 375 mL of the 50% solution.

**Molar, Molal, and Normal Concentrations**

See Concentrations in the General Notices.

**Molarity**—The molar concentration, \( M \), of the solution is the number of moles of the solute contained in one L of solution.

**Molality**—The molal concentration, \( m \), is the number of moles of the solute contained in one kilogram of solvent.

**Normality**—The normal concentration, \( N \), of a solution expresses the number of milliequivalents (mEq) of solute contained in 1 mL of solution or the number of equivalents (Eq, gram-equivalent weight) of solute contained in 1 L of solution. When using normality, the pharmacist must apply quantitative chemical analysis principles using molecular weight (MW). Normality depends on the reaction capacity of a chemical compound and therefore the reaction capacity must be known. For acids and bases, reaction capacity is the number of accessible protons available from, or the number of proton binding sites available on, each molecular aggregate. For electron transfer reactions, reaction capacity is the number of electrons gained or lost per molecular aggregate.

**EXAMPLES—**

1. How much sodium bicarbonate powder is needed to prepare 50.0 mL of a 0.07 N solution of sodium bicarbonate (NaHCO\(_3\))? (MW of NaHCO\(_3\) is 84.0 g per mol.)

In an acid or base reaction, because NaHCO\(_3\) may act as an acid by giving up one proton, or as a base by accepting one proton, one Eq of NaHCO\(_3\) is contained in each mole of NaHCO\(_3\). Thus the equivalent weight of NaHCO\(_3\) is 84 g. [Note—The volume, in L, \( \times \) normality of a solution equals the number of equivalents in the solution.]

\[
\text{The number of equivalents of NaHCO}_3\text{ required} = (0.07 \text{ Eq/L})(50.0 \text{ mL}/1000 \text{ mL/L}) = 0.0035 \text{ equivalents.}
\]

1 equivalent weight is 84.0 g.
0.0035 equivalents equals $84.0 \text{ g/Eq} \times 0.0035 \text{ Eq} = 0.294 \text{ g}$.

2. A prescription calls for 250 mL of a 0.1 N hydrochloric acid (HCl) solution. How many mL of concentrated hydrochloric acid are needed to make this solution? [NOTE—The specific gravity of concentrated hydrochloric acid is 1.18, the molecular weight is 36.46 and the concentration is 37.5% (w/w). Because hydrochloric acid functions as an acid and reacts by giving up one proton in a chemical reaction, 1 Eq is contained in each mole of the compound. Thus the equivalent weight is 36.46 g.]

The number of equivalents of HCl required is $0.250 \text{ L} \times 0.1 \text{ N} = 0.025$ equivalents.

1 equivalent is 36.46 g.

0.025 equivalents correspond to $0.025 \text{ Eq} \times 36.46 \text{ g/Eq} = 0.9115 \text{ g}$.

37.5 g of pure HCl are contained in 100 g of concentrated HCl. Thus 1 g of pure HCl is contained in $(100/37.5) \text{ g} = 2.666 \text{ g}$ of concentrated acid, and 0.9115 g is contained in $(0.9115 \times 2.666) \text{ g}$ or 2.43 g of concentrated acid.

In order to determine the volume of the supplied acid required, use the definition for specific gravity as shown below.

Specific gravity = (weight of the substance)/(weight of an equal volume of water).

$1.18 = \frac{2.43 \text{ g}}{(\text{weight of an equal volume of water})}$.

The weight of an equal volume of water is 2.056 g or 2.06 g, which measures 2.06 mL. Thus, 2.06 mL of concentrated acid is required.

**MILLIEQUIVALENTS AND MILLIMOLES**

NOTE—This section addresses milliequivalents (mEq) and millimoles (mmol) as they apply to electrolytes for dosage calculations.

The quantities of electrolytes administered to patients are usually expressed in terms of mEq. This term must not be confused with a similar term used in quantitative chemical analysis as discussed above. Weight units such as mg or g are not often used for electrolytes because the electrical properties of ions are best expressed as mEq. An equivalent is the weight of a substance (equivalent weight) that supplies one unit of charge. An equivalent weight is the weight, in g, of an atom or radical divided by the valence of the atom or radical. A milliequivalent is one-thousandth of an equivalent (Eq). Because the ionization of phosphate depends on several factors, the concentration is usually expressed in millimoles, moles, or milliosmoles, which are described below.
[NOTE—Equivalent weight (Eq.wt) = wt. of an atom or radical (ion) in g/valence (or charge) of the atom or radical. Milliequivalent weight (mEq.wt) = Eq.wt. (g)/1000.]

EXAMPLES—

1. Potassium (K⁺) has a gram-atomic weight of 39.10. The valence of K⁺ is 1⁺. Calculate its milliequivalent weight (mEq wt).

\[ \text{Eq wt} = 39.10 \text{ g}/1 = 39.10 \text{ g} \]

\[ \text{mEq wt} = 39.10 \text{ g}/1000 = 0.03910 \text{ g} = 39.10 \text{ mg} \]

2. Calcium (Ca²⁺) has a gram-atomic weight of 40.08. Calculate its milliequivalent weight (mEq wt).

\[ \text{Eq wt} = 40.08 \text{ g}/2 = 20.04 \text{ g} \]

\[ \text{mEq wt} = 20.04 \text{ g}/1000 = 0.02004 \text{ g} = 20.04 \text{ mg} \]

[NOTE—The equivalent weight of a compound may be determined by dividing the molecular weight in g by the product of the valence of either relevant ion and the number of times this ion occurs in one molecule of the compound.]

3. How many milliequivalents of potassium ion (K⁺) are there in a 250-mg Penicillin V Potassium Tablet? [NOTE—Molecular weight of penicillin V potassium is 388.48 g per mol; there is one potassium atom in the molecule; and the valence of K⁺ is 1⁺.]

\[ \text{Eq wt} = 388.48 \text{ g}/[1(\text{valence}) \times 1(\text{number of charges})] = 388.48 \text{ g} \]

\[ \text{mEq wt} = 388.48 \text{ g}/1000 = 0.38848 \text{ g} = 388.48 \text{ mg} \]

\[ (250 \text{ mg per Tablet})/(388.48 \text{ mg per mEq}) = 0.644 \text{ mEq of K⁺ per Tablet} \]

4. How many equivalents of magnesium ion and sulfate ion are contained in 2 mL of a 50% Magnesium Sulfate Injection? (Molecular weight of MgSO₄·7H₂O is 246.48 g per mol.)

Amount of magnesium sulfate in 2 mL of 50% Magnesium Sulfate Injection

\[ 2 \text{ mL of Injection} \times (50 \text{ g of magnesium sulfate/100 mL of Injection}) = 1 \text{ g} \]

\[ \text{Eq wt of MgSO₄·7H₂O} = \text{MW (g)}/(\text{valence of specified ion} \times \text{number of specified ions in one mole of salt}). \]

For the magnesium ion:
The number of equivalents is calculated as follows:

\[
\frac{246.48}{2(\text{valence}) \times 1 \times \text{(number of ions in the compound)}} = 123.24 \text{ g/Eq of magnesium ion}
\]

The number of equivalents in 1 g is
\[
\frac{1\text{ g}}{123.24 \text{ g/Eq}} = 0.008114 \text{ Eq}
\]

The number of mEq may be calculated as follows:

\[
\text{The mEq wt} = \text{Eq wt (g)/1000} = \frac{123.24 \text{ g/Eq}}{1000} = 0.12324 \text{ g}
\]

The number of milliequivalents of magnesium ion in 1 g is
\[
\frac{1\text{ g}}{0.12324 \text{ g/mEq}} = 8.114 \text{ mEq}
\]

For the sulfate ion:

The number of equivalents is calculated as follows:

\[
\frac{246.48}{2(\text{valence}) \times 1 \times \text{(number of ions in the compound)}} = 123.24 \text{ g/Eq of sulfate ion}
\]

The number of equivalents in 1 g is
\[
\frac{1\text{ g}}{123.24 \text{ g/Eq}} = 0.008114 \text{ Eq}
\]

The number of mEq may be calculated as follows:

\[
\text{The mEq wt} = \text{Eq wt (g)/1000} = \frac{123.24 \text{ g/Eq}}{1000} = 0.12324 \text{ g}
\]

The number of milliequivalents of sulfate ion in 1 g is
\[
\frac{1\text{ g}}{0.12324 \text{ g/mEq}} = 8.114 \text{ mEq}
\]

5. A vial of Sodium Chloride Injection contains 3 mEq of sodium chloride per mL. What is the percentage strength of this solution? (Molecular weight of sodium chloride is 58.44 g per mol.)

\[
1 \text{ mEq} = 1 \text{ Eq/1000} = \frac{58.44 \text{ g}}{1000} = 0.05844 \text{ g} = 58.44 \text{ mg}
\]

Amount of sodium chloride in 3 mEq per mL = 58.44 mg per mEq \times 3 \text{ mEq per mL} = 175.32 mg per mL

\[
175.32 \text{ mg/1 mL} = \frac{17532 \text{ mg}}{100 \text{ mL}} = 17.532 \text{ g/100 mL} = 17.5\%
\]

Using mols and mmols—
A number of countries have adopted the International System of Units and no longer calculate doses using mEq as described above, but instead use the terms moles (mol) and millimoles (mmol). In USP–NF or in the Pharmacists' Pharmacopeia the International System of Units is used except for the labeling of electrolytes.

**Definitions**

A mole equals one gram atomic weight or gram molecular weight of a substance.

A millimole equals 1/1000 of a mole.

**Examples**

1. Potassium (K) has a gram-atomic weight of 39.10. Calculate its weight in millimoles (mmol).

The weight of one mole is 39.10 g and the weight in millimoles is

\[
39.10 \text{ g}/1000 = 0.0391 \text{ g or } 39.1 \text{ mg}
\]

2. How many millimoles of Penicillin V are in a tablet that contains 250 mg of Penicillin V Potassium? (Molecular weight of penicillin V potassium is 388.48 g per mol.)

The weight of one mole is 388.48 g and the weight in millimoles is

\[
388.48 \text{ g}/1000 = 0.3848 \text{ g or } 388.48 \text{ mg}
\]

Thus there are 250 mg/388.48 mg/mmol = 0.644 mmol of Penicillin V ion per tablet.

**ISOOSMOTIC SOLUTIONS**

The following discussion and calculations have therapeutic implications in preparations of dosage forms intended for ophthalmic, subcutaneous, intravenous, intrathecal, and neonatal use.

Cells of the body, such as erythrocytes, will neither swell nor shrink when placed in a solution that is isotonic with the body fluids. However, the measurement of tonicity, a physiological property, is somewhat difficult. It is found that a 0.9% (w/v) solution of sodium chloride, which has a freezing point of −0.52°, is isotonic with body fluids and is said to be isoosmotic with body fluids. In contrast to isotonicity, the freezing point depression is a physical property. Thus many solutions that are isoosmotic with body fluids are not necessarily isotonic with body fluids, e.g., a solution of urea. Nevertheless many pharmaceutical products are prepared using freezing point data or related sodium chloride data to prepare solutions that are isoosmotic with the body fluids. A closely related topic is osmolarity (see Osmolality and Osmolarity). Freezing point data or sodium chloride equivalents of pharmaceuticals and excipients (see Table 1 below) may be used to prepare isoosmotic solutions, as shown in the examples below.
Table 1. Sodium Chloride Equivalents (E) and Freezing Point (FP) Depressions for  
a 1% Solution of the Drug or Excipient

<table>
<thead>
<tr>
<th>Drug or Excipient</th>
<th>E</th>
<th>FP Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine sulfate</td>
<td>0.13</td>
<td>0.075</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>1.00</td>
<td>0.576</td>
</tr>
</tbody>
</table>

EXAMPLE—
Determine the amount of sodium chloride required to prepare 60 mL of an isoosmotic 
solution of atropine sulfate 0.5% using the sodium chloride equivalent values and also 
the freezing point depression values.

Using the sodium chloride equivalent values—
The total amount of substances equivalent to sodium chloride (for a 0.9% solution) =

\[(0.9 \text{ g/100 mL}) \times 60 \text{ mL} = 0.54 \text{ g}.\]

The amount of atropine sulfate required = \[(0.5 \text{ g/100 mL}) \times 60 \text{ mL} = 0.3 \text{ g}.\]

1 g of atropine sulfate is equivalent to 0.13 g of sodium chloride.

0.3 g atropine sulfate is equivalent to \[0.3 \times 0.13 \text{ g} = 0.039 \text{ g} \text{ of sodium chloride}.\]

Thus the required amount of sodium chloride is \[0.54 - 0.039 = 0.501 \text{ g or 0.50 g}.\]

Using freezing point depression values—
The freezing point depression required is 0.52°.

A 1% solution of atropine sulfate causes a freezing point depression of 0.075°.

A 0.5% solution of atropine sulfate causes a freezing point depression of

\[0.075° \times 0.5 = 0.0375°\]

The additional freezing point depression required is

\[0.52° - 0.0375° = 0.482°\]

A 1% solution of sodium chloride causes a freezing point depression of 0.576°.

A (1%/ 0.576) solution of sodium chloride causes a freezing point depression of 1°.

A (1%/ 0.576) \times 0.482 = 0.836% solution of sodium chloride causes a freezing point 
depression of 0.482°.

The required amount of sodium chloride is

\[(0.836 \text{ g/100 mL}) \times 60 \text{ mL} = 0.502 \text{ g or 0.50 g}.\]

FLOW RATES IN INTRAVENOUS SETS
Some calculations concerning flow rates in intravenous sets are provided below.

[NOTE—Examples below are not to be used for treatment purposes.]

EXAMPLES—

1. Sodium Heparin 8,000 units in 250 mL Sodium Chloride Injection 0.9% solution 
are to be infused over 4 hours. The administration set delivers 20 drops per mL.

What is the flow rate in mL per hour?

In 4 hours, 250 mL are to be delivered.

In 1 hour, \[250 \text{ mL} / 4 = 62.5 \text{ mL are delivered}.\]
What is the flow rate in drops per minute?

In 60 minutes, 62.5 mL are delivered.

In 1 minute, 62.5 mL/60 = 1.04 mL are delivered.

1 mL = 20 drops.

1.04 mL = 1.04 × 20 drops = 20.8 drops.

Thus in 1 minute, 20.8 or 21 drops are administered.

2. A 14.5 kg patient is to receive 50 mg of Sodium Nitroprusside in 250 mL of dextrose 5% in water (D5W) at the rate of 1.3 µg per kg per minute. The set delivers 50 drops per mL.

Calculate the flow rate in mL per hour.

The dose for 1 kg is 1.3 µg per minute.

The 14.5 kg patient should receive 14.5 × 1.3 µg = 18.85 µg per minute.

50 mg or 50,000 µg of drug are contained in 250 mL of D5W.

18.85 µg are contained in 250 mL × 18.85/50,000 = 0.09425 mL D5W, which is administered every minute.

In 1 minute, 0.09425 mL are administered.

In 1 hour or 60 minutes, 60 × 0.09425 mL = 5.655 or 5.7 mL are administered.

Calculate the flow rate in drops per minute.

1 mL corresponds to 50 drops per minute.

0.09425 mL corresponds to 0.09425 × 50 = 4.712 or 4.7 drops per minute.

TEMPERATURE

The relationship between Celsius degrees (°C) and Fahrenheit degrees (°F) is expressed by the following equation:

\[ 9(\degree C) = 5(\degree F) = 160 \]

in which °C and °F are the numbers of Celsius degrees and Fahrenheit degrees, respectively.

EXAMPLES—

1. Convert 77 °F to Celsius degrees.
The relationship between the Kelvin and the Celsius scales is expressed by the equation:

$$K = °C + 273.1$$

in which $K$ and $°C$ are the numbers of Kelvin degrees and Celsius degrees, respectively.

### APPLICATION OF MEAN KINETIC TEMPERATURE

See *Good Storage and Distribution Practices for Drug Products* (1079) for the definition of mean kinetic temperature (MKT). MKT is usually higher than the arithmetic mean temperature and is derived from the Arrhenius equation. MKT addresses temperature fluctuations during the storage period of the product. The mean kinetic temperature, $T_K$, is calculated by the following equation:

$$T_K = \frac{\frac{-\Delta H}{R} \ln\left(\sum_{n=1}^{N} e^{-\frac{-\Delta H}{RT_n}}\right)}{N}$$

in which $\Delta H$ is the heat of activation, which equals $83.144$ kJ per mol (unless more accurate information is available from experimental studies); $R$ is the universal gas constant, which equals $8.3144 \times 10^{-3}$ kJ per degree per mol; $T_1$ is the average temperature, in degrees Kelvin, during the first time period, e.g., the first week; $T_2$ is the average temperature, in degrees Kelvin, during the second time period, e.g., second week; and $T_n$ is the average temperature, in degrees Kelvin during the nth time period, e.g., nth week, $n$ being the total number of temperatures recorded. The mean kinetic temperature is calculated from average storage temperatures recorded over a one-year period, with a minimum of twelve equally spaced average storage temperature observations being recorded (see *Good Storage and Distribution Practices for Drug Products* (1079)). This calculation can be performed manually with a pocket calculator or electronically with computer software.

### EXAMPLES

1. The means of the highest and lowest temperatures for 52 weeks are $25 °C$ each. Calculate the MKT.
\[
T_K = \frac{-\Delta H}{R} \ln \left( \frac{e^{-\Delta H/RT_1}}{n} + \frac{e^{-\Delta H/RT_2}}{n} + \cdots + \frac{e^{-\Delta H/RT_n}}{n} \right)
\]

\[
= \frac{-10,000K}{\ln[(52 \times e^{-33.5458})/52]}
\]

\[
= \frac{-10,000K}{\ln[(52 \times e^{-33.5458})/52]}
\]

\[
= 10,000K/33.5458 = 298.1K = 25.0°C
\]

The calculated MKT is 25.0 °C. Therefore the controlled room temperature requirement is met by this pharmacy. [Note: If the averages of the highest and lowest weekly temperatures differed from each other and were in the allowed range of 15 °C to 30 °C (see Packaging and Storage Requirements), then each average would be substituted individually into the equation. The remaining two examples illustrate such calculations, except that the monthly averages are used.]

2. A pharmacy recorded a yearly MKT on a monthly basis, starting in January and ending in December. Each month, the pharmacy recorded the monthly highest temperature and the monthly lowest temperature, and the average of the two was calculated and recorded for the MKT calculation at the end of the year (see Table 2). From these data the MKT may be estimated or it may be calculated. If more than half of the observed temperatures are lower than 25 °C and a mean lower than 23 °C is obtained, the MKT may be estimated without performing the actual calculation.

<table>
<thead>
<tr>
<th>n</th>
<th>Month</th>
<th>Lowest Temperature (in °C)</th>
<th>Highest Temperature (in °C)</th>
<th>Average Temperature (in °C)</th>
<th>Average Temperature (in K)</th>
<th>(\Delta H/RT)</th>
<th>(e^{\Delta H/RT})</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Month</td>
<td>Lowest Temperature (in °C)</td>
<td>Highest Temperature (in °C)</td>
<td>Average Temperature (in °C)</td>
<td>Average Temperature (in K)</td>
<td>(\Delta H/RT)</td>
<td>(e^{\Delta H/RT})</td>
</tr>
<tr>
<td>n</td>
<td>Month</td>
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<td>Highest Temperature (in °C)</td>
<td>Average Temperature (in °C)</td>
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<td>20</td>
<td>28</td>
<td>24</td>
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<td>33.659</td>
<td>2.411 × 10⁻¹⁵</td>
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<td>24</td>
<td>22</td>
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<td>25</td>
<td>298.1</td>
<td>33.546</td>
<td>2.699 × 10⁻¹⁵</td>
</tr>
</tbody>
</table>

a. To estimate the MKT, the recorded temperatures are evaluated and the average is calculated. In this case, the calculated arithmetic mean is 22.9 °C. Therefore, the above requirements are met and it can be concluded that the mean kinetic temperature is lower than 25 °C. Therefore, the controlled room temperature requirement is met.

b. The second approach is to perform the actual calculation.
The calculated MKT is 23.0 °C, so the controlled room temperature requirement is met. [NOTE—These data and calculations are used only as an example.]

3. An article was stored for one year in a pharmacy where the observed monthly average of the highest and lowest temperatures was 25 °C (298.1 K), except for one month with an average of 28 °C (301.1 K). Calculate the MKT of the pharmacy.

\[
T_K = \frac{-\Delta H}{R} \ln \left( \sum_{i=1}^{n} e^{-\Delta H / RT_i} \right) / n
\]

\[
= -10,000K / \ln \left( \frac{2.585 \times 10^{-14} + 2.033 \times 10^{-15} + ... + 2.699 \times 10^{-16}}{12} \right)
\]

\[
= -10,000K / \ln \left( \frac{2.585 \times 10^{-14}}{12} \right)
\]

\[
= 10,000K / 33.771 = 296.11K = 23.0°C
\]
The controlled room temperature requirement is not met because the calculated MKT exceeds 25 °C. (See Note in Example 2 above.)

4. Using the same calculation technique for controlled room temperature, the MKT for controlled cold temperatures can also be calculated.

a. For example, if the mean of the highest and lowest temperatures for each week over a period of 52 weeks was 8 °C (i.e., the same mean for each week), then the MKT can be calculated as follows:

\[ T_K = \frac{-10,000}{\ln(52e^{\frac{-\Delta H}{R \times 281.1}})/52} \]

\[ T_K = \frac{-10,000}{\ln(e^{\frac{-\Delta H}{R \times 281.1}})} \]

\[ T_K = \frac{-10,000}{\ln(3.548 \times 10^{-16})} \]

\[ T_K = 281.1 K = 281.1 - 273.1 = 8 °C \]

b. In another example, where a variety of average temperatures are used, as would be the case in reality, if the average of the highest and lowest temperatures ranges from 0 °C to 15 °C, then these averages would be individually substituted into the equation. For simplification of the mathematical process, 10 intervals are shown in Table 3 below. This illustration is intended for calculation of MKT at storage or in transit; i.e., during shipping or distribution of the critical drug product. These calculations can be performed manually or with a computer.

### Table 3. Sample Data for MKT Calculations

<table>
<thead>
<tr>
<th>Intervals</th>
<th>Low Temperature (in °C)</th>
<th>High Temperature (in °C)</th>
<th>Average Temperature (in °C)</th>
<th>Average Temperature (in K)</th>
<th>ΔH/RT</th>
<th>e^{ΔH/RT} x 10^6</th>
</tr>
</thead>
</table>
The purpose of this general chapter is to provide general information to assist pharmacists and support personnel in performing the necessary calculations for compounding and dispensing medications. This general chapter is not inclusive of all the information necessary for performing pharmaceutical calculations. For additional
information regarding pharmaceutical calculations, consult a pharmaceutical
calculations textbook. For additional information on pharmaceutical compounding and
drug stability, see: Pharmaceutical Compounding—Nonsterile Preparations (795),
Pharmaceutical Compounding—Sterile Preparations (797), and Packaging and
Storage Requirements (659); Quality Assurance in Pharmaceutical Compounding (1163)
and Stability Considerations in Dispensing Practice (1191).

Correct pharmaceutical calculations can be accomplished by using proper conversions
from one measurement system to another and properly placing decimal points (or
commas, in countries where it is customary to use these in the place of decimal points),
by understanding the arithmetical concepts, and by paying close attention to the details
of the calculations. Before proceeding with any calculation, pharmacists should do the
following: (a) read the entire formula or prescription carefully; (b) determine the
materials that are needed; and then (c) select the appropriate methods of preparation
and the appropriate calculations.

Logical methods that require as few steps as possible should be selected to ensure
that calculations are done accurately and correctly. A pharmacist should double-check
each calculation or have someone else double-check, e.g., a technician, if another
pharmacist is not available, before proceeding with compounding the preparation. One
expedient method of double-checking is estimation, which consists of convenient
rounding (e.g., 0.012 to 0.01, 0.44 to 0.5, 18.3 to 20, and 476 to 500) to approximate the
magnitude of answers.

2. CALCULATING AMOUNTS OF ACTIVE INGREDIENTS

The pharmacist must be able to calculate the amount or concentration of drug
substances in each unit or dosage portion of a compounded preparation at the time it is
prepared and again at the time it is dispensed. Pharmacists must perform calculations
and measurements to obtain, theoretically, 100% of the amount of each ingredient in
compounded formulations. Calculations must account for the active ingredient, or active
moiety, and water content of drug substances, which includes that in the chemical
formulas of hydrates. Official drug substances and added substances must meet the
requirements in general chapter Loss on Drying (731), which must be included in the
calculations of amounts and concentrations of ingredients. The pharmacist should
consider the effect of ambient humidity on the gain or loss of water from drugs and
added substances in containers subjected to intermittent opening over prolonged
storage. Each container should be opened for the shortest duration necessary and then
closed tightly immediately after use.

The nature of the drug substance to be weighed and used in compounding a
prescription must be known. If the substance is a hydrate, its anhydrous equivalent
weight may need to be calculated. On the other hand, if there is adsorbed moisture
present that is either specified on a Certificate of Analysis (CoA) or that is determined in
the pharmacy immediately before the drug substance is used in the preparation (see
chapter (731)), this information must be used when calculating the amount of drug
substance that is to be weighed to determine the exact amount of anhydrous drug
substance required.
There are cases in which the required amount of a dose is specified in terms of a cation (e.g., Li⁺), an anion (e.g., F⁻), or a molecule (e.g., theophylline in aminophylline). In these instances, the drug substance weighed is a salt or complex, a portion of which represents the pharmacologically active moiety. Thus, the exact amount of such substances weighed must be calculated on the basis of the required quantity of the pharmacological moiety.

The following formula may be used to calculate the theoretical weight of an ingredient in a compounded preparation:

\[ W = \frac{AB}{CD} \]

- \(W\) = actual weighed amount
- \(A\) = prescribed or pharmacist-determined weight of the active or functional moiety of drug or added substance
- \(B\) = molecular weight (MW) of the ingredient, including waters of hydration for hydrous ingredients
- \(C\) = MW of the active or functional moiety of a drug or added substance that is provided in the MW of the weighed ingredient
- \(D\) = the fraction of dry weight when the percent by weight of adsorbed moisture content is known from the loss on drying procedure (see chapter 731) or from the CoA. The CoA should be lot specific.

### 2.1 Active Ingredients

#### 2.1.1 Calculating Drugs Dosed as Salt Form and Hydrate

**Examples—Drugs dosed as salt form and hydrate**

1. Drugs dosed as salt form and hydrate
   Triturate morphine sulfate and lactose to obtain 10 g in which there are 30 mg of morphine sulfate for each 200 mg of the morphine–lactose mixture. [Note—Morphine is dosed as the morphine sulfate, which is the pentahydrate.]

   \[ W = \frac{1.5 \, \text{g} \times 759 \, \text{g/mol}}{759 \, \text{g/mol} \times 1} = 1.5 \, \text{g of morphine sulfate pentahydrate} \]

2. Active drug moiety and correction for moisture
   Accurately weigh an amount of aminophylline to obtain 250 mg of anhydrous theophylline. [Note—In this example, the powdered aminophylline dihydrate weighed contains 0.4% w/w absorbed moisture as stated in the CoA received by the pharmacy.]

   \[ W = \frac{AB}{CD} \]

   \(W\) = weight of aminophylline dihydrate (mg)
   \(A\) = weight of anhydrous theophylline, 250 mg
$B = \text{MW of aminophylline dihydrate, } 456 \text{ g/mol}$

$C = \text{MW of anhydrous theophylline, } 360 \text{ g/mol}$

$D = 0.996$

[NOTE—One mol of aminophylline contains 2 mol of theophylline. Theophylline has a MW of 180.]

To solve the equation:

$$W = (250 \text{ mg} \times 456 \text{ g/mol})/(360 \text{ g/mol} \times 0.996) = 318 \text{ mg of aminophylline dihydrate}$$

### 2.2 Hydrates, Salts, and Esters

#### 2.2.1 Calculating Hydrates, Salts, and Esters

**Examples—Hydrates, salts, and esters**

1. **Hydrates**

   If a prescription for 100 g of lidocaine hydrochloride 2% gel is to be made, 2 g of anhydrous lidocaine hydrochloride could be used, or the equivalent amount of lidocaine hydrochloride monohydrate could be calculated as follows:

   \[ W = \text{weight of lidocaine hydrochloride monohydrate (g)} \]

   \[ W = (2 \text{ g} \times 288.81 \text{ g/mol})/(270.80 \text{ g/mol} \times 1) = 2.133 \text{ g of lidocaine hydrochloride monohydrate} \]

   2. **Salts**

   A prescription calls for 10 mL of a fentanyl topical gel at a concentration 50 µg fentanyl/0.1 mL prepared from fentanyl citrate. The amount of fentanyl citrate required for the preparation could be calculated as follows:

   \[ W = \text{weight of fentanyl citrate in the prescription (µg)} \]

   \[ W = (50 \mu\text{g fentanyl}/0.1 \text{ mL}) \times 10 \text{ mL} = 5000 \mu\text{g of fentanyl} \]

   3. **Esters**
The amount of cefuroxime axetil contained in a single 250-mg cefuroxime tablet can be calculated as follows:

\[
W = \text{weight of cefuroxime axetil in tablet (mg)}
\]

\[
A = \text{weight of cefuroxime in the prescription, 250 mg}
\]

\[
B = \text{MW of cefuroxime axetil, 510.47 mg/mmol}
\]

\[
C = \text{MW of cefuroxime, 424.39 mg/mmol}
\]

\[
D = 1.0
\]

To solve the equation:

\[
W = (250 \text{ mg} \times 510.47 \text{ g/mol})/(424.39 \text{ g/mol} \times 1) = 300 \text{ mg of cefuroxime axetil}
\]

3. DOSAGE CALCULATIONS

3.1 Dosing by Weight

Doses are frequently expressed as mg of drug per kg of body weight per a dosing interval.

3.1.1 CALCULATING DOSING BY WEIGHT

Example—Dosing by weight

A physician orders azithromycin for oral suspension at a dose of 15 mg/kg/day, divided every 12 h, for a child that weighs 36 lb. Calculate the volume of oral suspension, in mL, that should be administered for each dose of a 200-mg/5-mL suspension as follows:

a. Calculate the child's weight in kg:

\[
36 \text{ lb} \times \frac{\text{kg}}{2.2 \text{ lb}} = 16.4 \text{ kg}
\]

b. Multiply the weight, in kg, by the dosing rate:

\[
16.4 \text{ kg} \times 15 \text{ mg/kg/day} = 246 \text{ mg/day}
\]

c. Divide the total daily dose by the number of doses/day:

\[
246 \text{ mg/2 doses} = 123 \text{ mg/dose}
\]

d. Calculate the volume of each dose using ratio and proportion:

\[
(123 \text{ mg/dose})/(200 \text{ mg/5 mL}) = 3.1 \text{ mL/dose}
\]

Some calculations may also be completed using dimensional units analysis (DUA). The DUA should begin at the left end with a factor containing the numerator answer units. All units other than those in the answer should cancel. If using DUA, the preceding equation would be as follows:
3.2 Dosing by Body Surface Area (Humans)

Some medications, including chemotherapeutic agents, require dosing by body surface area (BSA). The dose is expressed as amount of drug per meter squared (m²).

BSA may be calculated using the following formulas:

\[
\text{BSA (m}^2\text{)} = \sqrt{\left(\frac{\text{Height (in)}}{3131}\right) \times \left(\frac{\text{Weight (lb)}}{10,000}\right)}
\]

\[
\text{BSA (m}^2\text{)} = \sqrt{\left(\frac{\text{Height (cm)}}{3600}\right) \times \left(\frac{\text{Weight (kg)}}{10,000}\right)}
\]

3.2.1 Calculating by Body Surface Area (Human)

Example—Dosing by BSA (humans)

A physician orders rituximab at a dose of 375 mg/m² every week for 6 weeks for a patient who is 6 ft 2 in tall and weighs 183 lb. Calculate the volume, in mL, of 10-mg/mL rituximab injection needed to make each IV infusion dose as follows:

a. Calculate the patient’s BSA:

\[
\text{B} = \sqrt{\left(\frac{74 \text{ in}}{3131}\right) \times \left(\frac{183 \text{ lb}}{10,000}\right)} = 2.08 \text{ m}^2
\]

b. Multiply the BSA by the dosing rate:

\[2.08 \text{ m}^2 \times 375 \text{ mg/m}^2 = 780 \text{ mg/dose}\]

c. Calculate the volume of each dose using ratio and proportion:

\[
\frac{780 \text{ mg/dose}}{10 \text{ mg/mL}} = 78 \text{ mL/dose}
\]

The preceding calculation may also be completed using DUA as follows:

\[
2.08\text{-m}^2 \text{ patient} \times \frac{375 \text{ mg}}{\text{m}^2 \cdot \text{dose}} \times \frac{\text{mL}}{10 \text{ mg}} = 78 \text{ mL/dose}
\]

3.3 Dosing By Body Surface Area (Animals)

BSA for cats and dogs may be calculated using the following formulas. For other animals, consult an appropriate veterinary medicine reference.

Body surface area for cats:

\[
\text{BSA (m}^2\text{)} = \left\{10 \times \left[\text{body weight (g)}\right]^{0.667}\right\}/10,000
\]

Body surface area for dogs:

\[
\text{BSA (m}^2\text{)} = \left\{10.1 \times \left[\text{body weight (g)}\right]^{0.667}\right\}/10,000
\]

3.3.1 Calculating Dosing by Body Surface Area (Animals)
A veterinarian orders oral cyclophosphamide therapy at a dose of 50 mg/m² for a cat who weighs 5.8 kg. Calculate the dose of cyclophosphamide as follows:

a. Calculate the cat’s BSA:

\[
BSA (m^2) = \frac{[10 \times (5800 g)^{0.667}]}{10,000} = 0.324 m^2
\]

b. Multiply the BSA by the dosing rate:

\[
0.324 m^2 \times 50 mg/m^2 = 16.2 mg
\]

4. USE OF POTENCY UNITS

Because some substances cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency (see the *USP General Notices and Requirements 5.50.10, Units of Potency (Biological)*).

4.1 Calculating by Use of Potency Units

**Examples—Use of potency units**

1. Potency units-to-milligrams conversion

A dose of penicillin G benzathine for streptococcal infection is 1.2 million units administered intramuscularly. If a specific product contains 1180 units/mg, calculate the amount, in mg, of penicillin G benzathine in the dose as follows:

\[
\frac{1,200,000 \text{ units}}{1180 \text{ units/mg}} = 1017 \text{ mg of penicillin G benazathine}
\]

2. Potency units-to-milligrams conversion

A prescription calls for 60 g of an ointment containing 150,000 units of nystatin per gram. Calculate the quantity of nystatin with a potency of 4400 units/mg that should be weighed for the prescription as follows:

\[
60 g \times \frac{150,000 \text{ units of nystatin/g}}{4400 \text{ units/mg}} = 2045 \text{ mg of nystatin}
\]

5. VOLUME AND WEIGHT SUMS

Weights are additive in most mixtures of liquids, semisolids, and solids. Volumes in mixtures of miscible solutions and pure liquids may or may not be additive, based primarily on the effects of volume proportions and intermolecular hydrogen bonding. For example, mixtures containing equal or near-equal volumes of water and ethanol (and other miscible mono-hydroxy alcohols) will be exothermic and result in a volume contraction of <5%, e.g., 50 mL water + 50 mL ethanol yield 97–98 mL at 20°–25°.

Negligible volume contraction occurs between water and polyhydroxy or polyhydric alcohols, e.g., glycerin and propylene glycol. Volumes are additive with usually negligible error in aqueous mixtures that contain <10% of mono-hydroxy alcohols, i.e., there is <0.5% volume contraction.
6. DENSITY AND SPECIFIC GRAVITY

Density is defined as the mass of a substance in air at a specific temperature (typically 25°) per unit volume of that substance at the same temperature. Density may be calculated with the following equation:

\[
\text{Density} = \frac{\text{mass of substance}}{\text{volume of substance}}\text{ at a particular temperature and pressure}
\]

Specific gravity (SG) is the unitless ratio of the density of a substance to the density of water at 4°, or \([\text{(g of substance/mL)/1.00 g/mL}]\). Alternatively, SG can be calculated at a particular temperature in some common units of density from density of substance per density of water.

SG may be calculated with the following equation:

\[
\text{SG} = \frac{\text{weight of the substance}}{\text{weight of an equal volume of water}}
\]

6.1 Calculating Density and Specific Gravity

Examples—Density and specific gravity

1. Density calculation

2.3 g of activated charcoal powder occupies a bulk volume of 5.2 mL at 20° and 1 atm. The density of activated charcoal powder can be calculated as follows:

\[
\text{Density} = \frac{2.3 \text{ g}}{5.2 \text{ mL}} = 0.44 \text{ g/mL}
\]

2. SG calculation

125.0 g of glycerin occupies a volume of 99.0 mL at 25°. \([\text{NOTE—The density of water at 25° is 0.997 g/mL.}]\) The SG of glycerin can be calculated as follows:

\[
\text{SG} = \frac{125 \text{ g/99 mL}}{0.997 \text{ g/mL}} = 1.266
\]

3. Concentrated acid calculation

Hydrochloric acid is approximately a 37% w/w solution of hydrochloric acid in water. Calculate the amount, in g, of hydrochloric acid contained in 75.0 mL of hydrochloric acid as follows. \([\text{NOTE—The SG of hydrochloric acid is 1.18.}]\]

\[
37\% \text{ w/w} \times 1.18 = 43.7\% \text{ w/v}
\]

\[(43.7 \text{ g/100 mL}) \times 75 \text{ mL} = 32.8 \text{ g of hydrochloric acid}\]

7. MILLIEQUIVALENTS AND MILLIMOLEs

\([\text{NOTE—This section addresses milliequivalents (mEq) and millimoles (mmol) as they apply to electrolytes for dosage calculations. See also the 8. Concentrations Expressions section of this chapter.}]\]

The quantities of electrolytes administered to patients are usually expressed in terms of mEq. Weight units such as mg or g are not often used for electrolytes because the electrical properties of ions are best expressed as mEq. An equivalent (Eq) is the weight of a substance that supplies 1 unit of charge. An equivalent weight is the weight, in g, of an atom or radical, divided by the valence of the atom or radical. A mEq is \(1/1000\) of an Eq. The equivalent weight of a compound may be determined by dividing its formula or MW in g by the valence of its largest valence ion.
A mole equals one gram-atomic weight or gram-molecular weight of a substance. A millimole equals $1/1000^{th}$ of a mole.

### 7.1 Calculating Milliequivalents and Millimoles

#### Examples—Milliequivalents and millimoles

1. Calculate the mEq weight of calcium. \(\text{[NOTE—Calcium has a MW of 40.08, and the valence of calcium is 2\(^{+}\).]}\)

\[
\text{Eq weight} = 40.08 \text{ g/2} = 20.04 \text{ g}
\]

\[
\text{mEq weight} = 20.04 \text{ g/1000} = 0.02004 \text{ g} = 20.04 \text{ mg}
\]

2. Calculate the quantity, in mEq, of potassium in a 250-mg Penicillin V Potassium Tablet. \(\text{[NOTE—Penicillin V potassium has a MW of 388.48 g, there is one potassium atom in the molecule, and the valence of potassium is 1\(^{+}\).]}\)

\[
\text{Eq weight} = 388.48 \text{ g/1} = 388.48 \text{ g}
\]

\[
\text{mEq weight} = 388.48 \text{ g/1000} = 0.38848 \text{ g} = 388.48 \text{ mg}
\]

\[
(250 \text{ mg/tablet})/(388.48 \text{ mg/mEq}) = 0.644 \text{ mEq of potassium/tablet}
\]

3. Calculate the mEq of magnesium and sulfate in a 2-mL dose of 50% Magnesium Sulfate Injection. \(\text{[NOTE—Magnesium sulfate (MgSO\(_4\) \cdot 7H\(_2\)O) has a MW of 246.47, and the highest valence ion is magnesium 2\(^{+}\) and sulfate 2\(^{-}\).]}\)

\[
(50 \text{ g/100 mL}) \times (2 \text{ mL/dose}) = 1 \text{ g/dose}
\]

\[
\text{Eq weight} = 246.47 \text{ g/2} = 123.24 \text{ g/Eq}
\]

\[
(1 \text{ g/dose})/(123.24 \text{ g/Eq}) = 0.008114 \text{ Eq} = 8.114 \text{ mEq of both magnesium and sulfate per dose}
\]

This problem may also be worked using DUA as follows:

\[
\frac{50 \text{ g}}{100 \text{ mL}} \times \frac{2 \text{ mL}}{\text{dose}} \times \frac{2 \text{ Eq}}{246.47 \text{ g}} \times \frac{1000 \text{ mEq}}{\text{Eq}} = 8.114 \text{ mEq}
\]

4. A vial of sodium chloride injection contains 3 mEq/mL of sodium chloride. Calculate the strength, in % w/v, of the injection. \(\text{[NOTE—Sodium chloride has a MW of 58.44.]}\)

\[
\frac{3 \text{ mEq}}{\text{mL}} \times \frac{58.44 \text{ g}}{1 \text{ Eq}} \times \frac{\text{Eq}}{1000 \text{ mEq}} = \frac{0.1753 \text{ g}}{\text{mL}}
\]

\[
(0.1753 \text{ g/mL}) \times 100 \text{ mL} = 17.53 \text{ g in 100 mL} = 17.53\% \text{ w/v}
\]

5. Calculate the weight of potassium in mmol. \(\text{[NOTE—Potassium has a MW of 39.1.]}\)

The weight of 1 mol is 39.1 g and the weight in mmol is:

\[
39.1 \text{ g/1000} = 0.0391 \text{ g or 39.1 mg}
\]

6. Calculate the mmol of penicillin V potassium in a 250-mg Penicillin V Potassium Tablet. \(\text{[NOTE—Penicillin V potassium has a MW of 388.48.]}\)

The weight of 1 mol is 388.48 g, and the weight of 1 mmol is:

\[
388.48 \text{ g/1000} = 0.38848 \text{ g or 388.48 mg}
\]
The concentration expressions in this section refer to homogeneous mixtures of the following states of matter at a temperature of 20°–30° and pressure of 1 atm (29.92 in Hg, 760 mm Hg, 101.3 kPa, 1013.3 mb): gas in gas, gas in liquid, liquid in liquid, liquid in semisolid, solid in liquid, solid in semisolid, and solid in solid. Concentration expressions used in pharmacy practice and pharmaceutical research include, but are not limited to, those listed in Table 1. Common metric drug strength and clinical concentrations include, for example, µg/mL, mg/dL, g or mg per L, and ng/µL (see General Notices and Requirements 8.240, Weights and Measures).

### Table 1

<table>
<thead>
<tr>
<th>Title</th>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass in volume ratios</td>
<td>None is standard</td>
<td>Mass of a dispersed or dissolved ingredient per volume amount of mixtures containing that ingredient</td>
</tr>
<tr>
<td>mEq per volume</td>
<td>mEq/volume unit</td>
<td>mEq of an electrolyte or salt per unit of volume of solutions containing that electrolyte or salt</td>
</tr>
<tr>
<td>Molality</td>
<td>m</td>
<td>mol of a solute/kg of a solvent containing that solute</td>
</tr>
<tr>
<td>Molarity</td>
<td>M</td>
<td>mol of a solute/L of a solvent containing that solute</td>
</tr>
<tr>
<td>Normality</td>
<td>N</td>
<td>Equivalents (Eq) of a solute/L of a solvent containing that solute</td>
</tr>
<tr>
<td>Parts per million</td>
<td>ppm</td>
<td>Parts of a gas, liquid, or solid per 1 million part of another gas, liquid, or solid containing the first gas, liquid, or solid</td>
</tr>
<tr>
<td>% volume in volume</td>
<td>% v/v</td>
<td>mL of liquid per 100 mL of a solvent containing that liquid</td>
</tr>
<tr>
<td>% weight in volume</td>
<td>% w/v</td>
<td>g of a solute per 100 mL of a solvent containing that solute</td>
</tr>
<tr>
<td>% weight in weight</td>
<td>% w/w</td>
<td>g of a solute per 100 g of a mixture containing that solute</td>
</tr>
<tr>
<td>Ratio strength</td>
<td>X:Y</td>
<td>X parts of one ingredient per Y parts of another ingredient in a mixture</td>
</tr>
</tbody>
</table>

*a 1 mEq = Eq/1000.

*b The abbreviation for mole is mol.
<table>
<thead>
<tr>
<th>Title</th>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mol of solute per 1 kg of solvent is a 1 molal (1 m) solution.</td>
<td>( c )</td>
<td></td>
</tr>
<tr>
<td>1 mol of solute per 1 L of solution of that solute is a 1 molar (1 M) solution.</td>
<td>( d )</td>
<td></td>
</tr>
<tr>
<td>Normality = (Molarity \times \text{largest valence ion of a compound}), e.g., ((18 \text{ M} \ H_2\text{SO}_4 \times 2) = 36 \text{ N} \ H_2\text{SO}_4), where 2 derives from the 2(^{−}) valence of \text{SO}_4.</td>
<td>( e )</td>
<td></td>
</tr>
<tr>
<td>Eq of a compound = (1 mol \times \text{largest valence ion of a compound}), e.g., 1 mol of lithium citrate = 3 Eq of lithium citrate; 1 mol of Ca(gluconate)(_2) = 2 Eq of Ca(gluconate)(_2); and 1 mol of KCl = 1 Eq of KCl.</td>
<td>( f )</td>
<td></td>
</tr>
<tr>
<td>1 Eq of solute per 1 L of solution of that solute is a 1 normal (1 N) solution.</td>
<td>( g )</td>
<td></td>
</tr>
<tr>
<td>( R ), ( X ), and ( Y ) are whole numbers.</td>
<td>( h )</td>
<td></td>
</tr>
</tbody>
</table>

8.1 Calculating Normality

**Example—Normality**

Calculate the amount of sodium bicarbonate powder needed to prepare 50 mL of a 0.07 N solution of sodium bicarbonate (NaHCO\(_3\)). [\text{NOTE}—Sodium bicarbonate has a MW of 84.01.] In an acid or base reaction, because NaHCO\(_3\) may act as an acid by giving up one proton, or as a base by accepting one proton, one Eq of NaHCO\(_3\) is contained in each mole of NaHCO\(_3\).

\[
0.050 \text{ L} \times \frac{0.07 \text{ Eq}}{1 \text{ L}} \times \frac{1 \text{ mol}}{1 \text{ Eq}} \times \frac{84.01 \text{ g}}{1 \text{ mol}} = 0.294 \text{ g of sodium bicarbonate}
\]

8.2 Calculating Percentage Concentrations

Percentage concentrations of solutions and other homogeneous mixtures are usually expressed in one of three common forms in which numerator and denominator quantities are in g and mL measurement units.

1. Volume percent (\(\%\) v/v) = (volume of liquid solute/volume of solution or suspension) \times 100

or \(\%\) v/v = mL of liquid solute in 100 mL of solution or suspension

2. Weight percent (\(\%\) w/w) = (weight of solute/weight of mixture) \times 100

or \(\%\) w/w = g of ingredient in 100 g of mixture

3. Weight in volume percent (\(\%\) w/v) = (weight of solute/volume of solution or suspension) \times 100

or \(\%\) w/v = g of solute in 100 mL of solution or suspension

The preceding three equations may be used to calculate any one of the three values (i.e., weights, volumes, or percentages) in a given equation if the other two values are known (see also \textit{General Notices and Requirements 8.140, Percentage Concentrations}).

**Examples—Percentage concentrations**

1. Weight percent
A prescription order reads as follows (see Table 2):

### Table 2

<table>
<thead>
<tr>
<th>Component</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc oxide</td>
<td>7.5</td>
</tr>
<tr>
<td>Calamine</td>
<td>7.5</td>
</tr>
<tr>
<td>Starch</td>
<td>15</td>
</tr>
<tr>
<td>White petrolatum</td>
<td>30</td>
</tr>
</tbody>
</table>

Calculate the percentage concentration for each of the four components using the preceding weight percent equation as follows:

a. The total weight of ointment = 7.5 g + 7.5 g + 15 g + 30 g = 60.0 g
b. The weight percent of zinc oxide = (7.5 g of zinc oxide/60 g of ointment) × 100% = 12.5%
c. The weight percent of calamine = (7.5 g of calamine/60 g of ointment) × 100% = 12.5%
d. The weight percent of starch = (15 g of starch/60 g of ointment) × 100% = 25%
e. The weight percent of white petrolatum = (30 g of white petrolatum/60 g of ointment) × 100% = 50%

2. Volume percent
A prescription order reads as follows:
Rx: Eucalyptus Oil 3% v/v in Mineral Oil.
Dispense 30 mL.
Calculate the quantities of ingredients in this prescription using the volume percent equation as follows:

a. The amount of eucalyptus oil.

3% v/v = (volume of oil in mL/30.0 mL) × 100%

volume in oil = 0.9 mL of eucalyptus oil

b. The amount of mineral oil.

30 mL − 0.9 mL = 29.1 mL of mineral oil

8.3 Conversions of Concentration Expressions

8.3.1 SOLID-IN-LIQUID SOLUTION CONVERSIONS
The calculations used to convert from percent weight in volume, % w/v, to other concentrations and vice versa, using the same densities and formula or molecular weights, are illustrated as follows for calcium chloride, magnesium sulfate, and potassium chloride solutions in water.

8.3.1.1 Calculating solid-in-liquid conversions:
**Examples—Solid-in-liquid conversions**

1. Convert 10% w/v calcium chloride (CaCl₂ · 2H₂O) to molality (m). [NOTE—Calcium chloride has a MW of 147.01 g; 10% w/v solution has a density of 1.087 g/mL.]

   \[ \text{10% w/v} = \frac{10 \text{ g of calcium}}{100 \text{ mL of solution}} \]

   Using the density of the solution:

   \[ 100 \text{ mL of solution} \times 1.087 \text{ g/mL} = 108.7 \text{ g of solution} \]

   \[ 108.7 \text{ g of solution} - 10 \text{ g of calcium chloride} = 98.7 \text{ g of water} = 0.0987 \text{ kg of water} \]

   \[ \frac{10 \text{ g of calcium chloride}}{(147.01 \text{ g of calcium chloride/mol of calcium chloride})} = 0.068 \text{ mol of calcium chloride} \]

   \[ \frac{0.068 \text{ mol of calcium chloride}}{0.0987 \text{ kg of water}} = 0.689 \text{ m} \]

2. Convert 50% w/v magnesium sulfate (MgSO₄ · 7H₂O) to molarity (M). [NOTE—Magnesium sulfate has a MW of 246.47 g.]

\[ \frac{50 \text{ g}}{100 \text{ mL}} \times \frac{\text{mol}}{246.47 \text{ g}} \times \frac{1000 \text{ mL}}{1 \text{ L}} = 2.029 \text{ M} \]

3. Convert 10% w/v calcium chloride (CaCl₂ · 2H₂O) to normality (N).

\[ \frac{10 \text{ g}}{100 \text{ mL}} \times \frac{1 \text{ mol}}{147.01 \text{ g}} \times \frac{2 \text{ Eq}}{1 \text{ mol}} \times \frac{1000 \text{ mL}}{1 \text{ L}} = 1.36 \text{ N} \]

   *2 Eq/mol derived from the 2⁺ valence of calcium

4. Convert 10% w/v calcium chloride (CaCl₂ · 2H₂O) to mEq/mL.

\[ \frac{10 \text{ g}}{100 \text{ mL}} \times \frac{1 \text{ mol}}{147.01 \text{ g}} \times \frac{2 \text{ Eq}}{1 \text{ mol}} \times \frac{1000 \text{ mEq}}{1 \text{ L}} = 1.36 \text{ mEq/mL} \]

5. Convert 0.1% w/v calcium chloride (CaCl₂ · 2H₂O) to ppm.

\[ (0.1 \text{ g/100 mL}) \times (1 \times 10^4 \text{ ppm}) = 1000 \text{ ppm} \]

6. Convert 33% w/v potassium chloride (KCl) to 1:R ratio strength.

\[ (1/R) = (33 \text{ g/100 mL}) \]

\[ R = 3.03 \]

\[ 1:R = 1:3 \]

**8.3.2 LIQUID-IN-LIQUID SOLUTION CONVERSIONS**

The calculations used to convert from percent weight in weight, % w/w, and volume in volume, % v/v, to other concentrations and vice versa using the same densities and formula or MWs, are illustrated for glycerin and isopropyl alcohol in water. Besides liquid-in-semisolid, solid-in-semisolid, and solid-in-solid mixtures, % w/w is used for viscous liquids, such as coal tar, glycerin, and concentrated acids.

**8.3.2.1 Converting liquid-in-liquid solutions:**

**Examples—Liquid-in-liquid conversions**
1. Convert 50% w/w glycerin to % w/v. [NOTE—50% w/w glycerin has a density of 1.13 g/mL.]

\[
(50 \text{ g/100 g}) \times (1.13 \text{ g/mL}) = 56.5 \text{ g}
\]

\[
56.5 \text{ g/100 mL} = 56.5\% \text{ w/v}
\]

2. Convert 70% v/v isopropyl alcohol to % w/w. [NOTE—Isopropyl alcohol has a density of 0.79 g/mL, and 70% v/v isopropyl alcohol has a density of 0.85 g/mL.]

\[
70 \text{ mL of isopropyl alcohol} \times (0.79 \text{ g/mL}) = 55.3 \text{ g of isopropyl alcohol}
\]

\[
100 \text{ mL of solution} \times (0.85 \text{ g/mL}) = 85 \text{ g of solution}
\]

\[
(55.3 \text{ g of isopropyl alcohol}/85 \text{ g of solution}) \times 100 = 65.06\% \text{ w/w}
\]

3. Convert 70% v/v isopropyl alcohol to % w/v. The following values are from example 2.

\[
55.3 \text{ g of isopropyl alcohol}/100 \text{ mL of solution} = 55.3\% \text{ w/v}
\]

4. Convert 50% w/w glycerin to molality (m). [NOTE—Glycerin has a MW of 92.1.]

\[
50 \text{ g of glycerin}/(92.1 \text{ g/mol}) = 0.543 \text{ mol of glycerin}
\]

\[
100 \text{ g of solution} - 50 \text{ g of glycerin} = 50 \text{ g of water} = 0.05 \text{ kg of water}
\]

\[
(0.543 \text{ mol of glycerin}/0.05 \text{ kg of water}) = 10.86 \text{ m}
\]

5. Convert 70% v/v isopropyl alcohol to molality (m). [NOTE—Isopropyl alcohol has a density of 0.79 g/mL and a MW of 60.1; 70% v/v isopropyl alcohol has a density of 0.85 g/mL.]

\[
70 \text{ mL of isopropyl alcohol} \times (0.79 \text{ g/mL}) = 55.3 \text{ g of isopropyl alcohol}
\]

\[
100 \text{ mL of solution} \times (0.85 \text{ g/mL}) = 85 \text{ g of solution}
\]

\[
(85 \text{ g of solution} - 55.3 \text{ g of isopropyl alcohol}) = 29.7 \text{ g of water} = 0.0297 \text{ kg of water}
\]

\[
55.3 \text{ g of isopropyl alcohol}/(60.1 \text{ g/mol}) = 0.92 \text{ mol of isopropyl alcohol}
\]

\[
(0.92 \text{ mol of isopropyl alcohol}/0.0297 \text{ kg of water}) = 30.98 \text{ m}
\]

6. Convert 50% w/w glycerin to molarity (M). [NOTE—Glycerin has a MW of 92.1 g.]

From example 1, 50% w/w glycerin = 56.5% w/v glycerin

\[
(56.5 \text{ g/100 mL}) \times (\text{mol/92.1 g}) \times (1000 \text{ mL/L}) = 6.13 \text{ M}
\]

7. Convert 50% w/w glycerin to % v/v. [NOTE—50% w/w of glycerin has a density of 1.13 g/mL; 100% glycerin has a density of 1.26 g/mL.]

\[
50 \text{ g of glycerin}/(1.26 \text{ g/mL}) = 39.7 \text{ mL of glycerin}
\]

\[
100 \text{ g of solution}/(1.13 \text{ g/mL}) = 88.5 \text{ mL of solution}
\]

\[
(39.7 \text{ mL of glycerin}/88.5 \text{ mL of solution}) \times 100\% = 44.8\% \text{ v/v}
\]

9. Convert 50% w/w glycerin to 1 in R ratio strength.

\[
1/R = (50 \text{ g of glycerin}/100 \text{ g of solution})
\]

\[
R = 2
\]

\[
1 \text{ in } R = 1 \text{ in } 2
\]
8.3.3 SOLID AND SEMISOLID IN SOLID AND SEMISOLID MIXTURE CONVERSIONS

The calculations used to convert from percent weight in weight (% w/w) to ppm and ratio strengths are illustrated as follows for fluocinonide and tolnaftate in topical semisolids and powders.

8.3.3.1 Calculating solid and semisolid in solid and semisolid mixture conversions:

Examples—Solid and semisolid in solid and semisolid mixture conversions

1. Convert 0.05% w/w fluocinonide ointment to ppm.

\[
(0.05 \text{ g/100 g}) \times (1 \times 10^6 \text{ ppm}) = 500 \text{ ppm}
\]

2. Convert 1.5% w/w tolnaftate powder to 1:R ratio strength.

\[
1/R = (1.5 \text{ g of tolnaftate/100 g of powder})
\]

\[
R = 67
\]

\[
1:R = 1:67
\]

3. Convert 1% w/w tolnaftate in talcum powder to X:Y ratio strength.

\[
100 \text{ g of powder} - 1 \text{ g of tolnaftate} = 99 \text{ g of talcum}
\]

\[
X:Y = 1 \text{ g of tolnaftate}:99 \text{ g of talcum}
\]

8.4 Dilution and Concentration

A more concentrated solution can be diluted to a lower concentration to obtain appropriate strength and precision when compounding preparations. Powders and semisolid mixtures can be triturated or mixed to achieve lower concentrations. The amount of an ingredient in the diluted mixture is the same as that in the portion of the more concentrated source used to make the dilution; thus, the following equation can be applied to dilution problems \((Q_1)(C_1) = (Q_2)(C_2)\), where \(Q_1\) and \(Q_2\) are the quantity of solutions 1 and 2, respectively, and \(C_1\) and \(C_2\) are concentrations of solutions 1 and 2, respectively. Any quantities and concentration terms may be used but the units of those terms must be the same on both sides of the equation.

8.4.1 CALCULATING DILUTION AND CONCENTRATION

Examples—Dilutions and fortifications

1. Semisolid dilution

Calculate the quantity \((Q_1)\), in g, of diluent that must be added to 60 g of a 10% w/w ointment to make a 5% w/w ointment.

\[
(Q_1) = 60 \text{ g, } (C_1) = 10\% \text{ w/w, and } (C_2) = 5\% \text{ w/w}
\]

\[
60 \times 10\% \text{ w/w} = (Q_2) \times 5\% \text{ w/w}
\]

\[
(Q_2) = 120 \text{ g}
\]

\[
120 \text{ g} - 60 \text{ g} = 60 \text{ g of diluent to be added}
\]

2. Solid dilution

Calculate the amount of diluent that should be added to 10 g of a trituration (1 in 100) to make a mixture that contains 1 mg of drug in each 10 g of the final mixture.

\[
\text{Convert mg to g: } 1 \text{ mg of drug} = 0.001 \text{ g of drug}
\]
10 g of mixture should contain 0.001 g of drug

\( (Q_1) = 10 \text{ g}, \ (C_1) = (1 \text{ in } 100), \text{ and } (C_2) = (0.001 \text{ in } 10) \)

\[ 10 \times \frac{1}{100} = (Q_1) \times \frac{0.001}{10} \]

\( (Q_1) = 1000 \text{ g} \)

Because the final mixture of 1000 g contains 10 g of the trituration, 990 g (or 1000 g − 10 g) of diluent is required to prepare the mixture at a concentration of 0.001 g of drug in each 10 g.

3. Liquid dilution

Calculate the percentage strength \((C_2)\) of a solution obtained by diluting 400 mL of a 5.0% w/v solution to 800 mL.

\( (Q_1) = 400 \text{ mL}, \ (C_1) = 5.0\% \text{ w/v}, \text{ and } (Q_2) = 800 \text{ mL} \)

\[ 400 \times 5\% \text{ w/v} = 800 \times (C_2) \]

\( (C_2) = 2.5\% \text{ w/v} \)

4. Liquid fortification

Calculate the additional amount, in g, of codeine phosphate that need to be added to 180 mL of a 12 mg/5 mL elixir of acetaminophen with codeine to have a final concentration of 30 mg/5 mL of codeine phosphate.

\[ \text{Amount to add} = \text{Total amount required} - \text{Amount present} \]

\[ \text{Total amount required: } (30 \text{ mg/5 mL}) \times 180 \text{ mL} = 1080 \text{ mg of codeine phosphate} \]

\[ \text{Amount present } = (12 \text{ mg of codeine/5 mL}) \times 180 \text{ mL} = 432 \text{ mg of codeine phosphate} \]

\[ \text{Amount to add: } 1080 \text{ mg} - 432 \text{ mg} = 648 \text{ mg of codeine phosphate} \]

9. ALCOHOL

To achieve compliance with the statements in the General Notices and Requirements about Alcohol and the USP monograph for Alcohol, some conventions and special calculations are needed. See General Notices and Requirements 5.20.20.1, In Compounded Preparations, 8.30, Alcohol Content, and 10.40.80, Labeling Alcohol for information. The USP monograph for Alcohol states that it contains 92.3%–93.8% by weight corresponding to 94.9%–96.0% by volume of alcohol (C\(_2\)H\(_5\)OH) at 15.56°. The percent concentration for alcohol is generally taken to be 95% v/v of alcohol (C\(_2\)H\(_5\)OH) in water.

In summary:

- When the word alcohol is written on a prescription order or in a formula, as for example “alcohol 10 mL” or “dissolve in 5 mL of alcohol”, the compounder should use the Alcohol, USP [that is 95% alcohol (C\(_2\)H\(_5\)OH)].
- When the word alcohol is written with a percent, for example “alcohol 20%”, this means 20% v/v of alcohol (C\(_2\)H\(_5\)OH). If this percent is on a label of a commercial product, it means the product contains 20% v/v alcohol (C\(_2\)H\(_5\)OH). If this is part of a compounding formula, it means the compounder must add the equivalent of 20% v/v alcohol (C\(_2\)H\(_5\)OH), which may require special calculations.
Labels of products and compounded preparations are to include the content of alcohol (C₂H₅OH) in % v/v. For compounded preparations, this value must often be calculated based on the volume(s) of alcohol-containing ingredients added.

For calculations when preparing compounded drug preparations using Alcohol, USP, the first step is to determine the quantity, in mL, of alcohol needed, and the second step is to determine the % v/v of alcohol (C₂H₅OH) in the final preparation so that it can be properly labeled.

9.1 Calculating Alcohol

Examples—Alcohol

1. Determine the quantity of alcohol needed for the prescription (see Table 3):

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Purified water, a sufficient quantity to make 60 mL</td>
</tr>
</tbody>
</table>

a. In this prescription order, the alcohol 15% means the preparation contains 15% v/v of alcohol (C₂H₅OH).

b. For 60 mL of preparation, calculate the quantity of alcohol (C₂H₅OH) needed:

\[ 15\% \text{ v/v} \times 60 \text{ mL} = 9 \text{ mL of alcohol} \]

c. Because the source of alcohol (C₂H₅OH) is Alcohol, USP, calculate the volume, in mL, of Alcohol, USP needed to give 9 mL of alcohol (C₂H₅OH):

\[ 9 \text{ mL alcohol}/95\% \text{ v/v Alcohol, USP} = 9.5 \text{ mL of Alcohol, USP} \]

Therefore, add 9.5 mL of Alcohol, USP to this preparation.

d. Determine the % v/v alcohol content for labeling.

Because labeling of alcohol is in % v/v of alcohol (C₂H₅OH), the alcohol content of this preparation would be labeled: Alcohol 15%.

2. Determine the alcohol content, in % v/v, for the prescription (see Table 4):

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castor oil</td>
</tr>
<tr>
<td>Acacia</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Cherry syrup</td>
</tr>
</tbody>
</table>
Purified water, a sufficient quantity to make 100 mL

Because the USP monograph for Alcohol is to be used when alcohol is called for in formulas, measure 15 mL of Alcohol, USP.

95% Alcohol, USP × 15 mL = 14.25 mL of alcohol
14.25 mL of alcohol/100 mL of preparation = 14.25% alcohol

10. ALLIGATION ALTERNATE AND ALGEBRA METHODS

10.1 Alligation Alternate

Alligation is a method of determining the proportions in which substances of different strengths are mixed to yield a desired strength or concentration. Once the proportion is found, the calculation may be performed to find the exact amounts of substances required.

Set up the problem as follows.

1. Place the desired percentage or concentration in the center.
2. Place the percentage of the substance with the lower strength on the lower left-hand side.
3. Place the percentage of the substance with the higher strength on the upper left-hand side.
4. Subtract the lower percentage from the desired percentage, and place the obtained difference on the upper right-hand side.
5. Subtract the desired percentage from the higher percentage, and place the obtained difference on the lower right-hand side.

The results on the right side determine how many parts of the two different percentage strengths should be mixed to produce the desired percentage strength of a drug mixture. The total parts will equal the final weight or volume of the preparation.

10.1.1 CALCULATING BY USING THE ALLIGATION ALTERNATE

Examples—Alligation alternate

1. Determine the amount of ointment containing 12% drug concentration and the amount of ointment containing 16% drug concentration must be used to make 1 kg of a preparation containing a 12.5% drug concentration.

(higher) 16%  0.5 parts of 16%

12.5% (desired)

(lower) 12%  3.5 parts of 12%

4.0 parts of 12.5%
In a total of 4 parts of 12.5% preparation, 3.5 parts of 12% ointment and 0.5 parts of 16% ointment are needed.

4 parts correspond to 1 kg or 1000 g.
1 part corresponds to 250 g.
3.5 parts correspond to 3.5 × 250 g or 875 g of 12% ointment.
0.5 parts correspond to 0.5 × 250 g or 125 g of 16% ointment.

2. Determine the volume, in mL, of 20% dextrose in water and 50% dextrose in water needed to make 750 mL of 35% dextrose in water.

In a total of 30 parts of 35% dextrose in water, 15 parts of 50% dextrose in water and 15 parts of 20% dextrose in water are required.

30 parts correspond to 750 mL.
15 parts correspond to 375 mL.

Thus, use 375 mL of the 20% solution and 375 mL of the 50% solution to prepare the preparation.

10.2 Algebra Method

The following algebraic equation may be used instead of alligation to solve problems of mixing two different strengths of the same ingredient:

\[(C_s \times Q_s) + (C_w \times Q_w) = (C_f \times Q_f),\]

where \(C\) is concentration or strength, \(Q\) is the quantity; and the subscript \(s\) identifies the strongest strength, \(w\) identifies the weakest strength, \(f\) represents the final mixture with a strength less than \(s\) and greater than \(w\), \((Q_f + Q_w) = Q_s\), \(Q_f = (Q_s - Q_w)\), and \(Q_w = (Q_s - Q_f)\).

10.2.1 Calculating by using the algebra method

Examples—Algebra method

1. Determine the amount, in g, of 16% w/w drug ointment and 12% w/w drug ointment required to prepare 1 kg of 12.5% w/w drug ointment.

\[ (16\% \times Q_s) + [12\% \times (1000 \text{ g} - Q_s)] = 12.5\% \times 1000 \text{ g} \]

\[ 16\% \ Q_s + 120 \text{ g} - 12\% \ Q_s = 125 \text{ g} \]

\[ 4\% \ Q_s = 5 \text{ g} \]
\[ Q_s = 5 \text{ g/4\%} = 125 \text{ g of 16\% ointment} \]
\[ Q_s = 1000 \text{ g} - 125 \text{ g} = 875 \text{ g of 12\% ointment} \]

2. Determine the volume, in mL, of 10% dextrose injection and 50% dextrose injection needed to make 750 mL of 35% dextrose injection.

\[
(50\% \times C_s) + [10\% \times (750 \text{ mL} - C_s)] = 35\% \times 750 \text{ mL}
\]
\[
50\% C_s + 75 \text{ mL} - 10\% C_s = 262.5 \text{ mL}
\]
\[
40\% C_s = 187.5 \text{ mL}
\]
\[
C_s = 187.5 \text{ mL}/40\% = 468.75 \text{ mL} \text{ (470 mL practically)}
\]
\[
C_w = 750 \text{ mL} - 468.75 \text{ mL} = 281.25 \text{ mL} \text{ (280 mL practically)}
\]

11. ALIQUOT CALCULATIONS

When the quantity of drug desired requires a degree of precision in measurement that is beyond the capability of the available measuring devices, the pharmacist may use the aliquot method of measurement. It applies when potent drug substances are compounded, or when the total amount of the active drug in a single dose or individualized doses is less than the minimum accurately weighable quantity (MAWQ). Even if the amount of drug needed is greater than the MAWQ per unit, an aliquot will provide more material per unit, which will aid in handling and administration. Aliquot means “containing an exact number of times in something else”; the aliquot must be a proportional part of the total. Therefore, 5 is an aliquot part of 15, because 5 is contained exactly 3 times in 15. Both the total volume of solution or weight of powder triturate and the aliquot volume/weight should be easily and accurately measurable. If the solution or powder triturate is highly concentrated and a small error is made in measuring the aliquot, a large error can occur in the quantity of drug brought to the final formulation.

Aliquots can be: solid–solid, when the active drug and the diluents are solids; solid–liquids, when the active drug is solid and is to be incorporated into a liquid preparation, such as a solution, an emulsion, or a suspension; and liquid–liquid, when the active drug is liquid and the diluents are liquids. It can be a pure liquid or a concentrated solution of a drug. Aliquots of pure liquids are relatively uncommon because few drugs are liquid in their pure state. Aliquots involving concentrated solutions are more common.

There are two general methods to prepare aliquots:

1. Aliquot method 1 is applicable to drugs or substances that have to be within the degree of accuracy provided by the measuring device. It is the simplest method and can be applied to solid and liquid aliquots.

2. Aliquot method 2, also known as the dilution factor method, is useful when there is more flexibility in the amount of drug that may be measured.

Aliquot Method 1:

a. The MAWQ amount of drug is measured.
b. The drug is diluted with an arbitrary amount of diluent.
c. The amount of dilution that will give the desired amount of drug is calculated, and
   the amount is measured.

Aliquot Method 2:

a. The quantity of drug to be measured is determined by multiplying the amount of
drug needed by an appropriately determined factor, called the dilution factor.
The dilution factor must be a whole number more than or equal to the MAWQ
divided by the amount of drug needed.
b. An arbitrary amount of diluent is measured and added. The amount of diluent
used can be determined by different methods, provided the amount of diluent
chosen will give an aliquot greater than or equal to the MAWQ.
c. The amount of aliquot needed is determined by multiplying the weight or volume
of the dilution by the inverse of the dilution factor. Dilution factors are usually
chosen to be whole numbers.

The general calculations can be shown as:

\[ \frac{A}{B} = \frac{C}{D} \]

11.1 Calculating Aliquots

Examples—Aliquots
1. Solid-in-liquid dilution (Aliquot Method 1)
Prepare 100 mL of a solution containing 0.2 mg/mL of clonidine using water as the
diluent. To prepare this solution, 20 mg of clonidine is needed.

a. Select the weight of drug desired \((A)\) to be equal to or greater than the MAWQ. In
   this situation, the MAWQ of the balance is 120 mg.
b. Select the aliquot volume \((D)\) in which the desired amount of drug \((C)\) will be
   contained. This establishes the concentration of the solution to be prepared.
   Clonidine solubility is 1 g/13 mL, so if 5 mL is selected as the aliquot volume,
   the concentration in that solution will be 20 mg/5 mL. Therefore, solubility will
   not be a problem in this aqueous solution.
c. Using the preceding formula, calculate the volume of solution \((B)\) to be prepared.

\[ \frac{120 \text{ mg of clonidine}}{B} = \frac{20 \text{ mg of clonidine}}{5 \text{ mL of aliquot}} \]

\[ B = 30 \text{ mL} \]
d. Prepare the solution containing 120 mg of clonidine in 30 mL of Purified Water. Transfer a 5-mL aliquot from this solution to a final container, and add sufficient Purified Water to bring the formulation to a final volume of 100 mL.

2. Solid-in-solid dilution (Aliquot Method 2)
Prepare an individual dose of codeine phosphate 20 mg.

a. Select a dilution factor that will yield a quantity that is greater than or equal to the MAWQ, and weigh this amount. In this case, the dilution factor may be greater than or equal to 6 because $6 \times 20 \text{ mg} = 120 \text{ mg}$. The smallest dilution factor that may be chosen is 6 if the MAWQ of the balance is 120 mg.
b. Weigh an amount of diluent that will give an aliquot greater than or equal to the MAWQ. In this example, 600 mg of diluent is weighed.
c. Mix the two powders thoroughly by geometric trituration in a mortar.
d. Calculate the total weight of the dilution: $120 \text{ mg codeine phosphate} + 600 \text{ mg diluent} = 720 \text{ mg}$.
e. Calculate the aliquot part of the dilution that contains 20 mg of codeine phosphate by multiplying the total weight of the dilution by the inverse of the dilution factor: $720 \text{ mg} \times (1/6) = 120 \text{ mg}$.
f. Weigh this calculated amount of the dilution (120 mg) to get the desired 20 mg of codeine phosphate per dose.

12. POWDER VOLUME CALCULATIONS

12.1 Displacement in Suspension

12.1.1 CALCULATING POWDER VOLUME

Examples—Powder volume

1. Powder displacement in suspension

The directions to reconstitute a 150 mL bottle of an amoxicillin for oral suspension of 250 mg/5 mL require 111 mL of Purified Water. The physician has requested that the product be reconstituted at a concentration of 500 mg/5 mL. Calculate the amount of Purified Water required for the higher concentration.

a. Calculate the volume of the suspension occupied by the amoxicillin powder:

$$150 \text{ mL} - 111 \text{ mL} = 39 \text{ mL}$$

b. Calculate the quantity of amoxicillin present in the entire bottle:

$$150 \text{ mL} \times (250 \text{ mg/5 mL}) = 7500 \text{ mg}$$

c. Calculate the total volume of the suspension at the requested concentration (500 mg/5 mL):

$$7500 \text{ mg/(500 mg/5 mL)} = 75 \text{ mL}$$
d. Calculate the volume of Purified Water needed to reconstitute the powder by subtracting the powder volume calculated in step a:

\[ 75 \text{ mL} - 39 \text{ mL} = 36 \text{ mL of Purified Water} \]

NOTE—Such formulations may be too viscous to flow freely.

2. Powder volume in drugs for injection
If the powder volume of 250 mg of ceftriaxone for injection is 0.1 mL, calculate the amount of diluent that should be added to 500 mg of ceftriaxone for injection to make a suspension with a concentration of 250 mg/mL.

a. Calculate the total volume of injection:

\[ \frac{500 \text{ mg}}{250 \text{ mg/mL}} = 2 \text{ mL} \]

b. Calculate the volume occupied by 500 mg of ceftriaxone for injection:

\[ \frac{500 \text{ mg}}{250 \text{ mg/0.1 mL}} = 0.2 \text{ mL} \]

c. Calculate the volume of the diluent required:

\[ (2 \text{ mL of suspension}) - (0.2 \text{ mL of ceftriaxone for injection}) = 1.8 \text{ mL of diluent} \]

13. INTRAVENOUS FLOW OR INFUSION RATES
Intravenous (IV) solutions and emulsions may be administered by gravity flow and infusion or syringe pumps. Gravity-flow IV sets are regulated by an adjustable clamp on the tubing, and the approximate flow rate is determined by counting the number of drops per 10–15 seconds, then adjusting that to a per minute rate. Manufactured IV sets are typically calibrated to deliver from 15 to 60 drops/mL, depending on the particular set.

13.1 Solving by Multiple or Separate Steps
As in previous sections, the following examples may be solved by multiple separate steps, or a single-DUA procedure.

13.1.1 CALCULATING INTRAVENOUS FLOW OR INFUSION RATES
Examples—IV or infusion rates
1. An IV infusion of dextrose 5% in water with 20 mEq of potassium chloride is to be administered to a 6-year-old child at the rate of 12 mL/hour. An IV administration set that delivers 60 drops/mL is available. Calculate the flow rate in drops/minute:

\[ \frac{12 \text{ mL}}{\text{hour}} \times \frac{60 \text{ drops}}{\text{mL}} \times \frac{1 \text{ hour}}{60 \text{ minutes}} = 12 \text{ drops/minute} \]

2. A 63.6-kg patient is admitted to the Emergency Department and requires a dopamine hydrochloride infusion to maintain an adequate blood pressure. The drug is
ordered at an initial rate of 2 µg/kg/minute. A 400-mg/250-mL dopamine hydrochloride injection is available. Calculate the flow rate in mL/hour to be administered by infusion pump:

\[
\text{Flow rate (mL/hour)} = \frac{63.6 \text{ kg}}{\text{kg} \times \text{minute}} \times \frac{2 \mu g}{400 \text{ mg}} \times \frac{250 \text{ mL}}{60 \text{ minutes}} = 4.8 \text{ mL/hour}
\]

14. ISOOSMOTIC SOLUTIONS

The following discussion and calculations have therapeutic implications in preparations of dosage forms intended for ophthalmic, subcutaneous, intravenous, and intrathecal administration as well as for neonatal use.

14.1 Tonicity

Cells of the body, such as erythrocytes, will neither swell nor shrink when placed in a solution that is isotonic with body fluids. The measurement of tonicity, however, which is a physiological property, is somewhat difficult. A 0.9% w/v sodium chloride injection, which has a freezing point (FP) of −0.52°, is both isotonic and isoosmotic with body fluids. In contrast to isotonicity, FP depression is a physical property. Some solutions that are isoosmotic with body fluids are not isotonic, because they contain solutes to which cells are freely permeable rather than semipermeable. Freely permeable solutes (e.g., boric acid and urea) can cause erythrocyte lysis, i.e., behave as if they were hypotonic in concentrations that are hyperosmotic relative to body fluids. Nevertheless, many pharmaceutical products are prepared using FP data or related sodium chloride data to prepare solutions that are isoosmotic with body fluids. A closely related topic is osmolarity (see chapter Osmolality and Osmolarity).

FP data or sodium chloride equivalents of pharmaceuticals and excipients (see Table 5) may be used to prepare isoosmotic solutions, as shown in the following examples.

14.1.1 CALCULATING TONICITY

Example—Tonicity

Determine the amount of sodium chloride (NaCl) required to prepare 60 mL of an isoosmotic solution of atropine sulfate injection 0.5% using the E values and the FP depression values in Table 5.

<table>
<thead>
<tr>
<th>Drug or Excipient</th>
<th>E</th>
<th>FP Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine sulfate</td>
<td>0.13</td>
<td>0.075</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>1.00</td>
<td>0.576</td>
</tr>
</tbody>
</table>

Using the E values:

a. The total amount of substances equivalent to a 0.9% sodium chloride injection = (0.9 g/100 mL) × 60 mL = 0.54 g.

b. The amount of atropine sulfate required = (0.5 g/100 mL) × 60 mL = 0.3 g.

c. 1 g of atropine sulfate is equivalent to 0.13 g of sodium chloride.
d. 0.3 g of atropine sulfate is equivalent to \(0.3 \times 0.13\) g = 0.039 g of sodium chloride.

e. Thus, the required amount of sodium chloride is 0.54 g − 0.039 g = 0.501 g or 0.5 g.

Using FP depression values:

a. The FP depression required is 0.52°.
b. A 1% solution of atropine sulfate causes an FP depression of 0.075°.
c. A 0.5% solution of atropine sulfate causes an FP depression of \(0.5 \times 0.075° = 0.0375°\).
d. The additional FP depression required is 0.52° − 0.0375° = 0.483°.
e. A 1% solution of sodium chloride causes an FP depression of 0.576°.
f. Therefore, an FP depression of 1° is caused by a 1%/0.576 = 1.736% solution of sodium chloride.
g. 1.736% × 0.483 = 0.838% solution of sodium chloride causes an FP depression of 0.482°.
h. The required amount of sodium chloride is (0.838%) × 60 mL = 0.502 g or 0.5 g.

15. PH AND BUFFER CALCULATIONS

15.1 pH Calculations

See Appendix 1 for logarithmic definitions and applications.

\[\text{pH} = -\log [\text{H}_3\text{O}^+], \quad \text{and} \quad p\text{Ka} = -\log \left((\text{H}_3\text{O}^+)\text{[A}^-]/[\text{HA}]\right),\]

where \([\text{H}_3\text{O}^+]\) is the hydronium ion concentration in an aqueous solution, \([\text{A}^-]\) is the ionic form of the relevant acid, and \(\text{Ka}\) is the ionization constant of either a monoprotic acid or a particular proton from a polyprotic acid in aqueous solution. The \([\text{H}^+]\) = the antilogarithm of \((−\text{pH})\) or \(10^{−\text{pH}}\); and \(\text{Ka}\) = the antilogarithm of \((−\text{pKa})\) or \(10^{−\text{pKa}}\).

The pH of an aqueous solution containing a weak acid may be calculated using the Henderson–Hasselbalch equation:

\[\text{pH} = \text{pKa} + \log \left(\frac{\text{[base form]}}{\text{[acid form]}}\right)\]

The buffer equation symbol (↔) represents the equilibrium between conjugate base and acid forms or pairs of the same molecule. It is called the buffer equation, because small changes in the ratio of concentrations of the conjugate forms result in a logarithmically smaller change in pH. The salt form can be an acid or base, depending on structure; thus, its conjugate form is a base or acid, respectively.

Example 1:

B and BH+ represent a nonionized or “free” base and cationic acid pair, \(\text{BH}^+ \leftrightarrow \text{B}^+\text{H}^+\).

Example 2:

HA and A− represent a nonionized or “free” acid and anionic base pair, \(\text{HA} \leftrightarrow \text{A}^- + \text{H}^+\).

Example 3:

\(\text{H}_n\text{A}^-\) and \(\text{H}_{n-1}\text{A}^{2-}\), such as \(\text{H}_2\text{PO}_4^-\) and \(\text{HPO}_4^{2-}\), represent an anionic acid and anionic base relative to each other; the \(p\text{Ka} = 7.2\) for \(\text{H}_2\text{PO}_4^- \leftrightarrow \text{HPO}_4^{2-} + \text{H}^+\).

15.1.1 CALCULATING pH
A solution contains 0.020 mol/L of sodium acetate and 0.010 mol/L of acetic acid, which has a pKa value of 4.76. Calculate the pH and the [H+] of the solution as follows:

\[
pH = 4.76 + \log \left( \frac{0.020}{0.010} \right) = 5.06
\]

\[
[H^+] = \text{antilogarithm of } (-5.06) = 8.69 \times 10^{-6}
\]

### 15.2 Buffer Solutions

#### 15.2.1 Definition

A buffer solution is an aqueous solution that resists a change in pH when small quantities of acid or base are added, when diluted with the solvent, or when the temperature changes. Most buffer solutions are mixtures of a weak acid and one of its salts, or mixtures of a weak base and one of its salts. Water and solutions of a neutral salt, such as sodium chloride, have very little ability to resist the change of pH and are not capable of effective buffer action.

#### 15.2.2 Preparation, Use, and Storage of Buffer Solutions

Buffer solutions for Pharmacopeial tests should be prepared using freshly boiled and cooled water (see Reagents, Indicators and Solutions). They should be stored in containers such as Type I glass bottles and used within 3 months of preparation. Buffers used in physiological systems are carefully chosen so as to not interfere with the pharmacological activity of the medicament or the normal function of the organism. Commonly used buffers in parenteral products, for example, include: the nonionized acid and base salt pairs of acetic acid and sodium acetate, citric acid and sodium citrate, glutamic acid and sodium glutamate, and monopotassium or monosodium phosphate and dipotassium or disodium phosphate; and the acid salt and nonionized base pair tris(hydroxymethyl)aminomethane hydrochloride and tris(hydroxymethyl)aminomethane. Buffer solutions should be freshly prepared.

The Henderson–Hasselbalch equation, noted in 15.1 pH Calculations, allows calculation of the pH and concentrations of conjugate pairs of weak acids and their salts and weak bases and their salts in buffer solutions when the pKa of the acid form of the buffer pair is known. Appropriately modified, this equation may be applied to buffer solutions composed of a weak base and its salt.

#### 15.2.3 Buffer Capacity

The buffer capacity of a solution is the measurement of the ability of that solution to resist a change in pH upon addition of small quantities of a strong acid or base. An aqueous solution has a buffer capacity of 1 when 1 L of the buffer solution requires 1 g equivalent of strong acid or base to change the pH by 1 unit. Therefore, the smaller the pH change upon the addition of a specified amount of acid or base, the greater the buffer capacity of the buffer solution. Usually, in analysis, much smaller volumes of buffer are used to determine the buffer capacity. An approximate formula for calculating the buffer capacity is g equivalents of strong acid or base added per L of buffer solution per unit of pH change, i.e., (g equivalents/L)/(pH change).

#### 15.2.4 Calculating Buffer Capacity

Example—Buffer capacity
The addition of 0.01 g equivalents of sodium hydroxide to 0.25 L of a buffer solution produced a pH change of 0.50. The buffer capacity of the buffer solution is calculated as follows:

\[
\frac{0.01 \text{ Eq}}{0.25 \text{ L}}/0.50 \text{ pH change} = 0.08(\text{Eq/L})/(\text{pH change})
\]

### 16. TEMPERATURE

The relationship between Celsius or Centigrade (°C) and Fahrenheit (°F) temperature scale is expressed by the following equations:

\[
\begin{align*}
^\circ C &= (^\circ F - 32) \times \frac{5}{9} \\
^\circ F &= (^\circ C \times 1.8) + 32
\end{align*}
\]

#### 16.1 USP Temperatures

According to the *General Notices and Requirements 8.180, Temperatures*, temperatures are expressed in centigrade (Celsius) degrees, and all other measurements are made at 25° unless otherwise indicated. For instructional purposes, °F is shown in the examples.

#### 16.1.1 CALCULATING TEMPERATURES

**Examples—Temperatures**

1. Convert 77°F to Celsius degrees.

\[
^\circ C = (77^\circ F - 32) \times \frac{5}{9} = 25^\circ C
\]

2. Convert 30°C to Fahrenheit degrees.

\[
^\circ F = (30^\circ C \times 1.8) + 32 = 86^\circ F
\]

The relationship between the Kelvin or absolute (K) and the Celsius (°C) scales is expressed by the equation:

\[
K = ^\circ C + 273.1
\]

### 17. ENDOTOXINS

An endotoxin is a lipopolysaccharide that comes from a particular source, where species and strain number are usually indicated.

#### 17.1 Endotoxin Concentrations

For more information concerning endotoxins, see *Bacterial Endotoxins Test* 〈85〉.

#### 17.1.1 CALCULATING ENDOTOXINS

**Example—Endotoxins**

A 71.8-kg patient is to receive an intrathecal infusion of morphine sulfate at a rate of 0.3 mg/hour. The solution will be prepared by diluting preservative-free morphine sulfate injection, which contains 10 mg/mL of morphine sulfate, with 0.9% sodium chloride injection to produce an infusion rate of 2 mL/h.
1. Determine the volume, in mL, of morphine sulfate injection (10 mg/mL) and 0.9% sodium chloride injection needed to prepare a 24-hour infusion.

   0.3 mg of morphine sulfate/hour × 24 hours = 7.2 mg of morphine sulfate

   7.2 mg of morphine sulfate/(10 mg/mL) = 0.72 mL of morphine sulfate injection

   2 mL of infusion/h × 24 h = 48 mL of total volume

   48 mL total volume − 0.72 mL morphine sulfate injection = 47.28 mL of 0.9% sodium chloride injection

2. Calculate the maximum potential endotoxin load/hour for this preparation. [**NOTE—** USP monographs specify upper limits of 14.29 USP Endotoxin Units (EU)/mg of morphine sulfate in injections for intrathecal use, and 0.5 EU/mL for injections containing 0.5%–0.9% sodium chloride.]

   7.2 mg of morphine sulfate injection × 14.29 EU/mg of morphine sulfate = 102.89 EU from morphine sulfate

   47.28 mL of sodium chloride injection × 0.5 EU/mL = 23.64 EU from 0.9% sodium chloride injection

   \[ \text{Endotoxin load} = 102.89 \text{ EU} + 23.64 \text{ EU} = 126.53 \text{ EU} \]

   \[ \text{126.53 EU/24 hour} = 5.27 \text{ EU/hour} \]

3. Determine if the endotoxin load in step 2 exceeds the allowable USP limit for this patient. [**NOTE—** The maximum endotoxin load by intrathecal administration is 0.2 EU/kg/hour (see chapter 85).]

   Maximum endotoxin load = (0.2 EU/kg/hour) × 71.8 kg-patient = 14.36 EU/hour

   The endotoxin load of 5.27 EU/hour does not exceed the allowable limit of 14.36 EU/hour.

18. **STABILITY AND EXPIRATION DATE CALCULATIONS**

18.1 Stability Based on Rate Calculations

Calculation of a predetermined minimum percentage of initial drug strength or other quality parameter, e.g., in vitro dissolution of active pharmaceutical ingredients (APIs) or active drugs in solid oral dosage forms, is based on component-specific assays and other validated scientific testing. The expiration date or time elapsed until such minimum acceptable limits are reached for a specific manufactured product is exclusive to the specific formulation, packaging, and environmental conditions, e.g., temperature,
humidity, and illumination, to which the item is subjected. See also chapters 659, 795, 797, 1163, and 1191.

The degradation or concentration loss rates or kinetics of most APIs can be accurately represented or modeled by either zero order (constant) or first order (mono-exponential) rate equations. Zero order calculations are generally applicable to solids, semisolids, suspensions in which a majority of the drug strength is present as solid particles, and auto-oxidation in solutions. First order calculations are generally applicable for drug hydrolysis in solutions.

18.2 Zero Order Rate Calculations

The isothermal zero order or constant rate equation for a particular formulation is

\[ C = C_0 - kt \]

where \( C \) is the concentration of API at any time, \( C_0 \) is the concentration at origination or time zero, \( k \) is the reaction rate constant, and \( t \) is any time after origination or zero. The values and units of the rate, \( dC/dt \), and rate constant, \( k \), are the same for zero order processes, i.e., the units are concentration/time, such as mg/mL/day.

18.2.1 ZERO ORDER RATE EQUATION DERIVED FROM ORIGINAL DATA

The following examples illustrate calculations of the zero order rate equation from original concentration assay and time data, and an expiration date using that equation.

18.2.1.1 Calculating zero order rate:

**Examples—Zero order rate**

1. Calculate the zero order rate equation based on the assay results for a drug suspension at 25° (see Table 6):

<table>
<thead>
<tr>
<th>C (mg/mL)</th>
<th>t (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>3</td>
</tr>
<tr>
<td>47.5</td>
<td>8</td>
</tr>
<tr>
<td>44.8</td>
<td>17</td>
</tr>
<tr>
<td>42.3</td>
<td>26</td>
</tr>
</tbody>
</table>

Linear regression of the \( C \) (ordinate) versus \( t \) (abscissa) values yields the equation, \( C = 49.84 - 0.292t \) with a correlation coefficient of −0.9998.

2. Calculate the time when \( C = 0.9 \times C_0 \), i.e., the expiration date where the concentration will be 90% of the original concentration \( (t_{90}) \):

\[ C = 49.84 - 0.292t \]

\[ 0.9 \times 49.84 = 49.84 - 0.292(t_{90}) \]

\[ t_{90} = (44.86 - 49.84)/-0.292 = 17.05 \text{ days} \]

3. Using the previous linear regression equation, calculate the \( C \) of the drug suspension at 25° when \( t = 12 \) days:

\[ C = 49.84 - (0.292 \times 12) = 43.34 \text{ mg/mL} \]

4. Calculate \( t \) when \( C = 45 \text{ mg/mL} \):

\[ 45 = 49.84 - 0.292t \]
18.2.2 ZERO ORDER VALUES CALCULATED FROM A RATE EQUATION

The following are examples of expiration dates calculated from a rate equation derived from original concentration assay and time data.

18.2.2.1 Calculating zero order values from a rate equation:

Examples—Zero order from a rate equation

1. Calculate the \( t_{80} \) expiration date of a drug cream at 25° using the equation, \( C = 0.05 - 0.0003t \), where the \( C \) unit is % w/w and the \( t \) unit is months. At \( t_{80} \), \( C = 0.8C_0 \).

\[
0.8 \times 0.05 = 0.05 - 0.0003(t_{80})
\]

\( t_{80} = 33.3 \) months

2. Calculate the \( t_{80} \) expiration date of the drug cream formulation in example 1, but for which \( C_0 \) is 0.1:

\[
0.8 \times 0.1 = 0.1 - 0.0003(t_{80})
\]

\( t_{80} = 66.7 \) months

18.3 First Order Rate Calculations

The isothermal first order rate equation for a particular formulation in exponential form is \( C = C_0 e^{-kt} \), and in linear form is \( \text{ln}(C) = \text{ln}(C_0) - kt \), where \( C \) is the concentration of an API at any time, \( C_0 \) is the concentration at origination or time zero, \( k \) is the reaction rate constant, and \( t \) is any time after origination or zero. The constantly changing rate, \( dC/dt \), and rate constant, \( k \), are not the same for first order processes. The rate units are concentration/time, e.g., mg/mL/hour, but the rate constant unit is reciprocal time, time\(^{-1}\), e.g., hour\(^{-1}\).

18.3.1 FIRST ORDER LINEAR RATE EQUATION DERIVED FROM ORIGINAL DATA

The following examples illustrate calculation of the linear first order rate equation from original concentration assay and time data and calculation of an expiration date using that equation.

18.3.1.1 Calculating first order linear rate equations:

Example—First order linear rate

1. Calculate the linear first order rate equation based on the assay results for a drug solution at 27° (see Table 7):

<table>
<thead>
<tr>
<th>C (mg/mL)</th>
<th>t (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.3</td>
<td>2</td>
</tr>
<tr>
<td>11.9</td>
<td>6</td>
</tr>
<tr>
<td>11.5</td>
<td>14</td>
</tr>
<tr>
<td>10.6</td>
<td>24</td>
</tr>
</tbody>
</table>

Linear regression of the \( \text{ln}(C) \) (ordinate) versus \( t \) (abscissa) values yields the equation, \( \text{ln}(C) = 2.522 - 0.0065t \) with a correlation coefficient of 0.992.
2. From the linear regression equation, calculate the time when 95% of the original concentration is reached, \( t_{95} \), when \( C = 0.95C_0 \) which is the predetermined expiration date:

\[
\ln(C_0) = 2.522; \text{ thus, } C_0 = e^{2.522} = 12.45 \text{ mg/mL}
\]

\[
\ln(0.95 \times 12.45) = 2.522 - 0.0065(t_{95})
\]

\[
t_{95} = \frac{2.470 - 2.522}{-0.0065} = 8 \text{ hours}
\]

18.3.2 FIRST ORDER VALUES CALCULATED FROM A LINEAR EQUATION

The following are examples of an expiration date, concentration, and time calculated for the same drug solution at 22° from the rate equation, \( \ln(C) = 4.382 - 0.076t \), where the \( C \) units are \( \mu \text{g/mL} \) and the \( t \) unit is days, derived from the original concentration assay and time data.

18.3.2.1 Calculating first order values from a linear rate equation:

Examples—First order from a linear rate

1. Calculate the \( t_{90} \) expiration date:

\[
\ln(C_0) = 4.382; \text{ thus, } C_0 = e^{4.382} = 80
\]

\[
\ln(0.9 \times 80) = 4.382 - 0.076(t_{90})
\]

\[
t_{90} = \frac{4.277 - 4.382}{-0.076} = 1.4 \text{ days}
\]

2. Calculate the time at which \( C = 75 \mu \text{g/mL} \):

\[
\ln(75) = 4.382 - 0.076t
\]

\[
t = \frac{4.317 - 4.382}{-0.076} = 0.86 \text{ day}
\]

3. Calculate whether \( C = 70 \mu \text{g/mL} \) occurs before or after \( t_{90} \):

\[
\ln(70) = 4.382 - 0.076t
\]

\[
t = \frac{4.248 - 4.382}{-0.076} = 1.8 \text{ days}
\]

\( C = 70 \mu \text{g/mL} \) occurs at 1.8 days, after a \( t_{90} \) of 1.4 days

18.3.3 FIRST ORDER EXPIRATION DATE CALCULATED FROM TWO VALUES OF CONCENTRATION AND TIME

When degradation or other cause of concentration loss is known from experience or reference information to obey first order kinetics, the rate constant can be accurately estimated from accurate assays of only two concentrations at their respective times. In this case, the linear first order rate equation, \( \ln(C) = \ln(C_0) - kt \), may be transformed or integrated as \( \ln(C_t) = \ln(C_0) - k(t_e - t) \), which when rearranged is \( k = \ln(C_t/C_0)/(t_e - t) \). The following examples apply these equations to calculate expiration dates, concentrations, and times.

18.3.3.1 Calculating first order expiration date from two values:

Examples—First order expiration date from two values

1. At 25°, the concentration of an antibiotic in solution was 89 mg/mL after 3 hours and 74 mg/mL after 8 hours. Calculate the initial concentration at time zero:

\[
k = \ln(89/74)/(8 - 3) = 0.037 \text{ hour}^{-1}
\]
\[ \ln(89) = \ln(C_0) - (0.037 \text{ hour}^{-1} \times 3 \text{ hour}) \]
\[ \ln(C_0) = 4.489 + 0.111 = 4.6 \]
\[ C_0 = e^{4.6} = 99.5 \text{ mg/mL} \]

2. Calculate the \( t_{90} \) expiration date using the data in example 1. At \( t_{90} \), \( C = 0.9 C_0 \).
\[ \ln(0.9 \times 99.5) = \ln(99.5) - 0.037(t_{90}) \]
\[ t_{90} = (4.495 - 4.600)/(-0.037 \text{ hour}^{-1}) = 2.8 \text{ hour} \]

3. Calculate the concentration at 6 hour using the data in example 1:
\[ \ln(C) = \ln(99.5) - (0.037 \times 6) \]
\[ \ln(C) = 4.378 \]
\[ C = e^{4.378} = 79.7 \text{ mg/mL} \]

18.3.4 FIRST ORDER TIMES, \( T_n \) FOR 0.\( n \) FRACTION OR \( n\% \) OF REMAINING ORIGINAL CONCENTRATION

The two most common first order pharmaceutical \( t \) values are the \( t_{50} \), which is a primary parameter factor in clinical pharmacokinetics, and the \( t_{90} \), which is the most common stability shelf life or expiration date. Values of any \( t_n \), where \( 0 < n < 100 \), are derived from the linear first order equation, \( \ln(C) = \ln(C_0) - kt \). The equations for \( t_{50} \) and \( t_{90} \) in particular are derived in the following examples. The value of \( k \) by definition is constant for a specific drug chemical in a specific formulation at a specific temperature; thus, \( t \) values derived from such values of \( k \) are also constant.

18.3.4.1 Calculating first order times for remaining original concentrations:

Examples—First order times for remaining original concentrations

1. At \( t_n \), \( C = 0.\!n\times C_0 \).
\[ \ln(0.\!n\times C_0) = \ln(C_0) - kt_n \]
\[ t_n = [\ln(0.\!n \times C_0) - \ln(C_0)]/\!-k = \ln([0.\!n \times C_0]/C_0)/\!-k = \ln(0.\!n)/\!-k \]
\[ t_n = \ln(0.\!n)/\!-k \]

2. At \( t_{50} \), \( C = 0.5(C_0) \).
\[ \ln(0.5 \times C_0) = \ln(C_0) - kt_{50} \]
\[ t_{50} = [\ln(0.5 \times C_0) - \ln(C_0)]/\!-k = \ln([0.5 \times C_0]/C_0)/\!-k = \ln(0.5)/\!-k = -0.693/\!-k = 0.693/k \]
\[ t_{50} = 0.693/k \]

3. At \( t_{90} \), \( C = 0.9(C_0) \).
\[ \ln(0.9 \times C_0) = \ln(C_0) - kt_{90} \]
\[ t_{90} = [\ln(0.9 \times C_0) - \ln(C_0)]/\!-k = \ln([0.9 \times C_0]/C_0)/\!-k = \ln(0.9)/\!-k = -0.105/\!-k = 0.105/k \]
\[ t_{90} = 0.105/k \]

18.4 Stability Prediction Based on Arrhenius Theory

The basis of the Arrhenius theory is that reaction rates and rate constants change exponentially in the direction of arithmetic temperature change. The pharmaceutical application of the Arrhenius theory is based on scientifically accurate and statistically
valid assay data obtained at three or more temperatures that are ≥10° warmer than the intended drug storage temperature and each other. The Arrhenius equation may be expressed in an exponential form, \( k = A e^{-(E_a/RT)} \), a linear form, \( \ln(k) = \ln(A) - (E_a/RT) \), and an integrated form, \( \ln(k/k_i) = E_a(T_2 - T_1)/[R(T_2 \times T_1)] \), where \( k, k_i, \) and \( k_2 \) are isothermal rate constants, \( A \) is a thermodynamic factor, \( E_a \) is energy of activation for the degradation reaction, \( R \) is the gas constant (1.987 × 10⁻³ kcal mol⁻¹ K⁻¹ or 8.314 × 10⁻³ J K⁻¹ mol⁻¹), and \( T, T_1, \) and \( T_2 \) are absolute or Kelvin temperatures.

### 18.4.1 ARRHENIUS LINEAR EQUATION DERIVED FROM ORIGINAL DATA

The following examples illustrate derivation of a linear Arrhenius equation from original assay data and its application to predicting a drug stability expiration date at a cooler or lower storage temperature.

#### 18.4.1.1 Calculating Arrhenius equations:

**Examples—Arrhenius equations**

1. Calculate the linear Arrhenius equation based on the rate constants and temperatures for a beta-lactam antibiotic that decomposes in solution at a first order rate (see Table 8):

<table>
<thead>
<tr>
<th>( T (°C) )</th>
<th>( T (K) )</th>
<th>( 1/T (K^{-1}) )</th>
<th>( k ) (hour⁻¹)</th>
<th>( \ln(k) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>313</td>
<td>3.195 × 10⁻³</td>
<td>0.0014</td>
<td>-6.571</td>
</tr>
<tr>
<td>50</td>
<td>323</td>
<td>3.096 × 10⁻³</td>
<td>0.005</td>
<td>-5.298</td>
</tr>
<tr>
<td>60</td>
<td>333</td>
<td>3.003 × 10⁻³</td>
<td>0.016</td>
<td>-4.135</td>
</tr>
</tbody>
</table>

Linear regression of the \( \ln(k) \) (ordinate) versus \( 1/T \) (abscissa) values yields the equation, \( \ln(k) = 33.977 - (12,689/T) \) with a correlation coefficient of 0.99997.

2. Calculate the \( t_{90} \) shelf life expiration date, in days, at 25°C (298 K) using the equation in example 1:

\[
\ln(k_{25}) = 33.977 - (12,689/298) = 33.977 - 42.581 = -8.604
\]

\[
k_{25} = e^{-8.604} = 1.834 \times 10^{-4} \text{ hour}^{-1} = 4.402 \times 10^{-3} \text{ day}^{-1}
\]

\[
t_{90} = 0.105/k = 0.105/(4.402 \times 10^{-3}) \text{ day}^{-1} = 23.85 \text{ days}
\]

**18.4.2 STABILITY PREDICTIONS USING THE INTEGRATED ARRHENIUS EQUATION**

The following examples illustrate stability predictions based on one accurately determined isothermal rate constant and adherence to the same degradation rate order, e.g., first order, at temperatures at which stability is to be calculated from the equation, \( \ln(k/k_1) = E_a(T_2 - T_1)/[R(T_2 \times T_1)] \).

#### 18.4.2.1 Calculating stability prediction using integrated Arrhenius equation:

**Example—Stability using integrated Arrhenius equations**

1. Calculate the \( t_{85} \) stability expiration date at 4°C (277 K) for an ester hydrolysis with an \( E_a = 15 \text{ kcal/mol} \) and \( k = 0.0045 \text{ hour}^{-1} \) at 23°C (296 K):

\[
\ln(k_{277}/0.0045) = 15(277 - 296)/[1.987 \times 10^{-3} (277 \times 296)]
\]
\[
\ln(k_{277}) - \ln(0.0045) = -285/162.92
\]
\[
\ln(k_{277}) = -1.749 + \ln(0.0045) = -7.153
\]
\[
k_{277} = e^{-7.153} = 7.825 \times 10^{-4} \text{ hour}^{-1}
\]
\[
t_{50} = \ln(0.850)/k_{277} = -0.163/7.825 \times 10^{-4} \text{ hour}^{-1} = 208.3 \text{ hours}
\]
\[
t_{50} \text{ at } 4°C = 208.3 \text{ hours } (t_{50} \text{ at } 23°C \text{ is } 36.2 \text{ hours})
\]

### 18.4.3 Arrhenius-Based \( Q_{10} \) Stability Estimation

The temperature coefficient \( (Q_{10}) \) represents the multiplicative factor by which a chemical reaction rate constant changes in the same direction as the temperature for each 10°C change. For drug molecules, \( Q_{10} \) ranges from 2 to 5, corresponding to an \( E_{a} \) range of 10–25 kcal/mol or 42–105 kJ/mol. A \( Q_{10} \) of 3 yields reasonable estimates of drug stability in the equation, \( (t_n \text{ at } T_2) = (t_n \text{ at } T_1)/\{Q_{10}\} \), where \( n \) is a percentage of remaining \( C_n \), \( T_1 \) is the temperature at which \( t_n \) is known, and \( T_2 \) is the temperature at which \( t_n \) is to be estimated. Calculations using \( Q_{10} \) values of both 2 and 4 may be used to obtain the shortest or most conservative stability estimate, but \( Q_{10} = 3 \) is applied in the following two example.

#### 18.4.3.1 Calculating Arrhenius-based \( Q_{10} \) stability estimation:

**Example—Arrhenius-based \( Q_{10} \) stability**

1. Estimate the \( t_{90} \) expiration date in hours of an antibiotic suspension stored in a closed automobile at 57° for which the 8° refrigeration \( t_{90} \) is 14 days.

\[
t_{90} \text{ at } 57° = [14 \text{ days } \times (24 \text{ hours/day})]/\{3^{(57-8)/10}\} = 336 \text{ hours}/34.9 = 336 \text{ hours}/217.7 = 1.54 \text{ hours}
\]

\[
t_{90} \text{ at } 57° = 1.54 \text{ hours}
\]

### Appendix 1: Logarithms

The logarithm of a number is the exponent or power to which a given base number must be raised to equal that number. Thus, the logarithm of \( Y \) to the base, \( b \), equals \( X \), or \( \log_b(Y) = X \). The logarithm of 0 and all negative numbers is undefined or nonexistent. The logarithm of 1 is 0 and of numbers <1 is negative in all systems (see Table 9).

<table>
<thead>
<tr>
<th>Logarithmic System</th>
<th>Abbreviation or Symbol</th>
<th>Base Number</th>
<th>Format</th>
<th>Antilogarithm or Inverse Logarithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Log</td>
<td>10</td>
<td>\log Y = X</td>
<td>10^X = Y</td>
</tr>
<tr>
<td>Natural</td>
<td>Ln</td>
<td>e or 2.7183+</td>
<td>\ln Y = X</td>
<td>e^X = Y</td>
</tr>
</tbody>
</table>

* \( e \) is an irrational number derived from an infinite series of reciprocal whole number factorials, \( e = 1 + 1/1! + 1/2! + 1/3! + 1/4! ... + 1/n! \), where \( n = \infty \). \( e \) rounds to 2.7183 when \( n \geq 8 \).

2. The relationships between common and natural logarithms are the following:

a. \( \log Y = \ln Y/\ln 10 = \ln Y/2.303 \)

b. \( \ln Y = \ln 10 \times \log Y = 2.303 \times \log Y \)
3. Rules for some common calculations with logarithms are shown in Table 10.

Table 10. Rules for Calculating with Logarithms

<table>
<thead>
<tr>
<th>Formula</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Additions and multiplications</strong></td>
<td></td>
</tr>
<tr>
<td>( \ln(A) + \ln(B) = \ln(A \times B) )</td>
<td>( \ln(0.62) + \ln(1.73) = \ln(0.62 \times 1.73) = \ln(1.0726) = 0.070 )</td>
</tr>
<tr>
<td>( \log(A) + \log(B) = \log(A \times B) )</td>
<td>( \log(5.7) + \log(0.43) = \log(5.7 \times 0.43) = \log(2.451) = 0.389 )</td>
</tr>
<tr>
<td><strong>Subtraction and quotients</strong></td>
<td></td>
</tr>
<tr>
<td>( \ln(A) - \ln(B) = \ln(A/B) )</td>
<td>( \ln(0.5) - \ln(4) = \ln(0.5/4) = \ln(0.125) = -2.079 )</td>
</tr>
<tr>
<td>( \log(A) - \log(B) = \log(A/B) )</td>
<td>( \log(1.57) - \log(2.48) = \log(1.57/2.48) = \log(0.6330645) = -0.199 )</td>
</tr>
<tr>
<td><strong>Simple non-base exponentials</strong></td>
<td></td>
</tr>
<tr>
<td>( \ln(Y) = Z \times \ln(Y) )</td>
<td>( 13.6^z = 1.25 ) ( \ln(1.25) = -Z \times \ln(13.6) )</td>
</tr>
<tr>
<td>( \log(Y) = Z \times \log(Y) )</td>
<td>( Z = -\ln(1.25)/\ln(13.6) = -0.223/2.610 = -0.085 )</td>
</tr>
<tr>
<td><strong>Base exponentials</strong></td>
<td></td>
</tr>
<tr>
<td>( \ln(a \times e^b) = \ln(x) \leftrightarrow \ln(a) \pm b = \ln(x) )</td>
<td>( 67 \times 10^b = 15.1 ) ( \log(67) + b = \log(15.1) )</td>
</tr>
<tr>
<td>( \log(a \times 10^b) = \log(x) \leftrightarrow \log(a) \pm b = \log(x) )</td>
<td>( 1.826 + b = 1.179 ) ( b = 1.179 - 1.826 = -0.647 )</td>
</tr>
</tbody>
</table>