

Solvent Systems and Their Selection in Pharmaceuticals and Biopharmaceuticals

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Principles of Solubility

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Introduction

Solubility is defined as the maximum quantity of a substance that can be completely dissolved in a given amount of solvent, and represents a fundamental concept in fields of research such as chemistry, physics, food science, pharmaceutical, and biological sciences. The solubility of a substance becomes especially important in the pharmaceutical field because it often represents a major factor that controls the bioavailability of a drug substance. Moreover, solubility and solubility-related properties can also provide important information regarding the structure of drug substances, and in their range of possible intermolecular interactions. For these reasons, a comprehensive knowledge of solubility phenomena permits pharmaceutical scientists to develop an optimal understanding of a drug substance, to determine the ultimate form of the drug substance, and to yield information essential to the development and processing of its dosage forms.

In this chapter, the solubility phenomenon will be developed using fundamental theories. The basic thermodynamics of solubility reveals the relation between solubility, and the nature of the solute and the solvent, which facilitates an estimation of solubility using a limited amount of information. Solubility-related issues, such as the solubility of polymorphs, hydrates, solvates, and amorphous materials, are included in this chapter. In addition, dissolution rate phenomena will also be discussed, as these relate to the kinetics of solubility. A discussion of empirical methods for the measurement of solubility is outside the scope of this chapter, but is reviewed elsewhere (Grant and Higuchi, 1990; Grant and Brittain, 1995).

Units for the Expression of Solubility

A discussion of the thermodynamics and kinetics of solubility first requires a discussion of the method by which solubility is reported. The solubility of a substance may be defined in many different types of units, each of which represents an expression of the quantity of solute dissolved in a solution at a given temperature. Solutions are said to be *saturated* if the solvent has dissolved the maximal amount of solute permissible at a particular temperature, and clearly an *unsaturated* solution is one for which the concentration is less than the saturated concentration. Under certain conditions, metastable solutions that are *supersaturated* can be prepared, where the concentration exceeds that of a saturated solution. The most commonly encountered units in pharmaceutical applications are molarity, normality, molality, mole fraction, and weight or volume percentages.

The *molarity* (abbreviated by the symbol M) of a solution is defined as the number of moles of solute dissolved per liter of solution (often written as mol/L or mol/dm³), where the number of moles equals the number of grams divided by its molecular weight. A fixed volume of solutions having the same molarity will contain the same number of moles of solute molecules. The use of molarity bypasses issues associated with the molecular weight and size of the solute, and facilitates the comparison of different solutions. However, one must exercise caution when using molarity to describe the concentrations of ionic substances in solution, because the stoichiometry of the solute may cause the solution to contain more moles of ions relative to the number of moles of dissolved solute. For example, a 1.0 M solution of sodium sulfate (Na₂SO₄) would be 1.0 M in sulfate ions and 2.0 M in sodium ions.

The *normality* (abbreviated by the symbol N) of a solution is defined as the number of equivalents of solute dissolved per liter of solution, and can be written as eq/L or eq/dm³. Normality has the advantage of describing the solubility of the ionic compounds since it takes into account the number of moles of each ion in the solution liberated upon dissolution of a given number of moles of solute. The number of equivalents will equal the number of grams divided by the equivalent weight. For ionic substances, the equivalent weight equals the molecular weight divided by the number of ions in the compound. Equivalent weight of an ion is the ratio of its molecular (atomic) weight and its charge. Therefore, a molar solution of Na₂SO₄ is 2 N with respect to both the sodium and the sulfate ion. Since the volume of solution is temperature dependent, molarity and normality can not be used when the properties of solution, such as solubility, is to be studied over a wide range of temperature.

Molality is expressed as the number of moles of solute dissolved per kilogram of solvent, and is therefore independent of temperature since all of the quantities are expressed on a temperature-independent weight basis. The molality of a solution is useful in describing solubility-related phenomena at various temperatures, and as the concentration unit of colligative property studies. When the density of the solvent equals unity, or in the case of dilute aqueous solutions, the molarity and the molality of the solution would be equivalent.

Expressing solution concentrations in terms of the *mole fraction* provides the ratio of the number of moles of the component of interest to the total number of moles of solute and solvent in the solution. In a solution consisting of a single solute and a single solvent, the mole fraction of solvent, X_A , and solute, X_B , is expressed as:

$$X_A = \frac{n_A}{n_A + n_B} \quad (1)$$

$$X_B = \frac{n_B}{n_A + n_B} \quad (2)$$

where n_A and n_B are the number of moles of solvent and solute, respectively. Obviously the sum of the mole fraction of the two components must equal one:

$$X_A + X_B = 1 \quad (3)$$

Since mole fractions provide quantitative information of a mixture that can be readily translated down to the molecular level, this unit is most commonly used in thermodynamic studies of solubility behavior.

Volume fraction is frequently used to define the composition of mixed solvent systems, or to express the solubility of one solvent in another. However, since the volumes of solutions exhibit a dependence on temperature, the expression of concentrations in terms of volume fraction requires a simultaneous specification of the temperature. In addition, since volume defects may occur during the mixing of the solvents, and since these will alter the final obtained volume, defining the solubility of a solution in terms of volume fraction can lead to inaccuracies that can be avoided through the use of other concentration parameters.

The concept of *percentage* is widely used as a concentration parameter in pharmaceutical applications, and is expressed as the quantity of solute dissolved in 100 equivalent units of solution. The *weight percentage* (typically abbreviated as % w/w) is defined as the number of grams of solute dissolved in 100 grams of solution, while the *volume percentage* (typically abbreviated as % v/v) is defined as the number of milliliters of solute dissolved in 100 mL of solution. A frequently encountered unit, the *weight-volume percentage* (typically abbreviated as % w/v) expresses the number of grams of solute dissolved in 100 mL of solution. The choice of unit to be used depends strongly on the nature of solute and solvent, so the solubility of one liquid in another is most typically expressed in terms of the volume percentage. The use of weight or weight-volume percentages is certainly more appropriate to describe the concentration or solubility of a solid in its solution.

For very dilute solutions, solubility is often expressed in units of parts per million (ppm), which is defined as the quantity of solute dissolved in 1,000,000 equivalent units of solution. As long as the same unit is used for both solute and solvent, the concentration in parts per million is equivalent to the weight, volume, or weight-volume percentages multiplied by 10,000. The descriptive terms of solubility that is expressed in units of parts of solvent required for each part of solute can be found in each edition of the United States Pharmacopeia (Table 1).

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