

INTRODUCTION TO THE SERIES ON SOLUBILITY OF SOLIDS IN LIQUIDS: SUBSERIES ON PHARMACEUTICALS

Nature of the Project

The Solubility Data Project (SDP) has as its aim a comprehensive search of the literature for solubilities of gases, liquids, and solids in liquids or solids. Data of suitable precision are compiled on data sheets in a uniform format. The data for each system are evaluated, and where data from different sources agree sufficiently, recommended values are proposed. The evaluation sheets, recommended values, and compiled data sheets are published on consecutive pages.

For pharmaceuticals, the definitions, thermodynamics and methods of analysis are the same as those for the study of solubility of solids in liquids in general. For this subseries, special sections deal with matters of interest for pharmaceuticals, including discussions of polymorphism, factors influencing the rate of dissolution of drugs, and methods used to inhibit or enhance the rate of dissolution.

Definitions

A mixture (1, 2) describes a gaseous, liquid, or solid phase containing more than one substance, when the substances are all treated in the same way.

A solution (1, 2) describes a liquid or solid phase containing more than one substance, when for convenience one of the substances, which is called the solvent, and may itself be a mixture, is treated differently than the other substances, which are called solutes. If the sum of the mole fractions of the solutes is small compared to unity, the solution is called a dilute solution.

The solubility of a substance *B* is the relative proportion of *B* (or a substance related chemically to *B*) in a mixture which is saturated with respect to solid *B* at a specified temperature and pressure. Saturated implies the existence of equilibrium with respect to the processes of dissolution and precipitation; the equilibrium may be stable or metastable. The solubility of a substance in metastable equilibrium is usually greater than that of the corresponding substance in stable equilibrium. (Strictly speaking, it is the activity of the substance in metastable equilibrium that is greater.) Care must be taken to distinguish true metastability from supersaturation, where equilibrium does not exist.

Either point of view, mixture or solution, may be taken in describing solubility. The two points of view find their expression in the quantities used as measures of solubility and in the reference states used for definition of activities, activity coefficients and osmotic coefficients.

The qualifying phrase "substance related chemically to *B*" requires comment. The composition of the saturated mixture (or solution) can be described in terms of any suitable set of thermodynamic components. Thus, the solubility of a salt hydrate in water is usually given as the relative proportion of anhydrous salt in solution, rather than the relative proportions of hydrated salt and water.

For pharmaceuticals, the solubility of a drug substance in a given medium is of special importance in designing a suitable dosage form for a drug or in determination of a regimen for its administration. The solubility and rate of dissolution will determine the rate of appearance of the drug in various body fluids and at various sites of action. Therefore, the bioavailability of a drug is often determined by its solubility and rate of dissolution.

The solubility is a constant for a given substance in a given medium at constant temperature and pressure. Frequently it is possible to alter the solubility and rate of dissolution dramatically through changes in structure, degree of crystallinity or morphology, or by the addition of a solubilizing agent (cosolvent) to the dissolution medium. The appearance of a drug in adequate concentration at its site of action is a requirement for testing clinical efficiency; thus, enhancement of solubility may be required to render a substance clinically useful.

For reviews of recent literature on solubility and solubilization of

drug substances, see (3, 4).

Quantities Used as Measures of Solubility

1. Mole fraction of substance B, x_B :

$$x_B = n_B / \sum_{s=1}^c n_s \quad [1]$$

where n_s is the amount of substance of s , and c is the number of distinct substances present (often the number of thermodynamic components in the system). Mole per cent of B is $100 x_B$.

2. Mass fraction of substance B, w_B :

$$w_B = m_B' / \sum_{s=1}^c m_s' \quad [2]$$

where m_s' is the mass of substance s . Mass per cent is $100 w_B$. The equivalent terms weight fraction and weight per cent are not used.

3. Solute mole (mass) fraction of solute B (5, 6):

$$x_{s,B} = n_B / \sum_{s=1}^{c'} n_s = x_B / \sum_{s=1}^{c'} x_s \quad [3]$$

$$w_{s,B} = m_B' / \sum_{s=1}^{c'} m_s' = w_B / \sum_{s=1}^{c'} w_s \quad [3a]$$

where the summation is over the solutes only. For the solvent A, $x_{s,A} = x_A / (1 - x_A)$, $w_{s,A} = w_A / (1 - w_A)$. These quantities are called Jänecke mole (mass) fractions in many papers.

4. Molality of solute B (1, 2) in a solvent A:

$$m_B = n_B / n_A M_A \quad \text{SI base units: mol kg}^{-1} \quad [4]$$

where M_A is the molar mass of the solvent.

5. Concentration of solute B (1, 2) in a solution of volume V:

$$c_B = [B] = n_B / V \quad \text{SI base units: mol m}^{-3} \quad [5]$$

The symbol c_B is preferred to $[B]$, but both are used. The terms molarity and molar are not used.

Mole and mass fractions are appropriate to either the mixture or the solution point of view. The other quantities are appropriate to the solution point of view only. Conversions among these quantities can be carried out using the equations given in Table 1-1 following this Introduction. Other useful quantities will be defined in the prefaces to individual volumes or on specific data sheets.

In addition to the quantities defined above, the following are useful in conversions between concentrations and other quantities.

6. Density: $\rho = m/V$ SI base units: kg m^{-3} [6]

7. Relative density: d ; the ratio of the density of a mixture to the density of a reference substance under conditions which must be specified for both (1). The symbol d_t will be used for the density of a mixture at $t^\circ\text{C}$, 1 bar divided by the density of water at $t^\circ\text{C}$, 1 bar. (In some cases, 1 atm = 101.325 kPa is used instead of 1 bar = 100 kPa.)

8. A note on nomenclature. The above definitions use the nomenclature of the IUPAC Green Book (1), in which a solute is called B and a solvent A. In compilations and evaluations, the first-named component (component 1) is the solute, and the second (component 2 for a two-component system) is the solvent. The reader should bear these distinctions in nomenclature in mind when comparing nomenclature and theoretical equations given in this Introduction with equations and nomenclature used on the evaluation and compilation sheets.

Thermodynamics of Solubility

The principal aims of the Solubility Data Project are the tabulation and evaluation of: (a) solubilities as defined above; (b) the nature of the saturating phase. Thermodynamic analysis of solubility phenomena has two aims: (a) to provide a rational basis for the construction of functions to represent solubility data; (b) to enable thermodynamic