

Through selection of a different solubilizing agent or a different chemical salt form of the medicinal agent, alteration of the pH of a solution, or substitution in part or in whole of the solvent, a pharmacist can, in certain instances, dissolve greater quantities of a solute than would otherwise be possible. For example, iodine granules are soluble in water only to the extent of 1 g in about 3,000 mL. Using only these two agents, the maximum concentration possible would be approximately 0.03% of iodine. However, through the use of an aqueous solution of potassium iodide or sodium iodide as the solvent, much larger amounts of iodine may be dissolved as the result of the formation of a water-soluble complex with the iodide salt. This reaction is taken advantage of, for example, in Iodine Topical Solution, USP, prepared to contain about 2% iodine and 2.4% sodium iodide.

Temperature is an important factor in determining the solubility of a drug and in preparing its solution. Most chemicals absorb heat when they are dissolved and are said to have a positive heat of solution, resulting in increased solubility with an increase in temperature. A few chemicals have a negative heat of solution and exhibit a decrease in solubility with a rise in temperature. Other factors in addition to temperature affect solubility. These include the various chemical and other physical properties of the solute and the solvent, pressure, the pH of the solution, the state of subdivision of the solute, and the physical agitation applied to the solution as it dissolves. The solubility of a pure chemical substance at a given temperature and pressure is constant; however, its rate of solution, that is, the speed at which it dissolves, depends on the particle size of the substance and the extent of agitation. The finer the powder, the greater the surface area, which comes in contact with the solvent, and the more rapid the dissolving process. Also, the greater the agitation, the more unsaturated solvent passes over the drug and the faster the formation of the solution.

The solubility of a substance in a given solvent may be determined by preparing a saturated solution of it at a specific temperature and by determining by chemical analysis the amount of chemical dissolved in a given weight of solution. The amount of solvent required to dissolve the amount of solute can be determined by a

simple calculation. The solubility may then be expressed as grams of solute dissolving in milliliters of solvent; for example, "1 g of sodium chloride dissolves in 2.8 mL of water." When the exact solubility has not been determined, general expressions of relative solubility may be used. These terms are defined in the USP and presented in Table 13.1 (1).

Many of the important organic medicinal agents are either weak acids or weak bases, and their solubility depends on a large measure on the pH of the solvent. These drugs react either with strong acids or strong bases to form water-soluble salts. For instance, the weak bases, including many of the alkaloids (atropine, codeine, and morphine), antihistamines (diphenhydramine and promethazine), local anesthetics (cocaine, procaine, and tetracaine), and other important drugs, are not very water soluble, but they are soluble in dilute solutions of acids. Pharmaceutical manufacturers have prepared many acid salts of these organic bases to enable the preparation of aqueous solutions. However, if the pH of the aqueous solution of these salts is changed by the addition of alkali, the free base may separate from solution unless it has adequate solubility in water. Organic medicinals that are weak acids include the barbiturate drugs (e.g., phenobarbital) and the sulfonamides (e.g., sulfadiazine and sulfacetamide). These and other weak acids form water-soluble salts in basic solution and may separate from solution by a lowering of the pH. Table 13.2 presents the comparative solubilities of some typical examples of weak acids and weak bases and their salts.

**Table 13.1** RELATIVE TERMS OF SOLUBILITY (2)

DESCRIPTIVE TERM	PARTS OF SOLVENT REQUIRED FOR 1 PART OF SOLUTE
Very soluble	<1
Freely soluble	1–10
Soluble	10–30
Sparingly soluble	30–100
Slightly soluble	100–1,000
Very slightly soluble	1,000–10,000
Practically insoluble or insoluble	>10,000