

# PHYSICAL PHARMACY

Lec 1

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## Solubility and Distribution Phenomena

Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature, and in a qualitative way, it can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.

Solubility is an intrinsic material property that can be altered only by chemical modification of the molecule, in contrast to this, dissolution is an extrinsic material property that can be influenced by various chemical, physical, or crystallographic means such as complexation, particle size, surface properties, solid-state modification, or solubilization enhancing formulation strategies.

The solubility of a compound depends on the physical and chemical properties of the solute and the solvent as well as on such factors as temperature, pressure, the pH of the solution

The thermodynamic solubility of a drug in a solvent is the maximum amount of the most stable crystalline form that remains in solution in a given volume of the solvent at a given temperature and pressure under equilibrium conditions. Thermodynamic equilibrium is achieved when the overall lowest energy state of the system is achieved. This means that only the equilibrium solubility reflects the

balance of forces between the solution and the most stable, lowest energy crystalline form of the solid.

### **Solubility Expressions**

The solubility of a drug may be expressed in a number of ways. The United States Pharmacopeia (USP) describes the solubility of drugs as parts of solvent required for one part solute. Solubility is also quantitatively expressed in terms of molality, molarity, and percentage. The USP describes solubility using the seven groups listed in Table 1. The European Pharmacopoeia lists six categories (it does not use the practically insoluble grouping).

**Table 1 Solubility Definition in the United States Pharmacopeia**

<b>Description Forms (Solubility Definition)</b>	<b>Parts of Solvent Required for One Part of Solute</b>	<b>Solubility Range (mg/mL)</b>
Very soluble (VS)	<1	>1000
Freely soluble (FS)	From 1 to 10	100–1000
Soluble	From 10 to 30	33–100
Sparingly soluble (SPS)	From 30 to 100	10–33
Slightly soluble (SS)	From 100 to 1000	1–10
Very slightly soluble (VSS)	From 1000 to 10,000	0.1–1
Practically insoluble (PI)	>10,000	<0.1

### **Solvent-Solute Interactions**

The pharmacist knows that water is a good solvent for salts, sugars, and similar compounds, whereas mineral oil is often a solvent for substances that are normally only slightly soluble in water. These empirical findings are summarized in the statement, “like dissolves like.”

## **Polar Solvents**

The solubility of a drug is due in large measure to the polarity of the solvent, that is, to its dipole moment. Polar solvents dissolve ionic solutes and other polar substances. Accordingly, water mixes in all proportions with alcohol and dissolves sugars and other poly hydroxy compounds, however, that a consideration of dipole moments alone is not adequate to explain the solubility of polar substances in water.

A difference in acidic and basic character of the constituents in the Lewis electron donor–acceptor sense also contributes to specific interactions in solutions. The ability of the solute to form hydrogen bonds is a far more significant factor than is the polarity as reflected in a high dipole moment. Water dissolves alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds that can form hydrogen bonds with water

In addition to the factors already enumerated, the solubility of a substance also depends on structural features such as the ratio of the polar to the nonpolar groups of the molecule. As the length of a nonpolar chain of an aliphatic alcohol increases, the solubility of the compound in water decreases. Straight-chain monohydroxy alcohols, aldehydes, ketones, and acids with more than four or five carbons cannot enter into the hydrogen-bonded structure of water and hence are only slightly soluble. When additional polar groups are present in the molecule, as found in propylene glycol, glycerin, and tartaric acid, water solubility increases greatly. Branching of the carbon chain reduces the nonpolar effect and leads to increased water solubility. Tertiary butyl alcohol is miscible in all proportions with water, whereas n-butyl alcohol dissolves to the extent of about 8 g/100 mL of water at 20°C.

## Nonpolar Solvents

The solvent action of nonpolar liquids, such as the hydrocarbons, differs from that of polar substances. Nonpolar solvents are unable to reduce the attraction between the ions of strong and weak electrolytes because of the solvents' **low dielectric constants**. Nor can the solvents break covalent bonds and ionize weak electrolytes, because they belong to the group known as **aprotic solvents**, and they cannot form hydrogen bridges with non electrolytes. Hence, ionic and polar solutes are not soluble or are only slightly soluble in nonpolar solvents.

Nonpolar compounds, however, can dissolve nonpolar solutes with similar internal pressures through induced dipole interactions. The solute molecules are kept in solution by the weak van der Waals–London type of forces. Thus, oils and fats dissolve in carbon tetrachloride, benzene, and mineral oil. Alkaloidal bases and fatty acids also dissolve in nonpolar solvents.

## Semipolar Solvents

Semipolar solvents, such as **ketones** and **alcohols**, can induce a certain degree of polarity in nonpolar solvent molecules, so that, for example, benzene, which is readily polarizable, becomes soluble in alcohol. In fact, semipolar compounds can act as intermediate solvents to bring about miscibility of polar and nonpolar liquids. Accordingly, acetone increases the solubility of ether in water. Loran and Guth studied the intermediate solvent action of alcohol on water–castor oil mixtures. Propylene glycol has been shown to increase the mutual solubility of water and peppermint oil and of water and benzyl benzoate.

## **Solubility of Liquids in Liquids**

Frequently two or more liquids are mixed together in the preparation of pharmaceutical solutions. For example, alcohol is added to water to form hydroalcoholic solutions of various concentrations; volatile oils are mixed with water to form dilute solutions known as aromatic waters; volatile oils are added to alcohol to yield spirits and elixirs; ether and alcohol are combined in collodions; and various fixed oils are blended into lotions, sprays, and medicated oils. Liquid–liquid systems can be divided into two categories according to the solubility of the substances in one another: **(a)** complete miscibility and **(b)** partial miscibility. The term miscibility refers to the mutual solubilities of the components in liquid–liquid systems.

### **Complete Miscibility**

Polar and semipolar solvents, such as water and alcohol, glycerin and alcohol, and alcohol and acetone, are said to be completely miscible because they mix in all proportions. Nonpolar solvents such as benzene and carbon tetrachloride are also completely miscible.

### **Partial Miscibility**

When certain amounts of water and ether or water and phenol are mixed, two liquid layers are formed, each containing some of the other liquid in the dissolved state. It is sufficient here to reiterate that the mutual solubilities of partially miscible liquids are influenced by temperature.

In a system such as phenol and water, the mutual solubilities of the two conjugate phases increase with temperature until, at the critical solution temperature (or upper consolute temperature), the compositions become identical. At this temperature, a homogeneous or single-phase system is formed.

In the case of some liquid pairs, the solubility can increase as the temperature is lowered, and the system will exhibit a lower consolute temperature, below which the two members are soluble in all proportions and above which two separate layers form.

Another type, involving a few mixtures such as nicotine and water, shows both an upper and a lower consolute temperature with an intermediate temperature region in which the two liquids are only partially miscible.

A final type exhibits no critical solution temperature; the pair ethyl ether and water, for example, has neither an upper nor a lower consolute temperature and shows partial miscibility over the entire temperature range at which the mixture exists.