

**AL-Mustaqbal university college**  
**Pharmacy department**



# **Physical pharmacy II**

**lec1**

**Ghada Ali PhD candidate**  
**[ghada.ali@mustaqbal-college.edu.iq](mailto:ghada.ali@mustaqbal-college.edu.iq)**

# **Solubility and distribution Phenomena**

# Objective

- ❖ Define saturated solution, solubility, and unsaturated solution.
- ❖ Describe and give examples of polar, nonpolar, and semipolar solvents.
- ❖ Define complete and partial miscibility.
- ❖ Understand the factors controlling the solubility of weak electrolytes.
- ❖ Describe the influence of solvents and surfactants on solubility.
- ❖ Define thermodynamic, kinetic, and intrinsic solubility.
- ❖ Measure thermodynamic solubility.
- ❖ Describe what a distribution coefficient and partition coefficient are and their importance in pharmaceutical systems

***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 *thermodynamic solubility of drugs*** .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. The equilibrium involves a balance of the energy of three interactions against each other:

(1) solvent with solvent,

(2) solute with solute, and

(3) Solvent and solute. 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

## summary

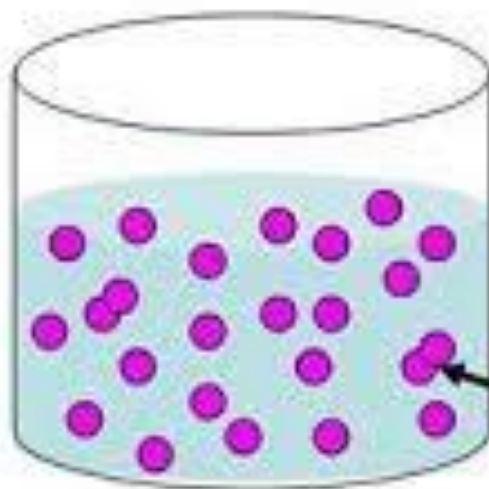
***A saturated solution*** is one in which the solute in solution is in equilibrium with the solid phase. Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature, and in a qualitative way, it can be defined as the spontaneous interaction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

***An unsaturated*** or *subsaturated* solution is one containing the dissolved solute in a concentration below that necessary for complete saturation at a definite temperature.

***A supersaturated solution*** is one that contains more of the dissolved solute than it would normally contain at a definite temperature, were the undissolved solute present.

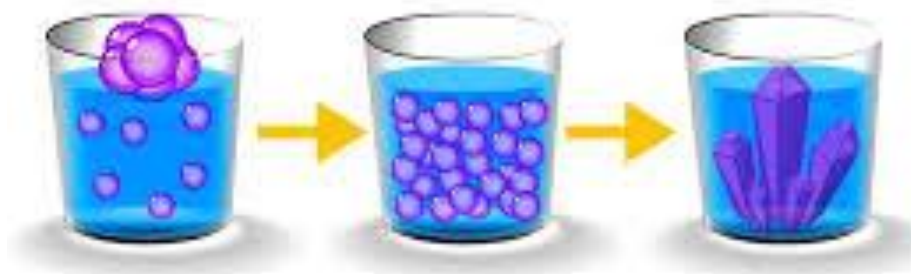


Unsaturated solution



Saturated solution

a solution with more dissolved solute at a given temperature, than a saturated solution



supersaturated solution

# 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(9-1)**.

The European Pharmacopoeia lists six categories (it does not use the practically insoluble grouping



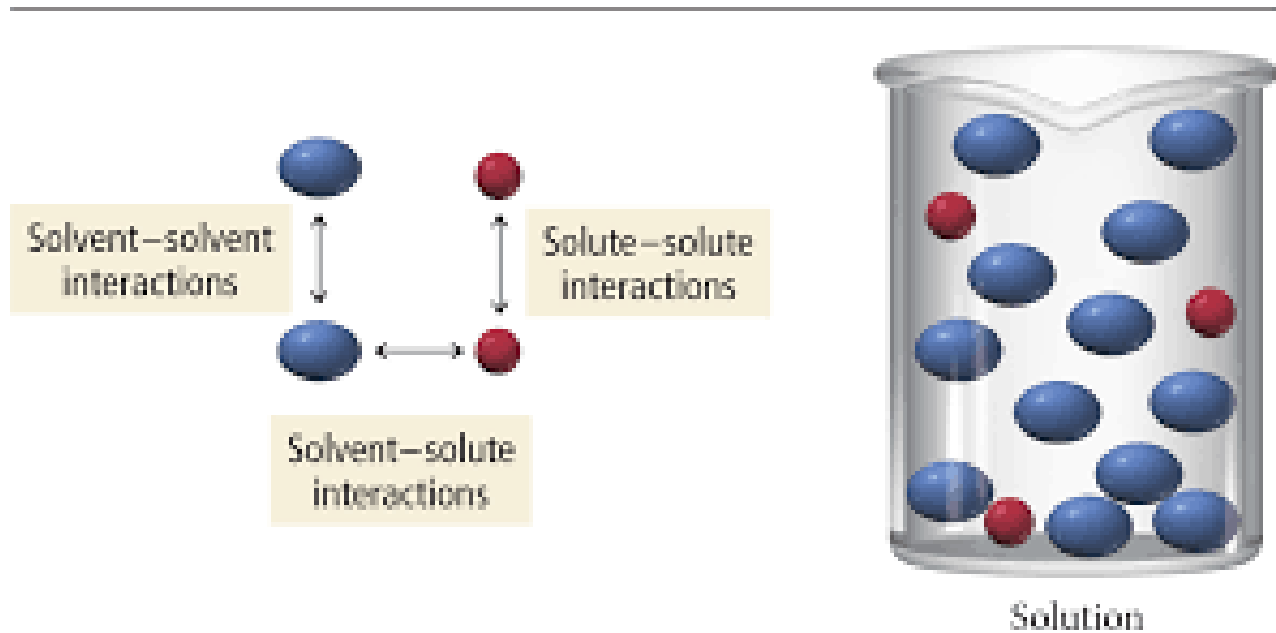
**TABLE 9-1****SOLUBILITY DEFINITION IN THE UNITED STATES PHARMACOPEIA**

Description Forms (Solubility Definition)	Parts of Solvent Required for One Part of Solute	Solubility Range (mg/mL)	Solubility Assigned (mg/mL)
Very soluble (VS)	<1	>1000	1000
Freely soluble (FS)	From 1 to 10	100–1000	100
Soluble	From 10 to 30	33–100	33
Sparingly soluble (SPS)	From 30 to 100	10–33	10
Slightly soluble (SS)	From 100 to 1000	1–10	1
Very slightly soluble (VSS)	From 1000 to 10,000	0.1–1	0.1
Practically insoluble (PI)	>10,000	<0.1	0.01

# 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 observed findings are summarized in the statement, “**like dissolves like.**”

## Solution Interactions



## 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 polyhydroxy compounds. 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 phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen containing compounds that can form hydrogen bonds with water

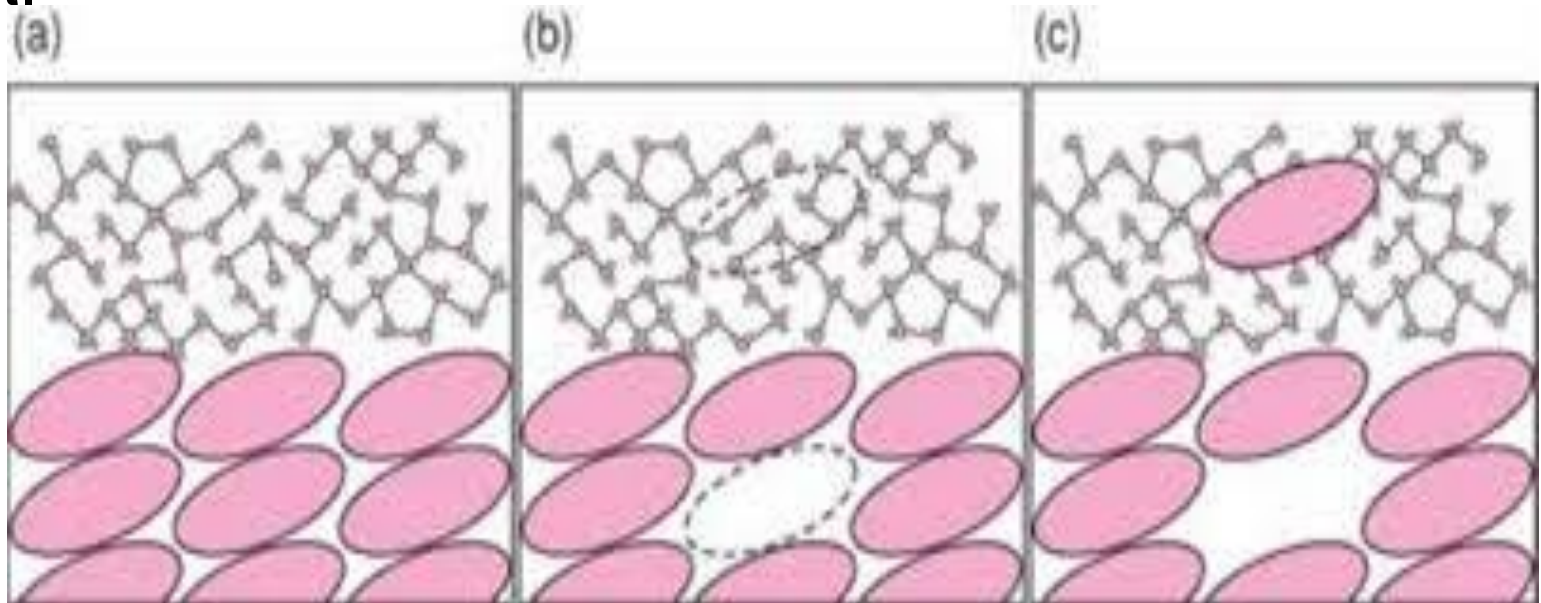
A difference in acidic and basic character of the constituents in the Lewis electron donor–acceptor sense also contributes to specific interactions in solutions. In addition the solubility of a substance also depends on structural features such as the ratio of the polar to the nonpolar groups of the 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 oil . Alkaloidal bases and fatty acids also dissolve in nonpolar solvents.

## 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 nonelectrolytes. 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

# Solubility

The simple maxim that *like dissolves like* can be rephrased by stating that the solubility of a substance can be predicted only in a qualitative way in most cases and only after considerations of polarity, dielectric constant, association, solvation, internal pressures, acid–base reactions, and other factors. In short, solubility depends on chemical, electrical, and structural effects that lead to shared interactions between the solute and the solvent.



## 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<sup>5</sup> 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. A number of common solvent types are listed in the order of decreasing “polarity” in **Table 9–2**, together with corresponding solute classes. The term *polarity* is loosely used here to represent not only the dielectric constants of the solvents and solutes but also the other factors enumerated previously

**TABLE 9-2****POLARITY OF SOME SOLVENTS AND THE SOLUTES THAT READILY DISSOLVE IN EACH CLASS OF SOLVENT**

	Dielectric Constant of Solvent, $\epsilon$ (Approximately)	Solvent	Solute	
Decreasing Polarity	80	Water	Inorganic salts, organic salts	Decreasing Water Solubility
↓	50	Glycols	Sugars, tannins	↓
	30	Methyl and ethyl alcohols	Caster oil, waxes	
	20	Aldehydes, ketones, and higher alcohols, ethers, esters, and oxides	Resins, volatile oils, weak electrolytes including barbiturates, alkaloids, and phenols	
	5	Hexane, benzene, carbon tetrachloride, ethyl ether, petroleum ether	Fixed oils, fats, petrolatum, paraffin, other hydrocarbons	
	0	Mineral oil and fixed vegetable oils		



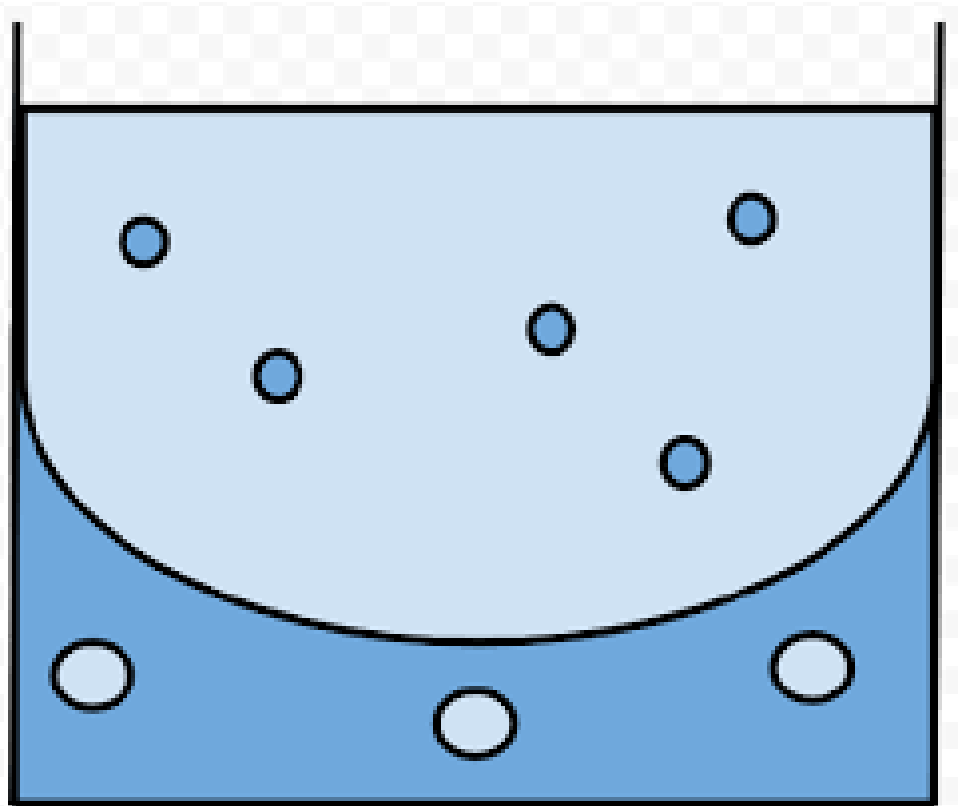
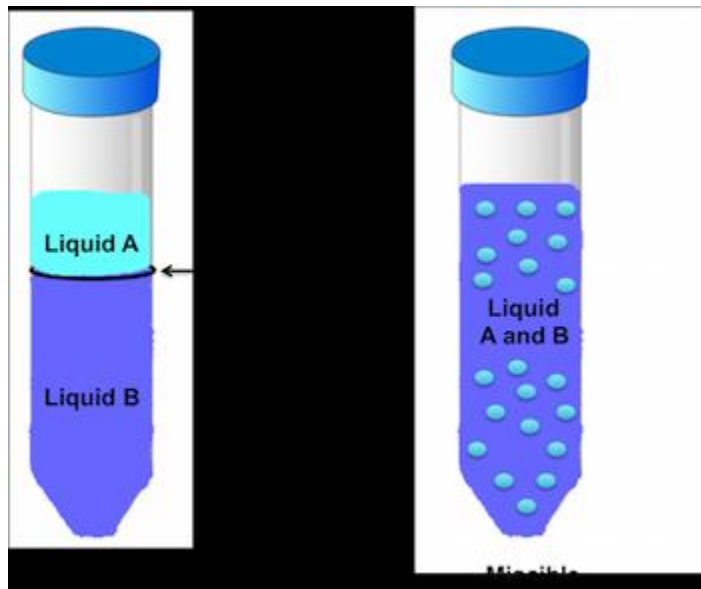
## Solubility of liquids in liquids

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 mixed 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 ( $\text{CCl}_4$ ) are also completely miscible.

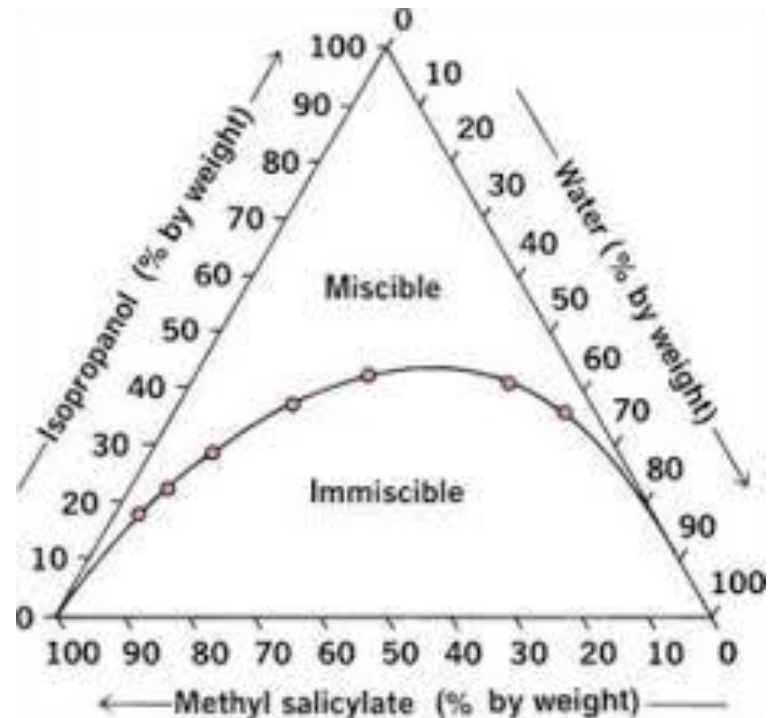


## Partial Miscibility

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 repeat the following points.

(a) 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. amount of one phase relative to the other.

(b) From a knowledge of the phase diagram, more especially the tie lines that cut the binodal curve, it is possible to calculate both the composition of each component in the two conjugate phases and the the amount of one phase relative to the other.



## Example

### Component Weights

A mixture of phenol and water at 20°C has a total composition of 50% phenol. The tie line at this temperature cuts the binodal at points equivalent to 8.4% and 72.2% w/w phenol. What is the weight of the aqueous layer and of the phenol layer in 500 g of the mixture and how many grams of phenol are present in each of the two layers?

Let  $Z$  be the weight in grams of the aqueous layer. Therefore,

$500 - Z$  is the weight

the percentages of phenol in the two layers must equal the overall composition of 50%, or  $500 \times 0.50 = 250$  g. Thus,

$$Z(8.4/100) + (500 - Z)(72.2/100) = 250$$

Weight of aqueous layer,  $Z = 174$  g

Weight of phenol layer,  $500 - Z = 326$  g

Weight of phenol in the aqueous layer,  $174 \times 0.084 = 15$  g

Weight of phenol in the phenolic layer,  $326 \times 0.722 = 235$  g

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## Phenol and water system phase diagram.

Temperature fixed at 50 °C

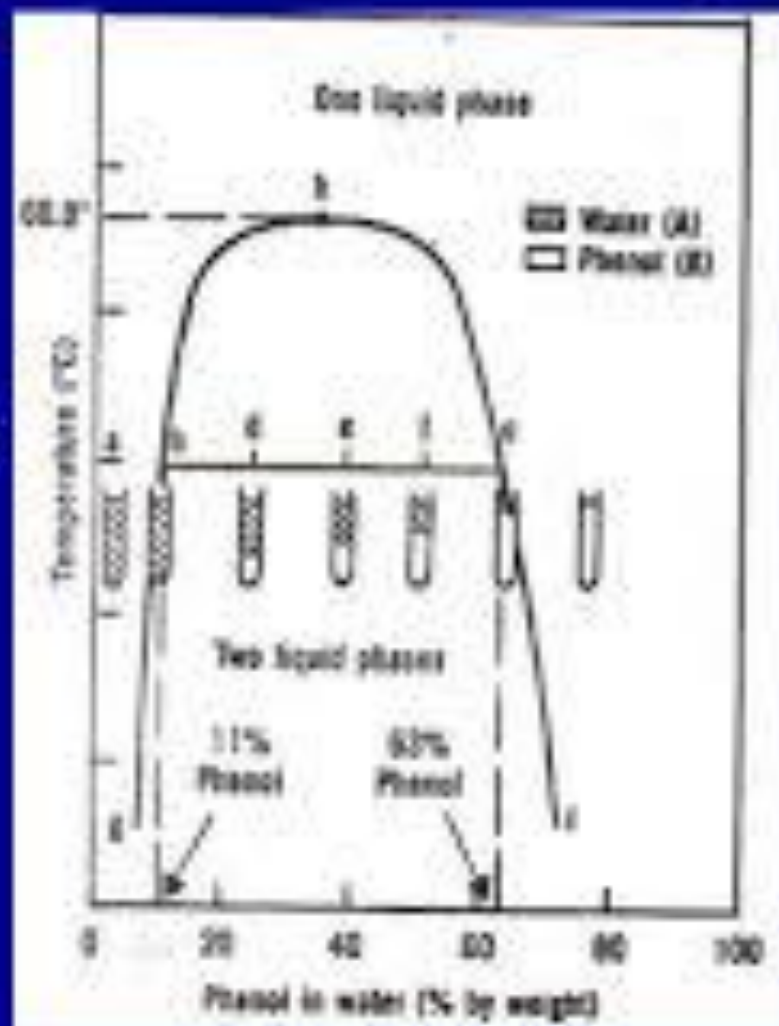
- ★ Point **a**, system containing 100% pure water.

Addition of phenol to water will result in the formation of a single liquid phase until the point **b** is reached.

- ★ At point **b**, appears a second phase.

**Phase A:** water rich phase containing 11% phenol

**Phase B:** phenol rich phase containing 63% phenol



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.

### Note

**consolute temperature** is the critical **temperature** above which the components of a mixture are miscible in all proportions





Thank  
you