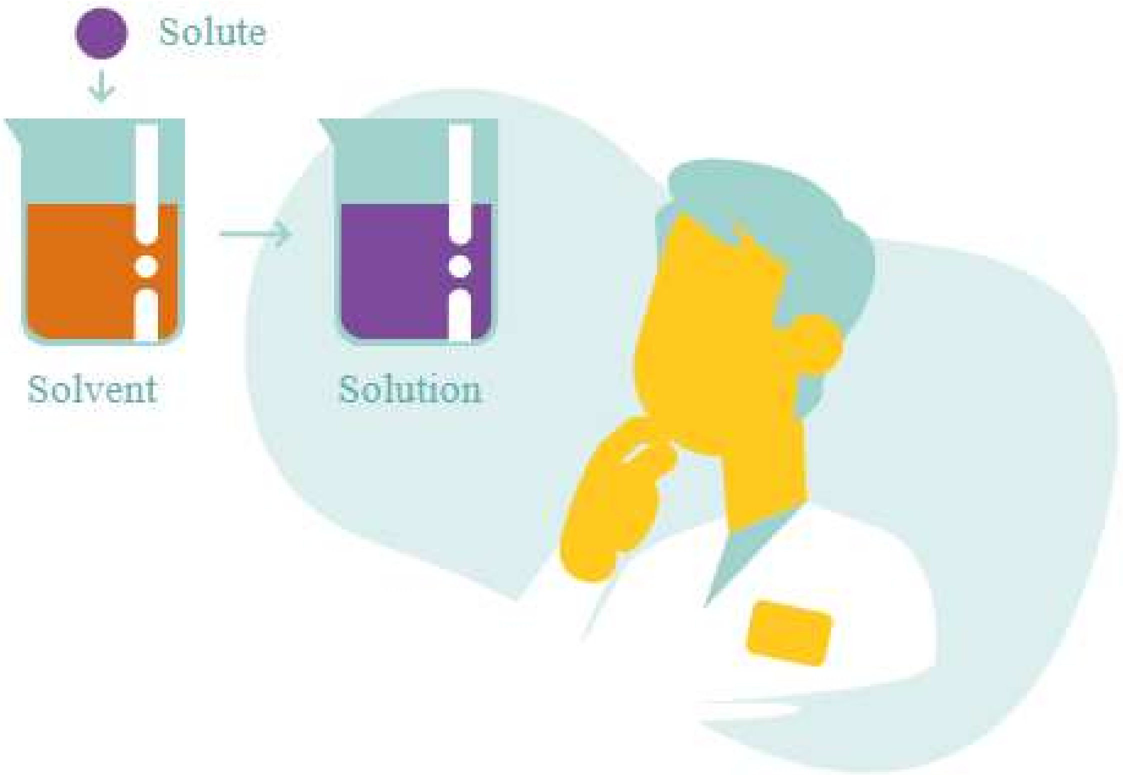
SOLUBILITY AND DISTRIBUTION PHENOMENA



GENERAL PRINCIPLES

- **Importance:**
  - Best solvent
  - Preparation
  - Purity
  - Structure and intermolecular forces

- **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.

- Solubility expressions:

SOLUBILITY DEFINITION IN THE UNITED STATES PHARMACOPEIA	
Description Forms (Solubility Definition)	**Parts of Solvent Required for One Part of Solute**
Very soluble (VS)	<1
Freely soluble (FS)	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble (SPS)	From 30 to 100
Slightly soluble (SS)	From 100 to 1000
Very slightly soluble (VSS)	From 1000 to 10,000
Practically insoluble (PI)	$>10,000$

SOLVENT-SOLUTE INTERACTIONS

- 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

A) 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.

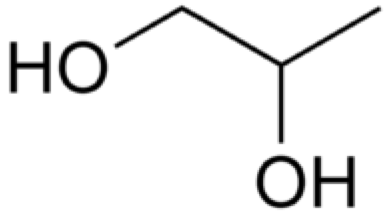
B) The ability of the solute to form hydrogen bonds is a far more significant factor than is the polarity as reflected in a high dipole moment.

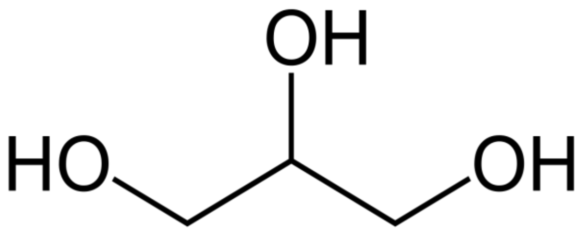
- ✓Water dissolves phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen containing compounds that can form hydrogen bonds with water

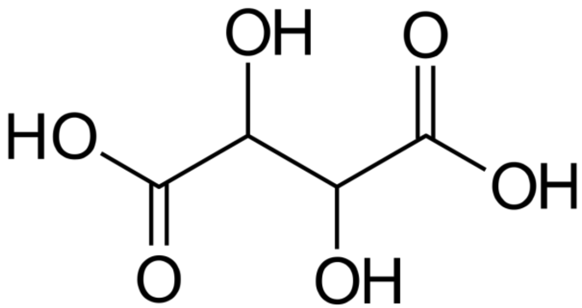
C) A difference in acidic and basic character of the constituents also contributes to specific interactions in solutions.

D) 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

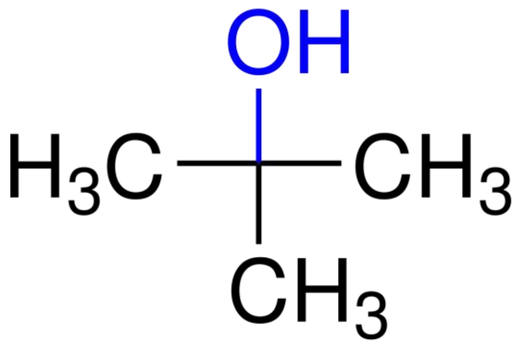


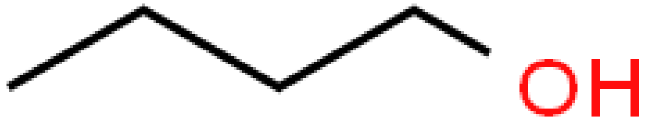




E) Branching of the carbon chain reduces the nonpolar effect and leads to increased water solubility.

- ✓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.

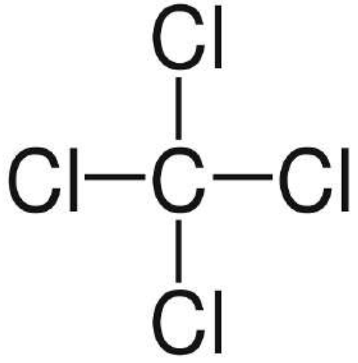


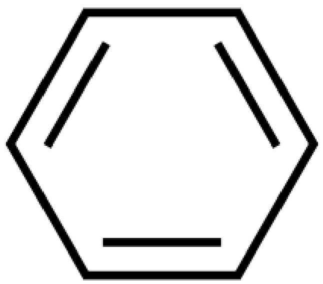


Nonpolar Solvents

- 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 type of forces.
- Thus, oils and fats dissolve in carbon tetrachloride, benzene, and mineral oil.





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.

- Propylene glycol has been shown to increase the mutual solubility of water and peppermint oil and of water and benzyl benzoate mixtures.

POLARITY OF SOME SOLVENTS AND THE SOLUTES THAT READILY DISSOLVE IN EACH CLASS OF SOLVENT

	Dielectric Constant of Solvent, ε (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
  - ✓ 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

(b) partial miscibility.

- The term miscibility refers to the mutual solubilities of the components in liquid– liquid systems.

A) Complete Miscibility

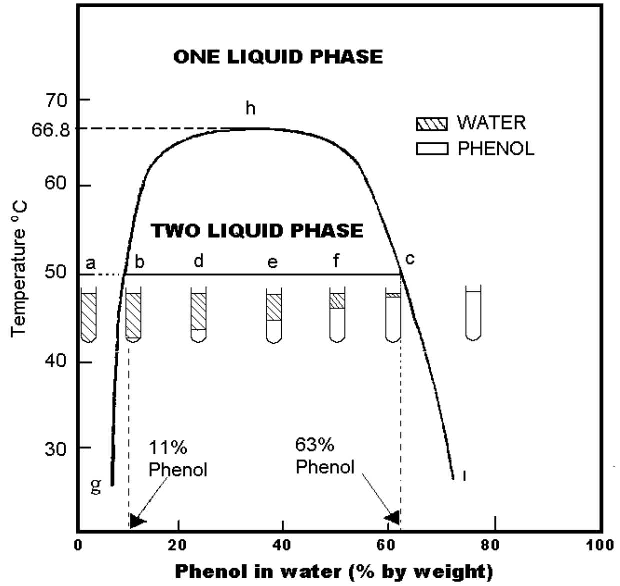
- Polar and semipolar solvents, such as water and alcohol, glycerin and alcohol, and alcohol and acetone, are said to be completely miscible because they **mix in all proportions.**
- Nonpolar solvents such as benzene and carbon tetrachloride are also completely miscible. Completely miscible liquid mixtures in general create **no solubility problems** for the pharmacist

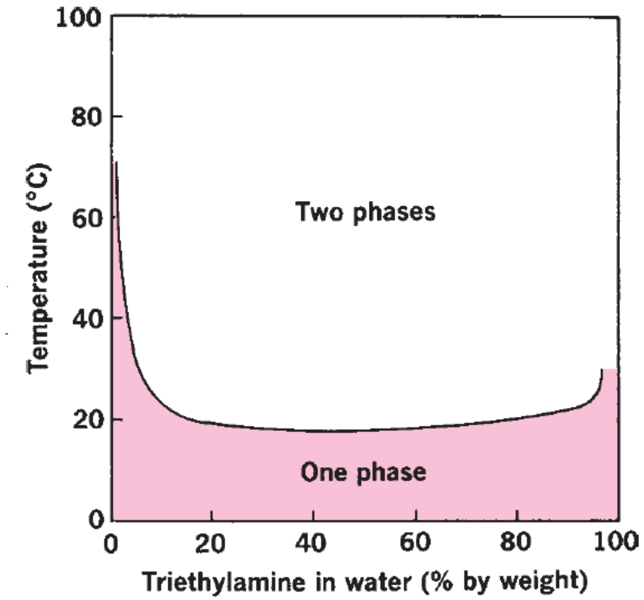
B) Partial Miscibility

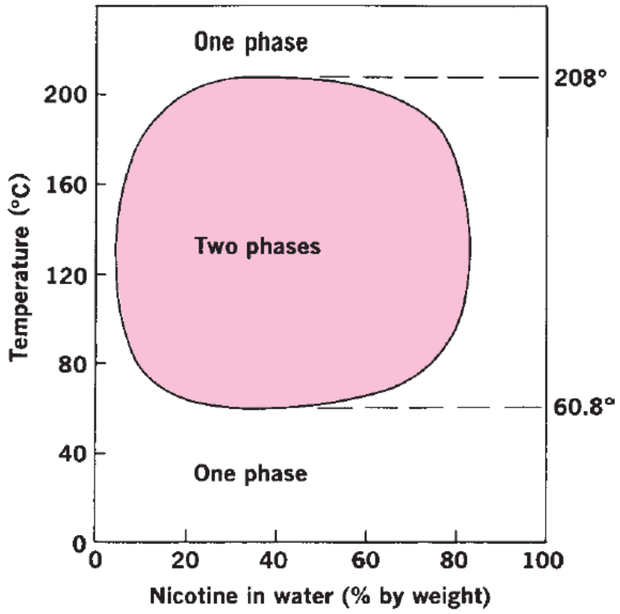
- When certain amounts of water and ether or water and phenol are mixed, two liquid layers are formed, each containing some of the other liquid in the dissolved state.

- 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.

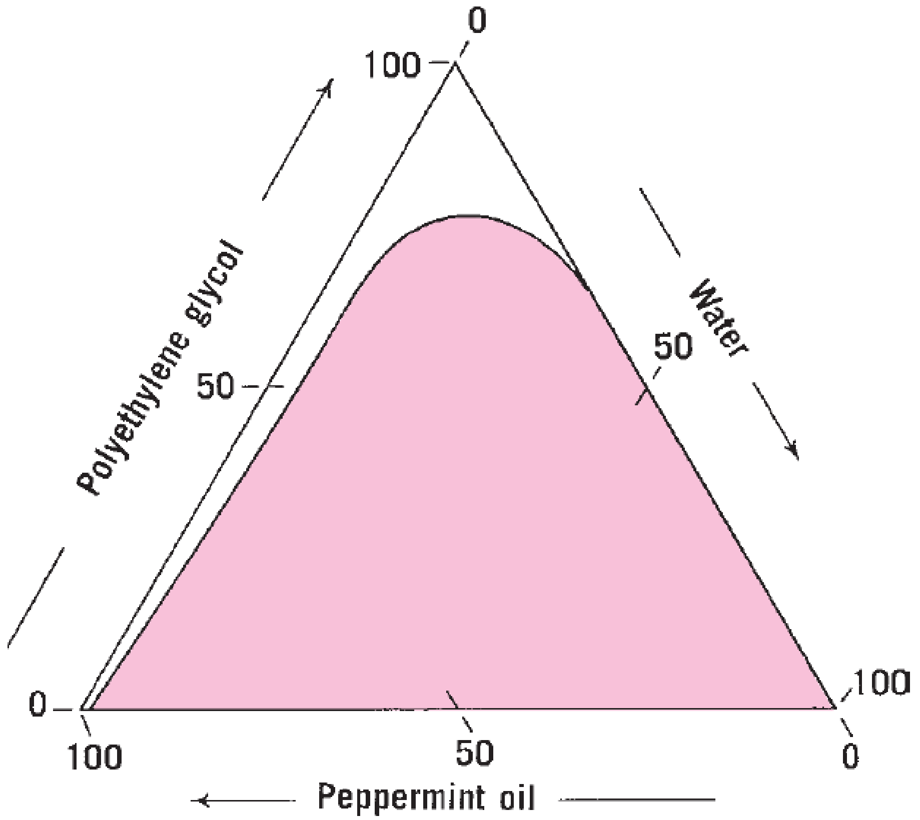
- Another type, involving a few mixtures such as nicotine and water, shows both an **upper and a lower consolute temperature** with an intermediate temperature region in which the two liquids are only partially miscible.
- A final type exhibits no critical solution temperature; the pair ethyl ether and 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.



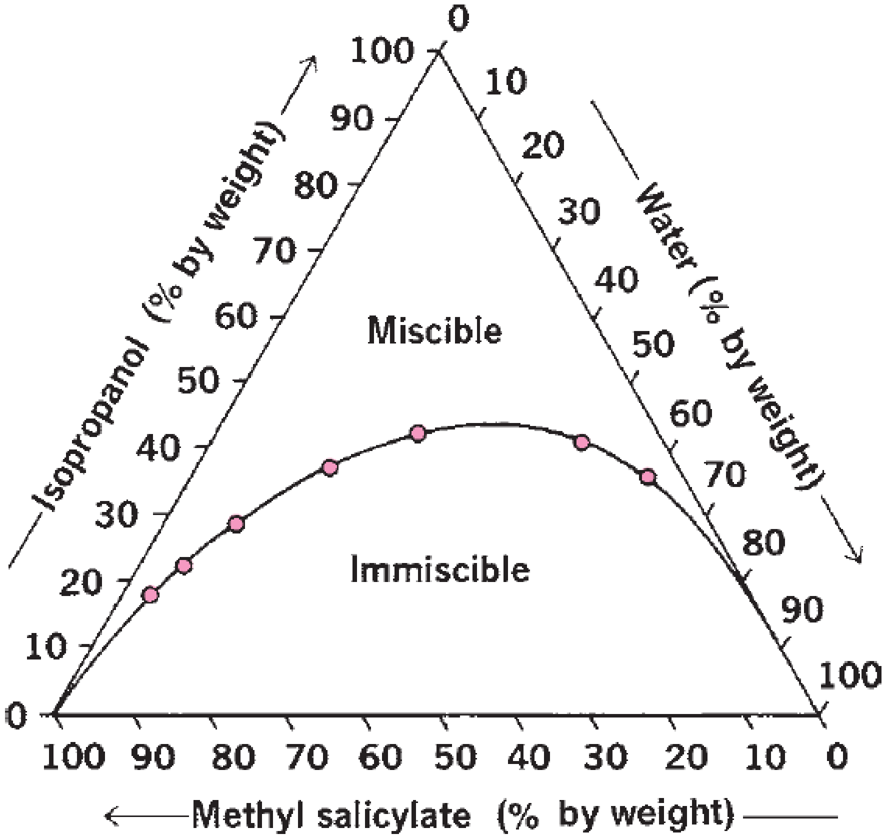




• ***Three-Component Systems***



A triangular diagram showing the solubility of peppermint oil in various proportions of water and polyethylene glycol.



Triangular phase diagram for the three-component system methyl salicylate–isopropanol–water.

SOLUBILITY OF SOLIDS IN LIQUIDS

- Systems of solids in liquids include the most frequently encountered and probably the most important type of pharmaceutical solutions.
- Factors affecting solubility of solids in liquids:

  1- Solvent

  2- pH

  3- Surfactant

  4- Complexation

  5- Size and shape of small particles: the solubility increases with decreasing particle size

  6- the configuration of a molecule and the kind of arrangement in the crystal: symmetric particle may be less soluble than an unsymmetrical one.

DISTRIBUTION OF SOLUTES BETWEEN IMMISCIBLE SOLVENTS

- If an excess of liquid or solid is added to a mixture of two immiscible liquids, it will distribute itself between the two phases so that each becomes saturated.
- If the substance is added to the immiscible solvents in an amount insufficient to saturate the solutions, it will still become distributed between the two layers in a definite concentration ratio.
- If C_1 and C_2 are the equilibrium concentrations of the substance in Solvent 1 and Solvent 2, respectively, the equilibrium expression becomes

$$\frac{C_1}{C_2} = K$$

- The equilibrium constant, K, is known as the distribution ratio, distribution coefficient, or partition coefficient.

- the distribution law: $\frac{C_1}{C_2} = K$ is strictly applicable only in dilute

solutions where activity coefficients can be neglected.

Example

When boric acid is distributed between water and amyl alcohol at 25°C, the concentration in water is found to be 0.0510 mole/liter and in amyl alcohol it is found to be 0.0155 mole/liter. What is the distribution coefficient?

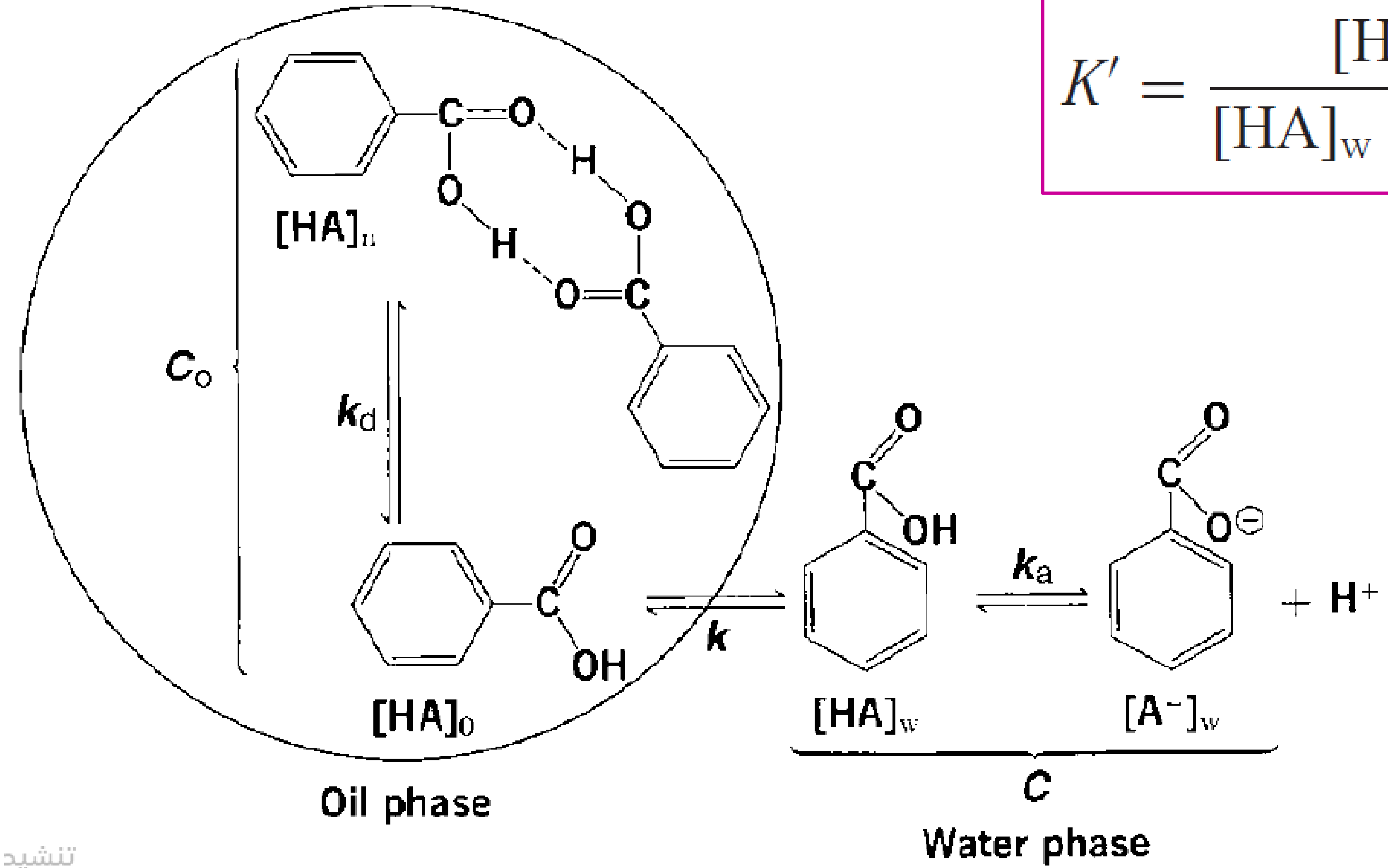
$$K = \frac{C_{H_2O}}{C_{alc}} = \frac{0.0510}{0.0155} = 3.29$$

$$K = \frac{C_{alc}}{C_{H_2O}} = \frac{0.0155}{0.0510} = 0.304$$

- Knowledge of partition is important to the pharmacist because the principle is involved in several areas of current pharmaceutical interest.

- These include preservation of oil–water systems, drug action at nonspecific sites, and the absorption and distribution of drugs throughout the body.

- Schematic representation of the distribution of benzoic acid between water and an oil phase.



$$K' = \frac{[HA]_o}{[HA]_w + [A^-]_w} = \frac{C_o}{C_w}$$

Extraction

- To determine the efficiency with which one solvent can extract a compound from a second solvent—an operation commonly employed in analytic chemistry and in organic chemistry

$$K = \frac{\text{Concentration of solute in original solvent}}{\text{Concentration of solute in extracting solvent}}$$