Pharmaceutical Technology I

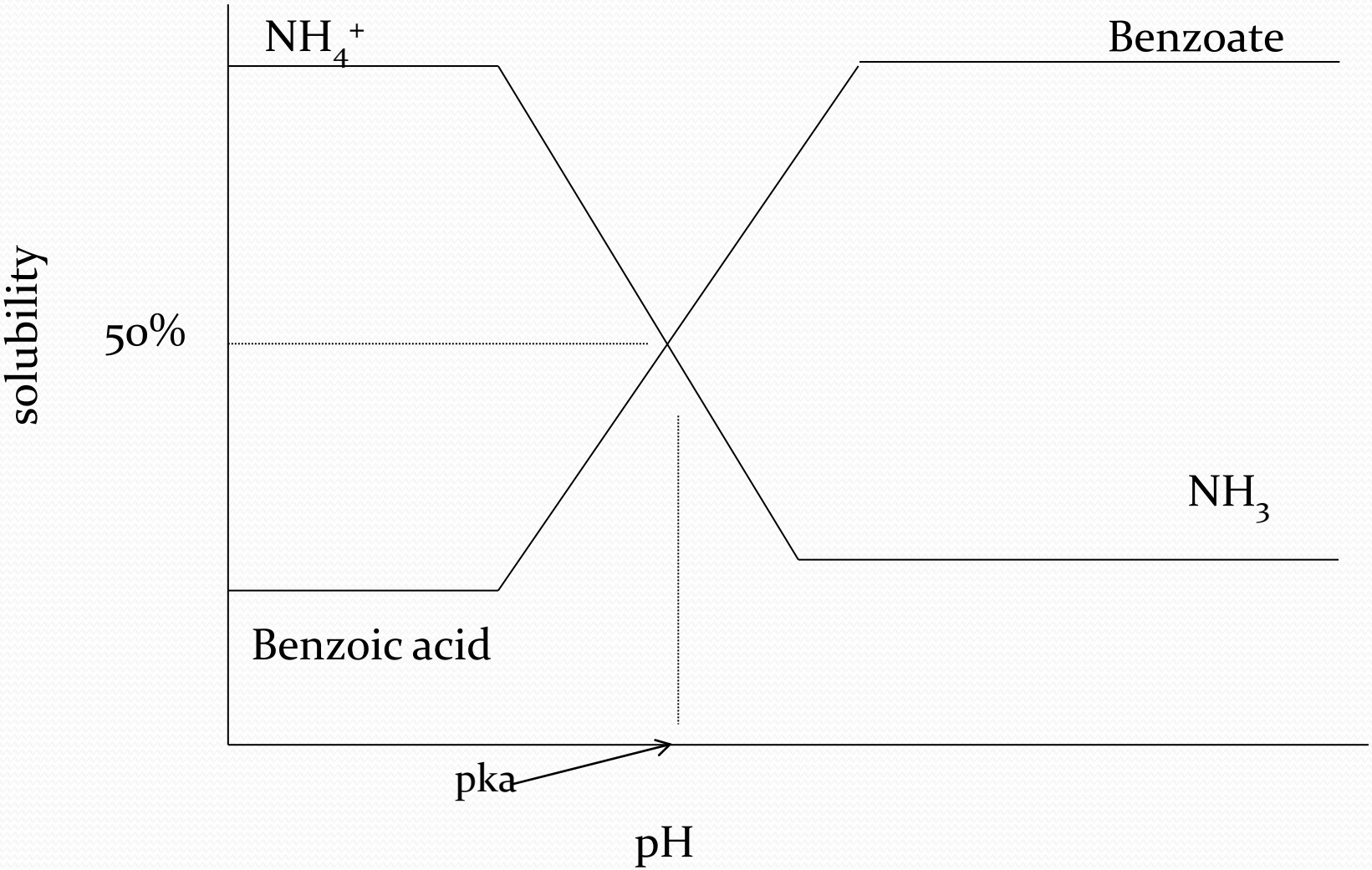
Lecture- 2

Factors affecting solubility

Part-II

4. Effect of pH on solubility:

- The pH of medium is important for certain compounds such as weak acid and weak base; it affects the degree of dissociation and the ratio of ionized to unionized form of the compound.
- The ionized form of drug is more soluble than unionized form in water, this affect on absorption and excretion rate.
- There is a curve called pH-solubility profile for weak acid and weak base.
- At pH = pka the ratio of ionized to unionized = 1, that 50% ionized or soluble in water (Figure 1).


NH_4^+
Benzoate
solubility
50%
NH_3
Benzoic acid
pka
pH

- The solubility in water of weak organic acids such as barbiturates & sulfonamides is increased as the pH increased by addition of base.
- This increase in solubility is due to the formation of water soluble salts. For example solubility of Phenobarbital (free acid) in water at pH 5.5, 25°C is 1.25 g /1000 mL. While, the solubility is increased to 1000 g/1000 mL due to soluble salt formation at pH 9.3, 25°C.
- If the pH of this solution is decreased by addition of strong acid, Phenobarbital (free acid) will precipitate.

- The solubility in water of weak organic base (e.g., alkaloids and local anesthetic) increases as the pH is decreased by addition of acid due to the formation of water soluble salts.
- Solubility of atropine in different pH media is shown in Table 1.

Table 1 solubility of atropine and atropine sulfate

Drug	Temperature	Solubility	pH
Atropine (Free base)	25°C	2.2g/ 1000mL	>10
Atropine Sulfate (Salt)	25°C	2500g/ 1000mL	5.4

5. Effect of other substances on solubility:

- The solubility of substance depends on the type and concentration of other substance in the solution.
- In general the solubility of slightly soluble electrolytes is reduced by addition of second salt which contains a common ion for example, when NaCl is added to a saturated solution of silver chloride AgCl, some of AgCl precipitate from the solution due to the presence of common ion (Cl^-).

$$AgCl \rightleftharpoons Ag^+ + Cl^-$$

$$NaCl \longrightarrow Na^+ + Cl^-$$

- The common ion may form complex with slightly soluble electrolyte may lead to increase the solubility of salts. e.g. Mercuric iodide is insoluble in water yet it dissolved by solution of soluble iodide.
- Another example is increase the solubility of iodine I_2 in an aqueous solution of KI due to the formation of soluble complex KI_3

Solubility expression

- The solubility of solute can 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 2.

Table 2. Relative terms of solubility

Descriptive term	Part of solvent required for 1 part of solute
Very soluble	< 1
Freely soluble	1-10
soluble	10-30
Sparingly soluble	100-1000
Slightly soluble	1000-10000
Practically insoluble or insoluble	> 10000

- **Solution of liquid in liquid**

1. Two liquids such as water/ alcohol, water/glycerin and water/ acetone. When are mixed, homogenous system is formed irrespective of the proportions in which the two are taken. Such pairs of liquids are said to be miscible.
2. Liquefied phenol/ water or ether /water are formed homogenous system only when mixed in a certain proportion. Such liquids are said to be miscible in certain proportion.
3. Water/mineral oil is insoluble in each other in any proportion so they are immiscible.

- **Solution of gas in liquid**

1. According to Henry's law the solubility of gas by weight in liquid is proportional to the pressure at constant temperature.
2. If there is a chemical interaction between the solute (gas) and the solvent (liquid), this will lead to high solubility as in case of gases NH_3 and HCl, their solubility will not be affected if the pressure is changed (increased or decreased).
3. Temperature: solubility of gas in liquid decreases as temperature increases, so the gas in solution should be cool down before opening and should be stored in cool places.

- Increase the temperature leads to decrease the solubility, e.g., CO_2 is twice soluble at 0^oC as it at 20^oC. So, the gaseous solutions should be stored at cool place (refrigerator).
- Containers holding strong ammonia solution should be cooled before they are opening in order to reduce liberation and expansion of gas since on cooling the solubility of gas increases.

- **Note:** When a salt is added to a liquid containing dissolved gas, liberation of gas occurs due to decrease solubility.
- This effect is referred to salting out of the gas.

Rate of dissolution

- Rate of dissolution: it is the speed at which the solute goes into solution.
- The unit of dissolution is equal to unit of concentration/ unit of time = $\Delta C/\Delta t$ = mg/ml/min.
- If the solubility increased, the rate of the dissolution will also be increased, but if the rate of dissolution increased, the solubility will not always increase.

Factors affecting rate of dissolution

1. Particle size of the substance: decreasing the particle size by comminution, the surface area will increase, and the rate of dissolution will increase also.

- The finer the powder, the greater the surface area, which comes in contact with the solvent, and the more rapid the dissolution process.

2. Temperature: the rate of dissolution increases when the temperature increased, because increasing the collisions between the solvent and the solute.

3. Agitation: the greater the agitation, the more unsaturated solvent pass over the drug and faster the formation of the solution. In other word, increases the interaction between the solute and the solvent.

- For many medicinal agents, the solubilities in the usual solvents are stated in the *United States Pharmacopeia-National Formulary* (USP-NF) as well as in the other reference books.

Solvents for pharmaceutical uses

- All pharmaceutical solvents should have the following properties:

1. Not toxic.
2. Not volatile.
3. Stable.

- Not toxic mean there is no harmful effect on body.
- In case of volatility, so it is volatile, so it evaporates and so lead to precipitate the active ingredient and it may become toxic or harmful. Therefore, it should store in cool place and in a well closed container.
- In case of stability, it should not interact with active ingredient or the added substances and should be stable on storage condition and protect the active ingredient stable.

Solvent used in pharmaceutical preparation

1. Water: it is a good solvent for most inorganic salts and for many organic compounds, its miscibility with other solvents such as alcohol and glycerin makes it a useful vehicle for many pharmaceutical preparations.
2. Alcohol USP: ethyl alcohol, ethanol, (94.9-96 % by volume C_2H_5OH): it is used as a solvent for certain drugs that are insoluble in water like organic substances (both natural and synthetic). It dissolves important plant constituents such as resins, volatile oils, alkaloids, glycosides and it is also used in liquid product as antimicrobial preservatives alone or as a co-preservative with other preservatives like parabens.

- Alcohol is frequently used with other solvents, as glycols and glycerin to reduce the amount of alcohol required. Since it has undesired pharmacologic and potential toxic effects when ingested in pharmaceutical products particularly by children, so the recommended alcohol content limit is as follows:
- For OTC oral products intended for children under 6 years of age, the recommended alcohol limit is 0.5%
- For product intended for children 6 to 12 years of age the recommended limit is 5%
- For products recommended for children over 12 year and for adults, the recommended limit is 10%.

3. Diluted Alcohol, NF 49-50%: is prepared by mixing equal volume of alcohol, USP, and Purified Water, USP and used in manufacture of certain preparation. Such hydroalcoholic liquid or solvent is useful in various pharmaceutical processes and preparations since it dissolves both alcohol-soluble and water-soluble substances.
4. Dehydrated Alcohol, USP: 99.5% by volume C_2H_5OH (absolute alcohol): it is practically free from water and its chief use in pharmacy is in research and analytic work and in the preparation of synthetic organic medicinal.
5. Isopropyl alcohol: Used in cosmetic and dermatologic formulation.

6. Glycerin, USP (Glycerol): it is a clear syrupy liquid with a sweet taste. It is miscible with both water and alcohol but not with chloroform, ether or fixed oil, it is an excellent solvent for tannins, phenol and boric acid. Because of its preservative qualities, sometimes it is used as a stabilizer for solutions prepared with other solvents. When it is used as a solvent, glycerin must be heated in order to reduce its viscosity. If this is not done it is difficult to dissolve substance in it. It is used as a stabilizer and as an auxiliary solvent in conjunction with water or alcohol. It is used in many internal preparations.

9. Propylene glycol: it is miscible with water, acetone, alcohol and chloroform, it will dissolve many essential oils, but it is immiscible with fixed oils. It has a wide range of usefulness as a solvent and is used as a replacement for glycerin in modern pharmaceutical and cosmetic formulations.
10. Polyethylene glycol 400: it is miscible with water, acetone, alcohol and other glycols. It dissolves many water soluble organic compounds as well as certain water insoluble substances such as acetyl salicylic acid.
11. Chloroform: it is miscible with alcohol, ether, benzene, solvent hexane and both fixed and volatile oils. It dissolves in 210 volumes of water. It is not flammable, but its vapor decomposes by naked flames producing harmful gases, it is a solvent for many alkaloids.

Question

- Which one of the following liquids must be heated when used as solvent?

1. Chloroform
2. Glycerin
3. Polyethylene glycol 400
4. Ethanol