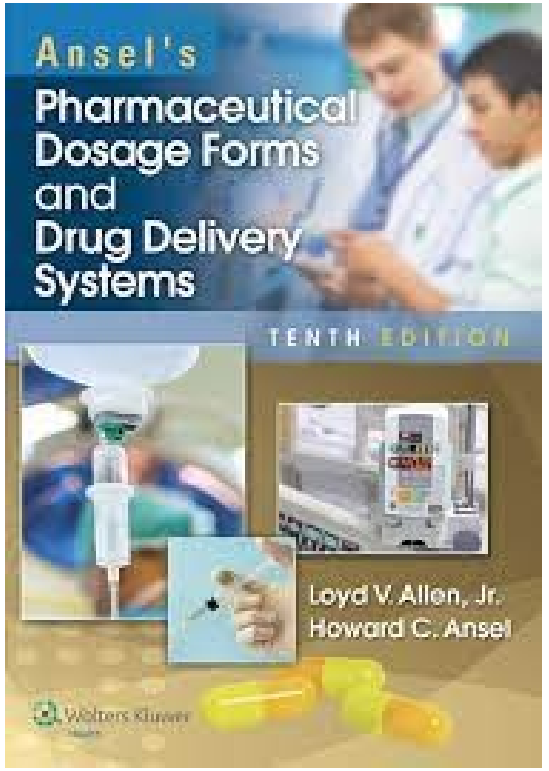
LEC 1
PHARMACEUTICAL TECHNOLOGY
SOLUTIONS

Stage: 3 / 1st course

Dr. Ameer S. Sahib

Solutions
Chapter 13



Reference:

Ansel’s pharmaceutical dosage forms and drug delivery systems

Solutions

- In pharmaceutical terms, solutions are “liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents ” (aqueous or non –aqueous).
- Prepared from any combination of solid, liquid, and gas.
- It may be classified by use to oral, otic, ophthalmic, or topical .
- Certain solutions prepared to be sterile and pyrogen free and intended for parenteral administration are classified as injections .

- Most common pharmaceutical solutions are aqueous solutions (why?) (also the biological systems are mostly aqueous).

- Medicated solutions contain drugs that are usually soluble in water and their absorption is higher than from suspension or solid dosage forms because any drug must be molecular dispersed (in-solution), before they can be absorbed across the biological membrane and be effective .

Solutions can be formulated for different routes of administration

- Orally: Syrups, elixirs, drops
- In mouth and throat: Mouth washes, gargles, throat sprays.
- In body cavities: Douches, enemas, ear drops, nasal sprays.
- On body surfaces: Collodions, topical solutions.
- Parenteral: Injectable dosage forms.

Pharmaceutical solutions classified according to their composition

Syrups

- Sweet thick oral solution
- Contains sucrose

Elixirs

- Hydro-alcoholic oral solutions
- Sweetened

Spirits, aromatic water

- Spirits are alcoholic or hydro-alcoholic solution of aromatic material
- Aromatic water the solvent is water

Fluidextracts Tinctures

- Aqueous or hydroalcoholic or alcoholic extract
- Plant or chemical origin
- Differ in concentration of the extract

Injections

Must be sterile, isotonic and buffered

Aqueous or non aqueous

Classification of solutions according to method of preparation

1-Solutions prepared by simple solution

- Gention violet solution1% in (10%alcohol) solution topical anti-infective

2-Solution prepared by chemical reaction

- Hydrogen peroxide solution 3% hydrolysis of persulfuric acid used as topical anti infective

3-Solutions prepared by simple solution with sterilization

- Atropine sulphate ophthalmic solution, also 0.9% w/v NaCl I.V. fluid

4- Solutions prepared by extraction

Ipecac, tolu

Advantages of solution

1. Easier to swallow
2. More quickly effective than solid dosage forms
3. Homogenous
4. Dilute irritant action of some drugs

Disadvantages of Solutions

1. Bulky
2. Unpleasant taste or odours are difficult to mask.
3. Needs an accurate spoon to measure the dose (drug activity?).
4. Less stable than solid dosage forms (why?).

Oral solutions

- Their absorption from the gastrointestinal tract into the systemic circulation may be expected to occur more rapidly than from suspension or solid dosage forms of the same medicinal agent.

(you have to differentiate between the rate and the extent of absorption)

- Solutes other than the medicinal agent are usually present in orally administered solutions.
- These additional agents are frequently included to provide color, flavor, sweetness, or stability.
- In formulating pharmaceutical solution, information on the solubility and stability of each solute with regard to the solvent or solvent system must be considered.
- Combinations of medicinal or pharmaceutical agents that will result in chemical and/or physical interactions affecting the therapeutic quality or pharmaceutical stability of the product must avoided .

Drug solubility

- The solubility of an agent in a particular solvent indicates the maximum concentration to which a solution may be prepared with that agent and that solvent at a given temperature, pH and pressure.

Very important scale

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

Expression of solubility

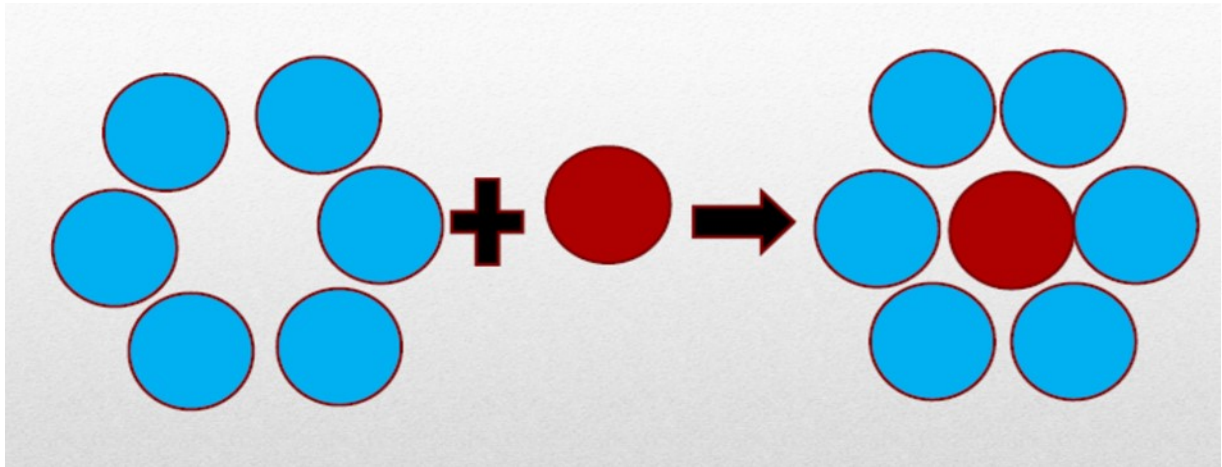
- Calcium Hydroxide Topical solution USP 140mg per 100ml of solution at 25°C
- Potassium iodide solution 100g per 100ml of solution

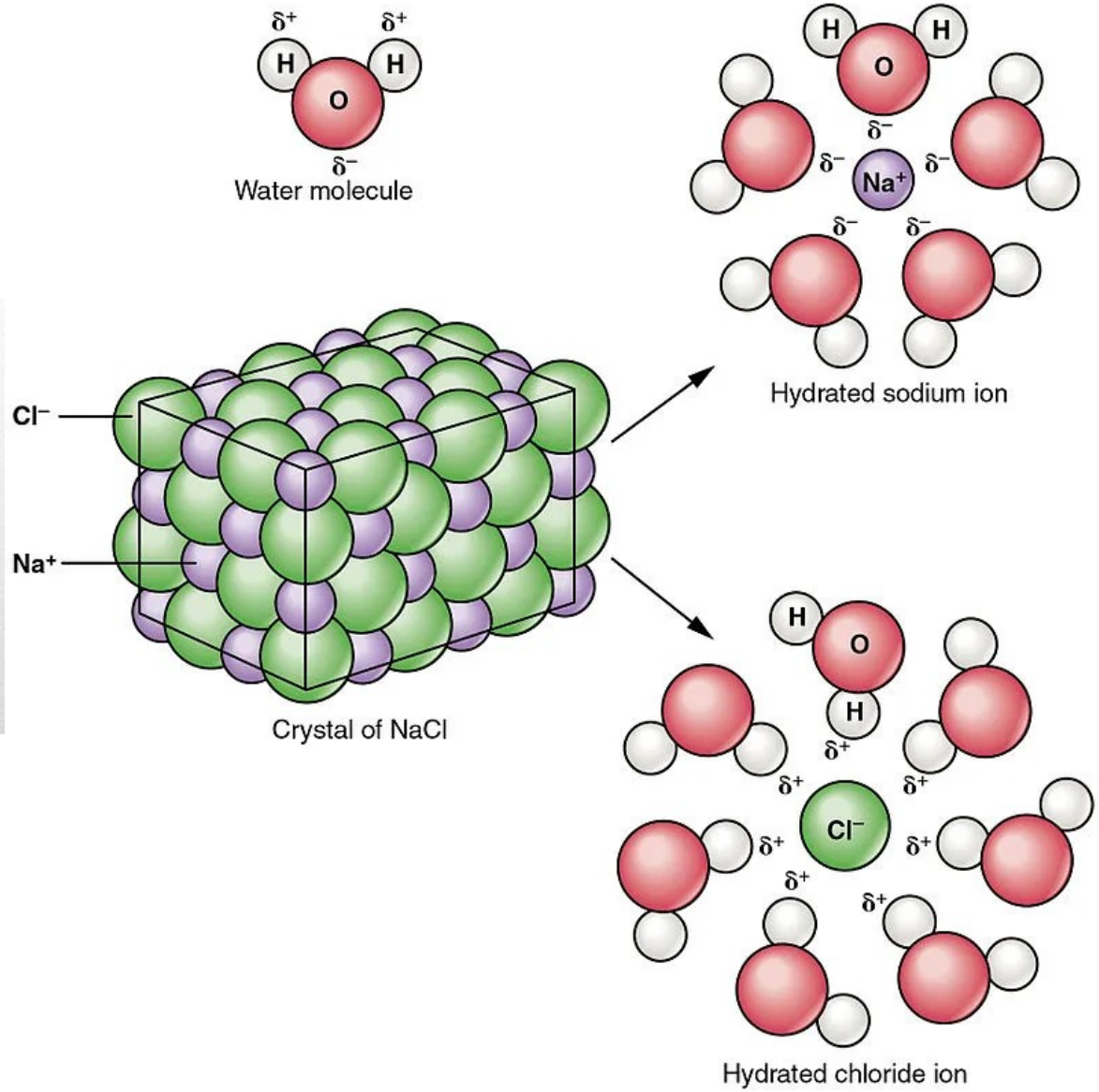
- The no. of ml. of a solvent required to dissolve 1 g of the solute (or 1 ml. of liquid)
- 1g of KI dissolves in 0.7 ml of water
- 0.5 ml boiling water
- Expressed using **physical units** w/w w/v, v/v
- Or **chemical units** milliequivalent mEq
- Used to express concentration of electrolytes depending on their ionic charge and valence activity

Theory of solubility

- When molecules interact, attractive and repulsive forces are in effect. The attractive forces cause the molecules to cohere, whereas the repulsive forces prevent molecular interpenetration and destruction. When the attractive and repulsive forces are equal, the potential energy between two molecules is minimal and the system is most stable.

- When a solute dissolve, the substance's intermolecular forces of attraction must be overcome by forces of attraction between the solute and the solvent molecules (solute-solvent intermolecular forces). This entails breaking the solute–solute forces and the solvent–solvent forces to achieve the solute–solvent attraction.




δ+
δ+
H
H
O
δ−
Water molecule
H
H
O
δ−
δ−
Na+
δ−
δ−
δ−
Hydrated sodium ion
Cl−
Na+
Crystal of NaCl
H
O
H
δ+
δ+
δ+
Cl−
δ+
δ+
δ+
δ+
Hydrated chloride ion

Excipients used in pharmaceutical solutions for oral administration

- 1. The vehicle
- Water types

Table 24.1 Different types of water, as defined by the *European Pharmacopoeia*

Type of water	Use
Purified Water	Used for the preparation of medicines that do not have to be sterile and apyrogenic.
Highly Purified Water	Used for the preparation of medicines where water of high biological quality is needed, except where Water for Injections is required.
Water for Injections	Used for medicines for parenteral administration. Must be pyrogen-free.
Sterilized Water for Injections	Used for medicines for parenteral administration. Water has been sterilized by heat and is suitably packaged.

Drinking water (potable)

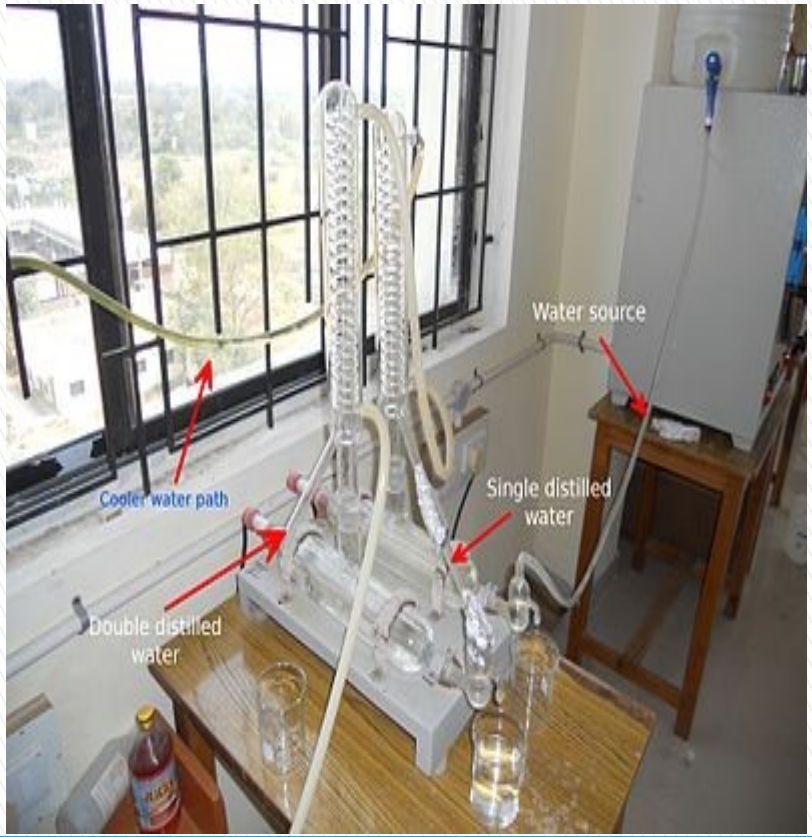
- Drinking water must be clear, colorless, odorless, and neutral or only slightly acid or alkaline
- Not accepted for manufacture of aqueous pharmaceutical preparations because of chemical compatibility of the dissolved solids with the medicinal agents (may lead to ppt., discoloration, effervescence)
- Used *for washing, in extraction of the crude vegetable drugs*

Purified Water USP

- Prepared from tap water complying with the Environmental Protection Agency for drinking water.
- Purified Water has fewer solids impurities than ordinary drinking water, when evaporated to dryness it must not yield more than 1mg solids per 100ml water
- Intended for *use in preparation of aqueous dosage forms* except those intended for parenteral administration.

Distilled water

- **Distilled Water DW**
- is water that has many of its impurities removed through distillation.
  Distillation
  involves boiling the water and then condensing the steam into a clean container



Definition

Typical laboratory distillation unit

Water for injection

- Pyrogen free water (polysaccharide byproduct of bacterial origin)
- Purified by distillation and used within 24 hr. after collection.
- Intended to be used as a solvent for parental products preparation to be sterilized after preparation
- Sterilization is achieved by autoclave (steam under pressure)

Sterile water for injection USP

- Water for injection sterilized and packed in suitable single dose container preferably Type I glass and not larger than 1000ml size.
- This water is intended to be used as a solvent, vehicle, or diluent for already sterilized and packaged injectable medications.
- They are used to reconstitute of antibiotics

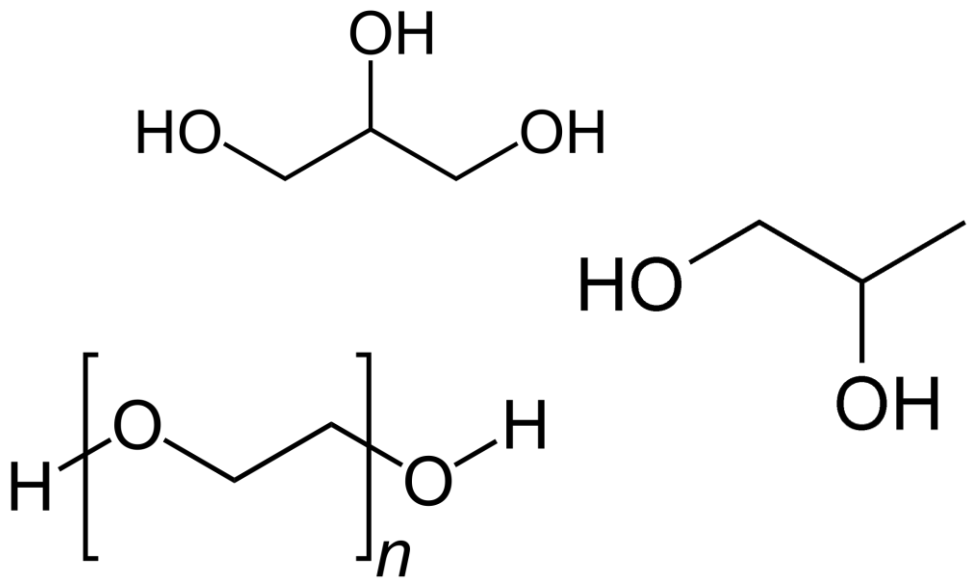
Bacteriostatic water for injection USP

- Sterile water for injection that contains bacteriostatic agent (benzyl alcohol)
- May be packed in single dose container (not larger than 5ml) or multiple dose containers (not larger than 30ml)
- Not used for neonates.

Other sterile liquids (as fluid supplement or for irrigation)

- Sodium chloride injection USP
- Bacteriostatic sodium chloride injection USP
- Ringer injection USP
- Lactated Ringer injection USP
- Dextrose 5% solution

2. Co -solvents
    - Glycerol
    - Alcohol (CH 3CH 2OH)
    - Propylene Glycol
    - Poly (ethylene glycol)(PEG)
3. Surface active agent
4. Complexing agent
5. Buffering agents
6. Sweetening agents
7. Viscosity enhancing agents
8. Antioxidants
9. Preservatives
10. Flavours and colorants



Taste masking

Taste of product	Suitable masking flavor
Salty	Apricot, butterscotch, liquorice, peach vanilla
Bitter	Anise, chocolate, mint, passion fruit, wild cherry
Sweet	Vanilla, fruits, berries
Sour	Citrus fruits, liquorice, raspberry

Additives: Flavors and perfumes

Product use	Flavor preferred
Relief of indigestion	Mint
Antiseptic activity	Terpineol
Oral mucosa anesthetic	Clove oil (eugenol)
Children	Fruity taste and smell
Adult	Flowery odours, acid taste

Additives: Colors

- The colour of the product is associated with the flavor

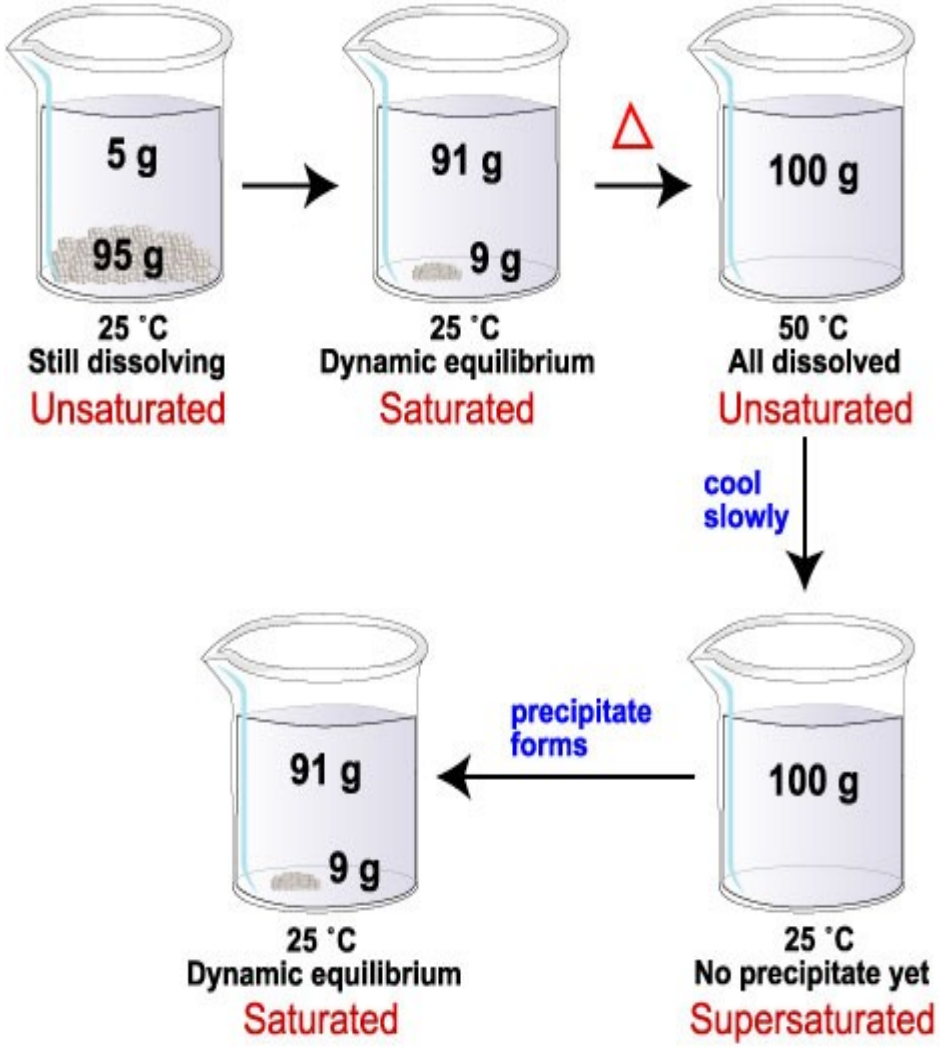
Flavor	Colour
Mint	Green
Chocolate	Brown
Cherry , strawberry	Pink – red

- Colouring agents used for:

1. Product identification
2. Safety and acceptability

Solubility

- The solubility of an agent in a particular solvent indicates the concentration to which a solution may be prepared with that agent and that solvent (solubility)
- When excess of solid (solute) is shaken with liquid (solvent) for a period of time, a maximum amount of it will be dissolved (saturated solubility).
- When excess amount of solute is added to saturated solution and the temperature is elevated more of solute will be dissolved (super saturated solution).



Rate of solubility enhanced by :

- Reducing the particle size of the solute (the finer the powder the greater the surface area, which comes in contact with the solvent, and the more rapid the dissolving process).
- Subjecting the ingredients to vigorous agitation (the greater the agitation the more unsaturated solvent passes over the drug and the faster the formation of the solution).
- Applying heat.

Factors affecting on extent of solubility

1. Temperature

Solids are usually more soluble in hot than in cold solvent.

In the process of solution we have three cases:

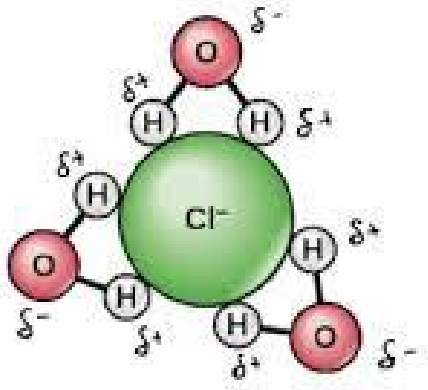
1. Endothermic reaction :Increase in the temperature lead to increase solubility.

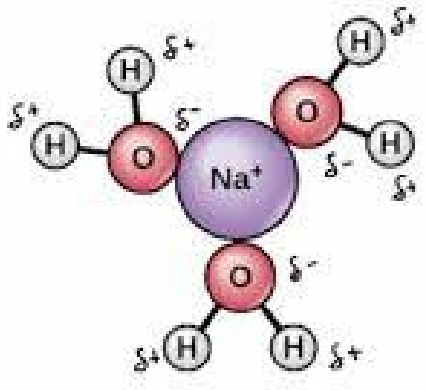
2. Exothermic reaction :Increase in the temperature result in decrease solubility .

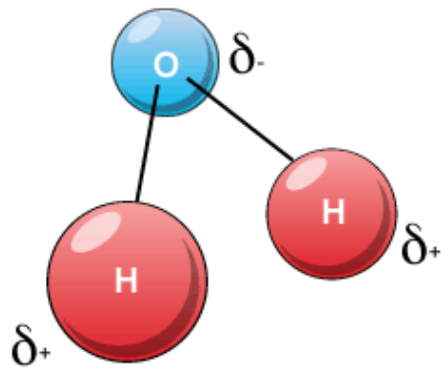
3. When heat is neither absorbed nor given off in the process of solution : Increase or decrease in the temperature results in no effect on the solubility .

2- Effect of molecular structure

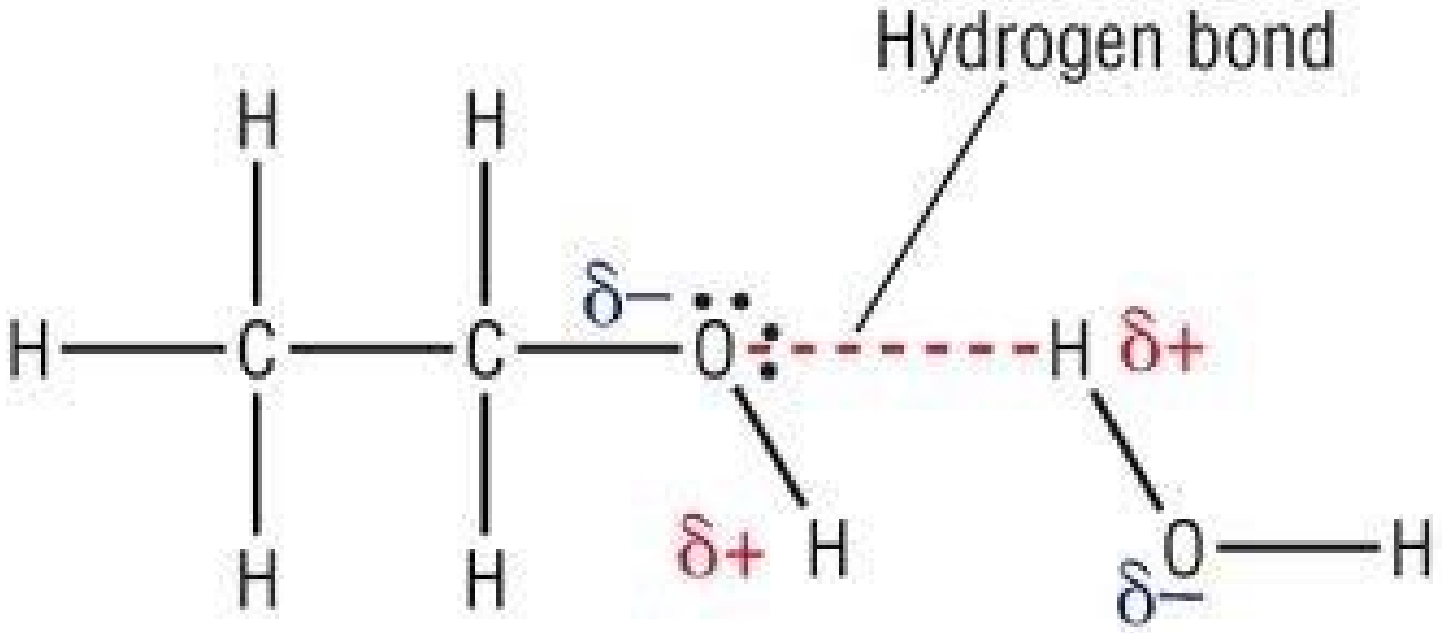
- The more nearly solute and solvent are a like molecular structure the greater solubility of one in the other.
- Water is composed of covalent molecules which are described as polar structures with strong dipole characteristics (negative and positive regions) .
- Polar solvents like water will dissolve salts and other electrolytes readily, so they are poor solvents for non polar substances.







- Polar liquids may act as solvent when it and solute are capable of complexation by H-bound formation e.g. water and alcohol of low M.wt . As the m.wt. of alcohol increased resulted in decrease polarity and decrease the solubility of water (why?).



❑**Carbon tetrachloride (CCl_4) is non polar . Non polar liquids don't dissolve polar or slightly polar substance.**

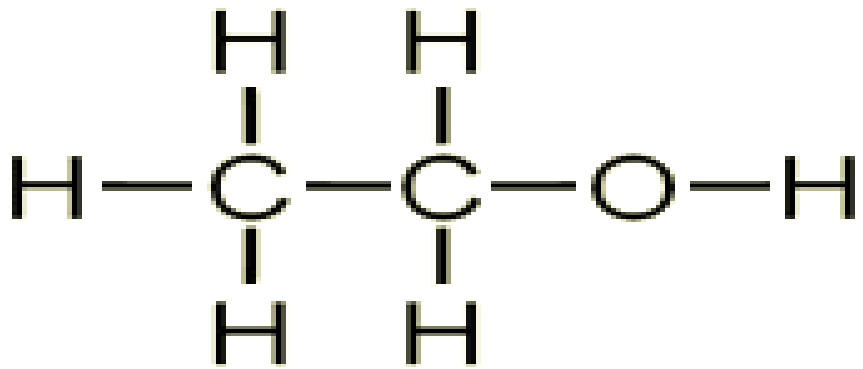
❑**Ethyl alcohol molecule have:**

▶**5 non polar carbon –Hydrogen bond**

▶**1 C-C bond (non polar)**

▶**C-O bond & H-O bond (polar)**

- **So it is considered as a good solvent for some polar and non polar substances due to the presence of distinct polar and non polar regions.**



How to predict solubility?

Like dissolve like

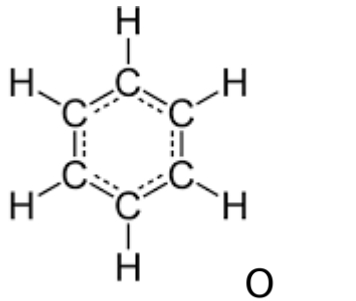
The more solvents and solutes are structurally alike the more rapid solution takes place.

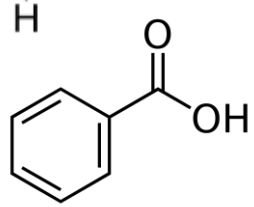
DRUG	MILLILITERS OF SOLVENT TO DISSOLVE 1 g OF DRUG	
	WATER	ALCOHOL
Atropine	455.0	2
Atropine sulfate	0.5	5
Codeine	120.0	2
Codeine sulfate	30.0	1280
Codeine phosphate	2.5	325
Morphine	5000.0	210
Morphine sulfate	16.0	565
Phenobarbital	1000.0	8
Phenobarbital sodium	1.0	10
Procaine	200.0	Soluble
Procaine hydrochloride	1.0	15
Sulfadiazine	13000.0	Sparingly soluble
Sodium sulfadiazine	2.0	Slightly soluble

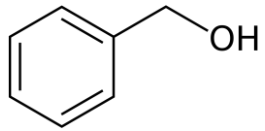
Chemical structure-solubility relationship.

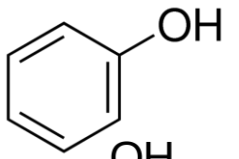
TABLE

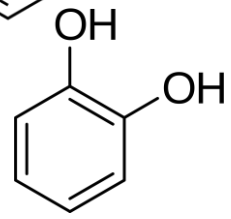
13.3 SOLUBILITIES OF SELECTED ORGANIC COMPOUNDS IN WATER AS A DEMONSTRATION OF CHEMICAL STRUCTURE–SOLUBILITY RELATIONSHIP

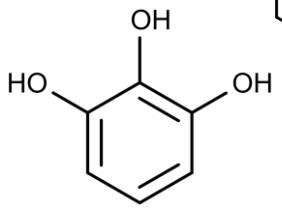












compound	Formula	MILLILITERS OF WATER REQUIRED TO DISSOLVE 1 G OF COMPOUND
Benzene	C6H6	1430
Benzoic acid	C6H5COOH	275
Benzyl alcohol	C6H5CH2OH	25
Phenol	C6H5OH	15
Pyrocatechol	C6H4(OH)2	2.3
Pyrogallol	C6H3(OH)3	1.7

Water soluble inorganic salts

- Salts of alkali metals(Na, K, Li,) are usually water soluble except Li_2CO_3
- Ammonium and quaternary ammonium salts
- Nitrates ,nitrites, acetates, chlorates lactates except silver and mercurous acetate
- Sulfates, sulfites and thiosulfates ,except calcium and barium salts
- Chlorides, bromides and iodides except salts of silver and mercurous ions

Solubility of organic molecules

- Molecules of 5 carbon chain length and one polar gp are usually soluble
- Branched chains are more soluble than the corresponding straight chain
- Increasing molecular weight will usually decrease solubility
- Increased structure similarity between solute and solvent is accompanied by increase solubility
- Polar function groups include OH, CHO, COH, CHOH, CH_2OH, COOH, NO_2, CO, NH_2 and SO_3H .

What is Lipinski's rule? (rule of five)

General notes

- The more nearly solvents and solutes are a like structurally, the more rapidly solution takes place.
- Polar liquids dissolve electrovalent compounds readily, but they are poor solvents for non polar substances. On other hand, non polar liquids are required for non polar solutes.
- Semi-polar liquids, such as ethyl alcohol posess some of properties of both polar and non polar solvents.

3- Effect of pH on solubility

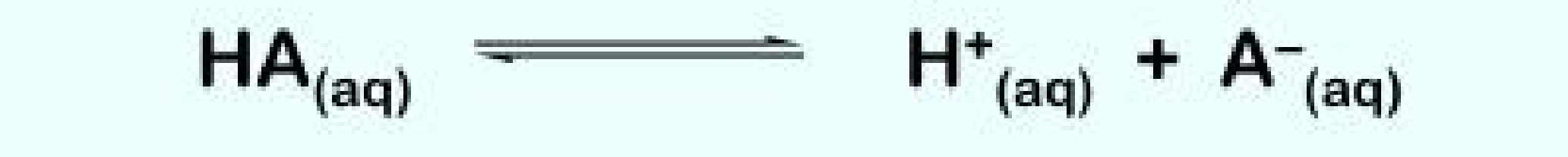
- Organic substances are either weak acids or weak bases. Their aqueous solubility depends on the pH of the solvent.
- The solubility in water of weak organic acids such as barbiturates & sulfonamides is increased as the pH increased by addition of base. This increase in solubility is due to the formation of water soluble salts.

- So:
- If the pH of Phenobarbital solution is increased above 5.5 by addition of strong base the solubility will increase.
- If the pH of Phenobarbital solution is decrease by addition of strong acid, Phenobarbital (free acid) will precipitate.

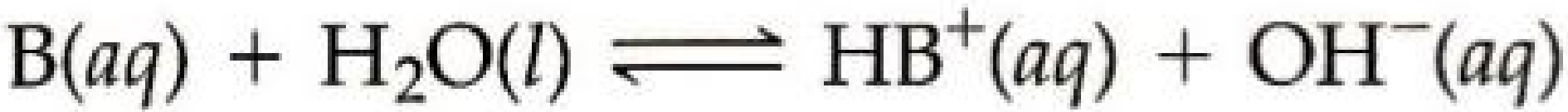
- ▶The solubility in water of weak organic base (alkaloids) increase as the pH decrease by addition of acid due to the formation of water soluble salts

- ▶If the pH of aqueous solution of salt is increased by addition of base atropine (free base will be precipitates).

For weak acid



For weak base



$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} + \log\frac{[\text{base}]}{[\text{acid}]}$$

- ▶At a given pH the degree of ionization weakly acid or basic drug depends on its pka value which is the –ve Log of its dissociation constant.
- **For weak acidic drugs:**

$$pH = pKa + \log \frac{S - So}{So}$$

- S=molar concentration of drug (dissociated and undissociated) species in solution.
- So=molar solubility of undissociated species.
- ▶This equation derived from Handerson–Hasselbach equation.

- **For weak basic drug:**

$$pH = pKw - pKb + \log \frac{So}{S - So}$$

- ▶**Note:** These equations may be used to calculate the pH at which a weak acids or bases will precipitate from solution of its salt.

Importance of pH on absorption and excretion

- ▶The unionized form can pass the biological membrane due to its lipid solubility and since the membrane is lipoprotein in nature. The ionized form can also pass the biological membrane by carrier mediated mechanism.
- ▶If toxic acidic substance is taken by patient, we give him basic compound to change it to ionized form that are more soluble and can not be reabsorbed by kidney tubules and will be excreted by kidney out of body, and vice versa if we have basic compound.

Oral solutions

- Effective
- Safe
- Stable
- Palatable

Final solution

- Drug
- Buffers
- Reducing agents
- Preservative
- Sweetening agent
- Flavoring agent (drug)
- Coloring agent (flavor)
- Density modifier
- Viscosity enhancers

Types of oral solutions

Oral solutions

- Mostly used for small and old aged patients
- Cold remedies and bronchodilators
- vitamins
- Laxative solutions
- Mist Diuretic

Dry for reconstitution

1. Unstable in aqueous media
2. Uniform dose

- ORS
- Orodispersible tablet (Halazone) or powder Voltafast ®
- Effervescent tablets or powder

Oral rehydration solution

ORS

- Used for diarrhea to replenish electrolytes
- This equates to
- 45 mEq sodium,
- 35 mEq chlorine, and
- 20 mEq potassium
- 30mEq citrate
- 25g dextrose per liter of fluid.
- These formulation are available in liquid or powder packet form for reconstitution

Oral colonic lavage solution

- Used before bowel procedures (colonscopy)
- Balanced solutions of electrolytes with PEG-3350

- Lactulose is a colonic acidifier that works by increasing stool water content and softening the stool. It is a man-made sugar solution laxative used to treat constipation.

Mouthwashes and gargles

- Mouthwashes/gargles are designed for the treatment of infection and inflammation of the oral cavity. Formulations designed for this purpose employ water as the vehicle, although a co-solvent, e.g. alcohol, may be employed to solubilize the active agent.
- The use of alcohol as a co-solvent may act to enhance the antimicrobial properties of the therapeutic agent.
- Other formulation components are frequently required to enhance the palatability and acceptability of the preparation. These include preservatives, colors, flavoring agents and non-cariogenic sweetening agents.

Douches (Internal vaginal solutions)

Used for irrigation, cleansing of the vagina for hygienic effect

- Astringents (Witch Hazel)
- Antimicrobials (povidone Iodine)
- Adjusting pH

Basic (sodium bicarbonate)

Acidic (vinegar, Lactic acid)

- Aiding normal flora growth

Liquid solutions or concentrates

Powders for solutions

External Feminine solutions

- Used for washing and cleaning
- Maintain hygiene
- pH between 3.5 and 4.5

Rectal solutions (Enemas)

1-Retention enemas

1. **Local effect**
   (hydrocortisone) as enemas for ulcerative colitis
2. **Systemic absorption**
   (aminophylline) rectal administration minimizes the undesirable GIT reaction, effective blood levels within 30 min after rectal instillation

Properties

Viscosity-enhancing agents, e.g. glycerol, may be included to aid retention of the formulation within the rectum and to reduce the incidence of seepage.

Rectal solutions (Enemas)

2-Evacuation enemas

Pharmaceutical solutions that are administered rectally and are employed to ensure clearance of the bowel,

Available in disposable plastic squeeze bottles containing a premeasured amount of enema solution.

1. Oil-based solutions and, in some formulations, the vehicle is the agent that promotes bowel evacuation, e.g. Arachis oil enema. **Softening the feces**
2. Aqueous formulations usually contain salts (e.g. phosphates) to alter the osmolality within the rectum, thereby increasing the movement of fluid to the rectal contents. Increasing the amount of water in the large bowel (**osmotic laxatives**).

Topical solutions (infection)

	conc	Vehicle
Hydrogen peroxide	3%	Aqueous
Chlorhexidine gluconate	4%	Aqueous
Iodine tincture	2%	Alcohol, water
Povidone Iodine	7.5%, 10%	Aqueous
Clindamycin phosphate	1%	Isopropyl alcohol Water
Erythromycin	2%	PEG/acetone/alcohol
Clotrimazole	1%	PEG400
Ketoconazole	1%	Water
Tolnaftate	1%	PEG

Topical solutions

Drug	Conc	Vehicle	Use
Fluorouracil	2.5%	PG	antineoplastic
Minoxidil	2 ,5%	Alcohol, water, PG	Baldness
Hydroquinone		Water Alcohol ,PG	
Podophyllum		Benzoin tincture	Warts
Fluocinolone acetonide Betamethasone Mometasone		PG	Adrenocortical steroid

THANK YOU

Lorem ipsum dolor sit amet, reque tacimates nec cu.