

### KEY CONCEPTS

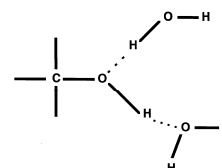
- What is Solubility and why is it important.
- Why do we need Solution dosage forms?
- What are the advantages and disadvantages of solution dosage form.
- How are pharmaceutical solutions formulated?

### SOLUBILITY

- Is a measure of the maximum amount of a substance that will dissolve in a liquid (at a constant temperature)
- Solutions are one or more substances dissolved in one or more miscible liquids.
- Review in Ansel's Dosage Form pages 112-113 on Solubility and factors affecting Solubility (Discussed in class).

### SOLUBILITY OF

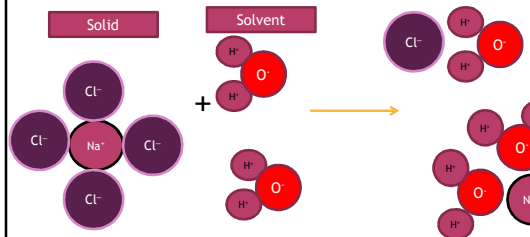
- If the solute molecules have the ability to form a bond with the solvent, this will increase its solubility.



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### Understanding Solubility

- Polar solvents:** polar solvents can dissolve polar solutes. HOW?
- Polar solvents reduce the forces of attraction between oppositely charged ions of the solute.



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### RULES USED TO PREDICT SOLUBILITY

- Water solubility increases with increasing the number of polar groups in a molecule ( $\text{NH}_2$ ,  $\text{OH}$ ,  $\text{SO}_3\text{H}$ ,  $\text{COOH}$ ).
- Water solubility decreases with increasing the C number in a molecule.
- Water solubility increases with increasing branching.
- Water solubility decreases with increasing MW.

### SOLUTIONS ARE:

Dosage forms prepared by dissolving the active ingredient(s) in an

Aqueous, non aqueous solvent or a combination of both( mixed solvent system).

### SOLUTIONS: FOR DIFFERENT ROUTES OF ADMINISTRATION

- Orally: Solutions either Syrups and Elixirs.
- In mouth and throat: Mouth washes, gargles.
- In body cavities: Douches, enemas, ear drops, nasal sprays.
- On body Surfaces: Topical Solutions, Collodions.

### ORAL PHARMACEUTICAL SOLUTIONS

- Drug is usually intended to provide a systemic effect or locally as mouth washes.
- Drug is soluble in the solvent.
- Excipients: flavoring agent, colorant, sweetener or preservative.
- Solubility and compatibility of each solute with regard to the solvent system needs to be known before compounding or formulating.

### GENERAL FACTS ABOUT PHARMACEUTICAL SOLUTIONS

- Solute (drug) is in solution and is expected to be absorbed quickly.
- Solutes other than the active ingredients may be also soluble in the solution: color, flavors, sweeteners, stability enhancers.

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### ADVANTAGES

1. Easier to swallow therefore easier for: children and elderly patients.
2. Their absorption into the systemic circulation occurs more rapidly than tablets and capsules. Why?
3. The active drug is homogeneously dispersed throughout the product : thus gives uniform dose than a suspension which needs shaking.
4. The dose of active drug is easily adjusted by measuring a different volume.
5. Dilute irritant action of some drugs (aspirin) thus minimize adverse effects in the GIT .

### DISADVANTAGES

1. The active ingredient in solution at a greater chance of chemical degradation mainly hydrolysis as compared to solid dosage form.
2. Bulky thus difficult to transport and store.
3. Unpleasant taste or odors are sometimes difficult to mask.
4. Needs an accurate spoon to measure the dose. Issue for vision impaired.
5. Less stable than solid dosage forms, major signs of instability:
  - i. color change,
  - ii. precipitation
  - iii. microbial growth

## ADMINISTRATION OF ORAL SOLUTIONS

Measured by calibrated cups or spoons

Patient history:

Diabetics and sugar content



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## SOLUTIONS

- Solution is homogenous, one phase system, has two or more components. Solute is dispersed as individual molecule unionized e.g sucrose or ionic salts  $K^+$ .
- Strength is expressed as mg/ml or mg/5ml
- Commercially available:
- Propranolol 80mg/ml
- Fluoxetine hydrochloride 20mg/5ml

## ELIXIR

Alcohol 10-12%  
is self preserving

- A type of solution. Homogenous one phase product. Has three or more components two of those are water and alcohol.
- Termed Hydroalcoholic solutions. Their alcohol content ranges from 5-40%.
- Non-medicated and medicated.
- Elixir is less efficient in masking taste than syrup, has higher dissolution ability and is easier to prepare.
- Traditionally alcohol used to solubilize and exert pharmacological effect as well preservative effect.
- At 10-12% alcohol is self preserving.

## ELIXIR

- Upon dispensing, patients need to be advised about potential side effect of alcohol.
- Alcohol content is a disadvantage for children.
- Currently manufacturers are limiting the amount of alcohol in their elixirs.
- Term may be used even if alcohol free e.g Tylenol Children's Elixir.
- Read ingredients prior to dispensing

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## (SYRUPS)

- Syrups are another type of solutions. Homogenous, one phase product.
- Medicated syrups are made of three or more components.
- Sucrose is commonly used (60-85%) maximum 85% Why?
- Sorbitol and fructose are being used as well.
- Concentrated solutions of sugar are stable and quite resistant to microbial growth. Why?
- Syrups possess remarkable masking properties for bitter and saline drugs.

## SYRUPS

- **Simple syrup:** when water is used alone for making syrup. E.g Syrup NF made of 85g of sucrose in purified water to make 100 ml of syrup. Used in compounding medicated syrups.
- **Medicated syrup:** when the aqueous preparation contains some added medicinal substance
- **Flavored syrup:** which contains aromatic or pleasantly flavored substances and is intended to be used as a vehicle or flavor for prescriptions.

- ✱ **In dilute solutions** sucrose provides an excellent nutrient for molds, yeasts, and other microorganisms.
- ✱ In concentration of 65 % by weight or more the solution will retard the growth of such microorganisms.

- ◉ Why is it important for the concentration of sucrose to approach but not quite reach the saturation point, WHY?



- ◉ A **saturated solution** may lead to crystallization of a part of the sucrose under conditions of changing temperature.

## SORBITOL BASED SYRUPS

- ✱ Sorbitol is used mostly in the form of a 70% w/w aqueous solution.
- ✱ Sorbitol solution is not irritating to the membrane of the mouth and throat and does not contribute to the formation of dental carries.
- ✱ Sorbitol is metabolized and converted to glucose; however, it is not rapidly absorbed from the GIT as sugars. No significant hyperglycemia has been found.
- ✱ Sorbitol solution does not support mold growth. Preservative should be used in solution containing less than 60% w/w sorbitol.
- ✱ It is chemically stable and inert with respect to drugs and other ingredients used in pharmaceutical preparation.

## FORMULATION COMPONENTS OF SOLUTION, ELIXIRS AND SYRUPS

1. Solvents
2. Preservatives
3. Antioxidants
4. Buffers
5. Flavors, colors and sweetening agents

## SOLVENT SELECTION

- ◉ Dissolution power
- ◉ Clarity
- ◉ Toxicity
- ◉ Compatibility
- ◉ Palatability, Color, Odor
- ◉ Price

## 1. SOLVENTS

1. Water
2. Alcohol
3. Glycerin
4. Propylene Glycol
5. Polyethylene Glycol 400

## WATER

Commonly used solvent, non toxic, compatible with body fluids and can dissolve most compounds.

**Tap water** is ONLY used in cleaning, extracting, and some external use products.  
May have up to 0.1 % solids

**Purified water USP Must Be used**

- ◉ Preparation: Distillation, ion exchange, or reverse osmosis.
- ◉ Solid content is less than 0.001%
- ◉ Used for aqueous dosage forms (except parenterals)

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## ALCOHOL

- ◉ Ethyl alcohol( Ethanol)
- ◉ Miscible with water, glycerin, propylene glycol and PEG 400.
- ◉ Second to water in terms of utility as a solvent pharmaceutically.
- ◉ Used to increase solubility of drug or added ingredients.

## FDA LIMITS OF ALCOHOL USE IN OTC PRODUCTS

Age	Restricted concentrations
Under 6 years	0.5%
6-12 years	5%
More than 12	10%

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## ALCOHOL

- ◉ Alcohol USP: 94.9- 96% ethyl alcohol
- ◉ Used as solvent or co-solvent, good water miscibility, good dissolution power, antimicrobial.
- ◉ Alcohol and water mixtures are called hydroalcoholic solutions
- ◉ Undesired pharmacological action

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## RUBBING ALCOHOL

- ◉ 70% ethyl alcohol by volume and the rest is water and denaturants
- ◉ bitter substances and organic additives that cannot easily be separated
- ◉ Rubefacient, soothing rub, germicide for instruments, skin cleaning.
- ◉ External use only.

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## GLYCERIN

- ◉ Clear, colorless, odorless viscous liquid.
- ◉ Miscible with water, alcohol, propylene glycol and PEG 400.
- ◉ No central nervous system depressant activity of ethanol.
- ◉ It is a humectant and has preservative properties.
- ◉ Used for both internal and external products.
- ◉ Solubilizing properties are comparable to alcohol but increased viscosity to the final product may be desirable or undesirable.

### GLYCERIN USP

- ◉ Comparable to alcohol in dissolution power
- ◉ Can be used to reduce alcoholic content of preparations
- ◉ Stabilizer
- ◉ Viscous

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### PROPYLENE GLYCOL

- ◉ Clear, odorless, colorless viscous liquid.
- ◉ Miscible with water, alcohol, glycerin and PEG 400.
- ◉ No central nervous system depressant effect.
- ◉ Has humectant and preservative effect such as glycerin.
- ◉ Used for both external and internal products.
- ◉ Replacing glycerin in modern formulations.

### POLYETHYLENE GLYCOL 400 NF

- ◉ A polymer composed of ethylene oxide and water.
- ◉ Clear, colorless and viscous liquid.
- ◉ Miscible with water, alcohol, propylene glycol and glycerin.
- ◉ Usually included in cosolvent system i.e two or more solvents used.

### 2. PRESERVATIVES

- ◉ Benzoates
- ◉ Parabens
- ◉ See your handout.

### PREPARATION OF SOLUTIONS

- ◉ Mixing
- ◉ Heating except with heat sensitive solutes
- ◉ *Reducing particle size is recommended*

### METHOD OF PREPARATION OF SYRUPS

1. **With the aid of heat**
  2. **By agitation**
  3. **By addition of sugar to medicated liquid**
  4. **By percolation**
- ◉ Most syrups are prepared with the aid of heat.
  - ◉ Caution must be exercised not to use excessive heat
  - ◉ Invert sugar where disaccharide is hydrolyzed to monosaccharide glucose (dextrose) and fructose (levulose).
  - ◉ Color is darker
  - ◉ Though sweetness is enhanced but more susceptible to microbial growth.

### SOLUTION WITH THE AID OF HEAT

- Quick
- Can be used for thermostable medications and non-volatile materials.
- Sugar inversion may happen.
- Darkening in color may happen too.

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### AGITATION WITHOUT HEAT

- Through placing all ingredients in a vessel larger than the volume of the syrup then agitation of the mixture
- Time consuming, maximum stability.
- Medication dissolved in the minimum solvent then incorporated into the syrup.

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### ADDITION OF SUCROSE TO THE PREPARED MEDICATED LIQUID

- Read page 419

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### PERCOLATION

- Either sucrose or the source of medication is percolated.
- Example the syrup of ipecac
- Read p 419

### ELIXIR PREPARATION

1. Simple agitation
  2. Prepare alcoholic solution and aqueous solution then add aqueous to alcoholic
- Filter if needed

Why?

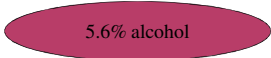
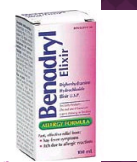


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### MEDICATED ELIXIR

- Mostly has one therapeutic agent for the ease of dose adjustment.
- **Antihistaminic Elixirs**
- Mostly as base amine prepared as salt (by interaction with acid), pH is critical when diluted.
- Diphenhydramine HCl

5.6% alcohol

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## MEDICATED ELIXIR

- ◉ Acetaminophen 160 mg/5mL (alcohol free)
- ◉ Digoxin Elixir
- ◉ 4.5-5.25 mg/ 100 mL elixir
- ◉ 10% alcohol
- ◉ Dose should be taken with high accuracy (bottle sold with calibrated dropper)
- ◉ Patient should not switch from product to another.

Analgesic Antipyretic



Cardiotonic



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## TINCTURES

- ◉ Alcoholic or hydroalcoholic solutions prepared from vegetable materials or chemicals.
- ◉ Tinctures have different:
  - Methods of preparation
  - Strength of drug
  - Alcoholic content.
- ◉ Contain alcohol 15-80% (for dissolution and preservation).

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## TINCTURES

- ◉ Due to high alcohol content, tinctures should be stoppered and protected from high temperatures.
- ◉ If it contains light sensitive materials it should be stored in light resistant containers.



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## ORAL TINCTURES EXAMPLES

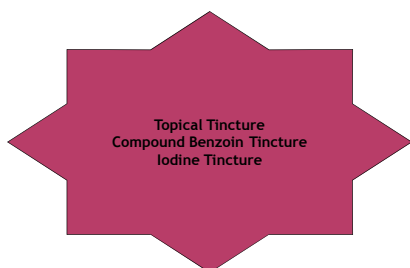
- Paregoric USP: camphorated tincture of opium (40 mg%) morphine.
- Opium Tincture: laudanum (1%) morphine
  - ◉ Both contain morphine.
  - ◉ But are not interchangeable.



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## NON-ORAL TINCTURES

- ◉ Tinctures may be topical



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## FLUIDEXTRACTS:

- ◉ Liquid preparations of vegetable drugs prepared by percolation.
- ◉ Alcohol (solvent or preservative)
- ◉ Concentrated solutions: 1ml contains 1 g of the standard drug.
- ◉ Too potent to be self administered,
- ◉ Bitter: Modified by flavorant, sweetener.
- ◉ Used as drug concentrate.
- ◉ Liquorice fluidextract.

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