Lecture 8
Introduction to Liquid dosage forms
PPP 211
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Classification of Liquid dosage forms

- Monophasic liquid D.F
  - Solutions
    - Aqueous solutions
    - Non-aqueous solutions
  - Suspensions
  - Colloids
    - Emulsions

- Polyphasic liquid D.F
Advantages of liquid dosage forms

1. Used for patients who cannot swallow.
2. Has fast absorption rate.
3. Is more flexible in achieving the proper dosing.
4. Best choice for young children and elders.
Disadvantages of liquid dosage forms

1. Has short shelf life due to low stability.
2. Has less accuracy.
3. Needs special storage and transferring conditions.
4. Is easily infected by microorganisms.
5. Has special storage requirements
Types of liquid dosage forms

1. Solutions
2. Suspensions
3. Syrups
4. Lotions
5. Tinctures
6. Spirits
7. Elixirs
8. Fluid extracts
9. Liniments
10. Aromatic water
11. Decoctions
12. Collodion
Preparation of Liquid dosage forms

• Liquid dosage forms are prepared:
  (1) by dissolving the active drug substance(s) in an aqueous or nonaqueous (e.g. alcohol, ether, glycerin) solvent.
  (2) by suspending the drug in appropriate medium.
  (3) by incorporating the drug substance into an oil or water phases.

• Additives:
  1. Antimicrobial agent
  2. Coloring agent
  3. Stabilizer
  4. Viscosity builder
  5. Flavoring agent
  6. Coloring agent
  7. Substances to keep the dose uniformity
  8. Substances to enlarge the total volume of the preparation
Liquid dosage forms

• Solutions: solutions are clear liquid preparations containing one or more active ingredients dissolved in a suitable vehicle.

• Suspensions (Solid in liquid dispersion): liquid preparations containing one or more active ingredients suspended in a suitable vehicle.

• Emulsions (liquid in liquid dispersion): emulsions are two phase system in which one liquid is dispersed throughout another liquid in the form of small particles.

• Colloids: A system in which finely divided particles, which are approximately less than 1 μm in size, are dispersed within a continuous medium in a manner that prevents them from being filtered easily or settled rapidly.
Liquid dosage forms can be administered:

- Topically: lotions or suspension applied to the skin, eye drops, nasal drops, ear drops
- Orally (p.o.): oral suspension and solution
- Parenterally: subcutaneous injection (s.c.), intramuscular injection (i.m.) and intravenous administration (i.v.)
Solution (solutio)

• Solutions are prepared by dissolving a solid or liquid drug in distilled water (aqua destillata)

• Solutions are intended for topical, oral, and parenteral administration. Solutions for local administration usually called lotions.
Classification of solutions

(i) According to the route of administration

- Oral solutions through oral route
- Otic solutions instilled in the ears
- Ophthalmic solutions instilled in the eyes
- Topical solutions applied over skin surface
Classification of solutions

(ii) According to composition and uses

- Syrups  aqueous solution containing sugar

- Elixir  sweetened hydro-alcoholic (combination of water and ethanol solution)

- Spirit  solution of aromatic materials in alcohol. Aromatic water solution of aromatic material in water.
Classification of solutions

(ii) According to composition and uses

-Tincture/fluid extract
solution prepared by extracting active constituents from crude drugs e.g compound cardamon tincture. They may also be solution of chemical substances dissolved in alcohol or in hydroalcoholic solvent e.g tincture of iodine.

-Injection
Certain solution prepared to be sterile and pyrogen-free and intended for parenteral administration.
Classification of solutions

(iii) **According to the vehicle**

- **Aqueous solutions**
  Solutions that contain water as the solvent. For example, sugar in water, carbon dioxide in water, etc.

- **Non-aqueous solutions**
  Solutions that contain a solvent other than water. Ether, benzene, petrol, carbon tetrachloride etc., are some common solvents. For example, sulphur in carbon disulphide, naphthalene in benzene, etc.
- Concentrated solutions and dilute solutions

Between two solutions, the solute quantity may be relatively more or less.

The solution that has a greater proportion of solute is said to be more concentrated than the other that has a lesser proportion. If the proportion of solute is less, the solution is said to be dilute.
Saturated and unsaturated solutions

- Saturated Solution
A solution in which no more solute can be dissolved at a given temperature is called a saturated solution.

- Unsaturated solution
A solution in which more solute can be dissolved at a given temperature is called an unsaturated solution.
A given solution that is saturated at a particular temperature may become unsaturated when the temperature is increased.
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. When a solvent at a given temperature has dissolved all of the solute it can, it is said to be saturated.

- The **solubility** of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature.

- How do substances dissolve? **Solvation** - there is an interaction between the solute and the solvent.
- The solute particles are usually surrounded by the solvent particles. This process is called solvation.

**Different substances have different solubility.**

- **Solubility** refers to the maximum amount of a solute that can be dissolved in an amount of solvent under specific temperature and pressure conditions.
- A substance that cannot be dissolved in another (or does so to a very limited extent) is said to be **insoluble**.
Factors affecting the solubility

Electrostatic attractions between water and solid ions/molecules play an important role in the solubility of solids in aqueous solutions. There are other factors that also play an important role to control solubility of a solute. These include the various chemical and other physical properties of both the solute and the solvent, pressure, the pH of the solution, the state of subdivision of the solute, and the physical agitation applied to the solution as it dissolves.

Temperature is an important factor in determining the solubility of a drug and in preparing its solution. Most chemicals absorb heat when they are dissolved and are said to have a positive heat of solution, resulting in increased solubility with an increase in temperature. The addition of more heat facilitates the dissolving reaction by providing energy to break bonds in the solid. A few chemicals have a negative heat of solution and exhibit a decrease in solubility with a rise in temperature.
SOLUBILITY

(2) Nature of the solute and the solvent

- The maximum possible concentration to which a pharmacist may prepare a solution varies greatly and depends in part on the chemical constitution of the solute. For example, calcium hydroxide topical solution, USP, and potassium Iodide oral solution, USP. The first solution prepared by agitation an excess amount of calcium hydroxide with purified water, contains only about 140 mg of dissolved solute per 100 ml of solution at 25°C, whereas, potassium iodide solution contains about 100g of solute per 100 ml of solution, more than 700 times as much solute as in the calcium hydroxide topical solution.

- The pharmacist can in certain instances dissolve greater quantities of a solute than be possible using different solubilizing agent or a different chemical salt form of the medicinal agent. For example using of an aqueous solution of potassium iodide or sodium iodide to increase the solubility of iodine granules in water such as in iodine topical solution prepared to contain about 2% iodine and 2.4% sodium iodide.

- Non polar solutes are soluble in non polar solvents; Polar or ionic solutes are soluble in polar solvents.

- The important organic medicinal agents are either weak bases or weak acids and their solubility depends to a large measure on the pH of the solvent. These drugs react either with strong acids or strong bases to form water-soluble salts.
- The weak bases including many of the alkaloids (atropine), local anesthetics (cocaine, procaine) and other important drugs are not very soluble in water, but they are soluble in dilute solutions of acids.
- Organic medicinals that are weak acids include barbiturate drugs (e.g. phenobarbital) and sulfonamides (e.g. sulfadiazine). These and other weak acids form water-soluble salts in basic solution. Substances with similar intermolecular attractive forces tend to be soluble in one another. This generalization is stated as "like dissolves like."

Salts of organic compounds are more soluble in water than are the corresponding organic bases. Conversely, the organic bases are more soluble in organic solvents, including alcohol, than are the corresponding salt forms.

Organic compounds are more soluble in organic solvents than in water. Organic compounds may be somewhat water soluble if they contain polar groups capable of forming hydrogen bonds with water.
## Nature of Solute and Solvent

<table>
<thead>
<tr>
<th>Solute</th>
<th>Polar Solvent</th>
<th>Non-polar solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polar</td>
<td>Soluble</td>
<td>Insoluble</td>
</tr>
<tr>
<td>Non-Polar</td>
<td>Insoluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Ionic</td>
<td>Soluble</td>
<td>Insoluble</td>
</tr>
</tbody>
</table>
Molecular size
The larger the molecules of the solute are, the larger is their molecular weight and their size. It is more difficult for solvent molecules to surround bigger molecules. The larger particles are generally less soluble. In the case of organic compounds the amount of carbon "BRANCHING "will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.
Certain combinations of anion and cation seem to be similar in makeup but do not have similar solubility characteristics. For instance, magnesium sulfate is soluble, but calcium sulfate is only slightly soluble, barium sulfate is very insoluble and is used as an opaque medium for x-ray observation of the intestinal tract, but barium sulfide and barium sulfite are more soluble and their oral use can result in poisoning. Mercurous chloride (HgCl) is insoluble and was formerly used as cathartic, but mercuric chloride (HgCl$_2$) is soluble in water and is a deadly poison if taken internally.

In many instances, solubility of drugs and their differentiation from other drugs are critical to the pharmacist for avoidance of compounding failures or therapeutic disasters.

The ability of a solvent to dissolve organic as well as inorganic solutes depends on its effectiveness in overcoming the electronic forces that hold the atoms of the solute together. During dissolution, the molecules of solvent and the solute become uniformly mixed, and cohesive forces of atoms replaced by new forces as a result of the attraction of the solute and solvent molecule for one another.
(3) Pressure
The effect of pressure is observed only in the case of gases. An increase in pressure increases the solubility of a gas in a liquid. For example carbon dioxide is filled in cold drink bottles (such as coca cola, Pepsi etc.) under pressure.

(4) Particle size
The solubility of a pure chemical substance at a given temperature and pressure is constant, however, its rate of solution depends on the particle size of the substance and the extent of agitation. The finer the powder, the greater the surface area that comes in contact with the solvent and the more rapid the dissolving process.

(5) Stirring or agitation
Agitation makes the solute dissolve more rapidly because it brings fresh solvent into contact with the surface of the solute. However, agitation affects only the rate at which a solute dissolves. It cannot influence the amount of solute that dissolves. An insoluble substance will remain undissolved no matter how much the system is agitated.
The solubility may be expressed as grams of solute dissolving in milliliters of solvent for example 1 gm 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.

Relative terms of solubility

<table>
<thead>
<tr>
<th>Descriptive term</th>
<th>Parts of solvent required for 1 part of solute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>1-10</td>
</tr>
<tr>
<td>Soluble</td>
<td>10-30</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>30-100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>100-1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>1000-10,000</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>&gt; 10,000</td>
</tr>
</tbody>
</table>
Solutions

Solutions can be formulated for different routes of administration
orally such as syrups, elixirs, drops.
In mouth and throat such as mouth washes, gargles, throat spray.
In body cavities such as douches, enemas, ear drops, nasal sprays.
On body surfaces such as lotions
Advantages of solutions

• Liquids are easier to swallow therefore easier for children, old age and unconscious people.
• A drug must be in solution before it can be absorbed (more quickly effective than tablets and capsules)
• A solution is an homogenous system, the drug will be uniformly distributed throughout the preparation (uniform dose than suspension and emulsion which need shaking)
• Some drugs can irritate the gastric mucosa if localized in one area. Irritation is reduced by administration of a solution of the drug
Problem associated with the manufacturing of solutions disadvantages of solutions

- Liquids are **bulky** and inconvenient to transport and store
- The **stability** of ingredients in aqueous solution is often poor than in solid dosage form
- Solution provide suitable media for the growth of microorganisms and may require the addition of **preservative**
- Accurate dose measuring depends on the ability of patient to measure the dose (needs an accurate spoon to measure the dose)
- The **taste** of a drug is always pronounced when it in solution (unpleasant taste or odours are difficult to mask)

Major signs of instability: color change, precipitation, microbial growth, chemical gas formation.
Suspension (suspensio)

• A suspension consists of a dispersion of relatively coarse particles, usually in aqueous vehicle.
• Suspensions may be used for oral and topical administration.
• Like solutions, oral suspensions are useful in children and patients who cannot tolerate a solid dosage form.
Drops (guttae)

• Drops are solutions, tinctures or mixtures of high-potent drug substances
• Drops are prescribed in small quantity (10–30 g)
- Drops are intended to be administered orally or externally (as eye drops, nasal drops and ear drops).

- **Eye drops (collyrium):** Timolol
- **Nasal (nose) drops:** Olynth 0,1%
- **Ear drops:** Furotalgin
Emulsion (emulsio)

- Emulsions are two-phase systems consist of liquid drug substances.
- They are classified as:
  - oil-in-water emulsion (O/W)
  - water-in-oil emulsion (W/O)
- Emulsions can be administered topically, orally, and I.M.
Liniment (linimentum)

- Liniments are milk-like liquids for topical administration.

- Example:
  - Carmolis fluid
  - Nival
Infusions and decoctions

- **Infusion (infusum)** is a dilute solution of the readily soluble constituents of crude drugs (from the soft parts of plants).
- Fresh infusions are prepared by macerating the drugs for a short period of time (15 min) with boiling water.
Decoction (decoctum)

• Decoctions is an extract of the water-soluble and heat-stable constituents of crude drugs (from the hard parts of plants) by boiling in water for 30 min, and cooling.
• Infusions and decoctions are of short duration (no more than 3 days).
Mixture (mixtura)

- Mixtures contain two or more active drug substance, dissolved, suspended, or dispersed in a suitable liquid base.
- Syrups are added as remedium corrigens, in quantity of 20% or 30% of the total volume.
- Oral and topical administration
Medical nail lacquers

• Such dosage form contains antifungal drugs for topical treatment of onychomycosis

• Example:
  - Batrafen nail lacquer 8%
  - Loceryl nail lacquer 8%
Medical shampoo

Selected topical formulations for the treatment of seborrheic dermatitis are:

• Nizoral shampoo
• Selsun shampoo
Sterile dosage forms for injection

These forms contain solutions, powder or lyophilized powder ready to be dissolve, suspensions, and emulsions. They are packaged in ampoules, vials, plastic bags, one-point cut ampoules, and prefilled disposable syringes.