LIQUID DOSAGE FORMS

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OBJECTIVES OF THE LECTURE

• At the end of this lecture, you will be able to explain:
  • What are the rationale of uses of Liquid dosage forms?
  • What are various types of liquid dosage forms?
  • What are advantages of Liquid dosage forms?
  • What are disadvantages of Liquid dosage forms?
  • What do you mean by solution, solubility and miscibility?
  • What are factors affecting solubility / miscibility?
  • What are various types of solutions?
  • What are various additives in pharmaceutical solutions?
  • How pharmaceutical solutions dosage forms are prepared?
Why Liquid Dosage Forms?

Provide a route for medication to those patients who can not swallow solid dosage forms.

Young
Elderly
After oral surgery
Types of Liquid Dosage Forms?

- **Homogeneous, Clear preparations** containing one or more active ingredients dissolved in a suitable vehicle.

- **Liquid dosage forms**
  - **Monophasic Liquid D.F Solutions**
    - Aqueous Solutions
    - Non-aqueous Solutions
  - **Polyphasic liquid D. F**

- **Solid drug suspended in Liquid/Vehicle**

- **Liquid preparations with 2 or more phases**
  - Finely divided particles suspended in Liquid/Vehicle

- **Drugs Dissolved in aqueous vehicle**

- **Drugs Dissolved in non-aqueous solvent.**

- **Emulsions**

- **Colloids**

- **Liquid drug dispersed Liquid/Vehicle**
Easier to swallow therefore easier for: children, old age and unconscious patients.

Flexibility in dosing.

May be designed for any route of administration like oral, topical, parenteral etc.

If given orally, more quickly effective than tablets and capsules as drug become available immediately for absorption.

Homogenous therefore give uniform dose than suspension or emulsion which need shaking.
Less stable than solid dosage forms.

Bulky therefore difficult to transport and store.

May require special storage conditions.

Difficulty in measuring the dose accurately.

Difficulty in administration.

Chances of dose variability is more.

**major signs of instability:**

- Color or odour change
- Precipitation of drugs
- Microbial growth
- Chemical gas formation
Solutions:

Homogenous One-phase Transparent system consisting of two or more components.

- The components do not separate on standing
- The components cannot be separated by filtration.

These are prepared by dissolving the active ingredient(s) in a solvent.

Aqueous (water, aromatic water or extracts)

Non aqueous (ethanol, glycerol, propylene glycol, certain oils)
The maximum amount of a solute that passes into solution (per ml) at a particular temperature.

A solute will dissolve best in a solvent that has a similar polarity to itself.

A drug is said to be soluble if more than 0.1 g dissolves in 100 mL solvent.

If less than 0.1 g dissolves in 100 mL solvent, the substance is said to be insoluble or, more exactly, sparingly soluble.

Solubility is a quantitative term whereas terms soluble and insoluble are relative.
## *Relative Terms of Solubility*

<table>
<thead>
<tr>
<th>Descriptive Term</th>
<th>Parts of Solvent required</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Soluble</strong></td>
<td>Less than 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>From 1 to 10</td>
</tr>
<tr>
<td>Soluble</td>
<td>From 10 to 30</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>From 30 to 100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>From 100 to 1000</td>
</tr>
<tr>
<td><strong>Very slightly soluble</strong></td>
<td>From 1000 to 10,000</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>From 10,000 and over</td>
</tr>
</tbody>
</table>

*Remington: The Science and Practice of Pharmacy*
• **MISCIBILITY**: when the two components forming a solution are either both gases, solids or liquids it is more usual to talk in terms of miscibility rather than solubility.

**Miscible**: water and alcohol are miscible.

**Immiscible**: two liquids do not mix e.g. water and oil.
Factors Affecting Solubility of Solute

1. Particle size – an increase in surface area to the solvent will increase rate of solution. So the particle size should be reduced by comminution before it is dissolved.

2. Agitation – increases the rate of solution by removing from the surface of the solute.

3. Temperature-- heating a liquid also causes solution to take place more rapidly by increasing the frequency which solvent molecules collide with the surface of the dissolving mixture.

4. pH – Many of the organic substances which are used medicinally are either weak acids or weak bases. And their aqueous solubility depend upon the pH of the solvent.
### Classification of Pharmaceutical Solutions

**Based on Vehicle Used**

<table>
<thead>
<tr>
<th>Aqueous</th>
<th>Sweet &amp;/or Viscid</th>
<th>Nonaqueous</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Douches</td>
<td>1. Syrups</td>
<td>1. Elixirs</td>
</tr>
<tr>
<td>2. Enemas</td>
<td>2. Honeys</td>
<td>2. Spirits</td>
</tr>
<tr>
<td>5. Nasal washes</td>
<td></td>
<td>5. Lotions</td>
</tr>
<tr>
<td>7. Sprays</td>
<td></td>
<td>7. OleoVitamin</td>
</tr>
<tr>
<td>8. Otic solutions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Inhalations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Classification of Pharmaceutical Solutions Based on Purpose

<table>
<thead>
<tr>
<th>Oral</th>
<th>In mouth &amp; throat</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Syrups</td>
<td>1. Mouth washes</td>
</tr>
<tr>
<td>2. Elixirs</td>
<td>2. Gargles</td>
</tr>
<tr>
<td>3. Spirits</td>
<td>3. Throat paint</td>
</tr>
<tr>
<td>4. Linctuses</td>
<td>4. Throat sprays</td>
</tr>
<tr>
<td>5. Drops</td>
<td></td>
</tr>
<tr>
<td>6. Draughts</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>On body Surfaces</th>
<th>In body Cavities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Collodions</td>
<td>1. Douches</td>
</tr>
<tr>
<td>2. Lotions</td>
<td>2. Enemas</td>
</tr>
<tr>
<td>3. Liniments</td>
<td>3. Ear drops,</td>
</tr>
<tr>
<td></td>
<td>4. Nasal sprays</td>
</tr>
</tbody>
</table>
Additives in solutions:

- Solvents (water, aromatic water, alcohols)
- Preservatives (Alcohols, acids, esters etc).
- Anti-oxidants
- Buffers
- Isotonicity modifiers
- Sweeteners
- Colors
- Flavours
Aqueous solutions are Homogeneous mixtures that are prepared by dissolving a solid, liquid or gas in an aqueous medium (vehicle). e.g. water, aromatic water or extracts.

Advantages of water:
✓ Cheap.
✓ Tasteless,
✓ Odourless,
✓ Inert (lack of pharmacological activity)
✓ Neutral
✓ Physiologically compatible
✓ Lack of toxicity

• DISADVANTAGES
✗ Support growth of microorganisms when contaminated
✗ Favorable medium for many chemical reactions.
✗ Some hydrolysable drugs such as glycosides and esters form unstable solutions when dissolved in water.
Tap Water ???
Potable Water: freshly drawn from the public water supply (main system) and suitable for drinking.

*It is not permitted to use tap water for the dispensing of pharmaceutical dosage forms due to its possible bacterial contamination and the presence of dissolved salts that destroy the active ingredients or enhance their decomposition.*

Freshly Boiled and Cooled Water ??
Boiling is seldom used to destroy vegetative bacteria. But, on storage for long time spores may yield vegetative microorganism.

**Purified Water Must be used**
*Drinking water PURIFIED further, by filtration, disinfection, UV radiation, distillation, deionization or reverse osmosis.*

*It is used as an excipients in the pharmaceuticals.*
Aromatic Waters

• Clear, saturated aqueous solution of aromatic /volatile oils or other volatile substances (camphor).
• An aromatic water is water enriched with both the essential oil and the water-soluble volatile components of a plant.
• Aromatic waters capture a broader range of both the water and fat-soluble volatile constituents of a plant, and this contributes to their efficacy and safety.
• They are used principally as flavored or perfumed vehicles.
• Aromatic waters have some advantages over pure essential oils and tinctures.
  • 1. A more gentle and balanced action –
  • 2. Presenting the essential oil in an aqueous medium –
  • 3. The convenience of a tincture without the alcohol –
  • 4. A highly convenient preparation –
  • 5. Traditional support for safety and efficacy –
  • 6. A gentle but effective external application – eg. Aromatic waters like chamomile, lavender, rose, make outstanding topical remedies for soothing, astringing, anti inflammatory, antiseptic, and cooling actions to the skin and mucus membranes.
• Volatile oils solutions represent an incompatibility problem of **salting out**. This occurs after the incorporation of a very soluble salt in their solution.
• Therefore sometimes talc is added as a distributing agent.
• Aromatic water deteriorates with time **therefore**: 
  • should be made in small quantities.
  • Should be protected from intense light and excessive heat by storing in air tight, light resistant containers.
  • should be discarded, if they become cloudy or otherwise deteriorate.
  • Deterioration may be due to volatilization, decomposition or mould growth.
  • Most aromatic waters have a shelf life of about 6-8 months.
(a) Distillation process (Stronger Rose Water NF)

- The drug is coarsely ground and mixed with sufficient quantity of purified water in the distillation unit.
- After distillation any excess oil in the distillate is removed by filtration.
- **Storage**: Air tight, light resistant container.
- **Advantage**: most satisfactory method.
- **Disadvantage**: slow and expensive
(b) Solution process (Peppermint water)

- Aromatic water may be prepared by shaking volatile substance with purified water for 15 minutes.
- The mixture is set aside for 12 hours & filtered.
- Talc (inert) may be used as distributing agent to increase the surface of the volatile substance, ensure more rapid saturation of the water and act as a filter aid.

CONCENTRATED AROMATIC WATERS

These products are alcoholic non-aqueous preparations containing 2% of volatile oils. These are approximately forty times stronger than the ordinary aromatic waters.
EXTRACTS:

- An extract is a substance made by extracting a part of a raw material, often by using a solvent such as water (aqueous Extract) or ethanol (alcoholic extract).
- Many spices, nuts, herbs, fruits, etc., and some flowers, are marketed as extracts.

**Extraction techniques**
- The majority of natural essences are obtained by extracting the *essential oil* from the *blossoms*, fruit, roots, etc., or the whole plants.
- *Expression* when the oil is very plentiful and easily obtained, as in lemon peel.
- *Maceration* is used to create smaller bits of the whole, as in making peppermint extract, etc.
- *Distillation* is used with maceration, but in many cases, it requires expert chemical knowledge.
Preservatives

Solution may become contaminated for a number of reasons:
1. Raw materials used in the manufacture of solutions are excellent growth media for bacterial substances such as gums, dispersing agents, sugars and flavors.
2. Equipment, environment and personnel contribute to product contamination.
3. Consumer use may result in the introduction of microorganism.

Preservative used should be:
1. effective against a wide spectrum of microorganisms
2. stable for its shelf life
3. non toxic, non sensitizing
4. compatible with the ingredients in the dosage form
5. free of taste and odour
**Alcohols (Ethanol & Propylene glycol)**

- **Ethanol** is useful as a preservative when it is used as a solvent. It needs a relatively high concentration (> 10%) to be effective.
- **Propylene glycol** preservative in the range of 15 to 30%.
- It is not volatile like ethanol.

**Acids: (Benzoic acid & sorbic acid)**

- They are used in a concentration range from 0.1 % to 0.5%.
- Only the non-ionized form is effective and therefore its use is restricted to preparations with a pH below 4.5.

**Esters:** Esters (methyl, ethyl, propyl) of p-hydroxybenzoic acid. Hence called as methyl, ethyl, propyl and butyl *parabens*.

- They are employed at concentrations up to about 0.2%.
- Effective and stable over a pH range of 4 to 8.

**Quaternary Ammonium Compounds: Benzalkonium chloride**

- Used at a relatively low concentration 0.002 to 0.02%.
- pH range of 4 to 10 and is quite stable at most temperatures.
- Because of the cationic nature of this type of preservative it is suitable for use in solutions...
**Antioxidants**

Vitamins, essential oils & almost all fats and oils can be oxidized. Oxidation reaction can be initiated by:

1. **heat**: maintain oxidizable drugs in a cool place
2. **light**: use of light-resistant container
3. **heavy metals** (e.g. Fe, Cu): effect of trace metals can be minimized by using citric acid or ethylenediamine tetraacetic acid (EDTA) i.e. sequestering agent.

Antioxidants as propyl & octyl esters of gallic acid, tocopherols or vitamin E, sodium sulfite, ascorbic acid (vit. C) can be used.

**Sweetening agents**

**Sucrose** is the most widely used sweetening agent.

Advantages: Colourless, highly water soluble, stable over a wide pH range (4-8), increase the viscosity, masks both salty and bitter taste, has soothing effect on throat.

**Polyhydric alcohols** (sorbitol, mannitol and glycerol) possess sweetening power and can be used for diabetic preparations.
Buffers: To resist any change in pH

Isotonicity modifiers: osmotic pressure
- Solutions for injection
- Application to mucous membrane
- Large-volume solutions for ophthalmic application

Most widely used isotonicity modifiers are: dextrose and NaCl

Viscosity enhancement
It is difficult for aqueous-based topical solutions to remain on the skin or in the eye (why?) therefore low concentrations of jelling agents are added to increase the viscosity of the product.

Flavours and perfumes: Mask unpleasant taste or odour
- Natural products: fruit juices, aromatic oil (peppermint, lemon etc.)
- Artificial perfumes are cheaper, more readily available and more stable than natural products.
(a) Simple Solution
(b) Solution by Chemical Reaction
(c) Solution by Extraction

(a) Simple Solution

- Prepared by dissolving the solute in a suitable solvent (by stirring or heating).

- Examples: Calcium hydroxide solution USP (lime water),

- Some times the solvent may contain other ingredients which stabilize or solubilize the active ingredient e.g. solubility of Iodine is 1: 2950 in water however, it dissolves in presence of KI due the formation of more soluble poly-iodides ($\text{KI}_2\text{I}_2$, $\text{KI}_2\text{I}_3$, $\text{KI}_3\text{I}_3$, $\text{KI}_4\text{I}_4$). Strong Iodine Solution USP (Lugol's Solution).
(b) Solution by Chemical Reaction
Prepared by reacting two or more solutes with each other in a suitable solvent
For example, Calcium lactate mixture is prepared by calcium carbonate and lactic acid.
Magnesium Citrate = prepared by reacting official magnesium carbonate with citric acid.

(c) Solution by Extraction
Plant or animal products are prepared by suitable extraction process. Preparations of this type may be classified as solutions but more often, are classified as extractives. Extractives will be discussed separately.
A solution must retain its clarity, colour, odour, taste and viscosity over its shelf life.

Both physical and chemical stability of solutions in their containers is very important.
THANK YOU FOR ATTENTION

GOOD LUCK ..