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Introduction

• Monophasic dosage form refers to liquid preparation containing two or more components in one phase system, it is represent by true solution.

• A true solution is a clear homogenous mixture that is prepared by dissolving solute in a suitable solvent.

• The component of the solution which is present in a large quantity is known as “SOLVENT” where as the component present in small quantity is termed as “SOLUTE”.
Advantage

• It is easier to swallow, therefore easier for children and old age people.
• Facilitate absorption of drug faster than solid dosage form as drug is already in solution form.
• It is homogenous therefore give uniform dose than suspension or emulsion which need shaking.
• Simple and fast to formulate
• It can be administered by various routes:
  Oral, Parenteral (injection), enema for rectal use, otic (ear), nasal and ophthalmic preparation.
Disadvantage

- They are bulky, so difficult to transport and store.
- Water is commonly use vehicle, which is prone to microbial growth. So addition of preservative is needed.
- When expose to direct sunlight it may undergo hydrolysis, so need to store in cool and dark place.
- Drug stability reduce by hydrolysis or oxidation. So, they have shorter expire date than solid dosage form.
- Other major sign of drug instability are color change, Precipitation, microbial growth etc.
Classification

Liquids meant for internal administration
- Syrups
- Mixtures
- Elixirs
- Linctuses

Liquids applied to the skin
- Lotions
- Liniments
- Collodions
- Paints

Liquids used in mouth
- Gargles
- Mouthwashes
- Throat paints

Liquids instilled into body cavities
- Douches
- Ear drops
- Nasal drops
- Eye drops
- Enemas
Liquids meant for internal administrations

- **Syrup**: Aqueous preparations of 60% to 85% sucrose with or without flavoring agents and medicinal substances. E.g. Chlorpheniramine maleate syrup, Chloral hydrate.

- **Elixirs**: Clear, aromatic, sweetened hydro alcoholic solutions with or without medicinal substances, intended for oral use. E.g: Dexamethasone elixir.

- **Linctuses**: Viscous, liquid and oral preparations that are generally prescribed for the relief of cough. E.g: Codeine Linctus.
Market available Syrup/Elixir/ Linctus
Liquids meant for external administration

Liquids used in the mouth

- **Gargles**: Aqueous solutions containing antiseptics or antibiotics used to treat throat infections. Available in concentrated form with direction for dilution with warm water before use. eg: Povidone Iodine gargle.

- **Mouthwash**: Aqueous solution with a pleasant taste and odor used to clean and deodorize the buccal cavity. Have antiseptic and astringent activity. eg: Antiseptics-phenol derivatives.

- **Throat paints**: Viscous liquid preparation used for mouth and throat infections. Eg: Phenol glycerine, Compound Iodine.
Market available Gargle, Mouthwash and Throat paints
Liquids meant for external administration
Liquids instill into body cavity

- **Eye drops**: Sterile, aqueous/oily solutions intended for instillation in eye. Eg: Timolol maleate eye drops.

- **Nasal drops** Administered through the nose to obtain local effect. Used during nasal congestion and upper-respiratory tract problem. Eg: Oxymetazolin Hydrochloride nasal drops.

- **Enemas**: Aqueous or oily solution that is introduced into the rectum and colon via the anus for cleansing, therapeutic or diagnostic purposes.
Market available Eye drop, Nasal drop and Enemas
Liquids meant for external administration

Liquid meant for skin

- **Liniments**: Oily liquid preparations, intended for external application with rubbing action to the affected area. Use to relief pain and stiffness, such as from muscles spasm and arthritis.

- **Lotions**: Topical preparation with a low to medium viscosity. Use to moisturize dry skin. Eg: Calamine Lotion, baby lotion

- **Paints**: Solutions used to sterilize the skin. Eg. Betadine antiseptic paint, Magenta paint
Market available Liniment, Lotion and Paint
Consideration

Formulation Consideration

- Solubility
- Stability
- Preservatives
- Pharmaceutical elegance
  - Viscosity modifiers
  - Sweetening agents
  - Flavouring agents
  - Colouring agents

Manufacturing Consideration

- Raw Materials
- Equipments
- Manufacturing Procedure
Approaches to increase the solubility of the drug

- **pH adjustment**: By addition of buffer to the formulation.
- **Co-solvency**: By addition of water miscible solvent in which drug has good solubility. The solvent known as co-solvent.
- **Micelle solubilization**: At high concentration surfactants are forced into water to form colloidal aggregate known as micelle. Drugs get adsorbed into micelle that increase drug solubility. Micelle form only at critical micelle concentration.
**Complexation**: Drug-complexing agent complexation formed when complexing agent is added to solution. It increase solubility of drug on the basis of Le Chatelier’s principle or “The equilibrium law”.

**Micronization**: 
The process involve size reduction of drug particle 1 to 10microns either by spray drying or fluid energy mill.

**Hydrotrophy**: Drug dissolve in the cluster of hydrotropic agent. Also there is drug- hydrotrophy agent complexation formation to increase drug solubility.
Preservative

Preservatives must have following criteria:
• Effective against broad spectrum of microorganisms.
• Physically, chemically, and microbiologically stable for lifetime of the product.
• Non toxic, non sensitizing, soluble, compatible and with acceptable taste and odour.

Types of Preservatives
• **Acidic**: phenol, benzoic acid, sorbic acid
• **Neutral preservatives**: chlorobutanol, benzyl alcohol
• **Quarternary ammonium compounds**: Benzalkonium chloride
Stability

Chemical Stability

✓ Chemical stability of a formulation is affected by:
  ◆ pH
  ◆ Temperature
  ◆ Ionic Strength
  ◆ Solvent effects
  ◆ Light
  ◆ Oxygen

✓ Instability can be prevented by use of:
  o Buffering agents
  o Antioxidants
  o Proper packaging (eg: use of amber bottle for light sensitive products)

Physical Stability

✓ A stable formulation retains its **viscosity, color, clarity, taste, and odour** throughout its shelf life

**Objective evaluation**

✓ Colour can be measured spectrophotometrically.
✓ Clarity can be determined by measurement of its turbidity or light scattering equipment.
✓ Viscosity can be measured by use of viscometers.

**Subjective evaluation**

✓ Taste and odour can be determined either by pharmaceutical investigator or by a panel of unbiased, taste sensitive individuals.
Pharmaceutical Elegance

Viscosity modifiers
- Enhance viscosity. Eg: Povidone, hydroxyethylcellulose

Sweetening agents
- To enhance palatability and mask the taste of the drugs. Eg: Sucrose, saccharin, aspartame

Flavouring agents

<table>
<thead>
<tr>
<th>Taste Sensation</th>
<th>Recommended flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt</td>
<td>Butter scotch, maple, apricot, peach, vanilla,</td>
</tr>
<tr>
<td>Bitter</td>
<td>Wild cherry, walnut, chocolate, mint.</td>
</tr>
<tr>
<td>Sweet</td>
<td>Fruit and berry, vanilla.</td>
</tr>
<tr>
<td>Sour</td>
<td>Citrus flavours, liquorice, raspberry.</td>
</tr>
</tbody>
</table>

Colouring agents
- To enhance the appearance of the vehicle; which matches well with the flavor employed in the preparation. Eg: green with mint, brown with chocolate flavor etc.
Manufacturing Consideration

**Raw Materials**: Incoming raw materials should be tested as per specifications that is identity, purity, uniformity and microbial contamination.

**Equipments**: The following types of equipments may be used in the manufacture of liquid formulations:
1. Mixing tanks (SS 316 Stainless Steel) equipped with an agitator.
2. Measuring devices for large and small amount of solids and liquids.
3. A filtration system e.g. filter press

**Cleaning of equipments**
✓ All equipments must be thoroughly cleaned and sanitized before use.
✓ Disinfectants used: Dilute solutions of $\text{H}_2\text{O}_2$, phenol derivatives.
✓ Sterilized by: Alcohol, boiling water, autoclaving, steam or dry heat.
Manufacturing of Monophasic Liquid

**Process flow**
- Addition of Raw materials (Active + excipients as per formula)
- Mixing: Jacketted vessel with variable speed mixer
- Filtration: Filter Press or Cartridge Filter
- Filling: Automatic Filling Machine

**Control Variables**
- Mixing time
- RPM
- Temperature
- Final Volume
- Pore size
- Filter integrity
- Filling Machine Speed

**Measured response**
- Clarity
- Viscosity
- Assay
- Clarity
- Volume
Filling / Packaging

Gravimetric
- Containers are filled with liquids to a given weight.
- Usually limited to large container filling or highly viscous products.
- Cannot be used in high speed, automatic equipments.

Volumetric
- Containers are filled with liquid to a given volume.
- Fill amount is measured by the stroke of the piston and cylinder assembly.
- Problems may arise when containers used are not dimensionally uniform.

Constant level
- Fill amount is verified by adjusting the height to which the container is to be filled.
- Variations in container dimension may result in variations in the net fill per unit.

Techniques of filling

Vacuum filling
Vacuum developed within the container causes liquid to flow from tank to container.

Gravity Vacuum filling
Bulk liquid tank is placed above filling stem so that liquid flows to the container due to force of gravity.

Pressure Vacuum filling
Pressure applied to bulk liquid tank and vacuum developed in the container results in pressure difference so that liquid flows to the container.
Recent Advance in Monophasic Liquid

• Recently developed method for the enhancement of solubility of drugs.
  – Nanocrystal
  – Nanomorph
  – Sonocrystallization
  – Supercritical Fluid Process

• Recent advances for the delivery of liquid dosage form
  – Novel Parenteral drug delivery
  – Novel ophthalmic drug delivery
Thank You...!!!!