LIQUID DOSAGE FORMS

Prof. S. B. Jadhav

K. K. Wagh College of Pharmacy, Nashik

Liquid Dosage Forms

Definition:

Pharmaceutical liquid dosage forms are those preparations that contains a combination of active ingredient or drugs and excipients *(emulsifying, dispersing, solubilizing, stabilizing, suspending, wetting, thickening agent, preservative, sweetening agent, flavoring agent, and coloring agent)* that are dissolved or suspended in appropriate solvents and used as a drug or medication

Liquid Dosage Forms

- It is the simplest type of pharmaceutical preparations for high absorption of medicinal drugs and rapid onset in which two components are enhanced to complete a liquid dosage form, solute (a component that dissolves) and solvents (the medium in which the solute will dissolve).
- *Solutions, Syrups, Suspensions, Elixirs, Emulsions, Linctus, Gargles, Mouthwashes, Lotions, Liniments, Nasal Drops, Eye drops, Throat Paints,*

Liquid Dosage Forms- Advantages

1. Easier to swallow liquid than solids, thus, more satisfactory and suitable for pediatrics and geriatrics
2. Solutions get absorbed easily, thus faster onset of action than solids
3. The drug n solution is uniformly distributed. In case of suspension and emulsion dose variation may occur resulting from phase separation during storage
4. If drug is administered in solution form, gastric irritation is reduced as it immediately gets diluted by the contents present in the gastric area
5. Manufacturing techniques are well established and low cost containers are available

Liquid Dosage Forms- Disadvantages

1. Transportation and storage of liquids is problamatic, as they are bulky. If any container breakage occurs during transportation, the whole formulated product is lost
2. Ingredients in liquids are liable to deteriorate and lose their potency, thus, they have limited stability. This is the reason why liquid dosage forms have shorter shelf- life
3. Liable to microbial contamination, hence, requires preservatives
4. Inconvenient: a) may spill, (b) require careful measuring, (c) special storage or handling requirement and (d) refrigeration and shaking before use

Liquid Dosage Forms- Classification

- Classified into two categories: 1. Monophasic 2. Biphasic

1. **Monophasic: a) Aqueous** :- *Syrups, Elixirs, Drops, Solutions, Tinctures, Aromatic Waters, Linctuses*

   b) Non-aqueous : *Lotions, Liniments, Gargles, Mouth Washes, Eye drps, Ear drops, Nasal drops, Inhalations*

2. Biphasic: a) Emulsions : *Oral, external, Parenteral, Opthalmic*

b) Suspensions: *Oral, external, Parenteral, Opthalmic*

Excipients Used in Formulation of Liquid Dosage Forms

- A number of substances are employed as additives in the formulation of dosage forms
- The primary function of these additives is to provide bulk to the preparation

Ideal Properties:

- Physiologically Inert
- Physiologically Stable
- Should not impart any undesirable taste, color and odour
- Non-toxic, non irritant and non- sensitizing
- Effective in low concentration
- Free from micro-organism
- Should not interfere with bioavailability of drug
- Accepted by regulatory authorities

Excipients Used in Formulation of Liquid Dosage Forms

- Excipients used in LDFs:

1. Vehicles
2. Surfactants
3. Hydrocolloids
4. Antioxidants
5. Complexing Agents
6. Preservatives
7. Coloring agents
8. Flavouring agents
9. Sweetening agents
10. Buffers

Excipients Used in Formulation of Liquid Dosage Forms

1. **Vehicles:** they are extensively required in preparations

- They can be divided into two categories: 1. Aqueous Liquids & 2. Non Aqueous vehicles

1. Aqueous Liquids : generally employed as diluents, solvents and includes:

a. Water: most commonly used vehicle

- Naturally occurring water contains may dissolved impurities. The quality of water used in pharmaceutical prepartions is very important.
- The water suitable for drinking purposes is known as potable water.

b. Distilled water: Obtained by distillation of potable water. It has now been replaced by purified water in all references of IP, BP, BPC & USP

Excipients Used in Formulation of Liquid Dosage Forms

c. Purified water: Obtained by distillation, ion exchange treatment, reverse osmosis or any other suitable process from potable water and contains no added substances.

- It is colorless, clear liquid without odour and taste having pH of 4.5 to 7.0
- It is not suitable for preparation of injections (water for injection is used)

d. Water for injection: it complies with all tests specified for purified water and additional tests for sterility and pyrogens

- 'Carbon dioxide free WFI ' is prepared by boiling the distillate for 10 minutes, cooling and transferring to final container and sterilization by autoclaving
- It is used in preparation intended for parentral administration or other sterile products

Excipients Used in Formulation of Liquid Dosage Forms

Advantages of using water as vehicle:

- Can be utilized as solvent
- Tasteless, chemically inert, no pharmacological activity
- Free of irritating substances

- It remains the most favorable vehicle in the preparation of pharmaceutical formulations. It is only when water cannot be used due to its failure to dissolve drugs or due to hydrolysis, instability or microbial growth in presence of water, that other vehicles are used

2. Aromatic Waters:

- Pleasant and flavoured vehicle
- Known to exhibit mild carminative property
- Besides being used as aromatic water, orange flower waterNF and peppermint water NF are also used as flavouring vehicles.

Excipients Used in Formulation of Liquid Dosage Forms

3. Syrups:

- Acacia, Cherry, coca, aromatic eriodictyon and simple syrups are frequently used as vehicles
- The less commonly used are citric acid, glycyrrhiza, etc.
- Can be used as vehicles, solvents, sweetening and flavoring agents

Excipients Used in Formulation of Liquid Dosage Forms

Non Aqueous Vehicles:

- As name suggest are free from water content and includes:

a. Oils or Oily materials: obtained from vegetable, animal or mineral source. Eg. Corn oil, cottonseed oil, castor oil, etc
   - Some vegetable oils can caused allergic reactions
   - Mineral oils like liquid paraffin of various grades have replaced vegetable oils

b. Hyroxylated compounds: comprising of compounds with one or more OH groups or their combination with other vehicles can be used to correct problems associated with solubility and stability of drugs

Alcohols: Ethanol, IPA, Glycerol

Excipients Used in Formulation of Liquid Dosage Forms

Non Aqueous Vehicles:

Alcohols: Dehydrated/Absolute Alcohol:

- Completely free of water and exert wider solvent action
- Frequently used in research and analytical works
- Also used in preparation of synthetic organic materials

Isopropyl Alcohol:

- Properties are same as ethanol
- Generally used as solvent in many cosmetics and skin preparation

Glycerol:

- Trihydric alcohol with unique solvent and preservative property
- Miscible with both water and alcohol
- Can be used as emollient and humectant
- Heated to reduce its viscosity prior to be used as solvent.
- Heating is requires since a highly viscous solvent may have difficulty in dissolving substances in it

Excipients Used in Formulation of Liquid Dosage Forms

Stabilisers:

Salicylic acid and Salicylates:

- Mild antiseptic
- Normally blended with benzoic acid in the preparation of whitfield ointment

Phenol

- In conc. Of 0.5%w/v it is employed as a bactericide in multi dose injectable, oily injectable, garles, and mouth washes
- In ear drop it is used in 6.4% w/w conc.

Excipients Used in Formulation of Liquid Dosage Forms

Stabilisers:

- Substances which confirms the stability of dosage form
- Stability can be attained by:
  - ✓ Selecting suitable buffer solution
  - ✓ Using only selective complexing agent
  - ✓ Using surfactant
  - ✓ Storing preparation at low temperature

Benzoic Acid: Used as a preservative in foodstuffs, drugs and cosmetics in the form of its sodium or potassium salt

- Mostly non toxic, except when consumed in huge amounts
- Added in conc. Of 0.1%w/v

Parahyroxy Benzoate : by – products of benzoic acid

- Esters of this is used widely as preservatives in dosage forms
- Eg. Methyl, ethyl & propyl paraben

Excipients Used in Formulation of Liquid Dosage Forms

Preservatives:

- Used in dosage forms to avoid contamination by microbial growth thus preventing their spoilage
- Microbial contamination in dosage form causes several chemical changes and may even lead to product spoilage.
- Thus, their preservation is necessary.
- Antimicrobail agent in sufficient quantities are added to parentral products packed in multi dose vials.
- Bacteriostatics abr used to inhibit microbial growth in multi dose injection.

Ideal Properties:

- It should be active against a broad range of pathogeic microbes
- The physical, chemical and microbiological stability of the preservative should remain constant for rest of the product's life

Excipients Used in Formulation of Liquid Dosage Forms

Preservatives:

Ideal Properties:

- It should be competant enough even in its small quantity
- It should show compatibility with the other constituents present in the formulation
- It should be stable, efficient and independent of pH
- Should not charecteristic odour, taste, colour and should besoluble in the vehicle used
- The partition coefficient of biphasic systems should favour that of the aqueous phase
- Non- toxic, non-irritant and non- sensitizing

Excipients Used in Formulation of Liquid Dosage Forms

Preservatives:

Mechanism of Action:

Generally involve one or more of the following mechanism to restrict the growth, multiplication and metabolism of micro-organism :

1. By altering membrane permeability
2. By denaturing the enzymes and the other cellular proteins
3. By cellular hydrolysis
4. By oxidising the cellular components

Benzoic Acid:

- Used as sodium or potassium salt
- Cocn : 0.1%w/v

Excipients Used in Formulation of Liquid Dosage Forms

Preservatives:

Parahyroxy Benzoate: *Same as above*

Mercurials:

- In the conc. Range of 0.001-0.1% w/v and 0.002 -0.005% w/v, different mercury containing substances like thiomerosal, phenyl mercuric acetate and nitrate can be used

Quaternary Ammonium Compound:

Benzalkonium chloride (BZK) in the conc. Range of 0.004-0.002%w/v can be used

Excipients Used in Formulation of Liquid Dosage Forms

Suspending Agent:

- Particles present in parentral suspension should be uniform and small in size
- Should not form cake on storage
- Easily re-dispersib;e and injected through an 18-20 gauge hypodermic needle
- All above can attained by controlling the degree of crystallisation , the particle size range and the method of drug sterilisation
- An even drug distribution is needed to guarantee safe and precise dose to the patients
- Suspending agent play an essential role in directing these processes
- These agent are generally used to uniformly disperse the particle present in suspension and prevent cake formation
- Eg. Carmellose sodium, povidone, gelatin, etc.

Excipients Used in Formulation of Liquid Dosage Forms

Suspending Agent:

Type of polymer	Examples
Cellulose Derivative Anionic	CMC (Carboxymethylcellulose) Microcrystalline cellulose blends
Non-Ionic	Methylcellulose (MC), Ehtylcellulose (EC), HEC, HPC, HPMC
Natural Polymers Anoinic	Alginates, carageenan, Xanthan Gum, Acacia, Tragacanth
Non ionic	Locust Bean gum, Guar gum
Synthetic Polymer Anionic	Carbomers
Non-ionic	PVP, PVA, Poloxamer
Clays	Magnesium Aluminum silicate, veegum, bentonite

Excipients Used in Formulation of Liquid Dosage Forms

Emulsifying Agent:

- Require to enhance the kinetic stability of an emulsion, thus improving its stability
- Surfactants or surface active agents ar e one of the most popularly used emulsifiers

Classification

1. **Natural (From Vegetable sources):** Acacia, Tragacanth, agar, pectin, starch
2. **Natural (Animal Sources) :** Gelatin, Egg yolk, Wool fat, Lecithin
3. **Semi Synthetic Polysaccharides:** Methyl Cellulose, Sodium CMC
4. **Synthetic: Anoinic-** Sodium dodecyl sulfate, SLS, **Catioic-** Benzalkonium chloride, **Non-ionic- PEG 400, span**
5. **Inorganic:** Milk of Magnesia, Mg Oxide, mg trisilicate, bentonite
6. **Saponins**
7. **Alcohols:** Cholestrol, Carbowaxes, Lecithins

Excipients Used in Formulation of Liquid Dosage Forms

Emulsifying Agent:

8. **Auxillary Emulsifiers:** used alongwith surfactants

- Comprises of finely divided solids which undergo interface adsorption
- Eg. Colloidal clays like bentonite (aluminum silicate) and veeguam (Mg aluminum silicate)

- **Uses:**
- Forms a condensed film around drplets of the dispersed phase
- Insufficient qty- fails to inhibit coalescence among dispersed phase
- High level- may negatively impact the product stability
- Hence should be used in optimum qty.
- Used as solubiliser, wetting agent, detergent, foaming and defoami9ng agent.

Excipients Used in Formulation of Liquid Dosage Forms

Colouring Agents:

- Coloring agents or colorants imparts an appropriate colour to p'ceutical preparations.
- Genrally used as sensory adjuvants to impart unique flavour to different products, thus, fulfilling the purpose of product identification.

Selection of colours:

Factors to be considered while selecting a colourant:

1. It should be checked for its quality and outer appearance
2. It should be monitored for their physical and chemical properties
3. Solution of the dye should possess a specific pH
4. It should be unaffected by light
5. It should be compliant to a large number of consumers

Excipients Used in Formulation of Liquid Dosage Forms

Classification of colours:

1. **Natural Colorants:** usually derived from mineral, plant and animal sources. These are mostly used for coloring foods, drugs, and cosmetics and are also required for making the p'ceutical preparation psychologically acceptable
   i. **Mineral colours:** known as **pigments**.
      - Used in preparation of **lotions, cosmetics and other topical preparations**
      - Currently their applications are substituted by synthetic ones
      - Eg. **Red & Yellow ferric oxides, titanium dioxide, carbon black, lead chromate prussian blue, etc**
   ii. **Plant colours:** they are obtained by extracting plant materials, chlorophyll, β carotenes, alizarin, indigo, anthocyanins and flavones
   iii. **Animal Colours:**

Excipients Used in Formulation of Liquid Dosage Forms

Classification of colours:

1. **Natural Colorants:**

   iii. **Animal Colours:**

   - Carminic acid (a brght red color) is obtained from cochineal of the insect *Coccus cacti*
   - Tyrian purple –air oxidation of *Murex brandaris* (a glandular secretion of a snail)
   - Due to increase availability of synthetic colours, animal colourant are rarely used.

2. **Synthetic Colours:**

   - Aniline was used to prepare synthetic colors.
   - Irrespective of their toxicity, a number of coal tar dyes were used in foods and beverages
   - The use of only few synthetic colours has been approved by the government of different countries, as most of them are harmful for human body
   - The approved synthetic colours are:

Excipients Used in Formulation of Liquid Dosage Forms

Classification of colours:

2. **Synthetic Colours:**
   - The approved synthetic colours are:
   a. **Natural colors:** Annatto, carotene, chlorophyll, cochineal, curcumin, red oxide of iron, yellow oxide of iron and titanium dioxide
   b. **Artificial colours:** Caramel

Excipients Used in Formulation of Liquid Dosage Forms

Flavours:

- Flavours are mixed sensations of taste, smell, sight and sound, which are required to produce a number of sensory perception for a substance
- In oral liquid dosage form, flavours play a significant role.
- Appropriate flavouring can conceal the obnoxious taste of drug added in liquid.
- Patient compliance for chewable tablets of antacids, antibiotics, vitamins is increased by adding flavourant and sweetners to them.
- The volatile nature of a flavour is an essential features affected by the warm and moist conditions of the mouth
- More volatile is the compound, the more prominent odour it will have

Excipients Used in Formulation of Liquid Dosage Forms

Sweetners

- Added for imparting sweet taste and concealing any obnoxious taste of certain constituents.

Examples:

1. **Sucrose:** it solublizes in water and remains physically and chemically consistent in pH range of 4-8. It is used as a preservative in concentration of 85%w/v sucrose solution
2. **Saccharin:** Generally used as a substituent for sugar. It is 250-500 times sweeter than sugars. But it also have slight bitter taste after its consumption
3. **Aspartame:** it is methyl ester of aspartic acid and phenylalanine. It is very stable dry powder, which is 200 times sweeter than sucrose

Excipients Used in Formulation of Liquid Dosage Forms

Flavours:

Selection of flavour:

1. It should be compatible with color and sweetner
2. Should be made keeping in mind whether it is intended for internal or external use
3. Should be made considering patient age
4. Common likings and dislikings of the user should be considered
5. The flavour used should be of optimum quality and taste

Examples: Pharmaceutical oral liquid preparations are usually flavoured with fruity or spicy flavours like pineapple, banana, ginger, cardamom, peppermint and cinnamon.

Likewise perfume blends of rose, jasmine, lavender, etc, are also used to impart floral smell to the topical preparations

Synthetic : Cinnaldehyde and benzaldehyde, simple ester like methyl salicylates, alcohols, glycerines, aldehydes(vanillin) and complex volatile oils like anise oil

Excipients Used in Formulation of Liquid Dosage Forms

Co-solvents

- These solvents are miscible with water and should be selected such that the drug gets solubilized in it.
- **Co-solvency** involves the utilization of co-solvent to enhance the solubility of weak electrolytes and non-polar molecules exhibiting low water solubility
- Eg. Etahnol, Sorbitol, glucerine, propylene glycol, etc

Buffers

These agents are dissolved in a solvent to stabilise the pH of a solution and to resist any pH changes.

Eg: Carbonates, citrates, phosphates, lactates and tartarates

Excipients Used in Formulation of Liquid Dosage Forms

Buffers

Ideal Properties of buffer:

- It should have a desired capacity in the desired pH range
- It should not affect or harm the stability of the final product
- It should be safe enough for biological applications
- It should not effect the flavours and coloring of the product
- It should show compatibility with the existing constituents of the solution
- It should be non toxic

Excipients Used in Formulation of Liquid Dosage Forms

Viscosity Enhancers:

- These are added to increase the viscosity of a liquid and thus:

a. Increase the solution pourability, &

b. Aid in making the product palatable

- Eg. **Natural Gums:** Acacia, Xanthan gum

  Cellulose derivatives: Sodium carboxy methyl cellulose, HPMC

Excipients Used in Formulation of Liquid Dosage Forms

Surfactants:

- Used to reduce the surface tension of a liquid or the interfacial tension existing between the two liquids
- These agents usually get adsorbed at the interface existing between the two phases.

Classification :

They are classified on the basis of their ionic behavior in solutions into four types:

1. **Anionic Surfactants:** they are known to ionize the liquid media

- Its surface activity is due to its anionic part
- Comprises of carboxylates, sulphonates and sulphate ions, termed as **soaps** and their preparation invovles saponification of natural fatty acid glycerides in alkaline solution

    i. Sulphates

        a) **Alkyl Sulphates:** Ammonium lauryl sulphate & sodium lauryl sulphate

        b) **Alkyl Ether Sulphates:** Sodium laureth sulphate (Sodium Lauryl Ether sulphates (SLES) & sodium myreth sulphate

Excipients Used in Formulation of Liquid Dosage Forms

Surfactants:

i. **Sulphates**
   a) **Alkyl Sulphates:** Ammonium lauryl sulphate & sodium lauryl sulphate
   b) **Alkyl Ether Sulphates:** Sodium laureth sulphate (Sodium Lauryl Ether sulphates (SLES) & sodium myreth sulphate

ii. **Sulfonates**
   a) **Docusates:** Dioctyl Sodium sulfosuccinate
   b) **Alkyl benzene sulfonates**
   c) **Sulfonate Fluorosurfactant:** perfluorooctanesulfonate (PFOS)

iii. **Carboxylates:**
   a) **Alkyl Carboxylates:** Fatty acid salts (SOAPS): sodium sterate
   b) **Sodium Lauroyl sarcosinate**
   c) **Carboxylate Fluorosurfactants:** Perfluorononanoate (PFOA)

Excipients Used in Formulation of Liquid Dosage Forms

Surfactants:

2. **Cationic Surfactants:**

- Frequently used
- They are quaternary ammonium compounds with antimicrobial properties.
- They exhibit bacteriostaticaction as they bind with carboxl groupo