Oral Liquids

By

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Introduction

- Oral Liquids are homogeneous liquid preparations, usually consisting of a solution, an emulsion or a suspension of one or more medicaments in a suitable vehicle.
- Liquid preparations for oral use are either supplied in the finished form or, with the exception of Oral emulsions, may also be prepared just before issue for use by dissolving or dispersing granules or powder in the vehicle stated on the label.

Classification of Liquid Orals

- Liquid dosage forms are broadly classified into two groups:

a) Monophasic liquid dosage forms

b) Biphasic liquid dosage forms

- Monophasic liquids dosage forms are one which contains only one phase i.e. mixtures, elixirs, syrups, linctuses, draughts and drops etc.
- Biphasic liquids dosage forms contains two phases i.e. suspensions and emulsions.

Advantages of Liquid Dosage Forms

- They are the most suitable dosage form for infants, children and geriatric patients.
- The unpleasant taste of the drugs can be masked by adding sweetening and flavoring agents.
- It is attractive in appearance and gives beneficial psychological effects.
- The drug is rapidly available for absorption.

Disadvantages of Liquid Dosage Forms

- The liquid dosage forms have less stability when compared to solid dosage forms.
- Liquids are bulky and therefore inconvenient to transport and store
- Accidental breakage of the container results in loss of whole dosage form.

Formulation consideration

The common excipients used in liquid formulation are

- Vehicles
- Solubilizers
- Preservatives
- Stabilizers
- Organoleptic agents

Vehicles

- **Solvents:**
- In liquid pharmaceutical formulations, vehicles are major components used as a base in which drugs and other excipients are dissolved or dispersed.
- They function by breaking of bond and reducing effective charge on ions thus increasing solute-solvent forces of attraction which are eventually greater than solute-solute and solvent-solvent forces of attraction.
- Eg; water, hydro-alcoholic liquid systems, polyhydric alcohols, acetic acid, ethyl acetate and buffers.
- **Co-solvent:**
- They are defined as water- miscible organic solvents that are used in liquid drug formulations to increase the solubility of poorly water soluble substances or to enhance the chemical stability of a drug.
- An ideal co-solvent should possess values of dielectric constant between 25 and 80. The most widely used system that will cover this range is a water/ethanol blend.
- It should not cause toxicity or irritancy when administrated for oral or parental use.
- Other co-solvents are sorbitol, glycerol, propylene glycol and syrup.

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- **Water:**

- For the preparation in pharmaceutical formulation IP refers water as clear, odorless, colorless and neutral with slight deviation in pH due to dissolved solids and gases.
- Purified water IP is commonly used as vehicle or as a component of vehicle for aqueous liquid formulations but not for those intended for parenteral administration.
- Ethanol, frequently referred as alcohol is the most commonly used solvent in liquid pharmaceutical formulation next to water.
- Diluted ethanol is prepared by mixing equal volumes of ethanol IP and purified water IP is a most useful solvent in various pharmaceutical processes and formulations to dissolve poorly soluble substances

Solubilizers

- To increase the solubility of the drug.
- **pH adjustment :**
- By addition of buffer to the formulation.
- Buffers act by binding hydrogen formulations to control potential changes in the pH.
- Buffers act by binding hydrogen ions in acids and donating hydrogen ions in bases.
- The selection of as suitable buffer should be based on suitability of acid-base form for use in oral liquids, stability of the drug and excipients in the buffer, and compatibility between the buffer and container.
- The stabilizing effect of buffers determines the potential reaction between excipients and drug.
- For example, buffers containing carbonate, citrate, tartarate and phosphate salts may precipitate with calcium ions by forming sparingly soluble salts.

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- **Co-solvency:** By addition of water miscible solvent in which drug has good solubility. The solvent known as co-solvent.
- **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". Eg disodium EDTA, dihydroxy ethyl glycine, citric acid.
- **Micronization:** The processes 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.
- **Wetting agents and surfactants:**
  - In pharmaceutical formulations wetting agents are routinely used, they air adsorbed at solid particles surfaces keep them away from vehicles which ultimately promotes penetration of the vehicle into pores and capillaries of the particles.
  - For non-aqueous based formulations mineral oils are commonly we use as wetting agents because hydrophobic drug particles are difficult to wet even after the removal of adsorbed air.
  - Surface active agents that work as wetting agents, comprises of branched hydrophobic chains with central hydrophilic groups or short hydrophobic chains with hydrophilic end groups.
  - For example- Sodium lauryl sulphate is one of the most commonly used surface-active agents as a wetting agent. When dissolved in water, it lowers the contact angle of water and support in spreading of water on the particles surface to remove the air layer at the surface and replace it with the liquid phase.

Preservatives

- Microbial contamination is major problem encountered by aqueous based liquid dosage forms.
- Use of preservatives becomes unavoidable in such cases to prevent the growth of microorganisms during production and over storage time.
- 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

Stabilizers

- Oxidation, photolysis, solvolysis and dehydration are common transformations taking place in liquid dosage forms.
- Amongst them for oxidation and photodecomposition of drug are very common pathways of drug decomposition and are very difficult to control due to low activation energies.
- Trace amounts of impurities, which are invariably present in the drug or excipient intitates the oxidation reaction.
- **Physical stability:**
  - A stable formulation retains its viscosity, color, calarity, taste and odour throughout its shelf life.
  - Color 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.
  - Taste and odour can be determined either by pharmaceutical investigator or by a panel of unbiased, taste sensitive individuals.

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- **Chemical stability** of the formulation is affected by pH, temperature, Ionic Strength, Solvent effects, Light, Oxygen.
- Instability can be prevented by use of: Buffering agents, Antioxidants, Proper packaging (eg: use of amber bottle for light sensitive products).
- **Antioxidants** act as chain terminators where it reacts with free radicals in solution to stop the free-radical propagation cycle.
- A combination of chelating agents with antioxidants is often used to exert synergistic effect.
- Oxidation of formulation component leads to products with an unpleasant odor taste appearance, ppt, discoloration or even a slight loss of activity. Some substances prone to oxidation include unsaturated oils/fats, compounds with aldehyde or phenolic groups, colors, flavors, sweeteners, plastics and rubbers, the latter being used in containers for products. Eg: acetone sodium bisulfite, acetylcysteine, ascorbic acid, thiourea.
- Emulsifying agents which prevent coalescence of the dispersed globules. Forms barriers at interface, and reduce interfacial tension Eg sodium lauryl sulphat, cetrimide, macrogols.

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- **Antifoaming agents:**

- The formation of foams during manufacturing processes or when reconstituting the liquid dosage forms can be undesirable and disruptive.
- Antifoaming agents are effective at discouraging the formation of stable foams of stable foams by lowering surface tension and cohesive binding of the liquid phase. Eg: Simethicone, organic phosphates, alcohols, paraffin oils etc.

- **Suspending and Viscosity Enhancing Agents:**

- The selection of an appropriate suspending agent is one of the most crucial factors in formulating a pharmaceutical suspension.
- Suspending agents impart viscosity and thus regard particle settling.
- Other factors considered in the selection of the appropriate suspending and viscosity enhancing agent include desired reheological property supendability in the system, chemical compatibility with other excipients, pH stability, hydration time, reproducibility, and the cost.
- Eg: clays, natural gums, synthetic gums In many formulations these excipients are employed in combination for enhanced effects.

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- **Humectants:** are hygroscopic substances that help to retard evaporation of aqueous vehicles from dosage forms.
- These excipients are used at 5% strength in aqueous suspension and emulsion for external application.
- They are also used to prevent drying of the product after application to the skin as well as prevent drying of product from the container upon opening.
- It also helps to prevent cap-locking caused by condensation onto neck of container-closure at first opening Eg propylene glycol, glycerol, polyethylene glycol.
- **Flocculating agents:** prevent caking. Addition of an electrolyte reduces the magnitude of zeta potential of dispensed particles Eg: Starch, sodium alginate.
- **Chelating agents:** are substances that form complexes with metal ion in activating their catalytic activity in oxidation of medicaments.
- These agents are capable of forming complexes with the drug involving more than one bond it's a complex compound contains one or more ring in its structure. Protect drug from catalysts that accelerate the oxidative reaction. Eg Disoium EDTA, dihydroxy ethyl glycine, citric acid and tartaric acid.

Organoleptic properties

- **Flavouring agents:** are agent in liquid pharmaceutical products is added to the solvent or vehicle component of the formulation in which it is most soluble or miscible. That is water soluble flavors are added to the aqueous component of a formulation and poorly water soluble flavors are added to the alcoholic or other non-aqueous solvent component of the formulation.
- **Sweetening agents:** Sucrose enhances viscosity of liquids and also gives a pleasant texture in the mouth. The term sugar free solution include sweetening agents such as sorbitol, mannitol, saccharin and aspartame as alternative to sugar such as sucrose, fructose.
- **Coloring agent:** A distinction should be made between agents that have inherent color and those that are employed as colorants. Colors used in liquid dosage form must be certified by FDA as per D&C Act 1940. Certain agents- sulphur (yellow), riboflavin (yellow), cupric sulfate (blue), ferrous sulfate (bluish green) cyanocobalamin (red) and red mercuric iodide (vivid red) have inherent color and not thought of as pharmaceutical colorants in the usual sense of the term.

Although most pharmaceutical colorants in use today are synthetic, a few are obtained from natural mineral and plant sources. For example, red ferric oxide is mixed in small proportions with zinc oxide powder to give calamine its characteristic pink color, which is intended to match the skin tone upon application.