CHAPTER 13

LIQUID ORAL PREPARATIONS

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Abstract

Liquid oral preparations are versatile dosage forms offering advantages in drug administration, especially for patients with swallowing difficulties. This section covers various types of liquid oral formulations, including solutions, suspensions, emulsions, and syrups. The principles of solubility and factors affecting drug dissolution in liquid media are explored. Formulation considerations, such as pH adjustment, use of co-solvents, and addition of preservatives, are discussed to ensure stability and palatability. The preparation methods for different types of liquid oral formulations are outlined, including techniques for achieving uniform dispersion in suspensions and emulsions. Challenges in liquid formulation, such as taste masking and ensuring dose uniformity, are addressed along with potential solutions. The role of excipients, including sweeteners, flavoring agents, and viscosity modifiers, in improving patient acceptability is examined. Quality control measures specific to liquid oral preparations, such as rheological properties, particle size analysis for suspensions, and stability testing, are detailed

Keywords: *Solutions, Suspensions, Emulsions, Solubility, Palatability, Dose uniformity*

Learning Objectives

After completion of the chapter, the student should be able to:

- Classify different types of liquid oral preparations and their uses.
- Explain the formulation principles of solutions, suspensions, and emulsions.
- Describe the role of various excipients in liquid oral preparations.
- Discuss the manufacturing processes for different liquid oral dosage forms.
- Outline the quality control tests and stability considerations for liquid orals.
- Analyze the challenges in formulating and preserving liquid oral preparations.
- Evaluate the factors affecting the bioavailability of drugs in liquid oral forms.

In pharmaceutical terms, solutions are liquid preparations that contains one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents.

Classification of solution

(i) According to the route of administration

a) *Oral solutions*—through oral route.
b) *Otic solutions*—instilled in the ears.
c) *Ophthalmic solution*—instilled in the eyes.
d) *Topical solutions*—applied over the skin surface.

(ii) According to composition and uses

a) *Syrup*—aqueous solution containing sugar.
b) *Elixir*—sweetened hydroalcoholic (combination of water and ethanol) solution.
c) *Spirit*—Solution of aromatic materials in alcohol.

d) *Aromatic Water*—Solution of aromatic material in water.
e) *Tincture / Fluid extract*—Solution prepared by extracting active constituents from crude drugs. e.g. Compound cardamom tincture. They may also be solutions of chemical substances dissolved in alcohol or in hydroalcoholic solvent. e.g. Tincture of Iodine.
f) *Injection*—Certain solution prepared to be sterile and pyrogen-free and intended for parenteral administration.

Formulation Consideration

1) **Solubility**
   a) pH
   b) Cosolvency
   c) Solubilization
   d) Complexation
   e) Hydrotrophy
   f) Chemical modification of the drug molecule
2) **Preservation**
   a) Preservatives
   b) Antioxidants
   c) Reducing agents
   d) Synergists
3) **Organoleptic consideration**
   a) Sweetening agents
   b) Flavoring agents
   c) Coloring agents
   d) Viscosity control
   e) Overall appearance
4) **Stability**
   a) Chemical stability
   b) Physical stability

SOLUBILITY

When a solid solute is dissolved in a liquid solvent two types of interactions are evident—one is the intra-molecular force between the solute molecules and the other is the intermolecular force between the solute and solvent molecules. When a solute dissolves, the substance's intra-molecular forces (cohesive force) must be overcome by the force of attraction between the solute and solvent molecules (adhesive force).This involves breaking the solute-solute forces and the solvent-solvent forces to achieve the solute-solvent forces attraction.

Expression of solubility

According to Indian Pharmacopoeia

Descriptive Phrase	Approximate quantities(ml) of solvent by volume for 1 part (1 gm) of solute by weight
Very soluble	less than 1 part
Freely soluble	from 1 to 10 parts
Soluble	from 10 to 30 parts
Sparingly soluble	from 30 to 100 parts
Slightly soluble	from 100 to 1000 parts
Very slightly soluble	from 1000 to 10,000 parts
Practically insoluble	more than 10,000 parts

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.

Determination of Equilibrium Solubility of a Drug

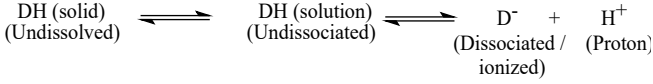
An excess of the drug (finely powdered to minimize the time required to attain the equilibrium) is placed in a vial along with a specific amount of the solvent. The tightly closed vial is then agitated at constant temperatures (preferably at temperature somewhat higher than room temperature e.g. 30^0C so that constant conditions can be maintained regardless of normal laboratory temperature variations), and the amount of drug in solution is determined periodically by assay (by some chemical method) of a filtered sample of the supernate. Equilibrium is not achieved until at least two successive samplings give the same result.

The *solubility* is generally expressed in mg of solute per ml of solvent at 25^0 C or per 100 ml etc.

Solubility of a drug depends on temperature, solvent, pH and the chemical nature of the molecule itself. By modifying these parameters the solubility of a drug can be manipulated according to the requirement of designing the dosage form.

pH

A large number of drugs are either weak acids or weak bases. The solubility of these agents can be markedly influenced by the pH of the environment. When a weakly acidic drug is dissolved in water it can remain in three states, namely undissolved, dissolved and ionized which can be expressed in the following reaction format:



The relationship between equilibrium solubility of a weakly acidic drug and the pH of the environment can be expressed by Henderson-Hasselbach equation:

$$pH = pKa + \log \frac{[D^-]}{[DH]}$$

where pKa = Dissociation constant of the acid

$[D^-]$ = Molar concentration of ionized drug

[DH] = Molar concentration of unionized drug

The same equation can be written in the following forms:

$$pH = pKa + \log \frac{[ionized]}{[unionized]}$$

$$pH = pKa + \log \frac{[base]}{[acid]}$$

where DH = Acid

D^- = Corresponding base of the acid (DH)

Weak Acid	**Weak Base**
DH (solid) $\rightleftharpoons$ DH(solutic	DOH (solid) $\rightleftharpoons$ DOH(solu
Dissolve	Dissolved
Unionis	Unionised
$pH = pKa + \log \frac{[D^-]}{[DH}$	$pH = pKa + \log \frac{[DOH^-}{[D^+]}$
$pH = pKa + \log \frac{[ion}{[unic}$	$pH = pKa + \log \frac{[unionis}{[ionise}$
$pH = pKa + \log \frac{[base}{[acic}$	$pH = pKa + \log \frac{[base]}{[acid]}$
DH = acid	DOH = base
D^- = corresponding base of DH	D^+ = corresponding acid of the base DOH

To maintain the drug in soluble state the solution of a drug must be done in a suitable buffer solution. The buffer must have the following properties:

1. The buffer must have adequate capacity in the desired pH range.
2. The buffer must be biologically safe for the intended use.
3. The buffer (or its pH range) must have minimum

interference on the stability of the final product.

4. The buffer should permit acceptable flavoring and coloring of the product.

e.g. Some commonly used buffer systems are ammonium chloride, diethanol amine, triethanolamine, boric acid, carbonic acid, phosphate buffer, glutamic acid, tartaric acid, citric acid buffer, acetic acid buffer etc.

COSOLVENCY

Weak electrolytes and nonpolar molecules frequently have poor water solubility. These types of solutes are more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as cosolvency; and the solvents that, in combination increases the solubility of the solute are called cosolvents.

To increase the water solubility of a drug another water miscible solvent in which the drug has good solubility is mixed.

Mechanism of action

It has been proposed that a cosolvent system works by reducing the interfacial tension between the predominantly aqueous solutions and the hydrophobic solute.

Examples of commonly used cosolvents

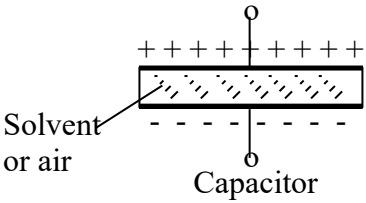
Ethanol, sorbitol, glycerin, propylene glycol and several members of the polyethylene glycol polymer (PEG200) series are the limited number of cosolvents (of water) those are used and are acceptable in oral preparation.

Use of cosolvents

Cosolvents are used to increase the solubility of weak electrolytes, non-polar molecules and volatile constituents used to impart a desirable flavor and odour to the product.

DIELECTRIC CONSTANT

One property of a solvent system is its dielectric constant. The dielectric constant of a solvent can be defined as the ratio of the capacitances of a capacitor filled with the solvent and air respectively.



$$\text{Dielectric constant } (\varepsilon) = \frac{C \text{ solvent}}{C \text{ air}}$$

where, C is the capacitance of the condenser filled with respective medium (solvent or air)
e.g dielectric water is 78.5

Every solute shows a maximum solubility in any given solvent system, at one or more specific dielectric constants.

To determine the relationship between solubility of a solute with dielectric constant(s) at which maximum solubility is attained is noted.

Pharmaceutical formulations of comparable dielectric constant can thus be prepared, and the most appropriate solvent system can be selected on the basis of solubility, stability and organoleptic characteristics requirements.

SOLUBILIZATION

Spontaneous increase of solubility of a poorly water-soluble solute molecules into an aqueous solution of surface active agents (or surfactants) in which a thermodynamically stable solution is formed.