ORAL LIQUID DOSAGE FORMULATIONS: A REVIEW

Humaira Rhim
Faculty of Pharmacy, INSC College of Pharmacy, India
Email: humaira45rahim@gmail.com

ABSTRACT
Oral dosage form as liquids are homogeneous liquid dosage forms, usually consisting of a solution, an emulsion or a suspension of one or more medicaments in a suitable vehicle. Modified-release dosage forms are developed for delivery of drug to maintain the drug concentration for prolonged duration of time. Drugs with short biological half life require multiple daily dosing to achieve the desired pharmacological effect. Frequent administration may lead result in poor patient compliance. Conventional immediate-release liquid dosage forms are administered more than once daily which require definite schedule usually demonstrate sequential peaks and troughs (valleys) associated with each dose. Modified-release liquid dosage forms are designed to release the drug at pre-determined rate for specific period of time in the body to achieve and maintain optimum therapeutic blood levels of drug.

KEYWORDS: Oral liquids, types, formulation, sustained release, suspension

INTRODUCTION
Pharmaceutical Oral Liquids
Oral liquids formulations are homogeneous liquid dosage forms which may be a solution/emulsion/suspension of one or more drug in a suitable vehicle. Oral liquids dosage forms are intended to administered orally with or without dilution [1]. Formerly liquid oral dosage forms were formulated just before issue by dissolving or dispersing drug granules or powder in the suitable vehicle. These vehicles are selected with regard to nature of the active pharmaceutical ingredient(s) as well as to enhance the organoleptic characteristics of the dosage form. Liquid oral dosage forms may contain suitable preservatives, antioxidants and other excipients like stabilizer, suspending, thickening, emulsifying, buffering, wetting, solubilizing, stabilizing,
coloring, flavouring and sweetening agents.

[2]

Classification of Oral Liquid Dosage forms

The oral liquid dosage forms can be classified as –

**Syrups**

Syrups are clear sweetened viscous solution of sucrose in water which contains one or more active pharmaceutical ingredients in this solution. The vehicle usually contains large amounts of sucrose or other sugars to which certain polyhydric alcohols may be added to inhibit crystallization or to modify solubilisation, taste and other vehicle properties. Sugarless syrups may contain sweetening agents and thickening agents. Syrups may contain ethanol (95%) as a preservative or as a solvent to incorporate flavoring agents. Antimicrobial agents may also be added to syrups [3].

**Elixirs**

Elixirs are clear, flavored oral liquids containing one or more active pharmaceutical ingredients (API) dissolved in a vehicle that usually contains a high concentration of sucrose or a suitable polyhydric alcohol [3].

**Linctuses**

Linctuses are viscous oral liquids which contain one or more active pharmaceutical ingredients. Linctuses are prepared by dissolving active pharmaceutical ingredients in a suitable vehicle containing sucrose, sugars derivatives or a suitable polyhydric. They are used to relief of cough, and are administered slowly without the addition of water [4].

**Mixtures**

Mixtures are oral liquids contain one or more active pharmaceutical ingredients. It is prepared by dissolving, suspending or dispersing API in a suitable vehicle. Suspended insoluble solids may settle down slowly on storage but can be easily re-dispersed upon shaking [5].

**Oral Solutions**

Oral solutions are oral liquids which contain one or more active pharmaceutical ingredients and excipients dissolved in a suitable vehicle [6]. Water as aqueous vehicle is the most preferred solvent. Organic solvents may also be used in combination with water or alone[7].

**Oral Suspensions**

Oral suspensions are biphasic liquids dosage forms in which insoluble active pharmaceutical ingredients are suspended in a suitable vehicle. These suspended insoluble solids may settle down slowly on storage to form a cake which can be re-dispersed upon shaking [8].

**Oral Emulsions**

An emulsion is a biphasic dosage form two or more liquids in which one phase is dispersed in another phase. These phases are aqueous
and lipid in nature. Phase separation is a problem associated with emulsion but can be easily rectified on shaking [9].

**Oral Drops**

Oral drops are oral liquids intended to be administered in small volumes for infants or children with the aid of a measuring device e.g. dropper [9].

**Universal Tests for Pharmaceutical Oral Liquid Dosage Forms**

At present 20% of all dosage forms are available as oral liquid dosage forms. Followings are tests which are generally applicable to pharmaceutical oral liquid dosage forms:

**Physical appearance**

This is a qualitative description of the pharmaceutical oral liquid dosage forms such as color, odor, taste etc [20, 21].

**Identification**

Identification test is done to verify the identity of the API used in the pharmaceutical oral liquid dosage forms. This test is done to discriminate between compounds of closely related structure that are likely to be present in the formulation [20, 21].

**Assay**

This test determines the strength or content of the API in the pharmaceutical oral liquid dosage forms and is sometimes called a content test [21].

**Impurities**

This test is used to observe the presence of any component other than API, or an excipient of pharmaceutical oral liquid dosage forms. The most common type of impurities that are measured is related substances, which are process impurities from the new drug substance synthesis, degradation products of the API, or both [10, 11].

**Quality Control Tests for Oral Liquid Dosage Forms**

- Visual Inspection
- pH
- Uniformity of content
- Weight variation
- Uniformity of weight
- Uniformity of mass of delivered doses
- Phase Separation
- Thermal Stress
- Sedimentation Volume
- Droplet Size
- Zeta Potential
- Degree of Flocculation
- Re-dispersibility
- Rheology
- Microbiological test
- Antimicrobial effectiveness testing[13,14]
1.5 Merits of Oral Liquid Dosage Forms

- Faster absorption than solid dosage forms.
- Suitable for patients like infants, geriatric, and mental health problems.
- Ease of dose adjustment.
- Flexibility in achieving the appropriate dose of the drug.
- Dispersion Improved patient compliance specially for children and old patient.
- Sweeteners and flavors can be added to mask the bitter or unpleasant taste as well as obnoxious odor [14].

Suspensions

Suspensions are the biphasic dosage form in which a finely divided insoluble solids are dispersed uniformly in a liquid dispersion medium [25]. Suspensions can be classified as coarse or colloidal, depending on the size of particles. Suspensions with particle size more than ~1 mm are known as coarse suspension, while below 1 mm are known as colloidal suspension.

A pharmaceutical suspension is prepared for following reasons as:

- When drug is insoluble in vehicle.
- When taste of drug is bitter,.
- Drug stability get increases.
- Requires controlled/sustained drug release.

Oral suspensions are highly viscous in nature and contain high concentration of dispersed solid. While parenteral suspensions have low viscosity (less than 5% solids).

Ideally, the dispersed phase should be uniformly dispersed within the continuous phase and should not settle down during storage but practically it is not possible because of the thermodynamic instability of the suspension. Solid particles of the suspension have surface free energy due to which system becomes unstable leading to sedimentation. Thus, in order to minimize the free energy, the system tends to decrease the surface area, which results into formation of agglomerates known as flocculation aggregation. Flocculation of particles depends upon the attractive and repulsive forces within the suspension. Particles of flocculated suspension are loosely attached with each other to form flocules. These aggregates are connected to each other by either by physical adsorption or by vanderwaal forces of attraction. Rate of settling of particles are rapid in a flocculated suspension, but advantage of this is that it can be easily re-dispersed upon gentle agitation thereby ensures stability as well as uniform dosing. In a deflocculated suspension particles remain suspended for a longer duration but when the sedimentation occurs; it leads to formation of
a closely-packed caking which can not redispersed easily by agitation. [16]

Table 1.1: Difference between Flocculated and Deflocculated Suspension [17]

<table>
<thead>
<tr>
<th>S.No</th>
<th>Deflocculated Suspension</th>
<th>Flocculated Suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>It do not consists floccules.</td>
<td>It consists floccules.</td>
</tr>
<tr>
<td>2.</td>
<td>Low rate of sedimentation.</td>
<td>High rate of sedimentation.</td>
</tr>
<tr>
<td>3.</td>
<td>Particles exist as separate entities</td>
<td>Particles form loose aggregates</td>
</tr>
<tr>
<td>4.</td>
<td>Low volume of sediment.</td>
<td>High volume of sediment.</td>
</tr>
<tr>
<td>5.</td>
<td>Form tightly packed hard cake.</td>
<td>Form loosely packed cake.</td>
</tr>
</tbody>
</table>

IMPORTANT CONSIDERATIONS IN FORMULATION OF SUSPENSION

The following are the most important factors to be considered during the formulation of pharmaceutical suspensions:

**Nature of suspended material:** The interfacial properties of the suspended material are an important consideration during the formulation of a suspension. Particles with low interfacial tension can be easily wetted by water, hence can be suspended easily. Particles which are having high interfacial tension cannot easily wet. Surfactants are used to increase the wetting property suspension by reducing their surface tension.

**Size of suspended particles:** Particle size reduction can be achieved by milling, sieving, and grinding. Particle size may affect rate and extent of absorption as well as dissolution.

**Viscosity of the dispersion medium:** It is observed that as the viscosity of dispersion medium increases, sedimentation rate get decreases; while it may affect desirable properties of sysytem such as syringability for parenteral suspensions, spreadability for topical suspensions, ease of administration for oral suspensions[18, 19, 20].

EXCIPIENTS USED FOR THE FORMULATION OF SUSPENSION

Excipients used to enhance the desired characteristics of the suspensions are as described below:

- Suspending agents/ Viscosity modifying agents
- Buffering agents
Surfactants / wetting agents

Antioxidants

Preservatives

Sweeteners

Flavouring agents

Vehicles

Suspending agents / Viscosity modifying agents

Suspending agents are used to improve viscosity to the solution. Suspending agents form micelle around particle to reduce inter particle attraction. Suspending agents used as thickening agents as they increases the viscosity of the solution to prevent sedimentation of the suspended particles as per Stoke’s’s law. The stability of the suspensions depends on the types of suspending agents rather than the physical properties of the drugs [20].

Buffering agents

To improve stability of liquid formulation suspension must have an optimum pH. Most liquid systems are stable at pH range of 4-10. Buffers are used in suspension to control the pH of the formulated dosage form. When buffers are used, they resist any change in pH when an acid or base is added in a system. Generally pH of suspension should be kept between 6-9.5,

Table 1.2 : Stability pH range and concentrations of most commonly used suspending agents/ viscosity modifying agents for suspension [30]

<table>
<thead>
<tr>
<th>S. No</th>
<th>Suspending agents/viscosity modifying agents</th>
<th>Stability pH range</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CMC</td>
<td>7-9</td>
<td>1-2</td>
</tr>
<tr>
<td>2.</td>
<td>Na-CMC</td>
<td>5-10</td>
<td>0.1-5</td>
</tr>
<tr>
<td>3.</td>
<td>Microcrystalline cellulose</td>
<td>1-11</td>
<td>0.6-1.5</td>
</tr>
<tr>
<td>4.</td>
<td>Tragacanth</td>
<td>4-8</td>
<td>1-5</td>
</tr>
<tr>
<td>5.</td>
<td>Xanthan gum</td>
<td>3-12</td>
<td>0.05-0.5</td>
</tr>
<tr>
<td>6.</td>
<td>Sodium alginate</td>
<td>4-10</td>
<td>1-5</td>
</tr>
<tr>
<td>7.</td>
<td>Methylcellulose</td>
<td>3-11</td>
<td>1-2</td>
</tr>
<tr>
<td>8.</td>
<td>Carageenan</td>
<td>6-10</td>
<td>0.5-1</td>
</tr>
<tr>
<td>9.</td>
<td>Hydroxypropylcellulose</td>
<td>6-8</td>
<td>1-2</td>
</tr>
<tr>
<td>10.</td>
<td>Hydroxypropylmethylcellulose</td>
<td>3-11</td>
<td>1-2</td>
</tr>
<tr>
<td>11.</td>
<td>Bentonite</td>
<td>&gt;6</td>
<td>0.5-5</td>
</tr>
<tr>
<td>12.</td>
<td>Hydroxyethylcellulose</td>
<td>2-12</td>
<td>1-2</td>
</tr>
<tr>
<td>13.</td>
<td>Guar gum</td>
<td>4-10.5</td>
<td>1-5</td>
</tr>
<tr>
<td>14.</td>
<td>Colloidal silicon dioxide</td>
<td>0-7.5</td>
<td>2-4</td>
</tr>
</tbody>
</table>
preferably between 7.4-8.4. Common examples of buffer salts used in pharmaceutical solutions are: acetic acid and sodium acetate (1–2%); citric acid and sodium citrate (1–5%); sodium phosphate and disodium phosphate (0.8–2%).

Main applications of buffers in a suspension systems are as:

- Prevent decomposition of API by change in pH.
- Control of tonicity
- Physiological stability is maintained
- Maintain physical stability [21].

**Antioxidants**

Antioxidants are used in suspensions/solution to enhance the stability of API and are susceptible to chemical degradation by oxidation. Typically in aqueous solution antioxidants are get degraded in preference to the therapeutic agent results in protecting API from decomposition. Antioxidants are available as water-soluble as well as water-insoluble antioxidants. Examples of antioxidants used are ascorbic acid, erythorbic acid, sodium ascorbate, thioglycerol, cysteine, acetylcysteine, cysteine etc [23].

**Preservatives**

Preservatives are use in pharmaceutical oral liquid dosage form to control the microbial bio burden of the formulation. preservatives should possess a broad spectrum of antimicrobial activity encompassing Gram-positive and Gram-negative bacteria and fungi. These should be chemically and physically stable over the shelf-life of the product and non-toxic. [24]

**Sweeteners**

Sweetening agents are used to impart sweetness in liquid formulations as well as to increase the palatability of the therapeutic agent. Examples are sucrose, liquid glucose, glycerol, sorbitol, saccharin sodium and aspartame. Artificial sweetening agents are saccharin sodium, aspartame, cyclamate etc are used alone.

**Flavouring agents**

Flavouring and coloring agents are added to increase patient compliance. The choice of color should be in contrast of flavour used. Sweeteners alone are not capable of complete taste masking of unpleasant drugs therefore, flavouring agents are used in formulation.

**Conclusion:**

Oral liquid dosage form are common oral dosage form which is used to improved patient compliance specially for geriatric and pediatrics patients. Now a days oral liquids are available as nano suspension and nano emulsion has become popular because of ease of administration, improved absorption and bioavailability of the drug.
### Table 1.3: List of preservatives and their optimal concentration [34]

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of preservative</th>
<th>Concentration range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Propyleneglycol</td>
<td>5-10</td>
</tr>
<tr>
<td>2</td>
<td>Disodium edentate</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>Benzalkonium chloride</td>
<td>0.01-0.02</td>
</tr>
<tr>
<td>4</td>
<td>Benzoic acid</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>Butylparaben</td>
<td>0.006-0.5</td>
</tr>
<tr>
<td>6</td>
<td>Cetrimide</td>
<td>0.005</td>
</tr>
<tr>
<td>7</td>
<td>Chlorobutanol</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>Phenyl mercuric acetate</td>
<td>0.001-0.002</td>
</tr>
<tr>
<td>9</td>
<td>Potassium sorbate</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>10</td>
<td>Sodium benzoate</td>
<td>0.02-0.5</td>
</tr>
<tr>
<td>11</td>
<td>Sorbic acid</td>
<td>0.05-0.2</td>
</tr>
<tr>
<td>12</td>
<td>Methyl paraben</td>
<td>0.015-0.2</td>
</tr>
</tbody>
</table>

### Table 1.4: List of sweetening agents [35]

<table>
<thead>
<tr>
<th>S.No</th>
<th>Bulk sweeteners</th>
<th>Artificial sweetening agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sugars: xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose</td>
<td>Sodium cyclamate</td>
</tr>
<tr>
<td>2</td>
<td>Hydrogenated glucose syrup</td>
<td>Na saccharin</td>
</tr>
<tr>
<td>3</td>
<td>Sugar alcohols: sorbitol, xylitol, mannitol, glycerin</td>
<td>Aspartame</td>
</tr>
<tr>
<td>4</td>
<td>Partially hydrolysed starch</td>
<td>Ammonium glycyrrhizinate</td>
</tr>
</tbody>
</table>

### Table 1.5: List of flavouring agents [25]
<table>
<thead>
<tr>
<th>S.No</th>
<th>Flavouring Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cocoa</td>
</tr>
<tr>
<td>2.</td>
<td>Strawberry</td>
</tr>
<tr>
<td>3.</td>
<td>Lemon oil</td>
</tr>
<tr>
<td>4.</td>
<td>Peppermint</td>
</tr>
<tr>
<td>5.</td>
<td>Vanilla</td>
</tr>
<tr>
<td>6.</td>
<td>Orange</td>
</tr>
<tr>
<td>7.</td>
<td>Mixed fruit</td>
</tr>
</tbody>
</table>

REFERENCES


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