LIQUID DOSAGE FORM

SYLLABUS

Definition and account of oral solutions, syrups and elixirs.
Their importance in the Medical field.
Components of the formulations with examples: Solvents, buffers, sweeteners, acidifiers, flavors, and preservatives.
Development of the formula.
Preparation, equipment in industrial scale.

SOLUTION

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) *Optic 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 hydro alcoholic (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:

$$\underset{\text{(Undissolved)}}{DH\ (solid)} \rightleftharpoons \underset{\text{(Undissociated)}}{DH\ (solution)} \rightleftharpoons \underset{\text{(Dissociated / ionized)}}{D^-} + \underset{\text{(Proton)}}{H^+}$$

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

$DH\ (solid) \rightleftharpoons DH(solution) \rightleftharpoons D^- + H^+$.

Dissolved
Unionised

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

$$pH = pKa + \log \frac{[ionised]}{[unionised]}$$

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

DH = acid

D^- = corresponding base of DH

Weak Base

$DOH\ (solid) \rightleftharpoons DOH(solution) \rightleftharpoons D^+ + OH^-$.

Dissolved
Unionised

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

$$pH = pKa + \log \frac{[unionised]}{[ionised]}$$

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

DOH = base

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

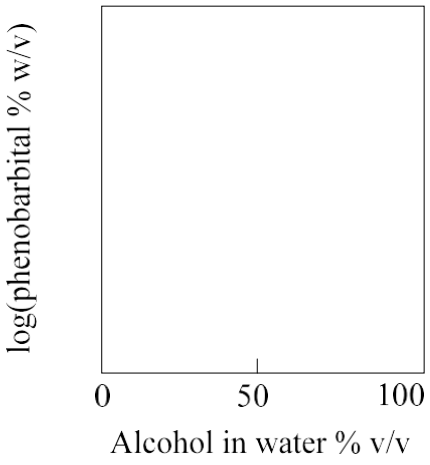
It has been proposed that a cosolvent system works by reducing the interfacial tension between the predominantly aqueous solutions and the hydrophobic solute.

Examples of commonly used cosolvents

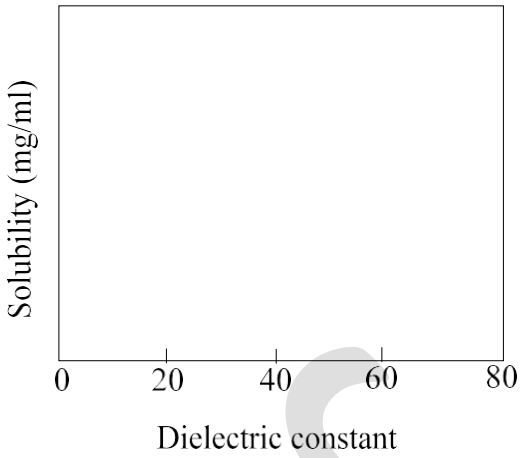
Ethanol, sorbitol, glycerin, propylene glycol and several members of the polyethylene glycol polymer (PEG200) series are the limited number of cosolvents (of water) those are used and are acceptable in oral preparation.

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.



The solubility of phenobarbital in a mixture of alcohol & water



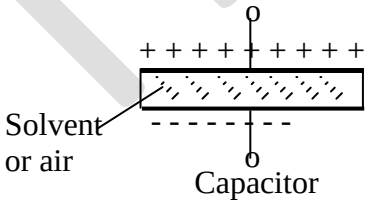
Caffeine in dioxane-water mixtures at solubility (mg/ml) plotted vs. dielectric constant of dioxane-water system.

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.

Mechanism

When surfactants are added to water at low concentrations, they tend to orient at the air-liquid interface.

As additional surfactant is added, the interface becomes fully occupied, and the excess molecules are faced into the bulk of the liquid.

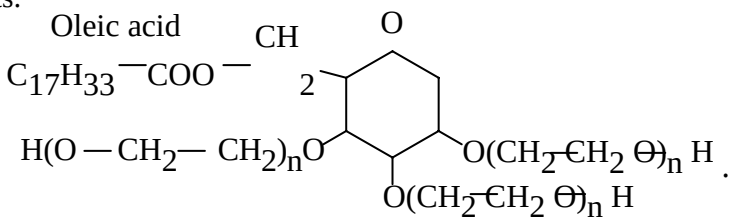
At still higher concentrations, the molecules of surfactant in the bulk of the liquid begin to form oriented aggregates or micelles, this change in orientation occurs abruptly (suddenly).

The concentration of surface active agent at which micelles occurs is called critical micelle concentration .

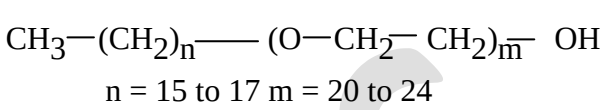
Solubilization is thought to occur by virtue of the solute dissolving in or being adsorbed onto the micelle. The water solubility of the solute increases with the concentration of the micelles.

Examples of some solubilizing agents:

Polyoxyethylene sorbitan fatty acid ester (Tween series)



Polyoxyethylene mono alkyl ether (BRIJ, MYRJ series)



n = 15 to 17 m = 20 to 24

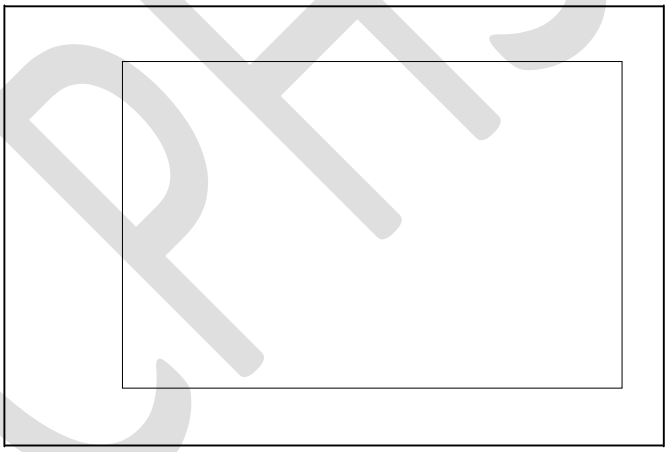
Other examples are Sucrose monoesters, Lanolin esters etc.

It has generally been found that surface-active-agents having HLB (Hydrophilic Lipophilic Balance) values higher than 15 acts better as solubilizing agents.

COMPLEXATION

Solubility of a compound may be increased by complexing with a complexing agent. e.g. solubility of para amino benzoic acid (PABA) may be increased by complexing with caffeine.

When an insoluble compound forms a complex which is more soluble in the solvent - the total solubility is equal to the inherent solubility of the uncomplexed drug plus the concentration of drug-complex in solution.



When a certain amount of drug is mixed in water some amount will get dissolved (A) and some amount will remain undissolved. If a complexing agent is added to it some drug will be complexed and become soluble in water. So the total solubility will be will be increased.

When more complexing agent is added total solubility will increase; at a certain concentration of complexing agent the solution will become saturated with respect to free drug and the complex (B). After this point if still complexing agent is used then remaining drug (undissolved) will form complex and the excess complex will be precipitated (C). When no drug is left for complexation, complexes of higher order may be formed.

e.g. I_2 is sparingly soluble in water. To dissolve it KI (potassium iodide) is added which makes a complex $KI.I_2$ (i.e. KI_3). After point C it forms $KI.2I_2$, $KI.3I_2$ etc.

HYDROTROPHY

The term hydrotrophy has been used to designate the increase in solubility in water of various substances due to the presence of large amounts of additives.

Mechanism of action

Not clear yet. Some workers have speculated that this phenomenon is more closely related to complexation involving a weak interaction between the hydrotrophic agent and the solute.

Another view is that the phenomenon must be due to change in solvent character because of the large amount of additive needed to bring about the increase in solubility.

Examples

Since a large concentration of hydrotrophic agent is required (in the range of 20 to 50%) to produce a modest increase in solubility, hence its pharmaceutical applications are very less in number.

Drug	Hydrotrophic agent
1. Benzoic acid	Sodium benzoate
2. Theophylline	Sodium acetate and sodium glycinate
3. Iodine	Polyvinyl pyrrolidone (PVP)
4. Adrenochrome mono semicarbazone	Sodium salicylate

SOLVENTS FOR ORAL PREPARATIONS

The solvents those are usually used in the oral liquid preparations are purified water, alcohol, glycerin and propylene glycol.

PURIFIED WATER (H_2O)

Naturally occurring water exerts its solvent effect on most substances. In oral preparations the water used is potable water or Purified Water USP.

Specifications of Purified Water USP

Method of preparations : By distillation or by ion-exchange.
Total solid : Less than 10 parts per million (ppm)
pH : Between 5 and 7.

ALCOHOL (ETHANOL)

Next to water, alcohol is the most useful solvent in pharmacy.

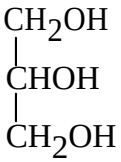
- It is used as a primary solvent for many organic compounds.
- With water it acts as a cosolvent and increases the solubility of drugs. Alcohol is often preferred because of its miscibility with water and its ability to dissolve many water-insoluble ingredients, including drug substances, flavorants, and antimicrobial preservatives.
- Alcohol is frequently used with other solvents, as glycols and glycerin, to reduce the amount of alcohol required.
- It also is used in liquid products as an antimicrobial preservative alone or as a co-preservative with parabens, benzoates, sorbates and other agents.

Disadvantages

It produces pharmacologic and potential toxic effects of alcohol when ingested in pharmaceutical products particularly by children. Hence, it should not be given to children below 6 years. For OTC (over the counter) oral product for children the recommended alcohol-content limit is 0.5 %.

Age of the patient	Permitted alcohol content
For children below 6 years	0.5 %
For children between 6-12 years	5.0 %
Children over 12 years and adults	10.0%

GLYCERIN (Glycerol)

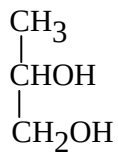


- Glycerin is a clear syrupy liquid with a sweet taste.
- It is miscible both with water an alcohol.
- Glycerin has preservative qualities.

Disadvantages

As a solvent, it is comparable to alcohol, but because of its viscosity, solutes are slowly soluble in it unless it is rendered less viscous by heating.

PROPYLENE GLYCOL



It is a viscous liquid, is miscible with water and alcohol. It is useful solvent with a wide range of application and is frequently substituted for glycerin in pharmaceutical formulation.

BUFFERS

A buffer is a compound or mixture of compounds that, by its presence in solution, resists changes in pH upon addition of small quantities of acid or base.

Buffering agents are necessary to resist the change of pH upon dilution or addition of acid or alkali in the liquid preparation.

The usual buffering agents used in oral liquid preparations are *acetate buffer* and *phosphate buffer*.

Buffer	Mixture of	Buffering Range
Acetate buffer	Glacial acetic acid Potassium, sodium, ammonium salt of acetic acid	pH 2.8 to 6.0
Phosphate buffer	Potassium dihydrogen phosphate Di-sodium hydrogen phosphate	pH 2.0 to 8.0

Buffering is required to:

1. Keeping weakly acidic or basic drug in solution
2. Increase the stability of the drug
3. Resist the change of pH upon dilution or addition of acid or alkali (e.g. leaching or alkali from glass container).

SWEETENERS

Solutions come in immediate contact with the taste buds (on the tongue). Drugs and other adjuvants are generally not good to taste (i.e. not palatable). To enhance palatability and to mask the taste of the drugs etc. sweeteners are used.

Example: Sucrose (sugar), saccharin, aspartame, liquid glucose.

Sucrose

Source Commercially sucrose is obtained from sugarcane, beet root and shorgum.

Advantages

1. It is soluble in aqueous medium.
2. It is available in highly purified form at reasonable price.
3. It is chemically and physically stable in the pH range of 4.0 to 8.0.
4. It is frequently used in conjunction with sorbitol, glycerin and other polyols.
5. Above 66.7 % mold growth will not take place.

Disadvantages

Concentration of sucrose solution above 66.7% (w/w) the sucrose crystallize making the solution hazy (i.e. reducing the gloss of the solution).

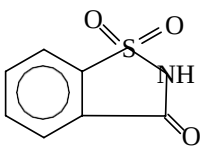
Caps of the containers are generally found to be locked due to this crystallization. Sorbitol, glycerin or other polyols are used to reduce the crystallization.

Liquid Glucose

Liquid glucose is an extremely viscid substance that imparts both body (i.e highly viscous) and sweetness to liquid formulations.

Preparation Partial hydrolysis of starch with strong acid produce liquid glucose. Its main component is dextrose and maltose.

Saccharin (Sodium and Calcium salts are soluble)



Advantages

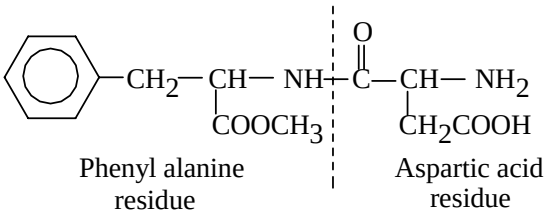
1. Saccharin is used to supplement sugars and polyols as sweeteners.
2. It is approximately 250 to 500 times as sweet as sugar.
3. It has no calorie value, hence can be given to obese patients and diabetic patients.

Disadvantages

It has a bitter after taste.

Aspartame

Aspartame is the methyl ester of aspartic acid and phenylalanine.



Advantages

1. It is approximately 200 times sweeter than sugar.
2. No bitter after taste.
3. Solubility in water is adequate for formulation purpose.

Disadvantage

Although it is very stable as dry powder, its stability in aqueous solutions is pH and temperature dependent. it is stable at pH between 3.4 and 5.0 and at refrigerated temperature.

COLORANTS

To enhance the appeal of the vehicle, a coloring agent is generally used which matches well with the flavour employed in the preparation e.g. green with mint, brown with chocolate flavor etc. The colorant used is generally water soluble, non-reactive with other components, and color-stable at the pH range and under the intensity of light that the liquid preparation is likely to be exposed during its shelf-life.

N.B. From the psychological point of view the scheme may be as follows:

Color Red ⟶ Orange ⟶ Yellow ⟶ Green ⟶ Blue ⟶ Violet

Psychological reactions ⟶ Exciting ⟶ Cheerful ⟶ Tranquilizing ⟶ Subduing ⟶

Desirable properties of a coloring agent

1. Must be harmless, should have no physiological activity
2. It should be a definite compound because then its coloring power will be reliable, its assay practicable.
3. Its tinctorial (coloring) power should be high so that only small quantities are required.
4. It should be unaffected by light, temperature, micro-organisms, pH changes.
5. It should not interfere with other adjuvants.
6. I must be free from objectionable odour and taste.
7. it must by inexpensive.

Example

- Coal tar colors e.g. Amaranth
- The permitted colors do not always give satisfactory shades when used alone but most popular tints and shades can be obtained by blending
  e.g. Green S and Tartrazine Solution B.P.C. contains GreenS (greenish blue) and Tartrazine (Yellow green)

PRESERVATION

Specific organisms generally recognized as undesirable in oral liquids include *Salmonella* species, *Escherichia coli*, *Enterobacter* species, *Pseudomonas* species (commonly *Pseudomonas aeruginosa*), *Clostridium* and *Candida albicans*.

Source of contamination:

Raw materials, processing containers and equipment, the manufacturing environment, operators, packaging materials and the user.

Characteristics of an ideal preservative

1. It must be effective against a broad spectrum of microorganisms.
2. It must be physically, chemically and microbiologically stable for the life-time of the product.
3. It must be nontoxic, non-sensitizing, adequately soluble, compatible with other formulation components, and acceptable with respect to taste and odour at the concentrations used.

Some pharmaceutically useful preservative

Class	Preservative	Usual concentration (%)
Acidic	Phenol	0.2 - 0.5
	Chlorocresol	0.05 - 0.1
	o-Phenyl phenol	0.005 - 0.01
	Alkyl esters of parahydroxy benzoic acid (e.g. Methyl and Propyl Paraben)	0.001 - 0.2
	Benzoic acid and its salts	0.1 - .0.3
	Boric acid and its salts	0.5 - 1.0
	Sorbic acid and its salts	0.05 - 0.2
Neutral	Chlorbutanol	0.5
	Benzyl alcohol	1.0
	β-Phenyl ethyl alcohol	0.2 - 1.0
Mercurial	Thiomersal	0.001 - 0.1
	Phenyl mercuric acetate and nitrate (PMA & PMN)	0.002 - 0.005
	Nitromersol	0.001 - 0.1
Quarternary ammonium compounds	Benzalkonium chloride	0.004 - 0.02
	Cetylpyridinium chloride	0.01 - 0.02

Preservatives	Uses
Acidic	
Phenol	Have characteristic odor and unstable when exposed to oxygen, hence used rarely.
Alkyl esters of parahydroxy benzoic acid (e.g. Methyl and Propyl Paraben)	Mostly used Adequately soluble in water Have both antifungal and antibacterial activity Methyl & Propyl ester at a ratio of 10 to 1 produce a synergistic effect.
Sodium salt of benzoic acid Sodium salt of sorbic acid	Mostly used Have antibacterial action and antifungal action Water soluble
Neutral	
Chlorbutanol Benzyl alcohol β-phenyl ethyl alcohol	The are volatile alcohols, hence, have odor and loss of preservative action on aging. Not used in oral liquid preparations. Used in ophthalmic, nasal and parenteral products.
Mercurials	Not used in oral liquid preparations Used in ophthalmic, nasal and parenteral products. *Disadvantage*: Mercurials readily reduced to free mercury.
Quartenary ammonium compounds	Not used in oral preparations Used in ophthalmic, nasal and parenteral solutions. *Disadvantages*: They are inactivated by variety of anionic substances.

SYRUPS

Syrups containing approximately 85% sucrose resist bacterial growth by virtue of their exosmotic effect on micro-organisms. Syrups that contain less than 85% sucrose, a sufficient concentration of polyol (e.g. sorbitol, glycerin, propylene glycol or polyethylene glycol) should be added to have the required osmotic pressure.

It is possible, however, for surface dilution to take place in a closed container as a result of solvent evaporation followed by condensation, with the condensate flowing back onto the liquid surface. The resulting diluted medium for bacterial and fungal growth. A sufficient concentration of preservative or 5 to 10% ethanol should be added to arrest the growth of microorganisms.

FLAVORS

An objectionable taste may lead to nausea, vomiting and refusal to take the preparation regularly or at all. On the other hand, an attractive flavour will encourage continuation of treatment.

The four basic taste sensations are salty, bitter, sweet and sour. A combination of flavoring agents is usually required to mask these taste sensations effectively.

Flavor selection

Taste sensation	Recommended flavor
Salty	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint.
Bitter	Wild cherry, walnut, chocolate, mint combinations, anise etc.
Sweet	Fruit and berry, vanilla
Sour	Citrus flavors, liquorice, root beer, raspberry

Flavor adjuncts

Menthol, chloroform and various salts frequently are used as flavor adjuncts.
Menthol and chloroform are sometimes referred to as *desensitizing agents*. They impart a flavor and odor of their own to the product and have a mild anaesthetic effect on the sensory receptor organs associated with taste.

MANUFACTURING CONSIDERATION

Raw materials

1. Incoming raw materials should be tested against some *specifications* regarding identity, purity, uniformity and freedom from excessive microbial contamination.
2. *Additional processing* may be required e.g. size-reduction or sterilization before manufacturing. It is usually much easier to begin with low microbial counts in the raw materials than to try to reduce these counts substantially during processing.
3. In oral liquid preparations *water* is the main vehicle. It should meet the USP requirements for **Purified water**. It may be obtained by distillation or ion-exchange treatment. To reduce the microbial burden water is passed through UV-rays and constant circulation in piping systems that have "dead ends" where micro-organisms can thrive.

EQUIPMENTS

The following types of equipments may be used in the manufacture of oral liquid solutions:-

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 for the final polishing - e.g. Sparkler filter.

Cleaning of equipments

All equipments must be thoroughly cleaned and sanitized before use.

Disinfectants used: Dilute solutions of H_2O_2, phenol derivatives and paracetic acid.
Sterilized by: Alcohol, boiling water, autoclaving, steam or dry heat.

Material of construction

- *Tanks* are usually constructed of polished stainless steel and are usually jacketed to allow for heating or cooling of the contents.
- Tanks are covered and equipped with see-through charging ports and illumination for easy observation of the contents. If the tanks are used for compounding of the bulk liquid, they have a built in agitation system.
- The compounded liquid may then be transported to the filling line, either manually by filling into portable transport tanks (fitted with wheels) or by pumping (or gravity flow) through a liquid delivery conduit.
- All the equipments and pipe lines should be easy to disassemble, clean and sanitise.

COMPOUNDING PROCEDURE

Objective Complete solution should usually be confirmed at every stage in the manufacture of a homogeneous liquid.

Formula

1. Active constituent / Drug
2. Vehicle (Water / Alcohol / Glycerol)
   Sweetening agents (viscosity building agents) Syrup, Sorbitol, Glycerol
3. Preservatives
4. Flavors
5. Colors (Dyes)

Steps of preparation

1. Purified water is heated to approximately 50^0C to facilitate the dissolution of the solid solutes. Solid solutes are added to the warm water and stirred to dissolve (e.g. sugar, drug).
2. If any additive is required in small amount then it should be dissolved separately and then mixed with the bulk mixture.
3. Any large volume liquids (e.g. glycerol, sorbitol solution) are added and mixed until homogeneous.
4. Before adding flavors the temperature should be reduced to 30^0C (since most of the flavors are volatile). The flavor should be dissolved in small amount of alcohol (since flavors are generally insoluble in aqueous medium) and then it is mixed with the bulk mixture.
5. Dye should be dissolved n small amount of water. Then transferred to the bulk mixture.
6. Finally volume is made up to the required volume. The total mixture is agitated thoroughly until homogeneity is obtained.
7. Finally the batch is filtered to obtain a polished, clear solution.

ORAL SOLUTIONS

Liquid system where all the solutes remain in dissolved state is known as *solution*. Solutions intended to be taken orally is called *oral solutions*.

Advantages

1. Absorption is instant from the gastro-intestinal tract.
2. Uniform dosage is certain.
3. They provide a safe means of administering substances like potassium iodide that cause gastric pain if taken dry, e.g. as powders or tablets.
4. The attractive appearance of a solution in a well polished bottle has a beneficial psychological effect.

PREFORMULATION

Oral solutions contain

1. Active constituents (Water soluble)
2. Preservative
3. Flavorant
4. Colorant
5. Chemical stabilizers (Antioxidant, reducing agent, synergists)

Dose

Liquid pharmaceuticals for oral administration are usually formulated such that the patient receives the usual dose of the medication in a conveniently administered volume, as 5 ml (one teaspoonful), 10 ml or 15 ml (one table-spoonful).

On the other hand many solutions used in paediatric patients are given by drop, utilizing a calibrated dropper usually furnished by the manufacturer in the product package.

Calculation

The strengths of pharmaceutical preparations are usually expressed in terms of % strength (w/w, w/v, v/v).

Formulation

Some chemical agents may be slowly soluble. In this case rate of dissolution may be enhanced by

1. application of heat: the temperature should not destroy other ingredients.
2. decrease the particle size to increase the specific surface area.
3. by agitation: but dissolution is delayed compared to heat application.

Chemical interaction

Chemical interactions which may occur between the various components of a solution which may result in a alteration in the preparation's stability and / or potency. For example, it has been demonstrated that esters of p-hydroxy benzoic acid (methyl-, ethyl-, propyl- and butyl- parabens) frequently used preservatives in oral preparations, have a tendency to partition into certain flavoring oils.

SYRUPS

- *Syrups* are concentrated, aqueous preparations of a sugar or sugar-substitute with or without added flavoring agents and medicinal substances.
- Syrups containing flavoring agents but not medicinal substances are called *flavored vehicles* (syrups).e..g Cherry Syrup, Cocoa Syrup, Orange syrup, Raspberry Syrup.
- Syrups containing medicinal agents are called *medicated syrups*. e.g. Chlorpheniramine maleate syrup, Ipecac syrup, Chloral hydrate syrup etc.

Components of syrups

Most syrups contain the following components in addition to the purified water and any medicinal agents present:

1. the sugar, usually sucrose, or sugar substitutes used to provide sweetness and viscosity,
2. antimicrobial preservatives,
3. flavorants, and
4. colorants.

Sucrose and non-sucrose based syrup

Sucrose is most frequently employed in syrups. In special circumstances it may be replaced by sugars, such as, *dextrose*, or non-sugars as *sorbitol, glycerin* and *propylene glycol*.

Methyl cellulose or hydroxyethyl cellulose –these two materials are not hydrolyzed and absorbed into the blood stream, and their use results in an excellent syrup-like vehicle.

Taste masking by syrup

The syrup imparts a characteristics "body" (viscosity) and together with the sweetness and the flavorants results in a type of pharmaceutical preparation that is quite effective in making the taste of added medicinal agents. When the syrup is swallowed, only a portion of dissolved drug actually makes contact with the taste buds, the remainder of the drug being carried past them and down the throat in the containment of the viscous syrup.

In the case of antitussive syrups (e.g. linctus) the thick sweet syrup has a soothing effect on the irritated tissues of the throat as it passes over them.

Preservative action of syrup

Simple syrup NF contains 85% w/v sucrose. At this concentration the syrup is resistant to microbial growth, due to unavailability of the water required for the growth of micro-organisms.

85% w/v syrup has a specific gravity of 1.313

i.e. 100 ml syrup contains 85 gm sucrose

Weight of 100 ml syrup = 100 x 1.313 = 131.3 gm

∴ Weight of water present in 100 ml syrup = (131.3 – 85) gm
= 46.3 gm

Volume of water present in 100 ml syrup =46.3 ml

∴ Volume of sucrose present in 100 ml syrup = (100 – 46.3) ml
= 53.7 ml

∴ 100 ml 85% syrup contains

	Weight	Volume
Sugar	85.0 g	53.7 ml
Water	46.3 g	46.3 ml
Syrup (total)	131.3 g	100.0 ml

The solubility of sucrose in water is 1 g in 0.5 ml

∴ to dissolve 85 g sugar required will be = 85 x 0.5 ml
= 42.5 ml

Thus, only a very slight excess of water (46.3 – 42.5 = 3.8 ml per 100 ml of syrup) is employed in the preparation of syrup. The sight excess of water permits the syrup to remain physically stable under conditions of varying temperature.

If the syrup were completely saturated with sucrose, under cool storage conditions some sucrose might crystallize from solution and, by acting as nuclei, initiate a type of chain reaction that would result in the separation of an amount of sucrose disproportionate to its solubility at the storage temperature. The syrup would then be very much unsaturated and probably suitable for microbial growth. However, the syrup NF is stable and resistant to crystallization as well as to microbial growth.

Preparation of Syrups

Syrups are frequently prepared by one of four general methods; depending upon the physical and chemical characteristics of the ingredients.

1. Solution of the ingredients with the aid of heat
2. Solution of the ingredients by agitation without the use of heat
3. Addition of sucrose to a prepared medicated liquid or to a flavored liquid and
4. by percolation of either the source of the medicating substance or of the sucrose.

Solution with the aid of heat

The sugar is generally added to the purified water, and heat is applied until solution is effected. Then other required heat-stable components are added to the hot syrup, the mixture is allowed to cool, and its volume is adjusted to the proper level by the addition of Purified Water.

The use of heat facilitates the rapid solution of the sugar as well as certain other components of syrups. If excessive heating occurs then sucrose may be hydrolyzed into dextrose (D-glucose), and fructose (levulose). This hydrolytic reaction is referred to as *inversion*, and the combination of the two monosaccharides is *invert sugar*. When heat is applied in the preparation of a sucrose syrup, some inversion of the sucrose is almost certain. The speed of inversion is greatly increased by the presence of acids, the hydrogen ion acting as a catalyst to reaction.

Invert sugar is more sweeter than sucrose, and normally colorless. Syrup darkens due to the effect of heat on the fructose. When the syrup is greatly overheated, it becomes amber colored due to the caramelization of the sucrose. Syrups so decomposed are more susceptible to fermentation and microbial growth.

Because of the prospect of decomposition by heat, syrups cannot be sterilized by autoclaving.

Solution by agitation without heat

Sucrose and other formulation agents may be dissolved in purified water by placing the ingredients in a vessel of greater capacity than the volume of syrup to be prepared, thus permitting the thorough agitation of the mixture.

Addition of sucrose to a medicated liquid or to a flavored liquid

Medicated liquid such as tincture or fluid extract is employed as the active ingredient in the preparation of syrup.

If the extract contains alcohol soluble ingredients and the alcohol amount is high then sucrose is added directly and stirred.

If alcohol content is low and all the ingredients are water soluble then the liquid extract is directly mixed with a prepared syrup.

Preparation of syrup by percolation

In this method purified water or an aqueous solutionis passed slowly through a bed of crystalline sucrose, thus dissolving it and forming the syrup. If required a poriton of the percolate is recycled.

Preparation of a multivitamin syrup

Formula: Each 15 ml contains

Active ingredients	Vitamin B1	4.5 mg
	Vitamin B2	2.5 mg
	Vitamin B6	1.5 mg
	Niacinamide	30 mg
	D-Pantothenol	5 mg
Sweeteners	Sorbitol	1 gm
	Glycerin	0.5 gm
	Sugar	7 gm
Preservative	Sodium benzoate	0.016 % (w/v)
	Methyl paraben sodium	0.015 % (w/v)
	Propyl paraben sodium	0.0015%(w/v)
Stabilizer	Disodium edetate	0.008%
Taste enhancer	Citric acid	0.008% (w/v)
	Flavours	q.s.
Colours	Caramel	q.s.
Vehicle	Purified water	15 ml

Procedure

1. Primary Syrup is prepared as usual, filtered and cooled to room temperature. The material is transferred to the mixing tank and stirring is started.
2. Vitamin B1 is dissolved in small volume of water and added to the syrup.
3. Vitamin B2 is slightly soluble in water, hence, it is dissolved with the aid of 10% sodium hydroxide. Vitamin B6 is also added to dissolve. The mixture is transferred to the mixing tank.
4. Niacinamide is dissolved in small amount of water and added to the mixing tank.
5. D-pantothenol is dissolved in hot water, cooled and transferred to the syrup.
6. Sorbitol and glycerin are added.
7. All the preservatives are dissolved in small volume of water and added to the syrup.
8. Citric acid and disodium edetate is dissolved separately in water and then mixed to the syrup.
9. Flavors and color are added and the final volume is made up with water.
10. Mixed for 2 hours and filtered.

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Questions

1. Short note on preservatives in pharmaceutical dosage forms.
2. Short note on syrups.
3. Give the importance of colorants, sweeteners, solvents, stabilizers, flavoring agents in pharmaceutical dosage forms.
4. Discuss the preformulatory and informulatory aspect of designing a multivitamin syrup.
5. What are syrups? Write about the preparation, properties and uses of at least two medicated syrups. Differentiate between solution and elixirs.
6. Classify organoleptic compounds with examples.

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