LIQUID DOSAGE FORMS

Lecture 1

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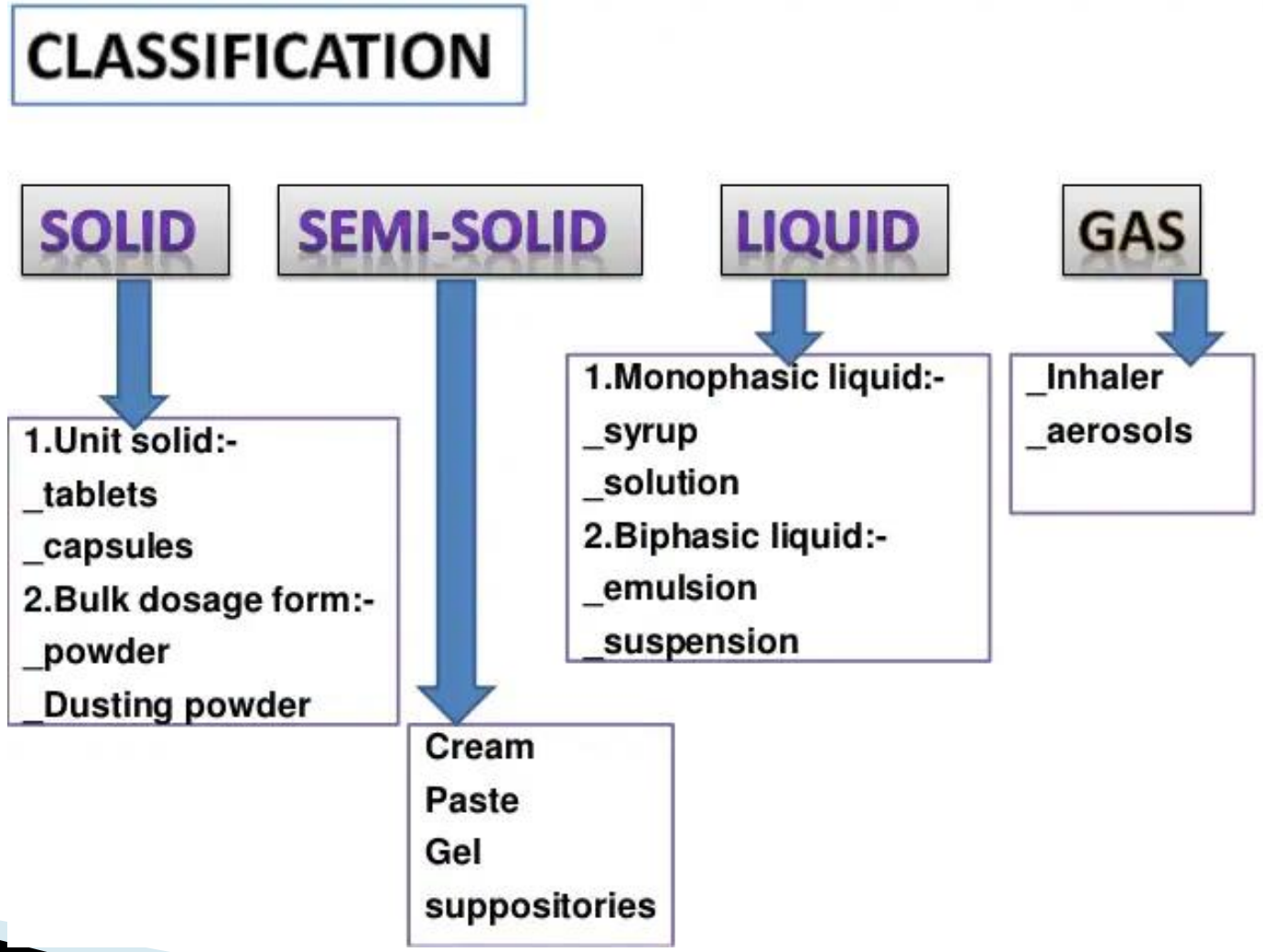
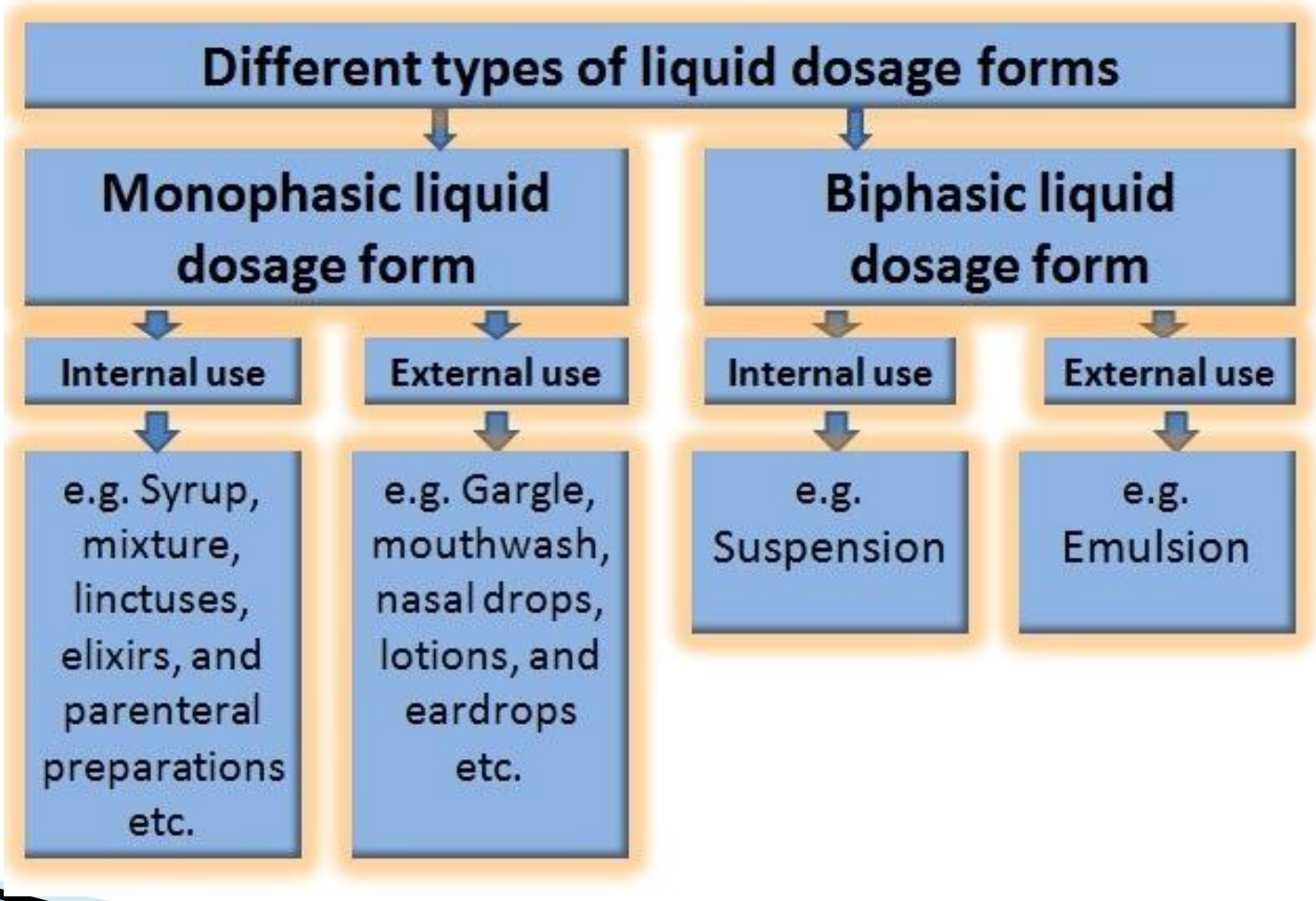
OUTCOMES OF THE LECTURE

- Liquid dosage forms (definition and administration).
- General types of liquid dosage forms
- Oral liquid dosage forms (advantages and disadvantages)
- Different types of oral solutions.
- Formulation of oral solutions
- Types of non-oral dosage forms

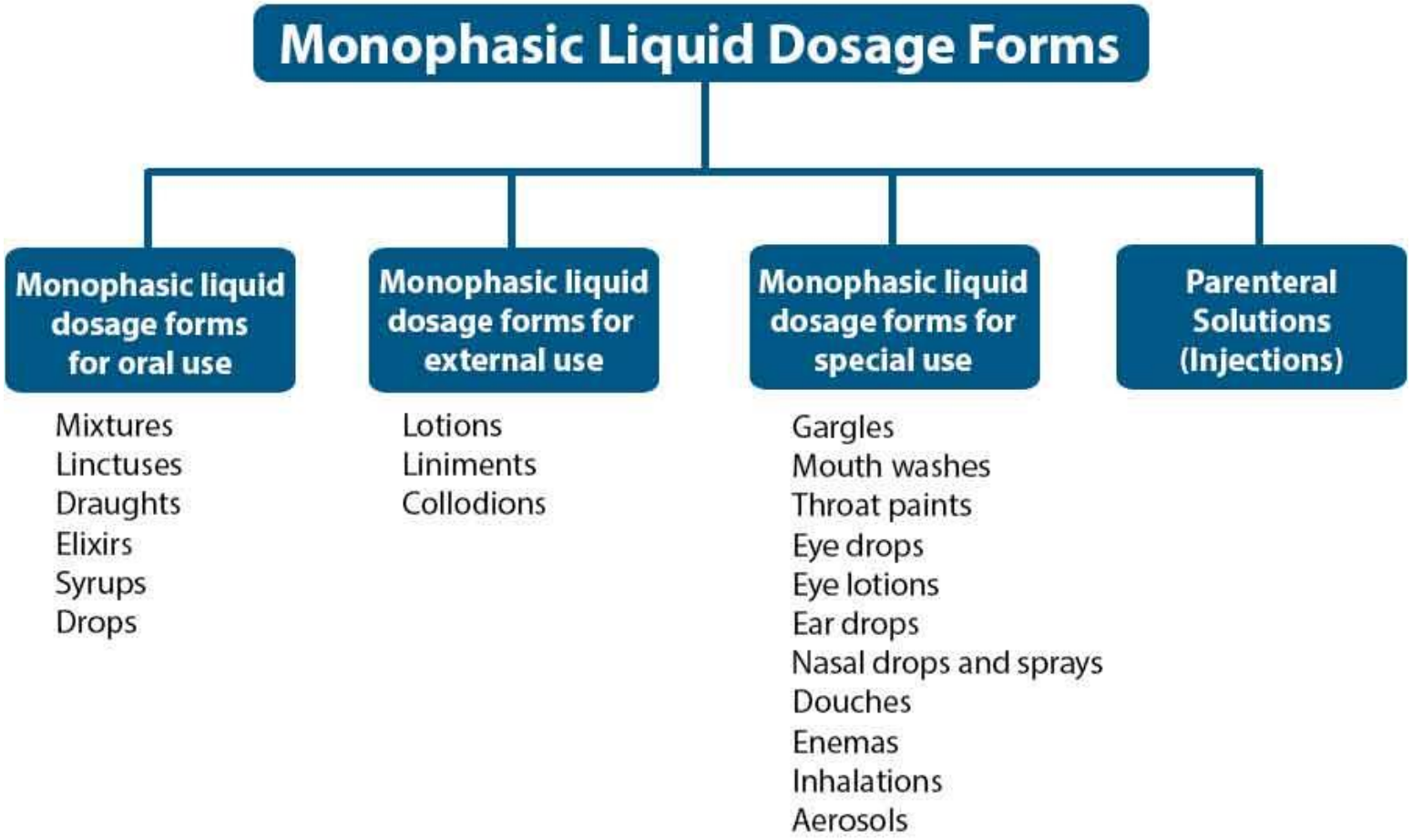
Dosage Forms



Liquid dosage forms (LDFs)



Another classification of monophasic DFs



Liquid dosage forms (LDFs)

- Liquid dosage forms are formulated to release the active principle immediately after oral or non-oral administration to obtain rapid and complete systemic drug absorption or local effect.

- It involves a mixture of active drug components and non-drug components (excipients).

Liquid dosage forms are prepared:

- By dissolving the active drug substance in an aqueous or non-aqueous (e.g. alcohol, ether, glycerin) solvent,
- By suspending the drug in appropriate medium , or
- By incorporating the drug substance into an oil or water phases

Administration of LDF

Liquid dosage forms can be administered:

- Topically – lotions or suspension applied to the skin, nasal drops, ear drops, eye solutions, mouth washes and gargles.
- Orally – oral suspension, emulsion & solution.
- Parenterally like :
  - subcutaneous injection (s.c.),
  - intramuscular injection (i.m.)
  - intravenous administration (i.v.)

General Types of LDFs

INTERNAL

- Syrups
- Suspension
- Emulsions
- Aromatic Water
- Collodions
- Spirit/Essences
- Elixir
- Mixtures
- Tinctures
- Draughts
- Fluid Extracts

EXTERNAL

mouth wash
gargles and throat paint
Nasal Preparation
ear drops
lotions
liniments
sprays
enemas

Oral Liquid Dosage Forms (OLDFs)

Definition:

OLDFs are homogenous preparations containing one or more active ingredients (API) in a suitable vehicle and are intended to be swallowed either undiluted or after dilution.

There are three main types of oral liquids:

- Solutions
- Suspensions
- Emulsions

✓ There are few examples of oral liquids such as a liquid paraffin which comprises a liquid active ingredient (laxative) .

✓ Some solutions or suspensions may be prepared in a powder form and reconstituted immediately before it is used by the patient (Powder for reconstitution).

Advantages of OLDFs

Advantages:

- Liquids are more easily swallowed than tablets or capsules. Therefore, they are more suitable for children and the elderly.
- The drug is more readily available for absorption, compared with solid dosage forms.
- More flexibility in achieving the proper dosage of medication.
- Palatable.
- Gastric irritation caused by certain drugs when administered with solid dosage forms could be reduced with liquid dosage forms.

Disadvantages of OLDFs

- Shorter shelf life than other dosage forms, and need special storage condition.
- The drug may be less stable in aqueous liquid formulations than tablets or capsules. However, this problem can be overcome by using suspension or using non-aqueous vehicles.
- Sometimes, masking the unpleasant taste of a drug is more difficult than when the drug is in a solid dosage form.
- Easily affected by microorganisms
- Liquid preparations tend be bulky and therefore inconvenient to store and transport.
- Easy to loss by the breakage of the container.
- Administration of the correct dose is less precise since it involves the use of 5 ml spoon otherwise, an oral syringe or sometimes a volumetric dropper can be used.

Oral Solutions and solubility issue

- Oral solutions usually contain one or more active ingredients dissolved in a suitable vehicle.
- The aqueous solubility of insoluble or sparingly soluble drugs can be enhanced by the addition of water soluble co-solvents such as ethanol, glycerol or propylene glycol which are suitable for oral administration.
- This technique is called **cosolvency**. **Other techniques** to improve the aqueous solubility of poorly soluble drugs are:

1. Addition of solubilizing agent such non-ionic surfactants (spans and tweens).
2. Salt formation for ionizable drugs by addition of acid or alkali to form salts.
3. By complexation, such as inclusion complexes using cyclodextrins.

Examples of oral solutions:

- Draughts
- Elixirs
- Linctuses
- Mixtures
- Oral drops
- Spirits
- Syrups

Oral solutions

- **Draughts:**

Old oral solutions (and some times suspensions)

intended to be administered as a single dose such as total volume 50 ml.

Ex. Digoxin and Black Draught Senna Laxative and ipecacuhana emetic draughts which are Oral draught preparations

- **Elixirs:**

Elixirs are clear, sweetended and flavored hydro-alcoholic liquids for oral administration. They contain one or more active ingredients dissolved in a vehicle that usually contains a high proportion of sucrose and alcohols (ethanol 5 - 40%) together with water, glycerine , propylene glycol and antimicrobial preservative. Typically, used in preparations of potent and unpalatable drugs. Like **antihistamines** and **antibiotics**

ELIXIRS

- **Elixirs are clear, sweetened hydroalcoholic solutions intended for oral use and are usually flavored to enhance their palatability.**

- **Nonmedicated elixirs are employed as vehicles, and medicated elixirs are used for the therapeutic effect of the medicinal substances they contain.**

- **In addition to alcohol and water, other solvents, such as glycerin and propylene glycol, are frequently employed in elixirs as adjunctive solvents.**

examples of medicated elixirs.

- **Antihistamine Elixirs**
- **Barbiturate Sedative and Hypnotic Elixirs**
- **Digoxin Elixir**

- brompheniramine and phenylephrine
- combination to relieve runny nose, congestion, and cough.

Promethazine is a first-generation antihistamine and antiemetic used to treat allergies, insomnia, and nausea

- **Linctus**
- Linctus is a viscous liquid for oral administration intended for treatment of cough for their demulcent, sedative and expectorant action. They must be sipped and swallowed slowly.
- They usually contain a high proportion of syrups and glycerol.

- Ex.1 **Simple linctus** contains Citric acid monohydrate, Aniseed Flavour, Propylene Glycol, Sodium Benzoate, Glycerol, Sucrose and Purified Water.
- Ex. 2: **Codeine linctus** used for TTT mild cough.

- The dose volume is small (5 ml) and to prolong the action it should be used undiluted

- **Oral Drops:**

Are liquid preparations for oral use. May be solutions or suspensions or emulsions that are intended to be administered in small volumes with the aid of a suitable measuring device.

Ex. The oil soluble vitamins such as vitamin B, A and D concentrations in fish liver oil

- **Official examples of oral solutions in drops:**

- Ammonium and Ipecacuanha oral solution BP
- Choloral mixture BP
- Alkaline Gentian oral solution BP
- Antihistaminic oral drops
- Vitamin B12

Formulation of Oral Liquids

- Oral liquids contain excipients (additives)in order to:
  - carry the active ingredients (**vehicle**),
  - enhance solubility (**solubilizing agents**),
  - maintain chemical and microbial stability such as **antioxidant and preservatives**, respectively.
  - or improve product elegancy (**sweetening and flavoring agents , colorants**).

Additives used in LDFs

Additives (excipients) are used in a liquid dosage forms for several reasons:

- To protect from the microbes.
- To make a stable preparation.
- To Improve the organoleptic properties.
- For Masking the bitter taste.
- To Enlarge the total volume of the preparation.
- For dose uniformity.

Example of additives

a. Vehicle
b. Antimicrobial agents(sodium benzoate, cresol, phenol)
c. Buffering agent (phosphate, glutamate, citrate)
d. Flavoring agent (almond oil, menthol)
e. Coloring agent (carminic acid)
f. Suspending agent (methyl cellulose, alginic acid, bentonite)
g. Emulsifying agent (gum acacia)
h. Stabilizing agent like sodium alginate, sodium carboxymethyl cellulose (CMC)
i. Diluent (starch)

- **Vehicles:**

Include water, aromatic waters , syrups and oils. The selection of the vehicle depends on:

- Intended use of preparation
- Physicochemical properties of the drug.

1- Water

✓ Potable water is mainly derived from surface sources such as lakes, rivers and streams or from underground .

✓ Potable water is palatable and satisfactory microbiologically and chemically.

✓ They may be used in preparations that are not intended to be sterile, provided that the mineral impurities that it contains do not react with medicaments or other ingredients.

Vehicles (Water cont.)

- **Distilled water**

Purified water that has been prepared by distillation.

- **Purified water**

Water prepared from a suitable potable water by distillation, followed by treatment with ion-exchange materials (deionizing resins).

- **Water for preparation**

It is potable freshly boiled and cooled purified water. It is used in preparing oral liquid preparations

2- Aromatic water

- Aromatic waters are saturated aqueous solutions of volatile oils or other aromatic oils that are used as vehicle for oral liquids.
- Some aromatic waters have a mild carminative action but they are used mainly for their flavoring properties.
- **Official examples:**
- Anise water BP (used to treat respiratory infections, nausea, constipation and other digestive issues)
- Camphor water BP(used to manage skin infections due to its antifungal and antibacterial properties).
- Chloroform water BP (is mainly used as antimicrobial preservative.)

3- Syrups:

✓ Syrups are concentrated aqueous solutions of sucrose (60% -80% w/v), other sugars or sweetening agents that are used as vehicles for their flavoring and sweetening properties.

✓ Glycerol, sorbitol , alcohols may be added to retard crystallization of sucrose or to increase the solubility of other ingredients.

✓ Syrup contains preservatives such as benzoic acid, hydroxybenzoate esters or ascorbic acid.

4- Oils

Suitable vegetable oils such as coconut oil, arachis oil have been used as vehicle for fat soluble substances like vitamin D or K or drugs that are unstable in aqueous media.

Flavoring agents (Spirits)

- Spirits are solutions of one or more substances usually of volatile nature (Essences) in ethanol 96% or dilute ethanol in content (62 - 85%).

- Spirits may be used pharmaceutically as flavoring agents and medicinally for the therapeutic value of the aromatic solute.

- Care should be taken when spirits are added to aqueous media as their high ethanolic content may result in precipitations of salts from aqueous media.

Uses of Spirits

A. MEDICINAL SPIRITS

AROMATIC SPIRIT OF AMMONIA

– reflex / respiratory stimulant (by inhalation)

B. FLAVORING SPIRITS

- Compound Orange Spirit

- Compound Cardamom Spirit

Syrups

- **Concentrated solution of sugar (e.g. sucrose) in water.**
- **Types of syrup:**

  1- Simple syrup; when water is used alone.

  2- Medicated syrup; contain drug

  3-Flavored syrup; contain no drug but aromatic or flavored substance

  ■Flavored syrup are accepted by both children and adults, and used as vehicles (e.g., Glycyrrhiza syrup and Raspberry Syrup BP 1988) for masking the salty taste of bromide, iodides, and chlorides and bitterness of preparation containing B- complex vitamins.

- **Glycerin or sorbitol may be added to:**

  1. Prevent crystallization of sucrose.

  2. Increase the solubility of other drugs.

- **Alcohol is included to act as:**

  1- Preservative **2-Solvent for the flavors.**

- **Types of Sugars used in Preparation of Syrups**

Glycogenic substances (materials converted to glucose in the body),

- **Sucrose is the sugar most frequently used in syrup, called nutritive syrup due to the high calories content.**
- **Non- sugar as glycerin, propylene glycol and sorbitol**

Non-glycogenic substances

- **These materials not hydrolyzed into the body and result in an excellent syrup - like vehicle for medication intended for use by diabetic patients**
- **Such as methylcellulose and hydroxymethylcellulose.**
- **Saccharine sodium**
- **Cyclomate sodium**
- **These syrups called non-nutritive syrup.**

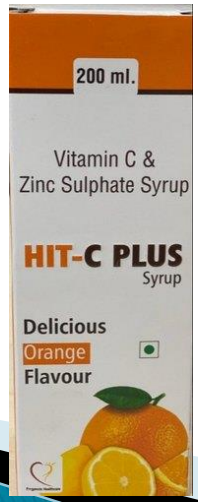
Methods of preparations of syrup

1. Solution with the aid of heat

- The usual method for preparing syrup, used for
    - Volatile substance (flavored substances).
    - Heat stable substances.
    - Rapid preparation of syrup.
- In this method, sucrose is added to the purified water and heat is applied until the solution is effected. Then, add the heat stable components to the hot syrup, the mixture is allowed to cool and its volume is adjusted to the required volume. If heat liable substance (volatile flavoring oils) are required to be added, they are added to the syrup after the solution rapidly cooled to the room temperature.
- Excessive heat must be avoided, because sucrose (disaccharide) may be hydrolyzed into monosaccharide, dextrose (glucose) and fructose (levulose). This hydrolytic reaction known as inversion and the produced sugars known as inverted sugars.

- **Invert sugar properties:**
  - More susceptible for fermentation and microbial growth.
  - Tend to darken in color.
  - Levulose formed is sweeter than sucrose.
  - But, decrease oxidation of other drugs (levulose formed is reducing sugar)

- Overheating cause caramelization of sucrose (amber color)
- Syrups cannot be sterilized by autoclaving without caramelization (amber color).



2. Solution by agitation without the aid of heat

- To avoid heat-induced inversion of sucrose.
- This process is used in those cases where heat would cause loss of valuable volatile constituents.
- The syrup is prepared by adding sucrose to the aqueous solution in a vessel of greater capacity than of syrup to be prepared. This permits active agitation and rapid solution.
- This process is time consuming than that using heat but result in a product has maximum stability.
- When solid agent are to be added to a syrup, it is best to dissolve the solid in a minimum amount of purified water and then incorporated in the syrup.
- When solid substances are added directly to the syrup, they dissolve slowly due to the viscosity of syrup and the limited amount of water available in the syrup.

- This method is used for preparation of
  - Cough syrups e.g., Codeine Phosphate Syrup

    R /

    Codeine phosphate 5 g

    Purified water 15 ml

    Chloroform spirit 25 ml

    Sufficient syrup to make 1000 ml.

- In case of diabetic patients, sorbitol solution can be used in the preparation instead of syrup. It has about half the sweetening power of syrup.

Preservation of syrups

- **Syrup can be preserved by:**
  - **Storage at low temperature not above 25°C.**
  - **Adding a preservative such as glycerin, benzoic acid, sodium benzoate, methyl paraben or alcohol in the formulation.**
  - **Autoclaving is not a suitable method for syrups .**

Syrups

Advantages of Syrups:

- Ability to mask bad taste of some medication.
- Thick character of syrup has soothing effect on irritated tissues of throat.
- Contain little or no alcohol.
- Easy to adjust the dose for a child's weight.

Types of non- oral liquids (Topical LDFs)

- Liquid to be applied to the skin: Liniments and lotions.

- Liquids meant for body cavity: Gargles, throat paints, mouth washes, eye drops, ear drops, nasal drops, sprays and inhalations