MODULE : 2

Lecture 9

DISCLAIMER

All the content material provided here is only for teaching purpose

Syrups

❖Syrups are concentrated, aqueous preparations of a sugar or sugar-substitute with or without added flavoring agents & medicinal substances.

There are 3 types:

1. A simple syrup contains only sucrose and purified water (e.g. Syrup USP). Saturated sugar solution without flavour or medicine.
2. Non-medicated : Syrups containing pleasantly flavored substances are known as flavoring syrups
3. Medicinal syrups: standard formula is a syrup containing medicinal agent.

EXAMPLES OF NONMEDICATED SYRUPS (VEHICLES)

Cocoa syrup

Suspension of cocoa powder in aqueous vehicle sweetened and thickened with sucrose, liquid glucose, glycerin; flavored with vanilla, sodium chloride. Particularly effective in administering bitter-tasting drugs to children

Orange syrup

Sucrose-based syrup uses sweet orange peel tincture, citric acid as the source of flavor and tartness. Resembles orange juice in taste; good vehicle for drugs stable in acidic medium.

Raspberry syrup

Sucrose-based syrup with raspberry juice about 48% by volume. Pleasant-flavored vehicle to disguise salty or sour taste of saline medicaments

Requirements for preparing syrups:

1. In these instances, drug solubility, stability, and bioavailability must be considered.
2. Medicated syrups are commercially prepared by:

Sucrose & purified water (simple syrup is obtained);

the therapeutic agent, of flavoring & coloring agents.

Addition other necessary & desirable ingredient.

Components of syrups:

1. Sugar (sucrose) or sugar-substitutes used to provide sweetness & viscosity.
2. antimicrobial preservatives.
3. Flavoring and colorants agents.
4. Some types of syrups, especially those prepared commercially, contain special solvents.
1. Thickeners, or stabilizers.

Sucrose & Non-Sucrose Based Syrups

Characteristics of simple sucrose syrup:

1. usually 60% to 80% (w/v)
2. Preservation (hypertonic solution)
3. High density & specific gravity (s.g. =1.313)

Specific gravity = $\frac{\text{weight of substance}}{\text{weigh of equal volume water}}$

1.313 = $\frac{w}{100}$, thus, weight of 100 mL syrup is 131.3

131.3g - 85g = 46.3 g or mL of water in the syrup.

Thus, 46.3 g of water are mixed with 85 g of sucrose to give syrup 65.5% w/w or 85%w/v.

Solubility of sucrose in water is 1g /0.5 ml of water, thus, 85 g of sucrose need 42.5 g of water.

Thus, the excess of water in 85% w/v syrup is 3.8 mL.

These 3.8 mL of water are free of sucrose.

This means that syrup is Not saturated .

If the syrup was completely saturated any variation of storage conditions (i.e. cooling) might produce sucrose crystals from the syrup.

Some sucrose might crystallize from solution and by acting as nuclei initiate a type of chain reaction that would result in separation of an amount of sucrose disproportionate to its solubility at the storage temperature.

The syrup would then be very much unsaturated & suitable for microbial growth.

In special circumstances sucrose may be replaced in whole or in part by:

I. Sucrose substances (materials converted to glucose in the body) replaced by Non-sugars (i.e. sorbitol, glycerin propylene glycol ..etc.).

II. nonglycogenetic substances such as methylcellulose (MC) or hydroxyethylcellulose HEC).

Characteristics of MC & HEC:

1. Not hydrolyzed and absorbed into the blood stream,
2. Excellent syrup-like vehicle for medications intended for diabetic patients
3. The viscosity is much like that of a sucrose syrup. more artificial sweeteners.

Antimicrobial Preservatives

The amount of required preservative for protection depends on:

1. Proportion of water available for microbial growth.
2. Nature & inherent preservative activity of some formulative materials (some oils sterile and possess antimicrobial activity);
3. The capability of the preservative itself.

- Some preservatives & correspondent usual concentration:

1.	Benzoic acid or Sodium benzoate	0.1 – 0.2%
2.	Combinations of m. b. parbens	total 0.1%
3.	Alcohol	15 – 20 %
4.	Propylene glycol & Glycerin	1 ml / 1ml.

Methods for Preservation of Syrups

I. Storage at ↓ temperature;

II. Addition of preservatives such as glycerin, parabens; alcohol,..etc.

III. Maintenance of a ↑ concentration of sucrose as a part of the formulation.

Example: Rx

Active drug	5 mL volume occupied
Other drug solids	3 ml volume occupied
Glycerin	15 mL
Sucrose	25 g
Ethanol 95 %	q.s. ???
Purified water	q.s. 100 mL

How much alcohol would be required to preserve this prescription?

Answer:

1. S. Syrup (85 %w/v) has s.g = 1.313, thus,
2. 85 g sucrose are in 100 ml 131.3 g of solution.
3. 131.3g – 85g = 46.3 g or 46.3 mL of water.
4. 100mL - 46.3 mL = 53.7 mL is the v. of 85 g of sucrose.
5. Thus, 85 g of sucrose preserves 46.3 mL of water.

   So, 85 g → 46.3 mL

   25 g → X, thus, X = 13.62 mL of water preserved.

   V. Of sucrose is:

   85g → 53.7 mL

   25g → x

   Thus, X = 15.7 mL
6. v. of active drug + v. of other drugs occupies 5 + 3 = 8 mL
7. 1 mL of glycerin preserves 1 mL of water & occupy 1 mL.

   So, glycerin preserves: 15 mL + 15 mL = 30 mL total.
8. The volume taken care = 13.62 + 15.7 + 8 +30 = 67.3 mL.
9. 100 ml – 67.3 mL of water preserved = 32.68 ml of water which need preservation.

10. Since it requires about 18% of alcohol to preserve water:

    So, $18 \rightarrow 100$ mL

    $x \rightarrow 32.68$ mL, $\rightarrow x = 5.88$ mL of alcohol 100%.

11. But the available alcohol 95%:

    So, $C_1 \cdot V_1 = C_2 \cdot V_2$

    $100 \cdot 5.9 = 95 \cdot V_2 \rightarrow V_2 = 6.2$ ml of alcohol 95% is required.

    So, add 6.2 ml of alcohol to the syrup and complete volume up to 100 mL with water.

Antihistamine Syrup

Chlorpheniramine maleate	0.4 g
Glycerin	25.0 mL
Syrup	83.0 mL
Sorbitol solutio	282.0 mL
Sodium benzoate	1.0 g
Alcohol	60.0 mL
Color and flavor	q.s.
Purified water, to make	1000.0 mL

Ferrous Sulfate Syrup

Ferrous sulfate	**135.0 g**
Citric acid	**12.0 g**
Sorbitol solution	**350.0 mL**
Glycerin	**50.0 mL**
Sodium benzoate	**1.0 g**
Flavor	**q.s.**
Purified water, to make	**1000.0 mL**

Flavorants or Flavoring agents

synthetic flavorants.

natural occuring flavorants as volatile oils (e.g. orange oil, vanilla ..etc.).

Flavorants must posses sufficient water solubility.

Alcohol may added to improve solubility of flavors.

Colorant

Enhance the appeal of syrup.

Selection of colorant in correlation with flavorant employed (i.e. green with mint, brown with chocolate, etc.).

Colorant must be:

1. water soluble
2. Non-reactive with other syrup components;
3. Color stable at the pH range & under the intensity of light

   that the syrup is likely encountered during its shelf-life.

Preparation of Syrups

Preparation of syrup depends on chemical & physical characteristics of the ingredients involved in formulation.

There are 3 methods for syrup preparation:

1. Solution of the ingredients with aid of heat
2. Solution by agitation
3. Percolation

Solution with the Aid of Heat

- Syrups are prepared by this method when it is desired to prepare the syrup as quickly as possible and when the syrup's components are not damaged or volatilized by heat.
- the sugar is generally added to the purified water, and heat is applied until the sugar is dissolved.
- Then, other heat-stable components are added to the hot syrup.
- Allow the mixture to be cool, the required volume is adjusted by the addition of purified water

Solution with the Aid of Heat

- If heat-labile agents or volatile substances, such as volatile flavoring oils and alcohol, are to be added after cooling of the syrup.
- hydrolytic reaction of sucrose known as inversion: Sucrose → glucose (dextrose) + (fructose).
- The combination of the two monosaccharide products is invert sugar.
- The speed of inversion is greatly increased by the presence of acids, the hydrogen ion acting as a catalyst to the reaction.
- the fructose sweetness of the syrup is altered because invert sugar which is sweeter than sucrose.
- The colorless syrup darkens because of the effect of heat on the fructose portion of the invert sugar.
- Syrups so decomposed are more susceptible to fermentation and to microbial growth than the non-decomposed syrups.

- Preparation procedure:

1. Weigh 85 g of sucrose;
2. Place them in 100 ml of volumetric flask
3. Add hot water & mix tell complete dissolution of sucrose
4. Add water up to volume.
5. Dissolve or add as dissolved other components such as flavor, color, medicine, & preservatives;
6. Fill in bottles then, close bottles after cooling.

Solution by Agitation without the Aid of Heat

- To avoid heat-induced inversion of sucrose.
- sucrose and other formulative agents may be dissolved in purified water by placing the ingredients in a vessel larger than the volume of syrup to be prepared, permitting thorough agitation of the mixture.
- It is more time consuming than the use of heat. but the product has maximum stability

- Preparation Procedure:

1.Put sugar & other formulative agents in large vessel to permit thorough agitation

2.Mix well tell complete dissolution of sugar & other soluble ingredients;

3.Drugs are dissolve them in minimal amount of purified water & then, added to syrup.

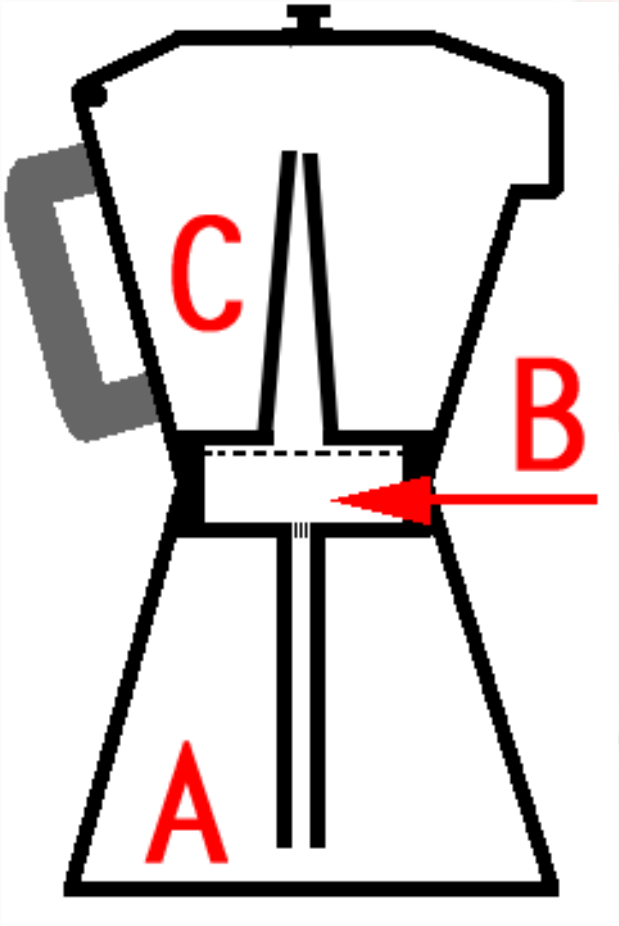
4.Add water up to volume;

5. When solid substances are added directly to a syrup, they dissolve slowly because the viscous nature of the syrup.

Addition of sucrose to Medicated liquid or to a Flavored Liquid

- Occasionally a medicated liquid, such as a tincture or fluid extract, is employed as the source of medication in the preparation of a syrup.
- Many such tinctures and fluid extracts contain alcohol-soluble constituents and are prepared with alcoholic or hydroalcoholic vehicles.
- If the alcohol-soluble components are undesirable, they are generally removed by mixing the tincture or fluid extract with water,
- The filtrate is the medicated liquid to which the sucrose is added in preparation of the syrup.
- If the tincture or fluid extract is miscible with aqueous preparations, it may be added directly to simple syrup or to a flavored syrup

Percolation



Percolation

- In this process, purified water or an aqueous solution is allowed to pass through a bed of crystalline sucrose. A pledged of cotton is put in the neck of the percolator and purified water or aqueous solution is added in the percolator containing sucrose. The flow rate is controlled by the stopcock and maintained in a fixed rate. If required, a small portion of liquid is re-passed through the percolator to dissolve the sugar completely in the liquid or aqueous solvent.

❖An example of a syrup prepared by percolation is ipecac syrup, which is prepared by adding glycerin and syrup to an extractive of powdered ipecac obtained by percolation by using a hydroalcoholic solvent.

❖ It consists of active alkaloids emetine, cephaeline, and psychotrine.

❖ It is an emetic syrup. Usual dose is 15 ml for poisoning in children when stomach evacuation is desired. Vomiting is achieved within ½ hour in 80% of treated children. Abuse of this syrup was in young women in attempt to lose weight.

❖Excess of emetine in tissue due to excess use cause cardiac muscle damage.

Elixirs

Elixirs are, sweetened, flavored, hydro-alcoholic solutions intended for oral use.

Types of elixirs:

1. Non-medicated elixir → employed as vehicle.
2. Medicated elixir → employed for therapeutic effect of the drug they contain.

❖The amount of alcohol in elixir depends on the solubility of dissolved agents.

❖ Each elixir requires a specific blend of alcohol and water to dissolve all of the components in solution.

- Adjuvant solvent as glycerin and propylene glycol frequently employed in elixir.
- Although many elixirs are sweetened with sucrose or with a sucrose syrup, some use sorbitol, glycerin, and/or artificial sweeteners.
- Elixir with 10 – 12 % alcohol don't need preservatives but such percent of alcohol is regarded unsuitable for Children and old patients
- Due to volatile oils and alcohol, elixirs should be stored in tight, light-resistant containers and protected from excessive heat

Preparation of Elixirs

1. By dissolving substance with agitation.
2. By mixture of 2 liquid ingredients

Dissolve alcohol soluble ingredients;

Dissolve water soluble ingredients separately;

- Add aqueous solution (water) to the alcoholic one (don't make the reverse).
- Add the desired up to volume with the solvent or vehicle specified for the formulation.
- Frequently the final mixture is not clear. What is the reason behind this?
- What can you do, if the obtained solution is cloudy?

Elixirs are mainly of two types

1. Non-medicated elixir:

❖ They are used purely as diluting agents or solvents for drugs containing approximately 25% alcohol, e.g., simple elixir, or low alcohol elixir (containing 8-10% alcohol), High alcoholic elixir (containing 75-78% alcohol)

❖If a hydroalcoholic vehicle is selected, the proportion of alcohol should be only slightly above the amount needed to effect and maintain the drug's solution.

2. Medicated elixirs:

- Elixirs containing therapeutically active compounds are known as medicated elixirs, e.g., Phenobarbital elixir USP, Dexamethasone elixir USP, Chlorpheniramine Maleate elixir USP, Diphenhydramine Hydrochloride elixir USP, Piprazine Citrate elixir, etc.

- when two or more therapeutic agents are present in the same preparation ??

What is the role of Glycerin; Syrup; Sorbitol & Propylene glycol in Elixir Formulation?

1. Contribution solvent effect of the Hydro-alcoholic solvent;
2. Assists in the dissolution of the solute and enhances stability of the preparation


RX
GLAXOSMITHKLINE
LANOXIN
(digoxin)
ELIXIR
PEDIATRIC
0.05 mg/mL
60 mL
Lanoxin® Elixir Pediatric
(digoxin)

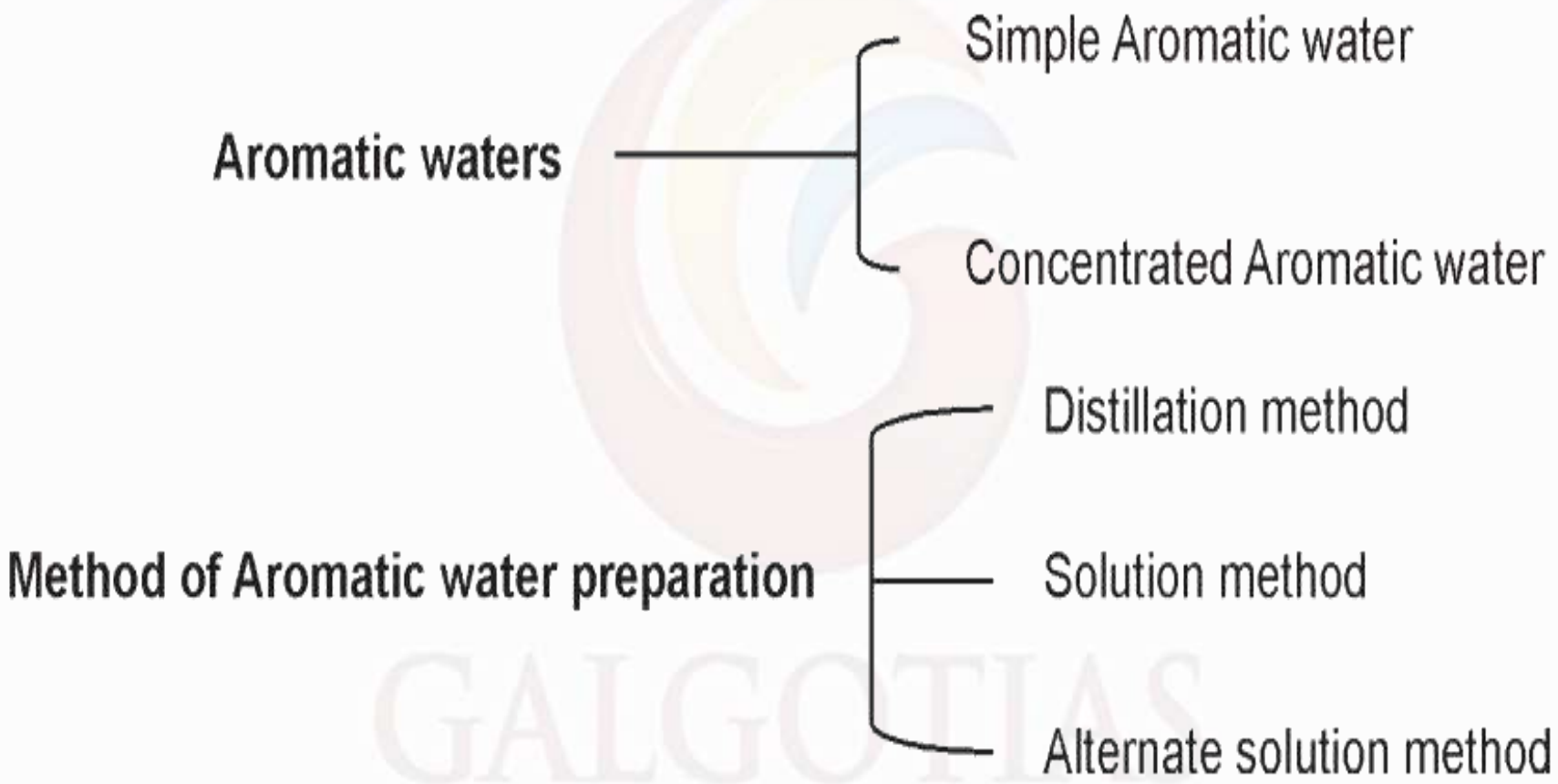

ELIXIR
LUMINAL
ELIXIR
LUMINAL

Aromatic waters

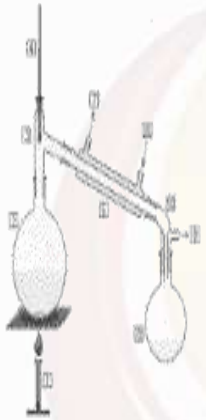
They are clear aqueous solution saturated with volatile Oils (e.g. rose oil, Peppermint oil, or other aromatic or volatile substances eg. camphor. Their odours and taste are of those of the drugs or volatile substances from which they are prepared.

Aromatic waters may be used for perfuming, flavoring or for special purposes for eg.

1. Camphor water has been used as the vehicle in ophthalmic solutions owning to its ability to contribute refreshing, stimulating effect to the preparation.
2. Hamamelis water known as witch hazel is employed as a rub, perfume and as an astringent in various cosmetic preparations, particularly in after-shave lotions.



1. Distillation Method:



The distillation method involves the placing of the coarsely ground odoriferous portion of the plant or drug from which the aromatic water is to be prepared in a suitable still, with sufficient purified water. Most of the volume of water is then distilled. The excess oils collected with the distillate rises to the top of the aqueous product and are removed. The remaining aqueous solutions, saturated with volatile material require clarification by filtration.

2. Solution Method:

Aromatic water is prepared by intermittently shaking 2ml (if liquid) or 2gm (if solid) of the volatile substance with 1000ml of purified water in suitable container for period of 15 minutes. After the period of agitation the mixture is set aside for 12 hours or longer to permit the excess oil and the solid substance to settle. Without further agitation the mixture is passed through a wetted filter paper and purified water added as needed to bring the volume of the filtrate upto the prescribed quantity.

3. Alternative solution Method:

By this method the volatile oil or suitably comminuted aromatic solid is thoroughly incorporated with 15gms of talc and to this mixture is added 1000ml of purified water. The resulting slurry is thoroughly agitated several times for the period of 30 minutes and then filtered.

Preparation of concentrated Aromatic water:

These products are alcoholic non aqueous preparations containing 2% of volatile oils They are forty times stronger than the ordinary aromatic waters. Many volatile oils contain aromatic part and non-aromatic part.

The aromatic portion is much more soluble in a weak alcohol than the non-aromatic portion. Hence when a solution of the oil in 90% alcohol is diluted with a limited amount of water the aromatic portion of the oil remains in solution while the non-aromatic portion is precipitated off, separating as an oilylayer. Therefore 50gms of talc is added for 1000ml of preparation which acts as a distributing agent, and Will absorbs the non-aromatic part. The solution is agitated and set aside for a few hours and filtered.

Storage: Aromatic water deteoriate with time and it should be made in small quantities and protected from intense light and excessive heat and stored in airtight, light resistance container.

SPIRITS

- Spirits are alcoholic or hydroalcoholic solutions of volatile substances.
- The alcoholic concentration of spirits is rather high, usually over 60%.
- Spirits can contain a greater concentration of Aromatic or volatile substances than the corresponding aromatic waters.
- When mixed with water or with an aqueous preparation, the volatile substances present in spirits generally separate from the solution and form a milky preparation.

- Spirits may be used pharmaceutically as flavoring agents and medicinally for the therapeutic value of the aromatic solute.
- Spirits may be taken orally, applied externally, or used by inhalation, depending upon the particular preparation.
- spirits may be prepared by simple solution, solution by maceration, or distillation.
- The spirits most recently official in the USP–NF are aromatic ammonia spirit, camphor spirit, compound orange spirit, and peppermint spirit.

Thank you.

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