LEC 2

PHARMACEUTICAL TECHNOLOGY

SYRUP

Stage: 3/ 1st course

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Syrups

Syrups are concentrated solutions of sugar (such as sucrose) in water or other aqueous liquids with or without added flavoring agents and medicinal substances. This mean there is three types of syrups

- 1. Simple syrup–concentrated solution of sucrose in purified water alone.
- 2. Medicated syrup–aqueous solution of sugar containing other substances as medication
- 3. Non-medicated/Flavored syrup–contained various aromatic and pleasantly flavored substances and is intended as a vehicle or flavor for other preparations.

Perhaps the most frequently found types of medications administered as medicated syrups are antitussive agent, antipyretics, analgesics, antihistamines, and others.

Main features of syrups

Sweet

- **Sweet so it mask the unpleasant taste of drugs**

Viscous

- Viscous will ensure physical concealment of the taste due to covering of the taste buds ,also the thick viscous nature of the medicine will sooth the irritated tissue of the throat as it passes over it (especially in case of antitussive syrups)

Flavored

- **Flavored will also aid in taste masking**

ADVANTAGE OF SYRUPS

- Exert high osmotic pressure – prevents the growth of MOs (bacteria, fungi, molds, etc)
- Palatable sweet – it is suitable as a vehicle for bitter/nauseous substances
- Appropriate for any patient, whatever the age is
- Economical and safe to the patient
- Retard oxidation because it (sucrose) partly hydrolyzed into dextrose & levulose (reducing sugary) so prevent decomposition of many substances

DISADVANTAGES

- Not suitable in emergency and for unconscious patients
- Not convenient for a patient with a gastrointestinal disorder such as diarrhea, constipation, ulceration, and hyperacidity in stomach
- Can’t avoid first pass metabolism

Examples of Non medicated syrups

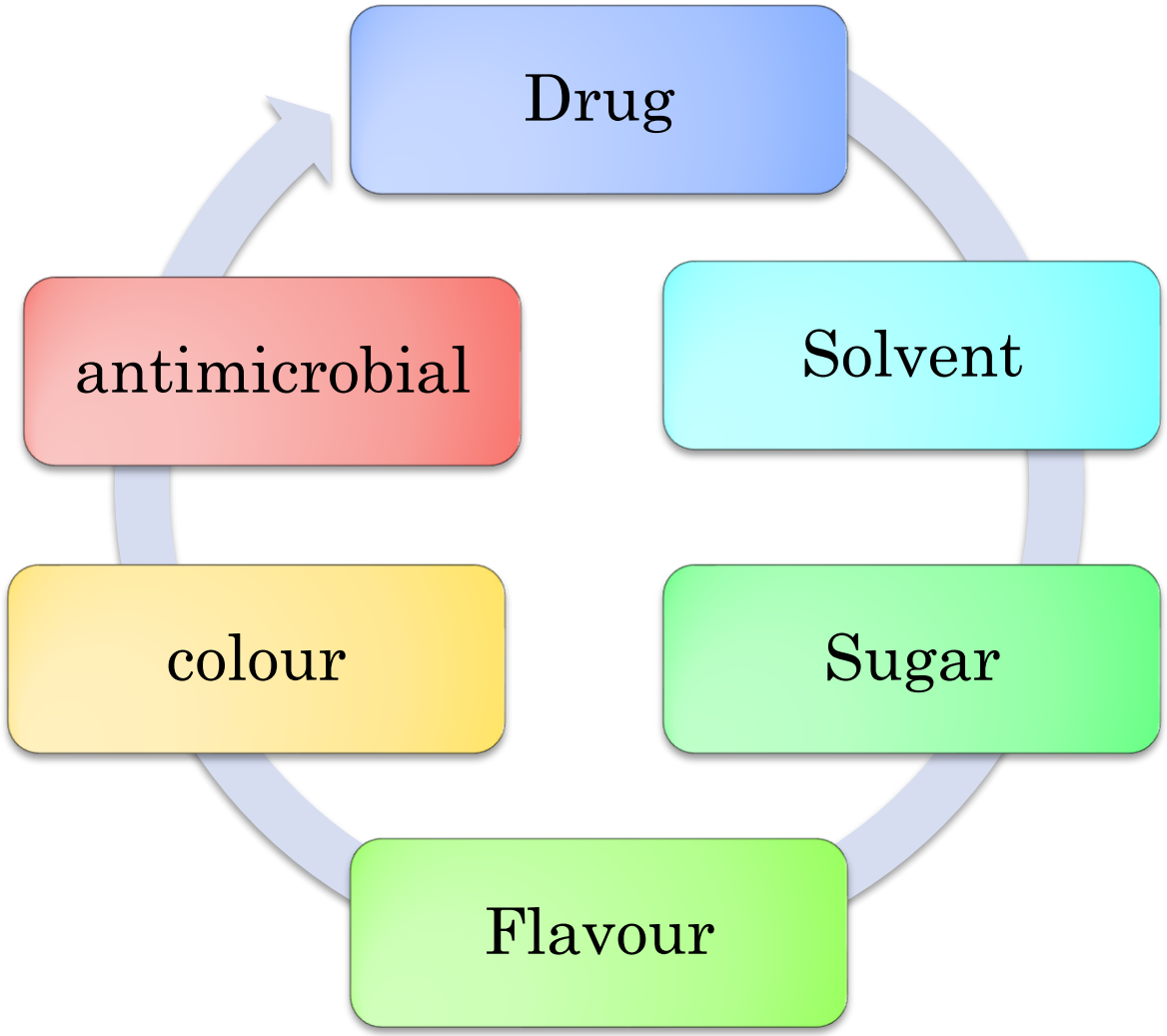
Syrup	Comments
Cherry syrup	Sucrose-based syrup with **cherry juice about 47% by volume**. Tart fruit flavor is attractive to most patients and acidic pH makes it useful as a vehicle for drugs requiring an acid medium
Cocoa syrup	Suspension of cocoa powder in aqueous vehicle sweetened and thickened with 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
Ora-Sweet, Ora-Sweet SF	Commercial vehicles for extemporaneous compounding of (Paddock Laboratories) syrups. Both have a pH of 4-4.5 and are **alcohol free**. **Ora-Sweet SF is sugar free**
Syrup	85% sucrose in purified water. Simple syrup may be used as the basis for flavored or medicated syrups

EXAMPLE (USING OF FLAVORED SYRUP) CAPTOPRIL ORAL LIQUID

- Preferred formula preparation by using unmedicated syrup
- Using a typical strength of 1 mg/mL as an example:
- * 4 captopril tablets 25 mg
- * Ora-Plus to 50mL
- * Ora-Sweet to 100 mL.
- Method guidance
- Tablets can be ground to a fine uniform powder in a pestle and mortar. A small amount of Ora-Plus may be added to form a paste, before adding further portions of Ora-Plus up to 50% of the final volume. Transfer to a measuring cylinder. The Ora-Sweet can be used to washout the pestle and mortar before making the suspension up to 100% volume. Transfer to an amber medicine bottle.
- Shelf-life

  7 days refrigerated in amber glass. Shake the bottle

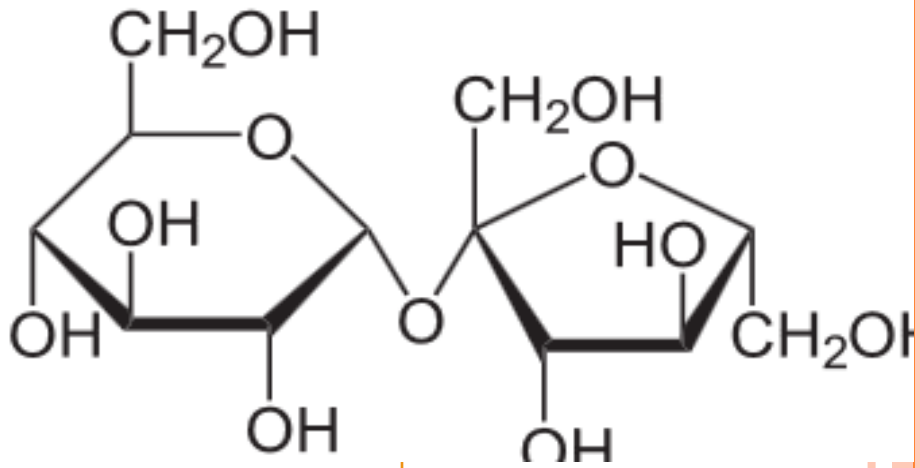
Syrup components



1. Sugar usually sucrose or sugar substitutes.
2. Antimicrobial preservative
3. Flavoring agent
4. Purified water, solvents, solubility agent, thicker, stabilizer
5. Drug
6. Also, it may contain a special solvents (including alcohol), solubilizing agents, thickeners, or stabilizers

Sucrose (why?)

- Purest compound commercially available
- sweet
- Lack of color
- Easy to handle



Simple syrup NF

Rχ	
Sucrose	85 g
Purified water q.s.	100 ml

- Sucrose 85% w/v
- This concentration requires no additional preservatives if the syrup is used soon and not stored or stored properly. (why?)
- **What is free water?**

Why simple syrup not required preservative?

The specific gravity of simple syrup is an important property to identify its concentration. Syrup has a specific gravity of about 1.313, which means that each 100 ml of syrup weighs 131.3 g.

- So,
  131.3g – 85g = 46.3g or mL of water in the syrup. Thus, 46.3 g of water are mixed with 85 g of sucrose to give syrup 85%w/v.

- **Solubility of sucrose is expressed as 1g in 0.5ml water**

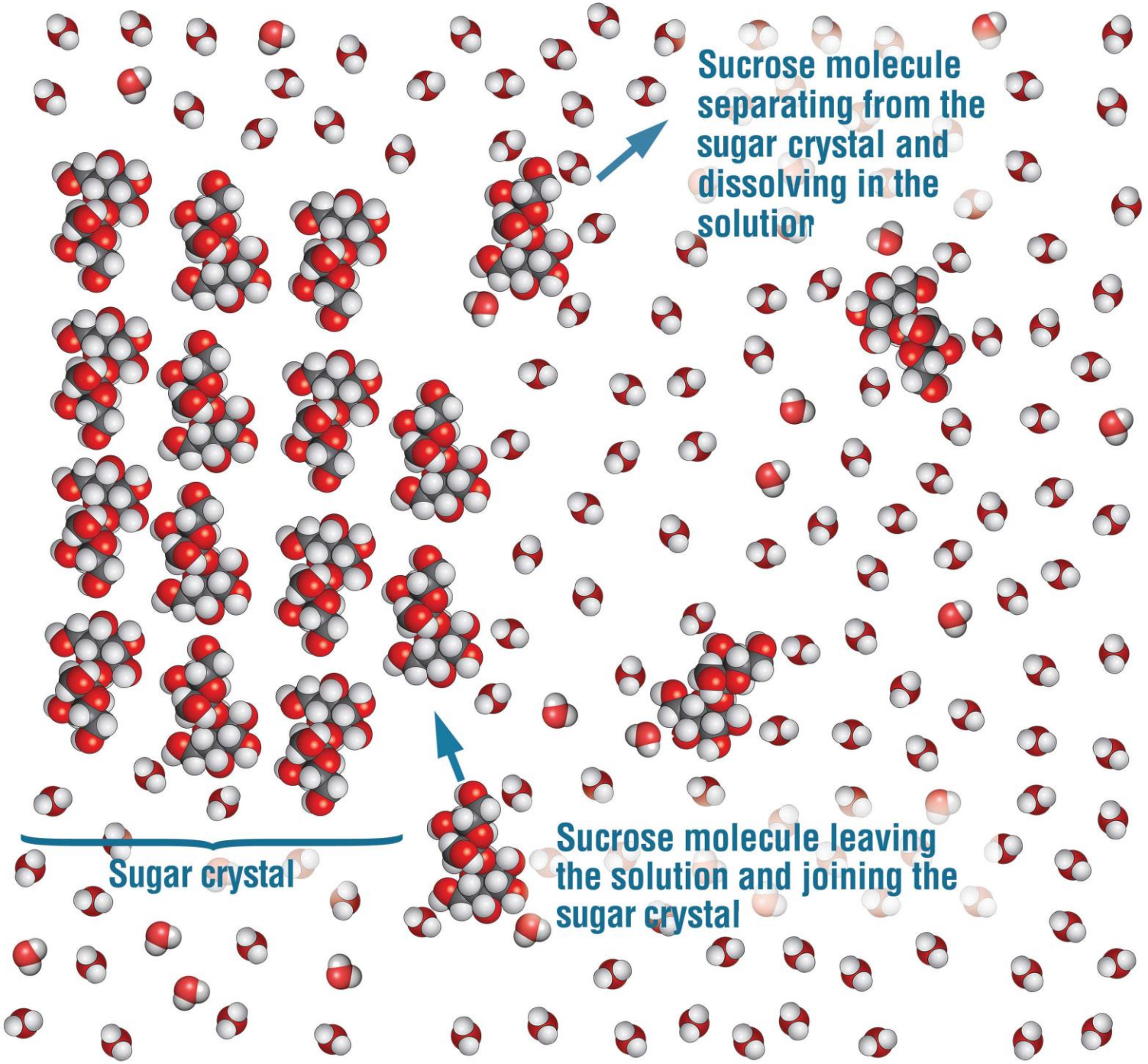
- **1g 0.5ml**
- **85 X X=42.5**
- **To dissolve 85g of sucrose 42.5ml of water is needed**

- 46.3 _ 42.5=3.8ml /100ml syrup excess water (these 3.8 mL of **water are free of sucrose**).
- Thus, only a very slight excess of water (about 3.8 mL per 100 mL of syrup) is employed in the preparation of syrup. Although it is not enough to be particularly amenable to the growth of microorganisms, the slight excess of water permits the syrup to remain physically stable in varying temperatures.

SATURATED SUCROSE SOLUTION

- If the syrup were completely saturated with sucrose, it might crystallize from solution upon cooling
- Thereby acting as nuclei that initiate chain reaction which result in separation of an amount of sucrose disproportionate to it's solubility at the storage temperature.
- If it is unsaturated (less concentrated), it will be suitable for microbial growth.

- Note: Simple syrup is a saturated solution at 4°C, so no crystallization should be observed unless the temperature drops below 4°C or super saturated


Sucrose molecule separating from the sugar crystal and dissolving in the solution
Sugar crystal
Sucrose molecule leaving the solution and joining the sugar crystal

Syrups containing sucrose

- Most syrups contain about 60-80% w/v sucrose. This percent is desirable for sweetness and viscosity.
- Dilute sucrose solution are prone to microbial growth which result in turbidity, fermentation, change in color.
- Concentrated sugar solution (85%w/v) are resistant to microbial growth.
- Syrups containing less than (85%w/v) sucrose, preservatives must be added.

Preservatives

High sucrose concentrations will usually protect an oral liquid dosage form from growth of most microorganisms.

- A problem arises, however, when pharmacists must add other ingredients to syrups that can result in a decrease in the sucrose concentration. This may cause a loss of the preservative effectiveness of the sucrose. This can be overcome, however, by calculating the quantity of a preservative (such as alcohol) to add to the formula to maintain the preservative effectiveness of the final product.

ANTI- MICROBIAL PRESERVATIVE

preservative	Concentration used as %
Benzoic acid	0.1-0.2
Sod benzoate	0.1-0.2
Butyl paraben (butyl p-hydroxybenzoate)	0.02
Propyl paraben 4-hydroxybenzoic acid propyl ester	0.05
Methyl paraben 4-hydroxybenzoic acid methyl ester	0.1
Sorbic acid	0.1
Alcohol 99%	15-20 (18)
Glycerin	45 (50)

Preservatives

- The benzoates and the parabens (hydroxyl-benzoic acids) and sorbic acid are most effective in acid solution
- Mixture of parabens are frequently employed to take advantage of their potentiating effect
- The amount of added preservative needed in syrups containing sucrose less than 85% w/v is estimated according to the calculated free water.
- If the syrups are diluted with water preservatives must be added

CALCULATE THE AMOUNT OF PRESERVATIVE

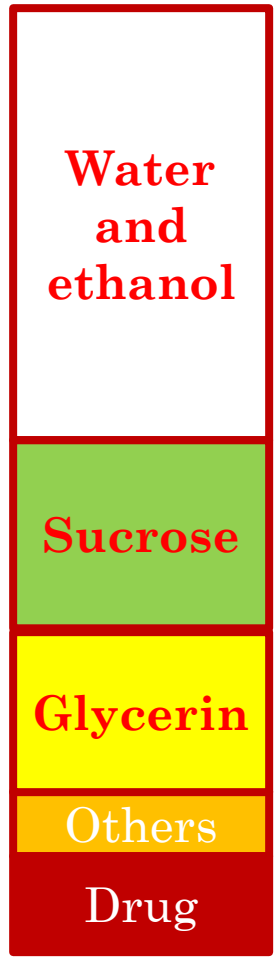
- Calculate the preservative amount required for 65% sucrose syrup knowing that 85%w/v sucrose will preserve 100ml solution (syrup)
- Answer
- 85g 100ml

  65g Xml X=76.5ml volume of solution preserved by 65%w/v sucrose.

- 100 - 76.5 = 23.5ml free water (not preserved)
- If 0.1% of benzoic acid used, so
- 0.1g 100
- X 23.5 X= 0.0235g of benzoic acid used
- **The amount of preservative added is calculated according to the volume of the free water**

Q CALCULATE THE VOLUME OF ETHANOL

Material	Quantity
Drug	5ml volume occupied
Solids (Other drug solids)	3ml volume occupied
Glycerin	15ml
Sucrose	25g
Ethanol 95%	q.s.
Purified water q.s.	100ml



Answer

- 85 / 100 = 25/v v=29.4ml volume of solution preserved
- 100 - 29.4 = 70.6ml volume of solution not preserved by sucrose

- Glycerin can preserve a double amount of water 15×2 =30ml
- 70.6 – 30 = 40.6ml (not preserved by sucrose and glycerin)
- Volume occupied by other components 5+3= 8ml
- 40.6 – 8 = 32.6ml (not preserved)
- 0.18 × 32.6 = 5.868 ≈5.9ml of alcohol(99%) required

18 100

X 32.6 X=5.9 ml of alcohol

- 5.9/0.95=6.21ml of alcohol 95% will be required

ANOTHER METHOD FOR CALCULATIONS

- Simple syrup 85g /100ml solution weighs 131.3g
- 131.3 - 85=46.3 wt. (g) or volume (ml) of water
- 100 - 46.3=53.7 ml volume occupied by sucrose
- 85g sucrose preserves 46.3 ml of water so that:
  - 1g of sucrose preserves 0.54ml of water
- Also 85g of sucrose will occupy a volume of 53.7ml so that :
  - 1g of sucrose will occupy 0.63ml
  - From these two facts we can complete the answer (how?).

ALCOHOL

- In sealed containers vaporization of water from the syrup and condensation will create a dilute solution of sucrose on the surface, which supports mold growth
- In some syrups alcohol is present in small amount as a solvent for alcohol soluble ingredients
- Although the concentration of alcohol is not sufficient for preservative effect but the alcohol concentrates in vapor above the syrup, thus preventing the growth of surface molds
- Syrups can withstand **10%** of alcohol not more.

FLAVORANT

- ❑ Synthetic flavorants
- ❑ Naturally occurring materials
- ❑ Volatile oils
- ❑ Vanillin

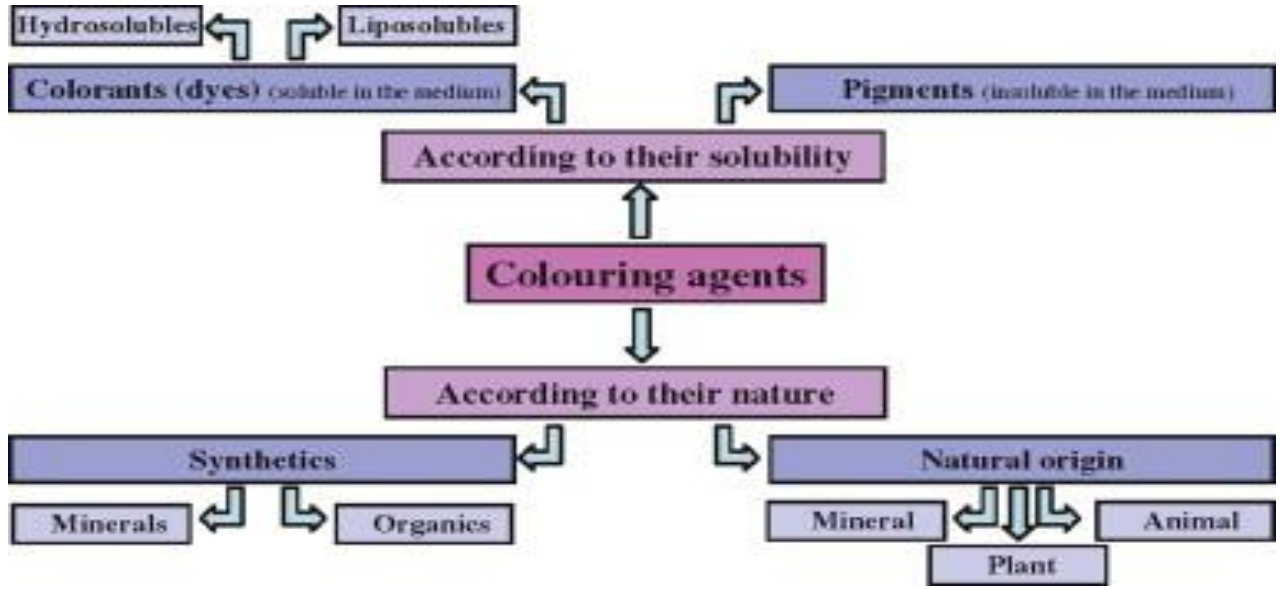
Because syrups are aqueous preparations, these flavorants must be water soluble.

COLORANT

The colorant is generally

- **water soluble.**
- **Non-reactive with the other syrup components (inert).**
- **Color stable at the pH range and under the intensity of light that the syrup is likely to encounter during its shelf life.**

Green with mint
Brown with chocolate



Syrups can be preserved by

1) Storage at **low temperature (not less than 4°C).**
2) Adding **preservatives** in the formulation
3) By the maintenance of a **high concentration** of sucrose as a part of the formulation

Home work

- Calculate the required amount of sodium benzoate, if you know 0.1% w/v is required to achieve preservation.
- State the function of each ingredient in the prescription.
- What do you predict pH of the formula, why?
- Predict the color of the formula.
- What is the meaning of NF, USP, and BP?
- If the patient is diabetic, re-write the formula accordingly without the weight of ingredient.

Rx	Amount
Drug	24ml volume occupied
Sod benzoate	q.s.
Glycerin	150ml
Alcohol	15ml
Sucrose	200g
Orange oil	2ml
Color	2ml
Purified water qs	1000ml

PREPARATION OF SYRUPS

Syrups are prepared by 4 different methods depending on the physical and chemical characteristics of the ingredients

1. Solution of ingredients with the ***aid of heat***, or called the hot process (Simple Syrup USP).
2. Solution of ingredients ***by agitation without heat***, *or called* (simple admixture of liquid component), e.g. Ephedrine Sulphate Syrup USP.
3. ***Addition of sucrose*** to a prepared medicated liquid or to a flavored liquid (Orange Syrup USP).
4. ***Percolation*** of either the source of the medicating substance or of the sucrose. Wild Cherry Syrup USP, Licorice syrup USP, Ipecac Syrup USP

1. SOLUTION WITH THE AID OF HEAT

Syrups are prepared by this method **for the following** reasons:

A. When desired to prepare the syrup as quickly as possible, and

B. When the syrups components are not damaged or volatilized by heat

Procedure:

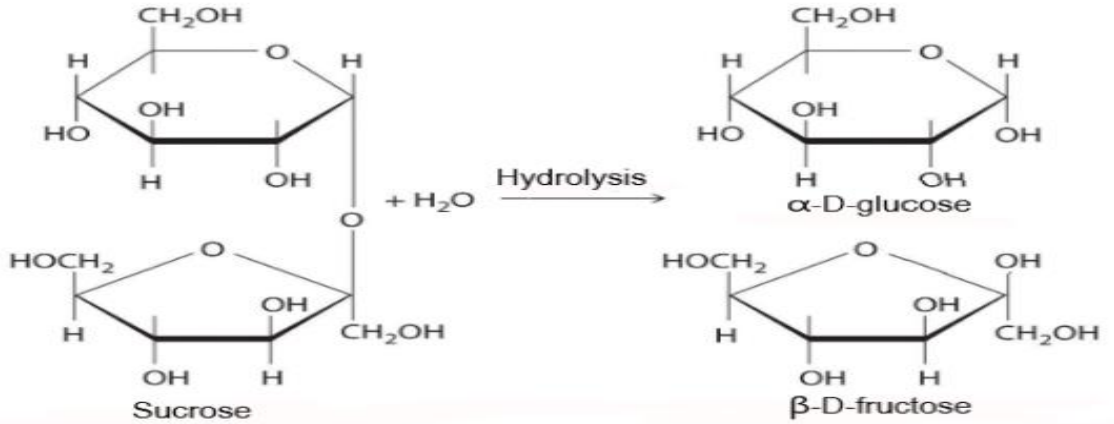
1. Add the sugar to the purified water and heat until solution is affected.
2. Heat stable components are added to the hot syrup
3. Cool and made up to volume.
4. If other components are heat labile, they are added after cooling, like alcohol and oil.

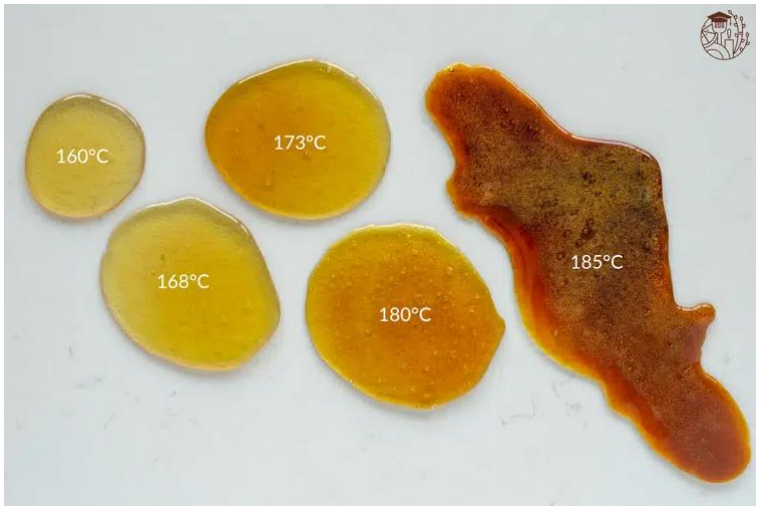
Caution: Do not apply excessive heat -inversion of sucrose causing discoloration due to caramelization may occurs (what is the cause of caramelization?).

Examples : Acacia syrup, NF; Cocoa Syrup, NF; Syrup USP (85% sugar, made by cold and hot process, percolation).

PRECAUTIONS

- Because of the prospect of decomposition by heat, syrups cannot be sterilized by autoclaving
- The use of excessive heat cause hydrolytic decomposition of sucrose to glucose and fructose (invert sugar)
- Inversion is increased by the presence of acids, the hydrogen ion acting as a catalyst to the reaction.
- Invert sugar is sweeter darker in color (caramelization) and more susceptible to fermentation





HYDROLYSIS OF SUCROSE (SPECIFIC ACID CATALYZED) CALLED INVERSION

Sucrose →	Glucose (dextrose) +	Fructose (laevulose)
Dextro -rotation	Dextro- rotation	Levo rotation of the light more pronounced than dextrose
Degrees of sweetness 100 (1)	74 (0.5-0.9)	173 (1.2)
Colorless liquid	Solution of invert sugar are more prone to microbial growth	Degradation leads to brown discoloration (caramelization)

2. Solution of ingredients by agitation without the aid of heat

- To avoid heat-induced inversion of sucrose, a syrup may be prepared without heat by agitation
- **Procedure:**
- 1. Sucrose and other formulative agents maybe dissolved in purified water.
- 2. Place the ingredients in a bottle of greater capacity than the volume of syrup.
- 3. Agitate the mixture
- **Examples**: Ferrous Sulfate Syrup, Ephedrine Sulfate, Citric acid Syrup, and Glycyrrhiza Syrup
- More time consuming than the use of heat but the product has maximum stability
- Miscible Liquid ingredients are incorporated during mixing
- **When solid agents are to be added to a syrup, it is best to dissolve them in a minimal amount of purified water and incorporate the resulting solution into the syrup,** this because (viscous nature of the syrup retards the dissolution of solids, also amount of free water is limited)

3-Addition of Sucrose to a Medicated Liquid or to a Flavored Liquid

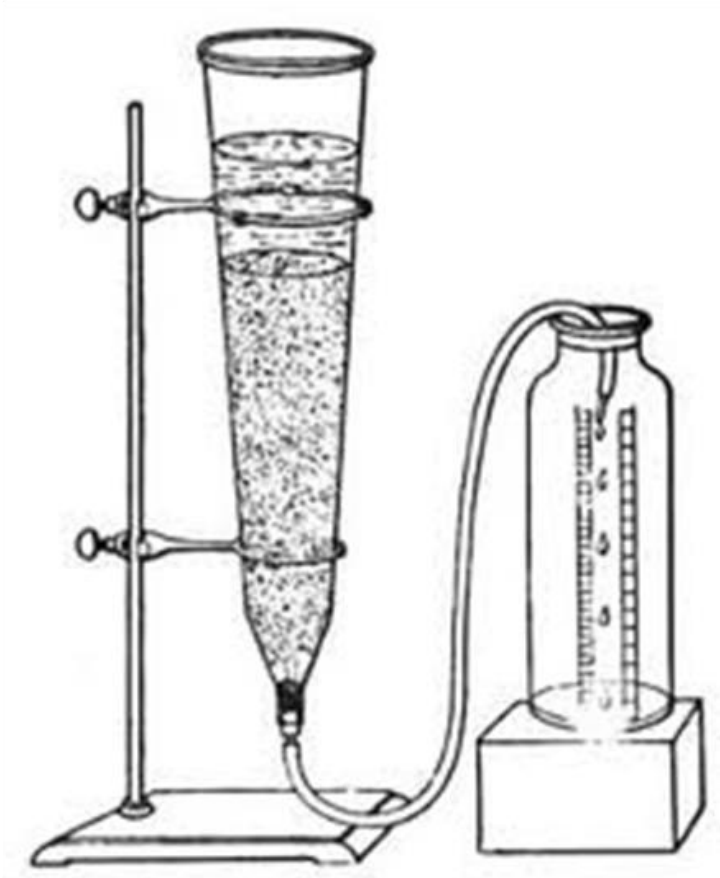
- This method is resorted to those cases in which fluid extracts, tinctures, or other liquids are added to syrup to medicate it.
- Syrups made in this way usually develop precipitates since alcohol is often an ingredient of the liquids and the resinous and oily substances dissolved by alcohol precipitate when mixed with syrup.
- A modification of this process consists of mixing the fluid extract or tincture with the water, allowing the mixture to stand to permit the separation of insoluble constituents, filtering and then dissolving the sucrose in the filtrate.

➔ This procedure is not permissible when the precipitated ingredients are the valuable medicinal agents.

4. Percolation

- It is an extraction method used glass percolator.
- In this method, either sucrose maybe percolated to prepare the syrup or the source of the medicinal component may be percolated to form an extractive to which sucrose or syrup may be added
- **Procedure:**
- 1. Purified water or aqueous solution of a medicating or flavoring liquid is allowed to pass slowly through a column of crystalline sucrose to dissolve it.
- 2. The percolate is collected and returned to the percolator as required until all of the sucrose has been dissolved.
- 3. Percolator with a pledge of cotton at the bottom is used
- **Example**: Tolu Balsam syrup -flavor for cough syrup

Percolator



EXAMPLE: IPECAC SYRUP USP

- Ipecac syrup, which is prepared by adding glycerin and syrup to an extractive of powdered ipecac obtained by percolation (2nd method of percolation).
- The drug ipecac, which consists of the dried rhizome and roots of *Cephaëlis ipecacuanha*, contains the medicinally active alkaloids emetine, cephaeline, and psychotrine.
- These alkaloids are extracted from the powdered ipecac by percolation with a hydroalcoholic solvent.
- The syrup is categorized as an emetic with a usual dose of 15ml.

★ This amount of syrup is commonly used in the management of poisoning in children when evacuation of the stomach contents is desirable. About 80% of children given this dose will vomit within half an hour.

Syrup examples

Dextrose-Based Syrups

- Dextrose may be used as a substitute for sucrose **(WHEN?)** in syrups containing strong acids in order to eliminate the discoloration associated with sucrose inversion.
- Dextrose forms a saturated solution in water at 70% w/v, which is less viscous than simple syrup.
- It dissolves more slowly than sucrose and is less sweet (0.7-0.8). Preservatives are required to improve the keeping qualities of such syrups. Glycerin is added in 30% to 45% v/v as preservative.

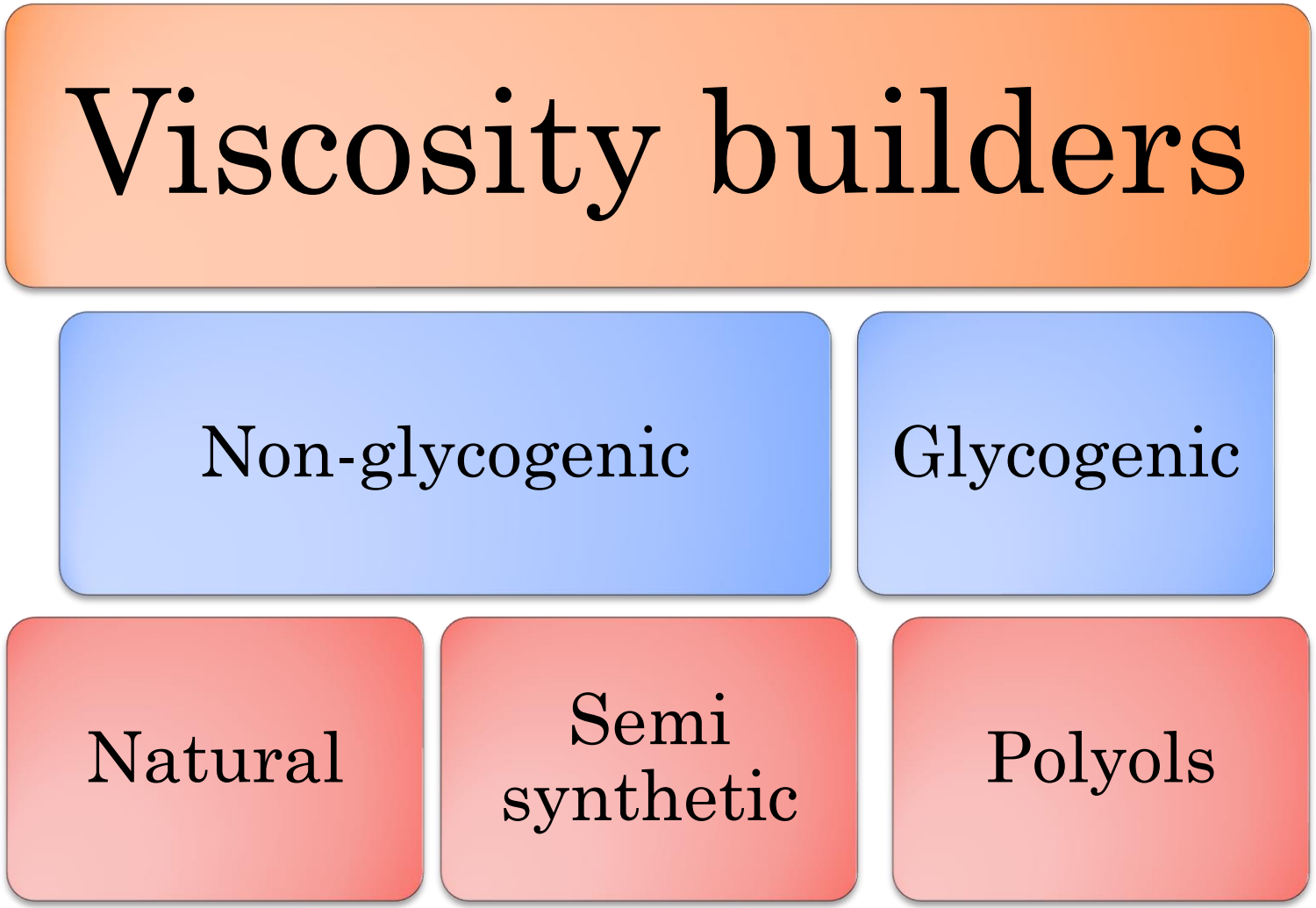
NON- SUCROSE BASED SYRUPS

Diabetic simple syrup

Artificial syrups (Non nutritive syrups)

- Intended as substitutes for syrups and to be administered to persons who must regulate their sugar and/or calorie intake accurately. e.g. persons suffering from diabetes mellitus. Some early formulae included glycerin, however, glycerin and propylene glycol are **glycogenetic** substances, i.e. they are materials which are converted into glucose in the body. An example of non–nutritive syrup is "Diabetic Simple Syrup". It contains compound sodium cyclamate (6% cyclamate sodium and 0.6% saccharin sodium) or saccharin . However, the cyclamate studies showed that the sweetener could produce cancer in animals and, as a result, this substance was removed from a wide variety of products. Similar studies have been carried out on saccharin. Much research has been done to find a safe synthetic substitute for sucrose. As a result, aspartame which is about 200 times sweeter than sucrose, is being used now in many commercial preparations as the sweetening agent.

NON- SUCROSE BASED SYRUPS REQUIRED



VISCOSITY BUILDERS

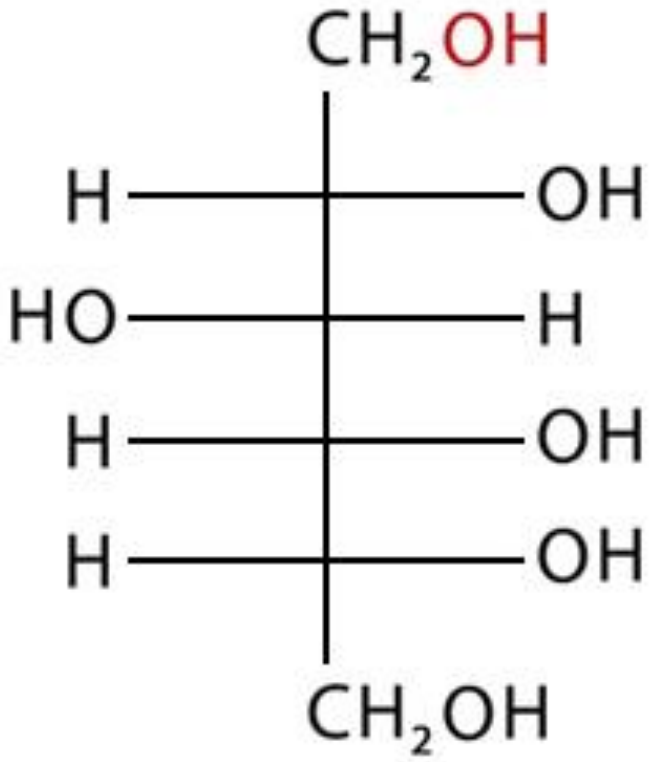
- 1-Glycogenic (Polyols) sorbitol (64%), glycerin, propylene glycol

- 2- Non- glycogenic , Polymers (Gums)
  a) Natural Tragacanth, Acacia
  b) Semi synthetic

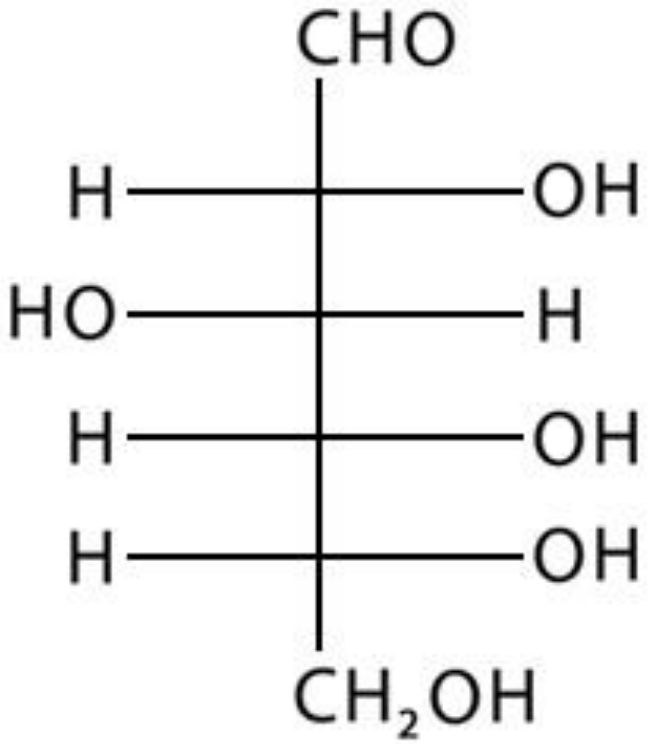
  - Methylcellulose MC (nonionic , exothermic)
  - Hydroxypropylmethylcellulose HPMC (nonionic)
  - Sodium Carboxymethylcellulose Sod CMC(anionic),
  - Sod Alginate (anionic) ,

Sorbitol-Based Syrups

- Sorbitol which is hexahydric alcohol made by hydrogenation of glucose has been used in the preparation of syrup.
- It is used mostly in the form of a 70% w/w aqueous solution.
- Sorbitol solution is not irritating to the membrane of the mouth and throat and does not contribute to the formation of dental carries.
- Sorbitol is metabolized and converted to glucose; however, it is not rapidly absorbed from the GIT as sugars. No significant hyperglycemia has been found (WHY?); it may be used as component of non-nutritive vehicles.
- Sorbitol solution does not support mold growth. Preservative should be used in solution containing less than 60% w/w sorbitol.
- It is chemically stable and inert with respect to drugs and other ingredients used in pharmaceutical preparation.



Sorbitol



Glucose

Advantage of sorbitol solution addition to simple syrup

Compatible with other polyols

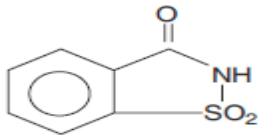
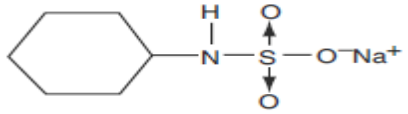
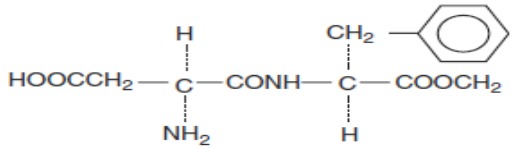
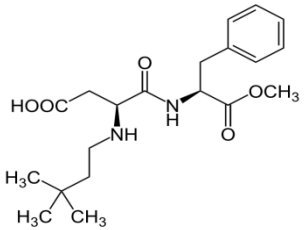
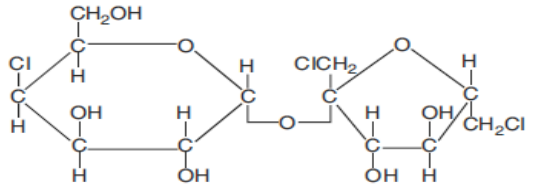
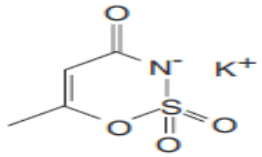
Can be added (30%) to simple syrup to reduce crystallization

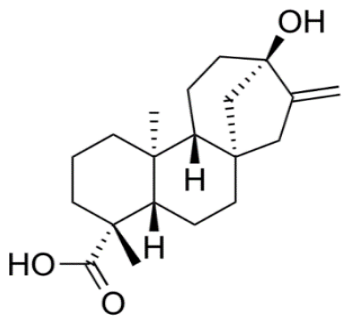
Sorbitol inhibits the sticking or locking of bottle caps which occur with high concentrations of sucrose

LINCTUSES

A syrupy or sticky preparation containing medicaments exerting a local action on the mucous membrane of the throat

- Linctuses are viscous preparations that contain the therapeutic agent dissolved in a vehicle composed of a high percentage of sucrose and, if required, other sweetening agents. (honey or glucose syrup)
- Linctuses are often used when the drug has a bitter taste
- These formulations are administered orally and are primarily employed for the treatment of cough, due to their soothing actions on the inflamed mucous membranes.
- Linctuses may also be formulated as sugar-free alternatives in which sucrose is replaced by sorbitol and the required concentration of sweetening agent

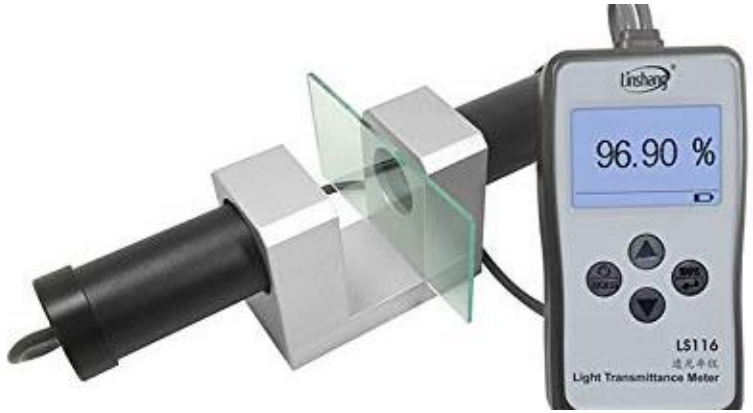
Sweetener	Degree of sweetness (sucrose reference)	Chemical structure	Comment
Saccharin Sweet "N" Low®	500		Bitter after taste
Sod cyclamate	30		Banned in USA
Aspartame Aspartyl phenylalanine methyl ester Canderel®	200		Unstable in hot solution,(PKU)
Neotame (N-[N-(3,3-dimethylbutyl)-L--aspartyl]-L-phenylalanine 1-methyl ester) Nutrasweet®	8000		
Sucralose Splenda®	600		Stable over a broad pH range
Acesulfame –K Nutrinova®	200		Heat stable

Natural Sweetener	Degree of sweetness	Chemical structure	Comments
Stevia	250		Extracts known as rebiana, Truvia, PureVia; mainly containing rebaudioside A, a steviol glycoside
Sorbitol	0.6		
Xylitol	1.0		
Mannitol	0.5		Derived from Mannose

Evaluation of syrup dosage form

1. Transmittance of light :

- A light transmittance meter is a newer tool that is used to check syrup color.
- In a light transmittance meter, a syrup sample is checked for color by passing light through the sample.
- The percent of light transmission is compared to light transmission rates set for different grades.
- When using one, it need to be sure there are no fingerprints on the syrup test bottle, and that the syrup sample has no bubbles or cloudiness.
- Any of these conditions may diminish the light that is transmitted through the sample and therefore lowers the grade of the sample.



2. Visual inspection:

• With visual inspection, the ingredients and the final products are carefully examined for purity and for appearance.

• Physical appearance of products for patient adherence and compliance is critical so it should be

- ✓ Good looking
- ✓ Elegance in appearance

3. pH measurement:

• The measurement and maintenance pH is also very important step in the quality control testing.

• Generally there are two different types of methods used in the measurement of pH:

➢ The simplest and cheapest is to dip a piece of pH paper into the sample. The paper is impregnated with chemicals that change color and the color may be compared to a chart supplied with the paper to give pH of the sample.

➢ If greatest accuracy is required a pH meter should be used. A typical pH meter consists of a special measuring glass electrode connected to and electronic meter that measures and displays the pH reading.

4. Sucrose concentration:

- The determination of sucrose concentrations is very important in quality control testing of syrups.
- If the concentration of sucrose in the syrup is very high it may crystallize the syrup and less sucrose concentrations give favor for the microbial growth.
- There is no specific method for the determination of sucrose in syrup, we use HPLC and UV-spectroscopy for this purpose.

5. Physical stability in syrups:

•The syrups are must be stable physically.

Example:

- ✓ Its appearance (no crystallization and microbial growth)
- ✓ Color must be completely soluble with other ingredients
- ✓ Odorant taste (palatable)
- ✓ Solid material is completely miscible in liquid.

Thank you