



Lecture 3

Syrups

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Oral Solutions

Definition
Excipients

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Oral Solutions

There are three principal types of solution formulations that are administered orally:

1. Oral solutions
2. Oral syrups
3. Oral elixirs

In addition, other solution formulations are employed for a local effect, e.g. mouthwashes/gargles.



Definition

Oral solutions are administered to the gastrointestinal tract to provide systemic absorption of the therapeutic agent.

Due to the resilience of the gastrointestinal environment, oral solutions may be formulated over a broad pH range.

Unless there are issues regarding the solubility or stability of the therapeutic agent, the usual pH of oral solutions is about 7.0.



Excipients

Typically the following classes of excipients are used in the formulation of oral solutions:

1. Buffers (e.g. citrate, phosphate)
2. Preservatives (e.g. parabens, benzoic acid, sorbic acid)
3. Antioxidants (water-soluble antioxidants are used, e.g. sodium metabisulphite 0.01–1.0% w/w)
4. Flavours and colours (the colour should be selected to complement the flavour of the formulation)
5. Viscosity-modifying agents (to affect the pourability of the formulation. For this purpose hydrophilic polymers are used, e.g. sodium alginate, hydroxyethylcellulose).

All components of the formulation should be soluble, with no evidence of precipitation to be classified as solution.



Oral Syrups

Definition

Compatibility

Components

Definition

Syrups are highly concentrated, aqueous solutions of sugar or a sugar substitute that traditionally contain a flavouring agent, e.g. cherry syrup, cocoa syrup, orange syrup, raspberry syrup.

Syrup NF, (also called simple syrup) is composed of an aqueous solution containing 85% sucrose (It is prepared by dissolving 85 g of sucrose in enough purified water to make 100 mL of syrup).



Definition

Medicated and Non-medicated Syrups

Syrups are classified according to their therapeutic effect into:

1. Non-medicated/Flavoring syrups (used as vehicles) .
2. Medicated Syrups (contain ingredients giving them therapeutic value) .

Therapeutic agents may either be directly incorporated into the non-medicated syrup or may be added as the medicated syrup is being prepared.

If the former method is employed, it is important to ensure that the therapeutic agent is soluble within the syrup base.



Compatibility

The choice of syrup vehicle must be performed with due consideration to the physicochemical properties of the therapeutic agent.

For example, cherry syrup and orange syrup are acidic and therefore the solubility of acidic or some zwitterionic therapeutic agents may be lowered and may result in precipitation of the drug substance.

Under these circumstances, the physical stability of the preparation will have been compromised and the shelf-life of the product will have been exceeded.

The use of acidic syrups may additionally result in reduced chemical stability for acid-labile therapeutic agents.



Components

The major components of syrups are as follows:

1. Purified water.
2. Sugar (sucrose) or sugar substitutes (artificial sweeteners).
3. Preservatives.
4. Flavors
5. Colors



Components

Sugar or Sugar Substitutes

The characteristic body that the sucrose and alternative agents seek to impart to the syrup is essentially the result of attaining the proper viscosity.

This quality, together with the sweetness and flavorants, results in a type of pharmaceutical preparation that masks the taste of added medicinal agents.



Components

Sugar or Sugar Substitutes

When the syrup is swallowed, only a portion of the dissolved drug actually makes contact with the taste buds, the remainder of the drug being carried past them and down the throat in the viscous syrup.

This type of physical concealment of the taste is not possible for a solution of a drug in an unthickened, mobile aqueous preparation.

In the case of antitussive syrups, the thick, sweet syrup has a soothing effect on the irritated tissues of the throat as it passes over them.



Components

Sugar or Sugar Substitutes

Pharmaceutically, syrups are classified into:

1. **Sucrose based syrups** (syrups which are concentrated solutions)
2. **Non-sucrose based syrups** (formulated with artificial sweetening agents and viscosity builders).



Components

Sugar or Sugar Substitutes

Sucrose Based Syrups

Traditionally syrups are composed of sucrose (usually between 60 and 80%) and purified water.

Due to the inherent sweetness and moderately high viscosity of these systems, the addition of other sweetening agents and viscosity-modifying agents is not required.

The aqueous sugar medium of dilute sucrose solutions is an efficient nutrient medium for the growth of microorganisms, particularly yeasts and molds.

On the other hand, concentrated sugar solutions are quite resistant to microbial growth because of the unavailability of the water required for the growth of microorganisms.



Components

Sugar or Sugar Substitutes

Sucrose Based Syrups

If the syrup were completely saturated with sucrose, in cool storage, 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 and probably suitable for microbial growth.

Many syrups are not intended to be as nearly saturated as Syrup, NF, and therefore must employ added preservative agents to prevent microbial growth and to ensure their stability during their period of use and storage.



Components

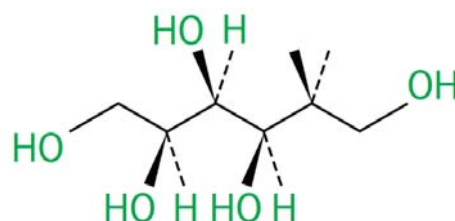
Sugar or Sugar Substitutes

Non-sucrose based syrups

In some formulations, other non-sucrose bases may replace traditional syrup.

One of the most popular is Sorbitol Solution USP, which contains 64% w/w sorbitol

These non-sucrose bases may be mixed with traditional syrups, if required, in the formulation of oral syrups that possess a low concentration of sucrose in comparison to traditional syrups.



Components

Sugar or Sugar Substitutes

Non-sucrose based syrups

More recently, many products have been formulated as medicated sugar-free syrups due to the glycogenetic and cariogenic properties of sucrose.

For the afore-mentioned reasons, all medicinal products designed for administration to children and to diabetic patients must be sugar-free.



Components

Sugar or Sugar Substitutes

Non-sucrose based syrups

Syrup substitutes must therefore provide an equivalent sweetness, viscosity and preservation to the original syrups.

To achieve these properties artificial sweeteners (typically saccharin sodium, aspartame), non-glycogenetic viscosity modifiers (e.g. methylcellulose, hydroxyethylcellulose) and preservatives (e.g. sodium benzoate, benzoic acid and parahydroxybenzoate esters) are included.



Components

Preservatives

As highlighted above, preservatives are not required in traditional syrups containing high concentrations of sucrose.

Conversely, in sugar-free syrups and in traditional syrups that contain lower concentrations of sucrose, the addition of preservatives is required.

Typical examples of commonly used preservatives include:

1. Mixtures of parahydroxybenzoate esters (usually methylhydroxybenzoate and propylhydroxybenzoate in a ratio of 9:1) (0.1–0.2%) .
2. Other preservatives that are employed include benzoic acid (0.1–0.2%) or sodium benzoate (0.1–0.2%).



Components

Flavors

These are employed whenever the unpalatable taste of a therapeutic agent is apparent, even in the presence of the sweetening agents.

The flavors may be of natural origin (e.g. peppermint, lemon, herbs and spices) and are available as oils, extracts, spirits or aqueous solutions.

Alternatively, a wide range of synthetic flavors are available that offer advantages over their natural counterparts in terms of purity, availability, stability and solubility.



Components

Flavors

Certain flavors are also associated with a (mild) therapeutic activity (e.g. many antacids contain mint due to the carminative properties of this ingredient).

Alternatively other flavors offer a taste-masking effect by eliciting a mild local anesthetic effect on the taste receptors (e.g. peppermint oil, chloroform and menthol).



Components

Colors

These are generally natural or synthetic water soluble, photo-stable ingredients that are selected according to the flavour of the preparation.

For example, mint-flavoured formulations are commonly a green colour, whereas in banana-flavoured solutions a yellow colour is commonly employed.

Such ingredients must not chemically or physically interact with the other components of the formulation.





Preparations of Syrups

Methods of Preparation of Syrups

Syrups are most frequently prepared by one of four general methods, depending on the physical and chemical characteristics of the ingredients:

1. Solution 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
4. Percolation of either the source of the medicating substance or the sucrose.



Solution with the Aid of Heat

Method

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.

1. The sugar is generally added to the purified water, and heat is applied until the sugar is dissolved.
2. Other 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.
3. If heat-labile agents or volatile substances, such as volatile flavoring oils and alcohol, are to be added, they are generally added to the syrup after the sugar is dissolved by heat, and the solution is rapidly cooled to room temperature.



Solution with the Aid of Heat

Inversion

The use of heat facilitates rapid solution of the sugar and certain other components of syrups

However, caution must be exercised against becoming impatient and using excessive heat.

Sucrose, a disaccharide, may be hydrolyzed into monosaccharides, dextrose (glucose), and fructose (levulose).

This hydrolytic reaction is inversion, and 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.



Solution with the Aid of Heat Inversion

When the syrup is greatly overheated, it becomes amber colored as the sucrose caramelizes.

Syrups so decomposed are more susceptible to fermentation and to microbial growth than the stable, undecomposed syrups.

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

The use of boiled purified water in the preparation of a syrup can enhance its permanency, and the addition of preservative agents, when permitted, can protect it during its shelf life.



Solution by Agitation Method

To avoid heat-induced inversion of sucrose, a syrup may be prepared without heat by agitation.

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.

This process is more time consuming than the use of heat, but the product has maximum stability.

Sometimes, simple syrup or some other non-medicated syrup, rather than sucrose, is employed as the sweetening agent and vehicle.



Solution by Agitation Method

When solid agents are to be added to a syrup, it is best to dissolve them in minimal amount of purified water and incorporate the resulting solution into the syrup.

When solid substances are added directly to a syrup, they dissolve slowly because the viscous nature of the syrup does not permit the solid substance to distribute readily throughout the syrup to the available solvent and also because a limited amount of available water is present in concentrated syrups.



Addition of Sucrose to a Medicated Liquid Method

Occasionally, a medicated liquid, such as a tincture or fluidextract that contain alcohol-soluble constituents, is employed as the source of medication in the preparation of a syrup.

If the alcohol-soluble components are unnecessary components of the corresponding syrup, they are generally removed by mixing the tincture or fluidextract with water, allowing the mixture to stand until separation of the water insoluble agents is complete, and filtering them from the mixture.

The filtrate is the medicated liquid to which the sucrose is added in preparation of the syrup.



Percolation Method

In the percolation method, either sucrose may be 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.

This latter method really is two separate procedures: first the preparation of the extractive of the drug and then the preparation of the syrup.

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.



References

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