Syrups

Syrups are concentrated aqueous preparations of a sugar or sugar substitute with or without flavoring agents and medicinal substances.

Syrups containing flavoring agents but not medicinal substances are called non medicated or flavored vehicles (syrups). Some official, previously official, and commercially available non medicated syrups are presented in the following table.

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.
Ora-Blend	A preblended combination of Ora-Sweet and Ora-Plus (1:1) and Ora-Sweet SF and Ora-Plus (1:1)
PCCA Acacia Syrup	A sweet, demulcent suspending vehicle with a mild vanilla flavor
PCCA-Plus Oral Suspending Vehicle	A preserved, buffered vehicle with demulcent qualities
PCCA Sweet SF	A sugar-free syrup containing sorbitol and can be used in diabetic patients as well as others
PCCA Syrup	A syrup vehicle with less sucrose than Syrup NF
Raspberry syrup	Sucrose-based syrup with raspberry juice about 48% by volume. Pleasant-flavored vehicle to disguise salty or sour taste of saline medicaments
SyrSpend™ SF Suspension Vehicle	A low osmolality suspending vehicle using modified starch technology. It is buffered at pH 4.2; it is sugar-free and paraben-free; it is available in unflavored, cherry, and grape formulations.
SyrSpend™ SF Alka	An alkaline suspension vehicle with a pH of about 7.0, when reconstituted as directed. It is low osmolality (<50 mOsmol), pleasant-tasting, sugar-free, alkaline medium available in unflavored and cherry formulas
Syrup	85% sucrose in purified water. Simple syrup may be used as the basis for flavored or medicated syrups.

These syrups are intended to serve as pleasant-tasting vehicles for medicinal substances to be added in the extemporaneous compounding of prescriptions or in the preparation of a standard formula for a medicated syrup, which is a syrup containing a therapeutic agent.

Components of Syrups:

Most syrup contains the following components in addition to the purified water and any medicinal agents present:

(*a*) The sugar, usually sucrose, or sugar substitute used to provide sweetness and viscosity;

(*b*) Antimicrobial preservatives;

(*c*) Flavorants; and

(*d*) Colorants.

Also, many types of syrups, especially those prepared commercially, contain special solvents (including alcohol), solubilizing agents, thickeners, or stabilizers.

Pharmaceutically syrups are classified best according to their basic formulas:

1. **Sugar based syrup:** which are concentrated solution of sugar.
2. **Artificial syrup:** which are formulated with artificial sweetening agents and viscosity builders.

Although there are many different sugars, sucrose and dextrose have been only used in the preparation of syrup, sucrose is obtained from sugar cone, sugar beet or less commonly sugar muple.

Sucrose is one of the purest of commercially available substances and is the preferred carbohydrate for syrup because of purity, degree of sweetness, lack of color & ease of handling.

Sucrose is the sugar most frequently employed in syrups, although in special circumstances, it may be replaced in whole or in part by other sugars or substances such as sorbitol, glycerin, and propylene glycol.

In some instances, all glycogenetic substances (materials converted to glucose in the body), including the agents mentioned earlier, are replaced by nonglycogenetic substances, such as methylcellulose or hydroxyethylcellulose.

These two materials are not hydrolyzed and absorbed into the blood stream, and their use results in an excellent syrup-like vehicle for medications intended for use by diabetic patients and others whose diet must be controlled
and restricted to nonglycogenetic substances. The viscosity resulting from the use of these cellulose derivatives is much like that of sucrose syrup.

Formulation of sugar based syrups:

Stability of aqueous sucrose solutions:

In order to formulate syrup properly, one must consider the properties of the basic vehicle particularly its stability, sucrose is subjected to two degradative pathways in aqueous solution fermentation and hydrolysis.

Most syrup contain a high proportion of sucrose, usually 60% to 80%, not only because of the desirable sweetness and viscosity of such solutions but also because of their inherent stability in contrast to the unstable character of dilute sucrose solutions.

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.

Syrup, NF, also called simple syrup. It is prepared by dissolving 85 g of sucrose in enough purified water to make 100 mL of syrup. The resulting preparation generally requires no additional preservation if it is to be used soon; in the official syrup, preservatives are added if the sucrose concentration is less than 85% or syrup is to be stored. When properly prepared and maintained, the syrup is inherently stable and resistant to the growth of microorganisms

Preservative used in syrup include benzoic acid ,butyl paraben ,sorbic acid ,glycerin ,alcohol etc. benzoates ,butyl paraben ,sorbic acid are most effective in acidic solution ,they in effective as preservative in alkaline solution mixtures of parabens are frequently employed to take advantage of their potentiating effect.

The amount of added preservative which is needed in those syrups containing reduced sugar concentration may be estimated from knowledge of calculated free water.e.g.100 mL of 65% w/v sucrose solution is equivalent to x76.5 mL of 85% w/v syrup and 23.5 mL of water.

85/100 = 65/X

X= 76.5 mL

100 – 76.5 =23.5 mL free water

The more free water the more preservative required in the product.

e.g 0.1% for preservative if 23.5 mL of free water ,so

0.1 × 23.5 /100 = 0.0235

Frequently, alcohol is used in syrups to assist in dissolving the alcohol-soluble ingredients, but normally, it is not present in the final product in amounts that would be considered to be adequate for preservation (15% to 20%).

In sealed container vaporization of water from syrup and its subsequent condensation on the syrup result in the formation of dilute solution of sucrose on the surface and this can support mold growth.

Incompatibilities:

1. If a preparation containing high concentration of alcohol sucrose will crystallize, simple syrup can tolerate 10% alcohol without crystallization.
2. When solution containing pectin are mixed with sucrose syrup .Gellation is observed since sucrose partially dehydrate pectin.
3. When syrup dehydrated with aqueous solution the necessity for additional preservative should be considered.

Generally syrup stored at room tempreture in tightly stoppered well filled bottles while refrigeration inhibits both mold growth and inversion and may be required for some syrup .It may cause crystallization of the sucrose .Large crystals which form are difficult to redissolve The supernatant liquid may contain significantly lower concentration of sucrose.

Preparation of syrup:

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

a) Solution of the ingredients with the aid of heat.
b) Solution of the ingredients by agitation without the use of heat or the simple admixture of liquid components.
c) Addition of sucrose to a prepared medicated liquid or to a flavored liquid.

d) Percolation of either the source of the medicating substance or the sucrose. Sometimes syrup is prepared by more than one of these methods, and the selection may simply be a matter of preference on the part of the pharmacist.

1. 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. In this method, 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, the mixture is allowed to cool, and its volume is adjusted to the proper level by the addition of purified water.

If heatlabile 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.

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.

When heat is applied in the preparation of 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 the reaction.

The sweetness of the syrup is altered because invert sugar is sweeter than sucrose, and the normally colorless syrup darkens because of the effect of heat on the levulose portion of the invert sugar.

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 syrup can enhance its permanency, and the addition of preservative agents, when permitted, can protect it during its shelf life. Storage in a tight container is a requirement for all syrups.

2. Solution by Agitation Without the Aid of Heat

To avoid heat-induced inversion of sucrose, syrup may be prepared without heat by agitation. On a small scale, 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 nonmedicated syrup, rather than sucrose, is employed as the sweetening agent and vehicle. In that case, other liquids that are soluble in the syrup or miscible with it may be added and thoroughly mixed to form a uniform product.

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 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 or to a Flavored Liquid

Occasionally, a medicated liquid, such as a tincture or fluidextract, is employed as the source of medication in the preparation of syrup. Many such tinctures and fluidextracts contain alcohol-soluble constituents and are prepared with alcoholic or hydroalcoholic vehicles. If the alcohol-soluble components are desired medicinal agents, some means of rendering them water soluble is employed.

However, if the alcohol-soluble components are undesirable or 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. If the tincture or fluidextract is miscible with aqueous preparations, it may be added directly to simple syrup or to flavored syrup.

Percolation

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. The drug ipecac, which consists of the dried rhizome and roots of *Cephaëlis ipecacuanha*, contains the medicinally active alkaloids emetine, cephaline, 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 15 mL.

Dextrose based syrup

Dextrose may be used as substitute for sucrose in syrup containing strong acids in order to eliminate the discoloration associated with carmelization e.g. hypophosphites and compound syrup of hypophosphites.Hydriodic acid syrup using dextrose. Ferrous iodide syrup containing dextrose have been formulated.Dextrose based syrups do not turn brown in acidic solution but they are subjected to other difficulties.

Dextrose forms a saturated solution in water at 70% (w/v) which is less viscous than simple syrup. Dextrose dissolves more slowly than sucrose and is less sweet.

The saturated solution of dextrose readily supports growth of microorganisms: consequently, it is more easily fermented .Preservative are required to improve the keeping quantities of such syrups. Glycerin may be added in 30 to 45 % (v/v) concentration to act as preservative, increase the viscosity and also give additional sweetness to the preparation. However syrups which contain glycerin and strong acids tend to develop a butyric odor on aging. Alternatively ,other preservative and artificial sweetening agents e.g saccharine sodium,could be use in place of glycerin.

Application of Solubilization to Syrup Formulation

Alternative formulations which are based on surfactant have been proposed for Tolu Balsam, Aromatic Eriodictyon and Orange syrup. Introduction of solubilizing agent in the formulation enable considerable simplification in manufacturing procedure. For e.g a Tolu Syrup could be prepared by combining simple syrup with Tween 20 (non ionic surfactant), glycerin and tincture of tolu balsam. No clarification is required .Relatively large amounts of surfactant (30%) are needed for this purpose.

The problems arising from the use of solubilizing agents in liquid formulation include: foaming, alteration in flavor (particularly the development of bitter aftertaste) and reduce stability with respect to mold growth.

Syrups prepared with solubilizers may separate into two layers, one rich in surfactant and the other rich in water .These difficulties may be partially eliminated by proper selection of solubilizing agent for the formulation and the addition of other substances (e.g. antifoaming agents) to counteract some of undesirable effects.

Formulation of Artificial Syrups

Non Nutritive Syrups

Several formulas have been published for sugar free vehicles which are intended as substitutes for syrups and are to be administered to persons who must regulate their sugar and/or caloric intake accurately. For e.g person suffering from diabetes mellitus, which characterized by hyperglycemia (higher than normal blood sugar levels), need such preparation.

Some early formulas included glycerin in order to take advantage of its viscosity and sweetness. However glycerin as well as alcohol and propylene glycol are glycogenetics substances, i.e., they are material converted into glucose in the body either directly or indirectly. Substances to be used as sugar substitutes should also be nonglycogenetic.

Sodium carboxymethyl cellulose

(Medium viscosity grade) 1.5%

Sweetening Agent qs.

Purified water qs

The carboxymethyl cellulose a derived gum function as bodying agent (viscosity builder).Some investigation have proposed the use of natural gum such as acacia and tragacanth for this purpose. However syrup prepared from these gums are not colorless (tragacanth produces opalescent product)and tend to change their characteristics upon aging. Sodium alginate and methylcellelose also have been used as the base for sugar free syrups. These substances are nonglycogenetic and produce clear colorless product .Unlike methyl cellulose which is nonionic ,the anionic alginate and carboxymethyl cellulose may exhibit incompatibilities with cationic drugs.

Strong dehydrating agents cause coagulation of aqueous dispersion of both natural and derived gums.Consequantly these syrups are incompatible with excessive amount of alcohol and electrolytes. Evidence of incompatibilities may be either simple increase or decrease in viscosity or in extreme cases gelation or precipitation. Solution of methyl cellulose unlike those of other gums, gel when heated, since methylcellelose is less soluble at elevated tempretures owing to dehydration of polymer. Preservative must be included in the formulation since aqueous solutions of gums readily support growth of microorganisems.

Non nutritive synthetic sweetening agents are required in the formulation .Saccharine sodium rated 300 to 550 times as sweet as sucrose.It may be used in concentration of 0.1-0.2 % but it is characterized by a bitter after taste which detracts from the desirable properties of syrup. Compound Sodium Cyclamate solution was the recommended sweetener in these formulas. It is 30 to 40 times as sweet as sucrose and has significantly less after taste than saccharine. The preferred sweetening agents combined both of these substances to make advantage of synergistic sweetening effect that saccharine has on sodium cyclamate,with minimum after taste. The main disadvantage of cyclamate that it has carcinogenic

effect on rat. New synthetic sweeteners will no doubt be developed ,which can included in this type of formulation.Aspartylphenylalanine methyl ester is a potential new low caloric sweetener reported to be about 160 times sweeter than sucrose in aqueous solution.

Sorbitol- Base syrup

Sorbitol is hexahydric alcohol ($C_6H_{14}O_6$) made by hydrogenation of glucose, has led to its use as a major component of proprietary syrup formulation .Crystaline sorbitol is white odorless and nonvolatile solid .It is used most in the form of a 70 % (w/w) aqueous solution.

Sorbitol solution is not irritating to the membrane of the mouth and the throat. Unlike sucrose it apparently does not contribute to the formation of dental caries.It is metabolized and converted to glucose: however it is not absorbed from GIT as rapidly as sucrose. No significant hyperglycemia has been found and consequently it may be used as component of non nutritive vehicle. On other hand ingestion of excessive quantities of it may have laxative effect.

Sorbitol solution is about 60% as sweet as sucrose and half as viscous as simple syrup. It has excellent mouth feel qualitities and lacks the acrid characteristics of some polyols (propylene glycol).Improved flavor characteristics and reduce sweetness may result when sorbitol solution is included in sugar based formulation .It is compatible with other polyols and simple syrups; as much as 10% (v/v) of alcohol can be added before crystallization is observed. Sorbitol in common with other polyols such as glycerin is also added to sucrose based syrups to reduce the tendency of concentrated sugar solution to crystallize.

Application of Syrups

Syrups are intensely sweet vehicles which lack significant amount of alcohol and can function to mask the taste otherwise salty or bitter drugs.Their effectiveness as vehicle is due also to their high viscosity and mouth feel qualities .Syrups are often described as having body and smoothness. For these reasons they constitute the vehicle most widly used for pediatric medication.

An important advantage of syrup is their acceptability and wide variety of flavors. Beside traditional flavors such as orange, lemon and peppermint, more exotic flavors are employed .Flavored syrup of pleasing taste can be prepared from fresh fruit such as peaches and from compounded imitation flavor concentrates such as maple ,tuti fruti grape etc. Cherry was preferred for antibiotics, cough preparation and sulfa antibiotics; chocolate for sulfonamides; and orange for vitamins.

Saline drugs (bromide, ammonium chloride, etc) are masked most effectively by spicy syrups such as ginger and cinnamonor by fruit syrup. The latter characterized by a tart taste arising from the presence of weak acids in syrup.

Fruit syrups prepared from imitation flavors (e.g. cherry) are not effective in masking salty taste unless weak acids are added. For this reason citric acid is a component of orange syrup USP .The tartness of these syrups is required to mask the saline taste. Fruit syrups are effective in masking sour drugs also , because of their natural association. On other hand fruit flavored syrups are not effective masking agents for bitter taste drugs. Whether or not a weak acid is present in the syrup makes little difference.

Preparation involving bitter drugs (e.g amines and their derivatives) present a major taste problem in the design of vehicles. Since the threshold for eliciting a bitter taste is very low and the taste itself is persistent.

Syrups which have proved most effective in masking bitter taste are compound sarsaparilla NF XI. Aromatic Eriodictyon and cocoa syrup. Eriodictyon syrup is believed to be effective because resinous constituents have mild anesthetic effect on the taste receptors. Because of its alkalinity this syrup may be incompatable with amine salt and cause their precipitation (which would go unnoticed in dark syrup).The alkalinity of this syrup may account for its effectiveness in reducing the bitter taste of alkaloids.

Cocoa syrup is the best vehicle for bitter drugs because of its high viscosity; in effect it coats the tongue and thus it tends to inhibit diffusion of the drug to the taste buds .Drugs which are present in low concentration may be adsorbed significantly by the high concentration of suspended cocoa solids, thus accounting for the effectiveness of the syrup in masking taste.