International Journal of Advances in Pharmaceutics
ISSN: 2320–4923; DOI: 10.7439/ijap
Volume 4 Issue 2 [2015]
Journal home page: http://ssjournals.com/index.php/ijap

Review Article

Review on artificial sweeteners used in formulation of sugar free syrups

Afaque Raza Mehboob Ansari*, Saddamhusen Jahangir Mulla and Gosavi Jairam Pramod

Department of Quality Assurance, D.S.T.S. Mandal's College of Pharmacy, Jule Solapur-1, Bijapur Road, Solapur- 413004, Maharashtra, India.

***Correspondence Info:**
Prof. Afaque Raza Mehboob Ansari
Department of Quality Assurance,
D.S.T.S. Mandal's College of Pharmacy, Jule Solapur-1, Bijapur Road, Solapur- 413004, Maharashtra, India
Email: afaque.ansari@rediffmail.com

Keywords:
Sugar free syrup,
Artificial sweeteners,
Diabetes mellitus,
Sucralose, and
Aspartame.

Abstract

Sweetening agents are employed in liquid formulations designed for oral administration specifically to increase the palatability of the therapeutic agent. The main sweetening agents employed in oral preparations are sucrose, liquid glucose, glycerol, Sorbitol, saccharin sodium and aspartame. The use of artificial sweetening agents in formulations is increasing and, in many formulations, saccharin sodium is used either as the sole sweetening agent or in combination with sugars or Sorbitol to reduce the sugar concentration in the formulation. The use of sugars in oral formulations for children and patients with diabetes mellitus is to be avoided. The present review discusses about the Artificial sweetening agents which are generally used while the preparation of Sugar-free Syrup.

1. Introduction

Syrups are highly concentrated, aqueous solutions of sugar or a sugar substitute that traditionally contain a flavoring agent, e.g. cherry syrup, cocoa syrup, orange syrup, raspberry syrup. An unflavored syrup is available that is composed of an aqueous solution containing 85% w/v sucrose (USP). Therapeutic agents may either be directly incorporated into these systems or may be added as the 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. It should also be remembered that 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.

2. The major components of syrups are as follows:

- Purified water
- Sugar (sucrose) or sugar substitutes (artificial sweeteners).

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 are not required. As the concentration of sucrose is reduced from the upper limit (e.g. through dilution), the addition of preservatives may be required. In some formulations, other non-sucrose bases may replace traditional syrup. One of the most popular is Sorbitol Solution, which contains 64% w/w Sorbitol although other alternatives are available that are based on mixtures of Sorbitol and glycerin. 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. 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. 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.

An important class of sugar substitutes is known as high-intensity sweeteners. These are compounds with many times the sweetness of sucrose, common table sugar. As a result, much less sweetener is required and energy contribution is often negligible. The sensation of sweetness caused by these compounds (the "sweetness profile") is sometimes notably different from sucrose, so they are often used in complex mixtures that achieve the most natural sweet sensation. [1]

In the United States, seven intensely sweet sugar substitutes have been approved for use. They are stevia, aspartame, sucralose, neotame, acesulfame potassium (Ace-K), saccharin, and advantame. Cyclamates are used outside the U.S., but have been prohibited in the U.S. since 1969. There is some ongoing controversy over whether artificial sweetener usage poses health risks [2]. The majority of sugar substitutes approved for use are artificially synthesized compounds. However, some bulk natural sugar substitutes are known, including Sorbitol and xylitol, which are found in berries, fruit, vegetables, and mushrooms. It is not commercially viable to extract these products from fruits and vegetables, so they are produced by catalytic hydrogenation of the appropriate reducing sugar. For example, Xylose is converted to xylitol, lactose to lactitol, and glucose to Sorbitol. Other natural substitutes are known but are yet to gain official approval for food uses.

Some non-sugar sweeteners are polyols, also known as "sugar alcohols". These are, in general, less sweet than sucrose but have similar bulk properties and can be used in a wide range of medicinal products. Sometimes the sweetness profile is 'fine-tuned' by mixing with high-intensity sweeteners. As with all food products, the development of a formulation to replace sucrose is a complex proprietary process [3].

3. Reasons for use

Artificial Sweeteners are used for a number of reasons including

3.1 To assist in weight loss –

Some people choose to limit their energy intake by replacing high-energy sugar or corn syrup with other sweeteners having little or no food energy. This allows them to eat the same foods they normally would while allowing them to lose weight and avoid other problems associated with excessive caloric intake.

3.2 **Dental care**

Sugar substitutes are tooth-friendly, as they are not fermented by the micro flora of the dental plaque. An example of a sweetener that can benefit dental health is xylitol. Xylitol works to prevent bacteria from adhering to the tooth surface, thus preventing plaque formation and eventually decay. The carbohydrates and sugars consumed usually adhere to the tooth enamel. Bacteria can feed upon this food source allowing them to quickly multiply. As the bacteria feed upon the sugar, they convert it to acid waste that in turn decays the tooth structure. Xylitol cannot be fermented by these bacteria, so the bacteria have difficulty thriving, thus helping to prevent plaque formation.

3.3 **Diabetes mellitus**

People with diabetes have difficulty regulating their blood sugar levels. By limiting their sugar intake with artificial sweeteners, they can enjoy a varied diet while closely controlling their sugar intake. Also, some sugar substitutes do release energy but are metabolized more slowly, potentially allowing blood sugar levels to remain more stable over time.

3.4 **Reactive hypoglycemia**

Individuals with reactive hypoglycemia will produce an excess of insulin after quickly absorbing glucose into the blood stream. This causes their blood glucose levels to fall below the amount needed for proper body and brain function. As a result, like diabetics, they must avoid intake of high-glycemic foods like white bread, and often choose artificial sweeteners as an alternative.

3.5 Avoiding processed foods

Individuals may opt to replace refined white sugar with less-processed sugars, such as fruit juice or maple syrup.

3.6 Cost

Many sugar substitutes are cheaper than sugar. Alternative sweeteners are often low in cost because of their long shelf-life and high sweetening intensity. This allows alternative sweeteners to be used in products that will not perish after a short period of time.[3]

4. Agents used as artificial sweetener

4.1 Aspartame

It is an odorless, white crystalline powder that is derived from the two amino acids aspartic acid and phenylalanine. It is about 200 times as sweet as sugar and can be used as a table top sweetener or in frozen desserts, gelatins, beverages, and chewing gum. When cooked or stored at high temperatures, aspartame breaks down into its constituent amino acids. This makes aspartame undesirable as a baking sweetener. It is more stable in somewhat acidic conditions, such as in soft drinks. Though it does not have a bitter aftertaste like saccharin, it may not taste exactly like sugar. When eaten, aspartame is metabolized into its original amino acids. Because it is so intensely sweet, relatively little of it is needed to sweeten a food product, and is thus useful for reducing the number of calories in a product.

The safety of aspartame has been studied extensively since its discovery with research that includes animal studies, clinical and epidemiological research, and post marketing surveillance, with aspartame being one of the most rigorously tested food ingredients to date. Aspartame has been subject to multiple claims against its safety, including supposed links to cancer as well as complaints of neurological or psychiatric side effects. Multiple peer-reviewed comprehensive review articles and independent reviews by governmental regulatory bodies have analyzed the published research on the safety of aspartame and have found aspartame is safe for consumption at current levels. Aspartame has been deemed safe for human consumption by over 100 regulatory agencies in their respective countries, including the UK Food Standards Agency, the European Food Safety Authority. [4,5]

4.2 Cyclamate

In the United States, the Food and Drug Administration (FDA) banned the sale of cyclamate in 1969 after lab tests in rats involving a 10:1 mixture of cyclamate and saccharin indicated that large amounts of cyclamates causes bladder cancer, a disease to which rats are particularly susceptible. Cyclamates are still used as sweeteners in many parts of the world, including Europe

4.3 Saccharin

Aside from sugar of lead, saccharin was the first artificial sweetener and was originally synthesized in 1879 by Remsen and Fahlberg. Its sweet taste was discovered by accident. It had been created in an experiment with toluene derivatives. A process for the creation of saccharin from phthalic anhydride was developed in 1950, and, currently, saccharin is created by this process as well as the original process by which it was discovered. It is 300 to 500 times as sweet as sugar (sucrose) and is often used to improve the taste of toothpastes, dietary foods, and dietary beverages. The bitter aftertaste of saccharin is often minimized by blending it with other sweeteners.

Fear about saccharin increased when a 1960 study showed that high levels of saccharin may cause bladder cancer in laboratory rats. In 1977, Canada banned saccharin due to the animal research. In the United States, the FDA considered banning saccharin in 1977, but Congress stepped in and placed a moratorium on such a ban. The moratorium required a warning label and also mandated further study of saccharin safety.

Subsequent to this, it was discovered that saccharin causes cancer in male rats by a mechanism not found in humans. At high doses, saccharin causes a precipitate to form in rat urine. This precipitate damages the cells lining the bladder (urinary bladder urothelial cytotoxicity) and a tumor forms when the cells regenerate (regenerative hyperplasia). According to the International Agency for Research on Cancer, part of the World Health Organization, "Saccharin and its salts was (sic) downgraded from Group 2B, possibly carcinogenic to humans, to Group 3, not classifiable as to carcinogenicity to humans, despite sufficient evidence of carcinogenicity to animals, because it is carcinogenic by a non-DNA-reactive mechanism that is not relevant to humans because of critical interspecies differences in urine composition."

In 2001 the United States repealed the warning label requirement, while the threat of an FDA ban had already been lifted in 1991. Most other countries also permit saccharin but restrict the levels of use, while other countries have outright banned it.

The EPA has officially removed saccharin and its salts from their list of hazardous constituents and commercial chemical products. In a December 14, 2010, release the EPA stated that saccharin is no longer considered a potential hazard to human health.[6]

4.4 Sucralose

Sucralose is a chlorinated sugar that is about 600 times as sweet as sugar. It is produced from sucrose when three chlorine atoms replace three hydroxyl groups. Unlike other artificial sweeteners, it is stable when heated and can therefore be used in baked and fried goods. About 15% of sucralose is absorbed by the body and most of it passes out of the body unchanged.

Sucralose is prepared from either of two sugars, sucrose or raffinose. With either base sugar, processing replaces three oxygen-hydrogen groups in the sugar molecule with three chlorine atoms.

There are few safety concerns pertaining to sucralose and the way sucralose is metabolized suggests a reduced risk of toxicity. For example, sucralose is extremely insoluble in fat and, thus, does not accumulate in fatty tissues; sucralose also does not break down and will dechlorinate only under conditions that are not found during regular digestion (i.e., high heat applied to the powder form of the molecule).[7]

4.5 Mannitol

Mannitol (also referred to as mannite or manna sugar) is a white, crystalline solid that looks and tastes sweet like sucrose. Mannitol is classified as a sugar alcohol; that is, it is derived from a sugar (mannose) by reduction. Other sugar alcohols include xylitol and Sorbitol. Mannitol and Sorbitol are isomers, the only difference being the orientation of the hydroxyl group on carbon 2. It is on the World Health Organization's List of Essential Medicines.

4.6 Xylitol

Xylitol is a sugar alcohol used as a sweetener. Xylitol is categorized as a polyalcohol or sugar alcohol (alditoll. Xylitol is roughly as sweet as sucrose (table sugar), with 33% fewer calories. Unlike other natural or synthetic sweeteners, xylitol is actively beneficial for dental health by reducing caries (cavities) to a third in regular use and helpful to remineralization.[3] Multiple studies utilizing electron microscopy have indicated that xylitol is effective in inducing remineralization of deeper layers of demineralized enamel.

Xylitol is naturally found in low concentrations in the fibers of many fruits and vegetables, and can be extracted from various berries, oats, and mushrooms, as well as fibrous material such as corn husks and sugar cane bagasse, and birch. However, industrial production starts from xylan (a hemicellulose) extracted from hardwoods or corncobs, which is hydrolyzed into xylose and catalytically hydrogenated into xylitol. A study in rats found that xylitol had reduced or nonexistent side effects compared to other artificial sweeteners, and lower caloric value and carcinogenicity than sucrose.

4.7 Maltitol

Maltitol is a sugar alcohol (a polyol) used as a sugar substitute. It has 75-90% of the sweetness of sucrose (table sugar) and nearly identical properties, except for browning. It is used to replace table sugar because it is half as caloric, does not promote tooth decay, and has a somewhat lesser effect on blood glucose. In chemical terms, Maltitol is known as 4-O-α-glucopyranosyl-D-sorbitol. It is used in commercial products under trade names such as Lesys, Maltisweet and Sweet Pearl.

4.8 Sorbitol

Sorbitol, also known as glucitol, is a sugar alcohol with a sweet taste which the human body metabolizes slowly. It can be obtained by reduction of glucose, changing the aldehyde group to a hydroxyl group. Most Sorbitol is made from corn syrup, but it is also found in apples, pears, peaches, and prunes. It is converted to fructose by Sorbitol-6-phosphate 2-dehydrogenase. Sorbitol is an isomer of Mannitol, another sugar alcohol; the two differ only in the orientation of the hydroxyl group on carbon 2.While similar, the two sugar alcohols have very different sources in nature, melting points, and uses. Sorbitol is a sugar substitute. It may be listed under the inactive ingredients listed for some foods and products. Sorbitol has approximately 60% the sweetness of sucrose.

4.9 Acesulfame K

Acesulfame K or acesulfame potassium was approved by the Food and Drug Administration in July 1988. Acesulfame K is an organic salt, containing sulfur and nitrogen, which is 150 to 200 times sweeter than sugar. It is marketed under the brand name Sunett and as Sweet One table-top sweetener. It is used in beverages, baked goods and candies. It has a good shelf life and is relatively temperature and pH stable.[8]

5. Conclusion

There are many over-the-counter combination syrups available for the management of cough. These are the mainstay of therapy in case of nonspecific cough and may act as adjuvant in addition to treatment of the specific cause, in case of cough associated with other conditions. Combination of drugs in a formulation i.e. multicomponent form increases patient compliance and provides better therapeutic action as compared to the other single component system Artificial sweeteners are also called non-nutritive sweeteners because they have very little, if any, caloric value. Because of this, they are commonly used in weight loss programs. They also have the advantage of being high intensity sweeteners, which make them more economic since the manufacturer uses very little to get the same result as table sugar or high fructose corn syrup. Artificial sweeteners are also great if you are diabetic, as they have very little or no affect on blood sugar. Artificial sweeteners such as xylitol are often used in gum because they don't contribute to dental decay or cavities. Common artificial sweeteners include aspartame, saccharine, sucralose, neotame and acesulfame potassium.

Acknowledgement

The authors are humbly thankful to D.S.T.S. Mandal's College of Pharmacy, Solapur for providing lab and library facilities.

References

[1] D Jones; Dosage form and Design pharmaceutical press, London, Chicago, 2012;17-18
[2] "High-Intensity Sweeteners". U.S. Food and Drug Administration. May 19, 2014. Retrieved September 17, 2014.
[3] http://en.wikipedia.org/wiki/Encyclopedia
[4] Aspartame. EFSA. Retrieved 23 September 2010.
[5] "Aspartame". Health Canada. Retrieved 23 September 2010
[6] J.J McKetta; Encyclopedia of Chemical Processing and Design: Volume 56, page no. 69-72.
[7] Merck Index, 11th Edition, 1989; 8854.
[8] Dr. K.O Donnell, Dr. M.W Kearsley; Sweeteners and Sugar Alternatives in Food Technology, Second Edition, 2012; page No-32-46.
[9] R.C Rowe, P.J Sheske, S.C Owen; Handbook of Pharmaceutical Excipients. The Pharmaceutical Press, fifth edition 2006.
[10] http://www.health.com/health/gallery/0,,20424821_3,00.html
[11] http://healthyeating.sfgate.com/