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SUGAR SUBSTITUTES: AN OVERVIEW

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ABSTRACT

Increased awareness of obesity-related health issues has resulted in greater use of sugar substitutes in food and pharmaceutical industry. Artificial sweeteners and sugar substitutes were developed to overcome these limitations and they have since then gone on to become a rapidly growing industry. Not only has the food industry, the pharmaceutical industry too benefitted from the research and development work done in this sector since they form an integral part of taste-masking technology. These substitutes not only mimic sugar in taste but also have lower calorific values. They can be used in pharmaceutical formulations for all age groups overcoming previous limitations for patients bearing risk factors such as diabetes and obesity. However, there exist divided opinions on the use of such sweeteners even though there have been extensive studies conducted on them over the years. This article covers the current FDA approved intense sweeteners viz. saccharin, aspartame, neotame, advantame, sucralose, acesulfame-K, stevia and swingle fruit and the bulk sweeteners viz. sorbitol, maltitol, mannitol, xylitol, erythritol, isomalt and lactitol. A brief review of their physiological effects, their safety and legal aspects is done.

KEYWORDS:- Sweeteners, sugar-substitutes, non-nutritive sweeteners, bulk sweeteners, low-calorie, Acceptable daily intake.

INTRODUCTION

The oral route is the simplest and safest route for systemic delivery of drugs. It is accepted by all age groups right from pediatrics to the geriatric population. However, palatability concerns govern this route of administration. To overcome this, various taste masking technologies have been developed over the years such as the use of flavorants, inclusion complexes, coatings, effervescent preparations, salt formations, solid dispersions and so on. One such simple, cost effective approach involves the use of sweeteners.

As per the European Food Safety Authority (EFSA) website, a sweetener is any substance that is used to impart a sweet taste in foodstuffs or may be used as a tabletop sweetener. Sweeteners can be classified broadly into nutritive and non-nutritive sweeteners as shown in figure 1. Over the years there has been a shift of trends towards non-cariogenic, low energy and low-insulinemic sugar alternatives due to increasing awareness on weight control and the importance of dental hygiene. Each sweetener has its own advantage and disadvantage in terms of sensory qualities and processibility. Some of the desirable attributes of a sweetener are a similar taste profile to sucrose, non/low-calorific value at normal use levels, non-cariogenic, safe, easily available, cost-effective and stable under desired processing conditions, compatible with other components, biodegradable and providing a pleasant mouthfeel.

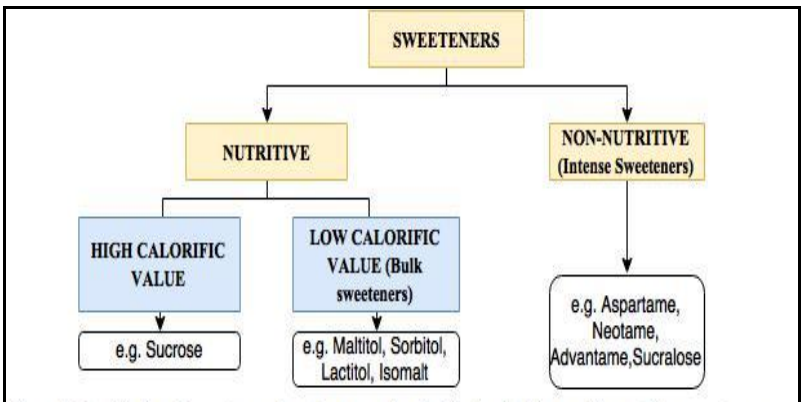

Figure 1. Classification of sweeteners. Sweeteners can be classified as Nutritive and Non-nutritive sweeteners. Low calorific nutritive sweeteners are used to give body and feel to pharmaceutical formulations whereas intense sweeteners being extremely potent make the preparations virtually sugar free.

Just like all food additives, a sweetener is a regulated substance and hence subject to safety evaluation prior to market approval. This approval is based on three main parameters i.e. the highest no-effect level, acceptable daily intake (ADI) and the estimated daily intake. Not all sweeteners bear the same global approval status from a regulatory perspective. One such famous example is that of cyclamate which was banned in the US shortly after its approval as it was found to cause bladder cancer in rats but continues to be used globally in over a hundred countries.[1]

LABELING REQUIREMENTS

Any product containing a sweetener shall bear on its label the name of the sweetener or the name of the sugar and the sweetener when used together. For products containing aspartame, it is mandatory to state on the label "PHENYLKETONURICS: CONTAINS

PHENYLALANINE". If more than 10% of added polyol is present, a warning label of "excessive consumption may produce laxative effects" should be used. The terms "calorie free", "zero calorie", "negligible source of calories", "without calories", etc. can be used on the label only if the product contains less than 5 calories per reference amount consumed and per labeled serving size and a claim of "reduced calorie" can only be used if there is an energy reduction of at least 1/3rd compared to normal (sugar containing) food (21 CFR 317.360).

This article gives an overview of 1) the 6 high-intensity sweeteners that are currently FDA approved: saccharin, aspartame, neotame, advantame, sucralose and acesulfame-K, 2) those bearing GRAS status: stevia and swingle fruit and 3) those commonly used as bulk low-calorie sweeteners: sorbitol, maltitol, xylitol, mannitol, erythritol, isomalt and lactitol.

A) HIGH-INTENSITY SWEETENERS

Saccharin

Necta Sweet®, Sweet 'n' Low®, Sweet Twin®, Sweetex®

Saccharin and its sweetness were discovered by Ira Remsen and Constantine Fahlberg at John Hopkins University in 1878. It derives its name from the latin word 'Saccharum' which means sugar. It is 300-700 times sweeter than sucrose.[1] Three forms of saccharin are commercially available: sodium saccharin, calcium saccharin and saccharin acid. Sodium saccharin is also known as soluble saccharin and is the most widely used form due to its high solubility. Calcium saccharin finds use in food products whereas saccharin acid is slightly soluble and is used in mouthwashes, toothpastes and pharmaceuticals.[2] It has a metallic aftertaste at normal use levels that is often masked by using it in combination with other sweeteners.[2]

Saccharin shows excellent stability to high temperatures and pH making it suitable for products requiring high processing temperatures. At acidic pH, the hydrolysis product is 2-sulfobenzoic acid while under alkaline conditions, degradation product is 2-sulfonamidobenzoic acid. Both are found as trace impurities in saccharin.[3]

Saccharin is slowly and incompletely absorbed from the intestine. It is not metabolized in humans and excreted almost completely by the kidneys with the remainder being removed in feces.[4] The JECFA has assigned saccharin an ADI of 5mg/kg BW/day.

Saccharin has been found to be safe for human consumption. Concerns related to its safety are primarily due to findings of bladder tumors in rats fed on diets high in saccharin.[5,6] However, it was later found that cancer causing mechanisms in rats are not applicable to humans. Hence in 2000, it was delisted from the National Toxicology Report on Carcinogens.[1] Another study on rats evaluated the relation between consumption of saccharin-sweetened beverages and weight gain. When used in specified quantities it is Generally Recognized as Safe (GRAS) listed by the FDA.

Aspartame

Natra Taste®, Nutrasweet®, Palsweet®, Equal®, Canderel®

Aspartame, discovered by J.D. Schlatter in 1965 at G.M. Searle is one of the most extensively studied food additives in the world. It is about 180-200 times sweeter than sucrose.[7] However; unlike other intense sweeteners because it is made from amino acids it has a calorific value of 4 kcal/g.[1] It is a dipeptide composed of two amino acids aspartic acid and phenyl alanine linked by a methyl ester.[8] The U.S. Food and Drug Administration (FDA) established an ADI of 50 mg/kg BW for aspartame (CFR, 2005) whereas the European Food Safety Authority (EFSA, 2006) after evaluating the long-term carcinogenicity of aspartame assigned it an ADI of 40 mg/kg BW/day.[9] The WHO has established an ADI of 0-40 mg/kg BW/day for aspartame, in both adults and children.[1]

In the case of aspartame Onset of sweetness often requires a slightly longer time than sucrose with a lingering taste which is often undesirable. To overcome this shortcoming it is often used as a blend with other intense sweeteners one such example is Twinsweet® an aspartame-acesulfame salt. Its solubility in water (pH 6-7 at 25˚C) is 1%.[2] Aspartame exhibits Lowest solubility at its isoelectric point of pH 5.4.[8] Stability of aspartame is a function of pH, temperature and time (stability decreases at elevated temperature and pH) with maximum stability at pH 4.2 and excellent stability in dry conditions (figure 2).[2] Aspartame loses its sweetness in solutions with a pH <3.9 and >4.3.[10]

Studies have shown that when the temperature of aspartame exceeds 86˚F the methanol in aspartame converts to formaldehyde and then formic acid, which in turn causes metabolic acidosis and blindness.[11] Methanol toxicity mimics multiple sclerosis and hence may often be misdiagnosed.[12] Aspartame is metabolized in the body to its constituent amino acids and methanol (Figure 3).

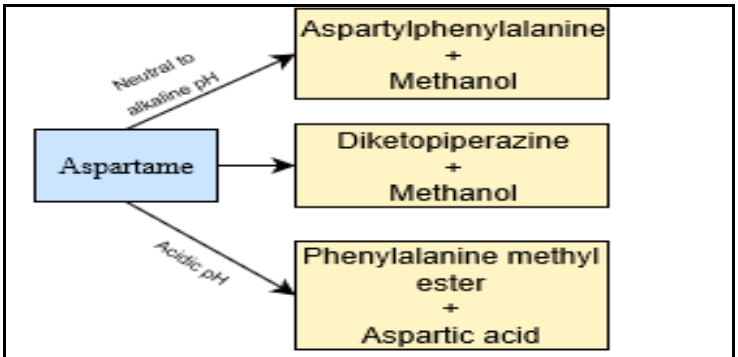

Fig.2.pH dependent decomposition of Aspartame

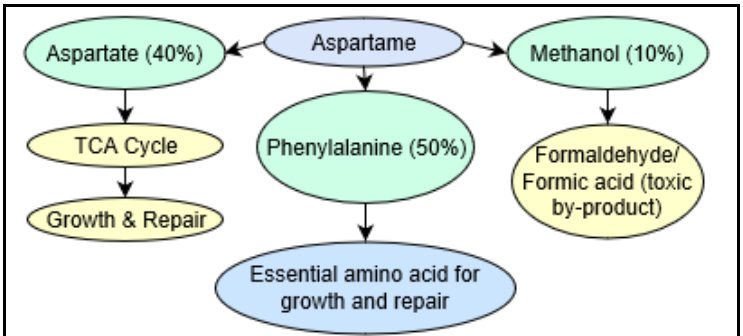

Fig.3. Aspartame on metabolism forms its constituent amino acids and methanol. These breakdown products are utilized by the body and hence unlike other intense sweeteners it has a calorific value.

The amino acids so formed are metabolized by the body accounting for its calorific value.[13] The three breakdown products of aspartame are all toxic if taken in higher doses. Phenyl alanine, an essential amino acid in the diet may lead to brain damage at elevated blood levels as observed in patients suffering from Phenylketonuria (PKU).[14] Studies in animal models have shown a positive correlation between aspartame consumption and seizure frequency which may be attributed to the phenylalanine levels, however, no such evidence was found in humans.[15,16]

High blood levels of aspartic acid were not found to exhibit any severe adverse effects.[14] Methanol in large doses is associated with toxicity. The methanol released on metabolism is oxidized in the liver to formaldehyde which has been shown to cause contact dermatitis of the eyelids.[17] However, when used in stated quantities the levels of methanol are inadequate to cause toxicity. Studies have also been conducted over the years on the effect of aspartame on the gut bacteria as its metabolite methanol is a known carcinogen which may alter this bacteria which forms the 1st line of intestinal defense.[18]

Several studies have been conducted over the years as a part of a post marketing surveillance program to identify the relation between aspartame and mutagenicity, genotoxicity, carcinogenicity, birth defects, attention deficit disorders but no strong evidence supporting any such claims have been found so far.[19,20] Due to the established safety information aspartame has been approved for use in more than 90 countries globally including United States, European Union (E951) and Japan.

Acesulfame-K

Sunette®, Sweet One®, Sweetex Plus®, Sweet and Safe®, Swiss Sweet®

Acesulfame- K was accidentally discovered by Clauss and Jensen in 1967 at a pharmaceutical company, Hoechst. It belongs to the class of dihydro-oxathiazinone dioxides. It is about 180-200 times sweeter than sucrose, but half as sweet as saccharin, hence, when used in quantities needed for adequate sweetness it leaves an aftertaste and so, is often used as a sweetener blend rather than as a single sweetener.[2] Such combinations not only provide a synergistic taste but also decrease the total amount of a sweetener that is used. It exhibits a rapid onset of sweet taste as compared to aspartame and sucralose without lingering.

It has been assigned an ADI of 15mg/kg BW by the JECFA. The actual consumption in the United States was found to be 20% of the ADI over a lifetime.[1] It is freely soluble in water. It has excellent long-term stability in the dry state. Stability in solution is a function of pH and temperature. At low pH and high temperatures (>200˚C) slight losses are detectable. Hydrolytic decomposition under extreme conditions may yield acetone, carbon dioxide, ammonium salts, sulphate and amino sulfonate.[21]

Acesulfame-K is absorbed quickly and excreted fast. It is not metabolized by bacteria in the oral cavity or the intestine. In humans, pharmacological effects that are attributable to potassium were seen. It passes through the body unmetabolised and is excreted primarily by the kidneys.[5] Acetoacetamide one of its breakdown products is toxic at high doses, however, like aspartame concentrations used for sweetening do not pose a safety hazard.[2]

Acesulfame-K was approved by the FDA despite poor-quality and inadequate test raising concerns over its potential toxicity and carcinogenicity. The National Toxicology Program (NTP) carried out toxicity studies on Genetically modified mice (GMM) rather than bioassays. The GMM test results were not considered as reliable determinants of the carcinogenicity of the compound.[22] There is a lack of sufficient data on the long-term effects

of acesulfame consumption. Despite multiple nominations over the years in the National Toxicology program bioassay program, such motions have been rejected and the compound has not been subjected to any such testing.[1]

Sucralose

Splenda®, SucraPlus®

Sucralose was discovered during a research program conducted at Queen Elizabeth College, at the University of London by Hough and his colleagues in 1976. Sucralose is a sucrose derivative (trichlorogalactosucrose) comprising of 2 chlorinated sugar molecules.[5] It is 600 times sweeter than sucrose with no unpleasant aftertastes.[14]

It is a white, crystalline, non-hygroscopic, free flowing powder.[23] Being a carbohydrate derivative, it retains 5 of its hydroxyl groups even after substitution of three by chlorine making it freely soluble in water.[5] Chlorination of fructose and glucose molecules makes it more resistant to acid as well as enzymatic hydrolysis. When exposed acidic conditions and high temperatures, dilute aqueous solutions slowly hydrolyze to constituent monosaccharides 1,6-dichloro-1,6-dideoxyfructose and 4-chloro-4-deoxygalactose.[24] Solutions show maximum stability at pH 5-6. At elevated temperatures, it may breakdown to carbon dioxide, carbon monoxide and traces of hydrogen chloride.[25]

A small amount of the ingested sucralose is absorbed and excreted mainly unchanged in feces. Two minor urinary metabolites have been identified in humans.[1] In 2006, FDA approved a health claim regarding the use of sucralose in the prevention of dental caries.[26] The ADI of sucralose was listed as 15mg/kg BW/day by the JECFA.

The safety of sucralose has been reviewed extensively and repeatedly over the years due to beliefs of the release of toxic chlorinated compounds. In a study published in 2013, it was seen that burning of sucralose at high temperatures resulted in the release of Polychlorinated dibenzo-p-dioxins and dibenzofurans, potentially toxic compounds.[27] Studies on rats have shown that sucralose may alter gut flora altering the bioavailability of nutrients and drugs. Grice and Goldsmith, 2000 have given an overview of the toxicity of sucralose. Studies on various animal groups have shown an increased number of lesions in the liver when administered with high-dose sucralose but, there was a lack of evidence on the progression of these lesions to neoplasms. Similar results were obtained in teratogenicity and neurotoxicity studies as well. No clinical or biochemical effects were observed in human volunteers during

clinical studies.[28] A recent study in 2014 showed that sucralose lowers blood glucose by enhancing GLP-1 release in presence of carbohydrates in healthy subjects but not those with type-2 diabetes.[29] Due to its safety background, sucralose has been strongly promoted among children to control childhood obesity, a global issue affecting the technologically driven world today.

Neotame

Newtame®

Neotame is a product of extensive research done to identify a high potency no-calorie sweetener. It was invented by the French scientist duo Claude Nofre and Jean-Marie Tinti by simple N-alkylation of aspartame.[8] It is 7000-13000 times sweeter than sucrose and about 40 times sweeter than aspartame. It has a clean sweet taste and shows the absence of any bitter or undesirable aftertastes. It is a crystalline solid with a solubility of 1% at 25˚C.[2] Solid form shows excellent stability with de-esterified neotame being a major degradant whereas solution stability is highly pH dependent with maximum stability at pH 4.5.[2] Neotame shows better heat stability than aspartame due to N-substitution which prevents intramolecular cyclization responsible for the formation of diketopiperazine derivatives. Divalent and trivalent cations and beta-cyclodextrins have been reported to improve the solubility of neotame.

Neotame is rapidly but incompletely absorbed (30%). Absorbed neotame is completely excreted in urine and feces. The major metabolite is de-esterified neotame which is excreted in feces.[30] Methanol is also formed as a by-product but levels are negligible and hence considered safe. Unlike aspartame, phenylalanine is not formed hence it is safe for consumption by patients suffering from PKU.[1]

Neotame has been approved for use in a number of markets including USA with an ADI of 2mg/kg body-weight daily assigned by the JECFA.[31] It has recently been approved in EU. Toxicity studies in dogs have shown elevated serum alkaline phosphatases, indicative of liver toxicity at 600mg/kg BW/day, with this in mind the EFSA has set the NOAEL at 200 mg/kg BW/day.[5] Another safety concern deals with the possibility of formation of nitrosamines (secondary amine of neotame reacts with nitrite from food/saliva) which are powerful carcinogens, however, all possible nitrosamines were synthesized by the producer and have been tested with the absence of any evidence of genotoxicity.[5]

Advantame

Advantame is the newest addition to the family of FDA approved (in 2014) high potency sweeteners developed by Ajinomoto Pharmaceuticals Company. It is an aspartame derivative comprising of aspartic acid, phenyl alanine, and vanillin.[32] It bears some structural similarity to the natural sweetener phyllodulcin. It is 20,000 times sweeter than sugar and 100 times sweeter than its parent compound aspartame.[33] It has a clean sweet taste with no undesirable aftertaste.

It has excellent stability in the dry state. In aqueous solutions, its stability is similar to aspartame with maximal stability at neutral to higher pH ranges. Unlike aspartame it is safe for use by phenylketonuric individuals and hence does not require special labeling.[5] Due to its potency, despite low water solubility, it does not pose a formulation problem as its usage levels are low enough to permit adequate solubility. Its stability is dependent on pH and temperature.

Advantame is rapidly absorbed mainly as de-esterified advantame (ANS9801-acid). Another metabolite found in humans is N-(3-(3-hydroxy-4-methoxyphenyl))-propyl-L-aspartic acid (HF-1) which is formed by hydrolysis of ANS9801-acid. It is excreted primarily in feces as its two major metabolite forms with minor quantities undergoing urinary excretion.[34]

Over the years advantame has been evaluated for its toxicity (including neurotoxicity), carcinogenicity, genotoxicity, teratogenicity in the rat as well as other animal models.[35,36,37,38] It has an ADI of 32.8mg/kg BW/day.

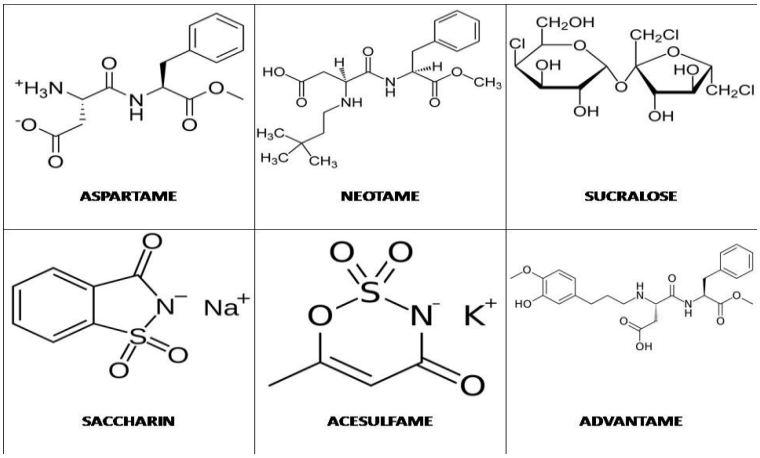

Figure 4: Structures of intense sweeteners.

Stevia

Truevia®, PureVia®, Enliten®

In the recent years, there has been increased consumer awareness about the potential benefits of herbal products over synthetic ones. This has spurred the food industry to look for non- or low-calorie sweeteners of herbal origin. One such sweetener is stevia.

As many as 8 sweet tasting diterpene glycosides have been identified in the leaves of *Stevia rebaudiana* Bertoni (Asteraceae) commonly known as ‘sweet herb', a plant native to South America. Crude extracts were first commercialized as a sweetener in Japan in as early as the 1970's. The glycosides being 200-400 times sweeter than sucrose serves as natural non-caloric sweeteners. All glycosides contain a common aglycone moiety- steviol, which differs in number and type of sugars attached. The leaves contain a complex mixture of glycosides including stevioside, steviobioside, rebaudiosides (A, B, C, D, E), and dulcoside A.[39] The major sweet constituents being stevioside (steviol, a diterpenic carboxylic alcohol + 3 glucose molecules) and rebaudioside A. Rebaudiosides being more polar than steviosides are more soluble and give a more sucrose like taste. These molecules are highly stable in aqueous solutions within a broad range of pH and temperature.[40,41] Crystalline forms of steviol glycosides have high melting points and exhibit polymorphism.

Metabolism studies in rats have shown that stevioside is hydrolyzed to release steviol. Some of this steviol is excreted unchanged in feces while a major portion is degraded by intestinal microflora to steviol, steviolbioside and glucose.[42] Absorbed steviol is excreted as a conjugate to bile in the liver. In one study on female Wistar rats, it was seen that stevia treated groups not only showed better control over body weight and decreased feed intake but also decreased levels of glucose, triglycerides, and low-density lipoproteins.[43] In a recent study evaluating the neurotropic effects of stevia in mice models, it was seen that stevia treated groups showed greater levels of cellular apoptosis in the hippocampus than control groups or groups fed with other artificial sweeteners.[44] In addition to sweetening the constituents also possess hypotensive, hypoglycemic, vasodilating, anti-inflammatory, anti-microbial and contraceptive properties.[45]

Although stevioside is not mutagenic its aglycone- steviol, formed on metabolism is known to be mutagenic in some tests with *Salmonella typhimurium* strains, however, no such conclusive evidence was found in humans.[46] Toxicological studies have shown the absence of teratogenic, carcinogenic effects or allergic reactions when used as a sweetener.

Accordingly, the Joint Food and Agriculture Organization/World Organization Expert Committee on Food Additives (JECFA) in 2008, established an ‘‘acceptable daily intake (ADI)” of steviol up to 4 mg/kg BW/day which is equivalent to 10 mg/kg BW stevioside.

Monk fruit (Swingle fruit)

Nectresse®, PureLo®

The leaves of an indigenous Chinese plant *Siraitia grosvenorii* of the Cucurbitaceae family contain triterpene type of sweet glycosides known as ‘mogrosides’. It derived its name swingle fruit after the botanist W.T. Swingle who provided its original botanical description. The process of making a useful sweetener from the fruit was later patented by Procter and Gamble (P&G) Company in 1995. It is 150 times more potent than sucrose. The major sweet constituents are Mogroside IV & V. Mogroside which bear the structural resemblance to steviol glycosides. Mogroside V is a polar compound readily soluble in water and the β-linkages ensure that the glycoside is a stable compound.[39] This sweetener has limited applications with the most common uses being in Chinese traditional remedies for a sore throat and cold. It also processes antioxidant properties.[18]

Not many safety studies have been done on this sweetener but, its long history of use suggests its safety. Its GRAS petition was approved in 2014. Hence it is now exempted from the requirements for premarket approval.

B) BULK SWEETENERS

These are sugar alcohols produced by replacing aldehyde group of aldose sugars with a hydroxyl group and can be hydrogenated monosaccharides, hydrogenated disaccharides and mixtures thereof. Polyols cause little or no insulin release after their ingestion and hence, are suitable for diabetics. They are used to provide volume or bulk to food preparations, often in combination with intense sweeteners to achieve sweetness quantum satis. Another marketing USP of polyols is their noncariogenicity, making them appropriate for sugar-free pediatric formulations. As they afford fewer calories compared to sugar, they can be useful as sugar alternatives in dietetic products. Polyols are classified as:

- Hydrogenated monosaccharides: Xylitol, Mannitol and Sorbitol.
- Hydrogenated disaccharides: Maltitol, Lactitol and Isomalt.
- Mixture of hydrogenated mono- and polysaccharides: Hydrogenated starch hydrolysates (Lycasin®).

The absorption and digestion of polyols are influenced by their amount ingested, concomitant intake of other food, which in turn dictates gastric emptying. Monosaccharides get absorbed passively whereas disaccharides first undergo hydrolysis into their corresponding monosaccharides to get absorbed. Excess intake causes unpleasant gastro-intestinal symptoms as well as decreases intestinal transit time which results in reduced absorption and consequently low energy value of sugar alcohols.[49]

All polyols are characterized by low glycemic index (GI) which is defined by the WHO/FAO as "the incremental area under the blood glucose response curve of a 50 g carbohydrate portion of a test food expressed as a percentage of the response to the same amount of carbohydrate from a standard food (typically glucose) taken by the same subject".

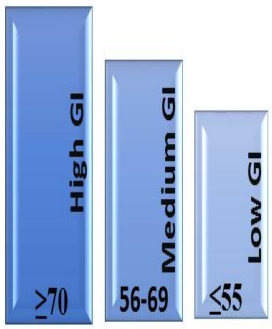

Figure 5: Glycemic index bands.

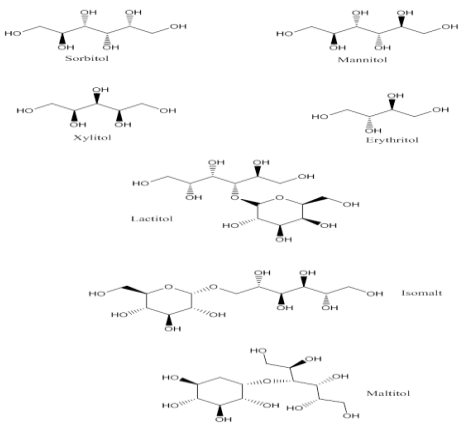

Figure 6: Structures of bulk sweeteners.

Monosaccharide polyol

Sorbitol

(Neosorb®, Sorbitab™)

One of the first polyols to be commercially available, sorbitol, also known as D-glucitol, is a hexahydric alcohol occurring as an odorless, white or colorless, crystalline, hygroscopic powder. It has four polymorphic forms viz., alpha, beta, gamma and delta with the gamma form being the most stable. It is stable chemically and doesn't partake in Maillard's reaction.[50] Sorbitol sweetness gets intensified at higher temperatures especially when it is present at low concentrations.[51]

Sorbitol gets absorbed passively although most of the ingested portion gets passed into the large intestine where the action of the resident microflora causes unpleasant flatulence.[52] The part of sorbitol that gets absorbed gets metabolized by oxidation by L-iditol dehydrogenase to give D-fructose which is then phosphorylated by fructokinase and which subsequently enters the fructose shunt pathway.[53] This oxidation is slow owing to delayed absorption of sorbitol compared to glucose. Hence, no significant spike in blood glucose level is seen after sorbitol ingestion.[54]

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) considered the adrenal medullary hyperplasia seen in rats fed high levels of sorbitol as the result of physiological stresses induced in aging rats because of the high dietary level of sorbitol. The JECFA thus considered sorbitol as safe and hasn't specified any ADI for it thus not limiting its consumption but acknowledging its laxative effect when taken in excess.[55] Sorbitol is considered as a food additive in EU (E420) and has been ascribed GRAS status in US (21CFR 184.1835).

Mannitol

(Pearlitol®, C*Mannidex™)

Mannitol, an isomer of sorbitol, is a white, odorless crystalline powder or granule. Like sorbitol, mannitol exhibits polymorphism having alpha, beta and delta form, the latter showing the moisture-induced transition to the beta form.[56] Among polyols, mannitol shows the least hygroscopicity and solubility (beta form).[57] At higher concentration levels, the sweetness of mannitol decreases both at higher temperatures and at colder temperatures.[51]

The metabolic pathway of mannitol is the same as that of sorbitol i.e. dehydrogenation to fructose and subsequent metabolism through glycolytic pathway. However, owing to less affinity to the L-iditol dehydrogenase enzyme, mannitol is incompletely metabolized, with most of it being excreted in urine.[53,58] Mannitol also has the least tolerability with 10-20g of its ingestion causing laxation. It is non-teratogenic, non-mutagenic and exerts no cytotoxic effect.[59] An ADI "Not specified" was given to mannitol by JECFA at its thirtieth meeting. Anaphylactic reactions have been known to occur when mannitol is used as an excipient, particularly in patients with a history of atopy.[60] Mannitol is listed as GRAS by FDA (21 CFR Section: 180.25). In the UK, it is permitted as a sweetener in cereal-based desserts, energy-reduced products or with no added sugar.

Xylitol

(Xylisorb®, Xylitab®)

Xylitol occurs as an odorless, white, granular solid crystalline particles or in powdered form. It is moderately hygroscopic and heat-stable, showing only slight discoloration when heated to 216°C under atmospheric pressure.[61] It is as sweet as sucrose (at a concentration of 10% solids) with equivalent bulk but providing only a quarter of calories provided by sucrose.[62]

Xylitol gets slowly absorbed to an extent of 25-50%.[63] It can get metabolized in the liver or by gut microflora.[62] In the liver, it gets oxidized by hepatic iditol-dehydrogenase to give xylulose which is then phosphorylated by xylulokinase to xylulose-5-phosphate which subsequently enters the pentose shunt pathway.[64]

On oral ingestion, xylitol causes a slight increase in blood glucose and no increase in plasma Gastric Inhibitory Polypeptide (GIP) or insulin concentration.[65] In one study done using diabetic subjects, xylitol was shown to cause no deterioration or an improvement in the diabetic state in terms of glucose tolerance and diabetic ketosis.[66] The open chain structure, as well as small molecular size of xylitol, affects the way it is metabolized by microorganisms.[67] Being a small molecule, xylitol doesn't serve as a substrate for oral microflora and is toxic to them because of the intracellular accumulation of its degradation product i.e. xylulose-5-phosphate which inhibits glycolysis.[68,69] It decreases the production of polysaccharide by these bacteria and increases production of soluble polysaccharides which decreases their adhesive power.[53] Moreover, it increases the concentration of ammonia in the extracellular phase of plaque which leads to less acidic plaque pH. In the study done by Makinen, et.al. using polyols containing dentifrices, the use of xylitol-

containing dentifrice was associated with the least plaque polysaccharide levels.[68] In another study done by Loesche, et.al. using polyols containing gums, the substantial reduction in the number of S.mutans in plaque or saliva of participants who chewed xylitol gums was found as opposed to those who chewed sorbitol or fructose gums.[70] Xylitol doesn't show any inhibitory effect on S.mutans when used concomitantly with easily fermentable carbohydrates.[71] Also, no appreciable adaptation occurs to the anticariogenic effect of xylitol.[72] Xylitol also plays a role in remineralization of demineralized enamel by restricting translocation of calcium and phosphate ions from lesions.[73,74]

Apart from laxation, other adverse effects were discovered in relation to xylitol in chronic toxicity studies done by Bär. These include bladder epithelium tumor and urinary tract calculi in male mice and pelvic nephrocalcinosis and adrenal medullary hyperplasia in male rats.[75] In mice and rats fed 10 and 20% dose of xylitol, elevated urinary excretion of oxalate and calcium ions were observed.[76] two of the factors responsible for the high incidence of bladder stone formation in these animals, the presence of which predisposed them to tumor formation. This calciuria was dose-dependent and occurred due to increased calcium absorption from the gut. However, no such bladder stone formation occurs in humans even at high dose levels of xylitol and therefore no bladder cancer risk.[75] Regarding Adrenal medullary hyperplasia, the JECFA in 1982 concluded that it was due to the gross dietary imbalance which may result in metabolic and physiologic disturbances. Also, the signs associated with pheochromocytoma in humans (increased catecholamines and their metabolites in urine, increased blood pressure) were not seen in rats. An ADI "Not specified" was given to xylitol by JECFA.[77] Xylitol was approved by FDA in 1986 (21CFR 172.395). It is also approved in over 70 countries including UK, Japan and Canada.

Erythritol

(Zerose™, C*Eridex™)

Erythritol occurs as a white or almost white powder, granular or crystalline material. It is non-hygroscopic, stable thermally and chemically and resists decomposition in acidic and alkaline media (pH 2-10).[78] Sweetness profile of erythritol is similar to sucrose, though it is accompanied by slight acidity and bitterness but no detectable aftertaste.[79]

About 60-90% of ingested Erythritol is absorbed rapidly and extensively from the proximal intestine, with peak plasma concentration occurring one hour after ingestion.[80] The unabsorbed portion is fermented by gut microflora, though not substantially, as evidenced by

insignificant dose recovered in expired carbon dioxide. Following absorption, it is rapidly distributed and then eliminated in urine (and trace level in feces) without undergoing the metabolic transformation.[81,82,83] When taken with food, absorption of erythritol is slowed due to delayed gastric emptying. Since it isn't metabolized there's no gastrointestinal side-effect apart from diuresis.[81] Erythritol intake doesn't have any significant effect on serum glucose.

Erythritol isn't an easy substrate for the oral microflora to metabolize.[84] In an experiment done by J. Kawanabe, et.al. using eight serotypes of S.mutans, it was found that the microbes didn't grow in media containing erythritol as the carbon source and it didn't serve as a substrate for plaque formation of these eight serotypes. Also, no lactic acid was produced from erythritol which is the main cause of lowering of dental pH and therefore demineralization.[85] In another study done using teenage participants, the use of erythritol containing chewable tablet and dentifrice was associated with lower salivary S.mutans as well as the amount of plaque, an effect comparable to that obtained using xylitol.[86]

On experimentations on rats, erythritol had no effect on any organ weight apart from cecum whose weight decreased in the rats fed 10% dose of erythritol.[87] All the adverse physiological impacts found in animal experimentations were thought to be physiological or adaptive reactions to the osmotic and diuretic effect of absorbed erythritol or in the case of rodents due to fermentation of the unabsorbed portion. According to the toxicological report of JECFA, erythritol didn't exhibit any mutagenic, clastogenic or teratogenic effect. The committee established an ADI "not specified" to erythritol for use as a sweetener.[88] Erythritol is permitted as a sweetener in nineteen countries including Japan, USA, Australia and Canada. In 2003, the EU Scientific Committee on Food (SCF) deemed erythritol as safe for use in food.

Disaccharides

Lactitol

(LACTY®)

Lactitol, composed of D-galactose and D-sorbitol, occurs as a white, odorless, crystals or in powder form. It has a relative sweetness less than sucrose, which increases on increasing its concentration and has no after-taste. The crystals can be anhydrous, mono- or dihydrate. The anhydrous form is hygroscopic while the monohydrate and dihydrate forms are non-hygroscopic.[89] Lactitol is stable to heat but hydrolyzes into D-sorbitol and D-galactose in

acidic media.[90] Solubility in alkali is more than lactose which it is derived from by reduction of its glucose part. On heating to 150-200°C, it shows only a slight discoloration, but heating to 170-240°C causes partial conversion of lactitol to its anhydrous derivatives viz. lactitan, sorbitol, and lower polyols.[91,92] Lactitol is miscible with other polyols like sorbitol and glycerol.[91]

On ingestion, a negligible part of lactitol is hydrolyzed and absorbed due to low activity of β-galactosidase in the human intestine.[64] This accounts for the lack of glycemic response to Lactitol. In a study done to assess metabolic response after ingestion of glucose, lactitol and xylitol in healthy, non-obese men, no change in glucose or insulin response was observed after lactitol ingestion substantiating the claim that it isn't absorbed by the small intestine. While xylitol caused a slight increase in plasma glucose and insulin response, only a little part of it was converted into glucose whereas, lactitol wasn't converted into glucose at all. No reactive hypoglycemia was observed after lactitol ingestion and no thermogenic effect was seen.[93] The lack of glycemic response isn't dose related.[64], thus making lactitol suitable for people with diabetes mellitus. In a study done by Hiele et.al. in six normal subjects using ^{13}C-labelled lactitol, a hike in the breath ^{13}C-CO_2 and H_2 gas was seen. Production of hydrogen gas was formed by fecal flora and no urinary secretion of lactitol was observed, confirming that lactitol isn't absorbed but undergoes extensive fermentation by colonic flora.[82] Lactitol can be regarded as bifidogenic or lactogenic since it stimulates the growth of lactobacillus and bifidobacteria species. The short chain fatty acids which are produced in its fermentation decreases intestinal pH and therefore inhibits adhesion of proteolytic bacteria which produce ammonia, endotoxins, etc., to epithelial cell walls, thus having a beneficial effect on the intestinal microenvironment.[89,94]

Lactitol, like xylitol and erythritol, is non-cariogenic. In an experiment done by Grenby et.al. using mixed cultures of dental plaque microorganisms incubated for 24 hours in six media containing different bulk sweeteners as energy sources, it was observed that the least fermentation occurred in lactitol and xylitol containing media, the pH of these media were high and consequently low enamel demineralization occurred.[95] Physiological effects similar to xylitol were seen in animal studies using lactitol as well, viz., calciuria, nephrocalcinosis, and adrenal medullary hyperplasia. However, as noted above these effects were nonspecific with no risk of being seen in humans. Therefore, an ADI of "not specified" was established

for lactitol as well.[77] Lactitol is GRAS listed and allowed as a food additive in EU, USA, Japan, Canada, etc.

Isomalt

(galenIQ™,C*IsoMaltidex™)

Isomalt is a mixture of two stereoisomers- 6-O-α-D-glucopyranosyl-D-sorbitol+1-O-α-D-glucopyranosyl-D-mannitol dihydrate. It occurs as a white powder, a granular or crystalline substance which has a sugar-like taste, with a sweetness intensity approximately 50-60% of that of sucrose and no off- or after-taste. When incorporated into beverages, its sweetness depends on its concentration and the matrix in which it is used viz., pH, texture, temperature, etc.[96] Isomalt has good thermal, enzymatic stability and is chemically inert.[97]

For isomalt to be absorbed, it first has to undergo hydrolysis into glucose, sorbitol, and mannitol. Hydrolysis of isomalt is dose dependent, with complete hydrolysis seen at low doses than after higher ones. Out of the three hydrolysis products, only glucose undergoes luminal absorption while the other two are only partially absorbed.[98] The unabsorbed portion undergoes colonic fermentation as evidenced by an increase in breath hydrogen after ingestion of isomalt (is less compared to sorbitol)[99] and results in complete disappearance of isomalt from feces. Like lactitol, isomalt was also shown to be prebiotic in an experiment done by Gostner et.al. which might contribute to the healthy colonic environment.[100]

In a study done by Thiébaud et.al. in healthy, normal weight subjects, effects of 30g loads of isomalt and sucrose was studied. In the subjects who received sucrose, significant changes in plasma glucose, insulin, and lactic acid were seen whereas isomalt produced no such effect.[101] In another study done by Holub et.al. using thirty-one people with type II Diabetes Mellitus, consumption of a diet containing 30g/day isomalt instead of high glycemic carbohydrates for twelve weeks with only metformin and thiazolidinediones used as antihyperglycemics, significant improvement in metabolic control of diabetes was observed.[102]

Isomalt isn't fermented by oral microflora and therefore causes no pH drop and consequently no cariogenicity.[96] Takatsuka et.al. studied the effect of isomalt on remineralization on bovine enamel lesions both in vitro and in vivo. Rinsing with 10% isomalt solution caused increased remineralization while the continuous presence of 10% isomalt inhibited both de-

and re-mineralization with significantly less overall mineral loss thus, having a positive de/remineralization balance.[103]

The JECFA established an ADI "not specified" in its 29th report considering the carcinogenicity, multigenerational reproduction studies and teratogenicity studies giving due attention to its laxative effect.[104] Isomalt is approved in over seventy countries including all the major ones.

Maltitol

(SweetPearl®, Maltidex™)

Maltitol consists of one glucose unit and one sorbitol unit linked together by an α-(1→4) bond and occurring as an odorless, white, anhydrous, crystalline powder. It has good chemical and thermal stability decomposing only when heated above 200°C. Maltitol is one of the least hygroscopic polyols and doesn't begin to absorb atmospheric moisture until 89% RH at 20°C.[105] It is sweeter than most polyols with only xylitol being sweeter and is commercially available as powder and syrup.

A small part of maltitol undergoes enzymatic metabolism which starts with its hydrolysis by maltase into glucose and sorbitol, which are then absorbed into the bloodstream. The latter is converted into fructose which then enters the glycolytic pathway.[106] The absorbed portion gets quickly excreted in urine unchanged. A significant portion of ingested maltitol undergoes microbial fermentation which results in increased hydrogen content of breath.[83] Ingested maltitol undergoes an extensive caloric utilization of approximately 90% as evidenced by low fecal levels of maltitol.[107] Maltitol causes a significantly lower blood glucose and insulin level compared to sucrose and doesn't cause rebound hypoglycemia.[108] Secchi et.al. studied the metabolic effects of increasing doses of maltitol in healthy subjects. Ten gram of maltitol caused no glycemic or insulinemic response, 25g maltitol caused a slight glycemia and insulinemia while 50g maltitol caused significantly lower glycemic and insulinemic response compared to sucrose. Moreover, these effects abated within 180min indicating the absence of late absorption and metabolic effect of maltitol.[109]

Maltitol and maltitol syrup are non-cariogenic. In an experiment done by Edwardsson et.al. comparing acid production from four polyols using different strains of streptococci and lactobacilli, lactitol was found to be fermented only by the lactobacillus species.[110] In another study done by Maguire et.al. it was observed that oral bacterial strains didn't adapt to

maltitol and xylitol after a 14-day exposure. This property combined with the low production cost of maltitol make it a viable alternative to xylitol.[111]

The JECFA in 1993 reviewed the toxicity and carcinogenicity study done in rats. No toxicity was seen in the study while the carcinogenicity study revealed incidences of benign and malignant pheochromocytomas in both male and female rats fed high maltitol diet. Adrenal medullary hyperplasia was seen in all animal groups while mammary gland adrenocarcinoma was seen in female rats fed 1.5 and 4.5g/kg BW/day maltitol. The committee didn't consider adrenocarcinoma to be treatment related since the incidences were in range reported in control groups in the same laboratories. As mentioned earlier, the adrenal medullary hyperplasia was considered nonspecific by the committee. In light of these findings, the committee established an ADI "not specified" to maltitol and maltitol syrup (containing 50-90 and 90-98% maltitol) that meet current specifications.[112] Maltitol and maltitol syrup are GRAS listed and are permitted for use in many countries, subject to the specifications and purity requirements of the respective countries.

CONCLUSION

The increasing health awareness among people has fuelled the growth of the sweetener industry. However, some section of the masses is still wary of using them despite approvals from various regulatory bodies. The adverse effects seen in animal studies are hard to ignore. Although "natural" does not necessarily mean safe, healthy or non-toxic the safety concerns over artificial substitutes has led to an increased demand for plant based alternatives. Mintel and Leatherhead food sales forecast skyrocketing growth of the stevia market from an estimated $110 million in 2013 to $275 in 2017.[113] Where the market for plant based sweeteners is expected to grow steadily, the market for artificial substitutes is dominated by acesulfame-K closely followed by sucralose. The pharmaceutical industry has slowly shifted from using sucrose to using artificial sweeteners as it can cater to a larger market comprising of pediatrics, adults and geriatrics, each group with its own set of population suffering from health conditions that demand on the cut down in the use of sucrose. This need is driven by the demise of sugar yet the demand for sweet products.

Newer sweeteners such as Alitame are yet pending USFDA approval. Whereas, studies are yet being conducted on newer herbal sweeteners such as brazzein, thaumatin and monellin. These 3 plant based sweeteners are essentially proteins formed by biochemical pathways and have complex mechanisms via which they elicit sweetness in humans. A major question in

the use of these sweeteners however continues to be its feasibility towards large scale extraction and production for the market. More research needs to be done to clear the air about the safety of these sweeteners. This requires collaboration between the government, industry and academic communities. Such collaboration would not only aid in better understanding of such additives and establishing the required guidelines and controls, but also help in understanding their role in the global food supply.

Table 1: Summary of high intensity sweeteners.

Property	Saccharin (E954)	Aspartame (E951)	Neotame (E961)	Advantame (E969)	Sucralose (E955)	Acesulfame-K (E950)	Stevia (E960)	Monk Fruit
Relative Sweetness[48]	300-600x	180-200x	7000-13000x	20,000x	600x	180-200x	200-400x	100-250x
Storage and Stability	Excellent stability under normal processing conditions.	Very good stability when dry (<8% moisture), less stable in liquids.	Excellent stability when dry, less stable in liquids.	Maximal stability at neutral to higher pH.	Unlike sucrose it exhibits resistance to hydrolysis under extreme acid and heat.	Very good stability under normal processing conditions	Sufficient stability in food processing applications	Sufficient stability in food processing applications
Regulatory Status US Europe (EU) JECFA	 Yes Yes Yes	 Yes Yes Yes	 Yes Yes Yes	 Yes Yes Yes	 Yes Yes Yes	 Yes Yes Yes	-GRAS Listed-	-GRAS Listed-
ADI(mg/kg bw/day).[31,47,48] USA EU JECFA	 5 5 5	 50 40 40	 2 2 2	 5 NA NA	 5 15 15	 15 9 15	 No ADI No ADI 4	 No ADI NA NA

Source: Compiled from [2], [24], [31], [47],[48].

Table 2: Summary of polyols.

Parameters	Sorbitol	Mannitol	Xylitol	Maltitol	Lactitol	Erythritol	Isomalt
Relative Sweetness (sucrose=100).[115]	50-60	50-60	80-100	80-90	30-40	53-70[116]	50-60
Glycemic Index.[64]	9	0	13	35	6	0	9
Insulinaemic index (Glucose=100).[64]	11	0	11	27	4	2	6
Calorific value.[114]							
USA	2.6	1.6	2.4	2.1	2	0.2	2
EU	2.4	2.4	2.4	2.4	2	1	2.4
Japan	3	2	3	2	2	0	2
Hygroscopicity.[64]	Median	Low	High	Median	Median	Very low	Low
Heat of solution(kJ/Kg).[64]	-111	-121	-153	-79	-53	-180	-39
Acid stability.[114]	2-10	2-10	2-10	2-10	>3	2-12	2-10
Regulatory approval.[114]							
EU	Yes	Yes	Yes	Yes	Yes	Yes	Yes
USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Japan	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Source: Compiled from [64], [114], [115] and [116].

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