REVIEW ARTICLE

LOW CALORIE ARTIFICIAL SWEETENERS AS AN ALTERNATIVE IN PHARMACEUTICAL DOSAGE FORM DESIGN

Pravin Guptaa* and Manish Kumb

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ABSTRACT

Tremendous research is going on in the field of preparing low calorie diet for diabetes, obesity, hypertension, and heart disease, providing potential area for growth to the food and pharmaceutical industry. Dosage forms prepared for diabetic patients lack sucrose as breakdowns into glucose and fructose which starts from the mouth itself and majority of it is digested in the small intestine. As soon as it is digested, it gives rise to blood glucose level. In order to control such glucose spikes in blood, their diet is immediately shifted toward low calorie food and medications with low glycemic index. Artificial intense sweeteners e.g. acesulfame potassium, sucralose, xylitol etc. in moderate amount, intensity of sweetness and physical characteristics were proved safe by USFDA. This review covers a brief description, stability conditions and pharmacokinetic analysis of artificial sugars.

Keywords: Acceptable daily intake, after taste, glycemic index, low calorie diet

INTRODUCTION

The serious complications of high blood glucose level are many, including diabetes, nerve damage and cardiovascular diseases. Higher sucrose intake also leads to obesity, health issues and even addiction. For avoiding these complications, artificial sweeteners are incorporated as advised by USFDA as per ADI (acceptable daily intake) values. This task is made easy by shift to artificial sugars having low glycemic index, as described in this paper. These sugars are either used alone or in combination, if problem of after taste persist. With the use of such sugars, consumers gets a free choice of food products and medications offering sweet taste without the calories as they are not at all metabolized. But later on, it was proved through clinical data obtained from populations under observation consuming heavy amount of these artificial sweeteners about altering their glucose metabolism. The threatening effects found were weight gain and diabetes mellitus Type II. When blood sample data was collected from US population under observation in 2018, the diagnosis concluded with Type II diabetes being present in ninety five percentage of population under study. Earlier research showed Type II diabetes to be present only in adults above the age of forty years. But now, the recent diagnosis has proved it to be very common in obese children and adolescents. Now, low calorie hexoses from glucose were developed by enzymatic interconversion of monosaccharides. Later, rare sugars and there analogs with enhanced therapeutic activities were developed.

Artificial sweeteners in smaller proportion may sweeten the formulation, hence may be named high intensity sweeteners. They are not carbohydrates and have no calories, hence impart sweetness without add on to calories. When taken in diet they show no effect on blood glucose level and fats with no sign of dental caries. The reported adverse effects were gastrointestinal discomfort and headache. Formulations made from artificial sweeteners are labeled as ‘sugar-free’ or ‘light’.

Acesulfame-K, neotame, saccharin, sucralose and aspartame are examples of approved artificial sweeteners. Alitame is under process of approval while cyclamate is example of banned sweetener. Changes in the electronic configurations and the distance between groups attached may alter the sweet taste of sweeteners.

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Sweeteners that are directly extracted from natural products as such without undergoing any change in their chemical structures are defined as natural sweeteners. They are divided into saccharides (sugar) and non-saccharides on the basis of their original structures. Terpenoids, sweet protein, steroidal saponine and dihydroisocumarines come under non-saccharide sweeteners. Liver metabolizes them into ATP (Adenosine triphosphate) necessary for cell building and energy source. The common side effects of natural sweeteners are hike in blood sugar, blood fats and increase in body weight. High sugar or carbohydrate based diet compels the pancreas to produce large amount of insulin, as a result person suffers from hypoglycemia. Such persons are advised to take artificial sweeteners.

MAJOR BENEFITS OF ARTIFICIAL SWEETENERS

Artificial sweeteners are used for the following major reasons:

Weight loss

Artificial sweeteners are non-nutritive, the amount needed to sweeten any product is too small in comparison to sucrose, they add virtually no calories to your diet. Examples of such sugars used are erythritol and xylitol, a sugar alcohol. This allows the patient to take the same desired food as he/she wishes without the risk of weight gain and other undesired complications.

Dental care

A dynamic relation exists between sugars and oral health. These sugar substitutes are mainly polyols, which are, basically hydrogenated carbohydrates in which aldehyde group at one end has been reduced to a hydroxyl or alcohol group. Xylitol is a pentose alcohol not fermented by cariogenic bacteria which feeds on sugars present on the enamel, avoiding their proliferation and eventually converts them to acid waste that in turn decays the tooth structure. The consistent use of optimum amount of xylitol sweetened gum reduces plaque accumulation bacteria, thus preventing enamel demineralization by working on plaque pH and enhancing the buffering effect by stimulating the flow of saliva. They don’t generate tooth cavities.

Diabetes mellitus

Diabetic patient often find difficulty in regulating their blood sugar levels. These artificial sweeteners are slowly metabolized and provides low calorie in contrast to carbohydrates. By shifting to these artificial sugars, one can enjoy varied diet without affecting their blood glucose level, while some of the sugar substitutes are slowly metabolized releasing energy and thus maintains potentially more stable sugar levels.

Reactive hypoglycemia

It results by release of excess amount of insulin by the pancreas in response to high sugar or carbohydrate based diet causing sudden rise in blood glucose level. This high insulin concentration immediately lowers the glucose level below their optimum concentration needed for normal body and brain function. It is commonly observed in both types of people, with or without diabetes, and also in overweight individuals. As a precaution, the diabetic patient must avoid such high glycemic foods and may choose these safe artificial sugars.

Avoiding processed foods

Processed food undergoes numerous mechanical and chemical operations for improvising organoleptic characteristics or to preserve them. They generally include unhealthy levels of sugars, sodium and fats just to make better in taste without any nutritional value. Too much use of such ingredients leads to complications like obesity, heart disease, high blood pressure and diabetes.

Cost

Artificial sweeteners are much cheaper then natural sweeteners as they are having longer shelf life and higher sweetening intensity. Products made from these intense sweeteners offers longer shelf life.

BRIEF DESCRIPTION OF SOME COMMONLY USED USDA APPROVED ARTIFICIAL SWEETENERS

Table I & II summarize certain important features of these high intensity sweeteners that might be useful in food and pharmaceutical industry.

Fig. 1 shows the structural formula and chemical name of non-nutritive sweeteners, while Fig. 2 shows polyols along with novel tagatose and thaumatin structural formulae along with their chemical names.

Acesulfame potassium

It is available in crystalline powder form and is characterized by its colorless or white-colored, odorless properties. It has high water solubility that increases with temperature, and shows sweetness 200 times when compared to sucrose with side effect of bitterness aftertaste. It remains stable at high temperature, which makes it suitable in cooking.
Table I: Properties of high intensity sweeteners

<table>
<thead>
<tr>
<th>Sweetener</th>
<th>pH at 20°C</th>
<th>Solubility at 20°C</th>
<th>Sweetness</th>
<th>Cal g⁻¹</th>
<th>GI</th>
<th>Source</th>
<th>ADI (up to)</th>
<th>After taste</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acesulfame K</strong></td>
<td>5.5 – 7.5</td>
<td>Freely soluble in water; slightly soluble in ethanol (95%)</td>
<td>180 - 200</td>
<td>calorie-free</td>
<td>Zero</td>
<td>Reaction between diketene and amidosulfonic acid in the presence of dehydrating agents, and neutralization with potassium hydroxide</td>
<td>15mg kg⁻¹</td>
<td>No after taste</td>
</tr>
<tr>
<td><strong>Alitame</strong></td>
<td>5.0 – 6.0</td>
<td>Freely soluble in water and ethanol (95%)</td>
<td>2000</td>
<td>1.4 kcal</td>
<td>Zero</td>
<td>It is an aspartic acid-containing dipeptide sweetener</td>
<td>40–300 mg kg⁻¹</td>
<td>No after taste</td>
</tr>
<tr>
<td><strong>Aspartame</strong></td>
<td>4.5 – 6.0</td>
<td>Sparingly soluble in water; slightly soluble in ethanol (95%)</td>
<td>180–200</td>
<td>4 kcal</td>
<td>Zero</td>
<td>By coupling together L-phenylalanine and L-aspartic acid, either chemically or enzymatically</td>
<td>40 mg kg⁻¹</td>
<td>No after taste</td>
</tr>
<tr>
<td><strong>Sodium cyclamate</strong></td>
<td>5.5 – 7.5</td>
<td>Freely soluble in water; slightly soluble in ethanol (95%)</td>
<td>30–50</td>
<td>calorie-free</td>
<td>Zero</td>
<td>Cyclamates are prepared by the sulfonation of cyclohexylamine in the presence of a base</td>
<td>11mg kg⁻¹</td>
<td>No after taste</td>
</tr>
<tr>
<td><strong>Saccharin sodium</strong></td>
<td>6.6</td>
<td>Freely soluble in water; slightly soluble in ethanol (95%)</td>
<td>300 -600</td>
<td>calorie-free</td>
<td>Varies</td>
<td>Saccharin is produced by the oxidation of o-toluene sulfonamide by potassium permanganate in a solution of sodium hydroxide</td>
<td>2.5mg kg⁻¹</td>
<td>After taste</td>
</tr>
<tr>
<td><strong>Sucralose</strong></td>
<td>5.0 – 6.0</td>
<td>Freely soluble in water and ethanol (95%)</td>
<td>300 - 1000</td>
<td>3.36 kcal</td>
<td>0-80</td>
<td>Selective substitution of three sucrose hydroxyl groups by chlorine</td>
<td>15mg kg⁻¹</td>
<td>No after taste</td>
</tr>
</tbody>
</table>

The drawback of residual taste could be masked and to get the release in controlled manner microencapsulation technique is applied. In solid form, it is most stable and also unaffected by light. In liquid form becomes unstable if not stored in optimum pH and temperature. No reduction in sweetness was observed when stored in pH between 3.0–3.5 and temperature above 25°C but degradation starts when pH goes down below 3.0 and temperature above 25°C when tested over a period of 2 years. For foods that undergo pasteurization, fermentation and baking this can be used as a sweetening agent. It is thermostable when used as a sweetener in baked food.
<table>
<thead>
<tr>
<th>Sweetener</th>
<th>pH at 20°C</th>
<th>Solubility at 20°C</th>
<th>Sweetness Cal g⁻¹</th>
<th>GI</th>
<th>Type</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythritol</td>
<td>5–7 (5% w/V aqueous solution)</td>
<td>Freely soluble in water; slightly soluble in ethanol (95%)</td>
<td>0.7</td>
<td>0</td>
<td>Sugar alcohol</td>
<td>Fermentation of glucose by <em>Moniliella pollinis</em>, a fungus</td>
</tr>
<tr>
<td>Glucose</td>
<td>6 - 8.5 (1% w/V aqueous solution)</td>
<td>Soluble in water, acetic acid and other solvents but sparingly soluble in methanol</td>
<td>0.5</td>
<td>4.0</td>
<td>100 Monosaccharide</td>
<td>Hydrolyzed starch</td>
</tr>
<tr>
<td>Fructose</td>
<td>5.35 (9% w/V aqueous solution)</td>
<td>Very soluble in water and soluble in ethanol and methanol</td>
<td>1.5–1.8</td>
<td>4.0</td>
<td>19–23 Monosaccharide</td>
<td>Enzymatically isomerized glucose</td>
</tr>
<tr>
<td>HFCS (High fructose corn syrup)</td>
<td>3.3 – 5.5 (24% w/V aqueous solution)</td>
<td>Soluble in water</td>
<td>1–1.2</td>
<td>4.0</td>
<td>60–65 Mixed gluc/fructose</td>
<td>Hydrolysis of corn starch and isomerization of glucose</td>
</tr>
<tr>
<td>HSH (Hydrogenated starch hydrolysates)</td>
<td>3 - 7 (20% w/V aqueous solution)</td>
<td>Very soluble in water and slightly soluble in ethanol</td>
<td>0.5–0.7</td>
<td>2–4</td>
<td>Varies Mixed polyols</td>
<td>Hydrogenated partially hydrolyzed starch</td>
</tr>
<tr>
<td>Isomalt/Isomaltitol/Palatinit™</td>
<td>3-10 (10% w/V aqueous solution)</td>
<td>Soluble in water and very slightly soluble in ethanol</td>
<td>0.45–0.65</td>
<td>2.0</td>
<td>2 Sugar alcohol</td>
<td>Hydrogenated isomaltulose; equal mixture of gluco-sorbitol and gluco-mannitol</td>
</tr>
<tr>
<td>Isomaltulose/Palatinose™</td>
<td>&lt; 3 (10% w/V aqueous solution)</td>
<td>Very soluble in water and slightly soluble in ethanol</td>
<td>0.3–0.4</td>
<td>2.0</td>
<td>32 Disaccharide</td>
<td>Enzymatic isomerization of sucrose with <em>Protoaminobacter rubrum</em>; GRAS (Generally recognized as safe) March 2006; a sucrose isomer</td>
</tr>
<tr>
<td>Lactitol</td>
<td>4.5 – 0.7 (10% w/V aqueous solution)</td>
<td>Freely soluble in water and slightly soluble in ethanol</td>
<td>0.35–0.4</td>
<td>2.4</td>
<td>6 Sugar alcohol</td>
<td>Hydrogenated lactose</td>
</tr>
<tr>
<td>Lactose</td>
<td>4.7 (10% w/V aqueous solution)</td>
<td>Soluble in water and sparingly soluble in ethanol</td>
<td>0.2–0.4</td>
<td>4.0</td>
<td>46-65 Disaccharide</td>
<td>Milk sugar</td>
</tr>
<tr>
<td><strong>Sugar</strong></td>
<td><strong>Concentration (10% w/V aqueous solution)</strong></td>
<td><strong>Solubility</strong></td>
<td><strong>Density</strong></td>
<td><strong>Brix</strong></td>
<td><strong>Notes</strong></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Lactulose</td>
<td>3.5 – 5.5</td>
<td>Miscible with water and formamide</td>
<td>0.6</td>
<td>0.2</td>
<td>0</td>
<td>Disaccharide</td>
</tr>
<tr>
<td>Leucrose</td>
<td>8.3 – 8.5</td>
<td>Soluble in water</td>
<td>0.5</td>
<td>2.0</td>
<td>-</td>
<td>Disaccharide</td>
</tr>
<tr>
<td>Maltitol</td>
<td>5.0 – 7.5</td>
<td>Freely soluble in water</td>
<td>0.5–0.9</td>
<td>3.0</td>
<td>35–52</td>
<td>Sugar alcohol</td>
</tr>
<tr>
<td>Maltose</td>
<td>4.5 – 6.5</td>
<td>Very soluble in water, slightly soluble in ethanol (95%)</td>
<td>0.4</td>
<td>4.0</td>
<td>105</td>
<td>Disaccharide</td>
</tr>
<tr>
<td>Maltulose</td>
<td>4.5 – 6.5</td>
<td>Soluble in water</td>
<td>0.3–0.42</td>
<td>-</td>
<td>32</td>
<td>Disaccharide</td>
</tr>
<tr>
<td>Mannitol</td>
<td>4.5 – 7.0</td>
<td>Freely soluble in water</td>
<td>0.5–0.72</td>
<td>1.6</td>
<td>0</td>
<td>Sugar alcohol</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>4.5 – 7.0</td>
<td>Very soluble in water</td>
<td>0.6</td>
<td>2.6</td>
<td>9</td>
<td>Sugar alcohol</td>
</tr>
<tr>
<td>Sucrose</td>
<td>8.3 – 8.5</td>
<td>Very soluble in water and slightly soluble in ethanol</td>
<td>1.0</td>
<td>4.0</td>
<td>61–65</td>
<td>Disaccharide</td>
</tr>
<tr>
<td>Tagatose</td>
<td>5.0 – 9.0 (10% w/V aqueous solution)</td>
<td>Very soluble in water and slightly soluble in ethanol</td>
<td>0.92</td>
<td>1.5</td>
<td>0</td>
<td>Galactose isomer</td>
</tr>
<tr>
<td>Trehalose</td>
<td>3.5 – 10 (4% w/V aqueous solution)</td>
<td>Soluble in ethanol, sparingly soluble in water (68.9g 100mL⁻¹)</td>
<td>0.5–0.7</td>
<td>3.6</td>
<td>45–50</td>
<td>Disaccharide</td>
</tr>
<tr>
<td>Xylitol</td>
<td>5.0 – 7.0 (10% w/V aqueous solution)</td>
<td>Freely soluble in water</td>
<td>1.0</td>
<td>3.0</td>
<td>7–13</td>
<td>Sugar alcohol</td>
</tr>
</tbody>
</table>
ACESULFAME POTASSIUM

6-Methyl 1,2,3-oxathiazin-4(3H)-one 2,2 dioxide potassium

ASPARTAME

N-L-a-Aspartyl-L-phenylalanine 1-methyl ester

SACCHARINE SODIUM

1,2-Benzisothiazol-3(2H)-one 1,1-dioxide, sodium salt

SUCRALOSE

1,6-Dichloro-1,6-dideoxy-b-D-fructofuranosyl-4-chloro-4-deoxy-a-D-galactopyranoside

ALITAME

L-a-Aspartyl-N(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate

SODIUM CYCLAMATE

Sodium N-cyclohexylsulfamate

**Fig. 1:** Structural formulae and chemical names of non-nutritive sweeteners\(^7,25\)

MALTITOL

4-O-\(\alpha\)-Glucopyranosyl-D-sorbitol

ERYTHRITOL

(2R,3S)-Butane 1,2,3,4-tetrol

LACTITOL

4-O-(b-D-Galactopyranosyl)-D-glucitol

MANNITOL

(2R,3R,4R,5R)-hexane-1,2,3,4,5,6-hexol

XYLITOL

xylo-pentane-1,2,3,4,5-pentol

TAGATOSE

(3S,4S,5R)-1,3,4,5,6-pentahydroxyhexan-2-one

SORBITOL

(2S,3R,4R,5R)-hexane-1,2,3,4,5,6-hexol

ISOMALT

(3R,4R,5R)-6-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy]hexane-1,2,3,4,5-pentol

THAUMATIN

N-[4-(4-cycloheptylpiperazin-1-yl) sulfonyl]phenyl]acetamide

**Fig. 2:** Polyols along with novel tagatose and thaumatin structural formulae along with their chemical name\(^66-68\)
Chewing gum is developed by microencapsulating the salt using fluid-bed coating and spray drying that imparts sustained release and higher drug loading without initial burst release. Later, prepared chewing gum using the same technique produced microcapsules with synergistic effect of both aspartame and acesulfame-K with gradual release of sweeteners. Due to its intense sweetness, it is preferred in cosmetic, foods, beverages and pharmaceutical preparations including dental formulations.

It is a relatively non-toxic and nonirritant material. Pharmacokinetic analysis proved that it is not metabolized and excretes out unchanged without affecting the potassium intake. Moreover, studies on rats and dogs have shown no mutagenic or carcinogenic symptoms. WHO recommends 15mg kg\(^{-1}\), whereas the European Union scientific committee recommends safe up to 9 mg kg\(^{-1}\).

In food and beverages, it is often blended with other sweeteners like aspartame and sucralose in order to mask its bitter sensation after taste. The blended powder gives intense sweetness more than the individual components. It is not at all metabolized, hence gives zero calories. USFDA in 2003 included it in the list of general purpose sweeteners and no further evidence is needed. Acetoacetamide is the breakdown product and gives toxic effects in large doses.

The microbial environment of the gut gets perturbed in case of acesulfame-K treated mice. Genus bacteriodes was in abundance in male mice than in the control with the variation using 16S rRNA sequencing and GC-MS metabolomics in their fecal metabolic profiles. The observed adverse effects in male mice were weight gain, changes in fecal metabolism, gut microflora composition changes and genetic changes responsible for energy metabolism. Methyl chloride is a known carcinogen present in acesulfame-K. Continuous use for extended time may cause kidney and liver effects, nausea, depression, mental confusion.

**Alitame**

Alitame is a non hygroscopic white crystalline odorless powder. Also, it is a non-toxic, non-carcinogenic and non-irritant sweetening agent. It is 2000 times sweeter than sucrose; each gram of alitame contributes 6KJ of energy. Food industry uses a maximum of 40-300 mg kg\(^{-1}\). It undergoes decomposition at elevated temperature and at low pH. Its use is restricted with oxidizing and reducing agents as it may chemically interact with them. The ADI of alitame is about 0.1mg kg\(^{-1}\). The metabolic breakdown results into aspartic acid and alanine amide, feces composition shows 7-22% unchanged. In this, the aspartic acid get further metabolized whereas alanine amide is excreted unchanged. FDA recommends it to be used, safely in cancer when analyzed on humans and animals for final approval.

**Aspartame**

With its intense sweetening effect, aspartame is used in food as well as pharmaceutical industries. It exists as an off white, non-toxic and almost odorless crystalline powder. It is added to mask the unpleasant taste of various dosage forms. It is also used as a nutritive supplemen with nutritive value such as 1g gives about 17KJ of energy. In comparison to sucrose, is 180-200 times sweeter and is easily metabolized in the body. In water, it is sparingly soluble whereas in ethanol it is slightly soluble. In acidic pH and higher temperature, it readily solubilizes. It loses its sweetness by undergoing hydrolysis in presence of moisture forming its degradation products. Upon breakdown in presence of water, its peptide linkage releases free amino groups. Its stability in aqueous solutions could be enhanced by adding cyclodextrin and polyethylene glycol 400. Moreover, its aqueous solution remains stable at pH 2 and becomes unstable as the pH rises to 3.5-4.5. Degradation occurs on prolonged heating, loss could be minimized by employing technique of high temperature for short duration of time followed by rapid cooling. It is not suitable for cooking as it readily loses its sweetness at elevated temperature. All metabolic components are metabolized in the same way as they might be derived from other food sources.

Aspartic acid, methanol, phenylalanine, formic acid, formaldehyde, and diketopiperazine were the metabolic products after oral ingestion. These metabolic derivatives give rise to various health problems such as eye problems, headache, blurred vision, nausea, brain tumors and memory loss. All metabolic components are metabolized in the same way as they might be derived from other food sources.

Methanol produced by the breakdown of aspartame is in very small amount, which is broken down in the body to give formaldehyde that in turn is converted into formic acid. Both formaldehyde and formic acid are toxic. Formic acid is rarely built up as body uses maximum...
formaldehyde to make other important substances. In excess, it is eliminated through urine or may be broken down into CO₂ and water⁴¹.

Aspartic acid is a well documented excitotoxin. Further, three amino acids produced, namely aspartate, cysteine and glutamate, are neurotransmitters and were responsible in stimulating our neurons to either damage or kill them. Adverse effects due to excitotoxins were hearing loss, spinal cord injury and stroke⁴². Moreover, another hydrolyzed component of aspartame, phenylalanine, has been reported to cause serious problem of brain damage. This amino acid plays an important role in neurotransmitter regulation⁴³.

In patients suffering from phenylketonuria, use of aspartame should be avoided. In this complication, the body of the patient lacks the enzyme phenylalanine hydroxylase responsible for the metabolism of this amino acid and is unable to break phenylalanine which is a degradation product of aspartame. As a result, phenylalanine gets accumulated and affects normal brain functions¹.

Increased rate of malignant tumors in male rats was demonstrated in research data. Higher rate of lymphoma and leukemia in both male and female rats was reported. Also there is an increased chance of mammary cancer in case of female rats⁴⁴. However, extensive research confirmed that aspartame has adverse effect of producing cancer in both animals and humans⁴⁵,⁴⁶. In order to minimize the adverse effects, it is often blended with other stable sweeteners like saccharine sodium⁴⁷.

Neotame

Neotame is an artificial sweetener and is derived from aspartame by incorporating a butyl group to the free amino group. As compared to sucrose, the sweetness of the derived product is 7000 times and with aspartame it is 30-60 times⁴⁸. As a general purpose sweetener, it was approved by FDA in 2002 for food and beverage manufacturers except in meat and poultry without a metallic after taste¹. Neotame is marketed by the name Nutrasweet™ with ADI of 18 mg kg⁻¹ per day⁴⁹. The potential benefits of this sweetener are higher heat stability and lower cost⁴⁹. In diseased condition, such as phenylketonuria, it reduces the concentration of phenylalanine which is the main cause of this disease. The peptide bond between aspartic acid and phenylalanine is broken by addition of t-butyl group that replaces the free amino group in order to lower the phenylalanine accumulation⁵⁰. In contrast, some research studies showed negligible relation between consumption of neotame and phenylketonuria⁵¹.

Dextrose monohydrate

It is available as dextrose anhydrous or as a monohydrate and is an odorless, colorless, white crystalline powder with sweet taste. Dextrose anhydrous, when kept in conditions at 25°C and relative humidity of 85%, absorbs tremendous amount of moisture, transforming it into monohydrate form. It shows pH between 3.5-5.5 with melting point of 83°C when a 20%w/V aqueous solution is prepared.

In pharmaceutical practice, it is used as a tonicity adjuster, sweetening agent, as a diluent and as a binder for granulation step preferably for chewable tablets. The tablet produced is less friable in comparison to lactose as diluent in tablets⁵²-⁵⁴. It protects the other ingredients from being oxidized during tableting process and thus imparts stability to them. It acts as a source of carbohydrate in parenteral preparations.

It remains stable in dry conditions and aqueous solutions of dextrose can be sterilized by autoclaving. At higher temperature, reduction in its pH causes caramelize of aqueous solution, so in order to maintain its stability it must be preserved in cool and dry condition.

It is contraindicated along with drugs such as warfarin sodium, cyanocobalamin, novobiocin sodium and kanamycin sulfate⁵⁵. Slight warm state decomposes the B-complex vitamins when administered along with it. Moreover, when used with aldehydes, dextrose undergoes reaction with amines causes brown coloration of solution along with its decomposition (Maillard reaction).

After absorption in GIT (gastrointestinal tract), it is completely metabolized, giving carbon dioxide and water with the release of energy in the form of ATP. It is administered intravenously as its concentrated solution causes nausea and vomiting orally, also local vein irritation occurs when greater than 5%w/V solution is given. The pH of its infusion may be raised to neutral by adding sodium bicarbonate that reduces the incidence of phlebitis.

Erythritol

Erythritol is considered as a nutritive sweetener and comes under natural compounds providing the body with energy under the category of sugar alcohols⁵⁶-⁵⁸. Fruits and vegetables contain sugar alcohols. Hydroxyl group replaces the aldo or keto group in fruits and vegetables⁵⁹.
Thermal and chemical stability of erythritol is good. It is available as non-hygroscopic, white crystalline substance offering mild sweet taste with sweetness 60-70% that of sucrose. Solubility study confirms that it is soluble in water with only slight solubility in ethanol but shows practical insolubility in ethers and fats. Erythritol is used as a sweetening agent; tablet and capsule diluents (30-90%w/V) and a taste-masking agent (0.5-3.0%w/V). Pharmaceutical applications include it in solid dosage forms, in their coatings, dry powder for inhalers, sugar-free lozenges and in chewing gums (5-10%w/V). In semi solid dosage such as tooth paste, it is recommended since it is a noncariogenic sweetener providing low calories. It has very high negative heat of solution resulting in cooling sensation. It is advantageous in preparing medicated chewing gums. The unpleasant aftertaste in liquid oral formulations such as mouth wash solutions could be masked with its inclusion in it.

Polyols such as erythritol are poorly absorbed through small intestine and come under low digestible carbohydrates. Excess intake may result in digestive discomfort such as gas and diarrhea. Increasing the internal osmotic potential along with its humectant and bulk forming properties elicit a laxative effect if taken in excess. In comparison to other sugars, it is less toxic if taken in large amount.

It shows incompatibility with strong acid and bases. Due to its lower molecular weight, 90% of it in humans is absorbed in the small intestine, providing low caloric value (0.8kJg⁻¹) and a excreted unchanged through urine as it is not metabolized. It is considered safe for diabetic patients with very low glycemic response after ingestion. FDA approved sugar alcohols are safe for human consumption. Examples of some commonly used sugar alcohols are sorbitol, mannitol, lactitol, maltitol and xylitol.

**Fructose**

Fructose is a monosaccharide sugar with functional category of sweetening agent, flavoring agent, dissolution enhancer and as a tablet diluents. It has higher solubility when compared with sucrose and is available as odorless white crystalline powder. This property of higher solubility and humectancy makes it a suitable candidate in solving the problem of cap locking due to crystallization of sucrose in syrups and elixir formulations. In conditions, where temperature is 25°C with relative humidity greater than 60%, it becomes hygroscopic, absorbs significant amount of moisture. Fructose solution remains stable at pH 3-4 and temperature of 4-70°C. It could be sterilized by moist heat method such as autoclaving.

Natural occurs fructose in honey and fruit in furanose form, it could be derived from inulin, dextrose and sucrose by various methods, but commercially it could be synthesized by crystallization of high fructose syrups obtained from cereal starch or cane and beet sugar as pyranose form.

In the preparation of tablets, syrups and solutions, fructose is used as a flavoring and sweetening agent. Since its sweetness is more readily perceived than other sugars, that makes it suitable for masking unpleasant taste of certain vitamins and minerals. It has solubility of about 95% in ethanol, so it is used as a sweetening agent in alcoholic preparations. Its sweetness effect in tablets when used as an excipient is more when compared to polyols such as mannitol and sorbitol. A desired hardness and friability could be achieved when crystalline fructose and sorbitol are mixed in the ratio 3:1. Fructose also acts as a water soluble carrier in enhancing the dissolution profile of certain hydrophobic drugs by reducing their wetting time such as digoxin by technique of coprecipitation with the drug. Tablet containing amines give brown coloration with fructose.

Metabolism yields dextrose as the major component along with metabolites lactic and pyruvic acids by insulin dependent phosphorylation mechanism. It is not suitable in diabetic diets as in excess it may cause acidosis. The recommended British Diabetic Association dose limit is 25g per day. In some parenterals it is used as an alternative to dextrose.

**Isomalt**

Isomalt is non hygroscopic as well as non cariogenic. It comes in the category of polyols and appears as white crystalline granules. It has sweetness of about 50-60% when compared to sucrose. It's pleasant sweetening taste or mouth feel with negligible negative heat of solution makes it a suitable candidate in formulations i.e. sugar-free chewing gum, chewable tablets, hard-boiled candies and lozenges. Moreover, it is also preferred in tablet and capsule preparations, their coating, in granules, suspension and also as a task masking agent in effervescent tablets. Thermal and chemical stability is proven through stability analysis.

Study on humans when ingested orally in adequate amounts does not raise the blood sugar level and thus isomalt shows lower glycemic response. It is mainly fermented in the large intestine with better tolerance but slight excess than the optimum recommended amount might cause laxative effect. During compression in tablet
formulation, isomalt generally adheres to the walls of the die cavities so inorder to reduce the friction, magnesium stearate as a lubricant are preferred. By this, the general problems of are capping, sticking and lamination in tablets also rectified.

**Lactilol**

Lactilol is a non-cariogenic, non-toxic, non-irritant odorless sweetening agent with cooling sensation, used as tablet and capsule diluent with slight solubility in 95% ethanol and ether. Therapeutically, lactilol is used as laxative and in treating hepatic encephalopathy. It could be produced by catalytic hydrogenation of lactose. It does not show brown coloration in presence of amines and thermally it is stable but gets hydrolyzed in acidic solution to sorbitol and galactose. It is resistant to bacterial fermentation in large intestine thus excreted unchanged without being absorbed.

**Maltilol solution**

Maltilol aqueous solution is a mixture of D-maltitol (≥ 50%w/W), D-sorbitol (≤8%w/W), and hydrogenated oligo-and polysaccharides. Physically, it appears as clear, colorless, odorless, viscous liquid with sweet taste. It has low calorific value, higher viscosity and is noncarcinogenic. Moreover, it is non-toxic, non-irritant and non-allergenic approved by WHO to be safely used in food products. It is soluble in ethanol, glycerine, propylene glycol and water. The viscosity decreases with increasing temperature and by decreasing the concentration of dry solids at a constant temperature. Desired viscosity could be achieved by mixing it with sorbitol solution. It's viscosity makes it a suitable suspending as well as sweetening agent when used alone or in combination with sorbitol.

It is preferred over sucrose to overcome the problem of cap-locking which is observed in sucrose based syrups and elixers as it has the property of noncrystallizing. Its consumption is restricted to below 50g per day as it may cause problems of flatulence and diarrhea. Maltilol solution is also reported in pharmaceutical lozenges, confectionary and food industry. At room temperature and at pH 3-9, it remains stable. Sodium benzoate and mixtures of parabens are used as antimicrobial preservatives in formulations containing maltitol.

**Mannitol**

Mannitol occurs as free flowing, white, odorless, crystalline granules. Along with the sweetness, it also imparts cooling sensation in the mouth. When crystallized out in alcohol and examined through the microscope, it appears as orthorhombic needles. It is used to adjust tonicity, as diluent in solid dosage form and as plasticizer to resolve the problem of brittleness. It is slightly soluble in ethanol, glycerine, propanol and water.

Mannitol has good stability with absence of Maillard reactions in dry condition as well as in aqueous solutions. It does not require the presence of catalyst in solution form, remains stable if kept in cold, dilute acids and alkali or if attacked by atmospheric oxygen. Aqueous solution could be sterilized by autoclaving or by filtration.

**Saccharine sodium**

The sodium salt of saccharine has higher solubility than the parent compound with sweetness power 300-600 times as that of sucrose. It is available as white colored efflorescent powder in crystalline form with problem of unpleasant metallic off taste. This aftertaste bitterness could be masked by blending it with other sweeteners such as cyclamates and aspartame giving synergistic response and also reduces the amount of saccharine sodium content used. The daily acceptable intake confirmed as safe is 2.5mg kg⁻¹. WHO confirms it to be used safely in sweetening pharmaceutical preparations such as tablets, powders, gels, suspensions and in liquid oral. However, its use in medicated confectionery, processed food and beverages as sugar alternate also follows certain interim regulations for ingredients declaration and specifying the maximum safe amount used. It remains stable without Maillard browning when stored at optimum temperature and humidity conditions. When exposed to higher temperature of 125°C and low pH (pH 2) for more than 1h it starts undergoing decomposition.

An article published in 1960 demonstrated that a higher dose of saccharine sodium is responsible for bladder cancer as a result of sediments in rat micturition which in turn hurts the cells of bladder. As a result, its use was banned in both animals and humans. But later on researchers concluded that it is safe for human, the bladder cancer in rats was due to presence of a mechanism not found in humans.

In 1994, a report on hepatotoxicity of saccharine was published. A patient took three different drugs having saccharine sodium as a common ingredient, so the overall dose exceeded the ADI. After the administration, patient report showed high levels of hepatic enzymes, which play a vital role in pathogenesis of the liver damage. Further studies concluded that high dose of saccharine sodium may increase body weight; affect the homeostatic and other physiological processes.
**Sorbitol**

Sorbitol is hygroscopic, colorless, odorless and crystalline powder with sweet cooling sensation after taste. It is used as a vehicle, humectant, plasticizer, tablet and capsule diluent and also as stabilizing and sweetening agent with sweetness power approximately 50-60% as that of sucrose. Glucose and fructose are the breakdown end products emerging out after metabolism. Its absorption is much slower in gastrointestinal tract; this property makes it a suitable vehicle for sugar free liquid formulations specially designed for diabetic patients. Sorbitol has greater impact on bioavailability/bioequivalence of drugs. It delays drug absorption by enhancing fluid influx and motility of gut. When used as a plasticizer, it reduces the brittleness of gelatin in capsule and also as a coating and film forming agent. In tablet formulation by wet granulation and direct compression methods, it is used as a diluent. However, in chewable tablets it imparts cooling sensation along with sweet taste.

In sugar free liquid formulations, sorbitol is used as a vehicle to stabilize drug, vitamins and antacid salts. In parenterals, when used as an excipient, it is reported to stabilize proteins in liquid form and has also been reported as a carrier to enhance the *in vitro* dissolution rate profile of indomethacin.

As an excipient, it is inert and compatible with majority of other excipient used. It is relatively stable at elevated temperatures and lacks Millard coloration in presence of amines. The parenteral solutions could be sterilized by autoclaving. With divalent and trivalent metal ions in strongly acidic and basic condition, it forms water soluble chelates and with iron oxides discoloration occurs. Ingestion of large quantities is avoided due to its osmotic laxative effect. Moreover, it is accepted for use in food additives and as an inert excipient in formulations, listed safe in GRAS (generally recognised as safe) and by FDA (Food and Drug Administration).

**Sucralose**

Sucralose is a crystalline, free-flowing, off-white powder with sweetness power 300-1000 times when compared to sucrose with no aftertaste. While evaluating the solubility parameter, it is freely soluble in water, methanol and 95% ethanol but only slightly soluble in ethyl acetate. FDA approved it to be a non-irritant and non-toxic food additive suitable for food, beverages and pharmaceuticals. In addition, it has no nutritional value, is non-cariogenic and shows negligible glycemic response that makes it a suitable sweetening agent for sugar free formulations. It is used as a sweetening agent in beverages, foods (0.03-0.24%w/V) and pharmaceuticals. Acceptable daily intake recommended by WHO is up to 15 mg kg⁻¹. Only 11-27% of the administered portion is absorbed and the rest is excreted unchanged in faeces as our body does not recognize it as a sugar. Thus neither does it undergo metabolism nor does it provide any calories, so it is safe to use as a sugar alternative. The small portion absorbed in blood is eliminated via kidney through urine.

It undergoes hydrolytic degradation when exposed to low pH and at high temperature conditions. During sterilization operations such as pasteurization and UHT (Ultra high temperature), no effect on its sweetness power is observed. The metabolites of sucralose are found to be non toxic and are insoluble in body fats as compared to other organic chlorides. After conducting several research on animals and humans through research studies FDA has not found any proof of serious conditions like cancer upon its consumption.

Gastrointestinal hormones such as GLP-1 released in response of carbohydrate intake shows adverse effects of suppression of appetite and slowing of gastric emptying. Therapeutic doses of GLP-1 hormone shows adverse effects of inhibiting glucagon secretion, slowdown of gastric emptying and suppresses of appetite in turn leading to serious weight loss in the long term administration. GLP-1 is one of the two known 'incretin' hormones that stimulate glucose-dependent insulin release. In healthy humans, GLP-1 and GIP account for at least 50% of the postprandial insulin response.

**Sodium cyclamate**

It is available as white odorless crystalline powder with slight solubility in ethanol, water and propylene glycol. Its dilute solution is stable towards heat, light and air over wide range of pH. Dilute solution with concentration 0.17%w/V gives sweetness 30 times that of sucrose whereas, when its concentration is further raised to 0.5%w/V, then it starts giving bitter taste. Generally, it is used to provide synergistic effect in resolving the aftertaste problem of certain sweeteners such as saccharine or acesulfame potassium used in the ratio 10:1. It is considered as non-carcinogenic, is excreted unchanged in urine and during bacterial decomposition in the gut it gets converted to the toxic metabolite cyclohexylamine. Prediction of ADI is difficult as metabolism differs from person to person. In some people, it is excreted unchanged while some people metabolize it to toxic cyclohexylamine. It is used as an inactive ingredient in oral powders, chewable tablets, and in suspensions. The acceptable daily intake suggested as safe by WHO for both sodium and calcium cyclamate.
Some studies proved the carcinogenicity of cyclamate in animals, and that it can lead to bladder cancer. Further work showed that there was no link between cyclamate and cancer, hence they filed petition for its approval.\(^93\)

**Xylitol**

It is used as an alternate to sucrose in providing the sweet cool sensation to the product. In solid dosage forms such as tablet and capsule it is used as diluent, in tablet coating (65%w/W). Use of Xylitol as an emollient and humectant in toothpaste, chewing gum and mouth rinses has been reported with reduction in the incidence of dental caries.\(^94\) Xylitol is found to be very effective in masking the unpleasant flavor and taste of certain actives and other excipients used in preparations. By its own bacteriostatic and bactericidal activity, it potentiates preservative efficacy in providing stability to the product. Also, its lower water activity and higher osmotic pressure keeps the product fresh and stable. The intravenous infusion given after trauma uses xylitol as an energy source.\(^95\) Chances of bacterial decomposition are less in the product made from it as only 25-50% of the orally administered dose is metabolized through microbial attack and fermentation.\(^96\) It also extends its application as a sweetening agent, and as a vehicle in sugar free preparations. Moreover, it also prevents product crystallization around the closures of bottles, thus the problem of ‘cap lock’ generally seen in sucrose containing syrups is resolved.

Its metabolism is independent to insulin, and provides very low calories. Daily intake of 100 mg in divided doses is well tolerated, as large doses may have a laxative effect. It remains stable over a wide pH range when used along with actives and excipients.

**TASTE-MASKING IN VIVO EVALUATION**

Bitterness of the formulation has been evaluated as:

a) The test performed inside the oral cavity by formulating it in the form of ODT (Oral Disintegrating Tablets) after getting approval from ethical committee.

b) Written consent of six healthy volunteers of both sexes in the age group 20-25 years were selected.

c) The optimized ODT formulation was evaluated for bitterness by comparing their results with the reference standard tablets and tabulated accordingly.

d) Volunteers were asked to put the tablet inside the buccal cavity till it got disintegrated.

e) The bitterness experienced by the volunteers was immediately recorded and analyzed over the bitterness intensity scale which ranged from 0-5 (0 = no bitterness, 1 = threshold bitterness, 2 = slight bitterness, 3 = moderate bitterness, 4 = bitterness, 5 = strong bitterness).

f) The BI is expressed in terms of following equation\(^97\):

\[
BI = \frac{BS - NC}{N}
\]

where, bitterness is indicated on ‘BS’, Higher the number on the scale higher will be the intensity of bitterness.

\(BI\): Bitterness intensity

\(BS\): Bitterness scale

\(NC\): Number of volunteers scored

\(N\): Total number of volunteers

**NOVEL SWEETENERS**

**Rare sugars**

Rare sugars such as allulose, allose, melezitose and D-tagatose are made by fermentation or enzymatic conversion. Their lower rate of metabolism provides lesser calories and leads to its use as an alternate to the traditional sugars such as sucrose, maltose, fructose or lactose. No objectionable after taste feature is applied in various pharmaceutical formulations, cosmetic, flavor and food industries.\(^98,99\)

**Tagatose**

It is a chemically inert sweetening agent with intense sweetening power of 92% as that of sucrose. It is very soluble in water and slightly soluble in ethanol. It is considered to be a potential drug candidate in treating Type II diabetes, since only 15% per day of the administered dose is absorbed in small intestine, larger portion of it is fermented in colon by indigenous microflora. In the colon, it gets converted to short chain fatty acids that are readily absorbed and metabolized.\(^100,101\) It has lower glycemic index value which is helpful in treating both body weight as well as metabolic disorders like diabetes. Being a reducing sugar, it reacts with primary amines which is indicated by yellow brown color thus confirms Millard reaction. As a dietary supplement it has been approved by FDA since 2003.

**L-and D-Nucleoside analogues**

L-and D-Nucleoside analogues of some rare sugars are utilized in the synthesis of some important biologically active antiviral and anticancer drugs. They are made...
from basic rare sugars which act as their building blocks. L-Nucleoside analogues are stable with powerful antiviral activity. Clevudine an anti-hepatitis B drug, is made from L-ribose, which is the D-ribose enantiomer. Further, purine nucleoside is synthesized from L-xyllose having same antiviral activity. Enantiomers of L-gulose and L-galactose are also used in the production of L-nucleosides. On the other hand, D-nucleosides such as D-allose are used as they show various therapeutically active responses such as anti-cancer, anti-inflammatory, anti-oxidant and immunosuppressant. An anti-tumor dehydroamino acid derivative is basically made from the rare sugar D-arabinose as the starting material[102].

CONCLUSION

This review might be useful to gain knowledge on the metabolism, health effects, formulation process, chemical structure and usage trends of artificial sweeteners. They serve as low risk alternatives to the natural sugars. Their usage above the recommended ADI for prolonged periods shows lethal effects such as headache and even brain damage. So, the assertion that they are safe is false. They are safe when used as per FDA recommended guidelines. Their low rate of metabolism giving out lesser calories makes them a suitable substitution.

REFERENCES


