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Review Paper

Artificial Sweeteners

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ABSTRACT

Artificial Sweeteners provide the sweetness of natural sugar without the calories and produce a low glycemic response. These sweeteners are used instead of sucrose (table sugar) to sweeten foods and beverages. Consumers and food manufacturers have long been interested in dietary sweeteners to replace sucrose in foods. This article goes into a lot of details about the different types of sweeteners such as saccharin, acesulfame potassium, aspartame, neotame and sucralose, their uses, chemistry and their potential effects on health. These sweeteners form acute and chronic effects on human health.

Keywords: Artificial sweeteners; adverse effects; potential toxicity

1. INTRODUCTION

Artificial sweeteners are many times sweeter than table sugar, smaller amounts are needed to create the same level of sweeteners, and which are either not metabolized in the human body or do not significantly contribute to the energy content of foods and beverages. Those provide the sweeteners of sugar without the calories and produce a low glycemic response. [1] Glycemic response to food is the effect that food has on blood sugar levels after consumption. [2] Consumers and food manufacturers have long been interested in dietary sweeteners to replace sucrose in foods. Because recently these products have received increased attention due to their effects on glucose regulation. These exceed the sweeteners of sucrose by a factor of 30-13,000 times because of these include substances from several different chemical classes. [1] These sweeteners are widely used in baked goods, carbonated beverages, powdered drink mixtures, jams, jellies and dairy products. [3] These are regulated by the Food and Drug Administration (FDA).

Sweeteners have been classified as natural sweeteners and artificial sweeteners. These artificial sweeteners further classified as nutritive and non-nutritive sweeteners depending on whether they are a source of calories. The nutritive sweeteners include the monosaccharide polyols (e.g., sorbitol, mannitol, and xylitol) and the disaccharide polyols (e.g., maltitol and lactitol). The non-nutritive sweeteners are better to known as artificial sweeteners. [1]

Artificial sweeteners have some ideal requirements. They should provide sweetness with no unpleasant aftertaste, should have little or no calories, should be economical to produce, should not be degraded by heat when cooked and should not be carcinogenic or mutagenic. Carcinogenic is having the potential to cause cancer, and mutagenic is a physical or chemical agent that changes the genetic material of the organism. [3]

The main reasons for using artificial sweeteners are weight lose, dental care, diabetes mellitus, reactive hypoglycemia and low cost. [1] Dental caries are also known as teeth decay or cavities. Breakdown of teeth due to activities of bacteria. This occurs due to acid made from sugar on the tooth surfaces. Simple sugars in foods are the primary energy source of these

bacteria. [4] Reactive hypoglycemia refers to low blood sugar that occurs after a meal usually within 4 hours after eating. This can occur in both people with and without diabetes and is thought to be more common in overweight individuals. Reactive hypoglycemia is known as the result of too much insulin being produced and released by the pancreas following a large sugar or carbohydrate based meals. [5] To reduce these activities, most of the people are using artificial sweeteners.

The main five sugar substitutes for use in a variety of foods are saccharin, acesulfame potassium, aspartame, neotame and sucralose. Characteristic features of these five artificial sweeteners are given in the Table 1.

Table 1. Characteristic features of artificial sweeteners [1]

Common name	Brand names	Number of times sweetener than sucrose	kcal/g	Common uses
Saccharin	Sweet'N Low Sweet Twin Necta Sweet	200-700	0	Soft drinks, Tabletop sweetener, Jams, Chewing gum, Baked goods
Acesulfame K	Sunett Sweet One	200	0	Tabletop sweeteners, Candies, Chewing gum, Dairy products
Aspartame	Nutra Sweet Natrataste Equal	180-200	4	Soft drinks, Yoghurt, Pharmaceuticals
Neotame	Neotame	7000-13000	0	Baked goods, Soft drinks, Chewing gum, Jams, Jellies, Puddings, Processed fruit and fruit juices
Sucralose	Splenda	600	0	Frozen deserts, Fruit juices, Chewing gum, gelatins

1.1 Structural requirements for sweetness

The generally accepted theory for the phenomenon of sweetness was developed by Shallenberger and Acree. According to this theory, a molecular system of a proton donor and proton acceptor is necessary. Changes in the distance between groups, as well as changes in electronic structure influence the occurrence of the sweet taste and may change the general taste perception, sometimes eliminating sweetness totally, or changing it to bitterness. [6]

1.2 General Uses

1.2.1 Foods and Beverages

Foods and beverages are the most important fields of application of artificial sweeteners, with calorie reduction being the main goal. Single sweeteners or combinations with other sweet substances. Artificial sweeteners can be used in diabetic foods and beverages; depending on the type of product, either as single sweetening agents or combined with bulk sugar substitutes suitable for diabetic consumption. Beverage uses of artificial sweeteners account for more than 50% of human consumption; sugar replacement by artificial sweeteners is simple, as carbohydrates do not play any important functional role in beverages. Other important applications are fruit flavored dairy products and desserts. [7]

1.2.2 Tabletop sweeteners

For household use, artificial sweeteners are formulated into table-top sweeteners, such as sweetener tablets, powders and spoon-by-spoon products, and liquids.

1.2.3 Pharmaceuticals

Artificial sweeteners are used to mask undesired flavors and tastes of active pharmaceutical ingredients, e.g., bitterness, whenever the pharmaceuticals are intended for use by diabetics. Sweeteners are used in syrups, and soluble tablets and powders.

1.2.4 Cosmetics

Several types of cosmetics, especially oral hygiene products, are sweetened to make them more pleasant for consumers. For oral hygiene products (e.g., toothpaste, mouthwash, etc.), noncariogenic ingredients have to be used. The desired sweetness level is adjusted with an additional quantity of artificial sweetener.

1.3 Saccharin

Saccharin is the first and oldest artificial sweetener that has been used for over a century to sweeten foods and beverages without adding calories. Saccharin has been approved by FDA for use in more than 100 countries. [3]

1.3.1 History

Saccharin was discovered by Fahlberg & Remsen in 1879 at John Hopkins University. This was found after those chemists were researching the oxidation mechanisms of toluene sulfonamide. They were working with coal-tar derivatives. During their research, a substance accidentally splashed on Fahlberg's finger and he noticed the substance had a sweet taste, which he traced to the chemical commonly known as saccharin. Saccharin enjoyed great commercial success in periods of short sugar supply, e.g., during world wars I and II. [8]

In 1997, the FDA proposed a ban on saccharin because of concerns about rats that developed bladder cancer after receiving high doses of saccharin. Foods containing saccharin were required to carry a label warning that sweetener could be a health hazard and that it was found to cause cancer in laboratory animals. That label contains "use of this product may be hazardous to your body". In 2000, the National Toxicology Programme determined that saccharin should no longer be listed as a potential cancer-causing agent because mechanistic studies have shown that these results apply only to rats. Mechanistic studies that examine have a substance work in a body. Human epidemiology studies have shown no consistent evidence that saccharin is associated with bladder cancer incidence. Because the bladder tumors in the rats are due to a mechanism not relevant to human and there is no clear evidence that saccharin causes cancer in humans. Epidemiology studies are that studies of patterns, causes and control of disease in groups of people. In 2001, saccharin was officially declared safe and the ban was removed. [9]

1.3.2 Chemistry

Saccharin is formed by an initial reaction between toluene and chlorosulfonic acid. Synthesis of saccharin is explained in Figure 1. [7]

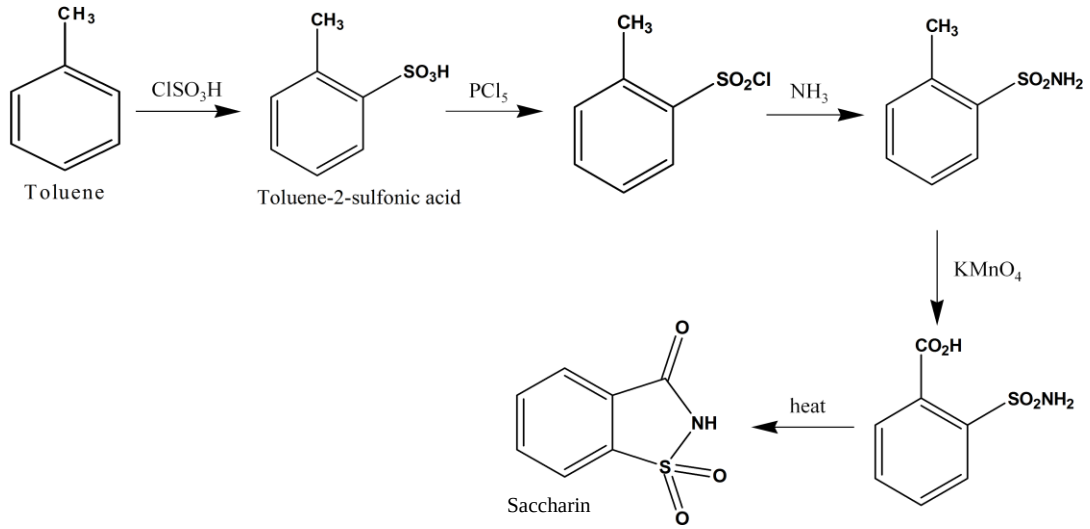

Figure 1. Synthesis of saccharin (Remsen-Fahlberg synthesis)

After ingestion, saccharin is not absorbed or metabolized. Instead, it is excreted, unchanged via the kidneys. [1] Slightly bitter taste and metallic taste and for this reason is sometimes combined with other sweeteners. For an example, saccharin is often used with aspartame in diet carbonated soft drinks. [3] The form used as an artificial sweetener is sodium salt and calcium salt, especially by people restricting their dietary sodium intake. [1]

1.3.3 Uses

Important fields of application are soft drinks, tabletop sweeteners, and desserts. For taste reasons, blends with other artificial sweeteners, or combinations with reduced sugar levels are preferred wherever such blends are approved. In oral hygiene products, saccharin masks undesired tastes of other ingredients. In starter feed for livestock, saccharin is used to avoid reduced feed intake after weaning. Besides its applications as an artificial sweetener, saccharin is used in electrolytic nickel deposition. Addition of saccharin to the nickel salt solutions increases the hardness and brightness of the nickel plate. This effect is apparently specific to saccharin. [10]

1.3.4 Toxicology

Saccharin causes a headache, breathing difficulties, skin eruptions and diarrhea.

1.4 Acesulfame potassium

This is a general purpose sweetener, white crystalline structure, high-intensity, non-nutritive sweetener, non-carcinogenic and stable under high temperatures. So it does not break down in heat, therefore often used in baked products. It is used in over 4000 products in approximately 90 countries. The "K" refers to the mineral potassium, which is naturally found in our bodies. [3]

1.4.1 History

Acesulfame-K was discovered in 1967 by chemist Karl Clauss and Jensen during investigations on oxathiazinone dioxides. The sweet taste was found by chance. Several other oxathiazinone dioxides taste sweet but have less favorable characteristics. Acesulfame-K was approved in the United States in 1988 for specific uses, including a tabletop sweetener. In 1998, the FDA approved acesulfame-K to be use in beverages. In specially, it has been used to decrease the bitter aftertaste of aspartame. FDA continues to support the use of acesulfame-K in diabetic and low-calorie food. [1]

1.4.2 Chemistry

Acesulfame-K is formed by an initial reaction between 4-chlorophenol and sodium. Synthesis of acesulfame-K is explained in Figure 2.

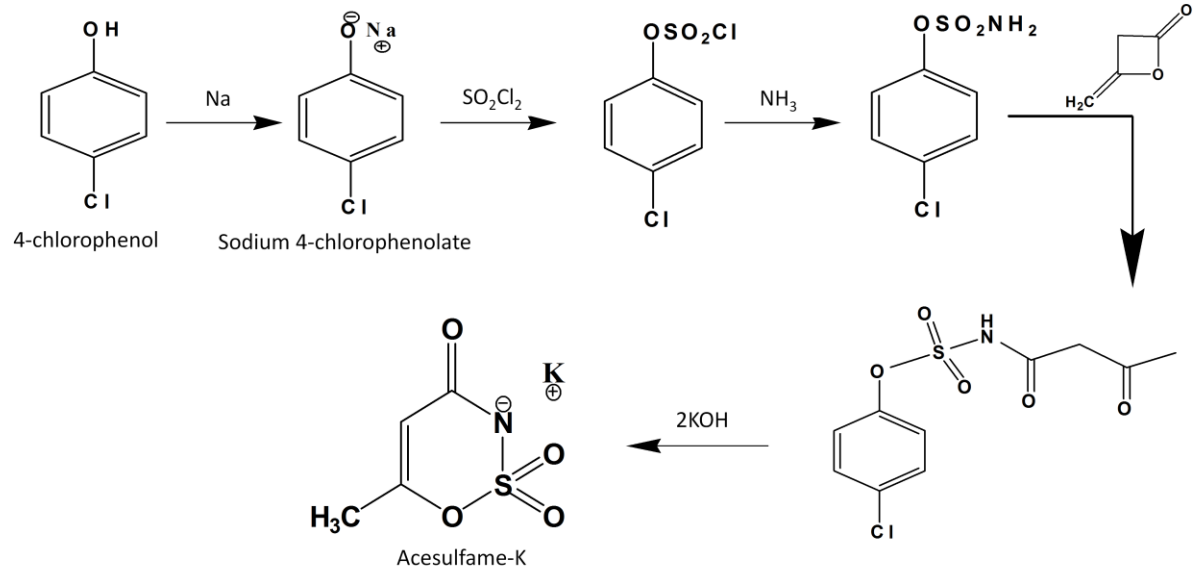

Figure 2. Synthesis of acesulfame-K

Acesulfame-K is not metabolized by the body and is not stored in the body. It is quickly absorbed and excreted in urine without undergoing any modification. Pharmacokinetic studies show that 95% of the consumed sweeteners basically ends up excreted in the urine. [11]

1.4.3 Uses

Acesulfame K is used in all fields of applications of artificial sweeteners. Common applications are table-top

sweeteners; beverages; foods, such as dairy products, desserts, bakery products, confectionery, chewing gum, pickles, and marinated fish; oral hygiene products and pharmaceuticals. Owing to its synergistic characteristics, acesulfame K is often used in sweetener blends, and in combination with bulk sweeteners in products requiring good stability, e.g., confectionery or bakery products.

1.4.4 Toxicology

Acesulfame-K contains methylene chloride which is a known carcinogen. Long-term exposure to methylene chloride can cause a headache, depression, nausea, mental confusion, liver and kidney effects. Acesulfame-K's breakdown in the body forms the byproduct acetoacetamide, which is toxic at high doses and which has been shown to cause tumor growth in the thyroid gland in rats, rabbits and dogs. Only 1% acetoacetamide is accumulated for three months. [3]

1.5 Aspartame

One of the most debated sweeteners. Aspartame has a sugar-like taste. It can be safely heated to high temperatures with some loss of sweeteners. It has been used in over 6000 different types of products. [12]

1.5.1 History

Aspartame was discovered in 1965 by G. D. Searle when he was studying new treatments for gastric ulcers. Tetrapeptide is normally produced in the stomach which was used by the biologist to test new anti-ulcer drugs. One of the most important steps in the process was to make an intermediate, aspartyl-phenylalanine methyl ester to synthesis tetrapeptide. When chemist was synthesis this tetrapeptide, accidentally, a small amount of the compound landed on the chemist's hand. Without noticing the compound, the chemist licked his finger and discovered a sweet taste. After realizing it was not likely to be toxic.

It was first approved by the FDA in 1981 as a tabletop sweetener; in 1996, it was approved as a general-purpose sweetener in all foods and drinks. Aspartame is sometimes blended with more stable sweetener saccharin. [13]

1.5.2 Chemistry

Aspartame is made by joining L-phenylalanine or L-phenylalanine methyl ester with L-aspartic acid. Synthesis of aspartame is explained in Figure 3.

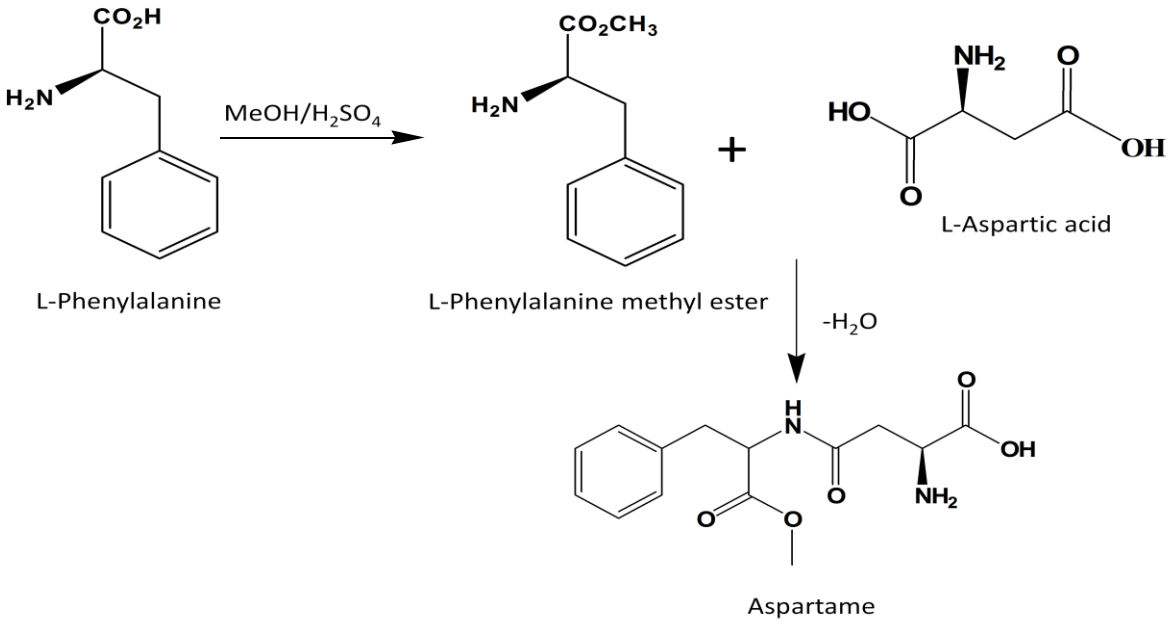

Figure 3. Synthesis of aspartame

Aspartame breaks down into small amounts of methanol, aspartic acid and phenylalanine during the digestion. Methanol is non-drinking alcohol, injecting of that can lead to toxicity and death within a few hours. The body also breaks down this methanol into formaldehyde which turns into formic acid in the liver. Formaldehyde and formic acid both are toxic.

Our body produces formaldehyde in amounts thousands of times greater than we get from the sweetener which is used by the body to make important substances. Formic acid rarely builds up because the body uses formaldehyde so quickly and if there were an excess, it would be eliminated through urine or broken down into CO_2 and water. Finally, the aspartame in diet produces so little amount of ethanol. [14]

1.5.3 Uses

The sensory characteristics of aspartame allow its use in all common sweetener applications. Limitations are imposed by its susceptibility to hydrolytic decomposition and limited temperature stability.

1.5.4 Toxicology

FDA has mandated packaging bear a warning label to prevent individuals with the rare genetic disorder phenylketonuria from ingesting the aspartame. Phenylketonuria is an inborn error of metabolism that leads to attenuated metabolism of the amino acid phenylalanine. Phenylketonuria can lead to behaviour problems and mental disorders. Individuals who suffer from this disease have an insufficient amount of the enzyme phenylalanine hydroxylase which is required to breakdown the phenylalanine. Without the presence of this enzyme, phenylalanine accumulates.

Due to the methanol, aspartic acid and phenylalanine which came from the digestion of aspartame can cause the following symptoms: headache, blurred vision, brain tumors, eye problems, memory loss and nausea. [15]

The aspartame consists of aspartic acid which is a well-documented excitotoxin. 3 amino acids such as glutamate, aspartate and cysteine that excite our neurons can be called as excitotoxin. These neurotransmitters (amino acids) excessively stimulate the nerve cells to either damage or kill. Excitotoxicity may be involved in spinal cord injury, stroke and hearing loss. [16]

1.6 Neotame

Neotame is the newest sweetener and a derivative of aspartame. A t-butyl group is added to the free amine group of aspartic acid. This could be a super sweet deal for food and beverage manufacturers, all the sweetness of sugar without a metallic after-taste plus at a fraction of the amount of sweetener needed compared to other sugar substitutes. The neotame was approved in 2002 as a general purpose sweetener, excluding in meat and poultry by FDA. [1]

1.6.1 History

After the success of aspartame in the market, there were calls for developing a novel sweetener possessing additional qualities such as higher heat stability, fewer restrictions and higher sweetener potency which means less amount to achieve the same sweetness at a lower cost. Therefore scientists synthesized thousands of compounds based on the simple structure of aspartame. End of the research, neotame came up with the desirable qualities among those synthesized compounds. Neotame was approved by FDA for general use in 2002. [17]

1.6.2 Chemistry

When we add the t-butyl group to the free amine group of aspartic acid, it leads to a second hydrophobic group and results in a product that is 30-60 times sweeter than aspartame. [18] Figure 4 shows the synthesis of neotame.

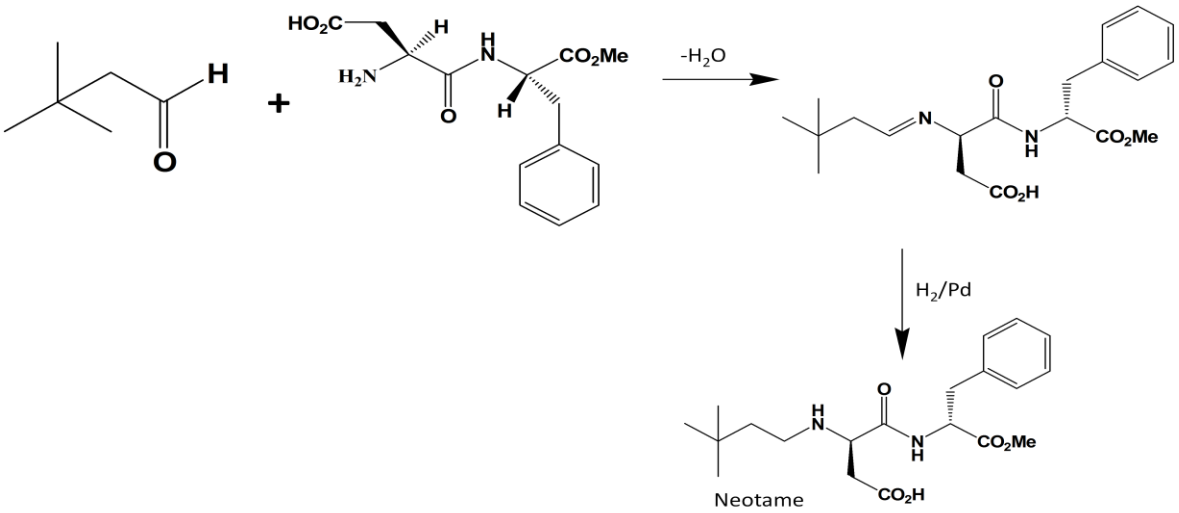

Figure 4. Synthesis of neotame

Neotame is rapidly metabolized by hydrolysis of the methyl ester via esterase present throughout the body. It forms a minor amount of methanol that the body absorbs. This process yields de-esterified neotame. Neotame and de-esterified neotame are rapidly clear from the plasma, which is completely eliminated from the body with recovery in urine and feces within 72 hours. It is safe for who suffer from phenylketonuria because t-butyl group is added to the free amine group of aspartic acid. This t-butyl group typically break the peptide bond between the aspartic acid and phenylalanine, thus reduce the availability of phenylalanine which is responsible for phenylketonuria. [19]

1.6.3 Toxicology

Neotame causes some of the toxic effects in the human such as it to reveal changes in body weight and food consumption, headache and hepatotoxicity at high dosages.

1.7 Sucralose

Sucralose is a sucrose molecule in which three of the hydroxyl groups have been replaced by Cl atoms. Sucralose is also heat stable which quality makes it a superb sweetener for cooking and baking. It retains its sweeteners significantly longer than aspartame. Figure 5 shows structures of sucrose and sucralose.

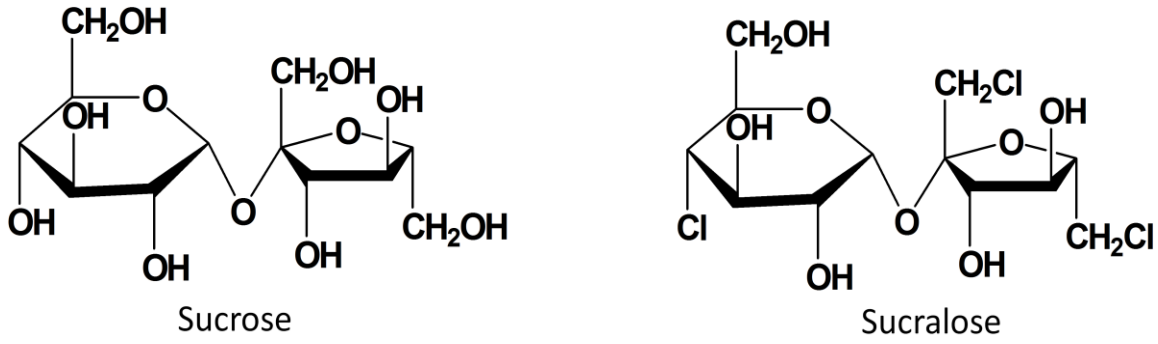

Figure 5. Structures of sucrose and sucralose

1.7.1 History

Sucralose was accidentally discovered by Tate & Lyle in 1976, was looking for ways to use sucrose as a chemical intermediate. Ironically, sucralose states out as cane sugar but ends up 600 times sweeter than table sugar. It came on the scene in 1976 and was approved by the FDA in 1999 for use in 15 food categories. After some laboratory experiments which

changes the sugar molecule, its structure now prevents it from being absorbed by the body. [20]

1.7.2 Chemistry

Synthesis of sucralose is shown in the figure 6.

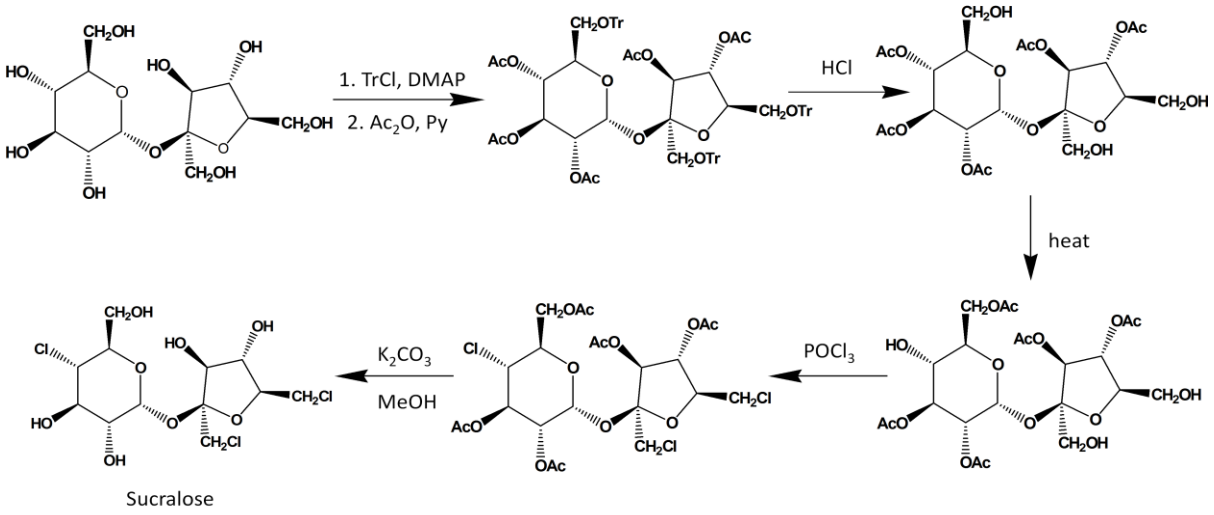

Figure 6. Synthesis of sucralose
TrCl = triphenylmethyl chloride; DMAP = 4-dimethylaminopyridine

Sucralose is poorly absorbed in the human and the majority of ingested sucralose excreted unchanged in the feces.

1.7.3 Toxicology

Sucralose is responsible for the shrunken thymus glands with diets of 5% sucralose, and also it causes diarrhea and dizziness.

2. HEALTH BENEFITS OF ARTIFICIAL SWEETENERS

Artificial sweeteners are not carbohydrates. So generally they don't raise blood sugar levels and cause diabetes. They have no calories. In distinction, every gram of normal table sugar contains four calories. They are suitable for obesity. They do not promote dental caries. [1]

3. ADVERSE EFFCTS OF ARTIFICIAL SWEETENERS

Saccharin, acesulfame-K and aspartame induced DNA damage in human peripheral lymphocytes. Sucralose has been well-tried through scientific experimentation to cause a decrease in beneficial micro-organisms. Under acidic conditions, acesulfame-K formed minute quantities of acetoacetamide and acetoacetamide-N-sulfonic acid. While under basic conditions, acetoacetic acid and acetoacetamide-N-sulfonic acid are formed. These degradation products may cause DNA strand breaks. [3]

Toxic potential of artificial sweeteners for the human body are shown in the Table 2.

Table 2. Toxic potential of artificial sweeteners [1]

Common name	Known metabolites	ADI (mg/kg)	Acute	Chronic
Saccharin	O-sulfamoylbenzoic acid	5	Nausea, vomiting, diarrhea	Low birth weight, bladder cancer, hepatotoxicity
Acesulfame-K	Acetoacetamide	15	Headache	Thyroid tumors
Aspartame	Methanol, aspartic acid, phenylalanine	50	Headache, dizziness, nausea, vomiting, thrombocytopenia	Lymphomas
Neotame	Methanol, de-esterified neotame	2	Headache, hepatotoxic at high doses	Lower birth rate, weight loss
Sucralose		5	Diarrhea, dizziness, stomach pain	Thymus shrinkage

ADI - Annual daily intake

Aspartame hydrolyzes into its components within the gut. The increase of these components was considered a possibility of gastrointestinal problems. Aspartame has been thought to cause brain damage because one of its hydrolyzed components is phenylalanine. Phenylalanine plays an important role in a neurotransmitter regulation. [3]

4. CONCLUSION

Artificial sweeteners provide some of the health benefits. However, commonly these sweeteners are toxic at high concentrations in the long term. Their consumption has been shown to cause mild to serious side effects ranging from headaches to life-threatening brain damages.

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