A Review on Artificial Sweeteners: Chemistry, Synthesis and Uses

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Abstract:

Artificial sweeteners use in weight loss, diet planning with no calories or low calories. In recent years, they are used in over 6000 or more products. This review reveals knowledge about the history, synthesis, brand products and uses of artificial sweeteners. These sweeteners are used instead of sucrose to sweeten the product. The artificial sweeteners play an important role in the patient with diabetes, obesity, etc. Now a day, the artificial sweeteners are most popular instead of natural sweeteners because of no calories and no chances of obesity.

Key words: Artificial sweetener, Aspartame, Saccharin, Neotame, Sucralose.

Introduction

Artificial Sweeteners

Artificial sweeteners are many times sweeter than table sugar. Smaller amounts are needed to create the same level of sweetness, 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. The main reasons for using artificial sweeteners are weight loss, dental care, diabetes mellitus, reactive hypoglycemia and low cost. Consumers and food manufacturers have long been interested in dietary sweeteners to replace sucrose in foods. [1] These sweeteners are widely used in baked goods, carbonated beverages, powdered drink mixtures, jams, jellies and dairy products. [2]This review gives the information about the sweeteners such as Aspartame, Saccharin, Neotame, Sucralose, Acesulfame Potassium and Sodium Cyclamate.

1. Aspartame

Aspartame is one of the most debated sweeteners. It has been used in 6000 different products. The FDA's approved ADI of aspartame is 50 mg/kg/day. [3]

History

Aspartame was discovered in 1965 by G. D. Searle when he was studying new treatment for the gastric ulcer. Tetra peptide is normally produced in the stomach which was used by the biologist to test new anti-ulcer drug. One of the most important steps in the process was to make an intermediate, aspartyl phenylalanine methyl ester to synthesize tetra peptide. When the chemist was synthesizing this tetra peptide, 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. He realizes that it was not likely to be toxic. It was the first artificial sweetener that was 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. [4]

Chemistry

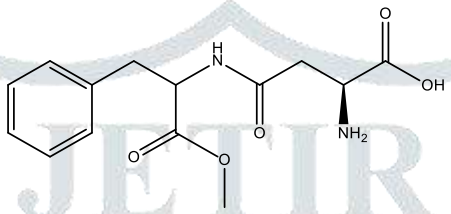

Figure 1. Structure of Aspartame

Under strongly acidic or alkaline conditions, aspartame may generate methanol by hydrolysis. Under more severe conditions, the peptide bonds are also hydrolyzed, resulting in free amino acids. [5] Two approaches have been used for synthesis of aspartame commercially. In the chemical synthesis, two carboxyl groups of aspartic acid are joined into an anhydride, and the amino group is protected with a formyl group as the formamide, by treatment of aspartic acid with a mixture of formic acid and acetic anhydride. Phenylalanine is converted to its methyl ester and combined with the N-formyl aspartic anhydride; then the protecting group is removed from aspartic nitrogen by acid hydrolysis. The drawback of this technique is that a byproduct, the bitter-tasting B-from, is produced when the wrong carboxyl group from aspartic acid anhydride links to phenylalanine, with the desired and undesired isomer forming in a 4:1 ratio. A process using an enzyme from Bacillus thermo proteolyticus to catalyze the condensation of the chemically altered amino acid will produce high yields without the B-from byproduct. A variant of this method, which has not been used commercially, uses unmodified aspartic acid, but produces low yields. Methods for directly producing aspartyl-phenylalanine by enzymatic means, followed by chemical methylation, have also been tried, but not scaled for industrial production. [6]

Synthesis

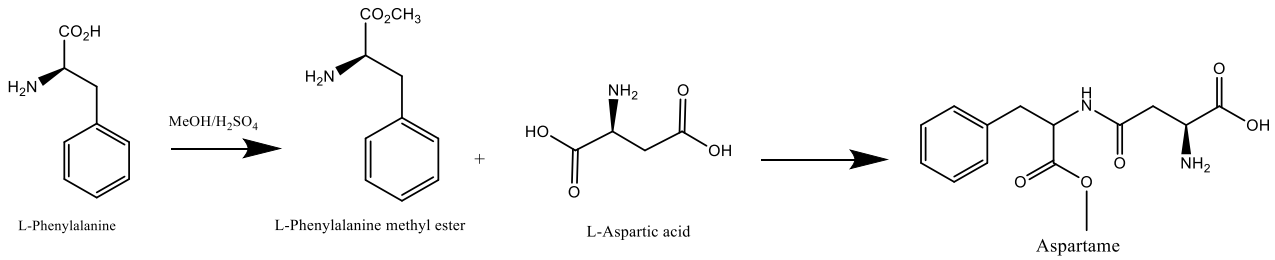

Figure 2. Synthesis of Aspartame

Products containing Aspartame

Table 4. Products containing Aspartame

Name of Product	Content of Aspartame in mg
Diet soda	225 mg
Powered drinks	100 mg
Yogurt	80 mg
Gelatin dessert	80 mg
Equal, 1 packet	22 mg

Equal **NutraSweet**

Figure 3. Aspartame containing products

Uses

Under the trade names Equal, NutraSweet and Canderel, aspartame is an ingredient in approximately 6,000 consumer foods and beverages sold worldwide, including diet sodas and other soft drinks, instant breakfast, breath mints, cereals, sugar-free chewing gums, coca mixes, frozen dessert, gelatin dessert, juices, chewable vitamin solemnest, milk drinks, pharmaceutical drugs and solemnest, shake mixes, tabletop sweeteners, teas, instant coffees, wine colors and yogurt. Aspartame is less suitable for baking than other sweeteners because it breaks down when heated and loses much of its sweetness. [7]

Metabolism and Health aspects

Upon ingestion, aspartame breaks down into natural residual components, including aspartic acid, phenylalanine, methanol and further break down products including formaldehyde, formic acid and diketo piperazine (George et al. 2010; Trocho et al. 1998). Each of which then metabolized just as it would be if derived from other dietary sources and are safe as consumed in normal diets.

2. 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. Saccharin is an artificial sweetener that has been widely accepted as a sugar substitute. It is three hundred to five hundred times sweeter than sucrose and is the most important and widely used sweetener, especially for diabetic patients, as it goes directly through the human digestive system without being digested. [8,9]

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 suly, e.g., during world wars I and II. [10]

Chemistry

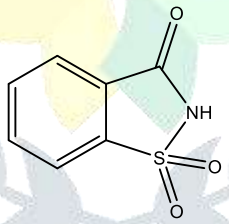

Figure 4. Structure of Saccharin

It is an NNS of 1, 2-benzoisothiazol-3-(2H) on 1, 1 dioxide. Saccharin has an unpleasant bitter or metallic off-taste. As the parent compound is only sparingly soluble in water, the sweetener is usually used as the sodium or calcium salt. Both salts are highly water-soluble, 0.67 g ml 1 of water at room temperature.

Synthesis

Saccharin can be produced in various ways. [11] The original route by Remsen and Fahlberg starts with toluene; another route begins with o-chlorotoluene. [12] Sulfonation of toluene by chlorosulfonic acid gives the ortho and para substituted sulfonyl chlorides. The ortho isomer is separated and converted to the sulfonamide with ammonia. Oxidation of the methyl substituent gives the carboxylic acid, which cyclizes to give saccharin free acid. [13]

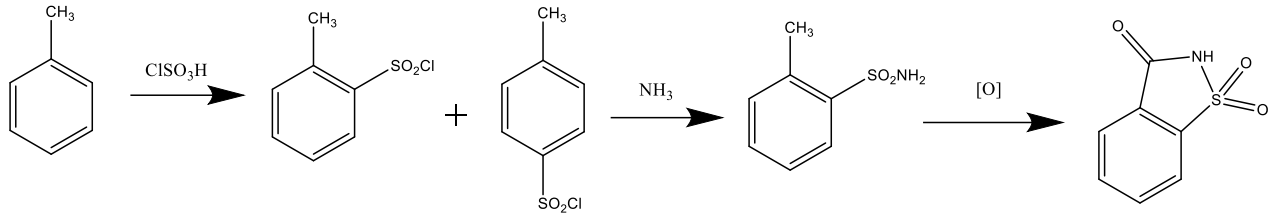

Figure 5. Synthesis of Saccharin

Product Containing Saccharin

Table 5. Product containing Saccharin

Product Containing Saccharin	Additional non Nutritive Sweeteners
Diet coke	Aspartame
Diet mountain Dew	Aspartame, Acesulfame K
Fanta Zero Soda	Aspartame, Acesulfame K
Fortuna Food Pound Cake- Marble Flavor	None
Gold's Low Calorie Borscht	None
Hainich Sweet Red Peers	None
IBC Diet Root Beer	Aspartame
Schwees Diet Tonic Water	None
Shasta Diet Grapefruit Soda	Aspartame
Tab Soda	Aspartame

Sweet'N Low **Sodium Saccharin**

Saccharin

Figure 6. Saccharin Containing Products

Metabolism

After ingestion, saccharin is not absorbed or metabolized. Instead, it is excreted, unchanged via the kidneys.

Uses of Saccharin

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.

Safety and Health effects

3. Neotame

Neotame is the newest sweetener and a derivative of aspartame. At-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 plusata 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. [14]

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 fewer amounts to achieve the same sweetness at 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 in2002. [15]

Chemistry

Neotame is formally a secondary amine of 3, 3-dimethylbutanal and aspartame. Latter is a dipeptide of phenylalanine and aspartic acid. Neotame has 2 stereo centers and 4 stereoisomers. Sweetness is due to the (2S), (3S) -stereoisomer. [16]

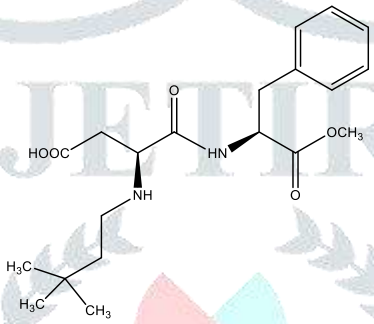

Figure 7. Structure of Neotame

Synthesis

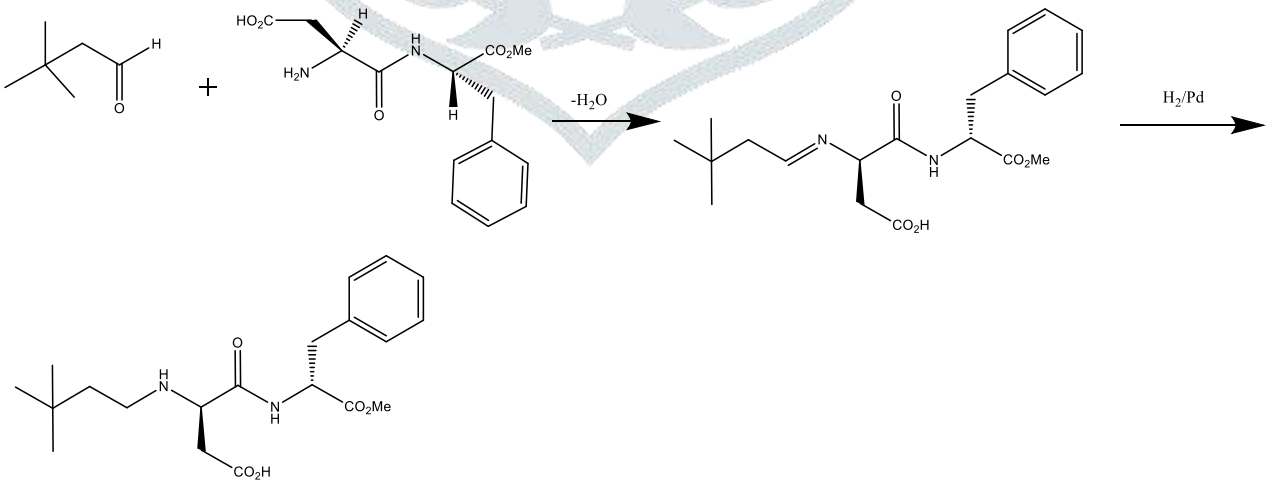

Figure 8. Synthesis of Neotame [17,18]

Figure 9. Neotame containing products [19]

Metabolism and health aspect

Neotame is rapidly metabolized, completely eliminated and does not accumulate in the body. The major metabolic pathway of neotame is hydrolysis of the methyl ester by esterase which is present throughout the body. This yields de esterifies neotame, the major metabolite and a significant amount of methanol. Due to the presence of the 3-3-di-methylbutyl group, peptidases which would typically break the peptide bond between the aspartic acid and phenylalanine moieties are essentially blocked, thus reducing the availability of phenylalanine. The amount of methanol derived from neotame is exceedingly small [20]. Neotame was approved by the USFDA as a general purpose sweetener in July 2002[21].It has also been favorably evaluated by JECFA [22] which established an ADI of 2mg/kg body weight/day. The ADI for neotame in the US is18mg/person/day [23].

Uses

Neotame is stable at high temperatures. It is a general all-purpose sweetener that has both cooking and baking applications. Neotame is used in baked goods, beverages, candies, chewing gum, dairy products, frozen desserts, puddings, and yogurt-type products and as a tabletop sweetener. [24]

In Drinks

Neotame's sweetness can be kept in cola carbonated drinks as long as 4-5 months, it can be applied in juice, vegetable juice and low alcohol wine, improve the taste and flavor of drinks, can also be applied in solid powdered beverage like lemon tea and milk powder.

In Starch, protein foods

Neotame can be mixed with other nutrition and non-nutrition sweeteners. It can resist starch's deceasing, prolong the products' duration. Also, can resist protein denaturation and keep good flavor in rich protein foods.

In Savory food

Neotame E 961 can be applied in high temperature short time (HTST) products including popcorn, cookie and cakes, because of the heating time is very little, and neotame concentration merely changes.

4. 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.

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. [25]

Chemistry

The only non-caloric sweetener prepared from sucrose. Although the name Sucralose ends in -ose, it is not a basic sugar like glucose or sucrose, so the name is rather misleading. Common brand names of sucralose-based sweeteners include Splenda®. Sucralose is also known as 4,1‟, 6‟-trichlorosucrose. Sucralose is made from sucrose (common table sugar) by the selective replacement of three hydroxyl groups with chlorine atoms, a process that occurs with inversion of configuration at the 4 positions of the galactoanalog. Its chemical formula is C12H19O8Cl3 (MW 397.35) Sucralose is a white, odorless crystalline powder and is readily dispersible and soluble in water, methanol, and ethanol. At 20°C, a 280 g/l solution of sucralose in water is possible. Sucralose presents Newtonian viscosity characteristics, a negligible lowering of surface tension, and no pH effects, and its solubility increases with increasing temperature. In ethanol, the solubility ranges from approximately 110 g/ l at 20°C to 220 g/l at 60°C and solubility of sucralose in ethanol facilitates in formulating alcoholic beverages and flavor systems. It has a negligible effect on the pH of solutions. [26]

Structure

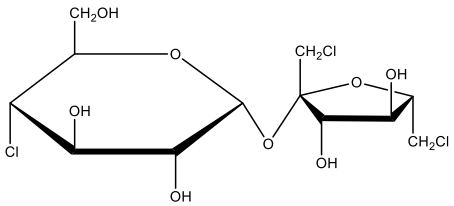

Figure 10. Structure of sucralose

Synthesis

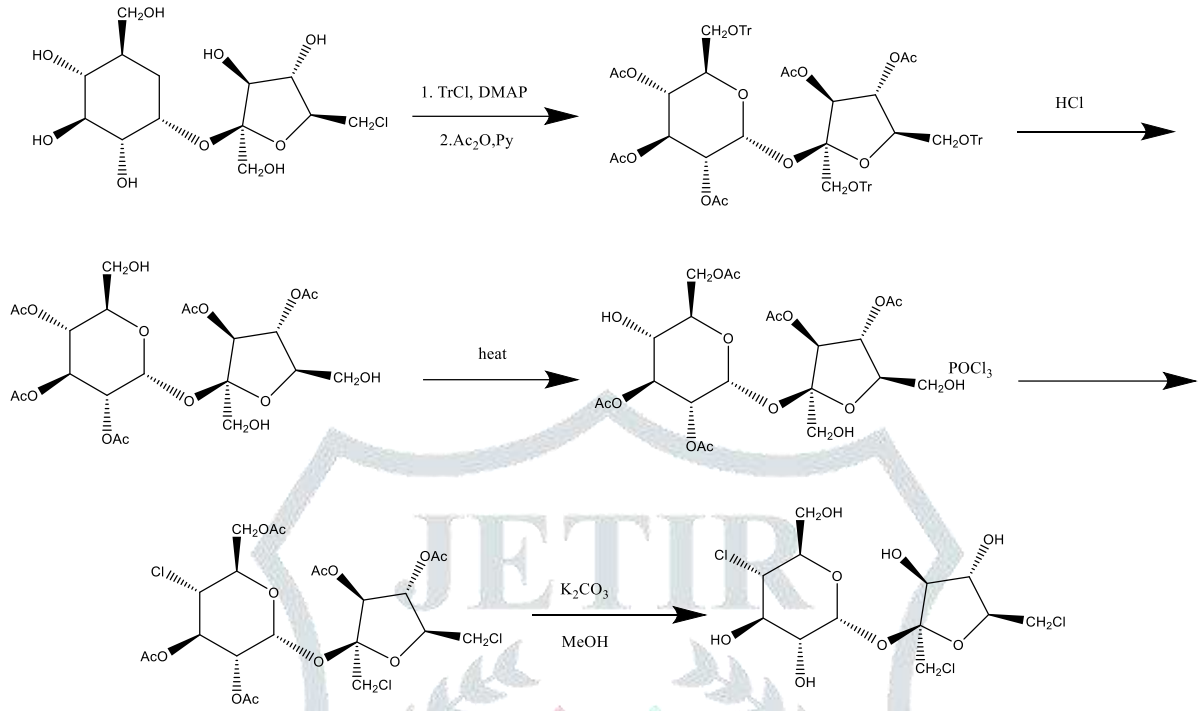

Figure 11. Synthesis of sucralose [27]

TrCl = triphenylmethyl chloride, DMAP = 4-dimethylaminopyridine

Sucralose is manufactured by the selective chlorination of sucrose in a multistep synthesis, which substitutes three of the hydroxyl groups of sucrose with chlorine atoms. This chlorination is achieved by selective protection of a primary alcohol group, followed by chlorination of the partially acetylated sugar with excess chlorinating agent, and then by removal of the acetyl groups to give the desired sucralose product. [28,29]

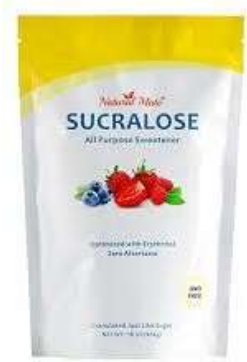

Figure 12. Sucralose Containing Products [30]

Metabolism and health aspect

Although sucralose is made from sugar, the human body does not recognize it as a sugar and does not metabolize it therefore it provides no calories. The bulk of sucralose ingested does not leave the gastrointestinal tract and is directly excreted in the feces while 11–27% of it is absorbed. The amount that is absorbed from the gastrointestinal tract is largely removed from the blood stream by the kidneys and eliminated in the urine. As it is an organo chloride and some of which are known to have significant toxicity [31] but sucralose is not known to be toxic. In addition, sucralose does not breakdown or dechlorinates. In determining the safety of sucralose, the FDA reviewed data from more than 110 studies in human and animals. Many of the studies were designed to identify possible toxic effects including carcinogenic reproductive and neurological effects but no such effects were found. Food and Drug Administration (FDA) approval are based on the findings that sucralose is safe for human consumption. U.S. Food and Drug Administration (USFDA) approved sucralose as a general-purpose sweetener. The acceptable daily intake (ADI) for sucralose in US is 5mg/kg body weight/day. The estimated daily intake for percentile consumers as calculated by USFDA is 1.6 mg/kg body weight/day [32].

Uses

Sucralose is used in many food and beverage products because it is a no-calorie sweetener, does not promote dental cavities [33] is safe for consumption by diabetics and nondiabetics, [34,35] and does not affect insulin level, although the powdered form of sucralose-based sweetener product Splenda (as most other powdered sucralose products) contains 95% (by volume) bulking agent's dextrose and maltodextrin that do affect insulin levels. Sucralose is a general-purpose sweetener that can be found in a variety of foods including baked goods, beverages, chewing gum, gelatins, and frozen dairy desserts. It is heat stable, meaning that it stays sweet even when used at high temperatures during baking, making it suitable as a sugar substitute in baked goods. [36]

5. Acesulfame-k

This is a general-purpose sweetener, white crystalline structure, high-intensity, non-nutritive sweetener, non-carcinogenic 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. And stable under high temperatures. So it does not break down in heat, therefore often used in baked products. It is used in over 4,000 products in approximately 90 countries. The "K" refers to the mineral potassium, which is naturally found in our bodies. [37]

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 after taste of aspartame. FDA continues to support the use of acesulfame-K in diabetic and low-calorie food. [38]

Structure

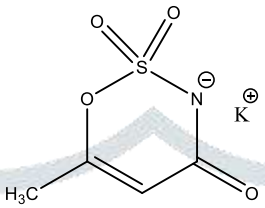

Figure 13. Structure of Acesulfame-k [39]

Synthesis

Acesulfame-K is formed by an initial reaction between 4 chlorophenol and sodium. Synthesis of acesulfame-K is explained in Figure 2. Pharmacokinetic studies show that 95% of the consumed sweeteners basically end up excreted in the urine.

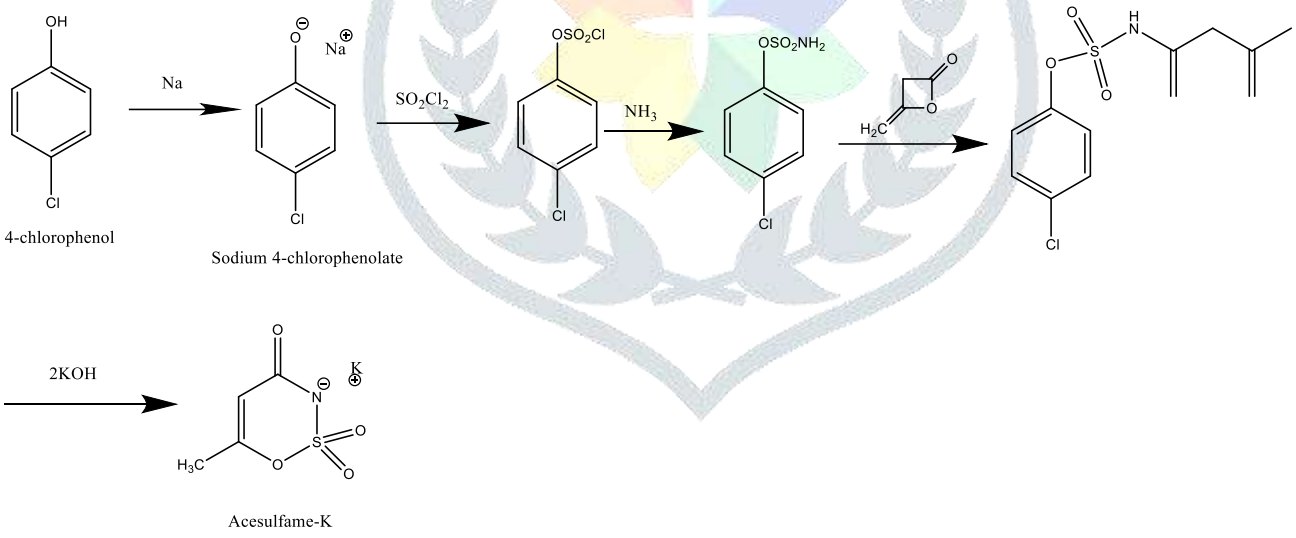

Figure 14. Synthesis of acesulfame-K[40]

Figure 15. Acesulfame contain product

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. [41] Ace-K is stable in dry preparation such as powdered beverages, desserts and tablet, as well as in products that have a low-water content, including hard candy or chewing gum. [42] Ace-K is stable under the normal heating condition during food processing including: [43] Production of fermented milk products, Spray-drying, form-mat drying and drying in a fluidized bed, Baking [44]

6. Sodium cyclamate

History

Cyclamate (Fig. 1e) was discovered in 1937. It was used as a low calorie sweetener in the United States in the 1950s and 1960s. It is a salt of cyclo hexyl sulfamic acid. Sodium cyclamate is used as none nutritive sweetener and the analogous calcium salt used specially in low sodium diets. Cyclamate is 30 times sweeter than sucrose. It has a bitter off taste, but has good sweetness synergy with saccharin. It is soluble in water, and its solubility can be increased by preparing the sodium or calcium salt. (Bo et al. 1986)

Chemistry

Cyclamate is the sodium or calcium salt of cyclamic acid (cyclo hexane sulfamic acid), which itself is prepared by reacting free base cyclo hexyl amine with either sulfamic acid or sulfur trioxide.[45] Prior to 1973, Abbott Laboratories produced sodium cyclamate (Sucaryl) by a mixture of ingredients including the addition of pure sodium (flakes or rods suspended in kerosene) with cyclo hexyl amine, chilled and filtered through a high speed centrifugal separator, dried, granulated and micro-pulverized for powder or tablet usage [46].

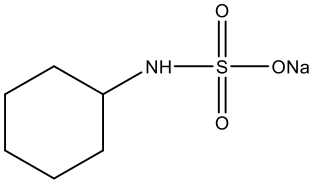

Figure 16. Structure of Sodium cyclamate

Synthesis

This process begins with the tri saccharide raffinose followed by chemical chlorination to form tetra chloro raffinose TCR. This TCR is then enzymatically treated with a galactosidase to move the 6-chloro-6-deoxygalactosyl moieties from the 6th position to yield cyclamate (Bennett et al. 1992) . There are another two methods available for synthesis of saccharin like bioorganic synthesis (Drasar et al. 1972) and regio selective deacylation.

Figure 17. Dairy products of sodium cyclamate

Use

Sodium Cyclamate is widely used as sweetener in food production. As sweetener: in cakes, baked foods, candied fruits and Pickles to improve sweetness. As sweetener: in soft drinks, juices and ice creams to improve sweetness. Sodium Cyclamate is widely used as sweetener in food production. As sweetener: in cakes, baked foods, candied fruits and Pickles to improve sweetness. As sweetener: in soft drinks, juices and ice creams to improve sweetness. Table-top sweeteners in the tablet, powder or liquid form.

- Soft drinks
- Breakfast cereals
- Dairy products
- Cakes and baked products
- Dried fruits, preserved vegetables
- Nuts
- Jams, jellies and marmalades
- Chewing gum and candies
- Salad dressings

General Uses

Possible Health Benefits of Artificial Sweeteners

Weight Control

One of the most annealing aspects of artificial sweeteners is that they are non-caloric. Although they are not a 'silver bullet', low calorie sweeteners can help people reduce their calorie intakes. Long-term trials consistently indicate that the use of low calorie sweeteners results in slightly lower energy intakes and that if low calorie sweeteners are used as substitutes for higher energy-yielding sweeteners, they have the potential to aid in weight management. [47]

Diabetes

People with diabetes have difficulty in regulating their blood sugar levels. Low calorie sweeteners offer people with diabetes broader food choices by providing the pleasure of the sweet taste without raising blood glucose. As low calorie sweeteners have no impact on insulin and blood sugar levels and do not provide calories, they can also have a role in weight loss and weight control for people with type II diabetes. [48]

Dental Cavities

When sugar-sweetened foods and drinks are consumed, the bacteria present in the mouth converts the sugar to acid. If this acid is not removed by teeth cleaning, it can wear away the surface enamel, eventually causing cavities to form. Low calorie sweeteners are not fermentable and do not contribute to tooth decay. By improving palatability, low calorie sweeteners can also encourage the use of toothpastes, mouthwashes and fluoride supplements that assist dental hygiene. [49]

Possible Health Concern of Artificial Sweeteners

Preterm Delivery

A prospective cohort analysis of 59,334 women from the Danish National Birth Cohort (1996-2002) concluded that daily intake of artificially sweetened soft drinks increased the risk of preterm delivery. [50]

Hepatoxicity

A case study of the hepatotoxicity of saccharin was published in 1994. A patient presented with elevated serum concentrations of liver enzymes after the oral administration of three different drugs, of which saccharin was the only common constituent. [51]

Thrombocytopenia

Additionally, a case report in 2007 revealed four individuals with thrombocytopenia attributed to products containing aspartame. [52]

Weight reduction

Although artificial sweeteners became popular for they can help reduce weight but epidemiologic data suggest an association between artificial sweetener use and weight gain. A prospective cohort study on drinkers of artificially sweetened beverages consistently had higher BMIs at the follow-up, with dose dependence on the amount of consumption. Average BMI gain was +1.01 kg/m2 for control and 1.78 kg/m2 for people in the third quartile for artificially sweetened beverage consumption. Similar observations have been reported in children, wherein a two-year diet soda consumption was associated with higher BMI Z-scores indicating weight gain. [53]

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