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Review Article

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Physical and chemical properties of High-Potency Sweeteners: A Review

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Abstract High-potency sweeteners are widely used in foods and beverages marketed as "sugar-free" or "diet," including baked goods, soft drinks, powdered drink mixes, candy, puddings, canned foods, jams and jellies, dairy products, and scores of other foods and beverages. In this review, physical and chemical properties of some high-potency sweeteners are given in detail.

Keywords Physical, chemical properties, High-Potency Sweeteners

1. Introduction

High-potency sweeteners are commonly used as sugar substitutes or sugar alternatives because they are many times sweeter than sugar but contribute only a few to no calories when added to foods. High-intensity sweeteners, like all other ingredients added to food in the United States, must be safe for consumption. Six high-intensity sweeteners are FDA-approved as food additives in the United States: Saccharin, Aspartame, Acesulfame potassium (Ace-K), Cyclamate, Neotame, and Advantame. High-potency sweeteners are widely used in foods and beverages marketed as "sugar-free" or "diet," including baked goods, soft drinks, powdered drink mixes, candy, puddings, canned foods, jams and jellies, dairy products, and scores of other foods and beverages. Given the widespread consumption of high-potency sweeteners in food industry, it is essential to understanding the physicochemical properties to manufacture of new products. The following are some of the features mentioned sugars.

2. Acesulfame K

Acesulfame K, the potassium salt of Acesulfame, was discovered accidentally in 1967 by Clauß and Jensen [19]. Acesulfame K belongs to the class of dihydro-oxathiazinone dioxides, which were then synthesized for the first time. Today, it is one of the most important intense sweeteners (see Figure 1).

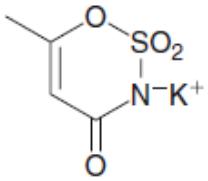

Figure 1: Chemical structure of Acesulfame K

2.1. Physical and Chemical Properties

2.1.1. Appearance

Acesulfame K forms white to colourless monoclinic crystals that are non-hygroscopic. Its bulk density is 1.81 g/cm^3. The molar mass is 201.2.

2.1.2. Solubility

Acesulfame K is freely soluble in water and also in aqueous alcoholic solutions with high water content. Its solubility is greater than required for practical application in both aqueous systems and in syrups of sorbitol, glucose or glucose–fructose (see Table 1). In addition to its use in a solid form, Acesulfame K can also be used in the form of a concentrated stock solution. In contrast, it is sparingly soluble in most organic solvents [10].

Table 1: Physicochemical properties and solubility of Acesulfame K

Appearance	Solid, crystalline (monocline), non-hygroscopic
Colour	Colourless to white
Colour in solution	Colourless
Dry matter	>99%
Melting point	>200°C (under decomposition)
Bulk density	1.81 g/cm^3
Equilibrium humidity	>80% RH
pH value (10% solution)	5.5–7.5
Solubility in water	~150 g/L at 0°C ~270 g/L at 20°C ~1300 g/L at 100°C
Solubility in ethanol	~220 g/L in 15% aqueous ethanol ~100 g/L in 50% aqueous ethanol
Solubility in sugar syrups (at 20°C)	≥100 g/L for sucrose syrup (62.5% dry matter) ≥160 g/L for invert sugar syrup (62.5% dry matter) ~150 g/L for fructose syrup (50% dry matter)
Solubility in sugar alcohol syrups (at 20°C)	≥75 g/L for sorbitol syrup (70% dry matter) ≥100 g/L for maltitol syrup (80% dry matter) ≥250 g/L for isomalt syrup (25% dry matter)

2.1.3. Stability

2.1.3.1. Storage stability

Acesulfame K can be stored for many years in solid form without visible or analytically detectable changes. Acesulfame K is, accordingly, stable in dry preparations like powdered beverages or desserts and tablets, but also in products having low-water content like hard candy or chewing gum.

2.1.3.2. Stability in solution

Under the normal storage and processing conditions of liquid foods and beverages, Acesulfame K is stable and at the common pH levels and customary storage conditions of beverages, the sweetness of Acesulfame K remains unchanged. At pH 3.0 and storage at 30◦C, even after several months, no perceptible loss in sweetness was observed. Within the common 'best before' period, sweetener loss is well below 10% of the original concentration and sweetness loss is not perceivable. Even storage at 40◦C results in perceptible losses only after several months [10, 11].Only at very low pH levels and continuing high storage temperatures can slight losses is detected analytically after prolonged storage. Investigation of reaction kinetics at 20◦C showed a half-life of 11.5 years at pH 5.77 and 6.95 years at pH 3.22 [6].

2.1.3.3. Temperature stability

Dry, solid Acesulfame K is stable at high temperatures. The decomposition limit depends on the rate of heating and is around 225◦C under conditions of melting point determination (rapid heating). Slow heating may result in decomposition at slightly lower temperatures. Acesulfame K is stable under the normal heating conditions used in the processing of foods. Pasteurization or ultra-high temperature (UHT) treatment used for dairy products do not

result in any loss of Acesulfame K. Drying processes like spray drying, foam-mat drying or drying in a fluidized bed are also possible without sweetener loss [2].

Similarly, canning and sterilization, as used for fruit and vegetables, do not result in Acesulfame K losses, when carried out under normal conditions. Temperatures in a baking process may be as high as 180◦C in the crust or outer parts of the product but only around 100◦C in the crumb or inner parts of the product. Accordingly, they remain far below the decomposition limit of Acesulfame K. In several studies on the baking stability of Acesulfame K, no loss on baking was found, even after excess heating that rendered the product very dark, and therefore, organoleptically unacceptable [7]. Microwave treatment of products containing Acesulfame K is possible without any loss of sweetness [24]. For sweets and confections, Acesulfame K can be added in the usual way before cooking if the acids are added after cooking. Kinetic investigations have shown that a decrease in sweetness is not anticipated even under extreme processing conditions and Acesulfame K has been found to be 'extremely stable' [6].

3. Aspartame

Aspartame is a nutritive intense sweetener produced by combining the amino acids l-phenylalanine and l-aspartic acid by a methyl-ester link (Figure 2). Its full chemical name is (35)-3-amino-N [alpha-S-alpha methoxycarbonylphenythyl]succinic acid but it is often described by its synonym L-aspartyl-L-enylalanine methylester (Figure 2).

In Europe, it is assigned the E number 951. Aspartame was discovered by Schlatter in 1965 in the laboratories of G.D. Searle and there followed a period of rigorous testing before it first appeared in the US market in 1981under the brand name of NutraSweet. The brand was heavily promoted and contributed to the phenomenal commercial success of aspartame as a sucrose replacement in the 1980sand 1990s.

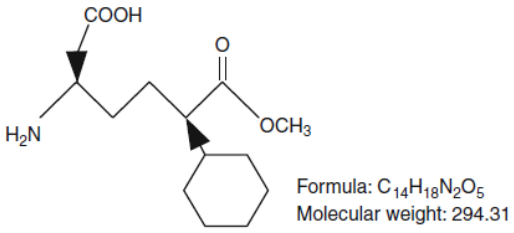

Figure 2: Aspartame structure (Ajinomoto)

3.1. Physicochemical properties

Aspartame is a white, colorless, crystalline substance, is regarded as ecologically safe and is a biodegradable non-regulated material [1].

3.1.1. Solubility

The solubility of aspartame in water (pH 6–7) at 25◦C is approximately 1% [1]. This can be increased by elevating the temperature and/or increasing the acidity.

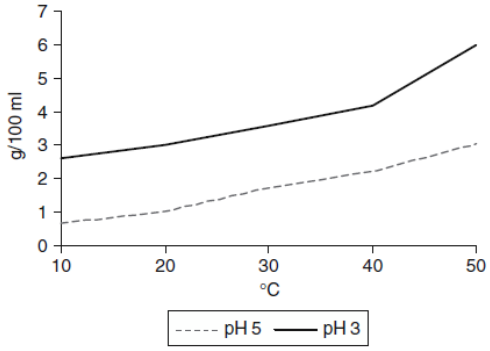

Figure 3: Aspartame solubility (Ajinomoto)

The use of some hydrocolloids, for example CMC, has also been reported to significantly increase solubility, even at low temperature [33]. The lowest solubility is at its isoelectric point at pH 5.4 [32]. Aspartame is sparingly soluble in other solvents [1] (Figure 3).

3.1.2. Stability

Dry

In solid form at ambient temperature and even at elevated temperature, aspartame has excellent stability (more than 5 years). In foods, optimum stability is achieved in systems with lower than 8% moisture [4].Stability decreases with increasing temperature and available moisture. It has been reported that addition of isomaltulose can improve the stability of aspartame over time [31].

Liquid

Aspartame is less stable in liquid systems and the stability is primarily a function of pH, temperature and time.

The aspartame molecule slowly hydrolyses at low pH to produce methanol and the tasteless molecule aspartyl-phenylalanine (AP). An alternative route at pH 5 and above is that aspartame may cyclise to form its diketo-piperazine (DKP) with the elimination of methanol [3]. These conversion products can be subsequently hydrolyzed to the individual amino acids – aspartic acid and phenylalanine (Figure 4) [5, 22-23]. In liquid systems, stability of aspartame at different pH follows a bell-shaped curve (see Figure 4). It is most stable in the range of pH 3–5 (with an optimum pH for stability at pH 4.2), which, fortunately, is the pH range of many food systems. Stability decreases with increasing temperature.

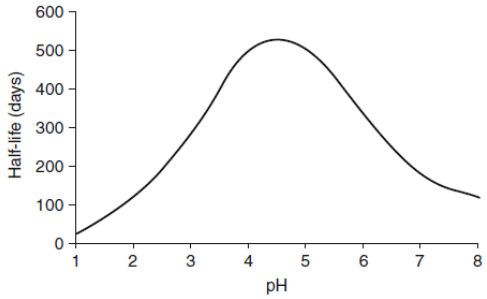

Figure 4: Aspartame stability changes with pH at 20 ◦C

4. Neotame

Although in the 1980s and 1990s aspartame was an impressive commercial success, a number of research groups around the world looked for the next-generation sweeteners that had greater sweetness, improved stability, good sweetness profile and could be produced at lower cost. Neotame, as it became branded, was a product of a research collaboration started in the mid-1980s between Tinti and Nofre at Claude Barnard University France and The NutraSweet Company [9, 30]. The French research group found a number of different compounds, which were many thousands of times sweeter than sucrose, and the NutraSweet Company selected compounds to take to the next stage of development and licensed the technology to produce them [9, 17]. In 1991, initial details of some of these compounds, including the one that would later be called Neotame, were released [17]. Neotame is n-[n-(3, 3-dimethylbutyl)-l-aspartyl]-l-phenylalanine-1-methyl ester [30](Figure 5).

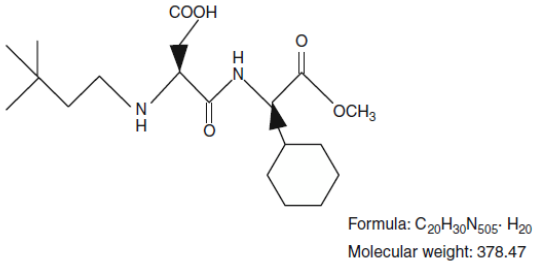

Figure 5: Neotame structure

4.1. Physiochemical properties

Neotame is a white/off-white crystalline powder with a melting point of 80.9–83.4◦C [25].

4.1.1. Solubility

Neotame is slightly more soluble than aspartame in water and significantly more soluble than aspartame in some solvents (ethanol). Solubility in water at 25◦C is 1.3% w/w and this increases with rising temperature (Figure 6) [25]. Formation of Neotame salts will also increase the solubility [13]. Dissolution rate in water at common use levels is quite rapid, for example 50 mg in 900 mL at 37◦C dissolves in 5 minutes [25].

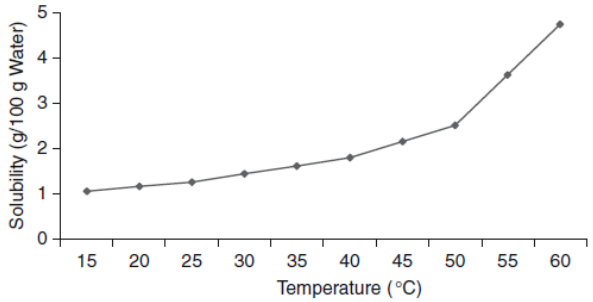

Figure 6: Solubility of Neotame in water

4.1.2. Stability

Dry stability of Neotame is good and in excess of 5 years. In dry conditions, the major degradation product is de-esterified Neotame (formed by the hydrolysis of the methyl ester group) [17]. Fluorescent lighting and polyethylene packaging have no effect on stability [8]. Neotame has similar stability to aspartame in many products and is more stable in neutral pH conditions (i.e. in baked and dairy products) [25]. Stability, over time, is dependent on three main variables: pH, temperature and moisture. Stability decreases with increasing temperature. The pH stability follows a bell-shaped curve similar to aspartame and the optimum pH for maximum stability is 4.5 [17]. Addition of divalent or trivalent cations and beta-cyclodextrin has been reported to improve stability [12, 18]. In aqueous solutions (pH 2–8), the main degradation product from Neotame is de esterified Neotame produced by hydrolysis of the methyl ester: n-[n-(3, 3-dimethylbutyl)-L-α aspartyl]-L-phenylalanine [15]. Neotame degradation does not produce DKP or phenylalanine. Stability in soft drinks utilizing Neotame should be managed in a similar way to aspartame beverages. Degradation can be minimized by formulation as close to the optimum pH for stability (pH 4.5) as possible and by maintaining a low temperature. As an indication, in a trial formulation at pH 3.2 and 20 ◦C, 89% Neotame remained after 8 weeks [8].

5. Advantame

While the NutraSweet Company was developing Neotame, Ajinomoto was also looking to develop the next generation of intense sweeteners. Ajinomoto is a major producer of aspartame and has an active sweetener discovery and development programmer.

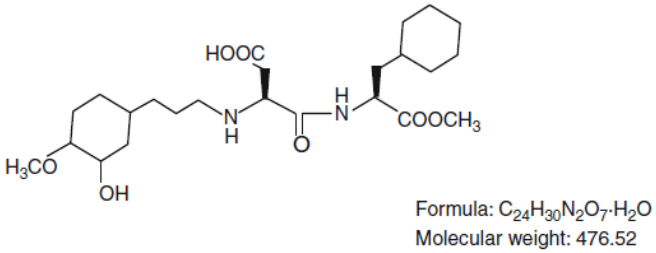

Figure 7: Advantame structure

The first product delivered by this programmer was Advantame and, like Neotame, it was discovered when Ajinomoto re-evaluated the lead compounds discovered by Nofre and also the Coca Cola Company [34]. Use of SAR, computer modeling followed by synthesis, screening for potency, taste profile, ease of manufacture,

physicochemical properties and likely metabolic fate, identified a compound initially designated ANS9801 and later named Advantame. Advantame is N-[N-[3-(3-hydroxy-4-methoxyphenyl) propyl-α-aspartyl]-l-phenylalanine 1-methyl ester monohydrate (Figure 7). Advantame shares certain structural characteristics with some natural sweeteners, for example Phyllodulcin [34]. Advantame has the empirical formula $C_{24}H_{30}N_2O_7 \cdot H_2O$and a molecular weight of 476 [12]. Its melting point is 101.5 ◦C and it is a white/yellow powder.

5.1. Physiochemical properties

5.1.1 Stability

Advantame is stable in dry form while in liquid systems (e.g. soft drinks), degradation does occur over time. In conditions of 25 ◦C/60% relative humidity, 60% of the Advantame remained after 20 weeks. The perceived decrease in sweetness was less than the actual decrease, which is to be expected since RS increases in high-intensity sweeteners as concentration of sweetener decreases [34].

5.1.2. Solubility

Solubility is quoted as 0.009 g/dL at 25◦C in 30 minutes and because of the very high RS, this is sufficient for most applications. A co-crystalline product with aspartame (Advantame: aspartame = 0.022:1), has been shown to have an increased rate of dissolution [34]. It is suggested by Ajinomoto that applications for Advantame would be as a sole or blended sweetener in a wide range of food products.

6. Saccharin

Saccharin (Figure 8), sometimes referred to as o-benzoic sulfimide, was the first commercially developed, sweet-tasting organic compound, which was significantly more potent than sucrose. The story of its commercial development and use as a non-caloric sweetener was reviewed in 2001 by Pearson (PMC Specialties Group, Inc.), a company long involved in saccharin manufacture, and more recently by Hicks (Pennsylvania State University) [16, 26]. Today, major manufacturers include Kaifeng and Shanghai Fortune of China and JMC of South Korea.

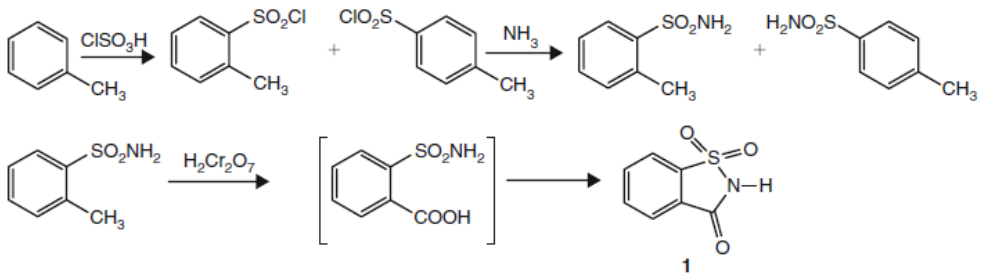

Figure 8: The Remsen–Fahlberg process for saccharin manufacture

6.1. Physical and chemical properties

Saccharin is commercially available in acid form as well as in sodium and calcium salt forms. All of these are white odourless solids. Saccharin in acid form is a strong acid with pKa of2.32 [14].

To be used in foods and beverages, a non-caloric sweetener must be sufficiently soluble and many non-caloric sweeteners do not meet this requirement. Commonly, sweetness intensity levels at least equivalent to 10% sucrose are required and in some systems (e.g. frozen desserts), sweetener levels matching the sweetness of 15–20% sucrose are needed. In addition, for many food systems, rapid dissolution is critical to comply with manufacturing requirements. For example, in carbonated soft drinks, concentrates of the sweetener-flavour system complex are prepared and it is important that all components rapidly dissolve. Thus, high solubilities and rapid dissolution rates are very desirable properties for non-nutritive sweeteners. In addition, a commercially viable non-caloric sweetener must be sufficiently stable to hydrolysis as well as to thermal and photochemical breakdown to be used in beverages, baked goods and confectionery. The performance of sodium saccharin relative to these metrics is as follows:

6.1.1. Solubility

Saccharin in its acid form is poorly soluble in water while its salt forms are highly soluble. The most commonly used form of saccharin is the sodium salt. As an example to illustrate the ample solubility of saccharin for common food or beverage products, if an application requires a sweetness level equivalent to 4% sucrose (a common situation in binary blends), from saccharin's C/R function, it can be calculated that a saccharin concentration of 75 mg/L is necessary. However, with a solubility of 1200 g/L, saccharin as its sodium salt is 16,000 times more soluble than necessary to meet this need. It is noteworthy that saccharin in its acid form is much less soluble than its salt forms and it is logical to be concerned about precipitation in acidic products such as soft drinks and reduced-calorie juices. However, this does not appear to be a problem. The only solubility problem observed is with the calcium salt in phosphoric acid-based beverages where $Ca_3 (PO4)_2$ may precipitate [28].

6.1.2. Stability

To be commercially viable, a non-caloric sweetener must be stable to degradation from hydrolytic, pyrolytic or photochemical processes that may be encountered in food or beverage applications. Stability is critical for three reasons. First, the rate of degradation must not be such that product shelf life is affected. Second, degradation must not cause any 'off'-taste or odor. And third, since non-caloric sweeteners are food additives, any degradation products formed must also be safe. In the United States, for any food or beverage application, if exposure to the degradation product may reach or exceed 12.5 µg/kg, then safety assessment studies equivalent to those required for the sweetener itself must be conducted before regulatory approval is granted [28].

7. Cyclamate

In 1944, the discovery that salts of cyclohexylsulfamic acid are sweet was reported by Sveda and Audrieth (University of Illinois) [21]. These cyclohexylsulfamic acid salts were prepared as illustrated in Figure 9 using chlorosulfonic acid as a sulfamating agent. Since this initial work, many alternative SO_3 sources (*i.e.* sulfamating agents) have been used including fuming sulfuric acid. These cyclohexylsulfamates are commonly referred to as cyclamic acid salts or, more simply, just as cyclamates. In the acid form, cyclamate has the chemical structure shown in Figure 9 and was the first of the sulfamate structural class of sweeteners to be discovered. Sweeteners of this class possess the -NH-SO_3− moiety as the common structural subunit. Cyclamate is generally used in foods as either the sodium or calcium salt. Since 1944, many other sulfamates have been synthesized, although none have been developed for use in foods.

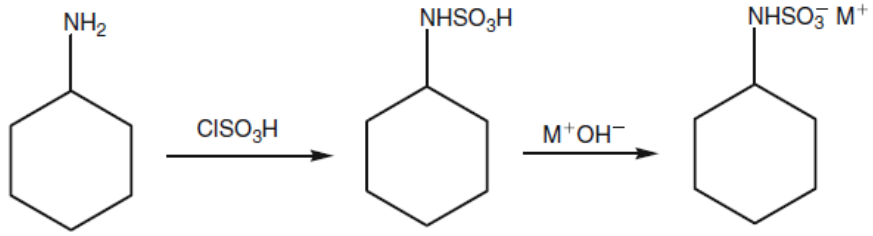

Figure 9: Audrieth-Sveda process for cyclamate manufacture

7.1. Physical and chemical properties

Solubility

Cyclamates exhibit excellent solubility characteristics for use in essentially all imaginable applications. Although the acid form is sufficiently water-soluble (133 g/L), its high acidity results in preference for the very soluble sodium (200 g/L) or calcium (250g/L) salts [20]. To illustrate the more than adequate solubility of sodium cyclamate, consider an application in which cyclamate is used in a binary blend with a sweetener such a ssaccharin. In such a situation, it is generally desired that cyclamate should provide half of the total sweetness desired that would typically be, allowing for sweetness synergy, sweetness equivalent to approximately 4% sucrose. Thus, the concentration of sodium cyclamate equi-sweet with 4% sucrose is 1120 mg/L; sodium cyclamate is about 180 times

more soluble than necessary for this level of sweetness. Cyclamate salts therefore have ample solubility for all food and beverage applications.

Stability

Hydrolytic degradation of cyclamate salts yields cyclohexylamine and inorganic sulfate. As a consequence of the adverse biological activity of cyclohexylamine, FDA scientists conducted a comprehensive evaluation of cyclohexylamine levels in arrange of food products [27]. Cyclohexylamine was found in the majority of these products, albeit at low levels. Interestingly, even in the most acidic samples (cola soft drinks); cyclohexylamine levels did not significantly change over 4 months of ambient-temperature storage. The trace levels of cyclohexylamine in food products appear to be substantially derived from trace levels present in the cyclamate sweeteners employed. Data have been reported on the hydrolysis of cyclamate under extreme conditions and are reported in Table 7.8 [29]. In summary, cyclamate sweeteners are quite stable. No significant loss of sweetness or generation of unsafe degradation products is expected in any common applications.

Reference

1. Ajinomoto. Aspartame Technical Bulletin, Ajinomoto AG, Zug, Switzerland; 2001/2002.
2. A. Lotz, C. Klug and G.-W. von Rymon Lipinski. Stability of Acesulfame K during high temperature processing under conditions relevant for dairy products. Zeitschriftf¨urLebensmittel technologie und Verfahrenstechnik 1992, 43(5), EFS 21.
3. B. Homler. Aspartame: Implications for the food scientist. In: L.D. Stegink and L.J. Filer (eds). Aspartame– Physiology & Biochemistry, Marcel Dekker, New York; 1984, pp. 247–262.
4. B.E. Homler. The properties and stability of aspartame. Food Technology 1984, 38(7) 50–55.
5. B.T. Carr, et al. Sensory methods for sweetener evaluation. In: C.T. Ho and C.H. Manley (eds). Flavour Measurement, Marcel Dekker, New York; 1993, pp. 226–227.
6. C. Coiffard, L.J.M. Coiffard and Y. de Roeck-Holtzhauer. Influence of pH on the thermodegradationofAcesulfame K in aqueous diluted solutions. STP Pharma Sciences 1997, 7(5), 382.
7. C. Klug, G.-W. vonRymon Lipinski and D. B¨ottger. Baking stability of Acesulfame K. Zeitschriftf¨urLebensmitteluntersuchung und Forschung 1992, 194(5), 476.
8. C. Nofre and J.M. Tinti. Neotame: discovery, properties, utility, Food Chemistry 2000, 69, 245–297.
9. European Patent Application, 894201359; 14 April 1989.
10. G.-W. von Rymon Lipinski. Properties and applications of Acesulfame-K. In: D.G. Mayer and F.H.Kemper (eds). Acesulfame K, Marcel Dekker, New York; 1991, p. 209.
11. G.-W. von Rymon Lipinski. Stability and Synergism – Important characteristics for the Application of Sunett (R) Food Ingredients Conference Proceedings, Maarssen, The Netherlands;1989; p. 249.
12. I. Prakash, I.E. Bishay, N. Desai and D.E. Walters. Modifying the temporal profile of the high-potency sweetener neotame. Journal of Agricultural and Food Chemistry 2001, 49(2), 786–789.
13. I. Prakash, et al. Neotame: the next-generation sweetener. Food Technology 2002, 56(7) 36–40.
14. J.A. Dean (ed.). Lange's Handbook of Chemistry, 13th edn, McGraw-Hill Book Company, New York; 1985, Section 5, p. 56.
15. J. Bergman, The NutraSweet Company – Personal Communication; 2005.
16. J. Hicks. The pursuit of sweet: A History of Saccharin. Chemical Heritage 2010, 28, 26–31.
17. J.M. Tinti and C. Nofre. Presentation at FIE Show Paris; 8 October 1991.
18. J.R. Garbow, et al. Structure, dynamics, and stability of cyclodextrin inclusion complexes of aspartame and neotame. Journal of Agricultural and Food Chemistry 2001 49(4), 2053–2060.
19. K. Clauß and H. Jensen. Oxathiazinone dioxides – a new group of sweetening agents. AngewandteChemie 1973, 85, 965.
20. K.M. Beck. Nonnutritive sweeteners: saccharin and cyclamate. In: T.E. Furia (ed). CRC Handbook of Food Additives, Vol. 11, 2nd edn, CRC Press, Boca Raton, FL; 1980, p. 125.

21. L.F. Audrieth and M. Sveda. Preparation and properties of some N-substituted sulfamic acids. Journal of Organic Chemistry 1944, 9, 89–101.
22. L.D. Stegink. Aspartate and glutamate metabolism. In: L.D. Stegink and L.J. Filer (eds). Aspartame: Physiology and Biochemistry, Marcel Dekker, New York; 1984, pp. 47–109.
23. L.D. Stegink, et al. Aspartame metabolism in human subjects. In: Health and Sugar Substitutes (ProcERGOB CoPnf), Karger AG, Basel, Switzerland; 1978.
24. M. Korb, B. Kniel and E. Meyer. Mikrowellenstabilit¨at der S¨ußstoffeAcesulfam und Aspartam. ZFLInternational Journal of Food Technology and Food Process Engineering 1992, 43(9), 494.
25. Neotame. Ingredient Overview, www.Neotame.com.
26. R.L. Pearson. Saccharin. In: L. O'Brien Nabors (ed). Alternative Sweeteners, 3rd edn, Marcel Dekker,New York; 2001, pp. 147–165.
27. T. Fazio, J.W. Howard and E.O. Haenni. Survey of cyclohexylamine content of food products containing cyclamates. Journal of the Association of Official Analytical Chemists 1970, 3, 1120–1128.
28. Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Usedin Food, US Food and Drug Administration, Bureau of Foods; 1982, pp. 1–19.
29. United States Congress, House of Representatives, Committee on the Judiciary Subcommittee No. 2.Cyclamates. Hearings before subcommittee no. 2 of the committee on the Judiciary House of Representatives, Ninety-Second Congress, 29, 30 September and 6 October 1971, Serial No.22.US Government Printing Office, Washington, DC; 1972.
30. US Patent, 4,935,517; 1990.
31. US Patent Application 20070160731A1; 12 July 2007.
32. W. Vetsch. Aspartame: technical considerations and predicated use Food Chemistry 1985, 16(3/4), 245–258.
33. W. Wafwoyo, et al. Interaction of aspartame with selected hydrocolloids: solubility of aspartame. Food Hydrocolloids 1999, 13, 299–302.
34. Y. Amino, K. Mori In: D.K. Weerasinghe and G.E. DuBois (eds). Sweetness and Sweeteners: Biology, Chemistry and Psycophysics (ACS Symposium Series), Oxford University Press, Washington DC; 2006, pp. 463–480.