The development and applications of sucralose, a new high-intensity sweetener[1]

I. KNIGHT

Redpath Specialty Products, 95 Queen's Quay East, Toronto, ON M5E 1A3, Canada

Received September 29, 1993

KNIGHT, I. 1994. The development and applications of sucralose, a new high-intensity sweetener. Can. J. Physiol. Pharmacol. 72: 435–439.

Sucralose is a new sweetener discovered during a collaborative research program between Tate & Lyle and Queen Elizabeth College of the University of London. It is made by selective substitution of sucrose hydroxyl groups by chlorine, resulting in a highly intense (600×) sugarlike sweetness and exceptional stability at both high temperature and low pH. The research leading to the discovery of sweetness in differently halogenated sucrose is described, as well as the development of sucralose and the process of safety testing and government approval. Finally, sucralose properties and applications in Canada's food and beverage industries are discussed.

Key words: sucralose, sweetener, stability, halogen, chlorine.

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Le sucralose est un nouvel édulcolorant découvert durant le programme de recherche conjointe de Tate & Lyle et du Collège Queen Elizabeth de l'Université London. Fabriqué à partir de la substitution sélective de groupements hydroxyles de la molécule de saccharose par le chlore, il possède une saveur sucrée très intense (600×) et un stabilité exceptionnelle tant à haute température qu'à faible pH. On décrit les étapes de la recherche ayant mené à la découverte de la saveur sucrée dans le saccharose différemment halogéné, au développement du sucralose, aux essais d'innocuité et à l'homologation gouvernementale. Enfin on discute de propriétés et des applications du sucralose dans les industries canadiennes des boissons gazeuses et de l'alimentation.

Mots clés : sucralose, édulcolorant, stabilité, halogène, chlore.

[Traduit par la rédaction]

Introduction

Sweetness as a sought-after sensation predates written history, although not pictorial history; in fact, a 20 000 year old painting depicts a man robbing a wild bee's nest. Although written records of the consumption of honey can be traced back to 2600 B.C., the sweetener of choice for many centuries has been sugar or sucrose.

For many years the majority of the population of developed countries has had to be less concerned with the inadequate availability of food than with the problems of excessive consumption. As a result, many individuals have been motivated to control and reduce the calories consumed, creating a new market for light and calorie-reduced foods and beverages. The U.S.-based Calorie Control Council 1991 national survey[2] shows that in the United States, 101 million people consume low-calorie foods and beverages.

Sugar has been the replacement focus of much of the work in the industry leading to low calorie sweetened foods and beverages. Many sweeteners having very high potency have been developed as sugar substitutes. Sweeteners available in the United States, Europe, and Canada prior to September 1991 are listed in Table 1. Saccharin was discovered in 1857 and was the first high-potency sweetener to be used, and it became used widely. Canadian studies indicated that saccharin caused bladder cancer in rats, and it was banned in Canada in 1977 (Arnold et al. 1980). However, in the United States, a similar Food and Drug Administration ban was never enacted as a result of a moratorium imposed by Congress. Saccharin has therefore remained widely available in the United States. Similarly cyclamates were implicated with carcinogenicity and essentially banned in both Canada and the United States (Price et al. 1970). Most European countries, with the exception of the United Kingdom and France, did not act to ban cyclamates. Hence Canada was unique in having only the one sweetener, aspartame, available for use in commercial food and beverage products.

Most of the recent growth in the low-calorie market has come from the introduction of aspartame, the first high-intensity sweetener having a broadly acceptable taste profile. However, it lacks stability in products requiring high-temperature processing and has a limited shelf life at low pH. Thus there was a significant opportunity for a new sweetener resistant to high-temperature processing and low pH systems.

The development of sucralose

In the 1960s, Tate & Lyle, Sugar Quay, Lower Thames Street, London SE1, the parent company of Redpath Specialty Products, Toronto, Ont., was investigating the use of sugar in nontraditional areas. As part of this initiative, a collaborative study was undertaken by Hough and Khan (1989) at Queen Elizabeth College, University of London. It was designed to investigate the sweetness functionality of derivatives of sucrose, specifically those substituted by halogens. It was found that selective halogenation can change the perceived sweetness of the molecule (Table 2), with chlorine and bromine being the most effective.

Derivatives substituted with the lighter halogens (i.e., chlorine, fluorine) retain a high water solubility, but fluorine, as well as being difficult to handle, has less effect than chlorine on sweetening power. The term galactosucrose was proposed by Hough and Khan (1989) to denote a sucrose derivative that had undergone inversion at the 4 position.

[1]This paper was presented at the CFBS symposium entitled Biotechnology and Nutrition, held June 17, 1993, at Windsor, Ont., and has undergone the Journal's usual peer review.

[2]Calorie Control Council. 1991. Dieting and low calorie/reduced product survey. Booth Research Services Inc., Atlanta, Ga. Unpublished.

Printed in Canada / Imprimé au Canada

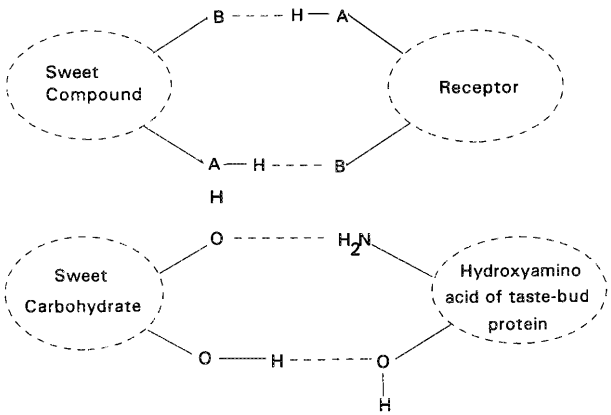

FIG. 1. Hydrogen bond interaction between AH/B units of sweet compound and the receptor site.

TABLE 1. Regulatory status of sweeteners in North America and Europe (September 1991)

United States	Europe	Canada
Saccharin[a]	Saccharin	Saccharin[b]
Aspartame	Aspartame	Aspartame
Acesulfame-K	Acesulfame-K	Cyclamates[c]
	Cyclamates[d]	

[a]Saccharin banned by Food and Drug Administration but overruled by moratorium imposed by Congress.
[b]Saccharin banned in Canada. Only permitted in tabletop sweeteners on request at pharmacies.
[c]Cyclamates banned in Canada. Only permitted in tabletop sweeteners.
[d]Restrictions in some countries, freely available in others.

For development as a sweetener, the most promising compound of the entire family was the 4,1′,6′-trichloro derivative, which is now known by its common name, sucralose. It was found to possess a sugarlike taste profile as well as exceptional stability both at high temperature and low pH.

Sucralose was subsequently developed and is presently available in Canada under the commercial brand name of SPLENDA® Brand Sweetener.

The mechanism of sweetness

The structural requirements of compounds possessing sweetness have been described (Fig. 1). Deutsch and Hansch (1966) suggested that generation of a sweet taste required a combination of hydrophobic bonding from one area on the molecule with electronic bonding from another. The highly intense sweeteners are more hydrophobic, giving rise to stronger absorption to the taste buds, in contrast to the simple sugars, which are more hydrophilic, less sweet, and weakly absorbed to the taste buds. Deutsch and Hansch (1966) observed a relationship between the sweetness of 2-amino-4-nitrobenzene derivatives and their partition coefficients between water and octanol. Shallenberger and Acree (1967, 1969) noted that sweetness depended upon the presence of two electronegative atoms, designated A and B, separated by 2.5–4.0 Å (260–300 nm), and a hydrogen atom covalently linked to A. In carbohydrates, a pair of hydroxyls on adjacent carbon atoms (a glycol group) is assigned as the AH/B unit, with one hydroxyl acting as the AH subunit and the oxygen atom of the other hydroxyl as the B

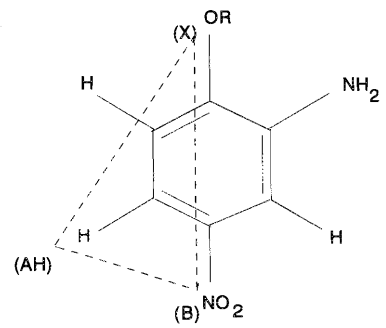

FIG. 2. 1-Alkoxy-2-amino-4-nitrobenzenes showing the triangle of groups important in conferring sweet taste.

TABLE 2. Halogenated derivates of sucrose and their relative sweetness

Derivative	Sweetening power (×sugar)
1′-Chlorosucrose	20
4-Chlorogaloctosucrose	5
6-Chlorosucrose	20
1′,6′-Dichlorosucrose	80
4,1′-Dichlorogalactosucrose	120
6,1′,6′-Trichlorosucrose	25
4,1′,6′-Trichlorogalactosucrose	650
4,1′,4′,6′-Tetrachlorogalactosucrose	2200
4,1′,6′-Tribromogalactosucrose	800
4,1′,4′,6′-Tetrabromogalactosucrose	7500
4,1′,6′-Trifluorogalactosucrose	40
4,1′,6′-Triiodogalactosucrose	120

subunit. Shallenberger and Acree (1967) suggested that the sweetness sensation is caused by formation of a pair of hydrogen bonds between the AH/B unit and the proteinaceous receptor site on the tongue.

It was noted in these early studies, however, that although this mechanism explained all sweet-tasting compounds, many compounds filled these structural requirements but possessed no sweetness. Hence it was thought that there must be additional criteria accounting for the mechanism of sweetness, and one was described by Kier (1972) in a study of 1-alkoxy-2-amino-4-nitrobenzenes. This study recognized the influence of a third site, which is hydrophobic and binds the sweet compound to the receptor site. This third site, designated X by Schallenberger and Lindley (1977) and van der Heijden et al. (1978), provides a triangle of groups important in conferring sweet taste, X, AH, and B, and is known as the glucophore (Fig. 2). This hypothesis to explain the mechanism of sweetness is supported by the work conducted on sucrose derivates by Hooft et al. (1991). In the case of sucralose, it appears that the two chlorine atoms present in the fructose portion of the molecule comprise the hydrophobic X-site, which is extended over the entire "outside" region of the fructose portion. The hydrophobic and hydrophilic regions are situated on the opposite ends of the molecule, similar to sucrose, apparently unaffected by the third chlorine on the C4 of the pyranose ring.

Development

Identification of a compound with high sweetening intensity is only the first step in developing a new product for human consumption. Regulatory agencies within national governments have strict standards for safety testing of a new product prior

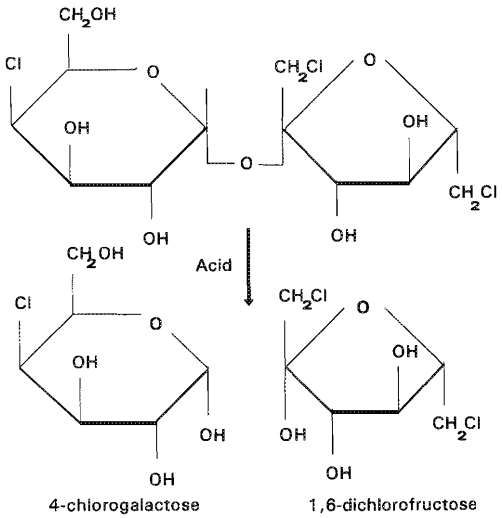

FIG. 3. Acid hydrolysis of sucralose in aqueous media.

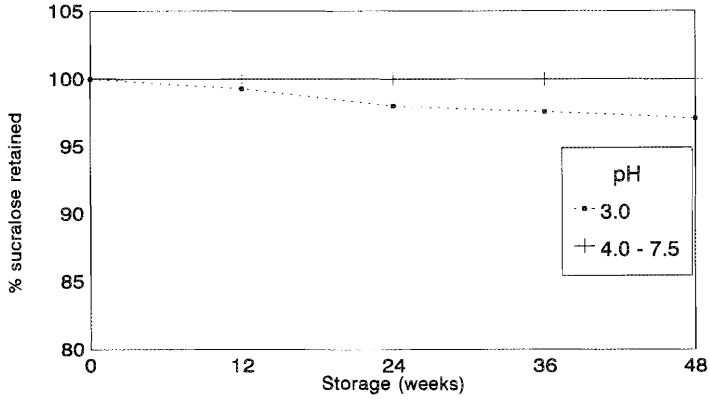

FIG. 4. Aqueous stability of sucralose, effect of pH at 30°C.

TABLE 3. Baking study using radiolabelled sucralose

	Concn. (ppm)	Temp. (°C/°F)	Time (min)	Recovery (±2%)
Sponge cake	312	180/356	25	100
Biscuits	256	210/410	8	100
Graham crackers	182	230/446	4	100

to its being granted approval. For the case of sucralose this program was jointly undertaken by Tate & Lyle Specialty Sweeteners Division (SSD), located in Reading, U.K., and its licensee, Johnson & Johnson of New Brunswick, N.J., U.S.A. The program was designed to provide data for the evaluation of safety and to estimate human consumption at both the mean and 90th percentile (i.e., level consumed by the highest consuming 10% of the population) levels. The studies covered acute, subchronic, and chronic exposure, as well as oncogenicity, mutagenicity, reproduction and teratology, and absorption, distribution, metabolism, and elimination (ADME) in animals. In addition, some clinical work was conducted that served to compare ADME data in animals with humans, demonstrating the appropriateness of the animal models. It took more than 7 years before the safety data package was ready for submission to the regulatory agencies.

Under section B, 16.002, of *The Food and Drugs Act and Regulation* (Health Canada 1991), the information required by the Canadian Government to adequately assess the acceptability of a new food additive includes chemical information (manufacturing methods, specifications, properties, etc.); anticipated levels of exposure, including recommendations and directions for use; a method of analysis; the entire safety database; data to demonstrate functionality; data to indicate potential breakdown products and the levels at which they may be present in foods; a proposed maximum limit for breakdown products in the finished food (if appropriate); specimens of labelling; and a sample of the product. Although not a stated requirement under section B, 16.002, the petitioner is encouraged to solicit "case for need" support from potential customers (i.e., food and beverage manufacturers). The regulatory agency then evaluates the information provided in the submission and challenges interpretations and conclusions reached, often requesting additional data.

Their review centres primarily on safety, by thoroughly examining the data from all of the animal studies leading to the identification of a "No Observable Adverse Effect Level" (NOAEL or NOEL), which is the highest dose in the most sensitive species that has no observable adverse effect. This is used to calculate the "Acceptable Daily Intake" (ADI), usually by applying a safety factor of 100, which comprises a factor of 10 for intraspecies variation and 10 for interspecies variation. The established ADI is compared with the projected intake at average and extreme levels. Provided the ADI is greater than the statistical projected intake for extreme users, no further adjustments are necessary. Note that Canada is more conservative than most other national regulatory agencies in that it permits only specific categories of use and it defines the maximum level of use for an additive for each category. Other countries such as the United Kingdom allow blanket approval, that is, in any category at any level, whereas the United States allows specific categories but without specifying a level of use.

Once the review has been completed and the evaluators are satisfied with product safety, a draft regulation is written, together with an analysis of potential social costs or benefits. The draft is published in Part I of the Canada Gazette (Canada Gazette Part I is published every week by Queen's Printer for Canada), along with an invitation for comments by any interested parties. It is most common to receive comments from professional or trade associations; however, comments may be received from foreign regulatory agencies or even private individuals. All comments received are assessed with a view to possibly changing the regulation if the comments are of a substantial nature, prior to its being published in final form in the Canada Gazette Part II (Canada Gazette Part II is published every 2 weeks by Queen's Printer for Canada). Once this happens, the regulation becomes official and the additive is permitted for use under the conditions stated.

Properties and applications

A subject of particular interest to both regulatory agencies and the food and beverage industry is the stability of sweeteners and the mechanism of and products resulting from breakdown. Although sucralose is exceptionally stable, some breakdown can occur under extreme conditions, and the mechanism for this has been characterized. Sucralose breakdown is remarkably similar to that of its parent molecule, sucrose. The reaction is

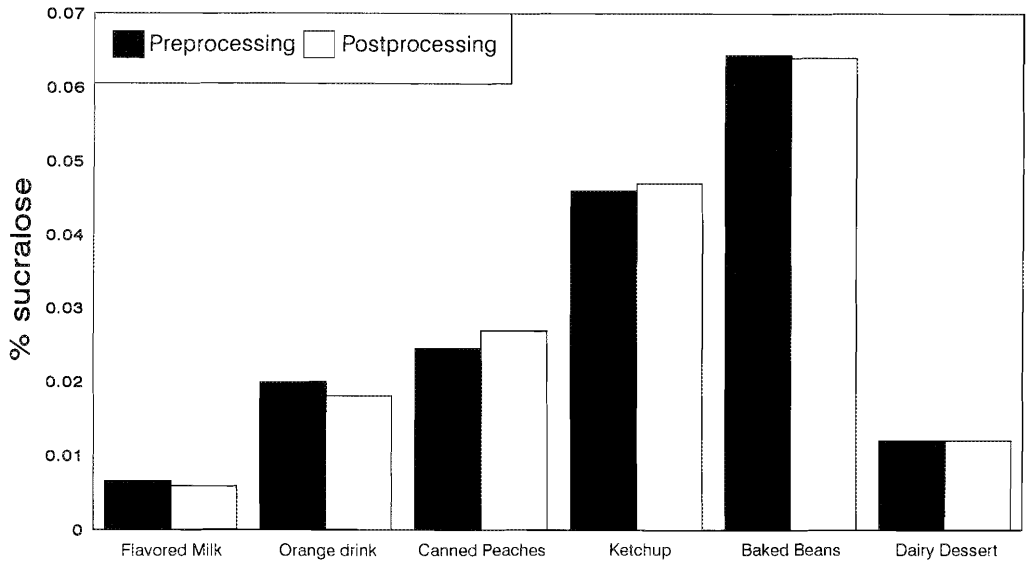

FIG. 5. Heat processing of products containing sucralose.

TABLE 4. Study of sucralose stability in heat processing

Product	Approx. % sugar	pH	Processing conditions	Type
Tropical beverage	7.5	2.8	93°C, 24 s	Pasteurization
Tomato ketchup	25.0	3.8	93°C, 51 min	Pasteurization
Canned fruit	20.0	3.3	100°C, 12 min	Pasteurization
Baked beans	4.0	5.6	121°C, 80 min	Sterilization
Dairy dessert	7.0	6.7	140°C, 15 s	Ultrahigh temperature
Vanilla milk	4.5	6.5	141°C, 3.5 s	Ultrahigh temperature

a first-order hydrolysis in which the glycosidic link is broken, incorporating a molecule of water, producing the two single-ring moieties (Fig. 3). This reaction is entirely analogous to the inversion of sucrose. The presence of the electronegative chlorine atoms reduces the rate of protonation of the glycosidic oxygen, resulting in a reaction rate more than 60 times slower than the corresponding inversion of sucrose, thus explaining the unusual stability of sucralose.

Even though sucralose has high stability, the nature of distribution systems for food and beverage products requires the recognition that there will be some small amount of breakdown products formed during extreme storage conditions. This recognition led to a safety testing program, almost as complete as that for sucralose, on the equimolar mixture of the sucralose hydrolysis products along with an estimate of the likely and extreme levels of exposure.

To assess the potential for sucralose breakdown when added to specific-product categories, stability studies in common products and processes were conducted (Quinlan and Jenner 1990). It was found that sucralose possesses extraordinary stability in aqueous systems, under conditions of both high heat and low pH. Model studies were initially conducted to quantify this stability (Quinlan and Jenner 1989), and then process-specific studies were run to quantify it in processes such as baking, pasteurization, sterilization, ultrahigh-temperature processing, and extrusion.

In addition, because of the enormous sales potential in carbonated soft drinks, separate studies were conducted to quantify the extent of breakdown on the shelf at the low pH levels normally found in these products. Figure 4 shows a model study in which the breakdown of sucralose at 30°C and various pH's is determined and expressed graphically (Jenner 1989). This covers two broad pH levels: 4.0–7.5, the pH of most conventional food systems, and 3.0, the pH of carbonated soft drinks and juice drink products. As can be seen, the breakdown over a year at the 4–7.5 pH level is so small as to be unmeasurable with HPLC. The breakdown at the more acidic pH, 3, is greater, but is still only approximately 3% over a full year of storage at what is actually warmer than usual room temperature.

Studies were also conducted to demonstrate that the baking process produces negligible breakdown of the sweetener. For example, three mixes, a cake, a biscuit, and a graham cracker, were spiked with the sugar sweetness equivalence of sucralose, which had been prepared with ^{14}C (Barndt and Jackson 1990). All of the radioactive-labelled material was recovered after processing and all as unchanged sucralose, demonstrating that sucralose can easily withstand the baking process (Table 3).

Many studies were conducted in actual food formulations to investigate stability in foods and beverages that rely upon high-temperature processing for their preservation (Table 4). Products were chosen to represent extreme ranges of pH and temperature conditions. Processing was carried out in actual industrial facilities in order to be faithful to the original objec-

TABLE 5. Approved categories of sucralose use and permitted levels

Category	Maximum level
Tabletop sweeteners	GMP
Breakfast cereals	0.1%
Beverages	0.025%
Desserts, toppings, fillings	0.025%
Chewing gum, breath mints	0.15%
Fruit spreads	0.045%
Salad dressings	0.04%
Confectionary	0.07%
Bakery products	0.065%
Processed fruits and vegetables	0.015%
Alcoholic beverages	0.07%
Puddings	0.04%
Table syrups	0.15%

NOTE: GMP, Good Manufacturing Practice.

tive. Processing had no significant effect on the integrity of the sucralose (Fig. 5).[3] All of these data were provided to Health and Welfare Canada to assist evaluation of the product.

Approval

On September 5, 1991, the Governor General of Canada signed the regulation permitting the use of sucralose in 13 categories of foods and beverages (Table 5). The publication in Canada Gazette Part II followed on September 25, 1991. This followed the endorsement of the safety of sucralose in June 1990 by the Joint Expert Committee on Food Additives of the WHO/FAO of the United Nations.

To date there are more than 100 products on the market containing SPLENDA® Brand Sweetener. At the present time sucralose is approved in Russia, Australia, and of course Canada, which was the first country to grant approval. Evaluations are ongoing in the United States, United Kingdom, Europe, and some Latin American countries.

Acknowledgments

The author acknowledges the efforts of Dr. M.R. Jenner from Tate & Lyle SSD, one of the original team working under Professor Hough at Queen Elizabeth College, for help in identifying the sources of data and in proofreading and ensuring the historical facts are correct.

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