

AN APPLICATION FOR THE ASSESSMENT OF

ASPARTAME-ACESULFAME SALT

PRIOR TO ITS AUTHORISATION

MAY 2002

I.1 THE APPLICANT

The Applicant is:-

Holland Sweetener Company
P.O. Box 258
6160 AG Geleen
The Netherlands

Tel: 00-31-46-476 4065
Fax: 00-31-46-476 4066

I.2 THE MANUFACTURER

The Applicant is also the manufacturer.

I.3 PERSON RESPONSIBLE FOR DOSSIER

The person responsible for this dossier, and to whom all enquiries should be directed, is:-

Dr C. Groeneveld
Product Development Manager

Holland Sweetener Company
P.O. Box 258
6160 AG Geleen
The Netherlands

Tel: 00-31-46-476 4065
Fax: 00-31-46-476 4066
Email: chris.groeneveld@dsm.com

I.4 CONTENTS OF DOSSIER

Part	Subject	Page
I	ADMINISTRATIVE DATA	1
I.1	THE APPLICANT	1
I.2	THE MANUFACTURER	1
I.3	PERSON RESPONSIBLE FOR DOSSIER	1
I.4	CONTENTS OF DOSSIER	2
II	TECHNICAL DATA	
II.1	NAME OF SUBSTANCE	3
	<i>IUPAC NAME</i>	3
	<i>OTHER NAMES</i>	3
	<i>CA INDEX NAME</i>	3
	<i>CAS NUMBER</i>	3
	<i>EMPIRICAL FORMULA</i>	3
	<i>STRUCTURAL FORMULA</i>	3
	<i>MOLECULAR WEIGHT</i>	3
II.2	JUSTIFICATION FOR USE OF ASPARTAME-ACESULFAME	4
II.2.1	<i>INTENDED USE AND PURPOSE</i>	4
II.2.2	<i>QUANTITY TO BE USED</i>	4
II.2.3	<i>EFFICACY OF ASPARTAME-ACESULFAME AT PROPOSED USE LEVELS</i>	4
	<i>(SWEETNESS OF ASPARTAME-ACESULFAME SALT)</i>	
II.2.4	<i>NEED FOR ASPARTAME-ACESULFAME, BENEFIT FOR CONSUMER</i>	6
	<i>BENEFIT 1) FASTER DISSOLUTION</i>	6
	<i>BENEFIT 2) NO MOISTURE UPTAKE</i>	8
	<i>BENEFIT 3) IMPROVED POWDER FLOW PROPERTIES</i>	10
	<i>BENEFIT 4) IMPROVED DISPERSION - SUGAR FREE HARD CANDY</i>	11
	<i>BENEFIT 5) IMPROVED CHEWING GUM</i>	11
	<i>BENEFIT 6) IMPROVED STORAGE STABILITY</i>	12
	<i>BENEFIT 7) WEIGHT SAVING</i>	13
II.3	EXPOSURE	14
	<i>FACTORS AFFECTING EXPOSURE</i>	14
	<i>CONCLUSION</i>	14
II.4	REACTION AND FATE IN FOOD	15
II.4.1	<i>INTRODUCTION: THE NATURE OF ASPARTAME-ACESULFAME SALT</i>	15
II.4.2	<i>STORAGE STABILITY</i>	15
II.4.3	<i>DISSOCIATION ON SOLUTION</i>	15
II.4.4	<i>CONCLUSIONS</i>	17

II.1 NAME AND STRUCTURE OF SUBSTANCE

IUPAC NAME

[2-carboxy-1-(N-(1-methoxycarbonyl-2-phenyl)ethylcarbamoyl)]ethanaminium
6-methyl-4-oxo-1,2,3-oxathiazin-3-ide-2,2-dioxide

OTHER NAMES

Common name	:	Aspartame-acesulfame
Trade name	:	Twinsweet™
Synonyms	:	Aspartame-acesulfame salt
Abbreviation	:	APM-Ace

CA INDEX NAME

L-Phenylalanine, L-.alpha.-aspartyl-, 2-methyl ester, compd. with 6-methyl-1,2,3-oxathiazin-4(3H)-one 2,2-dioxide (1:1)

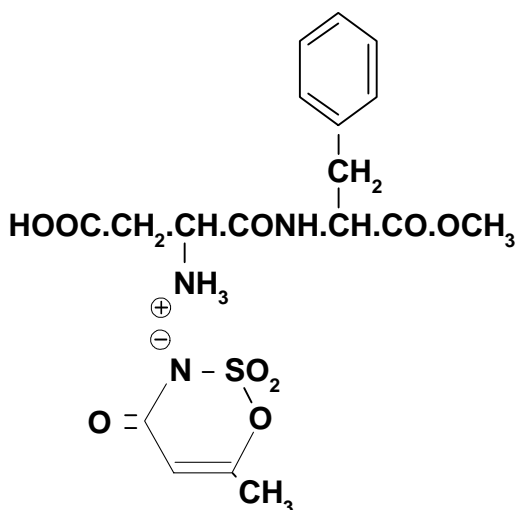
CAS NUMBER

106372-55-8

EMPIRICAL FORMULA

C₁₈ H₂₃ O₉ N₃ S

STRUCTURAL FORMULA



MOLECULAR WEIGHT

457.46

II.2 JUSTIFICATION FOR USE OF ASPARTAME-ACESULFAME

II.2.1) INTENDED USE AND PURPOSE

Aspartame-acesulfame salt is intended to be used as an intense sweetener. Its potential extends to all applications where the two existing sweeteners, aspartame and acesulfame-K, are already permitted to be used together. The salt may be used to replace the separate sweeteners either partially or entirely. No new uses are proposed.

II.2.2) QUANTITY TO BE USED

When aspartame-acesulfame dissolves it provides the same sweetening molecules as does a blend of the permitted sweeteners aspartame and acesulfame-K (**Part II.4**). The sweetening power of aspartame-acesulfame is the same as that of an equimolar blend of aspartame and acesulfame-K (**Part II.2.3**). Accordingly, the quantities of aspartame-acesulfame salt to be used will be those that furnish the same amounts of aspartame and acesulfame as would have been present had the separate sweeteners been employed.

In other words, aspartame-acesulfame salt contributes neither more nor less aspartame or acesulfame than is currently used. The salt is employed because it has technological and consumer benefits in comparison with the current practice of using a physical blend of the two permitted sweeteners.

The amount of aspartame-acesulfame salt to be used will be restricted by the quantitative limits currently in force for the category of foodstuff concerned. The maximum amount of aspartame-acesulfame will be such that the limits for both aspartame and acesulfame-K are respected.

II.2.3) EFFICACY OF ASPARTAME-ACESULFAME AT PROPOSED USE LEVELS (SWEETNESS OF ASPARTAME-ACESULFAME SALT)

Each molecule of aspartame-acesulfame contains one molecule of aspartame and one of acesulfame. In **Part II.4** evidence is presented to show that the salt APM-Ace dissociates in aqueous solution to release free aspartame and acesulfame. The sweetener molecules released by the salt are identical to those produced by dissolving separately the permitted sweeteners aspartame and acesulfame-K.

From these observations it is to be expected that the salt would exhibit the same sweetness as an equimolar blend of the two permitted, parent sweeteners. This is so in practice. Identical sweetness was found between various concentrations of APM-Ace salt and an equimolar blend of aspartame with acesulfame-K. The results hold true in both solvent systems tested, namely water and a citrate buffer, which were at widely different pH values. That these test systems were found to be equisweet in a double-blind trial gives an indirect indication that the same sweetener molecules were present in both solutions.

Figures II.2.3(1) and II.2.3(2) show how close the equivalence is.

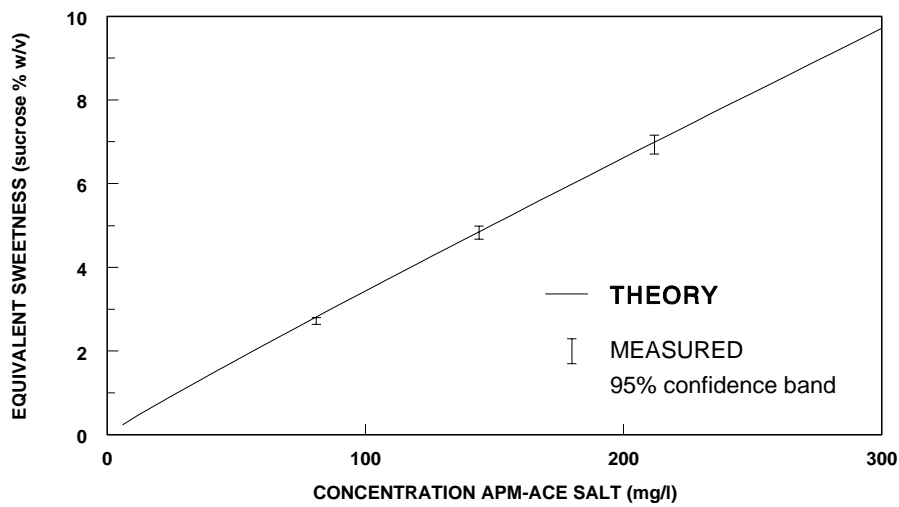


FIGURE II.2.3(1) Sweetness of APM-Ace in water, pH 7.0
Theoretical line calculated for an equimolar blend of aspartame and acesulfame-K, experimental points from taste panel

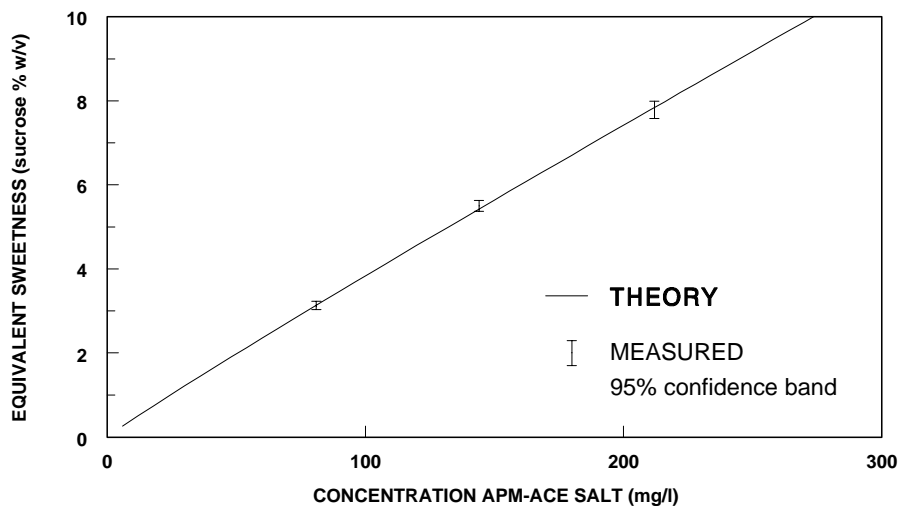


FIGURE II.2.3(2) Sweetness of APM-Ace in citrate buffer, pH 3.2
Theoretical line calculated for an equimolar blend of aspartame and acesulfame-K, experimental points from taste panel

II.2.4) NEED FOR ASPARTAME-ACESULFAME, BENEFIT FOR CONSUMER

Aspartame-acesulfame salt outperforms blends of single sweeteners in a number of technologically advantageous ways. These are listed below. The two key benefits - faster dissolution and no moisture uptake - are dealt with in more detail.

BENEFIT 1) FASTER DISSOLUTION

SUMMARY

Aspartame-acesulfame salt dissolves significantly more rapidly than an equimolar blend of aspartame and acesulfame-K. Instant powder products such as desserts, toppings, powder beverage mixes and some pharmaceuticals thus perform better during reconstitution. Similarly, table-top sweeteners dissolve faster, especially in cold beverages.

BACKGROUND

Consumers take for granted that powder products, such as desserts, toppings and beverage mixes, can be reconstituted almost instantaneously and that table-top sweeteners dissolve almost immediately. Achieving such performance in sugar-free and diet products containing intense sweeteners poses difficulties for the formulation technologist. In particular, aspartame is rather slow to dissolve, especially in cold systems such as might be involved in reconstituting a cold dessert or drink with refrigerated milk or cold water, or in sweetening ice tea.

The speed of dissolution can be improved by reducing the particle size, because this exposes a greater surface area to the solvent. However, in powder products, there are opposing constraints on particle size. Normally, manufacturers seek good powder flow and minimal dust content. These characteristics assist in the easy transport of powder mixes and minimise dust nuisance. They also contribute to accurate dosing of powders into packaging such as sachets, while preventing sealing problems due to fine particles becoming trapped in, and weakening, heat-seals. The normal route to achieving good powder flow and little dust is to use relatively large particles or granules. Fine powders are avoided. Aspartame is thus a source of potential difficulty in that large particles are desirable to assist powder flow and mixing properties, but large particles are unacceptable because they dissolve too slowly.

DISSOLUTION OF ASPARTAME-ACESULFAME SALT

APM-Ace salt dissolves markedly more quickly than aspartame. **Figure II.2.4(1)** contrasts the room-temperature dissolution of APM-Ace with that of aspartame of matched particle size. As the Figure shows, APM-Ace dissolves in about one quarter of the time required for aspartame. The difference is likely to be even more marked were the water cold.

Particles of 200-700 μm are actually granules, and the dissolution of aspartame in this form is such that it would be unlikely that a powder product manufacturer would consider using it. Instead, finer powders are employed, but APM-Ace outperforms these too, as explained below.

In the context of reconstitution of powder mix products, two factors have bearing on the quality of sweetness. Firstly, the speed with which the sweetener system dissolves governs the total sweetness perceived, especially if consumption follows immediately on reconstitution. Secondly, the quality of the sweetness sensation for blended sweetener systems is affected by the relative dissolution of the

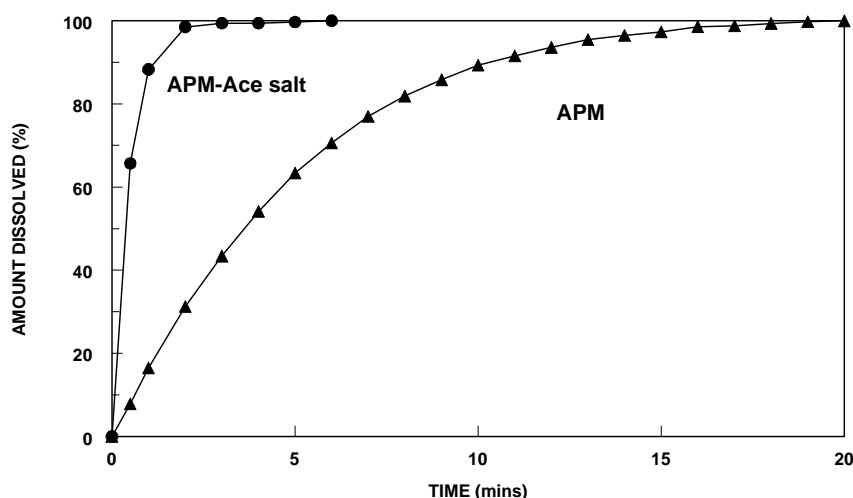


Figure II.2.4(1). Dissolution time of aspartame-acesulfame salt compared with that of aspartame in a laboratory test system. Particle size range of both samples 200-700 μm , solvent is water at 21°C.

components of the blend. That is to say, the desired ratio of blended sweeteners is not achieved until both are fully dissolved. Until dissolution is complete, there is a mismatch between the actual ratio in solution and that desired. Since consumers expect instantaneous reconstitution and often consume the product immediately, this mismatch can be significant, even though the overall dissolution time of the blend is only a few minutes.

Figure II.2.4(2) shows the release of sweetness on reconstitution of APM-Ace compared with that from an equimolar, equisweet blend of aspartame with acesulfame-K. The speedier dissolution of

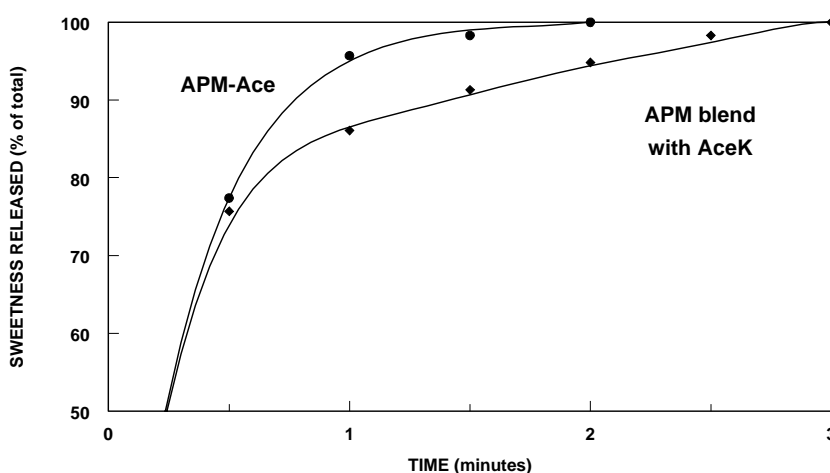


Figure II.2.4(2). Sweetness release during dissolution of aspartame-acesulfame salt compared with an equimolar blend of aspartame and acesulfame-K. Particle size range of both samples 50-250 μm , solvent is water at 21°C.

the salt is evident. In particular, the salt achieves 95% of target sweetness in less than half the time of the blend, for particles in the range 50-250 μm . The second aspect of blend dissolution, namely sweetness quality, is addressed in **Figure II.2.4(3)**, which contrasts the differing rates at which the salt and an equimolar blend deliver the target sweetener ratio. Owing to the differential dissolution of its components, the blend only achieves the desired ratio when completely dissolved. The APM-Ace, however, releases the same ratio throughout dissolution. The data are, again, for particles in the range 50-250 μm .

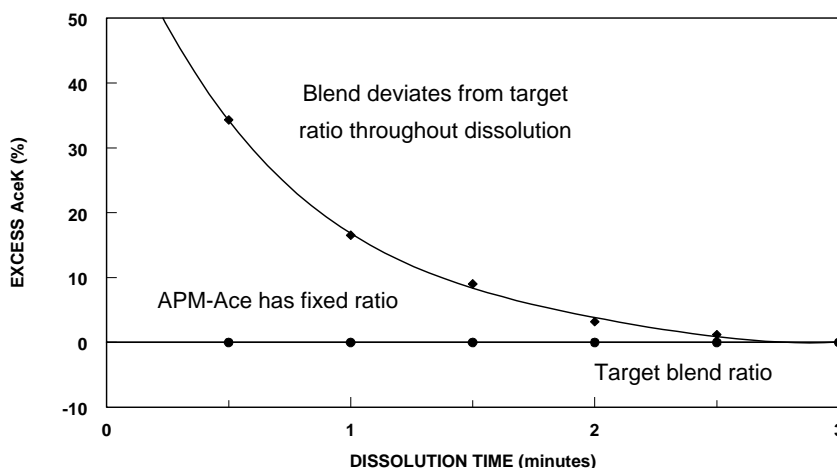


Figure II.2.4(3). Composition of sweeteners released during dissolution of aspartame-acesulfame salt compared with that of an equimolar blend of aspartame and acesulfame-K. Particle size range of both samples 50-250 μm , solvent is water at 21°C.

CONCLUSION

APM-Ace dissolves faster than either aspartame alone or a blend of aspartame and acesulfame-K. This is especially advantageous in the performance of powder mix products which aim for instant dissolution. In addition, the APM-Ace salt provides a fixed ratio of sweeteners throughout the dissolution process whereas a blend does not. The latter thus suffers a temporary failure to provide the desired sweetener ratio.

BENEFIT 2) NO MOISTURE UPTAKE

SUMMARY

In contrast to both blends of aspartame and acesulfame-K and to aspartame alone, the aspartame-acesulfame salt is not hygroscopic. Aspartame-acesulfame is thus much easier to store and to use in manufacture, especially during the preparation of powder mixes. The latter can be problematical, especially at times of high relative humidity in the atmosphere.

Use of the salt eases product handling and poses less stringent demands on packaging. The consumer receives a product more likely to be homogeneous (due to better mixing), and where the APM-Ace will not contribute to moisture uptake, which can lead to caking. The latter defect is particularly irksome where containers are intended for multiple use by the consumer, and the

repeated opening and closing of packaging allows ingress of atmospheric moisture and product deterioration.

BACKGROUND

Hygroscopicity - the tendency for materials to take up moisture from their surroundings - is an important property of food ingredients. Among the popular intense sweeteners, aspartame is a particularly effective desiccant. It can draw moisture from the atmosphere or from other ingredients with which it is combined in mixed powder products. The moisture taken up changes the properties of aspartame, especially its powder flow characteristics. This can lead to difficulties in making powder mixes as the aspartame can self-agglomerate, or clump, to form relatively large, aspartame-rich particles within the powder mix. These represent an inhomogeneity and can lead to undesirable segregation of the powder during manufacture and packaging. The agglomerates may even be visible and give rise to consumer complaint. Furthermore, on reconstitution of the powder, the agglomerates generally act as if they were single, large particles with all the negative consequences this has for dissolution rate (see Benefit 1).

ASPARTAME-ACESULFAME IS NOT HYGROSCOPIC

The tendency for aspartame to take up moisture from the atmosphere is shown in **Figure II.2.4(4)** and contrasted with the behaviour of aspartame-acesulfame. The latter has virtually no tendency to hygroscopicity at all and is remarkably immune to moisture uptake, even when exposed to very high relative humidities.

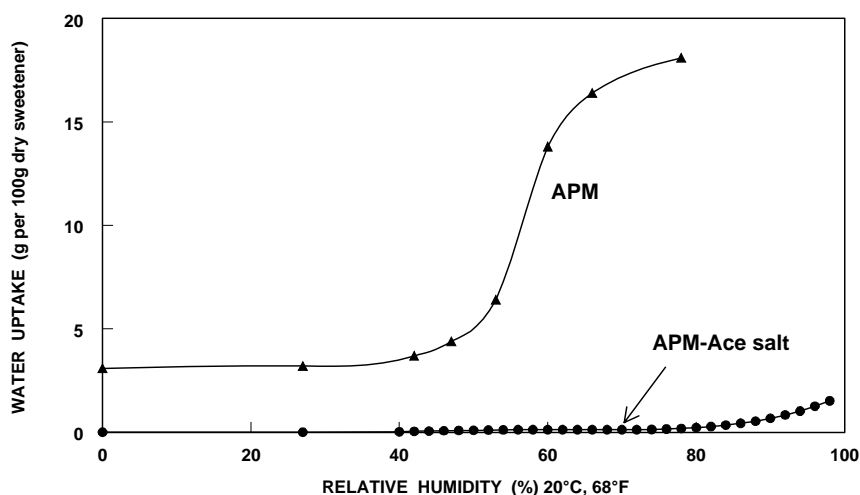


Figure II.5.4(4). Hygroscopicity of aspartame compared with absence of tendency for aspartame-acesulfame salt to take up moisture.

Figure II.2.4(5) compares the behaviour of the salt with that of an equimolar, equisweet blend of aspartame with acesulfame-K. The superior performance of the salt is clear.

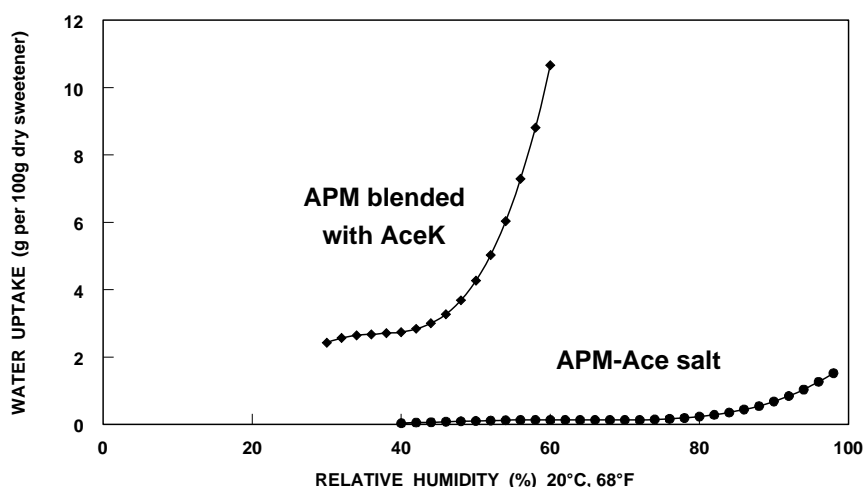


Figure II.2.4(5). Hygroscopicity of a blend of aspartame with acesulfame-K compared with absence of tendency for aspartame-acesulfame salt to take up moisture.

CONCLUSION

Aspartame-acesulfame has very low hygroscopicity, particularly in comparison with aspartame or a blend of aspartame with acesulfame-K.

BENEFIT 3) IMPROVED POWDER FLOW PROPERTIES

SUMMARY

The salt has superior powder-flow properties to those of a blend of aspartame and acesulfame-K. The use of blends can lead to inhomogeneities in powder products which the consumer may experience as variation in taste quality and/or sweetness level. Use of the salt assists in preparing products which are more uniform and acceptable to the consumer.

BACKGROUND

Aspartame-acesulfame salt has a single crystal type. Its semi-cubic crystals are easily grown and relatively sturdy. Consequently, free-flowing powders of controlled particle sizes - critical for powder mixing applications - can be made. In contrast, the needle-like crystals of aspartame are relatively difficult to grow and fragile. Aspartame powder flows poorly, and, in particular, its needle-shaped crystals do not lend themselves to the preparation of homogeneous, stable mixtures with the cubic crystals of acesulfame-K. Nevertheless, aspartame and acesulfame-K are a popular sweetener combination and there is growing demand for these two sweeteners to be used together in powder products. The salt overcomes their problems of powder incompatibility.

BENEFIT 4) IMPROVED DISPERSION - SUGAR FREE HARD CANDY

SUMMARY

Aspartame-acesulfame disperses easily in difficult applications, such as sugar-free hard candy, where a blend of sweeteners is difficult to employ. Superior product quality results.

BACKGROUND

Because of concerns about dental caries and its promotion in children by the consumption of candies in general, there is growing interest in the options for making sugar-free confectionery. Sugar-free hard candy is made by similar technology to that which is used for high-boiled sugar confectionery except that one or more polyols are used instead of sugars. Because the technologically-suitable polyols are less sweet weight-for-weight than sugar, it is usual to boost their sweetness by the addition of intense sweeteners.

It is considered to be undesirable to expose aspartame to the very high temperatures involved in preparing a polyol “mass” or “melt” prior to moulding individual candy pieces. Intense sweeteners are normally added to the hot mass at the same time as colour, flavour and any acid. All the ingredients are then mixed into the mass, which is then used to form candies. However, in many cases it is very difficult to obtain a homogeneous dispersion of aspartame. The sweetener may remain as individual particles which both spoil the appearance of otherwise transparent candies and, more particularly, represent discrete islands of concentrated sweetness embedded in the polyol matrix. For these reasons aspartame is sometimes avoided, even though it has taste quality advantages which recommend it.

APM-Ace, on the other hand, has been found to disperse easily to give transparent candies of homogeneous sweetness. The salt thus provides a simple and convenient means of introducing both aspartame and acesulfame into sugar-free hard candy.

BENEFIT 5) IMPROVED CHEWING GUM

SUMMARY

Aspartame-acesulfame salt surprisingly boosts the sweetness of chewing gum and gives it a very long-lasting quality without recourse to encapsulation of the sweetener. The consumer experiences an improved product quality at potentially lower cost.

BACKGROUND

Chewing gum leads the market in sugar-free or “tooth friendly” confectionery. The prolongation of chewing gum sweetness is the central aim of many gum development programmes. There is a strong interaction between gum sweetness and flavour, and gums which retain their sweetness are perceived also to be better flavoured. Because the consumer adapts to the sweetness released by a chewing gum, it is conventional wisdom that the sweetening system should, ideally, provide a distinct second boost to sweetness as the initial sweet impact is decaying.

Much ingenuity has been focused on the encapsulation of sweeteners in an effort to delay their solution and provide sweetness extension. A huge patent literature testifies to the effort devoted to this end. However, encapsulation - typically using one or more of a variety of polymeric coatings - is a costly process and difficult to control. Inevitably there is a substantial processing cost as well as waste.

Surprisingly, however, APM-Ace provides both a prolonged sweetness release and a distinct second boost to the sweetness profile. This is achieved simply by mixing the aspartame-acesulfame into the gum like any conventional ingredient. There is no need to resort to encapsulation. **Figure II.2.4(6)** gives an impression of this effect.

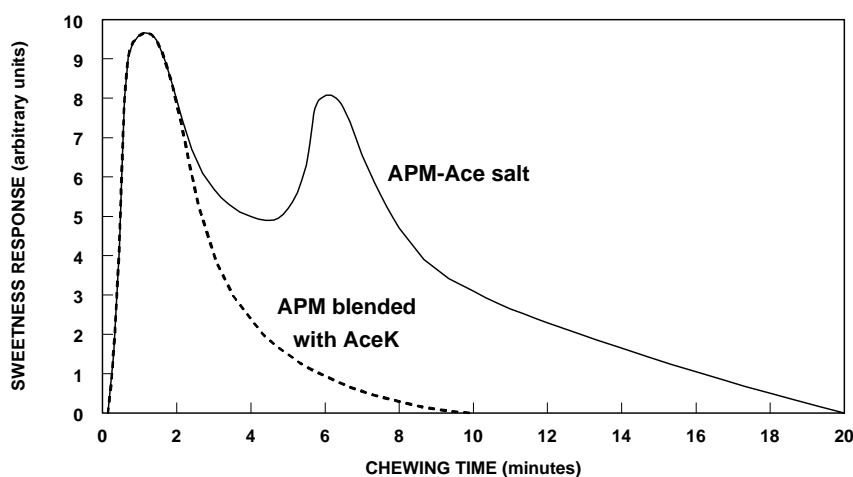


Figure II.2.4(6). Impression of the sweetness release profile of chewing gum sweetened with aspartame-acesulfame compared with a gum containing an equimolar amount of a blend of aspartame with acesulfame-K.

BENEFIT 6) IMPROVED STORAGE STABILITY

SUMMARY

Aspartame-acesulfame is more stable in certain applications towards certain reactive flavour compounds than aspartame alone. This means that the salt can be used in applications where aspartame has either required encapsulation for protection or has been substituted by sweeteners with a poorer taste. The consumer benefits from products of improved taste and prolonged shelf life.

BACKGROUND

Because of its sweetness quality, aspartame is favoured for the sweetening of sugar-free confectionery. While other intense sweeteners are used, their role is normally to supplement that of aspartame. It would be unusual, for example, to sweeten a product exclusively with acesulfame-K or saccharin because of those sweeteners' poorer taste profiles.

The major exception to this is where the flavour system is incompatible with aspartame. Such incompatibility can occur with flavours rich in aldehydes which react with aspartame, such as citral, vanillin, citronellal and anisaldehyde (*p*-methoxybenzaldehyde). An example of this phenomenon is cinnamon-flavoured chewing gum. This popular flavour contains a high concentration of cinnamaldehyde, an α,β -unsaturated carbonyl compound which reacts readily with free amino groups, such as are present on aspartame. As a result, aspartame-sweetened cinnamon-flavoured gum suffers a dual penalty in that the reaction both diminishes the concentration of the sweetener and of the flavour. The net effect is to limit the shelf-life of the product to such an extent that

manufacturers have felt obliged either to encapsulate aspartame in polymer systems, or to use less-attractive tasting sweeteners.

The structure of aspartame-acesulfame salt (see Part **II.1**) is such that molecular sites which play a role in reaction of aspartame with aldehydes are blocked by the adjacent acesulfame. The increased stability which results means that the solid salt can be used directly in difficult applications, such as cinnamon-flavoured gum.

Figure II.2.4(7) contrasts the sweetness stability on storage of cinnamon sugar-free chewing gums made using a blend of aspartame and acesulfame-K with the same gum made using an equimolar amount of aspartame-acesulfame salt. This demonstrates the enhanced stability of the salt in this environment, an improvement which results in a satisfactory shelf-life. Use of the salt thus allows aspartame to be included in the formulation so that the consumer can benefit from its particular sweetness quality.

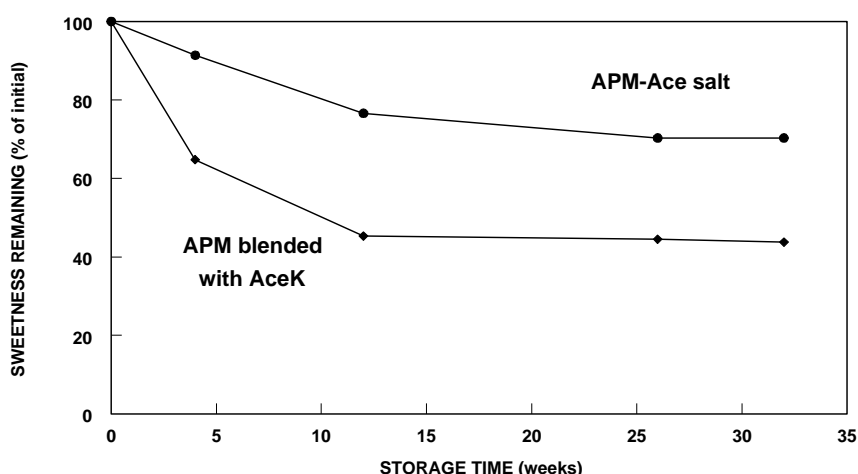


Figure II.2.4(7). Sweetness stability on storage of chewing gum made with aspartame-acesulfame salt compared with a gum containing an equimolar amount of a blend of aspartame with acesulfame-K.

BENEFIT 7) WEIGHT SAVING

SUMMARY

Aspartame-acesulfame weighs less than the equi-sweet amount of an equimolar blend of aspartame and acesulfame-K. The lower weight leads to savings on packaging, transport and storage of sweeteners which, in turn, can contribute to lower prices.

BACKGROUND

Aspartame-acesulfame salt is actually more effective on a weight-for-weight basis than a mere mixture of its parent sweeteners. This is because the molecule of the salt contains no potassium ions (see Part **II.1**), neither is there any water of crystallisation, nor any significant absorbed water. In contrast, aspartame may contain legally up to 4.5% moisture (strictly "loss on drying"), while by definition acesulfame-K comprises 19.4% by weight potassium. The salt thus represents a more concentrated source of sweetness, and comprises two pure sweeteners together, without the functionless presence

of potassium or water. A modest weight saving of about 11% results. This translates into a lowering of packaging, transport and storage costs, all of which are ultimately paid by the consumer.

II.3 EXPOSURE

FACTORS AFFECTING EXPOSURE

When considering potential exposure to aspartame-acesulfame it should be clearly understood that, when the salt dissolves, it provides the same sweetening molecules as does a mixture of aspartame and acesulfame-K (see **Part II.4**). In addition, the sweetening power of aspartame-acesulfame is the same as that of an equimolar blend of aspartame and acesulfame-K (see **Part II.2**). Accordingly, the quantities of aspartame-acesulfame salt used in foods are those which furnish the same amounts of aspartame and acesulfame as would have been present had the separate sweeteners been employed.

The salt thus represents an alternative source of aspartame and acesulfame to those which are already permitted. The salt's advantages over these lie in its different physical form and improved properties as a solid. Once dissolved, the salt ceases to exist and only permitted sweetening molecules are released into solution. It follows that "exposure to the salt" in practice means exposure to aspartame and acesulfame in amounts largely identical to those now in use.

Insofar as the technological advantages of the salt cause it to be more widely employed, it should be noted that no new applications are proposed. Thus use of the salt would fall within the existing regulatory limits on the joint use of aspartame and acesulfame-K. As a result, dietary exposure to aspartame or acesulfame will still fall well within the limits which were the basis for permitting their use as individual sweeteners.

CONCLUSION

Aspartame-acesulfame salt is an alternative source of the two permitted sweeteners, aspartame and acesulfame, and there are no grounds for expecting that use of the salt will lead to a substantial increase in exposure to these two sweeteners.

II.4 REACTION AND FATE IN FOOD

II.4.1) INTRODUCTION: THE NATURE OF ASPARTAME-ACESULFAME SALT

Aspartame-acesulfame is an ionically-bonded salt combining positively-charged aspartame with negatively-charged acesulfame. In effect, the potassium ion of acesulfame-K has been replaced by aspartame. The two sweetener molecules are combined in a fixed, equimolar ratio (**Part II.1, II.2**).

The manufacturing process of APM-Ace salt can in fact be regarded as a recrystallization process which significantly lowers the amounts of impurities carried over from the (permitted, food grade) raw materials. Also no new impurities have been detected in the salt.

It may be concluded that the composition of APM-Ace is effectively the same as that of a purified blend of the permitted sweeteners, aspartame and acesulfame-K, from which potassium has been removed.

In the following sections evidence is described of the dry stability of aspartame-acesulfame and of the dissociation of the salt in aqueous solution. These findings, in turn, support the conclusion that the reactions and fate of aspartame-acesulfame are the same as those of the two permitted sweeteners, aspartame and acesulfame-K. In particular, the solid salt is stable, even under abuse conditions, and dissociation on solution releases the same molecular species of sweetener as aspartame and acesulfame-K do. No new molecular types are available, and it follows that the subsequent reactions are limited to those already well established for these two sweeteners.

II.4.2) STORAGE STABILITY

The impurity levels in aspartame-acesulfame salt have been measured after storage at room temperature (circa 20°C) for various lengths of time. For comparison, the impurities have also been measured for aspartame and acesulfame-K, used as raw material to make the salt. In addition, the impurity levels in the salt and the raw materials after storage at higher temperatures (40 & 60°C) have been measured.

Within the limits of experimental error, the results show that the major components of the salt, as well as the minor impurities found remaining after synthesis, are unaffected by storage, also at higher temperatures. In addition special focus has been on acetoacetamide, diketopiperazine and aspartyl-phenylalanine, which are the principal indicators for potential breakdown of acesulfame-K and aspartame, respectively. Acetoamide was not found at all, which demonstrates that the acesulfame moiety in the salt is as stable as acesulfame-K itself. Furthermore the salt even appeared to be more stable than the parent aspartame. The reason for this is likely to reside in the fact that, in the salt, the amino group of aspartame is blocked by the presence of acesulfame (**Figure II.4.2(1)**) and is thus hindered from taking part in the principal breakdown reaction of aspartame.

II.4.3) DISSOCIATION ON SOLUTION

Aspartame-acesulfame is an ionically-bonded salt and would be expected, therefore, to dissociate in aqueous solution. The spectral properties of solutions of aspartame-acesulfame salt were compared with equimolar solutions of aspartame and acesulfame-K. The techniques used were nuclear magnetic resonance, Raman and infrared spectroscopy.

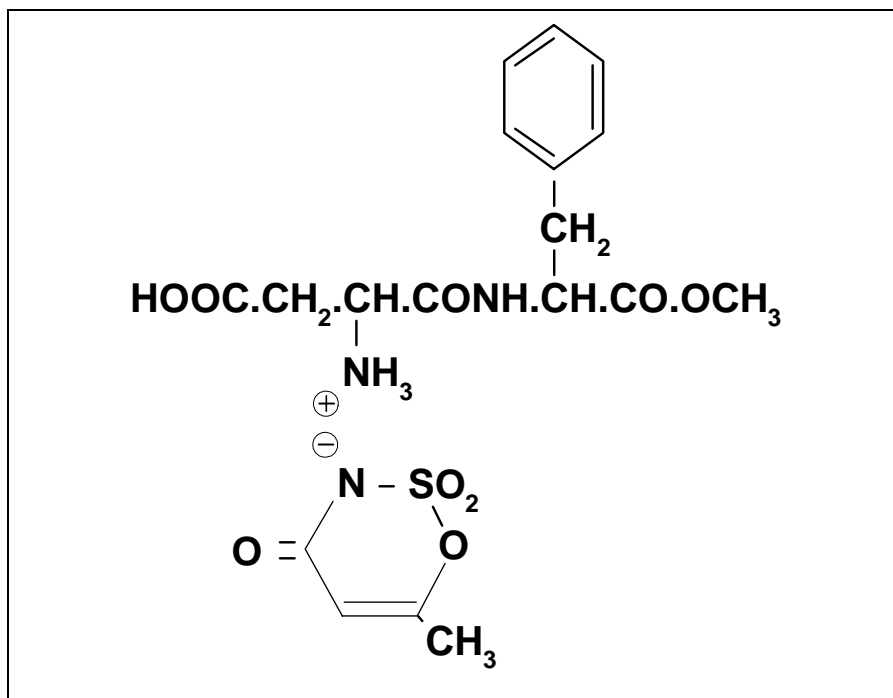


FIGURE II.4.2(1) Structure of aspartame-acesulfame salt.

Each of the spectroscopic methods used is a sensitive probe of molecular structure, and each failed to show any difference between solutions of the APM-Ace and those of the permitted sweeteners. Thus the sweetener molecules released by the salt are identical to those which appear in solution when a mixture of aspartame and acesulfame-K is dissolved. There was no evidence that the APM-Ace salt gives rise to new molecular species or compounds in solution.

It may be concluded that, when dissolved in aqueous solution, APM-Ace dissociates to give aspartame and acesulfame alone.

For completeness, the dissociation of APM-Ace in gastric juice was also investigated by means of ^1H -NMR which demonstrated that, even if it were not dissolved beforehand, APM-Ace dissolves in gastric juice to release the same sweetener molecules as does an equimolar mechanical blend of aspartame and acesulfame-K.

The gastric juice study was performed in two parts. In the first, the sweetener systems under investigation were dissolved up to a concentration which did not affect the natural pH of the gastric juice. However, this concentration was too low to allow very good spectra to be seen against the background of the gastric juice itself. In the second part, the concentrations of the sweeteners were increased to improve the quality of the spectra. However, it should be realised that the concentrations then used were far in excess of realistic levels. In addition, these concentrations were sufficiently high to cause pH differences between the test solutions, and these had to be eliminated by restoring the solutions to an identical pH with the aid of hydrochloric acid.

The above studies all indicate that APM-Ace, as an ionically-bonded salt, dissociates on solution to release aspartame and acesulfame, as shown in **Figure II.4.3(1)**.

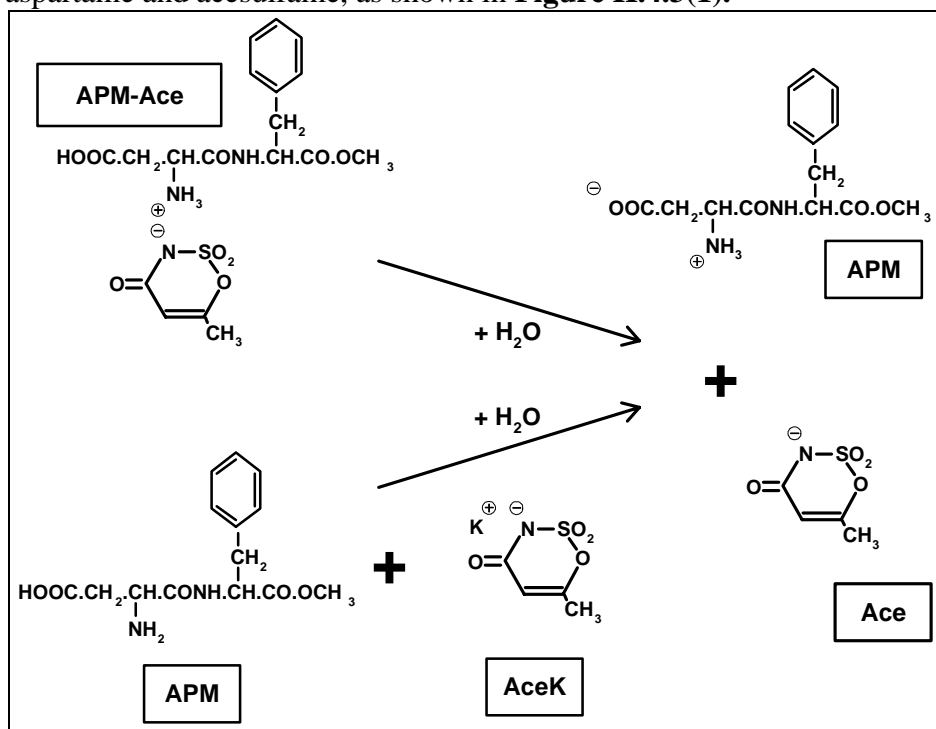


Figure II.4.3(1) Aspartame-acesulfame (APM-Ace) dissociates in aqueous solvents to release the same molecular species of sweetener as aspartame (APM) and acesulfame-K (AceK) do when dissolved separately.

II.4.4) CONCLUSIONS

APM-Ace releases only the same sweetener molecules as known, permitted sweeteners (**Part II.4.3**). No new substances are involved and no new applications are proposed. Accordingly, wherever the salt is dissolved in foods, its reactions and fate will be the same as those of the permitted parent sweeteners.

The molecular structure of the solid crystalline salt inhibits the principal breakdown reaction of the aspartame moiety thus making the solid form of APM-Ace even more stable chemically than aspartame itself (**Part II.4.2**). This higher stability as a solid has no toxicological consequences, because any physiological absorption is preceded by solution in saliva or digestive juices, even if the sweetener was not dissolved during preparation of the foodstuff. That is to say, the consumer is only exposed to the same molecular species as result from the use of existing, permitted sweeteners.