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Review

# Aspartame—General Review

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## Sweet Story of Success of G.D. Searle & Co.

As people develop and become affluent, they consume more sweet things, particularly in terms of sugar.[1] Sugar, if consumed in excess, will lead to obesity or diabetes, and sugar, being fermentable, does lead to dental decay, unless countered. The effect of sugar on these and the urgent need for those unable to consume sugar, i.e., diabetics, as well as those who wish to lose weight has led to the search for alternatives.

The ideal sweetener, as described by the Calorie Control Council,[2] should have the same or great sweetness as sucrose in addition to being colorless, odorless, readily soluble, stable, functionable, and economically feasible. The ideal sweetener should contribute reduced or no calories to the diet, be normally metabolized or resistant to digestion, and be non-toxic and non-promoting of dental caries. To date, many kinds of sweetener as an alternative to sugar have been introduced, such as saccharin, cyclamate, isomalt, acesulfam-K, thaumatin, xylitol, stevioside, dihydrochalcone, monellin, neosugar, hernandulcin, glycyrrhizin, ect.[3] However, none of them is ideal-each of them has the defective(s) in the aspect of heat or pH lability, distinct flavor profile, legal clearance, safety, and cost. Aspartame (APM), among the myriad of them, seems to be judged the best of the new high-intensity sweeteners because it meets the consumer demand for reduced calorie products, tastes sugar-like, and suits the application for various products.

APM is a white, odorless, crystalline powder that has a clean, sweet, sugar-like taste with a sweetness potency 180-200 times that of sucrose.[4,5] The story about the successful debut of APM in food ingredient industries is dated back to 1965. When James Schalatter at G.D. Searle & Co. working on the synthesis of gastrin tetrapeptide for ulcer therapy (to be used in a bioassay) was crystallizing L-aspartyl-L-phenylalaine from ethanol, the mixture bumped and spilled on his hand. Subsequently, when he licked his fingers to pick up weighing paper, he discovered the remarkable taste of this dipeptide ester. This event catapulated the researchers at G.D. Searle & Co. (Skokie, Ill) into an intensive research, and the company finally introduced a new high-intensity sweetener. Combined worldwide sales of NutraSweet and Equal (Searle's tabletop sweetners sweetened with APM only), being introduced at just the right time, were $500 million in 1984 and this figure nearly doubled in 1985.

This article delineates the sweetness, stability, metabolism/regulatory status, application and preparation of APM. The work of Homler, Stegink and Filer, and of several others gives more detaild information in this regard.[6,7]

## Sweetness

The taste of APM could not have been predited from its constituent amino acids, since L-aspartic acid is flat and L-phenylalanine is bitter. When the amino acids are combined in the form of $\alpha$-L-aspartylphenylanine and the phenylanlanine carboxy is converted to a methyl ester, a sweet product results. Basically, APM has a taste which is very similar to sucrose.[8] There is a slightly longer period of time required for APM to reach its peak sweetness compared with to that of sucrose. This difference is detectable at first contact, but distinction thereafter becomes tenuous. APM in aqueous solution and normally sweetened foods does not differ significantly from sucrose in bitterness, aftertaste, off-flavor, or general acceptability in concentrations comparable in sweetness to 4% sucrose solution.

APM is roughly 180-200 times as sweet as sucrose which has a relative sweetness of 1.0 as the standard against which all other sweeteners are compared, but the sweetness of APM is inversely related to the concentration of sucrose. For example, APM is 215 times the sweetness of 3% sucrose solution, while it has only 133 sweetness potency at 10% sucrose concentration.[9]

The sweentess potency mentioned above may not be applicable to product formulations because certain ingredients may affect the sweetness intensity of APM. For

example, the sweetness intensity of AMP is enhanced significantly in gelations, but it is not in gums.[9] Adversely, APM itself may affect the intensity of food component. Baldwin and Korschgen[10]reported in this segard that the intensity of fruit flavor of orange-and cherry-flavored beverages becomes significantly higher when the products are sweetened with APM. Other sensory properties of beverages and gelatins containing APM are descriptively analyzed by Larson-Powers and Pangborn.[11]

Variation of the sweetness potency of APM depending on the concentrations and the nature of food medium make it difficult to determine how much APM should be used in formulating the products. The problem, however, may be alleviated by the combined use of the high-intensity sweeteners, and this is in accordance with the recommendations of the Calorie Control Council.[12] A synergistic (greater than the sum of the individual parts) effect is sometimes observed when mixture of sweeteners (e.g., isomalt and APM) is used. This point of view is enough to attract the attention of processors who wish to cut the cost of using APM in their food products (The price of APM in the world market is $180-200/Kg). It makes the combined use of AMP with other sweeteners more feasible that the blends of the dipeptide ester with (i) sodium saccharin, (ii) sodim saccharin and sucrose, and (iii) sodium saccharin, sucrose, and cyclamate do not differ significantly from 4% sucrose solution in bitterness, aftertaste, or off-flavors.[4]

## Stability

Perhaps APM stability is the major factor that limits the wider range of application and so it is important. Under certain conditions, APM decomposes via a series of reactions that include ester and peptide bond hydrolysis and cyclization to the diketopiperazine (DKP).[13,14] Neither of the converted products, aspartylphenylalanine and DKP, is sweet. A loss of sweetness over time is all that is perceived-there is no off-taset.

The stability of APM depends on temperature, pH, moisture contend, and the system in which APM is used. APM in dry state is quite stable even under conditions far more severe than would be encountered in normal processing.[15] At temperatures above 120° C, however, it decomposes and this limits the use of APM in backed, fried, or retort processes.

The stability of APM in solution is a function of temperature, pH, and time. As the time and temperature increase at a given temperature and for a given processing time, respectively, the amount of APM remaining unconverted decreases. Decomposition follows simple first-order kinetics.

pH is especially important to APM stability. APM is most stable in the pH range of 3.0-5.0 where most moist or liquid food products exist. Above pH 5.0, it cyclohydrolyzes to DKP, and at pH 3.4 and lower, it hydrolyzes to aspartylphenylalanine.

The expected shelf life for classes of product may be an important criterion to the stability of products sweetened with APM. Carbonated soft drinks sweetened with APM are acceptably sweet for somewhat over 6 months at room temperature. This is satisfactory, since the expected shelf life of soft drinks is less than 6 months. The pH of ice cream is in the range of from 6.5 to above 7.0-outside the range where APM is normally considered stable. But stability for at least 6 months is obtained because the reaction rate is dramatically reduced due to the frozen state and the lower free moisture.

Fermentability of APM is an another subject of discussion in regard with stability. It is microbiologically stable. The Americna Dental Association has described that APM is not metabolized by *Streptococcus mutans,* the organism implicated in tooth decay and, therefore, APM is regarded as noncariogenic.

## Metabolism/Regulatory Status

When APM is injested orally, it is metabolized to yield aspartic acid, phenylalanine, and methanol by the same biochemical pathway as that of proteins in either the intestinal lumen or mucosa.[16] Some investrigators expressed concern about the safety of APM, since high blood levels of aspartic acid or phenylalanine are associated with toxicity.[17,18] Administration of high dose of APM to infant mice results in hypothalamic neuronal necrosis, presumably from elevated blood APM concentrations.[19] However, APM administration at 2g/Kg body weight to infant monkey does not produce neuronal necrosis, even though plasma APM level was elevated.[20]

Grossly high blood phenylalanine concentration in some individuals who are highly susceptible to excess phenylalanine (phenylketonuric) are associated with mental retardation.[21] Thus, it is desirable that the package

of the commercial products containing APM have labels warning the presence of phenylalanine.

All other considerations aside, the central concern about all low-calorie sweeteners has been safety. Effective on October 22, 1981, APM received regulatory clearance from the Food and Drug Administration for use in dry products and in tabletop sweeteners after Searle submitted evidence proving that APM consumption at the maximum projected levels of daily consumption would not pose a health risk. In mid-1983, FDA extended its approval to include carbonated beverages. Thus far, the foods in which APM can be used as sweeteners and flavor enhancer are cold breafkast cereals, chewing gum, dry beverage bases, instant tea and coffee, gelatin, puddings, fillings, and dairy product toppings. It can also be used as a prepackaged sugar substitute tablet. Petitions submitted to the FDA have also been filed for its use in refrigerated fruit-based drinks and frozen concentrates, asceptically packaged juice drinks and frozen confections. Its safety was further affirmed in July, 1985, when the American Medical Association Council on Scientific Affairs asserted that evidence sugests that consumption of APM by normal humans is safe and is not associated with serious adverse health effects.[22]

Accoding to FDA regulations, safe means that there is reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use (C.F.R. section 170.3i). All substances in our living environment have some type of harmful potential if ingested in excess. The basic question becomes not whether but how much of a given substance can be considered safe. Although APM is presently generally recognized as safe for use in foods, its content may not exceed those levels based on current good manufacturing practice.[23] The FAO/WHO Joint Expert Committee on Food Additives (JECFA) has established a working ADI of 40 *mg/kg* body weight/day.[24] In case of a person whose body weight is 50 *Kg*, the amount of APM that could be safely injested everyday is 2*g*, an amount judged as far below any level even suspected of being toxic, which roughly corresponds to 400*g* of sucrose. This is not of little quantity, considering that the amount of sugar consumption/day/person in our country was 32.1*g* in 1984.[25] So far, over the last few years, regulatory authorities in about 50 countries, including JECFA and Europan Economic Communities have approved the use of APM as a tabletop sweetener and/or a food additive.[26,27]

## Application

Although APM solubility is affected by pH (isoelectric point is pH 5.2), the APM solubility in water is about 10.0 *g/L* at 20°C and 40.0 *g/L* at 60°C. It seems to be low at first glance, but there is no problem in food formulations, taking the sweetness potency of APM into consideration. Packaged in sachets, APM as tabletop sweeteners is sold by Jeil Sugar Co. and Green Cross Co. as Fine Sweet and Green Sweet respectively in our country, as Equal in the US, Egal in Quebec and Canada, and Canderal in Europe and U.K. Since APM is too sweet to be used in a crystalline form, it is diluted with a bulking agent such as cyclodextrin,[28] acid hydrolyzed oligosaccharide,[29] polyglucose or polymaltose,[30] and especially polydextrose.[31-33] They also contribute to the stabilization and solubilization of APM.

Carbonated soft drinks are a major market for sugar and by far the largest application for low-calorie sweeteners. APM has a dramatic effect on the diet soft drink industry in U.S. Those brands containing 100% of the sweetener were introduced in early 1983 when saccharin-sweetened products comprised 5.35% of the category. With the presence of NutraSweet, the growth in this market segment has tripled in dollar volume, growing to $23 million in 1983. In the US, APM is now incorporated as the sole sweetening ingredient in virtually all diet soft drinks, but it may be blended with saccharin at a level close to 50% of the saccharin level in other countries. Combined use of APM with saccharin improves both the shelf-life and the taste of the product. APM/saccharin combinations have a synergistic sweetening effect, with less of each sweetener needed to produce the desired sweetness. Other products sweetened with APM are listed in the section of Metabolism/Regulatory Status.

## Preparation

### Chemical Process

Chemical abstract name of APM is N-$\alpha$-L-aspartyl-L-phenylalanine-1-methyl ester and the structure is shown in Fig. 1. Since the sweetness of APM was reported in 1969 by R. H. Mazur et al.,[4] many methods have been developed for preparing the compound.[34,39] APM can be synthesized by chemical methods which usually com-

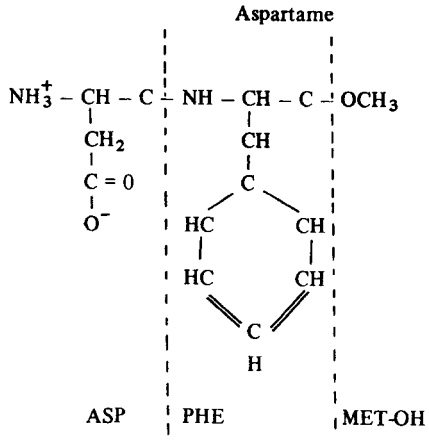


**Fig. 1. Structure of aspartame**

prise i) protection of amino group of L-aspartic acid, ii) esterification of carboxyl group of L-phenylalanine, iii) condensation of the N-protected aspartic acid and phenylalanine methyl ester, and iv) removal of the protecting group. APM is divided into two forms according to the carboxyl group of aspartic acid to which phenylalanine methyl ester is combined. If phenylalanine is condensed with $\alpha$-carboxyl group, it is $\alpha$-APM and if with $\beta$-carboxyl group $\beta$-APM.

Preparation of APM by chemical methods suffers from the formation of $\beta$-APM which must be removed because of its bitter taste.[4] According to one method, the $\beta$-carboxyl group as well as amino group of L-aspartic acid was both protected, converted to a very reactive ester, condensed with L-phenylalanine methyl ester, and the protecting groups were finally removed.[40] This method, however, is industrially disadvantageous because it involves many reacton steps and needs many kinds of auxiliary raw materials. There is another method. Ariyoshi et al.[41] can obtain a mixture of $\alpha$-and $\beta$-APM simply by mixing L-aspartic anhydride hydrochloride and L-penylalanine methyl ester in an organic solvent. The coupling reaction, however, always resulted in side reactions, such as the self-condensation of L-aspartic anhydride and the condensation between the unchanged anhydride and the resulting dipeptide ester, since the amino group of the aspartyl residue is unprotected. Under the well investigated reaction conditions, the yield of $\alpha$-APM in terms of L-aspartic acid anhydride was very low, 37%.[41] Some handicaps that chemical methods inherently have for the production of APM make the investigators contemplate an alternative-enzymatic method.

**Enzymatic Process**

In the last few years, the attention of the protease-catalyzed syntheses of peptides by reversing the hydrolysis reaction has been revived as an alternative to chemical methods. Commercial or pilot-scale production of such peptides as human insulin from the porcine hormone and the aspartame precursor has been started recently by Novo Industri A/S (Denmark) and Toyo Soda Manufacturing Co. Ltd. (Japan), respectively.

The enzymatic synthesizing process of APM comprises the exerting the effect of a protease on N-protected L-aspartic acid and phenylalanine methyl ester to obtain N-protected APM or the phenylalanine methyl ester adduct of N-protected APM and then removing the protecting group to form APM. Enzymatic condensation of N-protected aspartic acid with phenylalanine methyl ester has several advantages over chemical condensation. By enzymatic synthesis with cell extracts, the condensation gives exclusively the $\alpha$-isomer because only $\alpha$-carboxylic acid of aspartic acid participates in the condensation reaction due to the enzyme's strict spceificity.[42] Thus the difficult task to protect the $\beta$-carboxyl group can be avoided.[43] In contrast, all of the chemical methods is always accompanied with 20-40% production of the $\beta$-isomer.[44-46] Furthermore, enzymatic process gives the product in high yield within a reasonable time period, usually more than 90% and the reaction condition is mild. It makes the process more feasible that thermolysin and its family enzymes used for the coupling are thermostable[47] and resistant to organic solvent.[48] Therefore, they are suitable as industrial catalyst, as they are easy to handle and recover. A crude enzyme can be used without extensive purification.Chemical process and enzymatic process with industrial potential for the production of APM is compared in Table 1.

As has been done, thermolysin-catalyzed synthesis of APM was firstly performed in aqueous system.[49,50] However, the equilibrium of the system is in the side of the substrates, and the reaction rate is very low compared with that of hydrolysis. One of trials to shift the equilibrium position toward synthesis is the solubility-controlled accumulation of the product in the reaction mixture.[51,52] The further biotransformational approaches to the synthesis of $\alpha$-APM are the use of aqueous-organic biphasic systems.[53-55] and organic solvents[56] as en-

**Table 1. Comparison of chemical process and enzymatic process for the production of APM**

| | Chemical process | Enzymatic process |
|---|---|---|
| Energy cost | relatively high | low |
| Process lines & Equipment | complex | relatively simple |
| Reaction conditions | relatively severe | mild |
| Raw materials | L-Asp, L-Phe | D,L-Asp, D,L-Phe |
| Product | usually mixture of $\alpha$-and ß-APM | only $\alpha$-APM |
| Yield (%) | 50-70 | 90-99 |
| Separation | difficult | easy |
| Waste treatment | problematic | not problematic |
| Catalyst cost | – | high |

zymatic syntheses of various biologically active peptides.[57,58]

Immobilization of thermolysin is usually required not only to reuse but also to protect the enzyme from autolysis.[59] The enzyme can be immobilized either by adsorption to Amberlite XAD-series, by ionic bonding to Amberlite IRA-94 or by covalent bonding to the hydrophilic gel.[60] Oyama et al.[60] found that the enzyme is staying in the inner sphere of the porous carrier in water-saturated ethyl acetate. The reaction rate is, however, rather slow as compared with that in aqueous solution.[42,60,61] With the immobilized thermolysin to the synthetic adsorbant Amberlite XAD-7, a continuous reaction was performed in an organic solvent with both a plug flow reactor (PFR) and continuous stirred tank reactor (CSTR).[62] The immobilized enzyme CSTR was found more suitable for the continuous reaction than the PFR from the viewpoints of the long-term stability and ease of operation. Moreover, the addition of calcium to the substrate is not required and so one step for separation of calcium from the product can be obviated. Based on the various findings, a highly economical industrial process for the production of APM has been establsihed. The outline of the enzymatic process is shown in Fig. 2.[63]

Still, there is left a margin for further improvement of the enzymatic process. There is known a process for producing APM without using the protective groups which comprises contacting an appropriate microorganism or enzyme-containing fraction of said microorganism with L-aspartic acid and L-phenylalanine methyl ester in an aqueous medium. However, this is not always suitable for

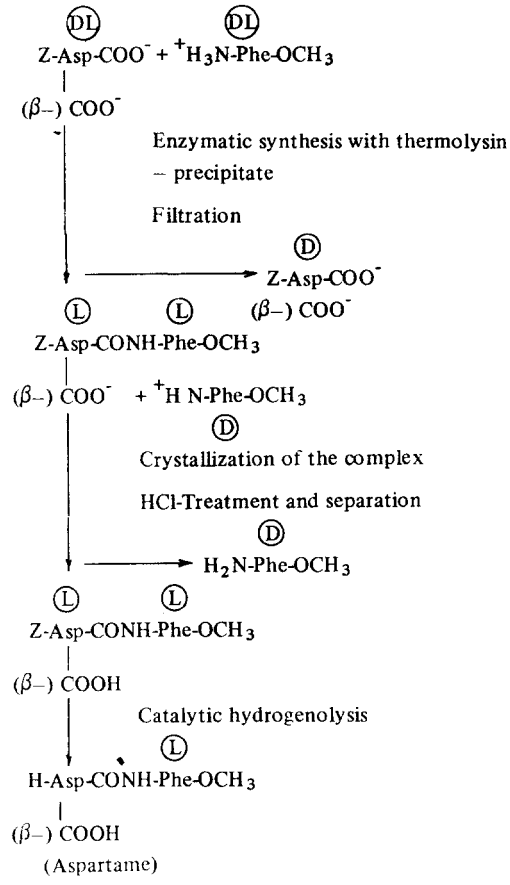


**Fig. 2. Thermolysin-catalyzed synthesis of L-$\alpha$-aspartame from benzyloxycarbonyl-D, L-aspartic acid and D,L-pheylalanine methylester**

the industrial production of APM because of the extremely low yields.[64] Almost all of the syntheses so far reported used endoproteinases. If exopeptidases could be ued, further advantages over chemical methods might be gained because two steps to protect the substrate and remove the protecting group after condensation would not be needed. However, in that case, there may exist a problem of how to shift the equilibrium toward the synthetic side. Superactivation of thermolysin through chemical modification[65-67] can increase the activity up to a factor of 400, and which, in turn, can contribute to the increase of productivity of the process. Stable and continuous supply of the enzyme at low price is an another point to be solved. The source microorganism of thermolysin is a thermophile, *Bacillus thermoproteolyticus rokko*, but the yield of the thermolysin is relatively low.

The companies with the most efficient processes for the production of APM will be able to hold much of the vast demand. The authors are being under the investigation to find another commercially advantageous process.

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# 아스파탐—총설

한대석 · 신현경
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아스파탐(N-*α*-L-aspartyl-L-phenylalanine-methyl ester)은 아스파르트산과 메칠 페닐알라닌의 펩티드결합 화합물로서 설탕의 180~200배의 감미도를 가지고 있으며 감미의 성상이 비교적 설탕에 유사하고 충치원인균에 의해서 발효가 되지 않으므로 새로운 설탕의 대체품으로서 국내외적으로 그 소비량이 급증하고 있다. 본고에서는 아스파탐의 감미도와 감미성상, 화학적 안정성과 위생적인 안전성에 대해서 살펴보고 각종 식품에서의 이용현황을 조사하였다. 그리고 현재 사용되고 있는 화학적 합성법을 소개하고 아울러 생산수율이나 제조공정상 화학적 합성법보다 유리할 것으로 생각되는 효소적 합성 방법에 대한 연구현황 및 가능성에 대해서 개략적으로 서술하였다.