

1 Nonproprietary Names

BP: Aspartame

PhEur: Aspartame

USP-NF: Aspartame

2 Synonyms

(3S)-3-Amino-4-[[[(1S)-1-benzyl-2-methoxy-2-oxoethyl]amino]-4-oxobutanoic acid; 3-amino-*N*-(α -carboxyphenethyl)succinamic acid *N*-methyl ester; 3-amino-*N*-(α -methoxycarbonylphenethyl)succinamic acid; APM; aspartamum; aspartyl phenylamine methyl ester; *Canderel*; E951; *Equal*; methyl *N*-L- α -aspartyl-L-phenylalaninate; *NutraTaste*; *NutraSweet*; *Pal Sweet*; *Pal Sweet Diet*; *Sanecta*; SC-18862; *Tri-Sweet*.

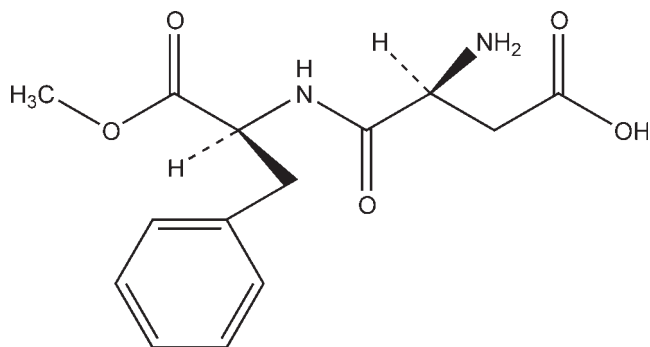
3 Chemical Name and CAS Registry Number

N-L- α -Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

4 Empirical Formula and Molecular Weight

C₁₄H₁₈N₂O₅ 294.30

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets,^(1,2) powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal). However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect.

8 Description

Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

SEM 1: Excipient: aspartame; magnification: 70 \times ; voltage: 3 kV.



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for aspartame.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Conductivity	$\leq 30 \mu\text{S}/\text{cm}$	—
Specific optical rotation	$+14.5^\circ$ to $+16.5^\circ$	$+14.5^\circ$ to $+16.5^\circ$
Related substances	+	—
Heavy metals	$\leq 10 \text{ ppm}$	$\leq 0.001\%$
Loss on drying	$\leq 4.5\%$	$\leq 4.5\%$
Residue on ignition	—	$\leq 0.2\%$
Sulfated ash	$\leq 0.2\%$	—
Impurities	+	—
Transmittance	—	+
Limit of 5-benzyl-3,6-dioxo-2-piperazineacetic acid	—	$\leq 1.5\%$
Chromatographic purity	—	+
Assay	98.0–102.0%	98.0–102.0%

10 Typical Properties

Acidity/alkalinity pH = 4.5–6.0 (0.8% w/v aqueous solution)

Brittle fracture index 1.05⁽³⁾

Bonding index

0.8×10^2 (worst case)⁽³⁾

2.3×10^2 (best case)⁽³⁾

Flowability 44% (Carr compressibility index)⁽³⁾

Density (bulk)

0.5–0.7 g/cm³ for granular grade;

0.2–0.4 g/cm³ for powder grade;

0.17 g/cm³ (Spectrum Quality Products).⁽³⁾

Density (tapped) 0.29 g/cm³ (Spectrum Quality Products)⁽³⁾

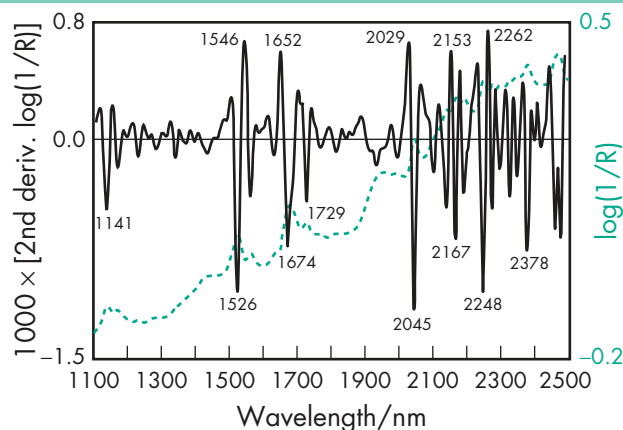


Figure 1: Near-infrared spectrum of aspartame measured by reflectance.

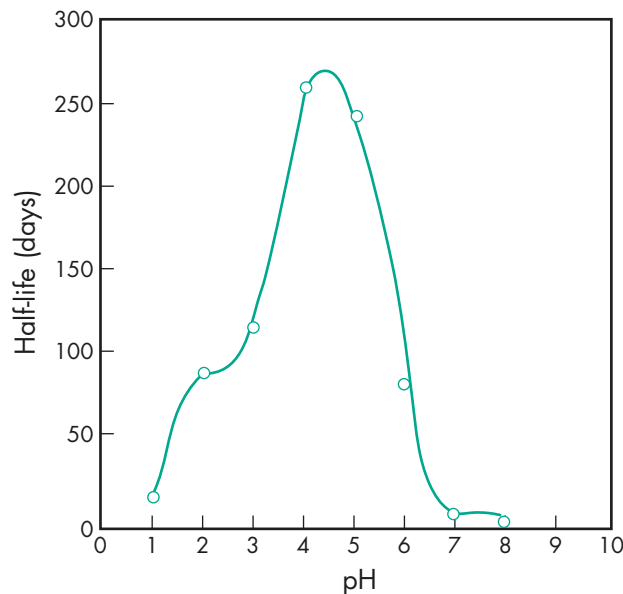


Figure 2: Stability profile of aspartame in aqueous buffers at 25°C.⁽⁸⁾

Density (true) 1.347 g/cm³

Effective angle of internal friction 43.0°⁽³⁾

Melting point 246–247°C

NIR spectra see Figure 1.

Solubility Slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C the solubility is 1% w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 20°C solubility is 10% w/v.

Specific rotation $[\alpha]_D^{22} = -2.3^\circ$ in 1 N HCl

11 Stability and Storage Conditions

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine with a resulting loss of sweetness. A third-degradation product is also known, β-L-aspartyl-L-phenylalanine methyl ester. For the stability profile at 25°C in aqueous buffers, see Figure 2.

Stability in aqueous solutions has been enhanced by the addition of cyclodextrins,^(4,5) and by the addition of polyethylene glycol 400 at pH 2.⁽⁶⁾ However, at pH 3.5–4.5 stability is not enhanced by the replacement of water with organic solvents.⁽⁷⁾

Aspartame degradation also occurs during prolonged heat treatment; losses of aspartame may be minimized by using processes

that employ high temperatures for a short time followed by rapid cooling.

The bulk material should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate.⁽⁹⁾ Reactions between aspartame and sugar alcohols are also known.

13 Method of Manufacture

Aspartame is produced by coupling together L-phenylalanine (or L-phenylalanine methyl ester) and L-aspartic acid, either chemically or enzymatically. The former procedure yields both the sweet α-aspartame and nonsweet β-aspartame from which the α-aspartame has to be separated and purified. The enzymatic process yields only α-aspartame.

14 Safety

Aspartame is widely used in oral pharmaceutical formulations, beverages, and food products as an intense sweetener, and is generally regarded as a nontoxic material. However, the use of aspartame has been of some concern owing to the formation of the potentially toxic metabolites methanol, aspartic acid, and phenylalanine. Of these materials, only phenylalanine is produced in sufficient quantities, at normal aspartame intake levels, to cause concern. In the normal healthy individual any phenylalanine produced is harmless; however, it is recommended that aspartame be avoided or its intake restricted by those persons with phenylketonuria.⁽¹⁰⁾

The WHO has set an acceptable daily intake for aspartame at up to 40 mg/kg body-weight.⁽¹¹⁾ Additionally, the acceptable daily intake of diketopiperazine (an impurity found in aspartame) has been set by the WHO at up to 7.5 mg/kg body-weight.⁽¹²⁾

A number of adverse effects have been reported following the consumption of aspartame,^(10,12) particularly in individuals who drink large quantities (up to 8 liters per day in one case) of aspartame-sweetened beverages. Reported adverse effects include: headaches;⁽¹³⁾ grand mal seizure;⁽¹⁴⁾ memory loss;⁽¹⁵⁾ gastrointestinal symptoms; and dermatological symptoms. However, scientifically controlled peer-reviewed studies have consistently failed to produce evidence of a causal effect between aspartame consumption and adverse health events.^(16,17) Controlled and thorough studies have confirmed aspartame's safety and found no credible link between consumption of aspartame at levels found in the human diet and conditions related to the nervous system and behavior, nor any other symptom or illness. Aspartame is well documented to be nongenotoxic and there is no credible evidence that aspartame is carcinogenic.⁽¹⁸⁾

Although aspartame has been reported to cause hyperactivity and behavioral problems in children, a double-blind controlled trial of 48 preschool-age children fed diets containing a daily intake of 38 ± 13 mg/kg body-weight of aspartame for 3 weeks showed no adverse effects attributable to aspartame, or dietary sucrose, on children's behavior or cognitive function.⁽¹⁹⁾

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Measures should be taken to minimize the potential for dust explosion. Eye protection is recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe and in the USA. Included in the FDA Inactive Ingredients Database (oral powder for reconstitution, buccal patch, granules, syrups, and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Alitame; aspartame acesulfame; neotame.

Aspartame acesulfame

Empirical formula $C_{18}H_{23}O_9N_3S$

Molecular weight 457.46

CAS number 106372-55-8

Comments A compound of aspartame and acesulfame approx. 350 times sweeter than sucrose. Aspartame acesulfame is listed in the USP32–NF27.

18 Comments

The intensity of sweeteners relative to sucrose depends upon their concentration, temperature of tasting, and pH, and on the flavor and texture of the product concerned.

Intense sweetening agents will not replace the bulk, textural, or preservative characteristics of sugar, if sugar is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported, e.g. aspartame with acesulfame potassium.

Aspartame can cause browning when used at high temperatures.

A specification for aspartame is contained in the Food Chemicals Codex (FCC).⁽²⁰⁾

The PubChem Compound ID (CID) for aspartame includes 2242 and 21462246.

19 Specific References

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- Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 69.

20 General References

- Marie S. Sweeteners. Smith J, ed. *Food Additives User's Handbook*. Glasgow: Blackie, 1991; 47–74.
- Roy GM. Taste masking in oral pharmaceuticals. *Pharm Technol Eur* 1994; 6(6): 24, 26–2830–3234, 35.
- Stegink LD, Filer LJ, eds. *Aspartame, Physiology and Biochemistry*. New York: Marcel Dekker, 1984.

21 Author

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22 Date of Revision

18 February 2009.

1 Nonproprietary Names

BP: Attapulgate

2 Synonyms

Actapulgate; *Attaclay*; *Attacote*; *Attagel*; attapulgis; palygorskite; palygorskite; *Pharmsorb Regular*.

3 Chemical Name and CAS Registry Number

Attapulgate [12174-11-7]

4 Empirical Formula and Molecular Weight

Attapulgate is a purified native hydrated magnesium aluminum silicate consisting of the clay mineral palygorskite, with the empirical formula $\text{Mg}(\text{Al}_{0.5-1}\text{Fe}_{0-0.5})\text{Si}_4\text{O}_{10}(\text{OH}) \cdot 4\text{H}_2\text{O}$.

5 Structural Formula

See Section 4.

6 Functional Category

Adsorbent.

7 Applications in Pharmaceutical Formulation or Technology

Attapulgate is widely used as an adsorbent in solid dosage forms. Colloidal clays (such as attapulgate) absorb considerable amounts of water to form gels and in concentrations of 2–5% w/v usually form oil-in-water emulsions. Activated attapulgate, which is attapulgate that has been carefully heated to increase its absorptive capacity, is used therapeutically as an adjunct in the management of diarrhea.

8 Description

Attapulgate occurs as a light cream colored, very fine powder. Particle size ranges depend on the grade and manufacturer.

9 Pharmacopeial Specifications

See Table I. See also Section 17.

Table I: Pharmacopeial specifications for attapulgate.

Test	BP 2009
Identification	+
Characters	+
Acidity or alkalinity (5% w/v aqueous suspension)	7.0–9.5
Adsorptive capacity	5–14%
Arsenic	≤ 8 ppm
Heavy metals	≤ 20 ppm
Acid-insoluble matter	≤ 12.5%
Water-soluble matter	≤ 0.5%
Loss on drying	≤ 17.0%
Loss on ignition	15.0–27.0%

10 Typical Properties

Acidity/alkalinity pH = 9.5 (5% w/v aqueous suspension)

Angle of repose 37.2–45.2°⁽¹⁾

Density 2.2 g/cm³

Density (tapped) 0.33 g/cm³ ⁽¹⁾

Flowability 20.9–29.6% (Carr compressibility index)⁽¹⁾

Particle size distribution

<2 μm in size for powder;

2–5 μm in size for aggregate.⁽¹⁾

11 Stability and Storage Conditions

Attapulgate can adsorb water. It should be stored in an airtight container in a cool, dry, location.

12 Incompatibilities

Attapulgate may decrease the bioavailability of some drugs such as loperamide⁽²⁾ and riboflavin.⁽³⁾ Oxidation of hydrocortisone is increased in the presence of attapulgate.⁽⁴⁾

13 Method of Manufacture

Attapulgate occurs naturally as the mineral palygorskite.

14 Safety

Attapulgate is widely used in pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. It is not absorbed following oral administration. In oral preparations, activated attapulgate up to 9 g is used in daily divided doses as an adjunct in the management of diarrhea.⁽⁵⁾

LD₅₀ (rat, IP): 0.34 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended. Attapulgate should be handled in a well-ventilated environment and dust generation should be minimized. When heated to decomposition, attapulgate emits acrid smoke and irritating fumes.

16 Regulatory Status

Included in nonparenteral medicines licensed in a number of countries worldwide including the UK and USA.

17 Related Substances

Activated attapulgate; magnesium aluminum silicate.

Activated attapulgate

Comments Activated attapulgate is a processed native magnesium aluminum silicate that has been carefully heated to increase its adsorptive capacity. Monographs for activated attapulgate are included in the BP 2009, USP 32, and other pharmacopeias. The USP 32 also includes a monograph for colloidal activated attapulgate.

18 Comments

The EINECS number for attapulgate is 302-243-0.

19 Specific References

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