WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.632
Volume 9, Issue 2, 195-201 Review Article ISSN 2278 – 4357

ASPARTAME SWEETENER

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Article Received on
13 Dec. 2019,

Revised on 02 Jan. 2020,
Accepted on 24 Jan. 2020

DOI: 10.20959/wjpps20202-15435

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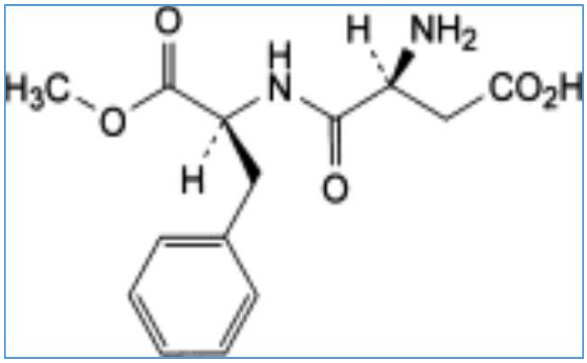
ABSTRACT

Artificial sweeteners have increasingly become an area of controversy in the world of food and nutrition. Consumers are oftenly barraged with a number of contradictory opinions and reports regarding the safety and efficacy of sweeteners. Artificial sweetener consumption may cause migraines or headache, skin eruptions, muscle dysfunction, depression, weight gain, liver and kidney effects, multiple sclerosis and blurred vision. On the other hand natural sweeteners like stevia and its products are safe and do not cause any health problem. Therefore, it is important for the consumer to choose sweeteners with great care. Aspartame (APM)) is composed of methyl ester of the dipeptideL-L-aspartyl-L-phenylalanine with molecular weight of 294.3 and a source of 4 kcal/g of energy (Food and Drug Administration, 2006).

INTRODUCTION

General Notices (Ph Eur monograph 0973) [(1)]

Structural Formula



General Formula and	$C_{14}H_{18}N_2O_5$	294.3	53906-69-7

Molecular Weight	
Action And Use	Sweetening agent.
Definition	(3S)-3-Amino-4-[[(1S)-1-benzyl-2-methoxy-2-oxoethyl] amino]-4-oxobutanoic acid.
Content	98.0 per cent to 102.0 per cent (dried substance).
Toxicity	Fingernail polish (dry), Rust.
Raw Materials	L-Phenylalanine Methyl Ester HCI N-Benzyloxycarbonyl-L-aspartic acida-p-nitrophenyl, β benzyl Diester[12] Hydrogen

Characters

In 1965:[14,19,21] James M. Schlatter, American chemist, combines two amino acids and obtains a sweet-tasting substance. This chemical is about 200 times[23] sweeter than sugar and is named aspartame. In 1983, it is approved for use in carbonated beverages. It becomes the most widely used artificial sweetener.[14-15-16-17]

Aspartame is a very low-calorie sweetener. It is made by joining two amino acids, aspartic acid and the methyl ester of phenylalanine.[23,24]

Appearance

White or almost white, slightly hygroscopic, crystalline powder.[1]

Solubility

Sparingly soluble or slightly soluble in water and in ethanol (96%), practically insoluble in hexane and in methylene chloride.[1,2]

Pharmacokinetics

Aspartame is hydrolysed in the gastrointestinal tract to its 3 primary constituents, methyl alcohol, aspartic acid, and phenylalanine.[2]

SAFETY

Adverse Effects and Precautions[2]

Patients with phenylketonuria should avoid[10,13] excessive use of aspartame since one of its metabolic products is phenylalanine.[20] Aspartame's sweetness is lost during prolonged cooking.

Aspartame hydrolysed in the gastrointestinal tract to methyl alcohol, aspartic acid, and phenylalanine.[12] However, even with extraordinary consumption, methyl alcohol toxicity stemming from aspartame use is extremely unlikely. Aspartate concentrations in blood do not rise significantly after a very large dose (50 to 100 mg/kg) and therefore toxicity related to aspartate is not expected to occur. Despite the similarity of aspartate to glutamate, studies in glutamate-sensitive persons have shown that they are not affected by aspartame consumption. Plasma concentrations of phenylalanine are also unlikely to be markedly elevated after modest consumption of aspartame by healthy persons but persons with phenylketonuria should avoid or limit their use of aspartame.[2,8,12,13,15,18]

A number of adverse effects have been reported after the use of aspartame; Most frequently reported problems have been headache, neuropsychiatric or behavioral symptoms, seizures, gastrointestinal symptoms, and hypersensitivity[22] or dermatological symptoms.[10,13] Available data do not provide evidence for serious widespread health consequences attendant upon the use of aspartame but it would appear that certain individuals might have an unusual sensitivity to the product. A safety review by the European Commission Scientific Committee on Food (ECSCF) concluded that no causal link could be established between the consumption of aspartame and the occurrence of epilepsy or seizures[10], or cognition, mood and behavior; this included individuals considered sensitive to aspartame.

An increased incidence of brain cancer was postulated to be related to aspartame use in one report; however, the FDA and the ECSCF maintained that the available evidence did not support an association. Multiple malignancies have been reportedin rats given doses lower than the current acceptable daily intake of 40 or 50 mg/kg. The European Food Safety Authority assessed this study and concluded, based on all current available evidence, that the increased incidence of cancers in the rats was unrelated to aspartame treatment, and that there was no need to further review the safety of aspartame, nor to revise the established acceptable daily intake for aspartame of 40 mg/kg.[2]

Breast-feeding

Aspartame 50 mg/kg given orally to healthy women resulted in small but significant increases in breast milk aspartate, phenylalanine, and tyrosine concentrations. However, it was noted that these levels were similar to postprandial milk samples and were unlikely to impact upon total amounts of amino acids ingested by the infant. Furthermore, the dose of

aspartame given in the study was considerably higher than the projected intake of about 7.5 to 8.5 mg/kg daily, assuming all sucrose intake were replaced by aspartame, and no aspartame abuse. Nonetheless, the American Academy of Pediatrics considers that caution is required when mothers ingest aspartame[3,4,5] where either the mother or breast-fed infant has phenylketonuria.[2,13,15]

Sickle-cell Disease

There is some preliminary evidence that aspartame may have beneficial effects in sickle-cell disease.[2]

Toxicity

Aspartame are virtually nontoxic in small to moderate exposures can caused Fingernail polish (dry) and Rust.[7]

Concern regarding possible carcinogenic effects of aspartame has mainly focussed upon tumours of the bladder and brain. The issue of bladder carcinogenesis arose mainly by analogy with saccharin, which is known to induce bladder tumours via a male rat specific mechanism involving 2- microglobulin. A number of epidemiological studies were conducted in the between the 1970s and the 1990s in an attempt to determine the relevance of these findings to humans; their results were variable but the majority did not indicate any increase in risk of bladder cancer in humans due to artificial sweetener consumption. None of these studies addressed aspartame directly and many of them were carried out in populations diagnosed before aspartame entered the market. The issue of brain tumour induction by aspartame arose partly because of the suggestion of increased brain tumour incidence in chronic rat studies and partly following the publication of a paper stating that an increase in brain tumour incidence in the USA had coincided with the release of aspartame. Subsequent epidemiological studies have not identified any association between brain tumour incidence and use of aspartame; indeed, studies of artificial sweetener use in which risks associated with saccharin and other sweeteners (presumed to represent mainly aspartame) are considered separately provide no evidence for an increased risk of any tumour type in humans.[25]

INTERACTION

Coumarins + Food

The rate of absorption of dicoumarol can be increased by food. Two reports describe antagonism of the effects of warfarin by ice cream, and another report attributes an increase

in prothrombin time to the use of aspartame. However, the most common food warfarin interaction is that due to foods containing vitamin K.[6]

Warfarin

A very brief report states that a patient taking warfarin had a raised prothrombin time, possibly due to the use of aspartame.[6]

Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent[9,16-20,22,23] in beverage products, food products, and in pharmaceutical preparations including tablets, 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.[2,13]

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).[2,21] However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect.[13]

Manufacturing Process

A solution of 88.5 parts of L-phenylalanine methyl ester hydrochloride in 100 parts of water is neutralized by the addition of dilute aqueous potassium bicarbonate then is extracted with approximately 900 parts of ethyl acetate. The resulting organic solution is washed with water and dried over anhydrous magnesium sulfate. To that, solution is then added 200 parts of N-benzyloxycarbonyl-L-aspartic acid α-p-nitrophenyl, βbenzyl diester, and that reaction mixture is kept at room temperature for about 24 hours, then at approximately 65°C for about 24 hours. The reaction mixture is cooled to room temperature, diluted with approximately 390 parts of cyclohexane, and then cooled to approximately -18°C in order to complete crystallization. The resulting crystalline product is isolated by filtration and dried to afford /β benzyl N-benzyloxycarbonyl-L-aspartyl-L-phenylalanine methyl ester, melting at about 118.5°-119.5°C.[11]

To a solution of 180 parts of β-benzyl N-benzyloxycarbonyl-L-aspartyl-L-phenylalanine methyl ester in 3,000 parts by volume of 75% acetic acid is added 18 parts of palladium black metal catalyst, and the resulting mixture is shaken with hydrogen at atmospheric pressure and room temperature for about 12 hours. The catalyst is removed by filtration, and the solvent is

distilled under reduced pressure to afford a solid residue, which is purified by recrystallization from aqueous ethanol to yield L-aspartyl-L-phenylalanine methyl ester. It displays a double melting point at about 190°C and 245°-247°C.[11]

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