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(54) Titre : CRISTAUX MELANGES COMPRENANT DE L'ASPARTAME ET UN DERIVE DE L'ASPARTAME, ET PROCEDE DE PRODUCTION ASSOCIE

(54) Title: MIXED CRYSTALS COMPRISING ASPARTAME AND ASPARTAME DERIVATIVE AND PROCESS FOR PRODUCING THE SAME

(57) Abrégé/Abstract:
There is provided a novel mixed crystal comprising aspartame (APM) and N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester, which can be used as a sweetener having considerably improved quality of sweetness , etc. The above mixed crystal can be easily produced industrially by subjecting a solution containing the above-mentioned APM and APM derivative to a crystallizing operation followed by the separation of the mixed crystal thus precipitated.

ABSTRACT

There is provided a novel mixed crystal comprising aspartame (APM) and N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester, which can be used as a sweetener having considerably improved quality of sweetness , etc.

The above mixed crystal can be easily produced industrially by subjecting a solution containing the above-mentioned APM and APM derivative to a crystallizing operation followed by the separation of the mixed crystal thus precipitated.

SPECIFICATION

MIXED CRYSTALS COMPRISING ASPARTAME AND ASPARTAME DERIVATIVE AND PROCESS FOR PRODUCING THE SAME

TECHNICAL FIELD OF INVENTION

The present invention relates to a novel mixed crystal comprising aspartame (APM) and N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester and a process for production thereof.

BACKGROUND OF THE ART

In recent years, as eating habits have improved significantly, obesity, and related diseases, caused by excessive sugar intake have been at issue. Consequently, the development of a low-calorie sweetening agent (sweetener) that replaces sugar has been in demand. Aspartame (APM) is widely used as a sweetening agent because of its quality and safety. However, APM is somewhat unstable, which is a problem.

Under these circumstances, in the specification of French Patent No.2697844, it is stated that derivatives in which an alkyl group is introduced on the amino group of aspartic acid which constitutes the APM are being studied in one approach to slightly improve their stability and their sweetening potency. Among them N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester, hereinafter abbreviated to "N-(3,3-dimethylbutyl)-APM" and simply referred to as "APM derivative", has a markedly improved sweetening

potency. Two processes are known for the production of N-(3,3-dimethylbutyl)-APM, the first being a process for alkylating APM reductively using 3,3-dimethylbutylaldehyde with sodium cyanoborohydride in methanol (refer to FR 2697844 specification), and the second being a process for alkylating APM reductively using 3,3-dimethylbutylaldehyde, with platinum carbon as the catalyst in a mixed solvent of water and methanol at a pH value in the range of 4.5 to 5 (refer to the above-mentioned WO95/30689 specification).

The sweetening potencies of N-(3,3-dimethylbutyl)-APM as a high sweetness sweetener and APM as an amino acid based sweetener, are reported to be respectively 10,000 times by weight ratio (refer to Japanese Patent Kohyou Publication JP-A-8-503206) and about 200 times by weight ratio (refer to Japanese Patent Kokoku Publication JP-B-47-31031) that of sucrose.

The qualitative properties of sweetness for N-(3,3-dimethylbutyl)-APM are not reported in details, it is known, however, that such compound is extremely weak in early taste (which means that a sweetener when put in the mouth tastes sweet as early as sucrose), and extremely strong in later taste (which means that a sweetener tastes sweet later than sucrose), according to the present inventors' findings. It has a strong astringent taste and unbalanced in terms of the quality of sweetness when compared to sucrose. On the other hand the quality of sweetness for APM is also weak in early taste, and strong in later taste, although not as bad as those in N-(3,3-dimethylbuty)-APM. Therefore, both compounds have the property for quality of sweetness which is weak in early taste, and strong in later taste.

There are various proposals for improvement of the sweetness quality and they are mainly concerned with later taste (For example, refer to Japanese Patent Kokai Publication JP-A-56-148255, JP-A-58-141760, JP-A-58-220668, etc.). Among these proposals, there are found methods for obtaining a natural quality of sweetness closer to that of sucrose, for example, by combining a compound with sucrose (refer to Japanese Patent Kokai Publication JP-A-57-152862). On the other hand, it is possible to intensify early taste, and weaken later taste and astringency in order to balance the quality of sweetness by combining homogeneously and properly N-(3,3-dimethylbutyl)-APM as a high sweetness sweetener with APM as an amino acid based sweetener, according to the findings in the present invention. For example, by combining homogeneously and properly N-(3,3-dimethylbutyl)-APM, which is weak in early taste, with APM, it is improved in early taste and thereby is expected to give a sweetener a good balance in terms of quality of sweetness, closer to that of sucrose, as compared to N-(3,3-dimethylbutyl)-APM or APM alone.

The sweetening potency of N-(3,3-dimethylbutyl)-APM is 10,000 times by weight ratio (refer to Japanese Patent Kohyou Publication JP-A-8-503206) more than that of sucrose, and therefore it is problematic to adjust its sweetness while using it. Accordingly, a combination of N-(3,3-dimethylbutyl)-APM with APM as sweetener is expected to provide improvement in quality of sweetness, and uses thereof. Under these circumstances, it may be considered that an improvement in quality of sweetness based on these proper combinations is a problem to be solved at present.

OBJECT OF INVENTION

An object of the present invention is, in considering the properties in quality of sweetness present in APM and N-(3,3-dimethylbutyl)-APM described in the previous section, to provide an appropriate combination of APM with N-(3,3-dimethylbutyl)-APM which is improved in quality of sweetness, and thereby solving the above-mentioned problem.

DISCLOSURE OF INVENTION

In order to solve the problem and achieve the object of the present invention, the present inventors have studied earnestly and found out that a novel mixed crystal comprising N-(3,3-dimethylbutyl)-APM and aspartame (APM) can be obtained by subjecting a solution containing N-(3,3-dimethylbutyl)-APM and APM to crystallization, and further that such obtained mixed crystal can achieve the object of the invention, is homogeneous and can considerably improve the quality of sweetness, compared to a simple mixture of both crystals, obtained separately.

In one embodiment, there is provided a mixed crystal comprising N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L- phenylalanine methyl ester and aspartame.

In one embodiment, the invention provides a process for producing a mixed crystal comprising N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine methyl ester and aspartame, which comprises:

subjecting a solution containing N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine methyl ester and aspartame to a crystallizing

operation.

In a further embodiment, there is provided a sweetners comprising the mixed crystal of the invention and a carrier for sweeteners.

The powder X-ray diffraction pattern for the crystal of the present invention (CuKα-ray; and so forth) is the same pattern as that of APM alone (For example, the wet crystal is a crystal of type IA, and the dry crystal is a crystal of type IB, as seen in the Japanese Patent Kokoku Publication JP-B-6-31312). However, in the high performance liquid chromatography analysis of the crystals, N-(3,3-dimethylbutyl)-APM is detected. On the other hand, in the case of a mixture wherein the crystals of N-(3,3-dimethylbutyl)-APM and the crystals of APM are simply mixed, the x-ray diffraction pattern show peaks both crystals therefore (i.e. N-(3,3-dimethylbutyl)-APM and APM). However, since N-(3,3-dimethylbutyl)-APM is detected in the high performance liquid chromatography analysis, although the powder X-ray diffraction pattern therefor is the same pattern as that for APM alone, it has been found that the obtained crystal mentioned above is a novel mixed crystal comprising N-(3,3-dimethylbutyl)-APM and APM.

Further, it has been found that mixed crystal of the invention comprising APM and N-(3,3-dimethylbutyl)-APM can be easily obtained by subjecting a solution containing APM and N-(3,3-dimethylbutyl)-APM to crystallization in a crystallizing operation followed by the separation of the crystals precipitated.

Based on these findings, the present invention has been completed.

The present invention is directed to a novel mixed crystal comprising

at least N-(3,3-dimethylbutyl)-APM and APM, and also to a process for producing a novel mixed crystal comprising at least N-(3,3-dimethylbutyl)-APM and APM, which comprises:

subjecting a solution containing the compound N-(3,3-dimethylbutyl)-APM) and APM to a crystallizing operation.

Further, the present invention contains the followings:

The above mixed crystal, wherein said APM and said APM derivative is contained in a weight ratio of APM to said APM derivative being about 100 to 0.1 - 10, and preferably about 100 to 0.3 - 3 for a sweetener.

The crystals containing the mixed crystal or the crystals made of the mixed crystal under these ranges can be easily produced by properly selecting a condition for crystallization thereof when producing the same, as described herein.

A solvent used in said crystallization operation for the process for production of the mixed crystal, is water or an alcohol alone or a mixed solvent containing more than one solvent optionally mixed, the solvent being selected from the group consisting of alcohol and water.

In one aspect, crystallization uses ethyl alcohol and methyl alcohol.

In one aspect of process, a ratio of APM to N-(3,3-dimethylbutyl)-APM at the initial concentration contained in the solution for said crystallizing operation is 4 or more (no less than 4), preferably in particular 10 or more (no less than 10) by weight.

In one aspect of process, said crystallizing operation comprises the steps of: adjusting an initial concentration (APM) of the solution for crystallization so that APM is present in about 10 grams or more (no less than about 10 grams), preferably about 20 to 100 grams, per 1 liter of solvent in the solution containing APM which should be precipitated after cooling the solution, and cooling the solution through heat transfer by conduction without providing a flowing or movement by force (such as a mechanical stirring or the like thereto) so that a pseudo-solid phase like an ice-confection or an ice-sweet (sherbet) may be produced in an entire solution from appearances, to form the pseudo-solid phase.

In a further aspect, there is provided a sweetener comprising the above mixed crystal, or comprising the above mixed crystal and a carrier usable for sweeteners, and a process for imparting sweetness, comprising the step of: using the mixed crystal for a material requesting sweetness, such as foods, buccal hygiene products (dental rinse, mouth wash, etc.), oral pharmaceutical products for animals (including humans).

EMBODIMENTS OF INVENTION

The novel mixed crystal of the present invention can be used as a sweetener, and when the crystal is produced, known methods for crystallization as are applied and carried out for the crystallizing operation.

A mixed crystal comprising N-(3,3-dimethylbutyl)-APM and APM can be produced by subjecting a solution containing the compounds

N-(3,3-dimethylbutyl)-APM and APM, to the crystallizing operation for crystallization and separating thus precipitated mixed crystal.

For the solvent employed in the crystallizing operation, a suitable solvent may be selected for the crystallization by studying or considering a solubility thereof for both compounds.

Example of solvent include solvent selected from water, ethyl acetate, methyl acetate, acetic acid, toluene, hexane, tetrahydrofuran, acetonitrile, dimethoxyethane, ethyl ether, isopropyl alcohol, ethyl alcohol, methyl alcohol, dichloromethane, chloroform and 1,2-dichiloroethane and the like, and a mixed solvent containing two or more of those solvents.

In case where the solvent remaining in the end product cause a material or serious problem or question, in view of quality of the product, water or a mixture of water and alcohol-based solvent(s), such as ethyl alcohol, methyl alcohol and the like may be preferably employed.

For the starting material employed in the crystallizing operation, (i.e., a solution containing N-(3,3-dimethylbutyl)-APM and APM), any solution containing at those two compounds may be employed. For example, a slurry or a solution thereof obtained in a course of production of each individual compound may be mixed therewith and used as starting material. Also a slurry or a solution containing N-(3,3-dimethylbutyl)-APM and APM obtained in the course of production for the N-(3,3-dimethylbutyl)-APM may be employed.

Thus obtained solution may be subjected to usual or conventional crystallizing operation for the crystallization, such as crystallization by cooling, crystallization by concentration, crystallization by neutralization. to obtain the mixed crystal of APM and N-(3,3-dimethylbutyl)-APM. In case there is much

APM therein, since it is known that minute or refined crystals may be formed under stirring the solution, it is preferable to subject the solution to crystallization under standing (static crystallization) or to crystallization under stirring, if required, following the crystallization under standing, in order to restrain a formation of minute crystals. On crystallization thereof under standing (static crystallization), the method for adjusting or controlling an initial concentration of the solution for crystallization so that APM therein may exist in about 10 grams or more, preferably about 20 to 100 grams, per 1 liter of the solvent in the solution containing APM which may be precipitated when cooling the solution, and cooling the solution through conductive heat transfer by conduction without giving the flowing or movement by force such as mechanical stirring or the like thereto so that a pseudo-solid phase like an ice-confection or an ice-sweet (sherbet) may be produced in an entire solution from appearances, to form the pseudo-solid phase, as described in Japanese Patent Kokoku Publication JP-B-03-025438, may be employed.

A complete mixed crystal does not form if the initial concentrations of APM and N-(3,3-dimethylbutyl)-APM in the solution subjected to the crystallizing operation, is in a ratio that is not 4 or more by weight. The ratio of APM to N-(3,3-dimethylbutyl)-APM to be employed preferably, may be no less than 4, more preferably no less than 10 by weight.

Advantageously, the mixed crystal is an homogeneously mixed form in comparison to a mixture obtained by mixing crystals of N-(3,3-dimethylbutyl)-APM with crystals of APM, each separately produced.

In relation to the sherbet or the slurry obtained in the crystallization, the end product can be obtained by subjecting the same to separation of a

solid material from a liquid, drying the solid material, and further granulating them, if required.

Examples of methods for the separation of a solid material from a liquid include a filtration and a centrifugation. Examples of methods for drying include vacuum dryer, fluidized-bed dryer, spray dryer, micron dryer and the like. Methods for granulation include, for example, a dry granulation, a wet granulation and the like. However, they are not limited to those exemplified.

There is no difficulty, when the mixed crystal obtained in the present invention may be used for a sweetener or production thereof. For example, it can be easily conducted by applying known methods for production of sweeteners or for use thereof in such case.

PREFERRED EMBODIMENTS

The present invention is further illustrated specifically by referring to the following examples and comparative example.

[EXAMPLE 1]

APM (15.6 g, 0.051 mol) in the water content of 3.9 % by weight and N-(3,3-dimethylbutyl)-APM (0.06 g, 0.15 mmol) in the water content of 5.5 % by weight were added to water (300 ml) and heated at 70°C for 1 hour to be dissolved. The concentration of APM and N-(3,3-dimethylbutyl)-APM in the solution were 5.2 g and 0.02 g per 100 ml of the solution respectively, the ratio of APM to N-(3,3-dimethylbutyl)-APM being 260 in the initial concentration. The solution was subjected to crystallization at 5°C for 3 hours under standing to prepare a sherbet (a sherbet-like material. The sherbet was stirred overnight to a slurry and was subjected to resolution of super saturation. The

slurry was filtrated through a filter paper of 1μm to separate wet crystals from the mother liquor. The wet crystals were dried under reduced pressure at 50 □ overnight to obtain 13.2 g of the dried crystals in the water content of 3.4 % by weight (APM: 97.4 weight %; N-(3,3-dimethylbutyl)-APM: 0.2 weight % as determined by the high performance liquid chromatography). The powder X-ray diffraction pattern (CuKα-ray) showed one type IB crystal.

[EXAMPLES 2 to 11]

The aqueous solutions containing APM and N-(3,3-dimethylbutyl)-APM described in the table 1 were subjected to the crystallizing operation. The compositions of solution for crystallization and the compositions of the dried crystals obtained are shown in table 1. All crystal thus obtained was in the form of the mixed crystal.

[Table 1]
Compositions of Solution for Crystallization and Compositions of Dried Crystals Obtained:

Example No.	Concentration of Solution for Crystallization [g/dl]		Ratio of APM to N-(3,3-dimethylbutyl)-APM in Initial Concentration	Composition of Dried Crystals [weight %]		
	APM	N-(3,3-dimethylbutyl)-APM		APM	N-(3,3-dimethylbutyl)-APM	Water
2	4.87	0.05	97	93.1	0.6	2.9
3	4.74	0.09	53	92.8	1.0	3.6
4	5.05	0.50	10	87.7	4.7	3.8
5	4.99	0.98	5	90.4	7.3	3.0

6	5.08	1.31	4	87.5	9.5	3.4
7	4.17	0.05	83	95.4	0.7	3.1
8	4.15	0.10	42	93.8	1.4	3.0
9	3.63	0.04	91	97.3	0.8	2.9
10	3.54	0.10	35	93.3	1.6	2.9
11	2.07	0.05	41	94.7	1.1	3.5
12	2.06	0.10	21	92.3	2.0	3.8

[COMPARATIVE EXAMPLE 1]

APM (5.31 g, 0.017 mol) in the water content of 3.9 % by weight and N-(3,3-dimethylbutyl)-APM (1.76 g, 4 mmol) in the water content of 5.5 % by weight were added to water (100 ml) and heated at 70°C for 1 hour to be dissolved. The concentration of APM and N-(3,3-dimethylbutyl)-APM thus dissolved in the solution were 5.1 g and 1.7 g per 100 ml of the solution respectively, the ratio of APM to N-(3,3-dimethylbutyl)-APM being 3 in the initial concentration. The solution was subjected to crystallization at 5°C overnight while standing to resolve super saturation. The crystals were filtrated through a filter paper of 1 μm to separate wet crystals from the mother liquor. The wet crystals were dried under reduced pressure at 50°C overnight to obtain 13.2 g of the dried crystals in the water content of 6.75 % by weight (APM: 80.0 weight %; N-(3,3-dimethylbutyl)-APM: 9.0 weight % as determined by high performance liquid chromatography). The powder X-ray diffraction pattern (CuKα-ray) did not show one type IB crystal.

EFFECTS OF INVENTION

The novel mixed crystal comprising N-(3,3-dimethylbutyl)-APM and APM obtained in the present invention, can be used as a sweetener having considerably improved quality of sweetness. The mixed crystal can provide a homogeneous and high quality sweetener in comparison with that obtained by producing separate crystals of N-(3,3-dimethylbutyl)-APM and APM and mixing the two crystals together.

The novel mixed crystal in the present invention can be easily produced industrially by subjecting a solution containing two kinds of the above-mentioned compounds to a conventional crystallizing operation followed by the separation of the mixed crystal thus precipitated.

CLAIMS

1. A mixed crystal comprising N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine methyl ester and aspartame.

2. The mixed crystal as defined in claim 1, wherein a ratio of said aspartame to said N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine methyl ester contained is 100 to 0.1 - 10 by weight.

3. A process for producing a mixed crystal comprising N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine methyl ester and aspartame, which comprises:

subjecting a solution containing N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine methyl ester and aspartame to a crystallizing operation.

4. The process as defined in claim 3, wherein said crystallizing operation is performed in water, alcohol or a mixture of water and alcohols.

5. The process as defined in claim 4, wherein said alcohol is ethyl alcohol and methyl alcohol.

6. The process as defined in claim 3, wherein an initial ratio of aspartame to N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine methyl ester contained in the solution for said crystallizing operation is 4 or more by

weight.

7. The process as defined in any one of claims 3 to 6, which comprises: adjusting an initial concentration of the solution for said crystallizing operation so that aspartame is in an amount of about 10 grams or more per 1 liter of solvent present in the solution containing said aspartame and cooling said solution through heat transfer by conduction without giving a forced fluidization thereto so that a pseudo-solid phase is produced in an entire solution from appearances, to form the pseudo-solid phase.

8. A sweetener comprising the mixed crystal as defined in claim 1 or 2 and a carrier for sweeteners.