AMENDED

AUSTRALIAN PATENT OFFICE Reg 76(3)

FORM 1

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A PATENT 603122

We TOSOH CORPORATION
of 4560, Oaza-Tonda, Shin-nanyo-shi, Yamaguchi-ken, Japan
hereby apply for the grant of a patent for an invention entitled:

"PROCESS FOR PRODUCING STABLE α-L-ASPARTYL-L-PHENYLALANINE METHYL ESTER"

which is described in the accompanying complete specification.

This application is a Convention Application and is based on the application(s) numbered: 188661/1986
for a patent or similar protection made in Japan
on 13th August, 1986.

Our address for service is C/- GRIFFITH HASSEL & FRAZER
71 YORK STREET
SYDNEY NSW 2000
AUSTRALIA

DATED this 18th day of April, 1988

TOSOH CORPORATION
By their Patent Attorneys

GRIFFITH HASSEL & FRAZER

TO: THE COMMISSIONER OF PATENTS,
COMMONWEALTH OF AUSTRALIA.

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 20 - 8 - 90

2326A/bm

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952 (AS AMENDED)

DECLARATION IN SUPPORT OF AN APPLICATION FOR A PATENT

(Name of applicant) In support of an Application made by:
Toyo Soda Manufacturing Co., Ltd.

(Title) for a patent for an invention entitled:
PROCESS FOR PRODUCING STABLE α-L-ASPARTYL-L-PHENYLALANINE METHYL ESTER

(Full name of signatory) I, Haruo Nakatani, Executive Vice President

(Address of signatory) of Toyo Soda Manufacturing Co., Ltd.
No. 4560, Oaza-tonda, Shin-nanyo-shi, Yamaguchi-ken, Japan

do solemnly and sincerely declare as follows:

1. I am authorised by the above mentioned applicant for the patent to make this Declaration on its behalf.

2. The name and address of each actual inventor of the invention is as follows:
(Insert details of inventor/s) Hidetoshi Wakamatsu, Shigeaki Irino, Tsuneo Harada, Akira Tokuda and Kiyotaka Oyama
of No. 2575, Oaza-tonda, Shin-nanyo-shi, Yamaguchi-ken, Japan,
No. 288, Oaza-hiraomura, Hirao-cho, Kumage-gun, Yamaguchi-ken, Japan,
No. 1774-14, Oaza-fukukawa, Shin-nanyo-shi, Yamaguchi-ken, Japan,
6-1, Madokoro 4-chome, Shin-nanyo-shi, Yamaguchi-ken, Japan and
15-12, Nijigaoka 7-chome, Hikari-shi, Yamaguchi-ken, Japan, respectively

(Insert details of assignment, etc.) and the fact(s) upon which the applicant is entitled to make this application are as follows:
The applicant is the assignee of the said invention from the said inventors

(Delete paragraphs 3 [illegible] Convention application) 3. The basic application(s) as defined by Section 141 of the Act was(were) made as follows:

Country Japan on August 13, 1986
in the name(s) Toyo Soda Manufacturing Co., Ltd.
and in ..... on .....
in the name(s) .....
and in ..... on .....
in the name(s) .....

4. The basic application(s) referred to in the preceding paragraph of this Declaration was(were) the first application(s) made in a Convention country in respect of the invention the subject of this application.

(Place and date of signing) Declared at Yamaguchi-ken, Japan this 23rd day of July, 1987

Signed: Haruo Nakatani
Position: Haruo Nakatani, Executive Vice President
Toyo Soda Manufacturing Co., Ltd.

GRIFFITH HASSEL & FRAZER, P.O. BOX 2133, G.P.O., SYDNEY, N.S.W. 2001
AUSTRALIA

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STABLE ASPARTAME

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(56) Prior Art Documents
AU 76820/87 C07K 005/06
AU 76819/87 C07K 005/06
AU 76147/87 C07K 005/06

(57) Aspartame has two types of crystal forms i.e. I and II types. The I type crystals are hygroscopic, and they are likely to undergo color change or decomposition during storage. Whereas, the II type crystals are less hygroscopic, and it has been taught that they have good flowability and storage stability.

It is an object of the present invention to solve such problems and to provide a process for producing Aspartame having excellent storage stability without requiring high temperature drying and redrying as required in the conventional processes.

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CLAIM

1. A process for producing stable α-L-aspartyl-L-phenylalanine methyl ester, which comprises heat-treating crystals of α-L-aspartyl-L-phenylalanine methyl ester having a water content of from 5 to 15% by weight based on wet crystals, at a temperature in the range from 50°C and lower than 80°C for at least 30 minutes.

3. The process according to Claim 1, wherein the crystals of α-L-aspartyl-L-phenylalanine methyl ester having a water content of from 5 to 15% by weight, are granulated by a granulator prior to the heat treatment.

5. The process according to Claim 1, wherein the crystals of α-L-aspartyl-L-phenylalanine methyl ester having a water content of from 5 to 15% by weight, are not treated by granulator.

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COMPLETE SPECIFICATION

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Related Art:

TO BE COMPLETED BY APPLICANT

AUSTRALIAN Reg 76(3) PATENT OFFICE

Name of Applicant: TOSOH CORPORATION. ~~TOYO SODA MANUFACTURING CO., LTD.~~

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Actual Inventor: Hidetoshi Wakamatsu; Shigeaki Irino; Tsuneo Harada; Akira Tokuda and Kiyotaka Oyama

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Complete Specification for the invention entitled:

PROCESS FOR PRODUCING STABLE α–L–ASPARTYL–L–PHENYLALANINE METHYL ESTER

The following statement is a full description of this invention, including the best method of performing it known to me/us:–
0962A:rk

Our Ref.: TS-230

PROCESS FOR PRODUCING STABLE α-L-ASPARTYL-L-PHENYLALANINE METHYL ESTER

The present invention relates to a process for producing α-L-aspartyl-L-phenylalanine methyl ester (hereinafter referred to as Aspartame) having excellent storage stability.

Aspartame has two types of crystal forms i.e. I and II types. The I type crystals are hygroscopic, and they are likely to undergo color change or decomposition during storage. Whereas, the II type crystals are less hygroscopic, and it has been taught that they have good flowability and storage stability.

Heretofore, a method has been proposed wherein wet Aspartame crystals are dried at a temperature of at least 80°C to obtain the II type crystals of Aspartame (Japanese Unexamined Patent Publications No. 172441/1984 and No. 37949/1985), or a method for preparing granules has been known in which dried II type crystals are hydrated to have a water content of from 35 to 45% by weight, followed by extrusion granulation and drying

again (Japanese Unexamined Patent Publication No. 95862/1984).

In the conventional processes, crystals are dried at a high temperature to obtain the II type crystals, and it is likely that a decomposition product of Aspartame i.e. a diketopiperadine derivative, is likely to form. Further, in order to obtain granules, a dried product of the II type crystals of Aspartame is required to be hydrated once, followed by granulation and drying again, such being disadvantageous from the viewpoint of the process control and a cost for energy.

It is an object of the present invention to solve such problems and to provide a process for producing Aspartame having excellent storage stability without requiring high temperature drying and redrying as required in the conventional processes.

The present inventors have conducted extensive research to solve the above-mentioned problems, and have found it possible to obtain stable II type crystals of Aspartame by heating I type crystals of Aspartame in a specific range of the water content without requiring high temperature drying or redrying.

Thus, the present invention provides a process for producing stable α-L-aspartyl-L-phenylalanine methyl ester, which comprises heat-treating crystals of α-L-aspartyl-L-phenylalanine methyl ester having a water content of from 5 to 15% by weight based on wet crystals,

at a temperature in the range from 50°C and lower than 80°C for at least 30 minutes.

Throughout the specification stable aspartame means that the aspartame comprises at least 70% of type II crystals.

Now, the present invention will be described in detail with reference to the preferred embodiments.

The wet Aspartame crystals prior to drying in accordance with the process of the present invention may be prepared by any precipitation and separation methods. There is no restriction as to the method for the preparation of the wet Aspartame crystals.

The wet Aspartame crystals thus obtained may or may not be treated by a granulator. When it is treated by a granulator, any type of granulator such as an extrusion type granulator or a compression type granulator may be employed. When the wet Aspartame crystals are treated by extrusion by means of an extrusion type granulator, granules of a cylindrical shape can be obtained by passing the wet Aspartame crystals through a screen having a mesh size of from 0.1 to 10.0 mm in diameter. It is preferred to pass the wet crystals through a screen having a mesh size of from 1.0 to 4.0 mm in diameter.

Such wet Aspartame crystals usually contain far more than 15% by weight of water. Therefore, the wet crystals are firstly dried to a water content of from 5 to 15% by weight. There is no particular restriction as to the temperature and the drying method for the drying of wet Aspartame crystals (which may or may not be granulated) to a water content of from 5 to 15% by weight based on

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wet crystals. For example, the drying machine may be of a usual type, but is preferably an air stream drier or a fluidized-bed drier whereby the retention time is long. If the temperature is too high, a diketopiperadine derivative as a decomposition product of Aspartame is likely to form. Therefore, the drying is preferably conducted at a temperature of lower than 80°C. The wet Aspartame crystals having a water content of from 5 to 15% by weight is then heat-treated at a temperature of higher than 50°C and lower than 80°C. The heat treatment may be conducted by an air stream drier or a fluidized bed drier. However, it is preferred to conduct the treatment in a sealed container for from 30 minutes to 48 hours. The heat treatment is continued until the crystal form of Aspartame is changed to the stable crystal form, and the heat treatment time is dependent on the water content and the temperature. Once the change to the stable Aspartame has been completed, further drying can be conducted at any temperature within a range where Aspartame udergoes no substantial decomposition. Thus, it is possible to obtain dry Aspartame having excellent stability.

Now, the present invention will be described in further detail with reference to Examples. However, it should be understood that the present invention is by no means restricted to such specific Examples.

In the Examples, the ratio of II type crystals (the

ratio (%) of the II type crystals to the total amount of the I and II type crystals) was determined as follows: Standard samples of the I and II type crystals were mixed at various ratios, and calibration curve was prepared based on the ratios in the strength of the specific peaks at the respective X-ray diffraction angles (2θ) of 4.4° (I type) and 5.0° (II type). Then, the ratio of the II type crystals was determined by compairing the strength ratio of each sample with the calibration curve.

Further, in the Examples, the hygroscopicity of Aspartame was determined by storing a sample in an air at a temperature of $25^{\circ}C$ under a humidity of 78%, and the storage stability was determined by placing from 2 to 3 g of Aspartame in a sealed container (20 ml), which was then stored in a constant temperature tank of $55^{\circ}C$ and measuring the water content and the diketopiperadine content after an expiration of a predetermined period of time.

EXAMPLE 1

Wet Aspartame crystals (5 kg) obtained by solid-liquid separation by means of a centrifugal separator, was extruded through a screen having a mesh size of 2.0 mm in diameter, and granulated. The wet granules (60 g) thus obtained were dried in an air stream drier by means of a hot air stream of $60^{\circ}C$ to a water content of 10.1% by weight. The granules (5 g) were placed in a sealed container and heat-treated at $60^{\circ}C$ for

about 1 hour, and then dried in an air stream drier by means of a hot air stream of 60°C. (Yield: 4.6 g, Example 1)

On the other hand, for the purpose of comparison, the above wet granules (60 g) were dried under reduced pressure at 40°C for 6 hours. (Yield: 24.6 g, Comparative Example 1)

The results of the storage stability and the hygroscopicity are shown in Table 1.

Table 1

Number of Example or Comparative Example	Ratio of II type crystals	Hygroscopicity Water content (%)		Storage stability Content of diketopiperadine (%)	
		Immediately after drying	After 24 hours test	Immediately after drying	After 79 days test
Example 1	100	2.0	5.4	0.20	0.94
Comparative Example 1	0	2.3	8.7	0.23	1.21

EXAMPLES 2 to 11

Wet Aspartame granules (250 g) prepared in the same manner as in Exmaple 1 were dried at 60°C under reduced pressure to obtain granules having water contents of (1) 19.5% by weight (20 g), (2) 15.4% by weight (17 g), (3) 10.1% by weight (23 g), (4) 5.5% by weight (18 g) and (5) 2.3% by weight (20 g), respectively. They were respectively treated by heating at various temperatures in sealed containers, followed by drying at 60°C under reduced pressure, to obtain dry Aspartame products having water contents of (1) 2.1% by weight (from 19.5% by weight), (2) 1.5% by weight (from 15.4% by weight), (3) 1.8% by weight (from 10.1% by weight) and (4) 2.0% by weight (from 5.5% by weight), respectively. The increases in the water contents of the dry Aspartame products during the storage were measured, and the results are shown in Table 2.

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Table 2

Number of Example or Comparative Example	Heat treatment		Water content at the initiation of heat treatment (%)	Ratio of II type crystals (%)	Hygroscopicity Water content increase (%) (After 48 hours test)
	Temperature (°C)	Time (hr)			
Comparative Example 2	40	17	5.5	0	9.9
Comparative Example 3	"	"	10.1	45	8.0
Example 2	50	3	"	78	5.3
" 3	"	"	10.1	100	4.0
Comparative Example 4	"	"	19.5	0	9.5
Example 4	60	1	10.1	100	3.7
" 5	"	3	5.5	"	4.1
" 6	"	3	10.1	"	4.0
Comparative Example 5	"	3	15.4	0	9.8
Example 7	70	1	5.5	100	3.8
" 8	"	1	10.1	"	3.8
Comparative Example 6	"	1	15.4	10	9.0
" 7	"	16	2.3	0	9.5
Example 9	"	"	5.5	100	3.8
" 10	"	"	10.1	"	3.8
Comparative Example 8	"	"	19.5	0	9.0
" 9	80	17	2.3	10	9.1
" 10	"	"	19.5	8	9.5

EXAMPLE 11

Wet Aspartame crystals (80 kg) prepared in the same manner as in Example 1, were dried in a conical drier as a sealed container at 60°C under reduced pressure, to a water content of 9.4% by weight. Then, the heat treatment was conducted at 60°C for 1 hour, followed by drying again under reduced pressure for 3 hours, to obtain 32.5 kg of a dried product of stable Aspartame (composed of 100% of II type crystals) having a water content of 1.8%.

As is apparent from the foregoing description, according to the present invention, it is possible to obtain dry Aspartame having excellent storage stability without necessity of high temperature drying, or reducing which is disadvantageous from the viewpoint of the process control and costs for energy.

The dry Aspartame product having excellent storage stability of the present invention is particularly useful when it is used as a table sweetener in the form of granules or tablets together with sugars or other substances.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for producing stable α-L-aspartyl-L-phenylalanine methyl ester, which comprises heat-treating crystals of α-L-aspartyl-L-phenylalanine methyl ester having a water content of from 5 to 15% by weight based on wet crystals, at a temperature in the range from 50°C and lower than 80°C for at least 30 minutes.

2. The process according to Claim 1, wherein the heat treatment is conducted within 48 hours.

3. The process according to Claim 1, wherein the crystals of α-L-aspartyl-L-phenylalanine methyl ester having a water content of from 5 to 15% by weight, are granulated by a granulator prior to the heat treatment.

4. The process according to Claim 3, wherein the granules have a diameter of from 0.1 to 10.0 mm.

5. The process according to Claim 1, wherein the crystals of α-L-aspartyl-L-phenylalanine methyl ester having a water content of from 5 to 15% by weight, are not treated by granulator.

6. The process according to Claim 1, wherein the heat treatment is conducted in a sealed container.

7. The process according to Claim 1, wherein the heat treatment is conducted in an air stream drier.

8. The process according to Claim 1, wherein the heat treatment is conducted in a fluidized-bed drier.

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9. A process for producing stable α-L-aspartyl-L-phenylalanine methyl ester substantially as herein described with reference to any one or more of Examples 1 to 13 (excluding Comparative Examples).

10. Stable α-L-aspartyl-L-phenylalanine methyl ester when produced by a process defined in any one of Claims 1 to 9.

Dated this 12th day of August 1987

TOSOH CORPORATION.
TOYO SODA MANUFACTURING CO., LTD.
By their Patent Attorney
GRIFFITH HASSEL & FRAZER

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