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**D E C I S I O N**  
of 9 March 1999

**Case Number:** T 0985/96 - 3.3.4

**Application Number:** 92118534.4

**Publication Number:** 0547342

**IPC:** C07K 5/06

**Language of the proceedings:** EN

**Title of invention:**

Method for crystallization of alpha-L-aspartyl-L-phenylalanine methyl ester

**Applicant:**

Ajinomoto Co., Inc.

**Opponent:**

-

**Headword:**

Crystallization/AJINOMOTO

**Relevant legal provisions:**

EPC Art. 56

**Keyword:**

"Inventive step (yes)"

**Decisions cited:**

T 0475/92

**Catchword:**

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Case Number: T 0985/96 - 3.3.4

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.4  
of 9 March 1999

**Appellant:** Ajinomoto Co., Inc.  
No. 15-1  
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Chuo-ku  
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**Representative:** Strehl Schübel-Hopf & Partner  
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**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 8 May 1996 refusing  
European patent application No. 92 118 534.4  
pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairperson:** U. M. Kinkeldey  
**Members:** L. Galliani  
W. Moser

**Summary of Facts and Submissions**

I. The appeal lies from the decision of the examining division dated 8 May 1996 whereby the European patent application No. 92 118 534.4 published as EP-0 547 342 was rejected pursuant to Article 97(1) EPC. The grounds of the refusal were that the subject-matter of the claims 1 to 5 then on file lacked an inventive step having regard to the following documents:

- (1) EP-A-0 405 273;
- (2) EP-A-0 399 605.

Claim 1 read as follows:

"A method for the crystallization of  $\alpha$ -L-aspartyl-L-phenyl-alanine methyl ester, comprising the steps of cooling and stirring a crystallizing solution of  $\alpha$ -APM, the cooling being conducted by indirect heat exchange with a coolant, circulating the coolant while continuously feeding an aqueous solution of  $\alpha$ -APM to the crystallizing solution of  $\alpha$ -APM, and withdrawing an amount of said crystallizing solution corresponding to the amount of said aqueous solution of  $\alpha$ -APM fed into said crystallizing solution, wherein the crystallizing solution of  $\alpha$ -APM has a temperature not greater than 20°C higher than the temperature of the coolant."

Dependent claims 2 to 5 concerned embodiments of the method according to claim 1.

- II. The examining division, while accepting the formal admissibility of said newly filed claim 1 under Article 123(2) EPC, considered that its subject-matter was obvious for a skilled person as the prior art documents (1) and (2) provided an incentive to operate at a temperature difference between crystallising solution and coolant not greater than 20°C.
- III. On 27 January 1999, the board sent a communication with a provisional, non-binding analysis of the case. The board referred inter alia also to the following document from the European search report:

(3) EP-A-0 091 787.

The appellants replied thereto on 22 February 1999 and filed new claims 1 to 5.

- IV. Oral proceedings took place on 9 March 1999. A new request was filed in substitution of the previous request. This consisted of claims 1 to 4 of which claim 1 read as follows:

"A method for the continuous crystallisation of  $\alpha$ -L-aspartyl-L-phenylalanine methyl ester on an industrial scale comprising cooling and stirring a crystallising solution of  $\alpha$ -APM while continuously feeding an aqueous solution of  $\alpha$ -APM to the crystallising solution of  $\alpha$ -APM and withdrawing an amount of said crystallising solution corresponding to the amount of said aqueous solution of  $\alpha$ -APM fed into said crystallising solution, the cooling being conducted by indirect heat exchange with a coolant in a crystalliser for industrial use having a metal heat exchange surface and by circulating the coolant, wherein the crystallising solution of  $\alpha$ -APM has a temperature not greater than 20°C higher than the temperature of the coolant."

Dependent claims 2 to 4 concerned embodiments of the method according to claim 1.

V. The appellants submitted in essence that in the decision under appeal the disclosure of documents (1) and (2) had been interpreted beyond the teaching in fact provided by them. Both documents dealt with small scale experiments with the aim to produce either crystals with better solubility (cf document (1)) or crystals with improved filtration properties and dehydration. They contained no statement about any temperature difference between the crystallising solution and the coolant. The specific temperature difference, which was an essential feature of the method of the present application, and which contributed in overcoming the need to use high temperature differences between the crystallising solution and the coolant in industrial crystallisers (cf declaration by Hisao Itoh dated 16 August 1994), would not have been suggested to the skilled person by the said documents, taken alone or in combination with each other or with document (3).

VI. The appellants requested that the decision under appeal be set aside and that the patent be granted on the basis of the following documents:

- (a) claims 1 to 4 submitted during oral proceedings,
- (b) description pages 1 to 3 and column 5 of page 4, lines 1 to 45 as published, and
- (c) drawings, Figures 1, 2(A) and 2(B) as published.

## Reasons for the Decision

### Article 123(2) EPC

1. Claim 1 results from the combination of the features of claims 1, 4 and 6 as filed and from the introduction of the features "continuous", "on an industrial scale" and "in a crystalliser for industrial use". The latter features have a basis in the application as filed which refers on page 4, first paragraph to "**continuous crystallization on an industrial scale**" (emphasis added) and in Example 1 to a crystalliser for industrial use. Thus, no objection under Article 123(2) EPC is seen by the board.

### Article 84 EPC

2. Although it can be said that the expression "on an industrial scale" per se is open to interpretation and thus questionable, the further indication "in an industrial crystalliser" renders the overall scope of claim 1 clear as the concept of "industrial crystalliser" is quite straightforward for a skilled person. This finding follows the finding in decision T 475/92 of 27 May 1997 which dealt with the same issue. No further clarity objections under Article 84 EPC against claim 1 are seen by the board.

### Novelty (Article 54 EPC)

3. None of the documents on file describes a method for continuous crystallisation of L- $\alpha$ -aspartyl-L-phenylalanine methyl ester characterised by the features recited in claim 1. Thus, novelty is acknowledged.

*Inventive step (Article 56 EPC)*

4. Three prior art documents are relevant for the evaluation of the inventive step of the claimed method, namely documents (1) to (3). Of them, documents (1) and (2) constituted the basis for the rejection of the application by the examining division (cf Section I supra).

5. All these documents are concerned with the crystallisation of  $\alpha$ -AMP and have as an objective the production of crystals with improved properties, although emphasizing different aspects of the process of crystallisation.

Of them, only document (3) is directly concerned with problems of continuous industrial operation, which are solved by way of a method in which crystallisation is carried out by cooling in an industrial crystalliser **without mechanical stirring**. The latter feature, which essentially characterises the process described in the document, is in direct contrast with the method of the claims at issue which requires stirring.

Document (1), which is primarily concerned with the production of crystals with better solubility, describes a **batchwise method** on a laboratory scale essentially consisting in adding a solution of  $\alpha$ -AMP to a stirred suspension of  $\alpha$ -AMP which is maintained at a temperature lower than the said solution.

In document (2), like in the present patent application, the main preoccupation is **avoiding the adhesion of the crystals** (scaling or scale formation) at the cooling surface of the crystalliser, in the perspective of industrial production. The method

proposed therein, which is essentially based on mixing a hot  $\alpha$ -AMP solution with a cold  $\alpha$ -AMP solution, is exemplified on a laboratory scale in a batch system, but is said to be apt to a continuous operation mode (cf page 3, lines 38 to 39).

6. In the board's view, document (2) constitutes the appropriate starting point for the evaluation of inventive step as it addresses the problem of the scaling on the heat exchange surface for cooling of the crystalliser. As said above, in order to prevent scale formation, the document proposes a crystallisation method based on mixing a hot solution of  $\alpha$ -AMP with a cold solution of  $\alpha$ -AMP in such concentrations and proportions that breaking of the supersaturation causes crystal precipitation. It is stated that mixing can be carried out either by introducing the two solutions simultaneously or one after the other eg in a mixing tank with stirrer in a batch system or continuously. However, in the examples the method is carried out batchwise, on a small scale, in glass containers. In particular, in the experiment of Example 1 a glass crystalliser was used with external cooling jacket and stirrer: one litre of the hot solution at 60°C was added to one litre of the cold solution (at 5°C) while stirring. The temperature of the mixture, which was 32.5°C, was lowered at the rate of 5°C per 10 minutes by circulating a cooling medium to the jacket while gradually lowering the temperature of the external water bath until the temperature of the solution reached 5°C. No substantial formation of adhered crystals was observed at the cooling surface of the crystalliser. Neither Example 1 nor any other examples nor the description report data about the temperature of the cooling medium or about the difference of temperature between the said cooling medium and the crystallising solution.

7. In the light of document (2), the problem to be solved by the patent in suit is the provision of a scaled-up cooling crystallisation method in which substantially no formation of scales takes place at the cooling surface of the crystalliser.
8. As a solution thereto, claim 1 proposes a continuous method essentially characterised by the fact that the crystallisation of  $\alpha$ -APM is carried out with stirring in a crystalliser for industrial use having a metal heat exchange surface, where the cooling is conducted by indirect heat exchange with a circulating coolant, wherein the crystallising solution of  $\alpha$ -APM has a temperature not greater than 20°C higher than the temperature of the coolant. The description of the patent in suit demonstrates that the technical problem is thereby satisfactorily solved as no serious (cf Example 1) or only slight (cf Example 2) scaling was observed after completion of the crystallisation, when working with volumes of 4 m<sup>3</sup> for four consecutive days.
9. The relevant questions in relation to inventive step are what measures the skilled person faced with the stated technical problem would have considered adopting, and whether these would have included a method covered by claim 1.
10. The skilled person knew from document (2) that scaling could be avoided by paying attention to the concentration, temperature and relative proportions of the two  $\alpha$ -APM solutions which are mixed. The importance of the difference in temperature between two  $\alpha$ -APM solutions to be mixed was also shown in document (1). The latter document taught a method in which a solution of  $\alpha$ -APM was added to a cooled, stirred slurry of  $\alpha$ -APM, the temperature difference between the two solutions being between from 10°C to 70°C, preferably

40°C to 70°C. Example 1 of document (1) reported **no adhesion of crystals** to the wall of the flask when in a one litre flask a solution of  $\alpha$ -APM at 60°C was added dropwise with stirring to an  $\alpha$ -APM slurry maintained at about 5°C by cooling the outside of the flask with ice water. The document advised the skilled person that about 5°C was the preferred temperature for the slurry, and that cooling could be achieved by usual means like eg a cooling coil at the outer surface (cf page 4, column 5, line 4 and lines 28 to 31).

11. The skilled person was aware of the fact that the scale-up of a crystallisation process from data obtained in small experimental units such as those of documents (1) and (2) was not a simple matter as it required the adjustment of the relevant parameters and factors through trial and error procedures before finding the correct operating conditions. Document (2), although projecting its teaching towards industrial production in a continuous operation mode, provided no assistance in respect of the adaptations necessary for scale-up. The skilled person knew, for example, that, while it was a relatively simple matter to mix batchwise two  $\alpha$ -APM solutions of different temperature under stirring and with external jacket cooling in a small experimental unit (eg 2 litres) as shown in the document in question, the same operation would have been more complicated when performed continuously on an industrial scale (eg 4000 litres). In fact, the large volumes of solutions involved required taking decisions eg as to the type of crystalliser, the concentration of the solutions, proportions of mixing, flow regimes, feeding rate, the manner of cooling etc..

As both document (2) and document (1) put emphasis essentially on the temperature difference between the two  $\alpha$ -APM solutions to be mixed, the **primary** preoccupation of the skilled person would have been

finding the correct parameters in relation to the mixing of the hot and the cold solutions (temperatures, concentrations, proportions etc.) and to the cooling of the resulting mixture.

12. As regards the cooling step, in the board's view, the skilled person would have relied on common wisdom according to which effective cooling could be achieved either by increasing the surface area of the cooling means or by increasing the temperature difference between the coolant and the crystallising solution, cf eg document (3) where the coolant has a temperature of 0°C and the crystallising solution a temperature of 55°C. However, nothing in the prior art would have readily provided an incentive to ensure during a continuous operation that a temperature difference between crystallizing solution and coolant not greater than 20°C is strictly maintained, as required by the claimed method.

13. In the board's judgement, contrary to the view of the examining division, the fact that in Example 1 of document (1) the experimental conditions were such that the temperature difference between crystallising solution and coolant (ice water) was not greater than 20°C would not have readily suggested adopting such conditions upon scale-up because no particular importance was attached to them in document (1) and, thus, upon scale-up little attention would have been paid to the non-emphasised cooling arrangements of an experiment carried out on a laboratory scale. Rather, cooling arrangements typical of industrial operations would have been adopted (cf point 12 supra) which would not have readily included the adoption of the measure referred to in the claims at issue.

14. For these reasons, the board is of the opinion that the method according to claim 1 and dependent claims 2 to 4 involves an inventive step.

### Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to grant a patent on the basis of the following documents:
  - (a) claims 1 to 4 submitted during oral proceedings, and
  - (b) description pages 1 to 3 and column 5 of page 4, lines 1 to 45 as published, and
  - (c) drawings, Figures 1, 2(A) and 2(B) as published.

The Registrar:

U. Bultmann

The Chairperson:

*U. Kinkeldey*  
U. Kinkeldey