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D E C I S I O N
of 27 May 1997

Case Number: T 0475/92 - 3.3.4

Application Number: 83301951.6

Publication Number: 0091787

IPC: C07K 3/12

Language of the proceedings: EN

Title of invention:
Process for crystallizing alpha-L-aspartyl-L-phenylalanine-methyl ester

Applicant:
AJINOMOTO CO., INC.

Opponent:
-

Headword:
Crystallizing/AJINOMOTO

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Novelty (yes) - after amendments"
"Inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0475/92 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 27 May 1997

Appellant: AJINOMOTO CO., INC.
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Tokyo 104 (JP)

Representative: Nash, David Allan
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Decision under appeal: Decision of the Examining Division of the European Patent Office posted 23 April 1992 refusing European patent application No. 83 301 951.6 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
S. C Perryman

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division dated 23 April 1992 whereby the European patent No. 0 091 787 (application No. 83 301 951.6) was revoked pursuant to Article 102(1) EPC. The grounds of the refusal were that the product claim of both the main and auxiliary requests then on file, which was directed to L-α-aspartyl-L-phenylalanine methyl ester (α-APM) crystals, lacked novelty having regard to the following document:

(1) JP-A-167268/1980

and that process claim 1 of both requests lacked an inventive step in the light of the same document.

Process claim 1 of both requests was identical to claim 1 as granted and read as follows:

" A process for crystallizing L-α-aspartyl-L-phenylalanine methyl ester from its aqueous solution by cooling, characterised in that it comprises adjusting the initial concentration of the ester so that the amount of precipitated solid phase formed after cooling is about 10 g or more per litre of solvent, cooling the solution by conductive heat transfer to form an apparently sherbet-like pseudo solid phase without effecting forced flow (that is to say without mechanical stirring or the like), and, if necessary, further cooling the system after formation of the pseudo solid phase."

II. With letter dated 12 January 1993, the only opponent withdrew its opposition.

III. With the statement of grounds of appeal, the appellants filed a new main request and four auxiliary requests. On 18 March 1996, the board sent a communication with an analysis of the case. The appellants replied thereto with letter dated 16 September 1996 which contained a new main request and seven new auxiliary requests. Following the summons to oral proceedings, the appellants filed copies of two videotapes already submitted during the opposition phase illustrating the invention and, later, a new main request and new auxiliary requests 1 to 9 in substitution of all previous requests.

IV. Oral proceedings took place on 27 May 1997. A new main request and five auxiliary requests in substitution of all previous requests were filed.

Claim 1 of the **main request** (claims 1 to 7) reads as follows:

" A process for crystallizing L-α-aspartyl-L-phenylalanine methyl ester on an industrial scale from its aqueous solution by cooling in an industrial crystallizer, which comprises adjusting the initial concentration of the ester so that the amount of precipitated solid phase formed after cooling is about 10 g or more per litre of solvent, cooling the solution by conductive heat transfer to form an apparently sherbet-like pseudo solid phase without effecting forced flow (that is to say without mechanical stirring or the like), and, if necessary, further cooling the system after formation of the pseudo solid phase, converting said pseudo solid phase to a slurry, subjecting the slurry to a solid-liquid separation, and drying the crystals of L-α-aspartyl-L-phenylalanine methyl ester; wherein said sherbet-like pseudo solid phase comprises bundle-like crystal aggregates of L-α-

aspartyl-L-phenylalanine methyl ester and the solvent, has no fluidity, and may be converted into a slurry by stirring."

Dependent claims 2 to 7 are identical to claims 2 to 7 as granted.

V. The appellants submitted that the claimed subject-matter was novel and inventive having regard to the prior art referred to during the opposition proceedings, in particular document (1) and the following document:

(2) JP-A-167267/1980 (N.B.:this document was referred to as document (11) during the opposition proceedings)

VI. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or one of first, second, third, fourth or fifth auxiliary requests submitted at the oral proceedings on 27 May 1997.

Reasons for the Decision

Main request

Article 123(2) and (3) EPC

1. Claim 1 of this request differs from claim 1 as granted in that it specifies:

- that the claimed process is carried out "on an industrial scale";

- that cooling takes place "in an industrial crystallizer"; and

- the further steps of "converting said pseudo solid phase to a slurry, subjecting the slurry to a solid-liquid separation, and drying the crystals of L-α-aspartyl-L-phenylalanine methyl ester; wherein said sherbet-like pseudo solid phase comprises bundle-like crystal aggregates of L-α-aspartyl-L-phenylalanine methyl ester and the solvent, has no fluidity, and may be converted into a slurry by stirring."

2. The introduction of the above mentioned features in claim 1 in comparison with the granted version does not result in an extension of the protection conferred so that there is no violation of Article 123(3) EPC.

3. The above mentioned features find support in the application as filed. In particular, reference to industrial production of α-APM is found on pages 1, 4 and 14 thereof. Crystallizers suitable for crystallization on an industrial scale are referred to in the figures and in the examples. The steps of converting the pseudo solid phase to a slurry, subjecting the slurry to a solid-liquid separation, and drying the crystals of L-α-aspartyl-L-phenylalanine methyl ester are referred to in the examples and on page 10, lines 17 to 24 and on pages 14 and 15 of the application as filed. Thus, no objection under Article 123(2) EPC is seen by the board.

Article 84 EPC

4. In the context of the subject-matter of the patent in suit, the expression "A process for crystallizing L-α-aspartyl-L-phenylalanine methyl ester on an industrial scale from its aqueous solution by cooling in an

industrial crystallizer" is clear to the skilled person in the art, who acknowledges a distinction between a process carried out in an "industrial crystallizer" (see eg KIRK-OTHMER Encyclopedia of Chemical Technology, 1979, 3rd edition, Vol.7, pages 243-285, John Wiley & Sons, New York, N.Y.,USA, in particular pages 263-269; this document was referred to during the opposition proceedings) and crystallization carried out in laboratory vessels. No further clarity objections under Article 84 EPC against the amended version of claim 1 are seen by the board.

Novelty (Article 54 EPC)

5. None of the documents on file describe a process for crystallizing L-α-aspartyl-L-phenylalanine methyl ester in which cooling is carried out **in an industrial crystallizer without mechanical stirring** and in which the sherbet-like pseudo solid phase thus formed is converted to a slurry that is subjected to a solid-liquid separation and the separated crystals of L-α-aspartyl-L-phenylalanine methyl ester are dried. In particular, documents (1) and (2) were extensively discussed during oral proceedings. In both documents the crystallization step is carried out without agitation (see Example 1 in both cases). However, crystallization is carried out in suitable vessels on a laboratory scale, **not** in an industrial crystallizer. Moreover, both documents refer to **wet** crystals, no reference being made to a drying step. For these reasons, the board concludes that the subject-matter of claim 1 (and, consequently, also of dependent claims 2 to 7) is novel.

Inventive step (Article 56 EPC)

6. In the board's judgement, document (2) constitutes the most appropriate starting point for the evaluation of inventive step. This document, which deals which the purification of L-α-aspartyl-L-phenylalanine lower alkyl esters, in particular of the methyl ester, for the purpose of industrial operation (see eg page 4 of the translated version, second full paragraph) describes the combination of an ion-exchange method with crystallization. In the only example given, the method was carried out on a laboratory scale (ie with small amounts of reagents and in small laboratory vessels). In order to achieve crystallization, the liquid passed through the ion-exchange column was kept at 5°C overnight. The thus precipitated crystals were collected by filtration and washed. Although no direct information is provided in the said document, in the board's view, both the fact that agitation is not mentioned and the manner used to describe the crystallization step ("depositing the crystals", "the precipitated crystals", "kept at 5°C overnight") unequivocally indicate that crystallization was carried out under static conditions, ie without mechanical stirring. As agreed by the appellants at oral proceedings, cooling without agitation of an aqueous solution of α-APM of the concentration stated in document (2) results inevitably in the formation of sherbet-like pseudo solid phase comprising bundle-like crystal aggregates of α-APM. Thus, such crystals must have necessarily formed there in consequence of the manner of operation. However, neither the occurrence of this phenomenon nor its implications are reported in document (2). The same applies to document (1) which also describes cooling of an aqueous solution of α-APM without agitation on a small laboratory scale. This

document is considered less appropriate as starting point for the evaluation of inventive step than document (2) as it is not directly preoccupied with problems of industrial operation.

7. In the light of document (2), the problem to be solved by the patent in suit is the scaling-up to an industrial scale of the process of recovering by crystallization L-α-aspartyl-L-phenylalanine methyl ester from an aqueous solution.

8. As a solution thereto, claim 1 proposes a method essentially characterised by the fact that crystallization is carried out by cooling in an industrial crystallizer without mechanical stirring. The description of the patent in suit as well as the evidence on file demonstrate that the technical problem is thereby satisfactorily solved.

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 process covered by claim 1.

10. The skilled person knew that scaling-up of a crystallization process from data obtained on a small scale unit is never a simple matter (see eg. KIRK-OTHMER, supra, page 271, first sentence under the heading "Scale-up and Operating Problems"). The evidence before the board (see in this respect eg the third declaration of Prof. J. W. Mullin, an expert for the appellants, in particular point 10, and KIRK-OTHMER, supra, page 264, "Unstirred Tanks") is that for crystallizing something such as L-α-aspartyl-L-phenylalanine methyl ester on an industrial scale from its aqueous solution, the skilled person would as a matter of routine have used an industrial crystallizer

in which stirring took place to prevent inhomogeneities arising and to speed up the cooling. Absence of stirring or other agitation would have been expected by the skilled person to adversely affect the cooling rate, to cause encrustation of the cooling surfaces, uncontrolled settling of the crystals and to cause difficulties when discharging the vessel. This is on the evidence the case when other substances are crystallized out of solution without agitation. Accordingly, his or her primary choice would have been a conventional **agitated** industrial crystallizer because it would have ensured inter alia a faster cooling rate, less encrustation and a better control of the distribution of the crystals in the mass and a somewhat purer product (see eg KIRK-OTHMER, supra, page 264, "Agitated Vessels").

11. Even if the skilled person had observed the crystals formed on cooling without agitation in the laboratory when repeating the teaching of documents (1) and (2), to be of a different form to the crystals formed on cooling with agitation, the solid form they took in a laboratory beaker would rather have lead the skilled person to believe that his or her problems would be worse without agitation than with agitation. As the skilled person would have had no experience with other substances of such sherbet-like crystals there would have been no pointer to the fact that for L-α-aspartyl-L-phenylalanine methyl ester this form of crystallization without agitation would produce any benefits, such as easier discharge and more easy drying. Thus, even if the skilled person had been dissatisfied as a result of difficulties of handling the crystals obtained from an agitated solution, there was nothing to point him or her to an industrial scale process without agitation as a way to avoid these difficulties.

12. For these reasons, the board is of the opinion that the choice of an unagitated industrial crystallizer in the cooling step of an aqueous solution of α-APM as now reflected by the process according to claim 1 and dependent claims 2 to 7 involved an inventive step. The main request is thus allowed.

Other matters

13. As the main request is considered allowable by the board, there is no need to consider the auxiliary requests. The main request contains no product claims. Thus, the description of the patent in suit, if necessary, should be amended to reflect this change. The adaptation of the description will have to be carried out at the level of the first instance to which the case is hereby remitted.

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 maintain the patent on the basis of the main request submitted at the oral proceedings on 27 May 1997 and a description to be adapted.

The Registrar: The Chairperson:

A. Townend U. Kinkeldey

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