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D E C I S I O N
of 7 December 2001

Case Number: T 0455/98 - 3.3.2

Application Number: 90312752.0

Publication Number: 0435450

IPC: A61K 9/18

Language of the proceedings: EN

Title of invention:
Crystalline sugar alcohol containing uniformly dispersed particulate pharmaceutical compound

Patentee:
SPI POLYLOS, Inc.

Opponent:
BASF Aktiengesellschaft Patente, Marken und Lizenzen

Headword:
Crystalline sugar alcohols/SPI POLYOLS

Relevant legal provisions:
EPC Art. 52(1), 54, 56, 84, 111(1), 123(2), (3)

Keyword:
"Main request and auxiliary requests 2 to 5: novelty (no); citation (10) when interpreted in the light of the specific reference to citation (11) destroys the novelty of process claim 7"
"First auxiliary request: filed late, admissibility (yes); inventive step (no), additional feature in claim 7 result of routine experimentation of the skilled practitioner"

Decisions cited:
T 0114/86

Catchword:
-

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Case Number: T 0455/98 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 7 December 2001

Appellant: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 5 March 1998 rejecting the opposition filed against European patent No. 0 435 450 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: G. F. E. Rampold
C. Rennie-Smith

Summary of Facts and Submissions

I. The respondent is proprietor of European patent No. 0 435 450. The patent was granted with 10 claims pursuant to European patent application No. 90 312 572.0. The two independent claims as granted read as follows:

1. A pharmaceutical composition comprising crystalline sugar alcohol derived from at least one mono- or polysaccharide and having uniformly dispersed within the crystal matrix of the sugar alcohol particles of at least one pharmaceutically active compound.

7. A process for producing pharmaceutical compositions having uniformly dispersed particulate active which comprises the steps of
   A) forming a molten sugar alcohol derived from at least one mono- or polysaccharide;
   B) dispersing particles of at least one pharmaceutically active material in said molten alcohol under conditions such that a homogeneous mixture is formed;
   C) cooling said homogeneous molten mixture while agitating until a viscous mass is formed; and
   D) cooling said mass slowly to a point where said alcohols become fully crystallised."

Claims 2 to 6 are dependent claims, directed to elaborations of the composition according to claim 1. Dependent claims 8 to 10 relate to specific elaborations of the process according to claim 7.

II. The appellant filed opposition to the grant of the European patent requesting its revocation in full pursuant to Article 100(a) EPC on the grounds of lack of novelty and inventive step. These grounds for opposition were supported, *inter alia*, by the following citations:

(10) FR-A-2 629 822;

(11) US-A-4 252 794.

III. The opposition was rejected pursuant to Article 102(2) EPC by a decision of the opposition division posted on 5 March 1998. The essence of the reasoning in the decision to reject the opposition was as follows:

As to novelty, the opposition division found that none of the documents cited in the course of the opposition proceedings disclosed clearly and unambiguously the pharmaceutical composition according to claim 1 or the process according to claim 7 with all the technical features of these independent claims.

Concerning inventive step, the opposition division considered citation (10) to represent the closest state of the art. It found, however, that citation (10), even if it is was read in the context of citation (11), pointed the skilled reader neither to the possibility of using a pharmaceutically active compound as the active ingredient in the claimed composition nor to the problem of avoiding segregation or separation of the active particulate material from the excipient mass. Moreover, it estimated that step C) of the process according to claim 7 was neither disclosed in the cited documents nor obvious to a person skilled in the art

trying to solve the problem of effectively preventing segregation of the dispersed particulate active material from the crystal matrix of the sugar alcohol so as to achieve uniform distribution of particles of a pharmaceutical material within the crystalline sugar alcohol matrix.

IV. An appeal was filed against the decision of the opposition division. Both the appellant (opponent) and the respondent (proprietor) requested oral proceedings.

V. In advance of the oral proceedings, scheduled for 7 December 2001, the respondent filed auxiliary requests 1 to 4 which became the second, third, fourth and fifth auxiliary requests as refiled during the oral proceedings before the board (see paragraph VI below). Each of the second, third and fourth auxiliary requests consists of an amended claim 1 and claims 2 to 10 as granted. The fifth auxiliary request consists of an amended claim 1 and claims 2 to 8 as granted (claims 9 and 10 being cancelled).

VI. In the introductory remarks at the oral proceedings, the chairman suggested that, for reasons of procedural economy, the patentability of process claim 7 be discussed first, since this claim was present in identical form in all requests on file at the beginning of the oral proceedings (see paragraphs I and V above). As a result of this discussion, the respondent filed towards the end of the oral proceedings a new first auxiliary request. This request consists of claims 1 to 10 as granted, step D) in claim 7 differing by the insertion of the words emphasised below: "cooling said mass slowly ***over a period of between about 6 and about 96 hours*** to a point where said alcohols become fully

crystallised."

VII. The appellant's arguments submitted in writing and during oral proceedings can be summarised as follows:

Citation (10) disclosed a process for the preparation of a solid composition based on crystalline sorbitol having uniformly dispersed within the crystall matrix particles of one or more alkali phosphates. The express incorporation of the disclosure of citation (11) in document (10) had the effect that the teaching of the cited state of the art was prejudicial to the novelty of the process according to claim 7.

The opposition division was, in the appellant's opinion, incorrect in both its conclusions in the decision under appeal, namely that citation (10) did not refer to the use of a pharmaceutically active compound for dispersion within the crystalline sorbitol matrix and that the cited state of the art did not mention the technical features of step C) in claim 7. On the contrary, alkali phosphates were clearly covered by the term "pharmaceutically active compound" in its broad sense used in the patent in suit. Similarly, the process disclosed in citation (11) included clearly and unequivocally the step of simultaneously cooling and kneading the molten sorbitol until a plastic magma was obtained and this procedure corresponded exactly to what was actually claimed in step C).

The requirement of cooling the extrudate resulting from step C) slowly to achieve crystallisation of the sorbitol matrix was likewise anticipated by the disclosure in the cited state of the art. The procedural steps used in the process of claim 7 for

cooling the viscous mass slowly to a point where the sorbitol becomes fully crystallised would be regarded by the skilled reader as clearly implied by the disclosure of citation (11).

The respondent's assertion that a uniform dispersion of the particulate material in the crystalline sorbitol matrix could not be achieved by the process disclosed in citation (10) was incorrect. On the contrary, what the respondent itself had demonstrated by the data provided in Table I of the patent in suit was nothing else than the finding that tablets produced by the claimed process contained *in toto* roughly the same amount of phenylpropanolamine hydrochloride as the active ingredient per one single tablet. The respondent's submission that these data showed the uniform dispersion of the active ingredient within the crystalline sugar alcohol matrix of the tablets was, however, a mere assertion which was in no way supported by the data presented in Table I.

VIII. The respondent disagreed and its arguments, in written submissions and during the oral proceedings, were in summary as follows:

The claimed invention was directed to the problem of achieving a uniform distribution of particles of a pharmaceutical material within a crystalline sugar alcohol matrix. From the description given in the background section of the patent in suit it would be appreciated that this problem was particularly acute with respect to pharmaceuticals in the form of fine powders because of the segregation problem encountered with prior processes. The claimed invention solved the problem by means of the process according to claim 7,

in which the pharmaceutical particles were dispersed in molten sugar alcohol followed by cooling of the mixture with continuous agitation thereby forming a viscous mass in which the distribution was fixed so that full crystallisation could be carried out subsequently. This process lead, for the first time, to a composition as defined in claim 1 of the patent in suit.

Citation (10) was concerned with a solid composition based on sorbitol and phosphates for the manufacture of a freezing adjuvant for foodstuffs based on minced meat and was thus not relevant to the problem solved by the invention. This citation contained no reference at all to a pharmaceutical composition. Thus the skilled person, faced with the problem of producing pharmaceutical compositions having a uniform distribution of particles of a pharmaceutical material within the crystalline sugar alcohol matrix, had no reason to consider citation (10) as a relevant piece of prior art.

The appellant’s combination of citations (10) and (11) to attack the patentability of the claimed process in the patent in suit was without foundation. The passage in (11) cited by the appellant, especially column 4, lines 30 to 45, described the procedure for producing a modified crystal form of sorbitol which was the precise subject-matter of the citation (11). There was no question of any other material being present in the process than sorbitol itself. There was a reference in (11) to the addition of compounding additives after the sorbitol product had been formed in the procedure described in (11).

In particular, there was no teaching at all in citation

(11) concerning the slow cooling of the viscous mass to a point where the sugar alcohol matrix becomes fully crystallised.

Citation (10) suggested the use of the apparatus described in document (11) in order to process a sorbitol/phosphate mixture. But (10) suggested only that the mixture was extruded with this apparatus so that it exited from the outlet at a temperature of 85°C- 100°C whereupon crystallisation of the sorbitol occurred. No previous controlled partial crystallisation of the sorbitol was mentioned and no reference was made to the operating conditions of the process in (11). It could not be assumed therefore that anything comparable to step C) of claim 7 was taught by this reference in (10).

IX. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the appeal be dismissed and that the patent be maintained either (main request) as granted or alternatively in accordance with one of the auxiliary requests filed during the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

Main request; auxiliary requests 2 to 5

2. As is apparent from paragraphs I and V above, process claim 7 is present in identical form in all sets of

claims forming the main request and auxiliary requests 2 to 5.

3. As regards the assessment of novelty of the process according to claim 7, the board considers it appropriate to make first the following general remarks: When assessing novelty, the disclosure of a particular prior document must normally be considered in isolation; in other words it is only the actual content of a citation (as understood by a skilled man) which destroys novelty. It is not permissible to "combine" **separate items** of prior art together. However, according to established case law of the boards of appeal, when determining the meaning to the skilled man of a citation (hereinafter referred to as the "primary citation") which contains a specific reference to a second citation, all or part of the disclosure of the second citation may need to be considered as part of the disclosure of the "primary citation" (see eg "Case Law of the Boards of Appeal of the European Patent Office", 3rd edition, 1998, I. C. 3.1, pp 70-71).

4. In the present case, step A) of the process according to claim 7 of the patent in suit comprises "forming a molten sugar alcohol derived from at least one mono- or polysaccharide". It has not been disputed throughoout the proceedings that the process for producing the solid composition of sorbitol and phosphates disclosed in citation (10) (ie the "primary citation") involves as the first step the provision of the desired quantity of sorbitol (ie a sugar alcohol derived from a polysaccharide) in the molten state (see eg page 2, lines 33 to 35).

5. Step B) of the claimed process requires "dispersing particles of at least one pharmaceutically active material in said molten alcohol under conditions such that a homogeneous mixture is formed" and corresponds thus exactly to what is described in the second step of the process disclosed in (10) as the provision of an intimate mixture of sorbitol and phosphates (see page 5, lines 14 to 15: "mélange intime de sorbitol et de phosphates").

5.1 The board cannot accept the respondent's argument that a difference is to be seen in the fact that, according to (10) phosphates are dispersed in the molten sorbitol, whereas the claimed process requires dispersion of a pharmaceutically active material in the matrix of the molten sugar alcohol. The term “pharmaceutically active material” is broadly defined in the patent in suit by reference to “an organic or inorganic orally ingestible compound which is taken for medicinal, dietary and/or nutritional purposes, and which is particulate in form. Illustrative of the pharmaceutically active compounds which may be beneficially formulated by the practice of the claimed invention are organic compounds such as aspirin, cimetidine, ibuprofen, aspartamine, atenolol, saccharine, acetaminophen, phenylpropanolamine hydrochloride and the like as well as inorganic compounds such as **salts and oxides of alkali metals,** alkaline earth metals and mineral supplements of iron, copper, zinc, and the like” (see patent specification, page 3, lines 25 to 30; claim 4 - emphasis added).

5.2 This broad definition of the pharmaceutically active material used for the dispersion in the molten matrix in the patent in suit clearly and unambiguously

includes materials or compounds encompassed by the technical term “phosphates” used in (10). The board concurs with the appellant's submission during oral proceedings that the use of phosphates, inter alia, for pharmaceutical and nutritional purposes forms part of the common general knowledge of a person skilled in the art and indeed of many with no particular skill in the art. Thus, to mention only two well-known examples, the skilled person would know that dibasic sodium phosphate, used as an orally ingestible compound, is a particulate material which is taken for dietary and/or nutritional purposes as a sequestrant, emulsifier or buffer in foods, or for medicinal purposes as a cathartic and in veterinary medicine as a laxative; and that monobasic sodium phosphate is an orally ingestible compound which is taken for medicinal purposes as an urinary acidifier in veterinary medicine. Consequently, the reference to a pharmaceutically active material in step B) of the claimed process cannot be considered, contrary to the respondent's assertion and the opinion of the opposition division in the decision under appeal, as a distinguishing feature over the state of the art according to (10).

6. The homogeneous molten mixture resulting from the above-mentioned process step B) is subsequently subjected, in step (C) of the process according to claim 7, to an operation which is broadly defined as “cooling said homogeneous molten mixture while agitating until a viscous mass is formed”.

6.1 The further processing of the molten intimate mixture of sorbitol and phosphates obtained in the above-mentioned second step of the process disclosed in (10) is referred to in the cited document as involving its

extrusion under conditions such that said mixture is brought, at the outlet of the extrusion apparatus, to a temperature of 85° C to about 100° C, whereby crystallization of the sorbitol is effected (see page 5, lines 14 to 19). In the following paragraph it is, however, explicitly specified and explained that the aforementioned extrusion may be performed, for example, on the machines disclosed in US-A-3 618 902 to TELEDYNE INC. and that their application **to the manufacture of powdered sorbitol** (emphasis added) has been disclosed in US-A-4 252 794 to I.C.I. [ie citation (11), the second citation]; in the following passage **it is explicitly stated that the text of the those patents is incorporated in citation (10) by reference** (see (10), especially page 5, lines 20 to 26).

6.2 Consequently, on the proper construction of citation (10) (ie the “primary citation”), the procedural steps and operating conditions used in the second citation (11) for the manufacture of powdered, crystalline sorbitol and their application for further processing the molten sorbitol/phosphate mixture into the final solid composition of crystalline sorbitol and phosphates have been incorporated by reference into the disclosure of citation (10) (see point 3 above). Furthermore, the successive procedural steps and operating conditions described in (11) (see especially column 3, line 64 to column 4, line 45) for the manufacture of powdered, crystalline sorbitol are exactly those suitable to prepare the compositions according to claim 7 of the patent in suit (see patent specification, especially page 4, line 42 to page 5, line 7). This identity of the successive procedural steps and operating conditions in the patent in suit and in citation (11) is clearly very relevant to the

actual scope of the disclosure of (10) in relation to those features of present claim 7 which are not explicitly and specifically mentioned in citation (10), but incorporated therein by reference.

6.3 The relevant method in citation (11) involves the steps of “continuously introducing a feed comprising molten sorbitol into an elongated mixing zone having shaft means and a plurality of kneader blades mounted on the shaft means, the configuration of the kneader blades being such as to provide restricted clearances between the blades and the adjacent walls; **simultaneously cooling and kneading the molten sorbitol as it passes through the mixing zone until a plastic magma of molten sorbitol and a substantial portion of gamma-sorbitol crystals is obtained and continuously discharging the blend from the mixing zone through an extrusion orifice”** (see especially column 4, lines 32 to 41). If this disclosure is compared with that starting from the penultimate line on page 4 to line 6 on page 5 of the patent in suit, it becomes unambiguously clear that the above-mentioned successive procedural steps and operating conditions disclosed in citation (11) and incorporated by reference into the disclosure of (10) correspond exactly to those which are used in the patent in suit and which are shortly referred to in step C) of claim 7, as "cooling said homogeneous mixture while agitating until a viscous mass is formed".

The term "viscous mass" used in the patent in suit for the product which is discharged from the extruder and the term "plastic magma" used in (11) (see column 4, lines 39 to 40) would be considered by the skilled

person as synonyms which designate the same physical state of the extrudate. Both, the "viscous mass" in the patent in suit (see especially page 4, lines 19 to 22) and the "plastic magma" in (11) (see especially column 4, lines 39 to 42) contain a substantial portion of the sugar alcohol in crystalline form. This mere difference in wording is insufficient to establish novelty of process step C) over the cited state of the art (see eg decision T 114/86, OJ EPO, 1987, 485).

6.4 The final step D) of claim 7 comprises the feature of "cooling said mass slowly to a point where said alcohols become fully crystallised". The disclosure in the description of the patent in suit referring to the above feature (see especially page 5, lines 6 to 7) reads "and further cooling the blend to ambient temperature forming the crystalline sugar alcohol containing included particulate" compared with the disclosure of the corresponding procedural step in citation (11) (see especially column 4, lines 43 to 45): "and further cooling the plastic magma to ambient temperature forming the modified gamma-sorbitol polymorph".

6.5 The respondent submitted repeatedly in writing and during oral proceedings, that step D) of the claimed process, requiring that the extrudate in the form of a viscous mass be cooled "slowly" to obtain the final product in crystalline form, was not disclosed in the cited state of the art. In this respect the board notes that the term "slowly" is a entirely relative term which may generally vary within extremely broad ranges when used in connection with a cooling process, especially if different sorts of materials are concerned. More specifically, the cooling process of

the hot extrudate from step C) is said in the patent in suit to vary typically within the specified **wide range** of about 6 to about 96 hours depending on the cross-sectional dimension of the extrudate mass and the effect of the added ingredient, including even longer periods for extruded shapes having a cross-sectional dimension of greater than 20 milllimeters.

Thus apart from the fact that the board considers in these circumstances the relative term "slowly" as entirely inappropriate and too vague to delimit the process of claim 7 from the cited state of the art and to establish novelty, it cannot recognise a real difference between the cooling procedure and operating conditions defined in step D) as "cooling said mass (ie the extrudate) slowly to a point where said alcohols become fully crystallised" and the cooling procedure as disclosed in (11) - see point 6.4 above. In the patent in suit, it is explained that the hot extrudate when permitted to stand (this would imply to a skilled person, in the board's opinion, cooling to ambient temperature) will fully crystallise (see page 5, lines 31 to 32). The equivalent procedural step in (11) involves entirely the same procedure and operating conditions, namely further cooling the plastic magma (hot extrudate) to ambient temperature forming the desired crystalline sorbitol.

6.6 Finally, the respondent argued during the oral proceedings that the uniform dispersion of the phosphates within the crystalline sorbitol matrix was not disclosed in the cited state of the art, whereas this uniform dispersion had been demonstrated by the data provided in Table I of the patent in suit. Since the procedural steps and operating conditions in the

cited state of the art and in the patent in suit are the same, there is no reason to assume that the products obtained would be different. The appellant argued during the oral proceedings, and the board is satisfied that kneading the molten mass, which is carried in the process disclosed in (11) (see especially column 4, lines 24 to 38) and in the patent in suit (see especially page 4, line 54, to page 5, line 3) using the same specifically equipped extruder, is responsible for the uniform dispersion of the particles of the active material within the crystalline sugar alcohol matrix.

As is apparent from the observations in paragraph VII above, the data presented in Table I of the patent in suit indicate merely the overall content of the active ingredient (phenylpropanolamine hydrchloride) in one single tablet. The board concurs therefore with the appellant's submission, that these data are inappropriate to demonstrate the uniform dispersion of the active ingredient within the crystal matrix of the tablets and to establish a potential difference between the composition resulting from the process according to claim 7 and that obtained by the process disclosed in document (10).

6.7 In conclusion, in the judgment of the board the disclosure of citation (10), when interpreted in the light of the specific reference to citation (11), destroys the novelty of the subject-matter of claim 7, and this claim therefore contravenes Articles 52(1) and 54(1) EPC. Since a decision can only be taken on a request as a whole, there is no need to consider the patentability of claim 1 of any of the main request and auxiliary requests 2 to 5.

First auxiliary request

7. Although this request was presented during the oral proceedings and was, accordingly, filed late, the board, exercising its discretionary power under Article 111(1) EPC, considers that it should be admitted into the proceedings. The respondent submitted that this request was prompted by the discussion in the oral proceedings and was reinforced by some additional submissions on the appellant's part during oral proceedings, namely that the feature "cooling said mass slowly" in step D) of the claimed process was relative and too vague to distinguish the claimed invention from the prior art. This assertion appears, *prima facie,* correct. Although the board does not condone such lateness *per se,* the exact meaning and impact of the proposed small amendment in claim 7 was immediately clear to the appellant and the board. Coupled with the fact that the appellant to a large extent prompted the amendment contained in the first auxiliary request by its own arguments during oral proceedings, the board exercises its discretion in favour of the respondent.

8. The board finds that amended claim 7 complies with the provisions of Article 84 and Articles 123(2) and (3) EPC. Since this finding was not disputed during oral proceedings, there is no need for further detailed consideration of this matter.

9. Claim 7 as amended requires in step D) that the extrudate from step C) be cooled slowly "over a period of between about 6 and about 96 hours" to a point where the sugar alcohols become fully crystallised. Since a cooling period falling within the period now specified in claim 7 is neither specifically disclosed in the

cited state of the art nor otherwise derivable therefrom, the board finds the subject-matter claimed in the first auxiliary request novel within the meaning of Article 54(1) EPC.

10. Starting from citation (10), when interpreted in the light of the specific reference to citation (11), as representing the closest state of the art, the technical problem underlying claim 7 may be seen as that of providing more precise cooling conditions for the extrudate obtained from step C) which allow the particular sugar alcohol in the desired crystalline form to be obtained (see patent specification, especially page 4, lines 31 to 35).

10.1 The solution of the problem consists of permitting the hot extrudate to stand for cooling "over a period of between about 6 and about 96 hours". On the basis of the data provided in the examples of the patent in suit and in the absence of any evidence to the contrary the board is satisfied that the stated technical problem is thereby solved. This was not disputed by the appellant.

10.2 The skilled person already knew that the successive procedural steps and operating conditions used in the state of the art cited in this decision for cooling the molten mixture of sorbitol and particulate material involved the steps of first cooling the mixture as it passes through the extrusion zone until a plastic magma of molten sorbitol and a substantial portion of sorbitol crystals is obtained, followed by cooling the extrudate to ambient temperature so as to obtain the sorbitol matrix in the desired crystal form (see points 6.3 to 6.6 above). For the skilled practitioner with that knowledge determination of the suitable

period required to do this would be merely a matter of routine experimentation, without any inventive effort. Moreover, the period specified in claim 7, which may extend over the extremely wide range from about 6 to about 96 hours, cannot be considered as providing an unexpectedly advantageous specific teaching or instruction saving the skilled person the necessity to perform his own experiments; on the contrary, such a wide range would suggest the experiments, albeit routine, could be extensive.

11. In view of the forgoing observations, in the judgment of the board the subject-matter of claim 7 does not involve an inventive step, and this claim therefore is contrary to Articles 52(1) and 56 EPC. Since a decision can only be taken on a request as a whole, there is no need, as regards the first auxiliary request either, to consider the patentability of claim 1.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

A. Townend U. Oswald