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**Datasheet for the decision
of 14 March 2017**

Case Number: T 1941/13 - 3.3.07

Application Number: 07729974.1

Publication Number: 2029110

IPC: A61K9/16, A61K31/505

Language of the proceedings: EN

Title of invention:

PROCESS FOR PREPARING SPRAY-DRIED FORMULATIONS OF TMC125

Patent Proprietor:

Tibotec Pharmaceuticals

Opponent:

Teva Pharmaceutical Industries Ltd.

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step - main request (yes)



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Case Number: T 1941/13 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 March 2017

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 1 July 2013 rejecting the opposition filed against European patent No. 2029110 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman R. Hauss
Members: A. Usuelli
 P. Schmitz

Summary of Facts and Submissions

- I. European patent No. 2 029 110, based on European patent application No. 07729974.1, was granted on the basis of 16 claims.

Independent claims 1, 14, 15 and 16 of the patent read as follows:

"1. A process for producing a solid pharmaceutical powder, comprising the steps of:

(a) providing a feed mixture of microcrystalline cellulose and a solution of a water-soluble polymer and TMC125;

(b) spray-drying the feed mixture from step (a) to form a solid dispersion of TMC125 and the polymer by introducing the feed mixture as droplets into a spray-drying chamber via an atomizing means."

"14. A solid dispersion of TMC125 in powder form obtainable by the process of any of claims 1 to 13."

"15. A pharmaceutical formulation comprising a powder as defined in claim 14 and further excipients."

"16. A solid dosage form comprising a powder as defined in claim 14 and further excipients."

- II. The patent was opposed on the ground that its subject-matter lacked inventive step. The following documents were cited during the opposition proceedings:

D1: WO 01/22938 A1

D2: US 2003/0185893 A1

D3: US 6,395,303 B1

III. By decision posted on 1 July 2013 the opposition division rejected the opposition.

In essence, the opposition division considered that the process defined in claim 1 of the opposed patent differed from the process of the closest prior art D1 in the use of microcrystalline cellulose in the spray-drying process. Taking into consideration the experimental results disclosed in the patent, the technical problem in respect of claim 1 was formulated as the provision of a process for preparing a solid powder composition of TMC 125 exhibiting a faster rate of dissolution and a higher percentage of release of TMC 125. The solution proposed by the patent, which consisted in adding microcrystalline cellulose to the feed mixture to be spray-dried, could not be derived in an obvious manner from document D1 in combination with the teaching of the other prior-art documents cited. The requirement of inventive step was therefore met.

For the same reasons, the subject-matter of claims 14 to 16, relating to a powder obtainable by the process of claim 1, was also inventive.

IV. The opponent (hereinafter: the appellant) lodged an appeal against that decision.

V. By letter dated 28 March 2014 the patent proprietor (hereinafter: the respondent) requested that the appeal be dismissed, or alternatively that the patent be maintained on the basis of an auxiliary request submitted with the same letter.

A further auxiliary request was submitted by the respondent by letter of 14 February 2017.

VI. Oral proceedings were held on 14 March 2017. Regarding the course of the oral proceedings, reference is made to the minutes.

VII. The appellant's arguments, as far as they are relevant for the present decision, can be summarised as follows:

Document D1 was the closest prior art for the assessment of inventive step. The process of claim 1 of the opposed patent differed from the process of D1 in that microcrystalline cellulose was added to the feed mixture to be spray-dried. The figures of the patent showed that the addition of microcrystalline cellulose resulted in a faster dissolution rate of the solid dispersion. However, they did not show whether microcrystalline cellulose had also the effect of increasing the total amount of TMC125 released from the composition, as alleged by the patent proprietor. The technical problem in respect of claim 1 was to be seen in the provision of a process for preparing a solid dispersion of TMC125 having a faster dissolution rate. From document D3, the skilled person knew that microcrystalline cellulose was used as tablet disintegrant. As explained in column 4 of this document, microcrystalline cellulose had the ability to draw fluid into a tablet by capillary action. This caused the disintegration of the tablet and therefore an increase in the surface area of the composition, which in turn resulted in an enhancement of the dissolution rate. The skilled person would have deduced that, by the same mechanism of action, microcrystalline cellulose could be used in the preparation of solid dispersions in order to enhance their dissolution rate. Moreover, document D3 disclosed in column 20 a spray-drying process involving the use of microcrystalline cellulose. The material obtained by this process was

mixed with other excipients and then compressed into a tablet. The solid dispersions described in the opposed patent could also be processed into tablets, as was clear from claim 15. Furthermore, microcrystalline cellulose was also disclosed in D2 as suitable excipient for solid dispersions. The subject-matter of claim 1 was therefore obvious. For the same reasons, product claims 14 to 16 were not inventive either.

VIII. The respondent's arguments, as far as they are relevant for the present decision, can be summarised as follows:

The figures of the patent demonstrated that the addition of microcrystalline cellulose to the mixture to be spray-dried not only improved the dissolution rate of the composition but also gave rise to an increase in the overall release of TMC125. The technical problem over D1 was therefore the provision of a process for preparing a solid dispersion of TMC125 having a faster dissolution rate and providing a higher release of active ingredient. Document D3 disclosed the use of microcrystalline cellulose as a tablet disintegrant. The appellant's argument was based on the assumption that tablet disintegration and the dissolution of solid powders were similar phenomena. This was pure speculation with no basis in the cited documents. As a matter of fact, a tablet was an aggregate of particles with a porous structure, whereas a powder was not porous. Hence, water could not penetrate a powder by capillary action as suggested by document D3. Furthermore, the spray-drying process was likely to modify the properties of microcrystalline cellulose due to contact with water, as suggested in D3. Hence, the skilled person could not foresee the properties of microcrystalline cellulose in a solid dispersion prepared by a spray-drying process. The

process of claim 1 was therefore inventive. For the same reasons, the product claims too met the requirements of Article 56 EPC.

- IX. The appellant requested that the decision under appeal be set aside and that the patent be revoked.
- X. The respondent requested:
- that the appeal be dismissed (i.e. that the patent be maintained as granted),
 - or, if the decision under appeal was set aside,
 - that the patent be maintained
 - according to auxiliary request 1 filed with letter of 28 March 2014, or
 - according to auxiliary request 2 filed with letter of 14 February 2017.

Reasons for the Decision

Main request (patent as granted)

1. Claim 1 - Inventive step

The patent in suit relates to a process for producing a spray-dried solid dispersion in powder form of the anti-HIV compound etravirine (TMC125) in a water-soluble polymer (see [0001] of the patent specification).

1.1 Closest prior art

The Board agrees with the parties and the opposition division that document D1 represents the closest prior art.

This document relates to pharmaceutical compositions comprising an antiviral compound and a water-soluble polymer in a solid dispersion which can, in one embodiment, be prepared by spray-drying a solution of the components (page 1, lines 11 to 13; page 39, lines 9 to 15). TMC125 is the compound prepared in example 2.B14 on page 66.

The parties do not contest the opposition division's finding that the process of claim 1 differs from the process of D1 in the addition of microcrystalline cellulose to the feed mixture containing TMC125 and a water-soluble polymer. The Board also agrees with this finding.

1.2 Technical problem

1.2.1 Example 1 of the patent in suit discloses the preparation of a spray-dried powder containing TMC 125, hydroxypropylmethyl cellulose and microcrystalline cellulose, according to the process of claim 1. This example furthermore discloses the preparation by a spray-drying process of a second powder containing only TMC 125 and hydroxypropylmethyl cellulose.

The two solid powders obtained in the process of example 1 have been assessed in a dissolution test whose results are disclosed in the figures of the patent. As accepted by the parties, the figures of the patent show that the solid dispersion containing microcrystalline cellulose presents a faster dissolution rate than the other composition.

In the light of this, the technical problem can be formulated as the provision of a process for preparing

a solid dispersion of TMC125 having a faster dissolution rate.

1.2.2 The parties disagree as to whether the figures of the patent demonstrate a further effect due to the addition of microcrystalline cellulose, namely an increase in the overall release of TMC125. However, having regard to the conclusion on inventive step on the basis of the technical problem defined in point 1.2.1 above (see below), there is no need to decide whether this further effect is present and therefore whether a more ambitious technical problem has been solved.

1.3 Obviousness

1.3.1 In the appellant's view, document D3 suggests adding microcrystalline cellulose to the feed of the spray-drying process in order to increase the dissolution rate of the composition.

1.3.2 Document D3 addresses the problem of providing a new type of microcrystalline cellulose, characterised by improved compressibility (column 4, lines 30 to 33). The new product is described as an agglomerate comprising a combination of microcrystalline cellulose and a "compressibility augmenting agent" such as silicon oxide (see column 6, 36-65).

Document D3 furthermore discloses some information concerning the properties and applications of "standard" microcrystalline cellulose. The appellant's arguments focus on this part of document D3. In particular, reference was made to column 4 (lines 61 to 67) mentioning that microcrystalline cellulose when used as a tablet excipient can act as a disintegrating agent. In the same passage it is furthermore stated

that "Microcrystalline cellulose...has the ability to draw a fluid into a tablet by capillary action. The tablets then swell on contact and the microcrystalline cellulose thus acts as a disintegrating agent."

In the appellant's opinion, the skilled person would deduce from this passage of D3 that microcrystalline cellulose, by virtue of its property of drawing fluid into the composition, would be useful to enhance the dissolution of an active ingredient from a solid dispersion.

- 1.3.3 However, neither D3 nor any other document on file indicates that the disintegration of a tablet and the dissolution of a solid dispersion are similar phenomena. In the Board's opinion, the skilled person would not equate these two processes, already in view of the differences between the two types of compositions. In this regard it is noted that the respective manufacturing processes are different: a tablet is prepared by compression whereas the solid powder of D1 is prepared by spray-drying. Thus, as pointed out by the respondent, a tablet is an aggregate of particles with a porous structure, whereas the solid dispersion envisaged in the patent in suit is a powder composition in which the active ingredient is molecularly dispersed throughout the water-soluble polymer (see also paragraph [0005] of the patent). The particles composing the solid dispersion are smaller than the particles of a tablet and have a larger surface area. Finally, as mentioned also in the decision under appeal, the disintegration of a tablet is a process whereby the tablet falls apart into smaller pieces, whereas dissolution requires the solubilisation of the active ingredient (paragraph 3.3 of the decision).

Considering these differences, a person skilled in the art would not assume, in the absence of any teaching, that a technical measure which is known to enhance the disintegration of a tablet would also be effective in enhancing the dissolution rate of a solid dispersion.

- 1.3.4 Moreover, document D3 indicates that microcrystalline cellulose has the ability to draw a fluid into a tablet by capillary action (column 4, lines 61 to 63). There is however no indication in the cited documents that a solid powder has a capillary structure. It is therefore at least doubtful whether capillary penetration of the fluid would be possible in such a composition.

In document D3 it is furthermore explained that the physical properties of microcrystalline cellulose may be altered during the manufacturing of a pharmaceutical composition, in particular due to the exposure to moisture in processes of wet-granulation (column 3, lines 29 to 33). Thus, microcrystalline cellulose which has been wet-granulated has reduced compactibility and particle porosity (column 5, lines 61 to 65). Considering this sensitivity of microcrystalline cellulose to handling steps, it would be difficult for a skilled person to foresee the properties of microcrystalline cellulose which has undergone spray-drying treatment, i.e. a process involving high pressures and temperatures and moisture. It is therefore unclear whether spray-dried microcrystalline cellulose would still retain certain abilities, such as that of drawing fluid into the composition.

Thus, also in the light of this lack of certainty in relation to technical issues, the skilled person would not consider using microcrystalline cellulose to

enhance the dissolution rate of a spray-dried solid dispersion solely because is known as a tablet disintegrant.

- 1.3.5 The appellant's argument that D3 discloses in column 20 (lines 41 to 54) the use of microcrystalline cellulose in a spray-drying process does not affect the considerations set out above. This spray-drying process of D3 involves the use of microcrystalline cellulose, a compressibility-augmenting agent and an active ingredient. The product obtained is an agglomerated material containing a modified form of microcrystalline cellulose in view of its intimate association with the compressibility-augmenting agent (see also column 6, lines 36 to 40). This modified microcrystalline cellulose, which is the main object of the invention of D3, has nothing to do with the "standard" microcrystalline cellulose mentioned in column 4 of D3 as a known tablet disintegrant. D3 does not teach that the modified microcrystalline cellulose enhances the dissolution rate of the agglomerated material prepared by the spray-drying process disclosed in column 20. Hence, the skilled person, confronted with the problem of increasing the dissolution rate of a solid dispersion would not find any relevant incentive to employ microcrystalline cellulose in this part of document D3.

The appellant's further argument that the solid dispersion of the opposed patent can be processed into tablets in the same manner as the agglomerated material obtained by the spray-drying process of D3 is of no relevance in the Board's view, since the experimental data of the patent shows that the solid dispersion of the patent in suit has an enhanced dissolution rate as

such, i.e. before any further processing into a tablet. This effect is not suggested by document D3.

1.3.6 As to document D2, the Board notes that it relates to a spray-dried solid amorphous dispersion of a drug and a polymer. In the context of this document microcrystalline cellulose is mentioned as an optional excipient of the composition, useful as a binder (see [0088]). There is no indication that microcrystalline cellulose could be useful for solving the technical problem of improving the release of TMC 125 (or of any other drug) from a solid dispersion. Thus, also D2 does not render obvious the subject-matter of claim 1.

1.4 In view of the above considerations, the Board concludes that the subject-matter of claim 1 meets the requirements of Article 56 EPC.

2. Claims 14 to 16 - Inventive step

2.1 Claim 14 relates to a solid dispersion obtainable by the process of claim 1. The appellant did not submit any specific argument in relation to the inventive step of claim 14.

As explained in the context of the discussion in respect of claim 1, the presence of microcrystalline cellulose in the solid dispersion results in an increase in its dissolution rate which is not suggested in the prior art. Thus, the product of claim 14 is inventive for the same reasons as those given for claim 1.

2.2 Claims 15 and 16 are likewise inventive since they relate to formulations comprising the solid dispersion of claim 14.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairwoman:



S. Fabiani

R. Hauss

Decision electronically authenticated