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Datasheet for the decision of 31 May 2021

Case Number: T 2135/17 - 3.3.07

Application Number: 09797033.9

Publication Number: 2367540

IPC: A61K9/20

Language of the proceedings: EN

Title of invention:
ORAL DISPERSIBLE TABLET

Patent Proprietor:
ratiopharm GmbH

Opponent:
Generics (U.K.) Limited

Headword:
Oral dispersible tablet / RATIOPHARM

Relevant legal provisions:
EPC Art. 123(2), 56

Keyword:
Amendments - allowable (yes)
Inventive step - (yes)

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Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2135/17 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 31 May 2021

Appellant: (Opponent)	Generics (U.K.) Limited Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Respondent: (Patent Proprietor)	ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm (DE)
Representative:	Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstraße 2 80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 24 July 2017 concerning maintenance of the European Patent No. 2367540 in amended form.**

Composition of the Board:

Chairman	E. Duval
Members:	J. Lécaillon
	Y. Podbielski

Summary of Facts and Submissions

I. European patent EP 2 367 540 (hereinafter "the patent") was granted on the basis of 11 claims. The independent claims of the patent as granted read as follows:

"1. Oral dispersible tablet comprising at least one filler selected from sugars and sugar alcohols, and microcrystalline cellulose, wherein the ratio of the at least one filler selected from sugars and sugar alcohols to the microcrystalline cellulose is in the range of 1:0.75 to 1:1.75 by weight, and wherein said tablet does not contain any disintegrant other than microcrystalline cellulose."

"10. Use of a pharmaceutical composition comprising a pharmaceutically active ingredient, at least one filler selected from sugars and sugar alcohols, and microcrystalline cellulose, wherein the ratio of the at least one filler selected from sugars and sugar alcohols to the microcrystalline cellulose is in the range of 1:0.75 to 1:1.75 by weight for the manufacture of an oral dispersible tablet, which does not contain any disintegrant other than microcrystalline cellulose."

"11. Method of preparing an oral dispersible tablet which comprises the steps of blending a pharmaceutically active ingredient, at least one filler selected from sugars and sugar alcohols, and microcrystalline cellulose, wherein the ratio of the at least one filler selected from sugars and sugar alcohols to the microcrystalline cellulose is in the range of 1:0.75 to 1:1.75 by weight, and processing the

obtained blend into tablets, preferably by direct compression, wherein said tablets do not contain any disintegrant other than microcrystalline cellulose."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as originally filed.

III. The opposition division took the interlocutory decision that, on the basis of the main request, the patent met the requirements of the EPC. The main request was filed by letter dated 24 August 2016 and contained the following 9 claims.

Claim 1 of the main request corresponded to claim 1 as granted wherein the following feature was added: "and further comprising a pharmaceutically active ingredient which is donepezil, memantine or a pharmaceutically acceptable salt thereof."

Dependent claims 2-7 of the main request corresponded to granted claims 2-6 and 9.

Independent claims 8-9 of the main request corresponded to granted claims 10-11 wherein the pharmaceutically active ingredient was specified as being "donepezil, memantine or a pharmaceutically acceptable salt thereof".

IV. The decision of the opposition division, posted on 24 July 2017, cited inter alia the following documents:

F1: WO 2008/057267 A2
D2: EP 1 839 650 A1

V. The opposition division decided in particular as follows:

(a) The main request complied with the requirements of Article 123(2) EPC, because the amendments to claim 1 were supported by the original application, in particular claims 8-9 and page 4 second paragraph.

(b) The subject-matter of the main request was sufficiently disclosed.

(c) The main request fulfilled the requirements of Article 54 EPC.

(d) D2 was the closest prior art to the claims of the main request. The distinguishing feature lay in the range for the ratio of the at least one filler selected from sugars and sugar alcohols to the microcrystalline cellulose. This resulted in tablets having a good combination of disintegration time (less than 26 seconds) and friability (less than 1%). The objective technical problem to be solved was thus the provision of orally dispersible donepezil or memantine tablets having an improved combination of disintegration time and friability. The claimed solution was not obvious in light of the prior art.

VI. The opponent (appellant) lodged an appeal against the above decision of the opposition division.

VII. With its reply to the appellant's statement setting out the grounds of appeal the patent proprietor (respondent) defended its case on the basis of the main request as maintained during first instance proceedings

(main request, see III. above), and on the basis of auxiliary requests 1-3 filed therewith.

VIII. By letter dated 5 May 2021, the appellant announced that it would not be attending the oral proceedings scheduled to take place before the Board of Appeal by videoconference on 20 May 2021.

IX. The oral proceedings were cancelled.

X. The appellant requests that the decision under appeal be set aside and that the patent be revoked.

XI. The respondent requests that the appeal be dismissed, *i.e.* that the patent be maintained as amended during first instance proceedings (main request), or that the patent be maintained on the basis of one of the auxiliary requests 1-3 filed with the reply to the statement setting out the grounds of appeal.

XII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) The amended weight ratio range and the specific pharmaceutically active ingredients were not originally disclosed in combination. Original claim 9 which disclosed the specific pharmaceutically active ingredients, did indeed provide, by way of interdependency with other original claims, support thereof only in combination with broader weight ratio ranges. The main request did thus not fulfill the requirements of Article 123(2) EPC.

(b) F1 was the closest prior art because it related to the same purpose as the patent in suit, namely short disintegration time, low friability and good

hardness and taught the present weight ratio of mannitol and microcrystalline cellulose (MCC). Moreover F1 mentioned direct compression while D2 did not. Finally the presence of the present pharmaceutically active ingredients was not decisive for the choice of the closest prior art, as it would be clear that they did not make any contribution to the desired technical effect.

(c) Even if D2 would be chosen as closest prior art, the claimed subject-matter would not involve an inventive step. Starting from D2, the distinguishing feature would reside in the specific weight ratio of the filler to MCC. No effect had been convincingly substantiated for said distinguishing feature compared to D2. The objective technical problem could consequently only be considered to be how to provide an alternative oral dispersible tablet. Following the teaching of D2 alone, the skilled person would have arrived at the present subject-matter by routine trial and error without exercising any inventive skills. Furthermore the skilled person would also have arrived at the presently claimed subject-matter in an obvious manner by combining the teachings of D2 and F1. Indeed the skilled person would have consulted F1 as it related to the same technical field and purpose as the present main request. The skilled person would have learned from F1 that varying the mannitol content influenced the physical characteristics of the resulting tablets and that a ratio of 1:1.00 (see table 4B and Figure 4 of F1) provided good physico-chemical properties. The main request did thus not fulfill the requirements of Article 56 EPC.

XIII. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) The amended weight range of claim 1 of the main request found basis in the original application (original page 4, second paragraph). Considering the subject-matter of original claims 1 and 9 also the combination of this range and the specific pharmaceutically active ingredients was originally disclosed. The main request thus met the requirements of Article 123(2) EPC.

(b) D2 represented the closest prior art because it indicated that an object of the invention was to provide a rapid disintegrating tablet showing improved strength and abrasion resistance. The purpose of D2 was thus the same as in the present patent. D2 additionally referred to the present pharmaceutically active ingredients.

(c) The claimed subject-matter differed from D2 in the specific weight ratio of the sugar/sugar alcohol to MCC. The references examples 1a, 2a and the examples 3-5 showed that if the content of sugar/ sugar alcohol was increased beyond the claimed ratio, the friability of the tablets got worse. The example 10 and the reference example 3a showed, that if the content of MCC was increased beyond the claimed ratio, there was a tendency to higher hardness. The patent thus revealed that, by using the claimed ratio, an improved balance of disintegration time, hardness and friability was obtained. This technical teaching was not obvious in the light of D2 whether taken alone or in combination with F1. The main request therefore met the requirements of Article 56 EPC.

Reasons for the Decision

Main request

1. Amendments - Article 123(2) EPC

1.1 Claim 1 of the main request is based on original claim 1 wherein:
(a) the tablet was specified as not containing "any disintegrant other than microcrystalline cellulose" (MCC),
(b) the ratio of the at least one filler selected from sugars and sugar alcohols to the MCC was amended to the range "of 1:0.75 to 1:1.75", and
(c) the tablet was specified as "further comprising a pharmaceutically active ingredient which is donepezil, memantine or a pharmaceutically acceptable salt thereof".

1.2 The appellant did not object to the introduction of feature (a), which finds basis in original claim 6.

1.3 Contrary to the appellant's view, the Board considers that the skilled person would have directly and unambiguously derived from the original application that features (b) and (c) may be combined, for the following reasons:

- Feature (c) is disclosed in original claims 8-9. Moreover donepezil and memantine are the sole active ingredients specified in the original examples. Donepezil and memantine as well as pharmaceutically acceptable salts thereof consequently constitute a preferred embodiment of the original application.

- Feature (b) is directly and unambiguously derivable from original page 4, second paragraph. The lower end point of the range was indeed disclosed as the lower end point of a preferred range on original page 4 second paragraph and the upper end point of the range was individually disclosed as a suitable ratio, combinable with any range. Feature (b) amounts thus to the selection of one of several possible ranges.

- The ratio of the filler selected from sugars and sugar alcohols to the MCC on the one hand and the nature of the active ingredient do not appear to be interrelated and concern separate components of the composition. This is not disputed by the appellant, who states in the statement setting out the grounds of appeal that "there is no technical interaction between the selection of APIs and the other components of the claimed ODTs". The skilled person would thus have directly and unambiguously derived from the original application that any disclosed sugar/sugar alcohol to MCC ratio may be used together with any disclosed API, in particular the preferred ones.

1.4 Claims 2-9 of the main request are further based on original claims 2-12.

1.5 Accordingly the main request fulfills the requirements of Articles 123(2) EPC.

2. Sufficiency of disclosure and novelty

The appellant did not pursue in the appeal stage its objections under Article 100(b) EPC and Article 100(a) EPC in combination with Article 54 EPC. The Board agrees with the opposition division that the subject-

matter of the main request fulfills the requirements of Articles 83 and 54 EPC.

3. Inventive step

3.1 Closest prior art

3.1.1 The main request relates to oral dispersible tablets comprising donepezil or memantine or a pharmaceutically acceptable salt thereof as well as two fillers in a specific ratio, a sugar or sugar alcohol and microcrystalline cellulose (MCC), wherein the tablet does not contain any further disintegrant other than MCC. The purpose of the patent is to provide oral dispersible tablets having a very short disintegration time in the mouth, a low friability, and a good hardness.

3.1.2 The parties disagreed as to the choice of the closest prior art document. The appellant considered that F1 represented the best starting point, while the respondent considered that it was D2.

3.1.3 F1 is concerned with tablets in general, *i.e.* not specifically with oral dispersible tablets, and discloses the use of co-processed MCC and sugar alcohol as excipients achieving good compactability, low lubricant sensitivity and low ejection force profile. In example 13 of F1 the disintegration time and hardness of the tablets were also reported in Tables 16-17. Some of the tablets of example 13 achieve a disintegration time in deionized water at 37°C of less than 30 seconds which seems to indicate that said tablets might be suitable as oral dispersible tablets (these tablets have however a different mannitol to MCC ratio than present tablets). Some examples contain MCC

and mannitol in the presently claimed ratio (Example 5 Table 4B), however neither the disintegration time nor a suitability as orally disintegrating tablet are reported. Moreover friability is not reported in F1, nor are donepezil or memantine mentioned as drugs suitable for being formulated as in F1. The key aspect of F1 lies in the co-processing of MCC and the sugar alcohol, which leads to tablets with better properties compared to a physical mixture of both fillers.

3.1.4 On the other hand, D2 relates to quick disintegrating tablets, in particular orally disintegrating tablets, having high tablet strength. These are achieved by using an acrylic copolymer excipient and applying a specific thermal treatment. Donepezil and memantine are mentioned as drugs suitable to be formulated as disclosed in D2. In addition, the examples of D2 describe tablets containing mannitol and MCC as further excipients.

3.1.5 It follows from the above analysis of the content of F1 and D2, that the purpose of D2 is similar to the one of the main request (namely providing orally dispersible tablets comprising a sugar alcohol and MCC with short disintegration time and good tablet strength), while the objective of F1 is slightly different (providing tablets with good compactability, low lubricant sensitivity and low ejection force profile). Furthermore, while some examples of F1 may appear closer in terms of common features to the subject-matter of the main request (ratio of mannitol and MCC of example 5 Table 4B falling under the presently claimed range), there is no information in F1 which allows to conclude that said examples relate to oral dispersible tablets. The Board is of the opinion that this functional feature of present claim 1 of the main

request cannot be ignored. The exemplified tablets of F1 are consequently not closer in terms of common features to the presently claimed subject-matter than the tablets of D2.

Accordingly D2 represents the most suitable starting point for the assessment of inventive step.

3.2 Distinguishing feature, effect and objective technical problem

3.2.1 The parties agreed that the tablets of the main request differ from those of D2 mainly in the specific ratio of sugar alcohol to MCC (1:0.75 to 1:1.75 in claim 1 of the main request versus 1:0.66 in all the examples of D2).

3.2.2 The parties however disagreed as to the effect linked to said distinguishing feature and thus the formulation of the objective technical problem underlying the subject-matter of the main request.

3.2.3 The respondent argued that the selection of the claimed range resulted in oral dispersible tablets with improved balance of disintegration time, hardness and friability. According to the respondent:
- The examples la, 2a and 3-5 show that, if the content of sugar is increased (i.e. ratio "below" the lower end-point of the claimed range), then the friability increases.
- If the content of MCC increases (i.e. ratio "above" the upper end-point of the claimed range) then the tablets tend to have increased hardness as revealed by example 10 and 3a, and the risk of incompatibility with other excipients and of unpleasant mouth feeling increases.

3.2.4 The Board observes the following:

- The examples la and 2a differ from examples 3-5 not only in the nature of the ratio of mannitol and MCC but also in several other features (presence of calcium silicate in example la, nature of the lubricant, tablet shape and/or tabletting machine). Any effect in terms of disintegration time and/or friability observed for examples 3-5 cannot therefore be attributed to the specific ratio of mannitol to MCC.
- Example 10 (according to the claims) and example 3a or reference example 3b (not according to the claims), on the other hand, differ from each other only in the ratio used, namely 1:1.17 in example 10 versus 1:2.00 in example 3a and 1:0.5 in reference example 3b. The tablets of example 10 have a lower hardness than those of example 3a and a shorter disintegration time (20 sec.) than those of reference example 3b (50 sec.). These examples substantiate some effects for the specific ratio used in example 10 (1:1.17), which falls within the claimed range. The patent does however not provide further data allowing to extrapolate these results to the entire claimed range, in particular to the end values thereof. Furthermore, as underlined by the appellant, the hardness value obtained for example 3a (not according to the claims) is comparable to the one obtained for examples 7-8 (according to the claims) and cannot therefore *per se* be considered as too high. Finally, the effect of reduced disintegration time has been shown versus a tablet having a different sugar in a higher content compared to D2 (isomalt in example 10 and 3b and mannitol in D2; ratio of 1:0.50 in reference example 3b but ratio of 1:0.66 in D2). The specific result obtained for example 10 when compared to example 3b cannot thus be considered as substantiating an effect versus D2.

These results are thus not appropriate to substantiate an improved effect over the entire claimed range versus the compositions of D2. The examples of the present patent however substantiate that good, even if not improved, disintegration times and friability are obtained when using the claimed fillers in the claimed ratio.

Starting from D2, the objective technical problem to be solved therefore resides in the provision of an alternative oral dispersible tablet containing donepezil or memantine or a pharmaceutically acceptable salt thereof and a sugar or sugar alcohol and MCC as fillers with good disintegration time and friability.

3.3 Obviousness of the solution

3.3.1 D2 teaches that good disintegration time and hardness are achieved thanks to the use of an acrylic copolymer and a specific thermal treatment. While mannitol and MCC are used as excipients in D2, the use of these excipients appears incidental as regards the objectives of D2. D2 does not teach whether different mannitol/MCC ratios would still lead to oral dispersible tablets with suitable disintegration time and friability. Furthermore F1 describes indeed a very broad range of mannitol:MCC ratio but does not focus on orally dispersible tablets, let alone any influence of mannitol:MCC ratio on friability and dispersion time. Finally, the data provided in the patent in suit, while not being suitable to substantiated an improved effect over the claimed range of ratio compared to D2, still show that modifying the sugar alcohol:MCC ratio has an influence on the friability and disintegration time of orally dispersible tablets. The Board is therefore of

the opinion that starting from D2, whether alone or in combination of F1, the skilled person would not have learned that the ratio of sugar alcohol to MCC can be modified within the claimed range while maintaining good disintegration time and friability.

3.3.2 In this context the appellant argued that D2 "provides no teaching that MCC and sugar alcohol should not be used in a specific ratio or that ranges of specific ratios of these components should be avoided in oral dispersible tablets". Thus, according to the appellant, already from D2 alone would the skilled person have arrived at the presently claimed subject-matter through routine trial and error without exercising any inventive skills. Furthermore, the skilled person, aware of the teaching of F1 that tablets with a broad sugar alcohol to MCC ratio have good friability, hardness and disintegration time, would have varied the sugar alcohol to MCC ratio without exercising inventive skills to solve the problem posed.

3.3.3 The Board cannot share this approach, for the following reasons:

- The absence of indication regarding the ratio of sugar alcohol to MCC in D2 cannot be considered as an indication that it can be varied as desired, while maintaining good friability and disintegration properties. D2 does not provide any link between said ratio and the desired physico-chemical properties. The Board considers that D2 alone does not provide the skilled-person with an incentive to modify the ratio between fillers to solve the problem posed.

- F1 does not concentrate on orally disintegrating tablets. While some of the tablets of example 13 of F1

might be suitable as oral dispersible tablets (see above 3.1.3), the preparation of orally dispersible tablets is not a purpose of F1. Moreover these specific fast disintegrating tablets of F1 contain MCC and mannitol in ratios falling outside the presently claimed range. It is undeniable that F1 describes a wide range of possible mannitol to MCC ratios. However F1 does not provide any hint towards a relationship between said ratio and good friability and disintegration properties of orally dispersible tablets. The key aspect of F1 lies indeed in the co-processing of MCC and the sugar alcohol, which leads to tablets with better properties compared to a physical mixture of both fillers. As detailed above (3.1.3), some examples contain MCC and mannitol in the presently claimed ratio (Example 5 Table 4B), however neither the disintegration time nor a suitability as orally disintegrating tablet are reported. It cannot therefore be concluded that F1 would have motivated the skilled person to modify the ratio of sugar alcohol to MCC in the examples of D2 to prepare alternative orally dispersible tablets having good friability and disintegration properties. The Board is of the opinion that any opposite conclusion can only be reached based on hindsight.

3.3.4 Accordingly, the main request fulfills the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero E. Duval

Decision electronically authenticated