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Datasheet for the decision of 28 April 2015

Case Number: T 0458/11 - 3.3.07

Application Number: 03700435.5

Publication Number: 1469832

IPC: A61K9/16, A61K9/14

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITIONS OF AMORPHOUS DISPERSIONS OF DRUGS AND LIPOPHILIC MICROPHASE-FORMING MATERIALS

Patent Proprietor:
BEND RESEARCH, INC.

Relevant legal provisions:
EPC Art. 54, 56, 123(2)

Keyword:
Amendments - added subject-matter (yes)
Novelty - auxiliary request (yes)
Inventive step - auxiliary request (yes)

Decisions cited:
T 0789/89

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Case Number: T 0458/11 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 28 April 2015

Appellant: (Patent Proprietor)	BEND RESEARCH, INC. 64550 Research Road Bend, OR 97701-8599 (US)
Representative:	Adam, Holger Kraus & Weisert Patentanwälte PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 15 December 2010 revoking European patent No. 1469832 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Semino
	P. Schmitz

Summary of Facts and Submissions

I. The appeal of the patent proprietor (appellant) lies against the decision of the opposition division announced at the oral proceedings on 10 November 2010 to revoke European Patent 1 469 832. The patent was granted on the basis of 13 claims, claims 1 reading as follows:

"1. A composition comprising:
(a) a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer, said concentration-enhancing polymer being selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethyl cellulose, hydroxypropyl methyl cellulose, poloxamers, polyvinylpyrrolidone, polyvinyl alcohols that have at least a portion of their repeat units in unhydrolyzed form, and mixtures thereof;
(b) a lipophilic microphase-forming material, said composition having a mass ratio of said lipophilic microphase-forming material to said low solubility drug of from 0.1 to 100;
(c) said lipophilic microphase-forming material being present in a sufficient amount so that said composition provides concentration enhancement of said drug in a use environment at least 1.25-fold relative to both a first control composition and a second control composition; wherein
(i) said first control composition consists essentially of an equivalent amount of said solid amorphous dispersion with no lipophilic microphase-forming material present;

(ii) said second control composition consists essentially of an equivalent amount of said low-solubility drug in undispersed form with an equivalent amount of said lipophilic, microphase-forming material but with no concentration-enhancing polymer;
wherein said solid amorphous dispersion and said lipophilic microphase-forming material are both present in a single dosage form which is an oral tablet or capsule;
wherein said lipophilic, microphase-forming material comprises from 10 wt% to 80wt% of said dosage form; and
wherein said lipophilic, microphase-forming material is selected from the group consisting of mixtures of polyethoxylated castor oils and medium-chain glyceryl mono-, di-, and/or tri-alkylates; mixtures of polyoxyethylene sorbitan fatty acid esters and medium-chain glyceryl mono-, di-, and/or tri-alkylates; mixtures of polyethoxylated castor oils and sorbitan esters; mixtures of sodium taurocholic acid and palmitoyl-2-oleyl-sn-glycero-3-phosphocholine and other natural or synthetic phosphatidyl cholines; and mixtures of polyglycolized glycerides and medium-chain glyceryl mono-, di-, and/or tri-alkylates."

II. Two oppositions were filed, based on Article 100 (a), (b), (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, the patent was not sufficiently disclosed and its subject-matter extended beyond the content of the application as filed. Opponent 2 withdrew its opposition during the opposition procedure.

III. The decision was based as main request on the granted patent, as auxiliary request 1 on a set of claims filed with letter of 5 November 2010 and as auxiliary request

2 on a further set of claims filed with letter of 4 December 2009 (then as the single auxiliary request).

Claim 1 of auxiliary request 1 corresponded to granted claim 1 with the further specification that "the lipophilic microphase-forming material is dispersed, along with the drug, in the concentration-enhancing polymer". Claim 1 of auxiliary request 2 was amended with respect to granted claim 1 in that the concentration-enhancing polymer was specified to be "hydroxypropyl methyl cellulose acetate succinate".

IV. In the decision the following documents were cited *inter alia*:

D1: WO-A-99/27946
D2: WO-A-03/004060
D3: WO-A-00/00179
D5: Data sheet filed by the patent proprietor with letter of 4 December 2009

V. The decision under appeal can be summarised as follows:

a) A basis was available in the application as filed for the deletion of two features in granted claim 1 with respect to claim 1 as filed. A suitable method for determining the concentration enhancement was disclosed in the patent in suit, so that also the objection of lack of sufficiency was not successful. Granted claim 1 was, however, not novel over documents D1 and D2 (the latter belonging to the state of the art under Article 54(3) EPC), which disclosed compositions with the same starting materials and the same processing steps as the patent in suit, so that also the not explicitly disclosed features (the amorphous

dispersion and the concentration enhancement) were implicitly disclosed.

b) Claim 1 of auxiliary request 1 was still not novel over D1 and D2.

c) Claim 1 of auxiliary request 2 was novel over D1 and D2, as they did not disclose hydroxypropyl methyl cellulose acetate succinate as the concentration enhancing polymer. It was, however, not inventive over document D3, taken as the closest prior art, which addressed a problem similar to the one of the patent in suit and from which the subject-matter of claim 1 differed in the particular combination of ingredients. Also taking account of the data sheet D5 a synergistic effect was not credible over the whole scope of the claim, so that the problem was the provision of alternative dosage forms of low-solubility drugs. All ingredients of the claimed composition were already cited in D3, so that the the proposed solution was not inventive in view of D3 alone.

VI. The appellant lodged an appeal against that decision. With the statement setting out the grounds of appeal, the appellant filed a single set of claims as new main request replacing all requests on file.

The main request included as claims 1 to 3 three independent claims which corresponded to granted claim 1 with the addition that "said lipophilic microphase-forming material is mixed but not included in said solid amorphous dispersion" (all three claims) and the further specification that said lipophilic microphase-forming material "is adsorbed on to a porous substrate" (claim 1), "is dispersed in a water soluble

or water dispersible matrix" (claim 2) or "is dispersed in a concentration-enhancing polymer" (claim 3).

VII. In a communication sent in preparation of oral proceedings, the Board expressed *inter alia* a number of concerns regarding "the basis in the original application indicated by the appellant for the features added to independent claims 1 to 3" (point 1 in the communication).

VIII. With letter dated 16 March 2015 the appellant filed six sets of claims as auxiliary requests 1 to 6.

The claims of auxiliary request 1 corresponded to the ones of the main request with the redefinition in claim 1 of the substrate onto which the lipophilic microphase-forming material is adsorbed as "a water-insoluble substrate". In auxiliary request 2 the same amendment was introduced, claim 3 was deleted and the dependent claims were renumbered accordingly.

IX. The remaining opponent (opponent 1), which had previously requested a transfer of the opposition, withdrew its opposition by letter of 22 April 2015.

X. Oral proceedings were held on 28 April 2015.

XI. The arguments of the appellant can be summarised as follows:

Main request - amendments

a) The common feature to the three independent claims, namely that the "lipophilic microphase-forming material is mixed but not included in said solid amorphous dispersion" was to be found on

page 17 of the original application as one of a number of options. However, it was described in detail in the following pages (page 19 and pages 25 to 28), so as to make it clear that it constituted a preferred embodiment of the invention. The further added features of claims 1 to 3 were disclosed on page 11 and on pages 25 to 28. In the latter citation the additional features of claims 1 and 2 were disclosed in combination with the embodiment wherein the lipophilic microphase-forming material was mixed, but not part of the dispersion. As to the wording used in claim 1 to define the substrate ("porous substrate"), even if it did not literarily correspond to the one used in the original application, it was still derivable therefrom, as it was specified that preferred substrates were "highly porous". As to the basis for the features added to claim 3 in combination, the third paragraph on page 11 provided a literal basis for the lipophilic microphase-forming material dispersed in a concentration-enhancing polymer and the previous paragraph introduced the idea of separating the lipophilic microphase-forming material from the dispersion. Moreover, the embodiment in which a single dispersion including the lipophilic microphase-forming material was present was a particularly preferred one, but not the only disclosed one. The alternative of claim 3 was at the same level of abstraction as the ones of claims 1 and 2 with respect to the disclosure in the application as filed.

Auxiliary request 1 - amendments

b) In auxiliary request 1 the precise wording used on page 26 with regard to the definition of the substrate onto which the lipophilic microphase-forming material is adsorbed was introduced in claim 1.

Auxiliary request 2 - amendments

c) The deletion of claim 3 rendered moot all the objections related to the embodiment covered by it.

Novelty and inventive step

d) Documents D1 and D2 were no longer relevant for lack of novelty, as they did not disclose the features added to the independent claims according to all requests with respect to granted claim 1. These features constituted further differences with respect to document D3, which was considered as the closest prior art in the decision under appeal. The effect of the features added to claim 1 was the minimisation of the effect of the lipophilic microphase-forming material on the glass transition temperature of the dispersion. The features added to claims 2 and 3 served to render the lipophilic microphase-forming material solid in order to aid its incorporation into solid dosage forms, to aid in dispersing the lipophilic microphase-forming material as a microphase and to provide additional concentration-enhancing polymer. These effects were technically clear and no further experimental evidence was needed. As there was no incentive in the available prior art

to add the distinguishing features in order to obtain these effects, the compositions according to all independent claims involved an inventive step.

XII. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims filed as main request with the statement setting out the grounds of appeal or, in the alternative, according to one of the six sets of claims filed as auxiliary requests 1 to 6 with letter of 16 March 2015.

Reasons for the Decision

Status of opponent

1. The opponent has withdrawn its opposition and is thus no longer a party to the proceedings (see Case Law of the Boards of Appeal, 7th edition 2013, IV.C.4.1.2, in particular T 789/89, OJ EPO 1994, 482).

Main request - amendments

2. Independent claims 1 to 3 of the main request include with respect to granted claim 1 an additional feature common to all three claims ("said lipophilic microphase-forming material is mixed but not included in said solid amorphous dispersion") and a further specific feature different in each of them (the lipophilic microphase-forming material "is adsorbed on to a porous substrate" in claim 1, "is dispersed in a water soluble or water dispersible matrix" in claim 2 and "is dispersed in a concentration-enhancing polymer" in claim 3).

2.1 As to independent claim 1, there is no disclosure in the original application of the lipophilic microphase-forming material as being adsorbed on to a "porous substrate". The two possible basis indicated by the appellant disclose that the lipophilic microphase-forming material may be adsorbed to the surface of a "solid material" (page 11, lines 8 to 21) or may be adsorbed to a "water insoluble substrate" (page 26, lines 3 to 19). While in both cases it is mentioned that "Highly porous materials such as calcium silicate are preferred" (page 11, lines 15 and 16; page 26, lines 11 and 12), this cannot be equated to the disclosure of a generic porous substrate (i.e. with any degree of porosity). Therefore the added feature is not directly and unambiguously derivable from the application as originally filed.

2.2 With regard to claim 3 reference was made by the appellant to the disclosure on pages 11 and 17.

2.2.1 On page 17 several options are disclosed regarding the collocation of the lipophilic microphase-forming material with respect to the dispersion comprising the low-solubility drug and the concentration-enhancing polymer, namely it may be included in the dispersion, it may be mixed with but not included within the dispersion or it may be co-administered with the dispersion (page 17, lines 12 to 24). In this context the alternative embodiments are not related to other features of the composition, nor to the presence of other ingredients or substrate in the composition. In the following pages some more details are given for the method of preparation of the composition, whereby the different alternatives are at times mentioned or implied (e.g. on page 23, lines 17 to 20 for the first embodiment and on the paragraph bridging pages 25 and

26 for the second embodiment) without presenting any of the alternatives as a preferred embodiment of the invention.

2.2.2 In the third paragraph of page 11 the further feature added to claim 3 ("the lipophilic, microphase-forming material is dispersed in a concentration-enhancing polymer") finds a literal basis (lines 23 to 25), however not in relationship to the presence of the lipophilic microphase-forming material as mixed with but not included within the dispersion. On the contrary it is said that it is preferred to have it dispersed with the drug and one or more concentration-enhancing polymers in a single dispersion (lines 29 to 33). The fact that in the previous paragraph mention is made of the advantage of separating the lipophilic microphase-forming material from the dispersion (lines 16 to 19) has no bearing, as it clearly refers to a different embodiment (with the lipophilic microphase-forming material adsorbed to the surface of a solid substrate, such as a highly porous material, see lines 7 to 16), which is unrelated to the presence of the lipophilic microphase-forming material dispersed in a concentration enhancing-polymer as described in the third paragraph (see in particular the word "Alternatively" at the beginning of the paragraph and the previously cited indication of the lipophilic microphase-forming material preferably present within a single dispersion with the further ingredients).

2.2.3 The combination of the features of claim 3 that the "lipophilic microphase-forming material is mixed but not included in said solid amorphous dispersion" and that it "is dispersed in a concentration-enhancing polymer" is therefore not directly and unambiguously derivable from the application as originally filed. In

this respect it is noted that the situation cannot be compared to the one of the embodiments of claims 1 and 2, for wich a separate part of the application is available as a basis for the combination of the added features (see points 4.1 to 4.3, below).

2.3 The requirements of Article 123(2) EPC are therefore not met for the main request in view of the expression "porous substrate" in claim 1 and of the combination of features in claim 3.

Auxiliary requests 1 and 2 - admittance

3. Auxiliary requests 1 and 2 were filed as a direct and clear reaction to the concerns under Article 123(2) EPC expressed by the Board in the communication (the wording "porous substrate" is amended in both requests, claim 3 is deleted in auxiliary request 2), which related to objections raised for the first time therein, so that the requests could not have been reasonably filed earlier. On that basis auxiliary requests 1 and 2 are admitted into the proceedings.

Auxiliary request 1 - amendments

4. As auxiliary request 1 still includes claim 3 with no amendments with respect to claim 3 of the main request, the requirements of Article 123(2) EPC are not met for the same reasons as given above (see point 2.2).

Auxiliary request 2 - amendments

5. In auxiliary request 2 the deletion of claim 3 and the amendment in claim 1 which no longer contains the expression "porous substrate" (amended to "water-insoluble substrate") overcome the objection under

Article 123(2) EPC on which the two previous requests failed.

5.1 The combination of features added to claims 1 and 2 with respect to the granted claims ("said lipophilic microphase-forming material is mixed but not included in said solid amorphous dispersion" in both claims and the lipophilic microphase-forming material "is adsorbed on to a water-insoluble substrate" or "is dispersed in a water soluble or water dispersible matrix" in claim 1 and 2 respectively) finds a basis in the paragraph bridging pages 25 and 26 and in the following paragraph on page 26 in the light of the first full paragraph of page 17.

5.2 As detailed above, the possibility of having lipophilic microphase-forming material mixed but not included in the solid amorphous dispersion of the drug and the concentration-enhancing polymer is disclosed as one of the possible alternatives on page 17 (see point 2.2.1, above). This embodiment is dealt with in the paragraph bridging pages 25 and 26 where the case is analysed "where the composition of the present invention is prepared by mixing the previously formed solid amorphous dispersion with the lipophilic microphase-forming material" and "the mixture can be prepared by any method resulting in a uniform mixture of the dispersion and the lipophilic microphase-forming material" (page 25, lines 29 to 32). In this context two alternatives are indicated in the following paragraph, namely "to disperse the lipophilic microphase-forming material in a water soluble or water dispersible matrix" or to have it "adsorbed to a water insoluble substrate" (page 26, lines 3 to 7).

5.3 The skilled person would therefore derive the combination of features added to claims 1 and 2 with respect to granted claim 1 directly and unambiguously from the application as filed. As to granted claim 1, the issue of a possible extension beyond the content of the application as filed had been dealt with in favour of the appellant in the decision under appeal (see point V a), above) and the Board does not see any need of any further analysis in this respect.

5.4 On that basis it is concluded that auxiliary request 2 meets the requirements of Article 123(2) EPC.

Auxiliary request 2 - novelty

6. Novelty with respect to documents D1 and D2 (the latter being prior art under Article 54(3) EPC), which were found to be novelty destroying for granted claim 1 in the decision under appeal (see point V a), above), is to be analysed.

6.1 Example 2 of document D1 (page 9, line 19 to page 10, line 2, also with reference to example 1 on page 9) discloses a preparation comprising a low-solubility drug (cyclosporin), concentration enhancing polymers (hydroxypropyl methyl cellulose phthalate and Poloxamer 124) and a lipophilic microphase-forming material, namely Cremophor RH 40 (polyethoxylated castor oil) and medium-chain triglycerides. The components of the mixture are dissolved in acetone and then the solvent is evaporated under reduced pressure. The obtained composition is powdered and formulated *inter alia* in capsules and tablets.

6.2 By means of the method of preparation where the ingredients are dissolved in a single solvent which is

then evaporated, a skilled person can only conclude that in example 2 of D1 a single dispersion is obtained, in which the drug, the concentration-enhancing polymers and the lipophilic microphase-forming material are present. The compositions of claims 1 and 2 of auxiliary request 2 are therefore distinguished therefrom at least in that the lipophilic microphase-forming material is "mixed with but not included in the dispersion". Moreover there is no mention in D1 of a separate dispersion of the lipophilic microphase-forming material in a water-soluble or water dispersible matrix, nor of its adsorption onto a water-insoluble substrate.

6.3 Example 15 of D2 (page 24, lines 8 to 19) discloses a preparation comprising a low-solubility drug (aceclofenac), a concentration enhancing polymer (polyvinylpyrrolidone) and a lipophilic microphase-forming material, namely Tween 80 (polyoxyethylene sorbitan monooleate, page 8, lines 12 and 13) and medium-chain triglycerides. These components are dissolved in a mixture of acetone and ethanol and the resulting solution is spray-dried. In example 19 (page 26, lines 10 to 16) the powder of example 15 (among others) is mixed with colloidal silicon dioxide (Cab-O-Sil) or magnesium stearate and then filled into empty hard-gelatin capsules.

6.4 Also in this case, by means of the method of preparation where dissolution of all the ingredients in a single solvent is accomplished followed by spray-drying, a skilled person can only conclude that a single dispersion is obtained, in which the drug, the concentration-enhancing polymer and the lipophilic microphase-forming material are present. This is not changed by the fact that, after preparation of the

powder, a water-insoluble substrate, such as colloidal silicon dioxide, is mixed with it, since this mixing takes place after the dispersion has already been formed and there is no information, nor any technical reason which could imply that the lipophilic microphase-forming material could separate from the already formed dispersion and become adsorbed onto the substrate. In view of this the compositions of claims 1 and 2 are distinguished from the disclosure in D2 at least in that the lipophilic microphase-forming material is "mixed with but not included in the dispersion". Moreover, in D2 there is no separate dispersion of the lipophilic microphase-forming material in a water-soluble or water dispersible matrix, nor any adsorption thereof onto a water-insoluble substrate.

6.5 On that basis the compositions of claims 1 and 2 of auxiliary request 2 are new over the disclosures of documents D1 and D2.

Auxiliary request 2 - inventive step

7. With regard to inventive step, the opposition division decided that the request of lowest ranking at that stage was not inventive over document D3, taken as the closest prior art (see point V c), above). With regard to auxiliary request 2 currently on file, the Board sees no reason to take a different starting point, but comes to a different conclusion, as the claimed subject-matter now relates to different embodiments.

7.1 Document D3 discloses in the context of improving the bioavailability of poorly water-soluble drugs (paragraph bridging pages 2 and 3) a solid dispersed preparation prepared by dissolving or dispersing the

drug in an oil, a fatty acid or a mixture thereof, mixing with a water-soluble polyol matrix and drying the mixture (claim 1). The obtained powder can be formulated in various forms, including tablets or capsules (page 5, lines 20 to 24). Caprylic/capric triglyceride and medium-chain glyceride are disclosed in a long list as examples of suitable oil (page 6, line 19 and page 7, lines 8 and 9); suitable water-soluble matrix materials are among others polyvinylpyrrolidone, hydroxypropyl methyl cellulose acetate succinate and cellulose acetate phthalate (page 7, lines 17 to 27); PEG-40 and PEG-60 hydrogenated castor oils may be added as surfactants (page 8, lines 1 to 16).

7.2 The compositions of claims 1 and 2 differ from the disclosure in D3 at least in the specific selection of ingredients (ingredients falling under those indicated in the claims are mentioned in D3 in different lists among many alternatives) and in that the lipophilic microphase-forming material is mixed with but not included in the dispersion and is adsorbed onto a water-insoluble substrate (claim 1) or dispersed in a (separate) water-soluble or water dispersible matrix (claim 2).

7.3 There is no evidence that the choice of the specific ingredients in combination has as such an effect over the preparation of D3 (i.e. with respect to the choice of polymers or oils different from those listed in claims 1 and 2). With respect to the lipophilic microphase-forming material not being included in the dispersion, but being mixed with it while being adsorbed onto a water-insoluble substrate, there is also no evidence that the effect claimed by the appellant (the minimisation of the effect of the

lipophilic microphase-forming material on the glass transition temperature of the dispersion) has been achieved by means of the added feature neither for specific embodiments, nor for the whole scope of the claim. As to the lipophilic microphase-forming material being dispersed in a (separate) water-soluble or water dispersible matrix, the effects invoked by the appellant (the solidification of the lipophilic microphase-forming material in order to aid its incorporation into solid dosage forms, the aid in dispersing the lipophilic microphase-forming material as a microphase and the provision of additional concentration-enhancing polymer with reference to page 11, third paragraph of the application as filed) do not appear to be related to the added feature, nor to be supported by evidence.

7.4 Under these circumstances, the problem solved can be seen in the provision of a further composition comprising a low-solubility drug and including a concentration-enhancing polymer and a lipophilic material.

7.5 While the choice of oils, polymers and surfactants specifically mentioned in D3 would be an obvious solution to the posed problem, no hint can be found in D3, nor in the prior art on file (in particular not in D1, see points 6.1 and 6.2, above) regarding the option of having the lipophilic microphase-forming material separate from the dispersion (mixed with it, but not included in it), while being adsorbed onto a water-insoluble substrate or dispersed in a (separate) water-soluble or water dispersible matrix.

7.6 In view of that the presence of an inventive step must be acknowledged for the compositions of claims 1 and 2 over the available prior art.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the instruction to maintain the patent on the basis of the claims of auxiliary request 2 and a description yet to be adapted.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated