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Datasheet for the decision of 18 January 2022

Case Number: T 0574/19 - 3.3.07

Application Number: 10705984.2

Publication Number: 2400954

IPC: A61K9/20, A61K9/28, A61K31/439

Language of the proceedings: EN

Title of invention:
PROCESS FOR FORMING SOLID ORAL DOSAGE FORMS OF SOLIFENACIN AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

Patent Proprietor:
KRKA, d.d., Novo mesto

Opponents:
Alfred E. Tiefenbacher (GmbH & Co. KG)
Patentree, Lda

Headword:
Process for forming solid oral dosage forms of solifenacin / KRKA

Relevant legal provisions:
EPC Art. 100(a), 56
RPBA 2020 Art. 13(2)

Keyword:
Late-filed evidence - admitted (no)
Inventive step - main request, auxiliary requests I, II (no) - auxiliary request III (yes)

Decisions cited:
T 2759/17, T 1112/19

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Case Number: T 0574/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 18 January 2022

Appellant: (Opponent 1)	Alfred E. Tiefenbacher (GmbH & Co. KG) Van-der-Smissen-Straße 1 22767 Hamburg (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Appellant: (Opponent 2)	Patentree, Lda Rua Salazares 842 4149-002 Porto (PT)
Representative:	Patentree Edificio Net Rua de Salazares, 842 4149-002 Porto (PT)
Respondent: (Patent Proprietor)	KRKA, d.d., Novo mesto Smarjeska cesta 6 8501 Novo mesto (SI)
Representative:	Hoefer & Partner Patentanwälte mbB Pilgersheimer Straße 20 81543 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 4 January 2019 rejecting the opposition filed against European patent No. 2400954 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	L. Basterreix

Summary of Facts and Submissions

I. European patent 2 400 954 (hereinafter "the patent") was granted on the basis of 13 claims.

Claim 1 of the patent read as follows:

"A process for the preparation of a solid oral dosage form comprising:
a.) an effective amount of crystalline solifenacin or its pharmaceutically acceptable salt,
b.) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms,
in the absence of a solvent,
said solid oral dosage form prepared by a process in the absence of a solvent, comprising one or more disintegrants and/or superdisintegrants in the range 1 to 90% by weight, preferably 1-40% by weight, more preferably 1-25% by weight, a binder in the amount 1 to 90% by weight, preferably 1-50% by weight, a lubricant in the amount 0.1 to 10% by weight, and a filler or diluent within a range 20-99% by weight, preferably 50-99% by weight, so that the total sum of the combination of components of the formulation is 100%, the main excipient being lactose monohydrate, microcrystalline cellulose or mannitol."

Claim 10 of the patent related to a solid oral dosage form defined in particular by the same components and prepared by a process in the absence of a solvent according to claim 1.

II. Two oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and

inventive step, and it extended beyond the content of the application as filed.

III. The opposition division took the decision to reject the oppositions filed against the patent.

IV. The decision cited in particular the following documents:

D1: EP 1 728 791 A1
D2: WO 2008/013851
D3: IN 1221 /DEL2007
D4: Ritschel et al., "Die Tablette-Handbuch der Entwicklung, Herstellung und Qualitatssicherung", Editio Cantor Verlag Aulendorf, 2002
D5: Augsburger et al., "Pharmaceutical Dosage Forms: Tablets" CRC Press, 2008, Ed.3
D7: WO 2008/128028 A2
D8: EP 2 018 850 A1
D19: J. Zheng, Formulation and Analytical Development for Low Dose Oral Drug Products, Wiley, 2008, chapters 5-7

V. The opposition division decided the following:

(a) The patent did not introduce added subject-matter.

(b) The claimed subject-matter was novel over D6 and D7.

(c) Regarding inventive step, there were two equally suitable starting points in D1, both relating to the preparation of solid oral forms of crystalline solifenacin, namely the wet granulation and the dry granulation.

Starting from the wet granulation embodiment of D1, the claimed subject-matter differed by the absence of solvent and the presence of 1 to 90% disintegrant. The objective problem was the provision of a process for the preparation of a solid formulation of crystalline solifenacin which comprises fewer degradation products. The claimed solution was not obvious in light of the prior art.

Starting from the dry granulation embodiment of D1, the claimed subject-matter differed by the presence of the main excipient selected from lactose monohydrate, microcrystalline cellulose or mannitol. The objective problem was the provision of an alternative dry process for the preparation of a solid formulation of crystalline solifenacin. The skilled person could not have predicted that the excipients recited in claim 1 would be suitable for preparing stable uniform solid compositions comprising crystalline solifenacin by a dry process.

Hence the claimed subject-matter involved an inventive step.

VI. Both opponent O1 (appellant 1) and opponent O2 (appellant 2) lodged an appeal against the decision of the opposition division.

VII. In its reply to the appeals, the patent proprietor (respondent) defended its case on the basis of the patent as granted as the main request, and filed auxiliary requests I-VII with its reply. The respondent also filed D20 with the same reply:

D20: page 19 of WO2005/092889

The respondent further filed auxiliary requests VIII-XI by letter dated 6 April 2020.

VIII. Claim 1 of auxiliary request I differed from claim 1 of the main request in that the pharmaceutically acceptable salt of solifenacin was selected from among several defined solifenacin salts.

Claim 1 of auxiliary request II was limited to the preparation of dosage form comprising an effective amount of crystalline solifenacin succinate.

Claim 1 of auxiliary request III contained the same limitation to solifenacin succinate as in auxiliary request II, and in addition incorporated the following feature:

> "pharmaceutical excipients being used in which, cumulatively, the average particle size of the main excipient is larger than 60 µm."

IX. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA dated 6 October 2021.

X. Appellant 1 filed further submissions on 22 November 2021.

XI. By letter dated 22 December 2021, the respondent filed D21a and D21b:

D21a: Pharmaceutical Dosage Forms, Tablets, edited by H. A. Lieberman et al., Second Edition, 1989, vol. 1, p. 196-197

D21b: Pharmaceutical Dosage Forms, Tablets, edited by H. A. Lieberman et al., Second Edition, 1989, vol. 3, p. 343-344

XII. The relevant arguments of the appellants may be summarised as follows:

(a) Admittance of D21a and D21b

The late filing of D21a and D21b was not justified by any exceptional circumstances. Hence D21a and D21b were not to be admitted into the proceedings.

(b) Main request

Added subject-matter:

Claim 1 of the main request resulted from the addition, to claim 1 as filed, of the features of claims 11 and 15 as filed, neither of which was dependent on said claim 1. This combination extended beyond the content of the application as filed.

Inventive step:

D1 addressed the problem of solifenacin stability by limiting the formation of amorphous material, and contained two equally suitable starting points, namely the wet granulation and the dry granulation.

The subject-matter of claim 1 of the main request differed from the dry granulation method of D1 by the presence of the main excipient selected from lactose monohydrate, microcrystalline cellulose or mannitol. The objective technical problem was either to provide a mere alternative to the dry process of D1, or to

provide appropriate excipients for the preparation of a crystalline solifenacin (salt)-containing solid formulation using direct compression. Lactose monohydrate, microcrystalline cellulose and mannitol were generally known for use in direct tableting (see D4, D5 and D19) or in the context of solifenacin compositions (see D2 and D3). Thus the claimed solution did not involve an inventive step.

Alternatively, starting from the wet granulation method of D1, the difference was the absence of solvent and the presence of 1 to 90% disintegrant. This had the effect of avoiding the degradation of solifenacin by reducing the moisture content. The objective technical problem was to avoid the degradation of solifenacin. Since D1 also disclosed that the absence of solvent avoided the amorphization of solifenacin and consequently increased stability, the claimed solution was obvious.

Lastly, D8 also rendered the claimed subject-matter obvious. D8 described the preparation of pharmaceutical compositions comprising solifenacin being amorphous for 95-95 wt%, thus implicitly disclosing the presence of 1-5 wt% crystalline solifenacin. D8 indicated that the crystalline form was more stable than the amorphous form. Thus the claimed subject-matter was rendered obvious by D8.

(c) Auxiliary requests

Since D1 described solifenacin succinate as the preferred salt, auxiliary requests I and II also lacked an inventive step over D1.

Regarding auxiliary request III, the patent contained no comparison showing that the average particle size of the main excipient was decisive in solving the problem of content uniformity. The use of lactose monohydrate or microcrystalline cellulose with the claimed particle size was common. Hence auxiliary request III also lacked an inventive step.

XIII. The respondent's arguments may be summarised as follows:

(a) Admittance of D21a and D21b

The filing of D21a and D21b, both reflecting common general knowledge, was in response to appellant 1's submission on 22 November 2021 and to the Board's preliminary opinion. Hence D21a and D21b were to be admitted into the proceedings.

(b) Main request

Added subject-matter:

The opposition division had rightly found that the product-by-process and the process claims were interlinked, such that introducing the product-by-process features of claims 11 and 15 into claim 1 did does not contravene the requirements of Article 123(2) EPC.

Inventive step:

D1 addressed the problem of stability, which was similar to the problem identified in the patent. Furthermore, D1 disclosed several processes for preparing solifenacin containing compositions,

especially wet granulation, compressing-molding, and melt granulation. In view of the preference expressed for the wet granulation in D1 (see paragraph [0038]), the skilled person would take this wet granulation embodiment as starting point for the assessment of inventive step.

The subject-matter of claim 1 of the main request differed from the wet granulation embodiments of D1 (see examples 1-4) at least in that the process was performed in absence of solvent, and by a different excipient composition. The objective problem to be solved was the provision of a process for the preparation of a solid formulation of crystalline solifenacin which comprises fewer degradation products. The claimed solution involved an inventive step because the skilled person found no hint, in D1 or in the other items of the prior art, to carry out the aqueous wet granulation embodiments of D4 in the absence of solvent.

The dry granulation embodiment briefly mentioned in D1 would be disregarded by the skilled person as a starting point, because D1 emphasized that this direct tableting procedure was associated with considerable drawbacks in terms of content uniformity and sticking of the mixture to punches during compression, and because it was not sufficiently disclosed as regards the combination of excipients to be used for this compressing-molding embodiment. Even if this embodiment was considered as starting point, the process of claim 1 of the main request provided not only a high bioavailability, less degradation, and excellent uniformity, but also overcame the problems of poor content uniformity and sticking to punches associated with direct compression, as shown by the successful

production of tablets in the examples of the patent. The objective problem was therefore the provision of an improved process for the preparation of a solid oral dosage form. D1 was silent on excipients to be used for the compressing-molding method. The skilled person would not arrive at the claimed subject-matter either when also taking D4, D5, D19, D2 or D3 into account.

D8 would also be disregarded by the skilled person as a starting point for solving the problem of the subject-matter defined in claim 1. D8 aimed at solving a different problem, namely the provision of a pharmaceutical composition wherein the solifenacin was in amorphous form and stabilised by a suitable excipient. Even if starting from D8, the skilled person would not deviate from its teachings and would not replace the amorphous solifenacin stabilized by suitable excipients of D8 by crystalline solifenacin.

(c) Auxiliary requests

In auxiliary request III, the most preferred features of claim 7 as granted had been introduced into claim 1. The main excipient particle size advantageously contributed to overcoming the problems caused by the strong aggregation properties of solifenacin salts leading to poor content uniformity and sticking of the mixture to the punches during compression, as well as contributed to an advantageous bioavailability (see paragraphs [0080]-[0082] and examples 1, 3, 5 of the patent). Hence auxiliary request III met the requirements of inventive step.

XIV. Both appellant 1 and appellant 2 request that the decision under appeal be set aside and that the patent be revoked in its entirety. Appellant 1 also request

that D21a and D21b not be admitted into the appeal proceedings.

XV. The respondent requests that the appeal be dismissed, i.e. that the patent be maintained as granted, or, alternatively, that the patent be maintained on the basis of one of auxiliary requests I-VII filed with the reply to the appeals, or auxiliary requests VIII-XI filed on 6 April 2020.

The respondent also requests that the new objection of lack of novelty over D8 be disregarded during the appeal proceedings.

Reasons for the Decision

1. Admittance of D21a/D21b into the proceedings

The respondent submitted D21a and D21b with its letter dated 22 December 2021, thus after notification of the summons to oral proceedings dated 10 May 2021. The admission of D21a and D21b is subject to the provision of Article 13(2) RPBA 2020. According to Article 13(2) RPBA 2020, any amendment to a party's appeal case made after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

The Board can identify no exceptional circumstances in the present case. The respondent contends that the filing of D21a and D21b is in direct response to appellant 1's submission dated 22 November 2021, and to items 2.3.1 and 3 of the Board's preliminary opinion. However, the respondent does not identify any specific element in the Board's preliminary opinion which would

justify this late filing. This opinion did not contain any novel objection. Furthermore, the submissions regarding D4 (page 254 and table 4/5) in appellant 1's letter dated 22 November 2021 (see page 3) had already been discussed in appellant 1's grounds of appeal. Lastly, despite the fact that D21a and D21b may reflect common general knowledge in the art, these documents still constitute new evidence and a change of the respondent's case.

Accordingly, neither D21a nor D21b were admitted into the appeal proceedings.

2. Main request (patent as granted), inventive step

2.1 The invention

The claimed invention relates to a process for the preparation of a solid oral dosage form containing crystalline solifenacin (see claim 1). According to the patent (see paragraphs [0005] and [0013]), the invention addresses the problems of:
- solifenacin stability, dissolution profiles and bioavailability, and also
- issues pertaining to the preparation of the solid oral dosage forms, in particular content uniformity and issues of sticking to the punches.

As stated in the patent, manufacturing solid dosage forms containing solifenacin or its pharmaceutically acceptable salts by using wet granulation can result in partial amorphisation of solifenacin, leading to decreased stability. In the present invention, this problem is solved by manufacturing processes in the absence of a solvent (see paragraphs [0015]-[0016]).

2.2 Starting point for the assessment of inventive step

2.2.1 The appealed decision identifies two embodiments in D1 as starting points for the assessment of inventive step.

Document D1 relates to compositions comprising crystalline solifenacin or a salt thereof (see [0001]). D1 recognises the problem of stability of the solifenacin formulations and that "amorphous solifenacin succinate generated during a manufacturing process of the drug products was the main cause of the degradation of the active pharmaceutical ingredient over time" (see [0011]). Thus D1 generally addresses the same problem of stability as the patent in suit.

To solve this problem, D1 provides methods for producing the crystalline solifenacin composition in which the amorphous content of solifenacin remains within a range with no influence on product stability (see paragraph [0034], [0035] and [0038]). These methods are in particular:
- a method with no use of any solvent, such as a direct tableting method or a melt granulation process (see claim 3), or
- a method with a reduced contact of solifenacin with a solvent, such as a wet granulation method (see e.g. examples 1-5).

2.2.2 The respondent contends that the solvent-free method of D1 is not a suitable starting point for the assessment of inventive step.

Firstly, the respondent points out that D1 only exemplifies the wet granulation method, and contains no actual example of any solvent-free method. Secondly, D1

expresses a clear preference for the wet granulation process because "solifenacin or a salt thereof has strong aggregation property so it is difficult to securely keep the content uniformity and the mixture sticks to punches during compression by the direct tableting process, and it is very difficult to control the amount of a substance with a low melting point to be dissolved by the melt granulation process" (see paragraph [0038]). The respondent, citing T 2759/17, concludes that the skilled person would not have realistically started from the solvent-free process of D1, because this process was inferior to the wet granulation method and because D1 did not disclose any actual complete formulation for the solvent-free process. In addition, the solvent-free method of D1 did not represent an equally suitable starting point, such that it was not to be seen as an alternative closest prior art to the wet granulation process.

2.2.3 The Board does not concur with the respondent's view.

The Board shares the opinion, expressed in e.g. T 1112/19 (see point 2.1.3 and decisions cited therein; see also the Case Law of the Boards of Appeal, 9th edition, 2019, I.D.3.1) that the claimed subject-matter must be inventive over any state of the art according to Article 56 EPC.

In the Board's view, it may sometimes be considered that a document or embodiment does not represent a suitable starting point, in the sense that it can be argued that the skilled person could not conceivably have modified it so as to arrive at the claimed invention. However, it is clearly not the case here for the solvent-free method of D1. As observed by the opposition division, this method is clearly and

unambiguously disclosed in D1, it aims at the preparation of crystalline solifenacin formulations, and it addresses at least one of the problems, if not the main one, stated in the patent, namely that of stability. Furthermore, solvent-free tableting processes such as direct tableting or melt granulation are commonly known. Consequently, the mere fact that D1 does not exemplify or specify the excipients to be used in the solvent-free process does not make it non-enabling.

2.2.4 It is a fact that D1 (paragraph [0038]) expressly indicates that the solvent free method fails to solve the problems of content uniformity and sticking of the mixture to punches during compression, which problems are mentioned in the patent (paragraph [0013]). In decision T 2759/17, the view was expressed that a disclosure within a prior art document could only be considered to represent a suitable starting point for assessing inventive step if the skilled person would have realistically started from it. An important consideration in this assessment was generally whether this disclosure aims at the same or a similar purpose or effect as that underlying the patent in question (see point 5.6 of the reasons). Referring to this decision, the respondent contends that the skilled person would not realistically start from D1.

The present Board however considers that such an approach would not lead to a objective assessment of inventive step here, because it would amount to disregarding the solvent-free method of D1 as starting point, on the ground that it does not represent the most promising - or a realistic - starting point for addressing the additional problems of content uniformity and stickiness, even before assessing

whether these problems are actually solved by the claimed method itself. The respondent cannot foreclose an assessment of inventive step starting from D1 just because the patent mentions, among others, also these technical problems.

2.3 Difference and effect

2.3.1 D1 generally discloses a solvent-free direct compression method for making crystalline solifenacin-containing solid formulations (see claims 3 and 1 of D1), but does not indicate which excipients are to be used in this method. The process of claim 1 of the main request differs by the choice of the excipients, namely 1-90% disintegrants and/or superdisintegrants, 1-90% binder, 0.1-10% lubricant, 20-99% filler or diluent, the main excipient being lactose monohydrate, microcrystalline cellulose or mannitol.

2.3.2 The respondent did not produce any comparison of e.g. a solvent-free method as claimed with one using different excipients. With respect to stability or bioavailability of the solifenacin, there is no evidence that the selection of the claimed excipients achieves any improvement over D1. However, D1 generally states that direct tableting of solifenacin is associated with drawbacks regarding poor uniformity and sticking to punches (see paragraph [0038]). In contrast, these issues do not arise in the examples of the patent, as shown by the successful production of large numbers of tablets (see e.g. example 1, paragraph [0105]). The Board consequently accept that the examples achieve an effect with respect to content uniformity and stickiness over the solvent-free methods generally described in D1.

2.3.3 The question is whether this effects can be extrapolated to the whole scope of claim 1. The examples are characterised not only by the presence of lactose monohydrate, microcrystalline cellulose or mannitol as main excipient, but also by further characteristics, and notably by given particle sizes (see paragraphs [0103] and [0108] of the patent). It is also noteworthy that the patent (see paragraphs [0080] and following) associates the improvements with respect to content uniformity and stickiness to the particle size of the main excipient. This particle size is not limited of claim 1. It is neither derivable from paragraph [0005] nor from paragraph [0080] of the patent that the mere choice of lactose monohydrate, microcrystalline cellulose or mannitol as main excipient, irrespective of their particle size, has any effect on content uniformity and stickiness.

2.3.4 Taking into account these elements, the Board comes to the conclusion that no effects are achieved, over the whole scope of claim 1, in comparison with the solvent-free process of D1.

2.4 Objective technical problem

The technical problem is the provision of an alternative dry process for the preparation of a solid formulation of crystalline solifenacin.

The Board does not agree with appellant 1's formulation of the problem as the provision of appropriate excipients for the preparation of a crystalline solifenacin (salt)-containing solid formulation using direct compression. Such a formulation anticipates that the differentiating feature lies with the excipients, and thus contains a pointer to the solution. Contrary

to appellant 1's opinion, formulating the problem as the provision of an alternative to the solvent-free process of D1 does not mean that the solution cannot be a solvent-free process, defined by further features.

2.5 Obviousness of the claimed solution

The first question is whether the skilled person would realistically consider carrying out the general teaching of D1 regarding a solvent-free process. This question cannot be answered without regard to the objective technical problem, which is simply to provide an alternative dry process for the preparation of a solid formulation of crystalline solifenacin. The skilled person does not seek to avoid the production issues such as content uniformity or stickiness. Accordingly, the skilled person would not be deterred by the statements in paragraph [0038] of D1, and would consider the solvent-free process as a promising route to solving the problem.

Secondly, the skilled person would chose the excipients defined in claim 1, and in particular use lactose monohydrate, microcrystalline cellulose or mannitol as main excipient. Lactose monohydrate, microcrystalline cellulose and mannitol are generally known for use in direct tableting (see e.g. D4, page 258, right column; D5, pages 183, 193 and 196; Dl9, pages 172-176) or in the context of solifenacin compositions (see D2, paragraph [0145]-[0146]; D3, page 7, third paragraph and paragraph bridging page 8). For instance, D2 proposes to prepare both crystalline and amorphous solifenacin formulations by dry blending or by direct compression using e.g. microcrystalline cellulose or spray-dried lactose as excipients. As to the remaining components, claim 1 only lists typical amounts of

functionally defined excipients. In view of the prior art, there is no reason for the skilled person to expect that the choice of the excipients of claim 1 would be unsuitable for the preparation of a solid formulation of crystalline solifenacin.

In conclusion, the Board finds that part of the claimed subject-matter consists in simply carrying out the solvent-free process generally taught in D1 with commonly known excipients, thus obtaining exactly the same results (a solid formulation of crystalline solifenacin) indicated in D1 and without showing to overcome the disadvantages (regarding content uniformity and stickiness) predicted therein.

Accordingly, the main request does not meet the requirements of inventive step

3. Auxiliary requests I and II, inventive step

D1 identifies solifenacin succinate as the preferred solifenacin salt (see page 5, line 9). Thus the limitation, in claim 1 of auxiliary requests I and II, to solifenacin salts including succinate, or to solifenacin succinate, does not change the conclusion of inventive step reached above for the main request.

Accordingly, neither auxiliary request I nor auxiliary request II meet the requirements of Article 56 EPC.

4. Auxiliary request III

4.1 Article 123(2) EPC

Like claim 1 of the main request, claim 1 of auxiliary request III combines the features of the solvent-free

process of claim 1 as filed with those of the solid oral dosage form prepared by a solvent-free process of claim 11, or page 14, and claim 15 of the application as filed. Appellant O2 had raised an objection of added subject-matter in this respect against the main request.

The Board however shares the respondent's view that this combination of features does not add subject-matter. In light of the general passages on page 4 (first paragraph) and page 3 (second paragraph) of the application as filed, the solvent-free process and the product resulting therefrom must be seen as two aspects of the same invention.

Accordingly, auxiliary request III meets the requirements of Article 123(2) EPC.

4.2 Inventive step

Against auxiliary request III, the appellants raised objections of lack of inventive step, starting from both alternatives in D1 or from D8.

4.2.1 Starting from the solvent-free method of D1

The subject-matter of claim 1 of auxiliary request III differs from the solvent-free method of D1 in that the excipients are 1-90% disintegrants and/or superdisintegrants, 1-90% binder, 0.1-10% lubricant, 20-99% filler or diluent, the main excipient being lactose monohydrate, microcrystalline cellulose or mannitol, and additionally in that, cumulatively, the average particle size of the main excipient is larger than 60 µm. The Board does not share the appellant's view that the average particle size parameter should be

disregarded as differentiating feature on account of its alleged lack of clarity. Neither the excipients nor any particle sizes at all are disclosed for the solvent-free process in D1.

As a result of this limitation, the Board considers that the processing improvements which can be inferred from the patent (see 2.3.2 above), in particular from examples 1 and 3 (in which the main excipient has the required particle size), are credibly achieved over the whole scope of the claim. In this respect, the statement in paragraph [0080] of the patent linking these effect to the particle size is supported by the examples. The Board accepts that some of the further parameters of the main excipient in the examples of the patent, namely the flowability, the angle of repose and the Hausner index (see table 1A, paragraph [0103]) could be expected, in view of the common general knowledge (reflected in particular in D19, page 180, table 7.9; D5, page 174; D4, page 704), to contribute to content uniformity. However, there is no indication that these further parameters could address the issues specifically resulting from strong aggregation properties of solifenacin (see paragraph [0038] of D1) and would account for the at least adequate stickiness of the mixture allowing the production of the tablets in examples 1 and 3 of the patent. No evidence or compelling reason was put forward to demonstrate that some parts of the claimed subject-matter would fail to exhibit any improvements in this respect.

Accordingly, the problem may at least be seen as the provision of a dry process for the preparation of a solid formulation of crystalline solifenacin addressing the issue of stickiness of the mixture.

The Board finds that the claimed solution is not rendered obvious by the prior art. Lactose monohydrate, microcrystalline cellulose or mannitol having an average particle size larger than 60 µm may be known from the prior art and could be used by the skilled person. However, the prior art does not give any hint that the use of these particular components as main excipient would lead to adequate processing properties and overcome the issues noted in paragraph [0038] of D1.

4.2.2 Starting from the wet granulation method of D1

Starting from the wet granulation method shown in D1, especially examples 1-4, the subject-matter of claim 1 of the main request differs at least in that the process is performed in the absence of a solvent.

As reasoned in the appealed decision (see section 4.2.1.1), tables 15-18 of the patent show that this difference leads to a higher stress stability, a lower amount of impurities and a shorter disintegration time as compared to granules prepared by wet granulation. The appellants do not contest that the problem may be formulated as the provision of a process for the preparation of a solid formulation of crystalline solifenacin which comprises fewer degradation products.

The appellants essentially argue that the skilled person would anticipate that a solvent free process, such as the dry compression method shown in D1, would lead to an even lower amount of amorphous solifenacin in the resulting formulation, and thus an even higher stability, as compared with the wet granulation process of D1.

The Board is not convinced by the appellants' reasoning. The data in D1 (see table 2 on page 12 of D1, and the equivalent passage in D20, the corresponding publication under the PCT) do not show any decrease in degradation when lowering the water content in the granules from 5.5% to 3.9%. In addition, D1 clearly sees the solvent-free methods and the wet granulation as separate processes. The skilled person, who has made the choice of starting from the wet granulation process, would not qualitatively change this process to a solvent-free method, and finds no indication in D1 that this modification would improve stability.

4.2.3 Starting from D8

D8 describes a process for the preparation of stable solifenacin formulations.

The subject-matter of claim 1 of auxiliary request III differs firstly by the excipients. Each of the disintegrant, binder, lubricant and diluent mentioned in D8 is optional (see the ranges including 0% in claim 10 and paragraphs [0029]-[0032]), and there is no disclosure in D8 that the lactose monohydrate and microcrystalline cellulose, recited among several other diluents in paragraph [0029] of D8, may be present as main excipient (see paragraph [0034]). Thus D8 does not disclose the combined features of claim 1.

In addition, D8 does not aim at preparing solid oral dosage forms comprising an effective amount of *crystalline* solifenacin. Rather, D8 relates to stable pharmaceutical compositions comprising solifenacin in amorphous form (see paragraph [0008]), where preferably no crystalline form can be detected (see paragraph

[0012]). The skilled person, starting from D8, may further develop its disclosure, but could not realistically be expected to take a step in the opposite direction without hindsight. Hence D8 does not lead to the claimed invention in an obvious manner.

4.2.4 Accordingly, the subject-matter of auxiliary request III involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of auxiliary request III filed with the reply to the grounds of appeal and a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated