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Datasheet for the decision of 10 November 2022

Case Number: T 1742/19 - 3.3.07

Application Number: 05852790.4

Publication Number: 1819323

IPC: A61K9/20, A61K9/48, A61K31/513

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITION CONTAINING AN ANTI-NUCLEATING AGENT

Patent Proprietor:
Merck Sharp & Dohme Corp.

Opponents:
Ter Meer Steinmeister & Partner Patentanwälte mbB
Georg Kalhammer/Stephan Teipel

Headword:
Pharmaceutical composition containing an anti-nucleating agent/ MERCK

Relevant legal provisions:
EPC Art. 83

Keyword:

Main request and auxiliary requests 1-5 - Sufficiency of disclosure (No)
Auxiliary request 6 - Sufficiency of disclosure (Yes)
Auxiliary request 6 - Inventive step (Yes)

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Case Number: T 1742/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 10 November 2022

Appellant: (Patent Proprietor)	Merck Sharp & Dohme Corp. 126 East Lincoln Avenue Rahway, NJ 07065-0907 (US)
Representative:	Merck Sharp & Dohme LLC 120 Moorgate London EC2M 6UR (GB)
Appellant: (Opponent 1)	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Strasse 4 80335 München (DE)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Appellant: (Opponent 2)	Georg Kalhammer/Stephan Teipel Lederer & Keller Unsöldstrasse 2 80538 München (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 13 May 2019 concerning maintenance of the European Patent No. 1819323 in amended form.**

Composition of the Board:

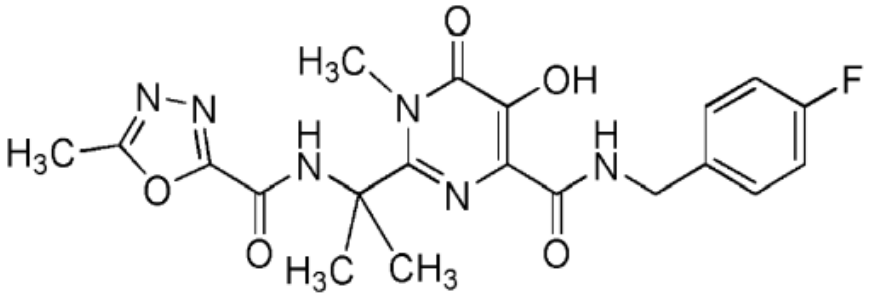
Chairman	A. Usuelli
Members:	D. Boulois
	A. Jimenez

Summary of Facts and Submissions

I. European patent No. 1 819 323 was granted on the basis of a set of 9 claims.

Claims 1, 2 and 6 as granted read as follows:

"1. A pharmaceutical composition for oral administration as a solid dose, which comprises: (a) from 0.5 to 20 wt.% of an anti-nucleating agent which comprises hydroxyalkylcellulose, and (b) an effective amount of from 5 to 75 wt.% of a potassium salt of Compound A, wherein Compound A is:



2. The pharmaceutical composition according to claim 1, wherein the potassium salt of Compound A is Form 1 potassium salt of Compound A.

6. The pharmaceutical composition according to claim 5, wherein the potassium salt of Compound A is Form 1 potassium salt of Compound A."

II. The patent had been opposed under Article 100 (a), (b), (c) EPC on the grounds that its subject-matter lacked inventive step, was not sufficiently disclosed and

extended beyond the content of the application as filed.

III. The appeal lies from the decision of the opposition finding that the patent in amended form meets the requirements of the EPC. The decision was based on the claims as granted as main request, on auxiliary requests 1-5 filed with letter of 5 February 2018 and auxiliary request 6 filed during the oral proceedings of 31 January 2019.

Claim 1 of auxiliary request 6 was identical to claim 1 as granted, this request differing only by the deletion of dependent claims 2 and 6.

IV. The documents cited during the opposition proceedings included the following:

D1: WO 03/035077;
D2: EP 1 904 067 B1;
D3: M. E. Aulton, Pharmaceutics, The Science of Dosage Form Design, 2nd Edition, 2002, Chapter 20, 289-305;
D4: Leuner Ch. et al, Eur. J. Pharm. Biopharm., 2000, 50, 47-60;
D5 : WO 03/086319;
D6 : Usui F et al, Int. J. Pharm., 1997, 154, 59-66;
D7: WO 2004/064846;
D8 WO 00/18384;
D9:Gao P et al., Drug Development And Industrial Pharmacy, 2004, 30, 221-29;
D10: WO 02/056878;
D11: WO 2006/060730;
D12: Overview of claim 1 of the main and auxiliary requests 1 to 5;
D13: Raghavan S.L. et al, Int. J. Pharmaceutics, 2001,212, 213-221

V. According to the decision under appeal, the main request met the requirements of Article 123(2) EPC.

The opposition division considered that the use of the term "anti-nucleating agent" was sufficiently disclosed, but that the subject-matter of claim 2 and 6 did not meet the requirements of Article 83 EPC. Neither the patent specification, nor the available prior art provided the skilled person with the information about how to prepare the seeds of the Form 1 crystalline Compound A potassium.

Auxiliary requests 1-5 did not meet the requirements of sufficiency of disclosure for the same reason.

Auxiliary request 6 was admitted into the opposition proceedings and the invention as claimed in auxiliary request 6 was sufficiently disclosed. With regard to inventive step, D1 was considered to represent the closest prior art, and the distinguishing feature resided in the use of a specific potassium salt of compound A in a specific amount, and in its combination with a specific amount of anti-nucleating agent comprising hydroxyalkylcellulose. In view of the data in the patent and those provided by the proprietor, the problem was defined as the provision of a novel pharmaceutical formulation comprising compound A having certain suitable bioavailability. The claimed solution was not obvious.

VI. The patent proprietor (hereinafter the appellant-proprietor), opponent 01 and opponent 02 (hereinafter respectively appellant-opponent 01 and appellant-opponent 02) filed an appeal against said decision.

VII. With its statement of grounds of appeal dated 19 September 2019, the appellant-proprietor requested that the decision under appeal be set aside and the patent be maintained according to the main request (patent as granted) or to the set of claims filed as auxiliary requests 1-11 during the opposition proceedings (auxiliary requests 1 to 5 filed with letter of 5 February 2018 and auxiliary requests 6 to 11 filed during the oral proceedings on 31 January 2019).

VIII. With its statement setting out the grounds of appeal dated 23 September 2019 the appellant-opponent 01 submitted the following item of evidence:

D14: WO2012/147101 A2

IX. With the letter dated 22 January 2020, the appellant-opponent 02 filed the following item of evidence:

D15: Bavin, Chemistry % Industry, 21 August 1989, 527-529
D16: Wikipedia, Polymorphism (material science)

X. A communication from the Board, dated 28 July 2022, was sent to the parties. In it, the Board expressed its preliminary opinion that the subject-matter of claims 2 and 6 of the main request was not sufficiently disclosed, but that the main request appeared to be inventive.

XI. Oral proceedings took place on 10 November 2022 in the presence of the appellant-proprietor and of appellant-opponent 02.

XII. The arguments of the appellant-proprietor may be summarised as follows:

Main request - Form 1 of potassium salt of Compound A - Sufficiency of disclosure

The method of obtaining Form 1 potassium salt of Compound A and its characterisation was described on paragraph [0093] of the opposed patent. The skilled person would have known that different crystalline forms of a particular compound were obtainable by crystallisation in different solvent systems and, knowing the solvent system for crystallisation, the skilled person could readily determine how to obtain small amounts of a seed crystal.

Furthermore, whilst seeding is preferred, it was not essential to effect crystallization which could be induced in other ways apart from adding seed crystal.

The skilled person would have expected that crystallization of the poorly soluble salt from a supersaturated solution might have occurred on standing with cooling and would have been motivated to investigate this.

In view of example 2 the skilled person might have expected that adding greater proportions of the more organic solvent (ethanol) might have promoted crystallisation and would have been prompted to investigate this.

The post-published document D11 (WO 2006/060730) provided proof that Form I potassium salt of Compound A could be obtained without seeding, which was indicated to be an optional step (see D11, page 15, lines 26-27).

Auxiliary request 6 - Anti-nucleating agent - Sufficiency of disclosure

The patent gave sufficient teaching on the anti-nucleating agent, which was anyway a known concept. The patent contained also sufficient teaching on how to choose other anti-nucleating agents, in addition to hydroxyalkylcellulose.

Auxiliary request 6 - Inventive step

D1 was the closest prior art and disclosed a large number of compounds, without any highlight to compound A. There were many choices to perform in D1 to arrive at the claimed subject-matter. This became even harder if it was considered that the addition of a hydroxyalkylcellulose could improve the bioavailability of the claimed compound A.

XIII. The arguments of the appellant-opponents 01 and 02 may be summarised as follows:

Main request - Form 1 of potassium salt of Compound A - Sufficiency of disclosure

According to the appellant-opponents 01 and 02, the compound of claims 2 and 6 of the main request related to Form 1 of the potassium salt of Compound A, and was characterized in paragraph [0026] and [0094] of the contested patent. However, seeds of Form 1 were used to prepare Form 1, but neither the patent, nor the available prior art did teach how to prepare said seeds.

Auxiliary request 6 - Anti-nucleating agent - Sufficiency of disclosure

According to appellant opponent 01, claim 1 defined a pharmaceutical composition comprising “an anti-nucleating agent which comprised hydroxyalkylcellulose”. Due to the term “comprises” the anti-nucleating agent, however, was not limited to hydroxyalkylcellulose. Thus, the mandatory presence of hydroxyalkylcellulose was required but additional anti-nucleating agents were permitted. The skilled person was not able to obtain substantially all embodiments falling within the ambit of the claims.

The skilled person was not able to identify what was an "anti-nucleating agent". According to the opposed patent, an anti-nucleating agent such as a water-soluble polymer prevented or minimized precipitation of the drug compound, e.g. raltegravir (compound A) in the gastrointestinal tract by providing prolonged supersaturation, e.g. by maintaining raltegravir in a solubilized form. Reference was made to the post-published international publication WO 2012/147101 A2 (D14) concerning pharmaceutical compositions comprising raltegravir. From the opposed patent and D14 it was apparent that both “anti-nucleating agent” and “solubilizing agent” were defined by the same functional terms even though completely different compounds were mentioned. It was an undue burden for the skilled person to isolate and characterize all the compounds potentially suitable as anti-nucleating agents and to test them.

Moreover, the term anti-nucleating agent was not well known to the skilled person.

This position was also endorsed by appellant-opponent 02 during the oral proceedings.

Auxiliary request 6 - Inventive step

D1 was the closest prior art. D1 explicitly described the preparation of Compound A and specifically hinted to the skilled person that Compound A was one lead compound of D1 for any drug formulation.

According to appellant-opponent 01, the solid formulations of the examples of the opposed patent comprised crystalline Form 1 of Compound A potassium salt. This salt was not sufficiently disclosed. Thus, these data were not suitable to show any technical effect. The tests of examples 4 and 5 were in any case not suitable to show any credible effect over the prior art. The difference between the composition according to claim 1 and the compositions of D1 was the use of Compound A in the form of its potassium salt, its specific amount and the presence of a specific amount of an anti-nucleating agent comprising hydroxyalkylcellulose. Starting from D1, the technical problem, therefore, could only be seen in the provision of an oral pharmaceutical composition comprising Compound A or pharmaceutically acceptable salts having a certain suitable bioavailability. In view of D1, the skilled person was motivated to provide Compound A potassium salt in such an oral dosage form so that enough solubility was obtained in acidic environment. In order to provide an oral dosage form resulting in sufficient bioavailability, the skilled person would have chosen excipients known to improve solubility and thereby bioavailability (see D4, D6, D9 or D13)). In D13, the addition of HPMC as anti-nucleating agent was in particular disclosed.

Document D1 was also the closest prior art for appellant-opponent 02. D1 disclosed compound A in example 19, compositions were disclosed on pages 55 and the salts on page 62. D1 did not disclose the presence of an anti-nucleating agent, the amount of anti-nucleating agent and the amount of compound A. The amount of active agent was not linked with any technical effect. With regard to the anti-nucleating agent, there was not evidence of any effect, since the experiments of examples 4 and 5 were given in the form of pure statements, and since it was not plausible that an effect was achieved over the whole scope ofclaim 1. The problem had to be defined as the provision of an alternative composition. The solution was obvious in view of the common general knowledge and D4, D9, D6, D3 and D13.

XIV. Requests

The appellant patent proprietor requested that the decision under appeal be set aside and the patent be maintained according to the main request (patent as granted) or to the set of claims filed as auxiliary requests 1-11 during the opposition proceedings (auxiliary requests 1 to 5 filed with letter of 5 February 2018 and auxiliary requests 6 to 11 filed during the oral proceedings of 31 January 2019).

The appellants opponents 1 and 2 requested that the decision under appeal be set aside and that the patent be revoked. The appellant opponent 2 further requested not to admit auxiliary requests 7 to 11 in the proceedings and any amendment to the patent proprietor's case regarding inventive step.

Reasons for the Decision

1. Main request - Sufficiency of disclosure

1.1 Claims 2 and 6 as granted relate to a specific form of compound A and read as follows:

"2. The pharmaceutical composition according to claim 1, wherein the potassium salt of Compound A is Form 1 potassium salt of Compound A.

6. The pharmaceutical composition according to claim 5, wherein the potassium salt of Compound A is Form 1 potassium salt of Compound A."

1.2 The description of the contested patent discloses the characteristics of From 1 crystalline potassium salt of compound A in paragraph [0026], without any teaching on how to prepare this specific compound. The only methods of preparation of the compound A are given in examples 1 and 2.

Example 1 discloses the preparation of the compound A and a crystalline potassium salt thereof, while example 2 relates specifically to the preparation of Form 1 crystalline potassium salt of compound A, i.e. the form mentioned inclaims 2 and 6.

Example 2 mentions explicitly in step A of the preparation that "the filtered solution was seeded with crystalline Form 1 Compound A K salt (1200 mg) at room temperature and then aged for 1 hour to build a good seed bed" (see par. [0093]). In view of this disclosure, a person skilled in the art would thus

consider this step of adding seed crystals as essential for obtaining the desired compound. This example is however the only disclosure in the patent in suit in respect of the preparation of crystalline Form 1 Compound A K salt, and it does not contain any information on how the seeds were obtained. The remaining part of the contested patent is also completely silent on this point

In addition, neither the source nor the synthesis of this seed crytsal form part of the skilled person's common general knowledge.

1.3 The appellant-proprietor argued that seeding is not essential, and that the skilled person will be able to make modifications to the experimental process and devise methods of inducing crystallisation without seeding, thereby enabling the small amounts of seed crystal required to be obtained for further crystallisation. The appellant-proprietor argued in particular that the skilled person would know that different crystalline forms are obtainable by crystallisation in different solvent systems. It explained that the crystallisation in a mixture of water and ethanol would result in the generation of Form 1 of Compound A potassium salt. Knowing the solvent system for crystallisation, the skilled person could readily determine how to obtain small amounts of a seed crystal which could then be used in subsequent crystallisation. The skilled person would expect that crystallization of the drug from a supersaturated solution might occur on standing with cooling and he would be motivated to investigate this.

In the Board's view,, these solutions proposed by the appellant-proprietor, remain unsupported hypothesis

and can only be regarded as an invitation to carry out a research program.

1.4 The appellant-proprietor also considered that the post-published document D11 provided proof that Form 1 potassium salt of compound A could be obtained without seeding (see D11, page 15, lines 26-27). Thus, it would have been possible for the skilled person to obtain Form 1 by simply carrying out the process of example 2 of the patent without seeding.

The Board notes in this regard that the skilled person was not aware of this information at the filing date.

Furthermore, D11 merely asserts in the cited passage that "the seeding steps forth above in Process P1 is optional in the sense that crystalline Compound A K salt can be obtained without seeding". However, process P1 (see page 8) is a broadly defined process that could be carried out in different solvents and under different conditions (see page 8 line 1 to page 15 line 20). There is however no evidence in this document that Form 1 potassium salt of compound A could indeed be obtained without seeding. In particular, there is no evidence that this crystalline form could be obtained without seeding in the solvent system and under the experimental conditions used in example 2 of the patent.

1.5 It follows that the main request does not meet the requirements of Article 83 EPC.

2. Auxiliary requests 1-5 - Sufficiency of disclosure

The subject-matter of claims 2 and 6 of the main request, relating to Form 1 potassium salt of Compound

A is present in the dependent claims of all auxiliary requests 1-5. The conclusion reached for the main request with regards to sufficiency of disclosure applies therefore also to auxiliary requests 1-5.

3. Auxiliary request 6 - Sufficiency of disclosure

3.1 The subject-matter of claim 1 has been objected by the appellant-opponents in view of the feature "anti-nucleating agent".

According to the appellant-opponents, the skilled person would not be able to identify "anti-nucleating agents" in the absence of any pointer to the identity of "anti nucleating agents", which is furthermore not limited to hydroxyalkylcellulose in view of the term "comprises".

3.2 In the claims, the functional feature "anti-nucleating agent" is directly associated with a defined class of compounds, i.e. the hydroxyalkylcelluloses. This provides an immediate and clear instruction to the skilled person on the compounds which achieve the claimed function.

Paragraphs [0016]- [0021] of the patent specification provides furthermore ample information and teaching with regard to the anti-nucleating agent. These passages refer to a solubility test for identifying anti-nucleating agents suitable for use with a particular salt. They also disclose that water-soluble polymers are suitable for use as anti-nucleating agents, and designate the hydroxylalkylcelluloses as preferred options, in particular hydroxypropylmethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose.

In view of this, the skilled person would be able to identify "anti-nucleating agents". Accordingly,the invention is sufficiently disclosed in relation to this aspect.

3.3 The fact that other anti-nucleating agents, not mentioned in the patent, may exist is irrelevant.

It is indeed sufficient that the skilled person can identify suitable "anti-nucleating agent" to fulfill the requirements of sufficiency of disclosure. In any case, D14 mentions the same "anti-nucleating agents" as the patent in suit, i.e water soluble polymers (see D14 page 14, lines 10-13).

3.4 With regard to the objection that "anti-nucleating agents" were not well known to the skilled person, the Board observes the following.

The term "anti-nucleating agent" is technically understandable as such, and relates to compounds inhibiting the formation of nuclei (crystals) or the nucleation of a compound. This is confirmed by the disclosure of paragraphs [0009] and [0010] of the specification which explains that said "anti-nucleating agents" improve the solubility of the drug Compound A in the gastrointestinal tract by inhibiting or delaying the conversion of the drug in a less soluble form under acidic pH.

Thus, anti-nucleating agents are well known to the skilled person. This is also illustrated by the teaching of several documents cited by the opposition division in its decision and cited by the appellant-opponent 01 for the assessment of inventive step for

deciding on the obviousness of using an anti-nucleating agent.

D6, D9 and D13 mention indeed explicitly the use of water-soluble polymers in the context of improvement of the solubility of poorly water soluble drugs by avoiding the formation of crystals or nuclei (see D6 abstract, D9, chapters "Introduction" and "Discussion"; D13, Abstract and page 214, left-hand col.).

3.5 With regard to the presence of the term "comprising" in claim 1 in relation to the "anti-nucleating agent", the Board observes that, as explained above, the description gives sufficient teaching on how to select further "anti-nucleating agent" in addition to hydroxyalkylcellulos.

3.6 Consequently, there is no lack of disclosure associated with the term "anti-nucleating agent" and auxiliary request 6 meets the requirements of Article 83 EPC.

4. Auxiliary request 6 - Inventive step

4.1 The claimed invention relates to a composition for oral administration that includes a drug that converts to a less soluble form under certain acidic conditions. The drug is the potassium salt of compound A, and the composition comprises an anti-nucleating agent for solving this problem (see par. [0005], [0006] and [0010] of the specification).

4.2 The opposition division considered D1 to be the closest prior art, in agreement with all the parties.

4.2.1 D1 relates to N-substituted hydroxypyrimidinone carboxamide as inhibitors of HIV integrase.

One of the compound disclosed in D1 is compound A in its free acid form, namely compound 24 on page 161, which is also exemplified on page 130 (example 19), and is mentioned in claim 28 on page 207, lines 18-20. Said Compound A is disclosed among a great number of alternative N-substituted hydroxypyrimidinone carboxamide.

D1 mentions the possibility to administer the compounds disclosed therein in the form of pharmaceutically acceptable salts, such as *inter alia* potassium salts (see page 62, lines 13-26), but also sodium, calcium, magnesium, quaternary ammonium salts.

Some ways and forms of administration are disclosed on page 62, lines 27-33. Page 63, lines 24-30 discloses tablets, capsules, nasal sprays, injectable suspensions as possible dosage forms.

The opposition division concluded in its decision that the differences between claim 1 and the closest prior art were the use of a specific potassium salt of compound A in the specific amount and in its combination with a specific amount of an anti-nucleating agent comprising hydroxyalkylcellulose.

The Board agrees with this conclusion, since document D1 does neither disclose compound A as potassium salt nor the presence of an anti-nucleating agent in the claimed amounts.

4.2.2 Appellant-opponent 01 disagrees with the identification of the distinguishing features between the claimed subject-matter and D1. In its view, D1 explicitly describes the preparation of Compound A and, by doing

so, specifically hints to the skilled person that Compound A is one lead compound of D1 for any drug formulation. In addition, D1 mentions that the compounds of D1 and pharmaceutically acceptable salts may be administered in the form of a unit dosage form (see D1, page 62). Hence, in its view D1 discloses pharmaceutical compositions comprising Compound A or pharmaceutically acceptable salts thereof with acceptable carriers for oral administration.

Appellant-opponent 02 had essentially the same position.

The Board disagrees with this argumentation. When the content of prior art document is considered, said content should not be considered as a reservoir from which it would be permitted to draw features belonging to distinct embodiments to artificially create a particular embodiment, unless the document itself suggests such a combination, In the present case, neither the compound A, nor its potassium salt, nor a particular dosage form are presented as preferred in D1, and there is no pointer in favour of any such combination in D1. In conclusion, the distinguishing features are as concluded by the opposition division in its decision.

4.3 According to the opposition division in its decision, the problem to be solved is the provision of a novel pharmaceutical formulation comprising compound A having certain suitable bioavailability. The appellant-proprietor agrees with the formulation of the technical problem by the opposition division.

Appellant-opponent 01 defines in its written proceedings the problem as the provision of an oral

pharmaceutical composition comprising compound A or pharmaceutically acceptable salts having a certain suitable bioavailability.

Appellant-opponent 02 defines the problem as the provision of an alternative formulation of the potassium salt of compound A.

4.4 As a solution to any of these problems, claim 1 of auxiliary request 6 proposes a composition for oral administration as solid dose comprising 0.5 to 20 wt.% of an anti-nucleating agent which comprises hydroxyalkylcellulose and 5 to 75 wt.% of a potassium salt of Compound A.

4.5 Examples 4 and 5 of the patent were discussed in the opposition proceedings and in the statement of grounds of appeal of the opponents in support of the existence of a technical effect.

4.5.1 Example 4 studies the in vitro dissolution properties of tablets containing 100 mg of Compound A and 0, 5, 10, or 15 wt. % HPMC. According to example 4, the tablets comprising HPMC showed prolonged drug supersaturation relative to the reference tablets containing no HPMC, wherein drug concentrations for the HPMC-containing tablets at dissolution times of 120 and 180 minutes were at least 2-fold greater than the drug concentrations achieved with the reference tablets. Moreover, tablets with 10 and 15 wt.% exhibited slower disintegration and drug release than the tablets with 5 wt.% HPMC, but nonetheless achieved prolonged supersaturation as well.

The same dissolution study performed with unformulated bulk Compound A K salt in granules and conducted at

37°C showed a more pronounced and favorable effect of HPMC. A 10 fold enhancement in drug solubility was observed at dissolution times of 60 to 180 minutes in the presence of HPMC versus dissolution in the absence of HPMC.

4.5.2 Example 5 studies the pharmacokinetics of a tablet comprising 100 mg of Compound A K salt with 5% wt.% of HPMC in vivo in Beagle dogs. Analogous study is performed with a 5 wt.% methylcellulose aqueous solution of the Compound A K salt, a dry filled capsule of bulk drug, and a reference tablet comprising no HPMC. The data showed a 2-fold improvement in $AUC_{0-24\ hrs}$ for the HPMC-containing tablet compared to the AUC value obtained for the reference tablet and the dry-filled capsule. The $AUC_{0-24\ hours}$ of the HPMC tablet was equivalent to that of the methylcellulose solution.

4.5.3 Hence, a direct comparison between a tablet comprising HPMC and a tablet without HPMC has been carried out in examples 4 and 5. In both examples, the comparison was made between a tablet with 0.0 wt.% of HPMC and at least 5.0 wt.% of HPMC.

An improvement linked with the presence of HPMC has been clearly shown in examples 4 and 5 of the patent. Example 4 shows indeed a two-fold improvement in the dissolution, and example 5 a 2-fold improvement in the AUC value. These results appear to show that the addition of HPMC as anti-nucleating agent has an effect on the solubility and bioavailability of the drug. Even if the results have been presented as a statement and not with direct experimental data, the Board does not see any reason to question them, in view of the detailed indications given for performing the experiments.

Moreover, the Board agrees with the opposition division in its decision that there is no evidence submitted by the opponents showing that the use of potassium salt of Compound A of hydroxyalkylcellulose at end points of the claimed range or the use of different types of hydroxyalkylcellulose other than the specific HPMC of the examples would lead to different results and prevent the skilled person from achieving the desired bioavailability.

The same conclusion applies when considering the possible presence of further anti-nucleating agents in view of the term "which comprises hydroxyalkylcellulose" in claim 1. The Board sees no reason to consider that the presence of an additional anti-nucleating agent would have a negative impact on the bioavailability. There is also no indication that the technical effect on the bioavailability would not be present if a different polymorphic form of compound A were used. Thus, in the absence of any specific arguments in this regard from the side of the opponents the Board consider that the results of the examples of the patent can be extrapolated to any crystalline form of compound A.

4.6 The Board concurs with the opposition division in its decision as to the existence of a technical effect. Accordingly, the problem is as defined by the opposition division in its decision (see point 4.3 above).

4.7 It remains to determine if the claimed solution is obvious.

4.7.1 Documents D4, D6, D9, D10, D13 were cited by the appellant-opponents to show that the claimed solution was obvious.

D4 relates to the improvement of the solubility of drugs for oral delivery by using solid dispersions in polymers, such as inter alia HPMC or HPC (hydroxpropylcellulose).

D6 discloses the effects of water-soluble polymers on precipitation of the drug RS-8359.

D9 teaches the inhibitory effect of HPMC on the precipitation of a poorly water soluble drug PNU-91325.

D10 describes the use of HPMC and other polymers for improving the solubility and bioavailability of water insoluble or poorly soluble drugs.

D13 discloses HPMC as anti-nucleating agent for decreasing the crystallization of hydrocortisone acetate.

It results from the teaching of all these cited documents that hydroxyalkylcellulose polymers were known and used for improving the water solubility of drugs or as anti-nucleating agents.

4.7.2 The question with regard to obviousness is in the present case whether the skilled person, starting from D1 as closest prior art, would have been incited to choose all the features disclosed therein and combine them with the teaching of the other cited documents to arrive at the claimed subject-matter, in order to provide a pharmaceutical formulation comprising compound A and having certain suitable bioavailability.

In the Board's view, there is no incentive neither in D1 nor in any other prior art document to combine the potassium salt of Compound A with an anti-nucleating agent comprising hydroxyalkylcellulose, not to mention to use this combination of substances in a solid dosage form for oral administartion; all documents D4, D6, D9, D10 and D13 focus on the use of hydroxyalkylcellulose for the improvement of bioavailability of poorly water-soluble drugs. However, the fact that Compound A and its potassium salt is a drug that converts to a less soluble form of the drug under certain acidic conditions was not known at the effective filing date of the contested patent. Therefore, as also concluded by the opposition division in its decision, unaware of this particular behaviour of Compound A, the skilled person, based on the common general knowledge would not have combined this drug with an anti-nucleating agent in order to solve the problem posed, i.e the provision of a pharmaceutical formulation comprising compound A having certain suitable bioavailability.

4.8 Consequently, the claimed solution is not obvious, and auxiliary request 6 meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated