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Datasheet for the decision of 11 February 2016

Case Number: T 2341/12 - 3.3.07

Application Number: 07120591.8

Publication Number: 1913939

IPC: A61K9/72, A61K9/14

Language of the proceedings: EN

Title of invention:
Formulations for use in inhaler devices

Applicant:
Vectura Limited

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

Keyword:
Amendments - added subject-matter (no)
Novelty - (yes)
Inventive step - (yes)

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Case Number: T 2341/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 February 2016

Appellant: (Applicant)	Vectura Limited 1 Prospect West Chippenham, Wiltshire SN14 6FH (GB)
Representative:	Clarke, Christopher John Vectura Limited Intellectual Property Department One Prospect West Chippenham Wiltshire SN14 6FH (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 6 June 2012 refusing European patent application No. 07120591.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	R. Hauss
Members:	A. Usuelli
	D. T. Keeling

Summary of Facts and Submissions

I. The appeal of the applicant (appellant) lies from the decision of the examining division announced at the oral proceedings held on 24 May 2012 to refuse European patent application No. 07120591.8.

II. The documents cited during the examination proceedings included the following:

D1: WO 96/23485
D3: WO 87/05213
D5: WO 00/28979

III. The invention underlying the application in suit relates to a pharmaceutical composition, preferably suitable for use in a dry powder inhaler, which comprises composite excipient particles.

The decision of the examining division was based on a main request and three auxiliary requests filed on 11 May 2012.

The examining division came to the conclusion that claim 1 of the main request and of auxiliary request 1 did not comply with the requirements of Article 123(2) EPC in view of the disclaimer introduced therein. Document D5, relating to dry powder formulations comprising a carrier, an active ingredient and magnesium stearate adhering to the particles of the carrier, was regarded as prejudicial to the novelty of claim 1 of auxiliary requests 2 and 3.

IV. With the statement setting out the grounds of appeal dated 16 October 2012, the appellant submitted two sets of claims as main request and first auxiliary request.

V. In a communication pursuant to Article 15(1) RPBA issued on 3 December 2015, the board *inter alia* expressed the opinion that the subject-matter of claim 1 of the main request was novel over document D5. As to the requirement of inventive step the board indicated that document D1 represented the closest prior art.

VI. By letter dated 24 December 2015, the appellant submitted a new set of claims as main request and withdrew the sets of claims submitted with the statement setting out the grounds of appeal.

A new set of claims was submitted on 10 February 2016 as first auxiliary request.

VII. Claim 1 of the main request submitted on 24 December 2015 read as follows:

"1. A pharmaceutical composition comprising composite excipient particles, each composite excipient particle comprising a particle of an excipient material and additive material applied to the surface of that particle of excipient material, the composite excipient particles having a mass median aerodynamic diameter of not more than 50 µm determined using an impinger, wherein the additive material is in the form of a coating on the surfaces of the particles of excipient material, and wherein the composition consists essentially of the composite excipient particles, particles of active material, and optionally a flavouring agent."

The main request also included two additional independent claims relating to a dry powder inhaler comprising a composition as claimed in claim 1

(claim 11) and to a pressurised metered dose inhaler comprising a composition as claimed in claim 1 which comprises a propellant (claim 12).

VIII. Oral proceedings were held on 11 February 2016.

IX. The appellant's arguments as to the inventive step of the main request can be summarised as follows:

Document D1 was the closest prior art. This document disclosed a method for producing a powder for use in dry powder inhalers, which included mixing carrier particles with additive material and milling the product. The additive material was in the form of particles adhering to the high energy sites of the carrier. The composition of claim 1 differed from the powders disclosed in D1 in the size of the composite particles and in the requirement that the additive material was in the form of a coating on the surface of the particles of the excipient. This coating was formed by a process of wet milling as explained in paragraphs [0022] and [0100] of the application in suit. This process was used for instance in the preparation of the composite particles of Method 7 which were then used in the preparation of Composition 4. This composition provided very good results in terms of fine particle fraction. Document D1 did not suggest providing excipient particles in which the surface of the carrier was coated by the additive. Quite to the contrary, the sentence bridging pages 16 and 17 of D1 indicated that an important feature of the excipient particles disclosed therein was that the additive did not form a coating on the surface of the carrier particles but instead the additive particles covered only limited portions of the surface. The concept of providing carrier particles coated by an additive was also not suggested by D5 and D3. The

subject-matter of the main request was therefore inventive.

X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request filed with letter of 24 December 2015 or on the basis of the claims of the auxiliary request filed with letter of 10 February 2016.

Reasons for the Decision

Main request

1. Article 123(2) EPC

1.1 In the decision under appeal the examining division came to the conclusion that the disclaimer introduced in claim 1 of the main request and in claim 1 of auxiliary request 1 resulted in an addition of subject-matter. The claims of the current main request do not contain any disclaimer. Therefore, the reasons leading the examining division to refuse the main request and auxiliary request 1 for non-compliance with the requirements of Article 123(2) EPC no longer apply.

1.2 The board is satisfied that the amendments to the claims of the present main request do not extend beyond the content of the application as filed. The requirements of Article 123(2) EPC are therefore met.

2. Article 54 EPC

2.1 Document D5 was considered by the examining division to anticipate the subject-matter of claim 1 of the then pending auxiliary requests 2 and 3.

2.2 Document D5 discloses dry powder formulations comprising an inactive carrier, magnesium stearate and an active compound (page 9, lines 16 to 27). Magnesium stearate is used as an additive to improve the resistance of the composition to moisture.

Document D5 also discloses excipient particles, i.e. particles containing only the carrier and magnesium stearate, which can be used in the preparation of the active particles containing also the drug (see for instance example 3). Like the composite excipient particles of claim 1 of the application in suit, the excipient particles of D5 comprise at least an excipient (the carrier) and an additive (magnesium stearate).

2.3 On page 15 of D5 (lines 30 to 32), it is stated that the mass median aerodynamic diameter (MMAD) of the carrier particles is approximately 10 to 500 µm and preferably approximately 50 to 200 µm. There is however no information with regard to the MMAD of excipient particles comprising the carrier and magnesium stearate. Thus, D5 is silent with regard to the MMAD of the particles corresponding to the composite excipient particles of claim 1 in suit.

2.4 Nor is it possible to determine the MMAD of these particles on the basis of the examples of D5 where only the carrier particle size is indicated.

2.5 Hence, the board considers that document D5 does not provide an unambiguous disclosure of a composition comprising excipient particles having a MMAD of not more than 50 µm.

The subject-matter of claim 1 is therefore novel over the disclosure of D5.

Since independent claims 11 and 12 are directed to inhaler products containing a composition of claim 1, the subject-matter of those claims is also novel.

2.6 The Board is satisfied that none of the other documents considered during the examination proceedings discloses the subject-matter of the present claims.

It follows that the main request complies with Article 54 EPC

3. Inventive step

3.1 The subject-matter of claim 1 relates to a pharmaceutical composition essentially consisting of composite excipient particles, an active agent and optionally a flavouring agent. The composite excipient particles comprise an excipient material and an additive forming a coating on the surface of the excipient material. The composition is preferably in the form of a dry powder suitable for use in dry powder inhalers. As explained in paragraph [0011] of the description, the additive material promotes the dispersal of the active particles on administration of the composition to the patient, for example via actuation of a dry powder inhaler device.

3.2 Closest prior art

3.2.1 The Board, in agreement with the appellant, considers document D1 to be the closest prior art.

D1 describes a powder for use in dry powder inhalers including active particles and carrier particles for carrying the active particles. The powder further includes an additive material on the surface of the carrier particles to promote the release of the active particles from the carrier on activation of the inhaler (page 6, lines 3 to 11).

Thus, like the application in suit, D1 concerns a pharmaceutical composition which includes excipient particles comprising an excipient material (i.e. the carrier) and an additive.

3.2.2 On page 7 of D1 (lines 7 to 25) it is explained that the surface of a carrier particle is not smooth but has asperities and clefts which are regarded as sites of high energy. The additive material is attracted to and adheres to these sites of high energy. As explained in the paragraph bridging pages 16 and 17 of D1, the consequence of this selective attraction for specific sites on the surface of the carrier is that the additive does not form a coating on the surface of the carrier particles. Indeed, in the same paragraph it is reported that inspection under an electron microscope of lactose carrier particles treated with leucine as additive "shows much of the surface of each lactose particle remaining exposed with leucine particles covering only limited portions of each lactose particle and forming a discontinuous covering on each lactose particle".

The discontinuous distribution of the additive and the very limited covering of the carrier surface are evident also from the representation made in figure 1 of D1 of a particle of dry powder material.

Hence, the requirement of claim 1 of the main request that the additive material is in the form of a coating on the surface of the excipient material represents a distinguishing feature over the subject-matter disclosed in D1.

3.2.3 D1 does not provide any information as to the size of excipient particles comprising particles of carrier and the additive. It is however stated on page 10 (lines 10 to 15) that the diameter of the carrier particles is preferably between 20 µm and 250 µm.

In the examples, the lactose used as carrier has a diameter above 90 µm. The addition of an additive to the carrier would very likely result in an increase of the particle size. The carrier particles with the additive may optionally be treated in a process of gentle milling. However, as explained on page 24 (lines 18 to 27), the size of the particles remains substantially unchanged during the treatment. It cannot be inferred from the above that the excipient particles disclosed in the examples of D1, comprising the carrier and the additive, have an MMAD of not more than 50 µm.

Thus, the subject-matter of claim 1 also differs from the disclosure of D1 on account of the requirement that the excipient particles must have an MMAD of not more than 50 µm.

3.3 Technical problem

3.3.1 The experimental part of the application describes the preparation of several pharmaceutical compositions and discloses for each of them the result of the measurement of the fine particle fraction (FPF). The FPF is a parameter used to evaluate the aerosol performance of a

formulation in that it provides an indication of the proportion of active particles capable of penetrating into the lung during inhalation.

The relevant data in the present context are those concerning compositions 3 to 9 which contain the composite excipient particles prepared in Methods 7 and Method 9. In these methods, the composite excipient particles are prepared by treating the excipient material and the additive in a process involving a step of wet milling. As explained in paragraph [0100] of the application in suit, the wet milling step ensures the deposition of the additive in the form of a coating on the surface of the additive material.

3.3.2 The FPF of compositions 3 to 9 evaluated with a twin-stage impinger or with a multi-stage impinger is always at least 50%. A strict comparison of these data with those disclosed in D1 is not possible because different active ingredients and additives are used in the tested compositions. It is however observed that the measurements made in D1 using a twin-stage impinger provide in many cases results below 50%.

3.3.3 The board notes that compositions 3 to 9 of the present application contain, in addition to the composite excipient particles and the active ingredient, also some amounts of coarse carrier material consisting of lactose. The wording of claim 1 (see point VII above) excludes the presence of significant amounts of additional carrier particles in the pharmaceutical composition. Hence, claim 1 does not cover compositions 3 to 9. It is nevertheless clear from the description that compositions essentially consisting of composite excipient particles and active material (i.e. compositions according to claim 1) and compositions

which in addition to these components contain also carrier particles, are both suitable for use in inhaler devices. This is clear for instance from paragraph [0054] of the description wherein it is stated that the "pharmaceutical compositions may comprise essentially only the composite excipient particles and active particles or they may comprise additional ingredients such as carrier particle". The same conclusion can be derived from the example relating to the preparation of composition 1 (paragraph [0087]). In the first part of this example composite excipient particles are mixed with micronised budenoside. Although in the second part of the example this mixture is blended with a coarse carrier lactose, it is explicitly reported that the mixture consisting of composite excipient particles and micronised budenoside "may be used in an inhaler directly". Finally, the board notes that paragraph [0066] of the application discloses the relative amount of composite excipient particles in compositions for use in dry powder inhaler which do not comprise carrier particles.

Thus, although the experimental data on the aerosol performance reported in the application relate to compositions comprising coarse carrier particles in addition to the composite excipient particles and the active ingredient, the board having regard to the general teaching of the application, sees no reason to doubt that also compositions essentially consisting of composite excipient particles and particles of active ingredient would be suitable for use in an inhaler device.

3.3.4 In view of the foregoing, the board considers that the technical problem underlying the invention can be formulated as the provision of a further pharmaceutical

composition containing particles comprising an excipient material and an additive suitable for use in inhalers.

3.4 Obviousness

3.4.1 As discussed in point 3.2.3 above, in the excipient particles of D1 the additive adheres to specific sites on the surface of the carrier material, thereby covering only a limited portion of it. On page 17 (lines 4 to 7) it is stated that the formation of a discontinuous covering by the additive, as opposed to a coating, represents an important and advantageous feature of the invention disclosed therein. This is in line with the indication on page 8 of D1, lines 7 to 14, to use only small amounts of additive material.

3.4.2 The emphasis put in D1 on the importance of a discontinuous covering by the additive would lead the skilled person to consider the formation of a coating as a measure going in the opposite direction of the teaching of D1 itself and possibly as being detrimental to the properties of the composition. The skilled person would therefore avoid modifying the excipient particles of D1 in this manner.

3.4.3 Nor is the concept of coating the excipient material with the additive suggested by the other cited documents.

In document D5 the additive is not used to promote the release of the active ingredient as in the compositions of the invention and of D1, but is used to improve the moisture resistance of the dry powder formulation. Accordingly, in the Board's opinion the skilled person would not combine the teachings of D1 and D5 in relation to aspects of the formulation which concern the

additive. In any case, document D5 does not clarify how the additive is distributed on the surface of the excipient material.

Document D3 relates to an excipient suitable for use in the preparation of powders for inhalation. The excipient takes the form of microgranules comprising a carrier and an additive material such as magnesium stearate. No information is given as to whether the additive is in the form of a coating of the carrier particles.

3.4.4 For the reasons set out above the Board comes to the conclusion that the skilled person would not modify the distribution of the additive material on the surface of the excipient particles of D1 by forming a coating in order to solve the technical problem defined in point 3.3.4 above.

In the light of this conclusion there is no need to consider whether the feature relating to the MMAD of the composite excipient particles would provide an inventive contribution to the subject-matter of claim 1.

3.4.5 Independent claims 11 and 12 are also inventive since they relate to inhalers comprising the composition of claim 1.

3.5 Thus, the subject-matter of the main request fulfils the requirement of 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 examining division with the order to grant a patent based on the claims of the main request, filed with letter of 24 December 2015, and a description to be adapted.

The Registrar: The Chairwoman:

N. Schneider R. Hauss

Decision electronically authenticated