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Datasheet for the decision of 22 November 2012

Case Number: T 0674/08 - 3.3.02

Application Number: 98965051.0

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Language of the proceedings: EN

Title of invention:
Microparticle inhalation formulations

Applicant:
Jagotec AG

Headword:
Inhalation formulations of dispersed microparticles/JAGOTEC

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0674/08 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 22 November 2012

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 12 October 2007 refusing European patent application No. 98965051.0 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: D. Boulois
R. Cramer

Summary of Facts and Submissions

I. European patent application No. 98 965 051.0 was refused by a decision of the examining division, pronounced on 13 September 2007 during oral proceedings, on the grounds of non-compliance with Article 56 EPC.

II. The decision was based on the main request filed on 9 August 2007.

Independent product claims 1, 7, 8, 9 of the main request read:

"1. An aerosol formulation consisting essentially of drug microparticles in a mean size range of 0.1 to 10 microns coated with one or more membrane-forming phospholipids and at least one surfactant selected from the group consisting of a polyoxyethylene-sorbitan-fatty acid ester, a polyoxyethylene fatty acid ester, a polyoxyethylene stearic acid ester, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, vitamin E, vitamin E D-a-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), a PEG glyceryl fatty acid ester, a propylene glycol mono- or di-fatty acid ester, a sorbitan fatty acid ester, a polyoxyethylene-polyoxypropylene co-polymer, glycerol triacetate, a monoglyceride, an acetylated monoglyceride, a bile salt, a polyethylene glycol, hydroxypropylmethylcellulose, sodium carboxymethyl cellulose, hydroxypropylcellulose and a carbomer, and dispersed in HFA 134a or HFA 227 propellant, wherein the density of the coated drug microparticles is substantially the same as the density of the propellant and the amount of coating on the drug

microparticles is more than 0.1% and less than 200% of the weight of the drug."

"7. A metered dose inhaler containing an aerosol formulation consisting essentially of drug microparticles in a mean size range of 0.1 to 10 microns coated with a mixture of phospholipids and at least one surfactant selected from the group consisting of a polyoxyethylene-sorbitan-fatty acid ester, a polyoxyethylene fatty acid ester, a polyoxyethylene stearic acid ester, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, vitamin E, vitamin E D-a-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), a PEG glyceryl fatty acid ester, a propylene glycol mono- or di-fatty acid ester, a sorbitan fatty acid ester, a polyoxyethylene-polyoxypropylene co-polymer, glycerol triacetate, a monoglyceride, an acetylated monoglyceride, a bile salt, a polyethylene glycol, hydroxypropylmethylcellulose, sodium carboxymethyl cellulose, hydroxypropylcellulose and a carbomer, and dispersed in HFA 134a or HFA 227 propellant, wherein the density of the coated drug microparticles is substantially the same as the density of the propellant and the amount of coating on the drug microparticles is more than 0.1% and less than 200% of the weight of the drug."

"8. Drug microparticles in a size range of from 0.1 to 10 microns coated with a membrane-forming phospholipid and at least one surfactant selected from the group consisting of a polyoxyethylene-sorbitan-fatty acid ester, a polyoxyethylene fatty acid ester, a polyoxyethylene stearic acid ester, polyoxyl 35 castor

oil, polyoxyl 40 hydrogenated castor oil, vitamin E, vitamin E D-a-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), a PEG glyceryl fatty acid ester, a propylene glycol mono- or di-fatty acid ester, a sorbitan fatty acid ester, a polyoxyethylene-polyoxypropylene co-polymer, glycerol triacetate, a monoglyceride, an acetylated monoglyceride, a bile salt, a polyethylene glycol, hydroxypropylmethylcellulose, sodium carboxymethyl cellulose, hydroxypropylcellulose and a carbomer, and dispersed in a pharmaceutically acceptable carrier for delivery to the upper or lower respiratory tract."

"9. A dry powder consisting essentially of drug microparticles in a mean size range of from 0.1 to 10 microns coated with a membrane-forming amphipathic phospholipid and at least one surfactant selected from the group consisting of a polyoxyethylene-sorbitan-fatty acid ester, a polyoxyethylene fatty acid ester, a polyoxyethylene stearic acid ester, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, vitamin E, vitamin E D-a-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), a PEG glyceryl fatty acid ester, a propylene glycol mono- or di-fatty acid ester, a sorbitan fatty acid ester, a polyoxyethylene-polyoxypropylene co-polymer, glycerol triacetate, a monoglyceride, an acetylated monoglyceride, a bile salt, a polyethylene glycol, hydroxypropylmethylcellulose, sodium carboxymethyl cellulose, hydroxypropylcellulose and a carbomer, for delivery to the upper or lower respiratory tract."

III. The documents cited during the examination proceedings included the following:
(1) WO91/04011

IV. In the decision under appeal, document (1) was considered to represent the most relevant state of the art. Document (1) discloses aerosols consisting of drug micro particles coated with a phospholipid or another surfactant. However, all other cited prior art documents were seen by the examining division as pertinent for inventive step as well, as they all disclosed compositions as claimed except the presence of an additional surfactant.

According to the examining division, all the claimed surfactants were known as stabilising agents in aerosol formulations. Alleged advantages without sufficient evidence to support a comparison with the closest prior art could not be taken into consideration for determining the problem underlying the invention. Therefore the problem to be solved by independent claims 1, 7, 8, 9 was regarded as how to provide alternative aerosol formulations.
The solution proposed appeared to be an obvious combination of known features, at which the skilled person would have arrived while optimising the formulation of document(1). As a consequence the presence of an inventive step for the subject-matter of independent claims 1, 7, 8 and 9 could not be acknowledged.

V. The appellant (applicant) lodged an appeal against that decision.

Arguments in support of inventive step of the main request filed before the examining division with the letter dated 9 August 2007 were provided with the grounds of appeal.

VI. With a letter dated 22 October 2012, the appellant provided further arguments and a further copy of the claims of the main request filed with the letter of 9 August 2007 before the examining division.

VII. With a letter dated 14 November 2012, the appellant informed the board that it would not be represented at the oral proceedings.

VIII. Oral proceedings before the board of appeal took place on 22 November 2012.

IX. The appellant's arguments can be summarised as follows:

Document (1) discloses drug microparticles coated with a phospholipid or a non-phospholipid surfactant and dispersed in HFA 134a. The skilled person would have to add a non-phospholipid or a phospholipid to the formulation disclosed in document (1).
When aiming to optimise the formulation of document (1), the skilled person would not have arrived at the claimed invention, since document (1) clearly teaches using only a single type of surfactant, and nothing would have prompted the skilled person to optimise the formulations by the addition of an additional phospholipid or non-phospholipid surfactant.
Furthermore, the skilled person would have been inclined to use the minimum number of non-active agents

in the compositions. Document (1) teaches away from the present invention.
The advantages offered by the formulation of the present invention should also be taken into account, especially the ability of the formulation to control the density of the particles as well as their polarities.
The use of a phospholipid with another surfactant allows the skilled person to adjust the density and the polarity of the coated drug microparticles to the propellant.

X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed before the department of first instance on 9 August 2007.

Reasons for the Decision

1. The appeal is admissible.

2. Main request - inventive step

2.1 The present invention relates to stable aerosol suspensions of drug microparticles having a mean particle size of from 0.1 µm to 10 µm dispersed in HFA 134a or HFA 227.

2.2 Document (1) constitutes the closest prior art, since it relates particularly to the stabilisation of dispersions of powdered medicaments in propellants. None of the other cited prior-art documents related to this particular problem.

Document (1) discloses medicinal aerosol formulations in the form of stable dispersions of micronised drug having a size distribution of 95% of particles below 10 µm and a mean size in the range of 1 to 5 µm (see page 11, lines 6-9). The micro particles are coated with a layer of surfactant, which constitutes 0.001 to 20% by weight of the coated solid medicament; this surfactant must be insoluble in the propellant 134a, and is preferably lecithin, sorbitan monolaurate or oleic acid (see page 3, lines 1-17; page 11, lines 9-10; page 7, lines 1-19 and the examples). The use of this surfactant provides a stable dispersion when using propellant 134a as propellant.
Examples 2 and 4-7 of document (1) show a suspension of coated active agent with a phospholipid content of 0.25% and 5% by weight. The examples, in particular example 2, show an improvement in the drug deposition and specify that the formulations are satisfactorily suspended, in particular in comparison to a formulation comprising a simple mixture with the same surfactant.

2.3 The problem as set out in the description of the present invention is to provide drug suspensions in the hydrofluorocarbon propellants HFA 134a or HFA 227 having an improved stability (see page 7, 2nd par.). It has to be investigated whether the application as filed contains evidence substantiating the alleged improvement.

2.4 As a solution to this alleged problem, claim 8 of the main request proposes in its broadest form, an aerosol formulation consisting essentially of drug micro particles in a mean size range of 0.1 to 10 microns

dispersed in a pharmaceutically acceptable carrier for delivery to the upper or lower respiratory tract characterised in that the micro particles are coated with one or more membrane-forming phospholipids and at least another surfactant selected from a specific list.

2.5 The application comprises six examples of aerosol formulations with phospholipids such as DPPC or DPMG in association with a second surfactant such as Myrj 52 or Poloxamer 188NF.
None of the examples shows any results or data regarding the stability of the drug dispersions. Nor does the description give any further data or indications about any achievement or improvement in respect of the stability of the drug dispersion.

As a consequence, none of the examples in the application or its description thereof succeeds in demonstrating a beneficial effect of the entirety of the claimed subject-matter over the prior art. It is therefore not credible that the alleged problem is solved. Consequently, the problem underlying the present invention as claimed in claim 8 of the main request can be seen only as the provision of a further aerosol dispersion of drug microparticles in the propellants HFA 134a or HFA 227.

In view of the information found in the description of the application, the board is convinced that the problem has been plausibly solved.

2.6 Thus, the question to be answered is whether the proposed solution(s) would have been obvious to the skilled person in the light of the prior art.

The coating with a second surfactant can only be seen as an arbitrary choice that would be made as a matter of routine by a skilled person.

Moreover, the subject-matter of claim 8 does not refer to any weight ratio or proportion between the phospholipid and the second surfactant used. The second surfactant can therefore be present in an amount varying from a high to a very low weight ratio to the phospholipid, and thus in a very low amount.

Consequently, the coating by a mixture of phospholipids and at least another surfactant is a common and obvious solution.

2.7 Further arguments from the appellant

- The appellant maintains that it would be desirable to match the density of the micro particles with the density of the propellant to avoid creaming or settling. This particular advantage offered by the formulation of the present invention must be taken into account, since it enables the specific formulation of the invention to control the density of the particles as well as their polarities.

The board could however not agree.
This technical feature is present in independent claims 1, 7 and 9, but is absent from the subject-matter of independent claim 8, and does not need to be taken into account for the assessment of inventive step. In any case, since the same active agents and excipients are used in both the invention and in document (1), the

density of the powder must inherently match the density of the propellant in the prior-art document (1).

- The appellant repeatedly argued that the skilled person might have attempted a combination of surfactants, but would not have contemplated the combination according to the invention.
This argumentation could not be taken into consideration, because the would-could approach is in general not meaningful when the problem is to find an alternative or further solution. If the problem is purely to find an alternative or further formulation, the skilled person would modify the existing product in any way he could by arbitrary choice.

2.8 Thus, the subject-matter of claim 8 of the main request is obvious vis-à-vis document (1). Consequently, the main request does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald