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Datasheet for the decision of 19 September 2017

Case Number: T 0476/14 - 3.3.07

Application Number: 09739150.2

Publication Number: 2268269

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Language of the proceedings: EN

Title of invention:
Sulfoalkyl ether cyclodextrin compositions

Applicant:
CyDex Pharmaceuticals, Inc.

Headword:
cyclodextrin/CYDEX

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - main and auxiliary requests (no)

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Case Number: T 0476/14 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 19 September 2017

Appellant: (Applicant)	CyDex Pharmaceuticals, Inc. 3911 Sorrento Valley Boulevard Suite 110 San Diego, CA 92121 (US)
Representative:	Harris, Jennifer Lucy Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 27 September 2013 refusing European patent application No. 09739150.2 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	D. Boulois
Members:	A. Usuelli
	I. Beckedorf

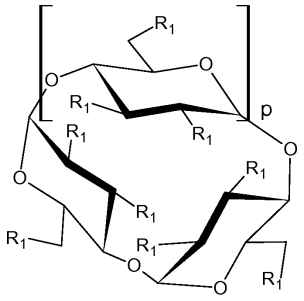
Summary of Facts and Submissions

I. The appeal of the applicant (appellant) lies from the decision of the examining division to refuse European patent application No. 09739150.2, published as WO 2009/134347.

II. The decision of the examining division was based on a main request and ten auxiliary requests.

Claim 1 of the main request read as follows:

"1. A sulfoalkyl ether cyclodextrin (SAE-CD) composition comprising a SAE-CD and less than 100 ppm of a phosphate, wherein the SAE-CD is a compound of Formula (1):



wherein p is 4, 5 or 6, and R_1 is independently selected at each occurrence from -OH or -O-(C_2-C_6 alkylene)-SO_3^--T, wherein T is independently selected at each occurrence from pharmaceutically acceptable cations, provided that at least one R_1 is -OH and at least one R_1 is -O-(C_2-C_6 alkylene)-SO_3^--T, wherein the SAE-CD has an average degree of substitution of 4.5 to 7.5, and wherein the SAE-CD composition has an absorption of less than 0.5 A.U. due to a drug-degrading agent, as determined by UV/vis

spectrophotometry at a wavelength of 245 nm to 270 nm for an aqueous solution containing 300 mg of the SAE-CD composition per mL of solution in the cell having a 1 cm path length".

III. The following documents were among those cited during the first-instance proceedings:

D8: Darco® KB-G; product datasheet;
D9: International Journal of Pharmaceutics, 330 (2007), 73-81;
D11: US 6,153,746;
D19: Declaration of Dr Antle dated 26 March 2013.

IV. In its decision, the examining division considered that document D11 was a suitable starting point for the assessment of inventive step. The composition defined in claim 1 of the main request differed from the compositions of D11 in that it contained a lower amount of phosphates. The technical problem was the provision of a sulfoalkyl ether cyclodextrin (SAE-CD) composition with less phosphate impurities. In the opinion of the examining division, removing these impurities was a matter of routine experimentation. Thus, claim 1 was considered obvious.

Claim 1 of auxiliary requests 1 and 6 to 10 was considered by the examining division to lack clarity and to be insufficiently disclosed. The amendments introduced in auxiliary requests 2 to 6 were considered not to meet the requirements of Article 123(2) EPC.

V. During the appeal proceedings the appellant submitted sets of claims with the statement setting out the grounds of appeal of 4 February 2014, with letter of 16 August 2017 and during the oral proceedings held on

19 September 2017. Some of these sets of claims were eventually abandoned during the proceedings.

At the end of the oral proceedings the following claims requests were maintained by the appellant:

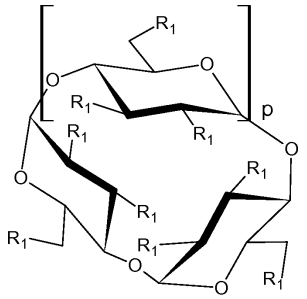
(a) Main request, filed on 16 August 2017
(b) Auxiliary request 1, filed during the oral proceedings held on 19 September 2017
(c) Auxiliary request 3, filed on 16 August 2017 (as sixth auxiliary request).

Claim 1 of the main request was identical to claim 1 of the main request pending before the examining division (see point II above).

Claim 1 of auxiliary request 1 differed from claim 1 of the main request in that the feature "...an aqueous solution containing **300** mg of the SAE-CD composition per mL of solution..." was replaced by "...an aqueous solution containing **500** mg of the SAE-CD composition per mL of solution..." (emphasis added).

Claim 1 of auxiliary request 3 read as follows:

"A sulfoalkyl ether cyclodextrin (SAE-CD) composition, wherein the SAE-CD is a compound of Formula (1):



wherein p is 4, 5 or 6, and R_1 is independently selected at each occurrence from -OH or -O-(C_2-C_6 alkylene)-SO_3^--T, wherein T is independently selected at each occurrence from pharmaceutically acceptable cations, provided that at least one R_1 is -OH and at least one R_1 is -O-(C_2-C_6 alkylene)-SO_3^--T, wherein the SAE-CD has an average degree of substitution of 4.5 to 7.5, wherein the SAE-CD composition is produced by a process comprising:
(a) mixing in an aqueous medium a cyclodextrin with a sulfoalkylating agent in the presence of an alkalizing agent to form an aqueous reaction milieu comprising a SAE-CD, one or more unwanted components, and one or more drug-degrading impurities;
(b) conducting one or more separations to remove the one or more unwanted components from the aqueous milieu to form a partially purified aqueous solution comprising the SAE-CD and the one or more drug-degrading impurities, wherein the one or more separations include a process selected from: ultrafiltration, diafiltration, centrifugation, extraction, solvent precipitation, or dialysis; and
(c) treating the partially purified aqueous solution with a phosphate-free activated carbon two or more times to provide the SAE-CD composition,
and wherein the SAE-CD composition has less than 100 ppm of a phosphate and an absorption of less than 0.5 A.U. due to a drug-degrading agent, as determined by UV/vis spectrophotometry at a wavelength of 245 nm to 270 nm for an aqueous solution containing 500 mg of the SAE-CD composition per mL of solution in the cell having a 1 cm path length".

VI. The following documents were submitted by the appellant during the appeal proceedings:

D16: Chemical stability of pharmaceuticals, 1979, pages 134-135
D17: Chemical stability of pharmaceuticals, 1986, pages 564, 565, 584, 585, 770, 771 and 776 to 779.

VII. For information on the course of the oral proceedings held on 19 September 2017, reference is made to the minutes.

VIII. The appellant's arguments, as far as they are relevant for the present decision, can be summarised as follows:

Document D11 was the closest prior art for the assessment of inventive step. The SAE-CD composition of claim 1 of the main request differed from the product prepared in example 1 of D11 in that it contained less than 100 ppm of phosphates. Moreover, D11 did not disclose directly and unambiguously the information that the SAE-CD composition had an absorption of less than 0.5 A.U. due to a drug-degrading agent. This information could also not be inferred from Figure 1 of the patent since it related to a process in which the purification was made with a different type of activated carbon than the one used in D11. The fact that D9 reported that the Ca salt prepared from the product Captisol® had an absorbance of approximately 0.8 A.U. was further evidence that the product of D11 did not meet the requirement of having an absorption of less than 0.5 A.U. due to a drug-degrading agent. The applicant had discovered that for an SAE-CD composition, there was a correlation between impurities having UV absorption in the wavelength range specified in the claims and degradation of the drug. This was demonstrated in the examples of the application. The technical problem was therefore the provision of an SAE-CD composition with reduced levels of impurities

which cause undesirable drug degradation. This problem was unknown before the priority date of the patent. There was therefore no teaching in the prior art on how to remove these impurities. There was also no teaching in the prior art on how to reduce the level of phosphates whilst maintaining low the amount of drug-degrading agents. Hence, claim 1 of the main request met the requirement of inventive step.

Claim 1 of the auxiliary requests defined SAE-CD compositions containing lower amounts of drug-degrading agent compared to the main request. In the process described in D11, the SAE-CD composition was purified by a single treatment with activated carbon. This was clearly not enough for reducing the amount of drug-degrading agent within the limit defined in the auxiliary requests. Hence, in respect of this request, it was even more evident that the feature concerning the UV absorption due to a drug-degrading agent represented a difference of the product of D11.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of a main request submitted on 16 August 2017 or, alternatively, on the basis of either auxiliary request 1 submitted during the oral proceedings or of auxiliary requests 3 submitted on 16 August 2017 as the sixth auxiliary request, and, in respect of all requests, amended pages 1 and 67 of the description submitted on 30 July 2015 and 4 February 2014 respectively.

Reasons for the Decision

Main request

Inventive step

1. The invention underlying the application in suit relates to a sulfoalkyl ether cyclodextrin (SAE-CD) composition of high purity. More particularly, the application addresses the problem of removing phosphate and drug-degrading impurities ([0005] and [0006]). The latter are substances that can cause the degradation of an active ingredient and are characterised by having an absorption at a wavelength of 245 nm to 270 nm.

2. Closest prior art

2.1 The closest prior art is document D11, which relates to a process for preparing SAE-CDs providing low levels of impurities (column 1, lines 7 and 8, column 2, lines 9 to 20). In example 1 of D11, a SAE-CD is prepared by a process comprising a step of purification carried out with Darco® KB-B activated carbon (column 7, lines 39 to 52).

2.2 According to paragraph [0113] of the present application, Darco® KB-B is an activated carbon in which the process of activation is made with phosphoric acid. This information is confirmed by the brochure D8.

In paragraph 3 of his declaration (document D19), Dr Antle states that because of the use of carbon activated with phosphoric acid, Captisol®, a commercial SAE-CD prepared according to the process of D11, has an average phosphate level of 155 ppm.

In view of this, the Board accepts the appellant's position that the product obtained in example 1 of D11 does not fulfil the requirement of claim 1 of containing less than 100 ppm of phosphates.

2.3 In the appellant's opinion, the SAE-CD composition of claim 1 differs from the product of example 1 of D11 also in the feature of having an absorption of less than 0.5 A.U. due to a drug-degrading agent, as determined by the method defined in the claim.

The Board notes that document D11 does not provide any information as to the UV absorption of the product obtained in example 1.

Example 28 of the present application describes the analysis by UV/vis spectrophotometry of SAE-CDs solutions that had been treated either once or twice with activated carbon. The UV/vis absorption spectra are reported in Figures 1 and 2. The spectra of Figure 1, concerning samples that have undergone a single treatment with activated carbon, clearly indicate that the absorption in the region of 245 nm to 270 nm is below 0.4 A.U., even when the sample contains high concentrations of SAE-CD up to 60%. These results are in line with those obtained by Dr Antle in the experiments described in D19. Exhibit 4 of this document shows that two SAE-CDs samples at 30% concentration (lots 10 and 29), purified by a single treatment with activated carbon, have an absorbance in the region of 245 nm to 270 nm below 0.35 A.U.

As discussed above, the SAE-CD of example 1 of D11 is purified by a treatment with an activated carbon, namely Darco® KB-B. In view of the evidence reported in

the present application and in D19, this product must have an absorption of less than 0.5 A.U. at a wavelength of 245 nm to 270 nm.

Hence, the feature of claim 1 concerning the absorbance in the range of 245 nm to 270 nm does not represent a further distinguishing feature over the disclosure of D11.

2.3.1 In paragraph 19 of D19, Dr Antle refers to the SAE-CD Ca salt prepared in document D9 starting from the commercial product Captisol®, which was prepared according to the process of D11. Dr Antle affirms that he had received this SAE-CD Ca salt from the authors of D9 and that he had determined that its absorbance in the region of 245 nm to 270 nm is approximately 0.8 A.U. In the appellant's opinion, this would indicate that Captisol®, obtained according to the process of D11, also has an absorption of approximately 0.8 A.U.

The Board notes in this respect that, according to D9, the process for preparing the Ca salt from the Na salt (i.e. Captisol®) took longer than three weeks (see paragraph 2.3). It appears that it cannot be excluded that some degradation of the SAE-CD occurred during the transformation of the sodium into the calcium salt. Thus, in the Board's view, the experiments disclosed in D19 in relation to the product of D9 cannot be used to infer that the product of D11 has an absorbance above 0.5 A.U. under the conditions defined in the claims of the present application.

2.3.2 For the above reasons, the Board concludes that the subject-matter of claim 1 of the application in suit differs from the disclosure of D11 only on account of

the requirement that the product must contain less than 100 ppm of phosphates.

3. Technical problem

3.1 As argued by the appellant in its submissions of 4 February 2014, it is known from documents D16 and D17, which can be considered to reflect the common general knowledge in relation to the chemical stability of pharmaceuticals, that the phosphates can catalyse the degradation of some drugs such as ampicillin, methicillin and triamcinolone. Thus, the teaching of these documents supports the statement in the description (see [0006]) that substantial removal of phosphate impurities provides highly stable formulations.

The technical problem is therefore to be seen in the provision of an SAE-CD product which makes it possible to prepare more stable formulations.

4. Obviousness

4.1 D16 and D17 indicate that the skilled person knew at the priority date that the presence of phosphate ions could be detrimental to the chemical stability of various substances. For instance, D17 teaches that the rate of hydrolysis of methyl paraben is sensitive to phosphate concentration (page 584) and that the hydrolysis of thiamine is catalysed by phosphate buffers (page 770).

He was furthermore aware that the activated carbon Darco® KB-B used in D11 was activated with phosphoric acid (see D8 and paragraph [0113] of the present description). Thus, faced with the task of providing a

SAE-CD product resulting in stable compositions, he would have reduced the amount of phosphates, e.g. by using an activated carbon containing low amounts of phosphates.

For these reasons, the Board considers that the subject-matter of claim 1 was obvious for a skilled person having regard to the cited prior art.

Auxiliary request 1

5. The SAE-CD composition of claim 1 of this request is characterised by the fact that it contains a lower amount of drug-degrading agent compared with the composition of the main request, since the requirement of having an absorption of less than 0.5 A.U. at a wavelength of 245 nm to 270 nm must be satisfied by a more concentrated SAE-CD solution (300 mg/mL in the main request vs 500 mg/mL in auxiliary request 1).

In the appellant's opinion, the product of example 1 of D11 does not meet the condition of having an absorption of less than 0.5 A.U. under the measurement conditions defined in claim 1, since it is obtained in a process involving a single step of purification with activated carbon whereas the product of the present application is purified by a double step of filtration with activated carbon.

5.1 To support its position, the appellant refers to page 67 of the present description, in which it is reported that an SAE-CD composition (lot No. 17CX01.HQ00025), obtained by a process comprising a single treatment with activated carbon, has an absorption, at a wavelength of 245 nm to 270 nm and 50% concentration, of

0.652 A.U., i.e. above the limit defined in claim 1 for a composition with the same concentration.

The Board notes in this respect that the present application provides the evidence that a single treatment with activated carbon may also be sufficient to reduce the amount of drug-degrading agent within the limit defined in claim 1 of the auxiliary request 1. Indeed, the experiments of page 67 referred to by the appellant show that a different lot of SAE-CD composition prepared by a single treatment with activated carbon (lot No. 17CX01.HQ00025) presents an absorption of 0.339 A.U. at 50% concentration. Furthermore, as discussed in point 2.3 above, Figure 1 shows that even a SAE-CD composition at 60% concentration, prepared by a single treatment with activated carbon, has an absorption below 0.4 A.U.

5.2 D11 does not provide information as to the absorption at a wavelength of 245 nm to 270 nm of the product prepared in example 1. However, it is the aim of this document to provide a method for preparing SAE-CD products of high purity (see column 3, lines 13 to 24 and column 6, lines 1 to 19) and at the end of example 1 it is stated that no β-cyclodextrin and sultone impurities were detected.

The Board therefore sees no reason to doubt that the SAE-CD product obtained in example 1 of D11 is of high purity.

5.3 The appellant decided to define the amount of drug-degrading impurity by the use of a specific parameter which does not appear to be commonly used in the prior art, namely the absorption at a wavelength of 245 nm to 270 nm of a solution containing 500 mg/mL of

SAE-CD. Under this circumstance, and considering that there are no specific reasons to doubt that the product of D11 fulfils the condition expressed by this parameter, the onus is on the appellant to prove that the amount of drug-degrading agent is a distinguishing feature over D11.

In this context, the Board also notes that, according to the declaration of Dr Antle (document D19, point 3), the appellant was responsible for supervising the production of Captisol® by the process disclosed in D11. Accordingly, it was apparently in a position to make a UV analysis of the product of D11.

In the absence of any evidence from the side of the appellant which might support its position, the Board considers that the feature of claim 1 concerning the absorption at a wavelength of 245 nm to 270 nm does not represent a distinguishing feature over D11.

5.4 Hence, the SAE-CD of claim 1 of auxiliary request 1 differs from the product of example 1 of D11 only in that it contains less than 100 ppm of a phosphate.

However, for the same reasons given above in respect of the main request, it would be obvious to the skilled person to reduce the amount of phosphates in the product of D11. Accordingly, auxiliary request 1 does not fulfil the requirements of Article 56 EPC.

Auxiliary request 3

6. Claim 1 of auxiliary request 3 differs from claim 1 of auxiliary request 1 in that it incorporates the features defining the process for preparing the SAE-CD composition. There is, however, no evidence that the

process defined in claim 1 imparts to the SAE-CD composition new characteristics over the composition defined in claim 1 of auxiliary request 1.
Hence, auxiliary request 3 does not comply with Article 56 EPC for the same reasons as set out in relation to auxiliary request 1.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Fabiani D. Boulois

Decision electronically authenticated