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D E C I S I O N
of 11 April 1994

Case Number: T 0896/91 - 3.3.2

Application Number: 86304044.0

Publication Number: 0205282

IPC: A61K 9/22

Language of the proceedings: EN

Title of invention:
Oral pharmaceutical composition

Applicant:
Euroceltique SA

Opponent:
-

Headword:
Oral composition/EUROCELTIQUE

Relevant legal norms:
EPC Art. 56

Keyword:
"Inventive step (yes)"

Decisions cited:
T 0002/83

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Case Number: T 0896/91 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 11 April 1994

Appellant: Euroceltique SA
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Decision under appeal: **Decision of the Examining Division of the European Patent Office dated 12 July 1991 refusing European patent application No. 86 304 044.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: P.A.M. Lançon
Members: L. Galligani
S.C. Perryman

Summary of Facts and Submissions

I. European patent application No. 86 304 044.0 published under No. 0 205 282 was refused by the Examining Division.

The decision was taken on the basis of a set of Claims 1 to 16 for all States except Austria and a set of Claims 1 to 15 for Austria filed by letter dated 19 November 1990 (received on 22 November 1990).

Claim 1 (all States except Austria) reads as follows:

"A sustained release, oral pharmaceutical composition in solid unit dosage form, for application to the mucosa of the oral or nasal cavity, comprising compressed granules characterised in that the granules comprise a drug, a C_{8-18} aliphatic alcohol and a hydrated water soluble hydroxyalkyl cellulose and further in that the granules are coated with a mucosa adhesive cellulose."

Claims 2 to 14 and Claims 15 to 16 relate, respectively, to specific embodiments of the composition according to Claim 1 and to the process for its preparation.

The claims for Austria are formulated as corresponding process claims.

II. The Examining Division refused the application under Article 97(1) EPC on the ground that the subject-matter of the claims did not involve an inventive step within the meaning of Article 56 EPC, having regard to the following documents:

(1) EP-A-0 032 004;
(2) EP-A-0 063 604;
(3) DE-A-1 907 546;
(4) DE-A-2 518 270.

The main reasons given for the decision are as follows:

(a) the composition disclosed in document (1) differs from that of Claim 1 essentially in that it does not mention *expressis verbis* the features "for application to the mucosa of the oral or nasal cavity" and "that the granules are coated with a mucosa adhesive cellulose". However, said features are not excluded by the teaching in (1);

(b) document (2) discloses a mucous membrane-adhering film preparation for drug delivery in which use is made of the mucous membrane adhesion property of the same cellulose derivatives of the present application. With respect to this known galenic form no surprising effect has been demonstrated by the Applicant in order to support inventive step;

(c) the mixing (coating) of granulated material with dry, powdered hydroxypropyl methylcellulose (HPMC) or sodium carboxy methylcellulose (CMC-Na) is known in the art [see documents (3) and (4)].

III. The Appellant lodged an appeal against this decision and paid the appeal fee.

The Appellant's arguments are essentially as follows:

(a) document (1) relates to the use of molecular coordination complexes formed between a cellulose polymer and a non-polar C_{8-18} aliphatic alcohol in controlled release formulations. The said document

does not suggest the preparation of formulations suitable for retention in the oral or nasal cavity nor does it disclose the coating of granules with a mucosa adhesive cellulose prior to compression;

(b) document (2) suggests at most that cellulose is a suitable mucosal adhesive. However, the said document does not teach controlled release oral compositions in solid unit dose form nor does it suggest the use of extragranular mucosa adhesive;

(c) the Appellant has found that by employing extragranular cellulose adhesive prior to compression the adherent properties of the resulting dosage form are significantly greater than those of a dosage form having intragranular adhesive only. This teaching could in no way be derived from (1) or (2);

(d) both documents (3) and (4) relate to the preparation of readily disintegrable dosage forms. The purpose of the added cellulose therein is not for promoting good adherence, but for promoting disintegration of the preparations. Thus, a skilled person seeking to produce an improved adhesive preparation would not have followed their teaching.

IV. In a communication pursuant to Article 110(2) EPC, the Board drew the Appellant's attention to a new citation, namely the Japanese open patent publication No. 100714/1981 [hereinafter document (6)] which was referred to in document (2) (see page 2, second paragraph). In the absence of a translation of document (6) the Board also referred to the abstract thereof retrieved through the Japanese Patent Abstract database [hereinafter document (5)].

In reply thereto, the Appellant provided a translation into the English language of the Examples of the said document (6) and observed that the tablet disclosed in (6) differed from that according to the present invention in that:

(a) the active ingredient was contained in a soft, pliable compression moulding produced under low pressure, **not** in granules tabletted under high pressure;

(b) the areas of the "tablet" from which absorption was to take place were **not coated** with the mucosa adhesive cellulose.

In its submission the prior art would have led the skilled person away from the present invention by requiring a construction having separate absorption and adhesive areas.

V. In a letter dated 28 April 1994 the Appellant, in reply to an inquiry by the Rapporteur, pointed out that the tablet product *MST CONTINUS* referred to in the clinical trials mentioned in the present application was made by a process involving the same ingredients and the same processing steps described in document (1).

VI. The Appellant requests the grant of a patent on the basis of the claims on file.

Reasons for the Decision

1. The appeal is admissible.

2. *Amendments (Article 123(2) EPC)*

The amended wording of the claims on file enjoys formal support in the application as originally filed (see page 4, first paragraph).

3. *Clarity (Article 84 EPC)*

The claims on file are comprehensible and contain all the essential features which characterize the invention. Moreover, the claims are supported by the description which provides examples of the preparation of the oral dosage form and clinical tests of its use. Thus, the requirements of Article 84 EPC are met.

4. *Novelty (Article 54 EPC)*

Novelty was not contested by the Examining Division.

None of the available documents affects the novelty of the claimed subject-matter. In particular, the claimed subject-matter is novel also *vis-à-vis* the newly cited document (6) which does not disclose a solid unit dosage form made of compressed cellulose-coated granules which comprise a C_{8-18} aliphatic alcohol and a hydrated water soluble hydroxyalkyl cellulose.

5. *Inventive step (Article 56 EPC)*

The Examining Division based the rejection on a lack of inventive step objection without explicitly identifying the closest prior art.

5.1 The closest prior art

In the Board's view the closest prior art is represented by document (1) which discloses controlled release pharmaceutical preparations *inter alia* for oral administration (see page 29, lines 25 to 26). The said preparations can be, for example, in the form of tablets (see Example 2, lines 15 to 18) made of compressed granules comprising a desired drug in a matrix formed between a cellulose polymer (e.g. a hydrated hydroxyalkyl cellulose, see Example 1) and a C_{8-18} aliphatic alcohol (see page 26, lines 6 to 16).

5.2 The technical problem and its solution

Administration of sustained and controlled release pharmaceutical preparations *via* the oral route can be effected by dosage forms which are either swallowed (in this case drug absorption takes place into the gastrointestinal tract) or held in the buccal cavity (in this case drug absorption can occur also through the oral mucosa). In the latter case there is the disadvantage that the oral preparation may be inadvertently swallowed [see introductory part of document (1)].

In the light of document (1) the technical problem underlying the present application can be seen in the improvement of the oral preparations described therein so as to obtain a prolonged bioavailability of the desired drug in the formulation.

As a solution to the said problem the Appellant proposes in the present claims a sustained release, oral pharmaceutical composition in solid unit dosage form (for example, a buccal tablet) made of compressed granules comprising a desired drug, a C_{8-18} aliphatic

alcohol and a hydrated water soluble hydroxyalkyl cellulose, wherein the granules are coated with a mucosa adhesive cellulose (e.g. hydroxyalkylcellulose) and a process for its preparation.

The application reports data on the duration of a tablet according to the present claims in the buccal cavity (see Table on page 17) as well as clinical trials which demonstrate that the subject buccal tablet displays a significantly prolonged bioavailability in comparison with an orally administered sustained release formulation prepared according to document (1) (*MST CONTINUS*; see description page 16 and Figure 2). It is observed that the prolonged bioavailability of the drug shown in the comparative test reported in Figure 2 can be ascribed exclusively to the extragranular cellulose because this is the only difference between the two tablets. The Board is, therefore, satisfied that the underlying technical problem has been solved.

5.3 Assessment of inventive step

In its assessment of inventive step, the Examining Division contended that, although document (1) did not mention *expressis verbis* the features "for application to the mucosa of the oral or nasal cavity" and "that the granules are coated with a mucosa adhesive cellulose", said features were not excluded by its teaching and, for this reason, an inventive step had to be ruled out.

The Board cannot accept this argument which is clearly based on hindsight because the said features reflect part of the problem and of its solution.

When assessing inventive step, the fundamental question to be answered, once the closest prior art has been determined [here: document (1)] and the objective

technical problem has been formulated, is whether the skilled person would have arrived at the claimed solution in a straightforward manner in the light of any other prior art document(s) and/or common general knowledge (see, for example, T 2/83 OJ EPO 1984, 265).

5.3.1 The step to the solution proposed in the present case

At the relevant priority date of the present application slow-releasing pharmaceutical preparations in the form of e.g. tablets, lozenges, films **adhering** to the mucosa of the oral or nasal cavity were known in the art [see page 1 of the present application; document (2), in particular pages 1 and 2; document (6)].

In the attempt to improve the oral pharmaceutical preparations of document (1), the skilled person would have certainly directed his attention to prior art documents concerned with buccal pharmaceutical preparations having mucous membrane adhesion properties.

Among the available documents the skilled person would have certainly considered the contents of documents (2) and (6).

(i) Document (6)

Document (6) deals in particular, as confirmed by document (5), with the problem of finding an alternative to the injection of insulin. For this purpose, document (6) discloses solid, sustained-release pharmaceutical preparations, e.g. tablets (see the example and Figure 2), for application to the mucosa of the oral or nasal cavity which consist of a compression molded core comprising the drug (insulin) covered with a shell comprising a hydroxypropyl cellulose

(optionally) in combination with an acrylic acid polymer (e.g. carbopol). The said core is eccentrically placed in the mucous membrane-adhering coating layer (see Figure 2).

In the Board's view, the skilled person would have readily derived from document (1) the teaching that the provision of a coating layer (a shell) of hydroxyalkyl cellulose (optionally) in combination with an acrylic acid polymer would have promoted the adhesion of oral tablets to the oral mucosa thereby permitting the absorption of the drug from the mucous membrane. Thus, the skilled person would at most have arrived at the idea of providing **the whole** of the solid oral dosage form of (1) with an outer layer such as that described in document (6). However, nothing in (6) would have readily suggested to the skilled person coating the component granules of the oral dosage form according to document (1) with extragranular mucosa adhesive cellulose.

(ii) Document (2)

Document (2) deals with the problem of finding an alternative to mucosa adhering tablets. For this purpose, document (1) proposes a film preparation comprising at least two layers, namely (a) a layer adhering to the mucous membrane made of a water-soluble cellulose derivative in which the drug is contained and (b) a layer consisting of a cellulose derivative which is only with difficulty soluble in water.

Document (2) points away from the use of large-sized preparations such as tablets by proposing

the use of film preparations (see description, page 2). Thus, the skilled person would have been led away from the solution proposed in the present claims.

Further, the Board notes that the teaching of (2) is directed to film preparations in which the desired drug is contained in the cellulose layer that adheres to the mucosa [layer (a)]. This is different from the arrangement in the present case where no drug is contained in the extragranular cellulose coating layer. Moreover, the purpose of layer (b) in (2) is to prevent elution of the pharmaceutical component from the layer (a) into the mouth (see page 14, second paragraph), **not** - as in the present case - to promote adhesion to the mucosa.

Thus, also document (2) would not have suggested to the skilled person coating the component granules of the oral dosage form according to document (1) with extragranular mucosa adhesive cellulose.

(iii) Other documents

Documents (3) and (4) referred to by the Examining Division in its decision relate to the preparation of disintegrable dosage forms. Thus, as correctly observed by the Appellant (see Section III, point (d), a skilled person would not have followed their teaching when seeking to solve the problem set out in Section 5.2 above.

5.3.2 Conclusion

For the above reasons, the Board considers that the subject-matter of the present claims involves an inventive step because neither document (2) nor document (6) rendered it obvious for the skilled person, who was faced with the technical problem as defined in Section 5.2 above, to make the known oral preparation of (1) adhere to the mucous membrane by providing its component granules with extragranular mucosa adhesive cellulose.

6. The main request is thus allowable subject to the description being amended by introduction of a reference to documents (1), (2) and (6) to comply with Rule 27 EPC. For this purpose the Board pursuant to its powers under Article 111(1) EPC remits the case to the first instance.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of the claims filed by letter dated 19 November 1990 (received on 22 November 1990) in the two versions for all States except Austria and Austria and a description to be amended.

The Registrar: The Chairman:

P. Martorana P.A.M. Lançon