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D E C I S I O N
of 29 July 2004

Case Number: T 0453/01 - 3.3.2

Application Number: 96940616.4

Publication Number: 0799028

IPC: A61K 9/20

Language of the proceedings: EN

Title of invention:
A controlled release formulation for poorly soluble basic drugs

Patentee:
Abbott Laboratories

Opponent:
Hexal Aktiengesellschaft

Headword:
Controlled release formulation/ABBOTT LABORATORIES

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - no: obvious combination"

Decisions cited:
-

Catchword:
-

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Case Number: T 0453/01 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 29 July 2004

Appellant: (Opponent)	Hexal Aktiengesellschaft Industriestrasse 25 D-83607 Holzkirchen (DE)
Representative:	TER MEER STEINMEISTER & PARTNER GbR Patentanwälte Mauerkircherstrasse 45 D-81679 München (DE)
Respondent: (Proprietor of the patent)	Abbott Laboratories Chad 0377/AP6D-2, 100 Abbott Park Road Abbott Park, Illinois 60064-3500 (US)
Representative:	Modiano, Guido, Dr.-Ing. Modiano, Josif, Pisanty & Staub, Baaderstrasse 3 D-80469 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 30 January 2001 rejecting the opposition filed against European patent No. 0799028 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
P. Mühlens

Summary of Facts and Submissions

I. European patent No. 0 799 028 based on application No. 96 940 616.4 was granted on the basis of a set of 14 claims.

Independent claim 1 as granted reads:

"1. A controlled release, solid pharmaceutical composition adapted for oral administration comprising:
a therapeutically effective amount of at least one basic drug having a water solubility of less than 1 part per 30 parts water;
a water-soluble alginate salt;
a complex salt of alginic acid, and
an effective amount of an organic carboxylic acid to facilitate dissolution of the basic drug."

II. Notice of opposition was filed against the granted patent by the appellant.

The patent was opposed under Article 100(a) EPC for lack of inventive step.

The following documents were *inter alia* cited during the opposition and appeal proceedings and remain relevant for the present decision:

(1) EP-A-188040

(3a) English translation of JP-A-60 163 823

III. The Opposition Division rejected the opposition under Article 102(2) EPC by its decision pronounced on 10 January 2001.

In its reasons for the decision under appeal, the Opposition Division found that document (1), which disclosed extended release compositions for soluble drugs comprising a matrix as the one of the patent in suit, represented the closest state of the art. The problem to be solved over said document was seen in the provision of a controlled release composition where a poorly soluble basic drug was released continually.

This problem was solved by the combination of the poorly soluble basic drug with an effective amount of an organic acid.

The Opposition Division considered that the available prior art documents were not relevant because they did not relate to the field of controlled release drugs and were concerned with the bioavailability of the drugs, so that the solution was regarded as inventive.

IV. The appellant (opponent) lodged an appeal against the said decision.

V. Oral proceedings were held before the Board on 29 July 2004.

VI. The appellant submitted that the subject-matter of the contested patent did not involve an inventive step.

In summary, in its view, the subject-matter of the contested patent was merely the result of an obvious

combination of the alginate matrix disclosed in document (1) with the drug formulation disclosed in document (3a), namely a mixture comprising 6-O-methylerythromycin A (6-ME) and citric acid.

VII. The respondent contested this view.

In its opinion, the skilled person would not combine document (1) and (3a) because they did not relate to the same technical field and because there was no pointer in these documents linking them.

Moreover, it argued that the skilled person had to overcome many technical prejudices in order to arrive at the claimed composition.
In fact, it submitted that the skilled person would not have used an organic acid in the claimed composition because it would have expected the drug and the alginate matrix to be degraded by the acid.

Moreover, it maintained that the increased bioavailability of the mixture disclosed in document (3a) would also prevent the skilled person from combining the teachings of documents (1) and (3a) as the purpose of the patent in suit was not the increase in the bioavailability of the drug, but to maintain the same bioavailability.

VIII. The appellant requested that the decision under appeal be set aside and the patent be revoked.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 56 EPC*

2.1 The patent provides for a peroral controlled release pharmaceutical composition where a poorly soluble basic drug may be released continually from the dosage form to reduce the daily dosage regimen. The composition comprises a therapeutically effective amount of at least one basic drug having a water solubility of less than 1 part per 30 parts water, a water-soluble alginate salt, a complex salt of alginic acid, and an effective amount of an organic carboxylic acid (page 2, lines 3 and 4; page 2, lines 57, to page 3, line 5).

Document (3a) discloses a peroral preparation comprising a therapeutically effective amount of at least one basic drug having a water solubility of less than 1 part per 30 parts water (6-ME) and an effective amount of an organic carboxylic acid (citric acid) (page 1, claim 1).

Both parties agreed that the preparation described in document (3a) was a conventional release dosage form, which needs to be administered several times within a twenty-four hour period and the Board sees no reason to differ.

The Board considers that this document, which concerns the same drug formulation as the one used in the matrix of the patent in suit, ie a mixture of a poorly soluble

basic drug with an organic carboxylic acid, represents the closest prior art.

2.2 Accordingly, the problem to be solved as against document (3a) can be seen as the provision of an improved formulation which allows a once-daily dose regimen.

2.3 This problem is solved by the subject-matter of claim 1 and, in the light of working examples of the patent in suit, the Board is satisfied that the problem has been plausibly solved.

2.4 Thus, the question to be answered is whether the proposed solution, ie the use of an alginate matrix of a water-soluble alginate salt and a complex salt of alginic acid, was obvious to the skilled person in the light of the prior art.

In that respect, document (1) discloses precisely an alginate matrix of sodium alginate (a water-soluble alginate salt)and sodium-calcium alginate (a complex salt of alginic acid). This matrix is, moreover, used for the preparation of a pharmaceutical tablet formulation to provide controllable, extended release profiles up to 24 hours. This matrix is described as being suitable for any active ingredients and in particular for pharmaceuticals which need to be administered frequently within a twenty-four hour period (page 3, line 29, to page 4, line 3).

Therefore, the Board is satisfied that the skilled person faced with the problem as defined under 2.3 would just have to follow the teaching of document (1)

to arrive at the subject-matter of the contested patent.

2.5 The Board does not share the respondent's submissions in favour of an inventive step for the following reasons:

As to the argument that the skilled person would not combine erythromycin with an organic acid because of the existence of a technical prejudice based on the knowledge that this drug is unstable under acidic conditions, the Board observes that, as the case law indicates, a prejudice arises from an opinion or preconceived idea widely or universally held by experts in the field.

In the present case, document (3a) shows that the concentration of 6-ME in blood, as indicator of its bioavailability, over a period of 10 hours is doubled when 6-ME is combined with citric acid (figures 1 and 2). In this document, it is accordingly concluded that the preparation containing citric acid may enhance the absorption of orally administered 6-ME from the digestive tract compared to the conventional dosage form without organic acid and that it is very useful (page 3, lines 11 to 13).

Under these circumstances, the conditions required for establishing the existence of a technical prejudice are not provided. To the contrary, document (3a) provides a clear hint to use 6-ME in combination with an organic acid since citric acid doubles the bioavailability of the drug over a period of at least 10 hours as demonstrated by the comparison of the curves

established for preparations with and without citric acid. As these curves show the same profile and as the document is silent about any detrimental effects, the Board is convinced that the skilled person would not have been dissuaded from using the drug in combination with citric acid.

In that respect, it is moreover pointed out that the mere fact that there exists no commercial preparation of that drug with citric acid does not change the teaching of document (3a) as far as the assessment of inventive step is concerned. Indeed, as a rule, commercial aspects are not influenced by technical considerations only.

As to the second technical prejudice, raised for the first time during the oral proceedings, the respondent referred to the passage in document (1) on page 9, third paragraph. which reads: "The mechanism of release of the active ingredient from the solid preparation is associated with the ability of the preparation [alginate matrix], upon exposure to the aqueous medium of gastric [acidic] juice, to hydrate (absorb water) and swell radially (and not decompose) to produce a viscous gel.".

From this explanation of the way the drug is released from the alginate matrix in the body, it cannot however be deduced that alginate salts are not stable in the presence of an organic acid in a solid pharmaceutical composition, ie in a dry form.

In the absence of any further element to that end, the Board is not convinced that such a prejudice does indeed exist.

Nor does the Board agree with the respondent's argument that the skilled person would not have taken the teaching of document (3a) into account because it related to preparations having an increased bioavailability compared to the conventional release form, whereas the aim of the contested patent was not to increase the bioavailability but to keep the same bioavailability as the conventional release form.

In fact, the Board is convinced that the skilled person would in any case use the more efficient preparation or at least both forms, since, as a rule, it is not possible to foresee the effect of a new dosage form on the bioavailability of a drug, as confirmed by document (3a) itself, which reports other unsuccessful attempts with other dosage forms (page 1, paragraph 3 of the description).

Finally, concerning the argument relating to the absence of a pointer to document (1) in document (3a), it is indeed correct that there is no reference to document (1) in this document and that this document deals moreover with a conventional release dosage form whereas document (1) deals with sustained release dosage forms.

The skilled person, who is an expert in pharmaceutical preparations in the present case, would however know the prior art dealing with any dosage form so that he would be aware of both documents. Moreover, even in the

absence of an explicit reference linking two documents, it remains within his skills to combine two teachings when there is a reason to do so, for instance in order to solve a problem.

This is precisely the case, since, as discussed above under 2.2 to 2.4, the skilled person is looking for a formulation to make a sustained release dosage form starting from the promising conventional release dosage combination of document (3a).

In view of the foregoing, the Board judges that the subject-matter of claim 1 of the set of claims as granted does not involve an inventive step as required by Article 56 EPC.

The Board wishes moreover to stress that the situation could not have been assessed differently when starting from the alginate matrix sustained release pharmaceutical preparation disclosed in document (1) as closest prior art since the above considerations also remain relevant. The Board is indeed convinced that the skilled person would, in any case, have used the improved combination of 6-ME with citric acid disclosed in (3a) in the alginate matrix of document (1) without inventive activity as there are no established technical prejudices preventing him from trying this promising preparation.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside

2. The patent is revoked

The Registrar: The Chairman:

A. Townend U. Oswald