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D E C I S I O N
of 16 September 1998

Case Number: T 0173/95 - 3.3.2

Application Number: 87301231.4

Publication Number: 0235986

IPC: A61K 9/16

Language of the proceedings: EN

Title of invention:
Slow release formulation

Patentee:
Ethical Pharmaceuticals Limited

Opponent:
Napp Laboratories Ltd.

Headword:
Double-matrix formulation/ETHICAL PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 83, 56

Keyword:
"Sufficiency of disclosure (yes) - improved effect not a feature of the claim"
"Inventive step (yes) - comparative tests"

Decisions cited:
-

Catchword:
-

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Case Number: T 0173/95 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 16 September 1998

Appellant: (Opponent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 24 January 1995 concerning maintenance of the European patent No. 0 235 986 in amended form.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: C. Germinario
R. E. Teschemacher

Summary of Facts and Submissions

I. European patent No. 0 235 986 was granted in response to European patent application No. 87 301 231.4 on the basis of a first set of 9 claims for all the designated contracting states except AT, ES and GR and a second set of 10 claims for AT, ES and GR.

II. Notice of opposition was filed by the appellant, requesting revocation of the patent in its entirety on the grounds of insufficiency of disclosure and lack of inventive step.

The following documents, cited during the proceedings before the opposition division, are relevant for the present decision:

(6) English translation of JP Patent No. 43 20006 (1968)

(7) D. A. Alderman, Int. J. Pharm. Tech. & Prod. Mfr., 5(3), 1984, p. 1-9 .

III. In its interlocutory decision, the opposition division held that the patent could be maintained in amended form, with independent claim 1 of the first set of claims reading as follows:

"A slow release formulation to be administered to human or animals, comprising (a) primary granules (1) which comprise particles (3) comprising an active ingredient and a primary matrix (4) of water soluble slow release material in which are dispersed the particles (3) comprising the active ingredient, and (b) a secondary matrix (2) of a water soluble slow release material in

which the granules (1) are dispersed, the secondary matrix (2) and the primary granules (1) forming secondary granules (6), wherein a polysaccharide material or alginate forms the slow release material of one or both matrixes (2,4)".

Independent claim 5 of the first set of claims and claim 1 of the set for AT, ES and GR were directed to a method of making the slow release formulation.

As regards the objection of insufficiency of disclosure, the opposition division was of the view that the examples in the description contained sufficient information to enable a person skilled in the art, supported by common general knowledge, to carry out the invention within the whole ambit of the independent claims.

The novelty of the claimed subject matter was not a ground for opposition.

The opposition division expressed the opinion that the comparative tests reported in the patent were not suitable for substantiating the alleged improved release profile of the claimed formulation. Nonetheless, it recognised as plausible, on the basis of other passages in the description, that the multi-matrix formulation according to the patent implied a longer sustained release of the active ingredient as compared with single matrix formulations. Having identified the closest prior art in document (6), the opposition division held that this document did not give any incentive to the skilled reader to modify the formulations therein disclosed by replacing the water insoluble slow release material comprised in said formulations by a water soluble alternative carrier.

The inventive step involved in the claimed subject matter was therefore recognised.

IV. The appellant (opponent) lodged an appeal against this decision. Oral proceedings were held on 16 September 1998. As previously announced in writing, the appellant was not represented. During the oral proceedings, the respondent filed a new set of 9 claims for the contracting states AT, ES and GR, in which an error in the text of claim 1 was corrected.

V. The appellant contested the reliability of the "comparative examples" described in the patent and produced new comparative tests. On the basis of the results of these tests, enclosed in the statutory declarations of T. J. Knott and J. M. Newton, the appellant concluded that no improvement in terms of the release rate of the active ingredient could be appreciated when the so-called double-matrix formulation according to the patent invention was compared with a single-matrix formulation comprising the same components in the same amounts. It was also maintained that the alleged difference in release profile observed by the respondent in subsequently submitted comparative tests was well within the normal and accepted experimental variability between different batches of the same substance and therefore had no statistical relevance.

The appellant's conclusion was that the patent specification did not describe how the alleged improved effect could be achieved and therefore did not describe the invention in a manner sufficiently clear and complete for it to be carried out.

In view of document (6), which disclosed a double-matrix formulation, the appellant contested, relying on the declaration of A. T. Florence, that a difference between the formulations according to the patent and document (6) could be recognised in the water solubility or insolubility of the slow release materials. In fact, among all the binders cited in (6), certain, such as casein or sodium and potassium salts of fatty acids, were water-soluble, while others, though insoluble at neutral pH, were water-soluble at basic pH. The appellant concluded that replacing the binders of (6) with the specific water-soluble materials cited in the patent, which were all well known from eg document (7), did not require the exercise of an inventive effort.

VI. In reply to the statement setting out the grounds of appeal and further communications, the respondent (patentee) produced new comparative tests, enclosed in D. J. Trigger's statutory declaration, and the following arguments.

With reference to the appellant's comparative tests, he pointed out, as a possible reason for the failure in reproducing the release profile characterising the claimed formulation, that both Knott's and Newton's tests were not carried out under the experimental conditions described in example 1 of the patent. Specifically emphasis was given to the type of shear mixer used in the tests. These arguments, however, were no longer developed during the oral proceedings, because, in the respondent's opinion, a more accurate evaluation of the results reported by Knott and Newton would, in any case, substantiate the improved release profile of the double-matrix formulation of the invention compared with a single matrix formulation.

With regard to document (6), the respondent argued that neither the formulation nor the manufacturing method therein described could be compared with the method and formulation of the present invention. In fact, the slow release materials employed in (6), being unable to swell in water, implied a totally different type of release of the active ingredient.

VII. The appellant (opponent) had requested in writing that the decision under appeal be set aside and European patent No. 0 235 986 be revoked.

The respondent (patentee) requested that the appeal be dismissed and that the patent be maintained in the version as maintained in the decision under appeal, the set of claims for AT, ES and GR being replaced by the set submitted during oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. The water soluble slow release material of claim 1 in both the first and the second sets of claims is defined as being a polysaccharide or alginate. The missing word "alginate" after "polysaccharide" in line 5 of claim 1 of the set for AT, ES and GR, was added in the claim of the set filed during the oral proceedings. The amendment, which removes an internal inconsistency and adapts the text of the claim to claim 1 of the first set of claims, is tantamount to a correction under Rule 88 EPC and, as such, allowable under Article 123(2) and (3) EPC.

3. *Sufficiency of disclosure*

Following the instructions given in the patent description, the experts acting for the appellant, T. J. Knott and J. M. Newton, manufactured slow release double-matrix formulations, whose release profile was considered substantially identical to the release profile of a single-matrix formulation comprising the same components in the same amounts. Therefore, since formulations showing the pretended advantage over those of the prior art could not be obtained, the appellant was of the opinion that the invention was not disclosed in a manner sufficiently clear and complete for it to be carried out.

The invention, as claimed in the patent at issue, is a slow release formulation having the claimed structural features and a method of making such a formulation. Beyond the feature of a "slow release of the active ingredient", the claim does not cite any other functional feature or advantageous effect over the compositions of the prior art. Hence, the "longer release time" is not part of the definition of the invention. For this reason, the alleged absence of this effect in formulations falling within the scope of the claim is totally immaterial to the repeatability of the invention, as long as the person skilled in the art can indeed produce such formulations, thus carry out the invention.

This is the case here, where the appellant himself, assisted by the instruction given in the patent description, was able to manufacture slow release formulations having the claimed structural features and being then used in the comparative tests.

For these reasons, the board's judgment is that the disclosure of the invention is in compliance with the requirements of Article 83 EPC.

4. *Inventive step*

The formulation of claim 1 comprises a primary and a secondary matrix of **water soluble** slow release material ... wherein a polysaccharide material or alginate forms the slow release material of one or both matrixes.

As illustrated by the respondent and confirmed by document (7) (chapter bridging pages 1 and 2), when the water soluble polymer materials of claim 1, such as alginate, methyl cellulose or other hydrophilic polysaccharide, are used as binders in a solid formulation, eg a tablet, and the formulation is placed in a dissolution medium, a gelatinous layer is formed on the tablet surface. At the outermost layer, the polymer is diluted to the point where it no longer has a structural integrity and dissolves or wears away. The gelatinous layer is an aggregate of polymer, active ingredient and excipient and controls the release of the drug.

4.1 The opposition division indicated document (6) as the closest prior art.

This document describes sustained release double-matrix compositions obtained by two steps of wet granulation of the active agent with a release delaying carrier, wherein different release delaying substances are used in the first and the second granulation (see claim).

These substances are chosen from the natural or synthetic polymers, fatty acids, their salts and esters, higher alcohols, proteins such as zein and casein and waxes (see page 1, first paragraph, page 2, fourth and fifth complete paragraphs and page 3 first paragraph).

The board is of the opinion, shared by the respondent, that these substances, either water insoluble or soluble, do not swell in water to give the characteristic gelatinous layer produced by the water soluble polysaccharide materials or alginate of the patent invention. This opinion is justified by the effect researched in (6). In fact, the release delaying substances are not expected to dissolve in the gastrointestinal tract, since they are resistant to disintegration but, on the contrary, break down giving a gradual dispersion in the body fluids (see page 1, third complete paragraph, page 2, second complete paragraph).

The board's opinion is further supported by the consideration that, though some water-soluble substances are also envisaged, nearly all the release-delaying substances cited in (6) are indeed water-insoluble hydrophobic materials, as is evident from the type of solvent suggested for both granulation steps which are always organic solvents, primarily of high hydrophobicity (see page 3, second full paragraph and examples).

For these reasons, the formulations of (6) will probably give, in an aqueous dissolution medium, a type of release completely different from the release characterising the claimed formulations and, for this reason, they are not comparable with the same.

Therefore, the board does not consider document (6) as the closest prior art.

In the board's view, the closest prior art is represented by compositions containing the same water soluble slow release materials of the claimed formulations though granulated in a single matrix, such as the compositions disclosed in document (7).

The reassessment of the closest prior art is consistent with the alleged purpose of the invention as illustrated in the description (page 3, lines 8 to 10) and in the examples. In fact, all the *in vitro* and *in vivo* studies investigating the properties of the claimed formulations compare these latter with water soluble single-matrix formulations as comparative terms. The board's view on what should be considered the closest prior art was implicitly shared by both parties, who submitted arguments and tests mainly intended to prove or deny the alleged advantageous effects of the claimed double-matrix formulations versus the single-matrix water soluble formulations known from the prior art, ie (7).

4.2 The intended purpose of all the experimental studies reported in the patent and all the tests produced by the respondent is to investigate whether the claimed formulations exhibited advantages, in terms of slower release, and *in vivo* performance, versus the known single-matrix formulations.

Therefore, starting from document (7), the underlying technical problem to be solved by the present invention is to provide slow release formulations exhibiting an improved release profile, while maintaining satisfactory pharmacokinetic and clinical performance.

4.2 The solution proposed by the patent is the soluble double-matrix formulation of claim 1.

4.3 The *in vivo* studies reported in the patent show, without having been contested by the appellant, that the tablets produced according to the present invention result in plasma theophylline concentrations similar to those obtained by the marketed single-matrix slow release formulations. Hence, these studies prove that the second aspect of the problem has been solved.

On the other hand, the *in vitro* dissolution tests reported in the patent are unsuitable for proving that the first aspect of the technical problem has been solved. In fact, as indicated in the decision under appeal and as admitted by the respondent, the tests comparing the claimed and the known formulations have been carried out under different experimental conditions. Therefore no meaningful comparison of the results can be made.

During the appeal proceedings, both parties submitted new *in vitro* release comparative tests, carried out by Knott and Newton for the appellant and by Trigger for the respondent. In all the tests, the formulations according to the present invention, made by double-granulation, are compared with the known formulations made by single granulation. The percentage of the released active ingredient is plotted on a curve versus time.

The results reported by Trigger, in his statutory declaration of 15 April 1996, in table 1 (double granulation) and 2 (single granulation), as summarised in table 3, show an indisputable difference in the

release profile characterising the two different formulations. The slower release of the active ingredient from the formulations according to the invention is confirmed by a second set of tests whose results are reported in tables 4 and 5.

The statistical relevance of the difference in dissolution rate showed by Trigger was contested by the appellant since, in his opinion, it was within the normal and accepted experimental variability observed between different batches of the same substance.

The board does not share this opinion. In fact, as calculated by the respondent (letter of 24 November 1997), the difference can still be appreciated, at least within the first hours of the dissolution test, after correction of the results by the highest value of tolerance (±10%) allowed by the European CPMP-Guidelines for the control tests of prolonged release oral solid forms. For this reason the results reported by Trigger cannot be attributed to the normal inter-batch variability or to experimental error.

In relation to the comparative tests carried out by Knott and Newton, the appellant held, in the accompanying commentary, that the results observed in both sets of tests did not evidence any improvement in release profile for the claimed formulations.

Faced with Knott's experiments 2 (double granulation) and 3 (single granulation), of 31 May 1995, both carried out under the same conditions, the board notes that the two plotted curves are not overlapping, but show a slightly different slope. It is worth noting that the gap between the curves, which shows a slower release from the double granulate, **increases with time**. Unfortunately, the experiments were not prosecuted until the total release of the active ingredient, thus

in a section of the diagrams where the gap between the curves could have been highly significant. The interruption of the tests by a value not exceeding the 75% release clearly prevents any final and statistically valid conclusion from being drawn.

For this reason, the results illustrated by Knott are unsuitable for giving any experimental basis to the appellant's contention that the release properties of the single- and double-matrix formulations are identical.

As to Newton's tests, the simple evaluation of the graphs in experiments 1 to 3 would allow the board to question the reliability of the results therein reported. The fact that the curves extend beyond the limit of 100% release evidences that the results are not reported on the correct scale, and no meaningful correlation between time and release is possible. To remove this flagrant inconsistency, admitted by the author himself, it was suggested that Newton's results had to be corrected by a coefficient taking account of the ratio of the nominal content (250 mg) and the real content (400 mg) of active ingredient in the tested tablets.

When corrected accordingly by means of the factor 0.625 (ie 250/400), as suggested by Knott, the diagrams of experiments 2 and 3, namely those carried out under the same operative conditions, suffer from the same deficiency already observed in relation to Knott's tests, that is that the monitoring of the release was not prosecuted until the total release of 100%. As seen above, this is not a minor factor, when slow release formulations having a very low release rate, thus a long 100% release time, are considered.

For these reasons, the board is primarily of the opinion that Newton's tests have not been carried out with the necessary accuracy and care to guarantee the reliability of the results and thus to offer a valid experimental support to the appellant's arguments.

Notwithstanding these considerations, the mere comparison of the curves of experiments 2 (double-matrix formulations) and 3 (single matrix formulation) indisputably shows that a difference in slope does indeed exist.

This difference, when quantified on the "corrected" graphs by means of the T50, ie time necessary for the 50% release, amounts to some 12%, as was admitted by the appellant in his Memorandum dated 19 May 1997. Comparable results are obtainable for all the other values on the release-percentage scale. On the other hand, when the results illustrated in experiments 2 and 3 are analysed per release-percentage versus time, eg 4, 8, 12 etc hours, the gap between the curves amounts to about 5 to 8%.

The statistical relevance of this difference was disputed by the appellant, since it was considered comprised within the normal and accepted variation observed among different batches of the same substance.

It remains, however, undisputed that the results reported by Newton confirm those observed by Knott, namely that the double-matrix formulation apparently releases the active ingredient more slowly than the single-matrix formulation. Now, since Knott's and Newton's experiments produced consistent results, and since it seams highly unlikely that both experts used, in 1995 and 1996 respectively, the same substances from the same batches for their experiments, the board considers that the effect underlined by both sets of

tests, ie the slower release from double-matrix formulations, cannot be attributed to the normal inter-batch variability or to experimental error, since in this case the outcome of the tests would have been influenced in a random way. Therefore the observed consistent effect is caused, in the board's opinion, by the common feature of having the same double-matrix structure.

As to the appellant's failure in obtaining results so conclusive and clear as those produced by Trigger, it should be considered that the release of the active ingredient from a sustained release formulation is influenced by many well known factors such as the granulometry of the components, the type of mixing, the content of active ingredient, the content of fillers, the type of dissolution test and many others (see document 7). The easy adaptation of these factors to the different situations, falls, in the board's view, within the competence of the skilled person. Therefore, assisted by the invention's teaching that a double-matrix formulation offers the advantage of a longer release of the active agent, the skilled person would be able to optimise the above cited factors in order to achieve the promised effect without exceeding his normal competence. However, it is reasonable to expect that the appellant, having an opposite motivation, did not engage himself in this effort of optimisation, but simply and rigidly applied the experimental conditions disclosed in example 1 of the patent. However, these conditions were not necessarily the best conditions for preparing the specific double-matrix formulations prepared by Knott or Newton and for emphasising the technical effect produced by the invention.

In conclusion, the experimental evidence submitted to the board is represented, on the one hand, by Trigger's comparative tests, which prove with a sufficient degree of certainty the stated effect of a longer release time from the claimed double-matrix formulation and, on the other hand, by Knott's and Newton's tests, which do not appear to give a reliable experimental support to the appellant's contentions that the release profile of single- or double-matrix formulations are essentially identical. Should, nevertheless, Knott's and Newton's results be considered, they would appear to point consistently to a slower release from the double-matrix formulation, and thus to confirm the technical effect obtained by the invention.

In view of the foregoing, the board is satisfied that the technical problem has been solved in all its aspects.

4.4 The skilled person, faced by the aforementioned problem to be solved, could not find in the closest prior art document, ie document (7), any suggestion or motivation to modify the structure of the single-granulation sustained release formulations therein described. On the contrary, the header "Granulation versus direct compression" on page 7, stresses that the sustained release matrix tablets can be made by direct compression or through conventional wet granulation methods without affecting the dissolution profile. This is a clear indication for the skilled reader that the manufacturing method, and the intimate structure of the matrix resulting therefrom, are not factors to be usefully considered in assessing the release profile of a sustained release formulation. In fact, in the teaching of (7), the release rate is primarily influenced by other factors such as the nature of the components and the size and form of the formulation.

On the other hand, document (6) describes sustained release double-matrix compositions consisting of a first granulate comprising a mixture of the active ingredient and a release delaying substance and second granulate comprising said first granulate and a second release delaying substance other than that used in the primary granulation. The use of two different release-delaying substances (or carriers) in the two granulation steps is an essential feature of the invention. Moreover, the document stresses that, not only do the two carriers have to be different, but also in order to obtain a product with excellent sustained release characteristics, the carriers used in the primary granulation step should preferably be insoluble or hardly soluble in the solvent employed in the secondary granulation step. It is in fact emphasised that if the carrier used in the primary granulation is also soluble in the solvent used in the secondary granulation, it may be dissolved away during the secondary granulation, exposing the drug and causing early release and loss of a reliable sustained effect (see page 2, third complete paragraph).

A further important point is that, though some water-soluble slow-release carriers are envisaged in (6), the teaching of this document is unambiguously directed to the use of water-insoluble substances, as is evident from the examples and from the type of solvents suggested for both granulation steps, which are all exclusively organic solvents.

Therefore, in the board's judgment, the skilled person, faced by the technical problem of providing sustained release formulations with improved release properties and assisted by the teaching in (6), would never have envisaged preparing a double-matrix formulation comprising, as slow release carrier for **both** the first and the second granulates, materials having the same

solubility properties, and, still less, materials being **both** water-soluble, since he would have expected, as indicated in (6), the loss or detriment of the sustained release effect rather than the desired improvement in the release profile. Thus the teaching in (6) would have pointed the skilled reader in a different direction to the one indicated by the patent at issue.

The board does not contest the appellant's view that (6) envisages the use of water-soluble carriers. This teaching, however, cannot be in contradiction to the whole general teaching in the document, that two different slow release carriers, having different solubility properties have to be used in the two granulation steps. Therefore the combined teaching in documents (6) and (7) would, at best, suggest to the skilled person that the water soluble material cited in (6) could be replaced by the hydrophilic polymers of (7) in **one** step of granulation, **but not in both** as required by claim 1 of the patent under consideration.

For all these reasons, the board's judgment is that none of the cited prior documents, either alone or in combination, affects the inventive activity involved in the formulation or method according to independent claims 1 and 5 or according to the dependent claims, which relate to practical realisation forms of the invention. The same reasons apply to the set of claims for AT, ES and GR.

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 maintain the patent in the version as maintained in the decision under appeal, the set of claims for AT, ES and GR being replaced by the set submitted during the oral proceedings.

The Registrar:

P. Martorana

The Chairman:

P. A. M. Lançon