BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

D E C I S I O N
of 13 June 2001

Case Number: T 0891/96 - 3.3.2

Application Number: 89309518.2

Publication Number: 0360562

IPC: A61K 9/22

Language of the proceedings: EN

Title of invention:
Directly compressible sustained release excipient

Patentee:
Edward Mendell Co., Inc.

Opponent:
The Boots Company PLC

Headword:
Sustained release excipient/MENDELL

Relevant legal provisions:
EPC Art. 54, 56, 84, 113(1), 123(2), (3)
EPC R. 57a

Keyword:
"Decision against the party absent during oral proceedings: no violation of Article 113(1) EPC: Novelty: yes, proper selection; Inventive step: yes, after limitation"

Decisions cited:
G0004/92, T 0012/81, T 0007/86

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0891/96 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 13 June 2001

Appellant: (Opponent)
The Boots Company PLC
1 Thane Road West
Nottingham NG2 3AA (GB)

Representative:
Thacker, Michael Anthony
The Boots Company plc
Group Patents Department D31
1 Thane Road West
Nottingham NG2 3AA (GB)

Respondent: (Proprietor of the patent)
Edward Mendell Co., Inc.
Route 52, R.D. 5
Carmel, NY 10512 (US)

Representative:
Brown, John David
Forrester & Boehmert
Franz-Joseph-Strasse 38
D-80801 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 30 July 1996 rejecting the opposition filed against European patent No. 0 360 562 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: G. F. E. Rampold
S. U. Hoffmann

Summary of Facts and Submissions

I. The respondent is proprietor of European patent No. 0 360 562 which was granted with 23 claims on the basis of European patent application No. 89 309 518.2.

II. The appellant originally filed notice of opposition requesting revocation in full of the European patent pursuant to Article 100(a) EPC on the grounds of lack of novelty and inventive step. Of the numerous documents cited during the first-instance opposition and subsequent appeal proceedings against the patentability of the claimed subject-matter in the patent in suit, the following remain relevant to the present decision:

(1) GB-A-2 188 843

(2) EP-A-0 234 670

(4) EP-A-0 180 364

(5) EP-A-0 182 772

(9a) H. M. Ingani et al, Abstract from "6th Pharmaceutical Technology Conference", 7-9 April, 1987, Volume II, 8 April 1987, pages 459 to 460

III. After considering the grounds for opposition, the opposition division rejected the opposition under Article 102(2) EPC at the conclusion of the oral proceedings.

IV. The appellant (opponent) filed a notice of appeal against the decision of the opposition division and

submitted a statement setting out the grounds of appeal. The respondent's observations on the appeal statement were accompanied by a declaration by Mr Troy W. McCall including a comparison of the dissolution rates of tablets, containing either xanthan gum or locust bean gum as the sole hydrophilic material (hereinafter also referred to as gum) of the slow release excipient, with the dissolution rates of tablets containing a combination of both xanthan gum or locust bean gum, as claimed in the patent in suit.

V. On 13 June 2001, oral proceedings took place before the board in the presence of representatives of the proprietor (respondent); the duly summoned appellant had informed the board in advance that it did not wish to attend the hearing.

VI. During the hearings the respondent submitted in substitution for its previously filed request, that the appeal be dismissed and that the patent be maintained unamended, a modified request concerning maintenance of the patent in amended form on the basis of claims 1 to 14 and 18 to 23 as granted. The set of claims 1 to 20 in the respondent's current request differs from the claims as granted in that claims 15 to 17 have been deleted completely, that claims 18 to 23 have been renumbered as claims 15 to 20, and that their appendance has been amended consequentially. The independent claims read as follows:

"1. A free-flowing , directly compressible slow release granulation for use as a pharmaceutical excipient, comprising from 20 to 60 percent by weight of a hydrophilic material comprising a heteropolysaccharide and a polysaccharide material

capable of cross-linking said heteropolysaccharide in the presence of aqueous solutions, and from 40 to 80 percent by weight of an inert pharmaceutical filler, selected from the group consisting of a monosaccharide, a disaccharide, a polyhydric material, and mixtures thereof, the ratio of said inert pharmaceutical filler to said hydrophilic material being from 4:1 to 0.67:1.

15. A slow release tablet for oral administration of a therapeutically active ingredient in the gastrointestinal tract comprising:

from 20 to 60 percent by weight of a hydrophilic material including a controlled release excipient comprising a hydrophilic gum matrix which includes a xanthan gum and a galactomannan gum capable of cross-linking said xanthan gum when exposed to gastric fluid, the ratio of said xanthan gum to said galactomannan gum being from 3:1 to 1:3, and an inert pharmaceutical filler, the ratio of said inert pharmaceutical filler to said hydrophilic matrix being from 4:1 to 0.67:1, and an effective amount of a therapeutically active ingredient, the ratio of said therapeutically active ingredient to said hydrophilic gum matrix being 1:10 or less.

19. A method for providing a universal tableting granulated excipient which is free-flowing and directly compressible for a controlled release of a relatively soluble or insoluble therapeutically active medicament comprising:

determining the solubility of a therapeutically active medicament which is to be tableted;

mixing an effective amount of said therapeutically active medicament with a premanufactured granulated slow release excipient comprising from 30 to 50 percent by weight of a hydrophilic material comprising a heteropolysaccharide and a polysaccharide material capable of cross-linking said heteropolysaccharide in the presence of gastric fluid, and from 50 to 70 percent by weight of an inert pharmaceutical filler;

providing a final mixed product having a ratio of said pharmaceutically active medicament to said hydrophilic material of 1:3-7 and a sufficient amount of said hydrophilic material such that a gel matrix is created when said tablet is exposed to gastric fluid and such that at lowest 3.5 hours are required for 50 percent of said therapeutically active medicament to be released following exposure to gastric fluid, and thereafter directly compressing the resulting blend to form a tablet."

Claims 2 to 14 are dependent on claim 1, claims 16 to 18 on claim 15, and claim 20 is dependent on claim 19. The dependent claims relate to specific elaborations of the subject-matter as claimed in the respective independent claims on which they depend.

VII. The appellant’s submissions in the statement setting out the grounds of appeal can be summarised as follows:

Concerning novelty, the appellant maintained its assertion that claim 18 as granted (present claim 15) lacked novelty under Article 54(2) EPC in view of the disclosure of citation (2) or (5) either alone or considered in the light of the general specialist knowledge as represented by a number of citations filed

in the first-instance opposition and subsequent appeal proceedings.

More specifically, citation (2) disclosed in Example 4 a slow release tablet containing 35.7% flurbiprofen as the active ingredient, 20% xanthan gum, 43.3% lactose and 1% magnesium stearate. At page 7, line 10 onwards, it disclosed further that other sustained release polymers, including locust bean gum, may partially replace the xanthan gum in the tablets of (2). The synergistic increase in viscosity of xanthan gum and locust bean gum had been known for many years and was, at the priority date, even part of the common specialist knowledge. It was thus clear that locus bean gum would be the prime choice for combination with xanthan gum.

As to inventive step, the appellant essentially relied on two principal arguments as follows:

First, the single comparative example were the drug was propranolol submitted as evidence by the respondent in the McCall declaration did not support the inventiveness of all drugs in all therapeutic areas. Thus, all drugs had different drug loading in a tablet, solubility, half-lives, sites of absorption in the gastrointestinal tract, interaction with the carrier, therapies, flow properties and all these factors had an effect on the release profile of the drug. A change in any of these factors resulted in a different release profile. The variation in the T_{50} values (denotes the time needed for 50% of the medicament to be released) and T_{90} values (denotes the time needed for 90% of the medicament to be released) in the patent in suit also demonstrated that the single release profile provided

as the comparative example did not reflect all the release profiles in all drugs in the sustained release excipient system claimed in the contested patent.

Second, no inventive step was involved if the drug was omitted from the compressible mixture disclosed in (2), comprising a compressible sustained release excipient, a compressible inert filler and a drug, so as to arrive at a directly compressible granulation. It was within the knowledge of the skilled person that the inert diluents specified in the claims of the contested patent were all compressible excipients and, if used in a sufficient amount in a formulation, the formulation would be capable of direct compression.

Citation (4) admittedly related to buccal tablets and the specific conditions for release of the drug were thus different from the specific conditions encountered in the gastrointestinal tract. Nevertheless, in the examples of (4), all the ingredients including xanthan and locust bean gum and the inert compressible diluents were mixed together and directly compressed. (4) therefore provided a good reason when combined with the disclosure of (2), for preparing a mixture comprising drug, xanthan gum, locust bean gum and one or more inert fillers for sustained release in the gastrointestinal tract.

VIII. The respondent disagreed with the appellant's view and argued in its written submissions and during the oral proceedings essentially as follows:

While the appellant contended that it would not be novel to select locust bean gum for combination with xanthan gum, not one example in (2) disclosed the

combination of xanthan gum with locust bean gum. Based on the statements in (2) that locust bean gum had undesired variations in chemical structure, one could not conclude that there was a clear and unambiguous disclosure pointing to the combination of xanthan and locust bean gums so as to obtain what was claimed. Moreover, there was nothing in (2) which taught that locust bean gum was capable of cross-linking the xanthan in the presence of an inert diluent.

Faced with the McCall declaration and the correct conclusion by the opposition division that the results in the declaration were accurate and reflected unexpected results, the appellant did not submit any test results of its own which contradicted the results presented by the respondent. The burden was not on the respondent to disprove the negative, but rather on the appellant to provide support for its allegations made on appeal.

Citation (2) failed to disclose or suggest a directly compressible slow release granulation for use as a pharmaceutical excipient, much less those comprising xanthan and locust bean gums in combination with an inert diluent. Moreover, the cited state of the art did not suggest to a skilled person to omit the drug from the known slow release formulations. In general, slow release excipients, including gums, previously known to the art were characterized by poor cohesive properties and were unsuitable for direct compression with therapeutic ingredients. The subject-matter of claims 1, 15 and 19 was accordingly also patentable under Article 56 EPC vis-à-vis citation (2) and the supplemental references introduced into the proceedings.

IX. The appellant requested in writing that the decision be set aside and the patent be revoked.
The respondent requested that the appeal be dismissed and that the patent be maintained as amended with the claims in the respondent's request filed during the oral proceedings on 13 June 2001.

Reasons for the Decision

1. The appeal is admissible.

2. The amendment to the respondent's current request (see paragraph VI above) can fairly be said to be occasioned by a ground for opposition specified in Article 100(a) EPC and is accordingly admissible under the terms of Rule 57a EPC.

2.1. The amended version of the claims does not give rise to any objections under Articles 84 and 123(2) or (3) EPC.

3. As regards the novelty of the claims under consideration in this appeal, the board has no reason to depart from the reasoning and the conclusion of the opposition division in the impugned decision.

3.1 In its submissions during the appeal proceedings the appellant limited its novelty attack to the assertion that the subject-matter of present claim 15 (claim 18 as granted) lacked novelty in comparison with the prior art of citation (2) or (5).

3.2 Citation (2) discloses solid sustained release pharmaceutical formulations in which xanthan gum is

employed as the hydrophilic material, optionally in combination with an inert filler or diluent, as the sustained release carrier. It states in this context that the sustained release carrier should comprise a major proportion of xanthan gum (see eg page 6, lines 29 to 30; claim 1). In particular, citation (2) describes 18 examples of oral dose tablets in which xanthan gum serves to provide sustained release properties for tablets containing various active substances and in which a relatively minor proportion of the xanthan gum may optionally be replaced by one or more other polymers having sustained release properties. However, as emphasised by the respondent, none of the examples in (2) describes the combination of xanthan gum with a galactomannan gum capable of cross-linking said xanthan gum, as required for the controlled release excipient of the tablet claimed in present claim 15.

More specifically, citation (2) discloses in Example 4, to which the appellant particularly refers, a tablet containing 200.0 mg (35.7% by weight) flurbiprofen as the active ingredient, 112 mg (20% by weight) xanthan gum, 242.4 mg (43.3% by weight) lactose and 5.6 mg (1% by weight) magnesium stearate.

In this context, at page 7 of (2), line 1 onwards, reference is made that "**if desired**, a proportion of the xanthan gum may be replaced in the sustained release carrier by one or more additional polymers having sustained release properties". From line 10 onwards a list is provided comprising 11 different examples of such additional polymers, including locust bean gum and guar gum, without any further indication of whether or not any of these polymers would indeed be capable of

cross-linking with xanthan gum.

3.3 The controlled release excipient is generically described in (2) by at least two variable parameters, the possible combinations of which result in a substantial number of different compositions suitable for the pharmaceutical excipient disclosed in (2). Thus, the first variable parameter includes the options of using either xanthan gum as the sole hydrophilic material or a mixture wherein a certain proportion of the xanthan gum is replaced by one or more additional polymers having sustained release properties. The second variable parameter includes 11 different options of such additional polymers which are specified in the list on page 7.

Consequently, in order to arrive, starting from Example 4 in (2), at the subject-matter of claim 15 two independent selections would be required, namely from the first variable parameter the selection of a mixture having a certain proportion of the xanthan gum replaced by one or more additional polymers and from the second variable parameter the selection of a galactomannan gum capable of cross-linking said xanthan gum, ie either locust or guar gum, which are the only cross-linking polymers within the group of the options specified in the list on page 7. The particular result of this sequence of selections introduces into claim 15 a **new element** which as such is not disclosed in (2) and which is indispensable for the acknowledgment of the novelty of a selection for patent purposes (see T 12/81, OJ EPO, 1982, 296; T 7/86, OJ EPO 1988, 381).

3.4 The appellant relied for its lack of novelty objection on a substantial number of supplemental references in

addition to citation (2) to show that to those skilled in the art locust bean gum would have been the immediate choice for combination with xanthan gum. However, apart from the fact that it is not permissible in assessing novelty to combine general information from various references with the specific disclosure of one particular prior art reference, a particular choice, even one striking the skilled reader as the most straightforward, would not be prejudicial to novelty, if that choice was the result of a "multiple selection" from more than one variable parameters.

3.5 As to the state of the art according to citation (5), this citation does not disclose the combination of xanthan gum with a galactomannan gum capable of cross-linking said xanthan gum as the hydrophilic material of the controlled release pharmaceutical excipient, but rather the combination of xanthan gum with either mannans or galactans or with a mixture of both mannans and galactans. As emphasised by the respondent, the galactomannans form a distinct class of polysaccharides having a well defined structure and a high molecular weight of 220,000 ± 20,000 daltons. Both, the mannans on the one hand, and the galactans on the other, are polysaccharides which are composed, as opposed to the galactomannans, solely of mannose or galactose units and have, moreover, a considerably lower molecular weight.

Further, there is no disclosure in (5) of mixing together the individual components in the stated ratios set forth in claims 1 and 15 and 19 or adding the therapeutically active ingredient to the hydrophilic gum matrix in a ratio of 1:10 or less.

In view of the above-mentioned differences, the novelty of the present claims over the prior art of (5) is beyond doubt.

3.6 In the absence of any further objections to the novelty of the present claims, the board does not consider further discussion of this issue to be necessary or appropriate.

4. The slow release granulation according to the claimed invention (see claim 1) and the slow release tablet prepared therefrom (see claims 15 and 19) are designed for oral administration of a therapeutically active ingredient so as to provide, upon oral ingestion of the tablet and its contact with gastric fluid, a constant rate of sustained release of the medicament in the gastrointestinal tract (see patent specification, especially page 6, lines 1 to 24; Figures 1 to 6).

4.1 Citation (2) already discloses sustained release, solid oral dosage forms, preferably tablets, which likewise release the drug after oral ingestion during their passage through the gastrointestinal tract (see especially the paragraph bridging pages 11 and 12). The observations in points 3.2 and 3.3 above also make it clear not only that the sustained release tablets disclosed in citation (2) correspond with regard to their particular intended use to the claimed invention, but also that such tablets are closely related to the subject-matter of the independent claims 1, 15 and 19 in the patent in suit with regard to the proportions and the nature of both the hydrophilic material (gum) and the inert filler or diluent of the excipient by which the sustained release of the medicament in the gastrointestinal tract is achieved.

Consequently, the board arrived at the conclusion that the above-mentioned Example 4 of citation (2) comes closer to the claimed subject-matter in the patent in suit than any other state of the art available in the present proceedings and represents therefore the closest state of the art. Both parties seemed to share the board's opinion in this respect.

4.2 From the release rate reported in Table 4 for the tablets disclosed in Example 4 of citation (2) and, more precisely, from the dissolution profiles shown in Figure 3 of the patent in suit and the test results provided in Tables 1, 2 and Figures 1 and 2B of the McCall declaration, it may be seen that tablets containing xanthan gum as the sole hydrophilic material in combination with an inert filler such as lactose, sucrose or dextrose do not provide a sufficiently constant releasing rate of the medicament over the entire releasing period and that, in particular, an increase in the dissolution rate T_{50} would be desirable. Consequently, in the light of the closest state of the art according to (2), the technical problem may be seen as that of providing a slow release formulation for oral administration of a wide variety of therapeutically active medicaments in the gastrointestinal tract, allowing for an improved and more constant release of the medicament over the entire releasing period.

4.3 The solution to the problem was the provision of the free-flowing, directly compressible slow release granulation according to claim 1 and the slow release tablet according to claims 15.

The claimed granulation and the tablet in the patent in

suit basically differ from that in Example 4 of citation (2) in

- that xanthan gum which is used in Example 4 as the sole hydrophilic material (gum) of the slow release excipient is replaced by one comprising a combination of a heteropolysaccharide, including xanthan gum, and a polysaccharide material, including galactomannan gum, capable of cross-linking said heteropolysaccharide when exposed to gastric fluid (see for more details points 3.2 to 3.3 above);

- that the slow release granulation is provided in the form of a pre-granulate which does not contain the therapeutically active ingredient and to which the active ingredient is added only prior to the direct compression of the resulting blend to form a tablet; and in

- that the free-flowing slow release granulation is a universal tableting excipient suitable for direct compression with a broad variety of medicaments to form a slow release tablet;

4.4 The exactly comparative data reported in the McCall declaration (see especially Table 1, Column 3, Figures 1 and 2C) provide appropriate evidence that a tablet according to the invention, which contains in the slow release excipient the combination of 15% xanthan gum/15% locust bean gum in a 1:1 ratio, releases the therapeutically active medicament (propranolol) at a controlled rate, allowing for a continuous, more or less uniform release over the entire releasing period of 20 hours, as opposed to an

excipient comprising either gum alone, ie 30% xanthan gum (see especially Table 1, Column 2, Figures 1 and 2B) or 30% locust bean gum (see especially Table 1, Column 1, Figures 1 and 2A).

Moreover, the results reported in the McCall declaration show an improved, increased dissolution rate T_{50} of the medicament for a tablet which includes the combination xanthan gum/locust bean gum in the above-mentioned 1:1 ratio, in comparison with a tablet containing the same proportion of either xanthan gum or locust bean gum alone. Specifically, the dissolution rate T_{50} for the tablet according to the claimed invention was 9.7 hours (see especially Table 2, Test C). In contrast, the dissolution rate T_{50} for a tablet containing xanthan gum as the sole hydrophilic material was 7.5 hours (see especially Table 2, Test B) and that for locust bean gum alone was 2.9 hours (see especially Table 2, Test A).

4.5 The appellant suggested in the appeal statement that it was at least doubtful whether the comparative data in the patent in suit and the McCall declaration would provide adequate evidence of the claimed improved release properties for all drugs in all therapeutic areas, but did not substantiate this with any evidence. In this context the appellant referred to the results reported in citation (9a), which includes, *inter alia*, a comparison of the release properties of theophylline tablets containing 25% by weight xanthan gum alone with the properties of tablets containing 25% by weight mixtures of xanthan/locust bean gums at ratios 4:1, 3:1, 2:1 and 1:1.

Citation 9(a) states in the penultimate paragraph on page 459 in general terms that **"increasing the locust bean gum content** in the formulations induces an increase of the liquid uptake rate by the tablets and also **an increase of the theophylline release during the first hour of the dissolution test,** due to partial erosion".

However, the respondent has explained to the satisfaction of the board that the tablets disclosed in (9a) comprised neither an inert filler nor a pre-granulated (pre-manufactured) sustained release carrier and that the results reported in (9a) were therefore neither comparable with, nor in contradiction to, the results provided in the patent in suit and the McCall declaration. Moreover, the board observes that these results in (9a) appear to be in line or at least comparable with certain results derivable from the examples given in (2), namely that the substitution of various other gum ingredients for a portion of xanthan gum leads to a more rapid release of the drug (see for

more details point 5.2 below).

4.6 Consequently, the data provided in the McCall declaration make it, in the board's judgment, sufficiently and plausibly clear that the significantly improved release properties indeed result from the use of the combination of xanthan gum and locust bean gum with an inert filler in the stated proportions, as compared to the use of the same inert filler with xanthan or locust bean gums alone. These data are, moreover, consistent with the data presented in the application as filed and the patent as granted. Therefore on the basis of the comparative data provided and in the absence on any evidence to the contrary, the board considers it sufficiently plausible that the beneficial effects reported in the McCall declaration can be achieved with a broad variety of different drugs and is accordingly satisfied that the technical problem is solved in its entirety.

5. It still remains to be determined whether the requirement of inventive step is met by the claimed subject-matter.

5.1 In citation (2), it is stated that the use of xanthan gum or a carrier comprising a major proportion of xanthan gum allows lower levels of sustained release carrier to be used than heretofore suggested and generally provides a slower release of active ingredient into the body as compared to the use of naturally occurring hydrophilic gums (see especially page 3, lines 11 to 22; page 6, lines 13 to 31). Galactomannan is specifically mentioned in (2) as one of the sustained release carriers which "must, in general, comprise a large proportion of the dosage form

to provide a suitable sustained release" (see page 1, lines 24 to 30). Further, citation (2) goes on to say that "not all gums having hydrophilic properties will be suitable per se to provide sustained release formulations" (see page 1, lines 30 to 33). Consequently, there is no technical teaching or suggestion citation (2) encouraging the skilled man to take into account the proposed solution of the patent in suit.

5.2 Moreover, a comparison of the release characteristics of three different oral dosage forms for the same medicament (ibuprofen), reported in Examples 1 to 3 of (2) [see Example 1, sustained release material: xanthan gum as the sole gum component; Example 2, sustained release material: xanthan gum in combination with hydroxypropylcellulose and carrageenan gum; Example 3, sustained release material: xanthan gum in combination with sodium alginate], reveals that the substitution of other gum ingredients for a proportion of xanthan gum (see Examples 2 and 3) lead to a more rapid release of the drug, as opposed to the xanthan gum/locust bean gum combination suggested in the patent in suit.

Similarly, all the Examples 7, 10 and 11 in (2) comprise a total amount of 15% gum and are otherwise identical but for the proportion of sodium alginate substituted for xanthan gum. Nevertheless, the substitution of increasing proportions of sodium alginate for xanthan gum causes the dissolution rate T_{50} and accordingly the release characteristics to decrease from 7.8 hours [Example 7; sustained release material: 15% xanthan gum as the sole gum component], to 7 hours [Example 11; sustained release material: 10% xanthan gum in combination with 5% sodium alginate] and further

to 5.7 hours [Example 10; sustained release material: 7.5% xanthan gum in combination with 7.5% sodium alginate].

5.3 In view of the aforementioned observations, there is clearly no teaching or hint in citation (2) suggesting to a person skilled in the art that there would be any benefit in combining the essential hydrophilic slow release material used in (2), ie the heteropolysaccharide xanthan gum, with any other material, let alone that any beneficial effects could be achieved by combining xanthan with a polysaccharide material, such as locust bean gum or gear gum, capable of cross-linking the xanthan gum when exposed to aqueous solutions and, in particular, to gastric fluid.

5.4 As far as the technical teaching of citations (1) and (4) is concerned, both citations relate only to buccal tablets for administration of drugs by absorption through the buccal mucosa of the mouth. The appellant itself admitted in the appeal statement (see especially paragraph 9.3) that a substantial distinction exists between the conditions for release of the drug in the mouth through the buccal mucosa and the conditions in the gastrointestinal tract. This has moreover already been acknowledged on page 2 of citation (2), where it is stated in lines 20-31 as follows: " Xanthan gum is also known to have a synergistic swelling action in combination with locust bean gum. This combination is disclosed in (1) which relates to a tablet adapted to dissolve in the mouth over a period up to two hours. These tablets require the presence of a very large proportion of monosaccharide or disaccharide (ie of the order of 70% or more), but only a very small amount of the xanthan/locust bean gum combination in order to

function effectively to satisfy the particular requirements of a buccal tablet."

As a consequence of the different physical and physiological conditions in which a buccal tablet is designed to perform versus the conditions in the gastrointestinal tract, a buccal tablet would be completely unsuitable for satisfying the particular requirements of an oral dose tablet which is used to provide, upon oral ingestion and contact with gastric fluid, a constant rate of sustained release of the medicament in the gastrointestinal tract over a period of up to 20 hours or more. Consequently, one skilled in the art also had no reason or incentive to combine the teaching of (1) or (4) with that of (2).

5.5 As can be derived from the observations in point 3.5 above, citation (5) does neither disclose nor in any way suggest the use of the combination of xanthan gum and galactomannan gum as a sustained release excipient for oral tablets.

Moreover, the proper function of the sustained release tablet in (5) necessarily depends on the use of very specific excipients or diluents in substantial amounts, in addition to xanthan and the mannans or galactans or their mixture, namely silicic acid, dimethylpolysiloxane and micronized seaweed. None of them is used for the slow release granulation or the tablet according to the claimed the invention. Consequently, the teaching of citation (5), taken either individually or in combination with that of (2), failed to provide any useful suggestion or hint whatsoever leading those skilled in the art in the direction of the claimed invention.

5.6 The results reported in citation (9a) for a theophylline tablet containing the xanthan gum/locust bean gum or xanthan gum/gear bean gum combination as the hydrophilic slow release material in various rates provide clear evidence that such combinations themselves do not necessarily lead to an improvement in the sustained release properties of the tablet carrier or a sustained release tablet containing such carrier (see for more details point 4.5 above). To the contrary, based on the results in (9a), one skilled in the art would necessarily conclude that drug release utilizing a carrier having an xanthan gum/locust gum or gear gum mixture would be undesirably faster than with xanthan gum alone.

Consequently, there is no suggestion in (9a) by which one could foresee the unexpectedly beneficial results obtained with an oral dosage tablet for sustained release of the medicament in the gastrointestinal tract having the particular xanthan/locust bean gum carrier as called for in claims 1, 15 and 19 of the patent in suit.

5.7 The appellant relied repeatedly on the argument that the synergistic increase in the viscosity of xanthan gum and locust bean gum had been known for many years and was, at the priority date, even part of the common specialist knowledge. According to the appellant, those skilled in the art were likewise aware of the optimum viscosity requirements for the sustained release carrier in-vivo and knew the explicit statement in (2) according to which 50% xanthan gum could be replaced by another sustained release polymer, including locust bean gum. The skilled person, having this combined knowledge and seeking to improve the release properties

of the known slow release tablets, would have reasonably concluded, in the appellant’s opinion, that for maximum flexibility of the release profile xanthan gum, acting through the gastrointestinal tract, would be best complemented with locust bean gum.

However, contrary to what the appellant appears to suggest, the results in citations (9a) and (2) provide appropriate evidence that the mere knowledge of the synergistic increase in the viscosity of xanthan gum and locust bean gum or the synergistic swelling action of xanthan gum with locust bean gum would not open the way to a sustained release carrier or tablet having the advantageous release properties shown in the patent in suit. Instead, the teaching in the cited prior art makes it clear that the desired release properties are not only based on the sole effect of using the xanthan/locust bean combination as the hydrophilic material, but also result from the advantageous interaction of all the technical features in claims 1, 15 and 19. There is no prior art available in the proceedings suggesting to a person skilled in the art that the technical problem posed could successfully be solved by the particular combination of the technical features of the present claims.

5.8 The appellant's argument in the appeal statement that the omission of the active ingredient from the formulations in citation (2) yields the subject-matter of present claim 1 is unfounded and therefore unacceptable. Citation (2) and all the other citations as well fail to disclose a directly compressible pre-manufactured (pre-granulated) slow release granulation for use as a pharmaceutical excipient (see claims 1, 19) which can be mixed with the desired amount of any

desired therapeutically active medicament to provide a final blend suitable for direct compression into a tablet (see claims 15, 19).

The skilled reader of the citations on the one hand, and the disclosure of the claimed invention, on the other, would, in the board's judgment, immediately realise that a different distribution of the active drug in the pharmaceutical excipient is achieved, depending on

(i) whether the powdery components of the excipient are first mixed with the drug and the resulting blend is then either directly compressed into tablets or subjected to granulation prior to its compression into tablets [either one of these methods is used in all prior art documents available in the proceedings],

(ii) or a method is used wherein the powdery components are mixed in the absence of the drug and a pre-manufactured granulation is formed, which is subsequently mixed with the drug, and the resulting final blend is then directly compressed to form a tablet [as is the case in the claimed invention].

In the first case (i) the active drug will be randomly distributed within the powdery blend or each single granule of the granulate and accordingly also within the completed tablet, while in the second case (ii) the active drug will be located mainly on the outer shell of the pre-manufactured granules, resulting in a particular distribution of the drug in the tablet. The respondent has explained during the oral proceedings to

the satisfaction of the board that the specific swelling properties of the hydrophilic slow release material used in the patent in suit in combination with the particular distribution of the active drug in the matrix, resulting from the provision of a pre-manufactured granulated slow release excipient, jointly contribute to the improved release properties of the medicament in the gastrointestinal tract and accordingly to the successful solution of the stated problem.

There is absolutely nothing in the cited state of the art to suggest to a person skilled in the art the method of blending the powders including gums and inert ingredients in the absence of the drug, as claimed in the patent in suit, to provide a premanufactured, free-flowing granulation (see claim 1), which can later be mixed with a broad variety of different drugs and subjected to direct compression to form a sustained oral dosage tablet (claims 15, 19), allowing for a more constant rate of sustained delivery of the medicament in the gastrointestinal tract.

5.9 For all these reasons, the subject matter of claims 1 and 15 does involve an inventive step and is allowable pursuant to Article 52(1) and Article 56 EPC.

Claim 19 is directed to a method for preparing the new and inventive slow release tablet according to claim 15 by mixing the medicament with the new and inventive premanufactured slow release granulation and direct compression of the resulting blend into the tablet. Thus it is also allowable.

Dependent Claims 2 to 14, 16 to 18 and 20 relate to

specific elaborations of the subject-matter as claimed in the respective independent claims on which they depend and are therefore also allowable.

6. The Enlarged Board of Appeal has interpreted the provisions of Article 113(1) EPC concerning the right to be heard as meaning that a decision against a party which has been duly summoned but which fails to appear at oral proceedings may not be based on facts put forward for the first time during those oral proceedings (see decision G 4/92, OJ EPO 1994, 149, Conclusion 1). Notwithstanding this, in its decision the Enlarged Board of Appeal clearly viewed the possibility of holding hearings in a party's absence, as provided for in Rule 71(2) EPC, in relation to the need for proper administration of justice, in the interests of which no party should be able to delay the issue of a decision by failing to appear at oral proceedings (see especially point 4 of the reasons). This can only mean that parties to the proceedings must expect that, on the basis of the established and plainly relevant facts, any decision may go against them. It can further be inferred from this, in the board's opinion, that a decision against an absent party may be based on a modified request discussed for the first time during oral proceedings, at least if the stage reached is such that the absent - albeit duly summoned - party could have expected such a modified request to be filed and discussed and was aware from the proceedings to date of the actual bases on which it would be judged. Applying the principles elucidated above to the present case, the board's conclusions are the following:

6.1 First, in the appeal statement the appellant maintained

its objections, *inter alia*, to the patentability of the subject-matter of claims 15 to 17 as granted. In these circumstances, it could legitimately have expected that the respondent would amend the patent by deletion of the attacked claims 15 to 17 and that the case would be discussed during the hearings before the board on the basis of a consequentially modified request.

6.2 Second, the extent of the patent was amended during the oral proceedings before the board in a restrictive way and only in so far as the subject-matter of Claims 15 to 17 as granted was deleted completely. While this amendment has the effect that the scope of the protection afforded has been considerably reduced, claims 1 to 14 and 18 to 23, which have been maintained as renumbered claims 1 to 20, remain entirely unchanged as compared to the corresponding claims forming the basis for the decision under appeal. This being the case, the appellant had in the course of the appeal proceedings a sufficient opportunity to present in writing its comments on the subject-matter of virtually all remaining claims 1 to 20 forming the respondent's current request.

6.3 Thirdly, the decision to maintain the patent in amended form is entirely based on grounds, facts and evidence which were already known to the appellant from the proceedings before the opposition division and which were again brought to the appellant's attention during the appeal proceedings. If the appellant preferred not to attend the oral proceedings - which it too had requested - it availed itself of the opportunity to present its comments during the oral proceedings before the board.

6.4 On the basis of the above considerations, the board is of the opinion that, in the circumstances of the present case, considering and deciding in substance on the maintenance of the patent in amended form in no way conflicts with the conclusions of the Enlarged Board of Appeal in decision G 4/92 and does not contravene the appellant's procedural rights as laid down in Article 113(1) EPC, in spite of its absence during oral proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent as amended with the claims in the respondent's request filed during the oral proceedings on 13 June 2001 and any adaptation of the description considered necessary by the opposition division.

The Registrar: The Chairman

A. Townend P. A. M. Lançon