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D E C I S I O N
of 3 August 2005

Case Number: T 0663/00 - 3.3.02

Application Number: 94115465.0

Publication Number: 0647448

IPC: A61K 31/485, A61K 9/16, A61K 9/50

Language of the proceedings: EN

Title of invention:
Orally administrable opioid formulations having extended duration of effect

Applicant:
Euro-Celtique S.A.

Opponent:
-

Headword:
Oral solid dosage form/EURO-CELTIQUE

Relevant legal provisions:
EPC Art. 52, 54, 56, 83, 84, 106, 107, 108, 123(2)
EPC R. 29(1), 64, 86(3)
RPBA Art. 10b

Keyword:
"Main request, first and second auxiliary requests - compliance of the amended claims with Articles 84 and 123(2) - no: relevant functional feature omitted"
"Third auxiliary request - inventive step - no - technical teaching of the prior art leads those skilled in the art directly to the claimed solution of the problem posed"

Decisions cited:
T 0060/89

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0663/00 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 3 August 2005

Appellant: Euro-Celtique S.A.
122, Boulevard de la Pétrusse
L-2330 Luxembourg (LU)

Representative: Maiwald, Walter, et al
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 17 February 2000 refusing European application No. 94115465.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: G. Rampold
C. Rennie-Smith

Summary of Facts and Submissions

I. The appellant is the applicant of European patent application No. 94 115 465.0 ("the application"). The application was filed on 30 September 1994, claiming priority from an earlier US application on 7 October 1993, and is entitled "Orally administrable opioid formulations having extended duration of effect". The application as filed contained, *inter alia*, claims directed to:

"1. A sustained release oral analgesic dosage form for once—a—day administration, comprising:
a unit dose of a plurality of inert pharmaceutically acceptable substrates comprising an analgesically effective amount of an opioid analgesic or a salt thereof in sustained release form, each of said substrates having a diameter from about 0.1 mm to about 3 mm, said unit dose being bioavailable and providing effective blood levels of said opioid analgesic for at least about 24 hours.

2. The dosage form of claim 1, wherein said substrates are selected from the group consisting of spheroids, beads, microspheres, seeds, pellets, ion-exchange resin beads, granules, and mixtures thereof.

4. The dosage form of claim 2, wherein said substrates comprise matrices of a substantially uniform mixture of said opioid analgesic and a hydrophobic material.

9. The dosage form of claim 1, further comprising release-modifying agents, said release-modifying agents comprising on or more hydrophilic polymers such as hydroxypropylmethylcellulose.

18. The dosage form of claims 1-17, which further comprises a non—steroidal anti—inflammatory agent selected from the group consisting of ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and mixtures of any of the foregoing."

II. By a decision pronounced at the close of the oral proceedings on 21 January 2000, with written reasons notified on 17 February 2000, the examining division of the EPO refused the application pursuant to Article 97(1) EPC. The decision was based on an amended set of claims 1 to 32 filed at the oral proceedings before the examining division. Claim 1 read as follows:

"1. The use of an opioid analgesic in the preparation of a medicament for a method of therapy by once-a-day administration to achieve and maintain therapeutic levels, wherein the medicament is a bioavailable sustained-release oral analgesic

dosage form for once-a-day administration, comprising:
a unit dose of a plurality of pharmaceutically acceptable substrates comprising an analgesically effective amount of an opioid analgesic or a salt thereof in sustained release form, each of said substrates having a diameter from 0.1 mm to 3 mm, said dosage form being bioavailable and providing effective treatment of pain for about 24 hours,

with the exception that the dosage form is not an oral pharmaceutical preparation containing a therapeutically effective amount of a salt of morphine for administration once daily characterized in consisting of a material number of individual particles, each having a core containing a salt of morphine coated with a barrier layer, and said barrier layer being derived from a solution, dispersion, suspension, emulsion or melt, and containing at least one water-insoluble component selected from the group consisting of ethyl cellulose, copolymers synthesised from acrylic and methacrylic esters and natural or synthetic waxes, and a plasticizer, and in that the mean serum concentration of morphine obtained is at least *50%* of the maximum serum concentration during at least 12 hours after the administration of a single dose of said preparation,

with the exception that the dosage form is not an orally administrable sustained release dosage unit form containing morphine, or a pharmaceutically acceptable salt thereof, as active ingredient,

which composition gives a peak plasma level at 1.0 to 3.5 hours after administration, and

with the exception that the dosage form is not a solid release, oral dosage form, the dosage form comprising an analgesically effective amount of an opioid analgesic or a salt thereof, coated with a controlled-release coating or in a controlled-release matrix, wherein the dissolution rate in-vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C is from about 12.5% to about 42.5% (by wt) opioid released after 4 hours and greater than 60% (by wt) opioid released after 8 hours, the in-vitro release rate being substantially independent of pH and chosen such that the peak plasma level of said opioid obtained in-vivo occurs from about 2 to about 6 hours after administration of the dosage form."

III. Of the numerous documents cited during the first-instance examination and subsequent appeal proceedings against the patentability of the claimed subject-matter in the application, the following are also referred to in the present decision:

(1) EP-A-0 377 518
(2) EP-A-0 548 448
(3) WO 94/22431
(4) EP-A-0 636 370
(6) EP-A-0 631 781
(8) EP-A-0 630 646
(10) EP-A-0 636 366
(12) EP-A-0 553 392

(13) EP-A-0 535 841.

IV. In the decision under appeal, the examining division found that claim 1 as amended lacked clarity under Article 84 EPC because there was an ambiguity as to the technical features required to prepare a medicament providing effective treatment of pain for about 24 hours. It also found that the claimed subject-matter in the application did not meet the requirements of novelty and inventive step in the light of the closest state of the art according to citation (2).

V. An appeal against this decision was filed on 27 March 2000, with the appeal fee being paid at the same time. The statement of grounds of appeal, filed on 16 June 2000, contested the finding in the decision under appeal that the claims before the examining division did not comply with the requirements of Articles 54, 56 and 84 EPC.

VI. With a letter dated 16 August 2001 a third party filed observations under Article 115(1) EPC. This party alleged that the application was not entitled to claim priority from its priority document, US patent application Serial No. 08/133503 of 7 October 1993 and was, therefore, only entitled to its European filing date of 30 September 1994, and that the disclosure of citations (8) and (10) was, therefore, state of the art under Article 54(3) EPC; such disclosure deprived all claims of novelty.

VII. In the board's first communication of 25 February 2002, the appellant was invited to submit its comments on the observations made by the third party.

VIII. With its reply of 22 May 2002, the appellant filed an amended set of claims 1 to 32. Claim 1 read as follows:

"1. The use of an opioid analgesic in the preparation of a medicament for a method of therapy by once-a-day administration to achieve and maintain therapeutic levels, wherein the medicament is a bioavailable sustained-release oral analgesic dosage form for once-a-day administration, comprising:
a unit dose of a plurality of pharmaceutically acceptable substrates comprising an analgesically effective amount of an opioid analgesic or a salt thereof in sustained release form, each of said substrates having a diameter from 0.1 mm to 3 mm, said dosage form being bioavailable and providing effective treatment of pain for about 24 hours,

with the exception that the dosage form is not an oral pharmaceutical preparation containing a therapeutically effective amount of a salt of morphine for administration once daily characterized in consisting of a material number of individual particles, each having a core containing a salt of morphine coated with a barrier layer, and said barrier layer being derived from a solution, dispersion, suspension, emulsion or melt, and containing at least one water insoluble component selected from the group consisting of ethyl cellulose, copolymers synthesised from acrylic and methacrylic esters and natural or synthetic waxes, and a plasticizer, and in that the mean serum concentration of

morphine obtained is at least *50%* of the maximum serum concentration during at least 12 hours after the administration of a single dose of said preparation,
with the exception that the dosage form is not an orally administrable sustained release dosage unit form containing morphine, or a pharmaceutically acceptable salt thereof, as active ingredient, which composition gives a peak plasma level at 1.0 to 3.5 hours after administration,

with the exception that the dosage form is not a solid release, oral dosage form, the dosage form comprising an analgesica1ly effective amount of an opioid analgesic or a salt thereof, coated with a controlled-release coating or in a controlled-release matrix, wherein the dissolution rate in-vitro of the dosage form, when measured by the US Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7,2) at 37°C is from about 12.5% to about 42.5% (by wt) opioid released after 1 hour, from about *25%* to about *65%* (by wt) opioid released after 2 hours, from about *5%* to, about *85%* (by wt) opioid released after 4 hours and greater than 60% (by wt) opioid released after 8 hours, the in-vitro release rate being substantially independent of pH and chosen such that the peak plasma level of said opioid obtained in-vivo occurs from about 2 to about 6 hours after administration of the dosage form,

with the exception that the dosage form is not a controlled release formulation comprising a substrate comprising an active agent in an amount

sufficient to provide a desired effect in an environment of use, the substrate being coated with a aqueous dispersion of plasticized pharmaceutically acceptable hydrophobic acrylic polymer in an amount sufficient to obtain a controlled release of said active agent when said formulation is exposed to an environment fluid, and cured at a temperature greater than the glass transition temperature of the aqueous dispersion of a plasticized acrylic polymer for a sufficient period of time until a curing endpoint is reached at which the coated substrate provides a stable dissolution of the active agent which is unchanged after exposure to accelerated storage conditions; and

with the exception that the dosage form is not, a controlled release formulation, comprising a substrate containing an active agent in an amount sufficient to provide a desired effect in an environment of use, said substrate coated with an aqueous dispersion of plasticized ethylcellulose in an amount sufficient to obtain a controlled release of said active agent when said formulation is exposed to an environmental fluid, the coated substrate being cured at a temperature greater than the glass transition temperature of the aqueous dispersion of plasticized ethylcellulose and at a relative humidity from about 60% to about 100% for a sufficient period of time until a curing endpoint is reached at which said coated substrate provides a stabilized dissolution of said active agent which is unchanged after exposure to accelerated storage conditions, said

endpoint being determined by comparing the dissolution profile of the formulation immediately after curing to the dissolution profile of the formulation after exposure to accelerated storage conditions."

IX. Following a second change of representative, the appellant requested on 20 March 2003 that the proceedings be suspended for a period of at least three months to give the reappointed original representative enough time to study the case and to prepare further submissions. A letter containing a newly amended set of claims 1 to 28 was filed by the appellant on 22 August 2003. Claim 1 read as follows:

"1. A sustained release oral analgesic dosage form for once-a-day administration,
comprising a unit dose of a plurality of inert pharmaceutically acceptable substrates comprising an analgesically effective amount of an opioid analgesic or a salt thereof in sustained release form, each of said substrates having a diameter from about 0.1 mm to about 3 mm,
said unit dose being bioavailable and providing effective blood levels of said opioid analgesic for at least about 24 hours and wherein the analgesic dosage form comprises an effective amount of opioid in immediate release form,

except dosage forms wherein said substrates are coated with an aqueous dispersion of plasticized pharmaceutically acceptable acrylic polymer and cured at a temperature greater than the glass transition temperature of the aqueous dispersion

of the plasticized polymer for a sufficient period of time until a curing endpoint is reached at which the coated substrate provides a stable dissolution of active agent which is unchanged after exposure to accelerated storage conditions."

X. The communication of 22 February 2005 annexed to the summons for oral proceedings outlined the board's preliminary opinion on the amended set of claims. In particular, the board noted that claim 1 did not fulfil the requirements of Article 123(2) EPC. In this respect the appellant's attention was drawn to the fact that the application as filed disclosed, at page 24, lines 3 to 13, that "in certain embodiments of the present invention an effective amount of opioid in immediate release form is included in the unit dose comprising the substrates", but this was expressed in claim 1 by the feature "wherein the analgesic dosage form comprises an effective amount of opioid in immediate release form". This feature was, in the board's judgment, broader than the original disclosure because it did not necessarily reflect what had been originally disclosed, namely that an effective amount of opioid in immediate release form may in fact be included in the unit dose of the substrates.

The board further noted that, for several reasons explained in detail in the said communication, neither did the disclaimer in claim 1 provide a clear definition of the subject-matter to be excluded from claim 1 nor was it possible for a skilled person to define clearly and unambiguously the subject-matter remaining in the claim or, differently expressed, to

define the matter for which protection was sought, contrary to the requirements of Article 84 EPC.

Finally the board drew attention to the fact that, in the course of the first instance and appeal proceedings, the appellant had already had sufficient time and opportunity to present its arguments and to file amendments to the application. Nevertheless, even at this very late stage of the proceedings, the board agreed, in the exercise of its discretion under Rule 86(3) EPC and Article 10b RPBA, to give the appellant one further opportunity to file amendments in order to overcome the objections raised in the said communication.

XI. In reply thereto, the appellant filed on 21 April 2005 observations and four amended sets of claims, forming its new main request and first, second and third auxiliary requests.

Claim 1 of the main request reads as follows:

"1. A sustained release oral analgesic dosage form for once-a-day administration, comprising a unit dose of an analgesically effective amount of opioid analgesic or a salt thereof, the unit dose comprising a plurality of inert pharmaceutically acceptable substrates comprising the opioid analgesic or a salt thereof in sustained release form, each of said substrates having a diameter from about 0.1 mm to about 3 mm, and wherein the unit dose includes an amount of the opioid analgesic or a salt thereof in immediate release form, said unit dose being bioavailable and

providing effective blood levels of said opioid analgesic for at least about 24 hours,

except dosage forms including sugar beads, comprising 63 % ± 1% by weight of morphine sulfate, coated with a retardant coating, comprising acrylic resins, and overcoated with a coating, comprising additional immediate release morphine sulfate, and

except dosage forms including a unit dose of 8 mg hydromorphone hydrochloride which include sustained and immediate release beads, wherein the sustained release beads include sugar beads coated with hydromorphone hydrochloride and overcoated with a sustained release coating including ethyl cellulose and the immediate release beads include sugar beads coated with hydromorphone hydrochloride without being overcoated with a sustained release coating including ethyl cellulose."

Claim 1 of the first auxiliary request is worded as follows:

"1. A sustained release oral analgesic dosage form for once-a-day administration, comprising a unit dose of an analgesically effective amount of opioid analgesic or a salt thereof, the unit dose comprising a plurality of inert pharmaceutically acceptable substrates comprising the opioid analgesic or a salt thereof in sustained release form, each of said substrates having a diameter from about 0.1 mm to about 3 mm, and wherein the

unit dose includes an amount of the opioid analgesic or a salt thereof in immediate release form, said unit dose being bioavailable and providing effective blood levels of said opioid analgesic for at least about 24 hours,

except dosage forms including a plurality of inert pharmaceutically acceptable substrates comprising an opioid analgesic overcoated with a controlled release coating comprising an aqueous dispersion of hydrophobic acrylic or alkylcellulose polymer and additional opioid analgesic in either the controlled release coating or an additional overcoating coated on the outer surface of the controlled release coating, and

except dosage forms including a unit dose of 8 mg hydromorphone hydrochloride which include sustained and immediate release beads, wherein the sustained release beads include sugar beads coated with hydromorphone hydrochloride and overcoated with a sustained release coating including ethyl cellulose and the immediate release beads include sugar beads coated with hydromorphone hydrochloride without being overcoated with a sustained release coating including ethyl cellulose."

Claim 1 of the second auxiliary request is worded as follows:

"1. A sustained release oral analgesic dosage form for once-a-day administration, comprising a unit dose of an analgesically effective amount of opioid

analgesic or a salt thereof, the unit dose comprising a unit dose of a plurality of inert pharmaceutically acceptable substrates in the form of a multiparticulate sustained release matrix comprising the opioid analgesic or a salt thereof in sustained release form, each of said substrates having a diameter from about 0.1 mm to about 3 mm, and wherein the unit dose includes an amount of the opioid analgesic or a salt thereof in immediate release form, said unit dose being bioavailable and providing effective blood levels of said opioid analgesic for at least about 24 hours."

XII. Oral proceedings were held on 3 August 2005. The discussion at the hearing focussed on several formal deficiencies of the claims in the main request and first and second auxiliary requests and both the formal aspects and substantive merits of the claims in the third auxiliary request filed on 25 April 2005. As a consequence of this discussion, the appellant presented towards the end of the hearing an amended third auxiliary request replacing its previously filed third auxiliary request. Claim 1 of the actual third auxiliary request reads as follows (lettering of features added by the board):

"**(a)** A sustained release oral analgesic dosage form
(a1) for once-a-day administration,
(b) comprising a unit dose of a plurality of inert pharmaceutically acceptable substrates
(c) comprising an analgesically effective amount of an opioid analgesic or a salt thereof

(d) in sustained release form,

(e) each of said substrates having a diameter from about 0.1 mm to about 3 mm,

(f) said unit dose being bioavailable and providing effective blood levels of said opioid analgesic for at least about 24 hours,

(f1) said dosage form further comprising a non-steroidal anti-inflammatory agent selected from the group consisting of ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and mixtures of any of the foregoing,

(g) wherein the substrates are coated with a sufficient amount of a hydrophobic material,

(h) further comprising release-modifying agents, said release-modifying agents comprising one or more hydrophilic polymers such as hydroxypropylmethylcellulose."

XIII. The appellant's submissions in writing and during oral proceedings, so far as relevant to this decision, can be summarised as follows (all references below

presented by the appellant in support of the current version of the claims are to the application as originally filed):

(A) The following feature added to claim 1 of the current main request and first and second auxiliary requests - "and wherein the unit dose includes an amount of opioid analgesic or a salt thereof in immediate release form" - could be derived from the disclosure at page 24, lines 3 to 6, where it was stated that "in certain embodiments of the invention an effective amount of opioid in immediate release form is included in the unit dose comprising the substrates of the present invention". This statement had to be interpreted in the light of the disclosure in the application as a whole. The reference to a "unit dose" in the above statement meant the total amount of substrates needed to administer the desired dose of opioid analgesic to a patient. In accordance with the claimed invention, the desired dose of opioid analgesic was generally administered in the form of sustained-release substrates. However, in one specific embodiment of the invention, namely that disclosed at page 24, the unit dose included in addition to opioid analgesic associated with the sustained-release substrates an effective amount of opioid analgesic in immediate release form. In this particular embodiment, the claimed dosage form in the application comprised a unit dose of an analgesically effective amount of opioid analgesic, that effective amount comprising the opioid analgesic partly in sustained release form and partly in immediate release form. The disclosure of the application did not require that, in this particular embodiment of the invention, the effective amount of

opioid analgesic in immediate release form was necessarily associated with the substrates, but could be present elsewhere in the claimed analgesic oral dosage form. For example, it was disclosed at page 24, lines 26 to 32, that the immediate release portion of the opioid dose might be incorporated into a gelatin capsule via inclusion of the sufficient amount of immediate release opioid as a powder or granulate within the capsule. Or, the gelatin capsule itself might be coated with an immediate release layer of the opioid. Thus, in the appellant's opinion, the newly introduced feature - "and wherein the unit dose includes an amount of opioid analgesic or a salt thereof in immediate release form" - was explicitly disclosed in the application as filed and thus did not give rise to an objection under Article 123(2) EPC.

(B) Claim 1 of the third auxiliary request resulted from a combination of claims 1, 4, 9 and 18 as originally filed and thus complied with the requirements of Articles 84 and 123(2) EPC.

(C) The claimed subject-matter in the third auxiliary request was novel because none of the citations available in the proceedings disclosed a sustained-release oral analgesic dosage form for once-a-day administration comprising an analgesically effective amount of opioid analgesic or a salt thereof in sustained release form in combination with a non-steroidal anti-inflammatory agent.

(D) The problem to be solved by the claimed invention was to provide an oral opioid analgesic dosage form suitable for once-a-day administration. This problem

was solved by providing a dosage form which comprised an effective amount of opioid analgesic in a plurality of inert pharmaceutically acceptable substrates in sustained release form having a diameter from 0.1 mm to 3 mm, and further comprised a non-steroidal anti-inflammatory agent selected from the group specified in claim 1.

(E) Neither citation (2) nor citation (12) disclosed a dosage form suitable for once-a-day administration. There was no information in the cited documents about the *in-vivo* effect of the dosage forms disclosed in (2) and (12) when administered to a human patient. The lack of correlation in general between *in-vitro* dissolution profiles, such as those disclosed in (2) and (12), and *in-vivo* blood plasma profiles and the duration of an analgesic effect of a medicament in a patient did not enable the skilled person to deduce from the cited state of the art any reliable information about the *in-vivo* releasing rates of the dosage forms disclosed in (2) or (12). Since a skilled person would not have considered feasible, at the priority date of the application, the preparation of oral opioid analgesic dosage forms for once-a-day administration, there was nothing in (2) and (12) to suggest the present invention.

(F) Moreover, none of the cited documents suggested combining in a sustained-release oral analgesic dosage form for once-a-day administration an effective amount of an opioid analgesic or a salt thereof in sustained release form with an effective amount of a non-steroidal anti-inflammatory agent in order to improve

the effectiveness of the medicament in treating pain and inflammations of chronic medical conditions.

(G) In the appellant's opinion, the acknowledgment of an inventive step for the subject-matter of the third auxiliary request was thus justified.

XIV. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims in the main request or the first or second auxiliary requests all filed on 25 April 2005 or the third auxiliary request filed in the oral proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.

2. *Main request, first and second auxiliary requests: amendments (Article 123(2) EPC); clarity and support (Article 84 EPC)*

2.1 The underlying idea of Article 123(2) EPC is clearly that an applicant should not be allowed to improve his position by adding subject-matter not disclosed in the application as filed, which would give him an unwarranted advantage and could be damaging to the legal security of third parties relying on the content of the original application.

2.2 In order to limit the scope of the claimed-subject-matter in the application to certain specific

embodiments of the invention and thereby establish novelty over a series of citations in the proceedings, claim 1 in all three requests has been amended after filing, *inter alia*, by insertion of the additional features "and wherein the unit dose includes **an amount** of the opioid analgesic or a salt thereof in immediate release form" (see I vs XI above).

2.2.1 According to the consistent case law of the boards of appeal, introduction into a claim of a particular technical feature, which is not properly supported by the disclosure of the application as filed contravenes Article 123(2) EPC, even if the introduction results in a limitation (see Case Law of the Boards of Appeal of the EPO, 4th ed. 2001, pages 197 ff).

2.2.2 The appellant alleged in writing and at the hearing that the proposed amendment (limitation) finds a basis on page 24, lines 4 to 6, of the application as filed. The relevant disclosure in the application as filed referred to by the appellant reads in the whole context of the description as follows:

*"In certain embodiments of the present invention, an **effective amount** of opioid in immediate release form is included in the unit dose comprising the substrates of the present invention. The immediate release form of the opioid is included **in an amount which is effective** to shorten the time to maximum concentration of the opioid in the blood (e.g., plasma), such that the T_{max} is shortened to a time of, e.g., from about 2 to about 4 hours. This causes the blood concentration curve to have an early peak*

rather than the substantially flattened curves currently recommended by those skilled in the art. It has been discovered that by including such an ***effective amount*** *of immediate release opioid in the unit dose, the experience of relatively higher levels of pain in patients is significantly reduced. In such embodiments, an* ***effective amount*** *of the opioid in immediate release form may be coated onto the substrates of the present invention"* (see page 24, lines 3 to 19; emphasis added by the board).

2.2.3 Hence, the person skilled in the art, when reading the application as filed, will immediately and unambiguously recognise the **relevance** of the functional technical feature disclosed in the description stipulating that in certain embodiments of the invention the immediate release form of the opioid analgesic be "included in the unit dose in an amount **which is effective**" [i.e. to shorten the time to maximum concentration of the opioid in the blood (e.g., plasma), such that the T_{max} is shortened to a time of, e.g., from about 2 to about 4 hours - see 2.2.2 above], i.e. **its essentiality** to the quality or quantity of the effect obtained and thereby to its distinguishing power against the relevant prior art.

2.2.4 By omitting this relevant functional technical feature (i.e. "**an amount which is effective** ....."") from claim 1 in the current main request and the first and second auxiliary requests, the amended claims in all three requests now cover the possibility of including the opioid analgesic in immediate release form in the unit dose in an any conceivable amount within the broad indefinite range

from ineffective, infinitesimal amounts to unduly large amounts. It follows that claim 1 in all three requests has been amended (broadened) in such a way that it contains subject-matter which extends beyond the content of the application as filed.

2.2.5 Moreover such claims, generally relating to "**an amount** of the opioid analgesic or a salt thereof in immediate release form" without further specification, do not define the claimed subject-matter by reference to all its essential technical features and, consequently, lack both clarity and proper support in the description. The requirements of Article 123(2) EPC and Article 84 EPC in conjunction with Rule 29(1) and (3) EPC are accordingly not met.

2.3 If only for the sake of completeness it should also be pointed out that during oral proceedings the board drew attention to further violations of Articles 123(2) and 84 EPC in the claims of the above-mentioned requests. However, since the deficiencies mentioned in 2.2.2 to 2.2.5 above prejudice the grant of a European patent on the basis of the main request or the first or second auxiliary requests, the board does not need to consider any of the further objections under Articles 84 and 123(2) EPC which have been raised during oral proceedings to the claims in the requests mentioned above.

2.3.1 Since a decision can only be taken on a request as a whole, none of the further claims in these three requests needs to be examined. In these circumstances, the appeal in so far as it relates to the main request and the first and second auxiliary requests

must be dismissed, as claim 1 in all three requests does not meet the requirements of Articles 84 and 123(2) EPC.

3. *Third auxiliary request - admissibility; amendments*

3.1 The appellant's assertion that the third auxiliary request with the amendments to claim 1 filed during oral proceedings formed a direct response to certain objections under Articles 84 and 56 EPC raised by the board in the course of said proceedings appears *prima facie* correct. Since claim 1 as amended results from a combination of claim 1 with dependent claims 2 and 12 of the third auxiliary request already filed in writing and it was immediately apparent that the amendments do not contravene Article 123(2) EPC (cf. claims 1, 2, 9 and 18 as originally filed - see I above), the board exercises its discretion in favour of the appellant and admits the amended third auxiliary request into the proceedings, despite being filed at the latest possible moment, namely toward the end of the oral proceedings, and in spite of the fact that in the course of the written appeal proceedings six previous attempts have already been made by the appellant to file amended claims.

3.2 *State of the art*

3.2.1 Citation (1) discloses a pharmaceutical pellet composition comprising a core element including at least one active ingredient of high solubility; and a core coating for the core element which is partially soluble at a highly acidic pH to provide a slow release of active ingredient, e.g. an opioid

analgesic, and wherein the active ingredient is available for absorption in the intestine over an extended period of time, such that blood levels of active ingredient are maintained with the therapeutic range over an extended period of time, e.g. from 8 to 24 hours (see page 14, lines 7 to 8).

3.2.2 Citations (2) and (12) disclose (lettering of features and emphasis added by the board):

(a) **a stabilized controlled release solid oral dosage form** (see (2): page 3, lines 51-52; (12): page 3, lines 35 to 36),

(b) comprising
a plurality of inert pharmaceutically acceptable substrates (beads) (see (2): page 3, line 52; (12): page 3, line 36);

(c) comprising a therapeutically active agent selected, *inter alia*, from
an analgesically effective amount of an opioid analgesic, e.g. morphone, codeine, hydromorphone, hydrcodone, oxycodone, dihydrocodeine, dihydromorphine, (see (2): page 6, lines 13 and 24 to 26; (12): page 5, lines 43 and 54 to 56),
or
an anti-inflammatory agent, e.g. naproxin, diclofenac, ibuprofen, indomethacin (see (2): page 6, line 14; (12): page 5, line 44);

(d) **in sustained release form** (see (2): page 3, lines 53 to 54: "..... beads coated with a therapeutically active agent, and an ethylcellulose overcoat of a suitable thickness to obtain a controlled release of said therapeutical active agent when the solid dosage

form is exposed to aqueous solutions"; page 6, line 54 to page 7, line 1: "a sufficient amount of the aqueous dispersion of ethylcellulose to obtain a predetermined controlled release of said therapeutically active agent when said coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physically characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc."; see (12): page 3, lines 37 to 38: "..... beads coated with a therapeutically active agent, and an overcoat of a an acrylic resin of a suitable thickness to obtain a controlled release of said therapeutical active agent when the solid dosage form is exposed to aqueous solutions");

(e) **each of said substrates having a diameter from about 0.1 mm to about 3 mm** (see (2), page 6: lines 27 to 28, and page 7, lines 54 to 55, "nu pariel 18/20 beads"; (12): page 6, lines 1 to 2, "nu pariel 18/20 beads");

(f) the *in-vitro* release profiles (see (2): page 8, lines 42 to 48 and Tables 3 to 6) indicate that from 91.6 to 81.3 of hydromorphone HCl dissolved after **24 hours**; thus the ***in-vitro* dissolution rates obtained in (2) are entirely comparable to the examples in the present application** (see e.g. Tables 3, 6, 9 11); similar *in-vitro* release profiles are shown in (12): Tables 3, 8 and 15);

(g) **wherein the substrates are coated with a sufficient amount of a hydrophobic material** (see **(d)** above and (2): page 4, lines 7 to 9: "the present invention is related to a method for

obtaining a stabilized controlled release formulation comprising a substrate coated with an aqueous dispersion of a hydrophobic polymer, comprising preparing an aqueous dispersion of ethylcellulose ....."; lines 37 to 39: "in order to obtain a controlled release formulation, it is usually necessary to overcoat the substrate comprising the therapeutically active agent with a sufficient amount of the aqueous dispersion of ethylcellulose ....."; (12), page 3, lines 52 to 53: ".....overcoating the substrate with a sufficient amount of the dispersion of acrylic polymer to obtain a predetermined controlled release of the therapeutically active agent .....");

(h) **further comprising release-modifying agents, said release-modifying agents comprising one or more hydrophilic polymers such as hydroxypropylmethylcellulose** (see (2): page 4, lines 24 to 29: "ethylcellulose, which is a cellulose ether that is formed by the reaction of ethyl chloride with alkaline cellulose, is completely insoluble in water and gastrointestinal juices, and therefore to date has been considered not to be suitable by itself **for tablet coating. It [ethylcellulose]** has, however, been commonly used **in combination with hydroxypropylmethylcellulose [HPMC]** and other film-formers to **toughen or influence the dissolution rate of the film**. Due to the stability characteristics of **ethylcellulose**, this polymer has been mainly applied to the above-mentioned formulations from organic solutions").

3.2.3 Citations (3), (4), (6), (8) and (10), which have been cited against the novelty of the claimed subject-matter either by the examining division or the third party at various stages in the examination of the present application, are all comprised in the state of the art under Article 54(3) and (4) EPC.

3.3 Novelty

3.3.1. After examination of the citations uncovered by the search report and those introduced by the third party and the appellant during the proceedings, the board is satisfied that none of them discloses a sustained release oral analgesic dosage form including all the features stated in claim 1. In particular, none of the citations relates to a sustained release oral analgesic dosage form comprising as active ingredients an effective amount of an opioid analgesic or a salt thereof **in combination with** ("further comprising") a non-steroidal anti-inflammatory agent selected from the group specified in claim 1 (see XI above, feature **(f1)**). Therefore, the subject-matter as set forth in claims 1 to 20 is novel within the meaning of Article 54(1) EPC.

3.4 The closest state of the art

3.4.1 In the present case it is readily apparent from a comparison of the claimed sustained release oral analgesic dosage form defined in claim 1 (see XI above) and that disclosed in the state of the art according to citation (2) (see 3.2.2 above) that the former does not differ from the cited state of the

art in any essential technical feature of the dosage form; the relevant technical features **(a)** to **(e)** and **(g)** to **(h)** are the same in claim 1 and in citation (2)(see XI above *vs.* 3.2.2 above).

Hence, the sole difference between the dosage form defined in claim 1 and the disclosure of (2) may be seen in that claim 1 explicitly refers to effective blood levels of the opioid analgesic for at least about 24 hours [as compared to the 24 hours *in-vitro* releasing rates disclosed in both the present application and citation (2) - see XI above, feature **(f)** *vs.* 3.2.2 **(f)** above] and stipulates the presence of a non-steroidal anti-inflammatory agent selected from the group specified in claim 1 in addition to an opioid analgesic as the active ingredients [as compared to the alternative use of non-steroidal anti-inflammatory agent as the active ingredient proposed in (2) - see XI above, feature **(f1)** *vs.* 3.2.2 **(c)** above].

3.4.2 In view of the fact that the features **(a)** to **(e)** and **(g)** to **(h)** of the claimed dosage form are clearly of a technical nature in that their function in citation (2) as well as in the present application is to enable the skilled person to control and regulate both the in vitro and in vivo release profiles of an opioid analgesic in order to provide sustained-release products which provide effective blood levels of said opioid analgesic over the desired delivery period, citation (2) represents the closest state of the art under Article 54(2) EPC available in the proceedings.

3.5 *The problem and the solution*

3.5.1 Departing from citation (2), the problem to be solved by the application can be seen in the provision of a further sustained release oral analgesic dosage form comprising an opioid analgesic or a salt thereof and providing effective blood levels of said opioid analgesic for at least 24 hours. The solution proposed is a sustained release oral analgesic dosage form including the features stated in present claim 1.

3.5.2 The examining division objected, *inter alia*, in the decision under appeal (see Reasons, point 4) to claim 1 in the version on which its decision was based, citing Article 84 EPC, on the grounds that "if as argued D2 [i.e. citation (2)] does not provide a 24 hours release preparation, the reader would be required to repeat the endeavour shown in the Applicant's examples in order to produce alternative products within the scope of claim 1. This renders claim 1 unclear under Article 84 EPC as it represents a result to be achieved (Guidelines C-III, 4.7)". The board considers that, by its objection, the examining division referred to the fact that claim 1 did not contain all the technical features which are essential in order to achieve the desired result, that is to say providing effective blood levels of an opioid analgesic or a salt thereof over the desired delivery period stated in the claim.

3.5.3 During oral proceedings the board raised a similar objection, namely that present claim 1 is too broad because it does not, even after amendment by introducing the additional features **(g)** and **(h)**,

contain all the technical features which the appellant itself considered in its submission at the hearing to be essential in order to provide effective blood levels of an opioid analgesic over the desired delivery period of 24 hours as stated in claim 1. However, the claim was sufficiently clear and complete that this issue was not crucial to an understanding of the other issues and, in view of the board's decision on the further matters referred to below, no final decision on this issue is necessary in this case.

3.5.4 Such an objection under Article 84 EPC is likely to raise a further objection under Article 83 EPC. However, since the question of adequate disclosure within Article 83 EPC must be assessed on the basis of the application as a whole - including the claims and the description - the board is satisfied that the disclosure in the application as a whole enables those skilled in the art to solve the technical problem defined in 3.5.1 above.

3.6 *Inventive step*

3.6.1 The board adopts the view expressed in decision T 60/89 (OJ EPO 6/1992, 268, see especially Reasons, point 3.2.5) that the same level of skill has to be applied when, for the same invention, the two questions of sufficient disclosure within the meaning of Article 83 EPC and inventive step within the meaning of Article 56 EPC have to be considered.

3.6.2 A person having the level of skill mentioned above and seeking a solution to the problem in the state of

the art would certainly take into account the statement in the last paragraph on page 3 of the application that "notwithstanding the diverse factors influencing both dissolution and absorption of a drug substance, a strong correlation has been established between the in—vitro dissolution time determined for a dosage form and (in-vivo) bioavailability. The dissolution time and the bioavailability determined for a composition are two of the most significant fundamental characteristics for consideration when evaluating sustained-release compositions".

In this context, the appellant essentially alleged that, if two formulations possess similar *in-vitro* dissolution rates, it does not mean that they will **necessarily** have the same *in-vivo* release profile. Nevertheless, in the absence of any evidence to the contrary in the present case, those skilled in the art, faced with the problem posed and seeking a solution to this problem in the state of the art, would take into consideration and carefully study the *in-vitro* dissolution rates determined for the sustained-release oral opioid analgesic dosage forms described in the examples of citations (2) and (12). In doing so, they would be given sufficient instructions as to the relevant technical details required for a sustained release oral dosage form in order to achieve effective blood levels of said opioid analgesic over the desired delivery period. Such technical details are, for example:

- the advantage of using a sustained-release multiparticulate system ("substrates");

- the nature and size of the "substrates", i.e. spheroids, beads, microspheres, seeds pellets, etc, of said multiparticulate system;
- the nature and effective amount of opioid analgesic in sustained release form comprised in the substrates;
- the nature, amount and thickness of the hydrophobic retardant overcoating material necessary to control and regulate both the *in-vitro* and *in-vivo* release profiles of an opioid analgesic;
- the nature and amount of the "various additives" (plasticizers, film-forming agents etc.) to be included in the retardant coating required effectively to control and modify the *in-vitro* and *in-vivo* release profiles so as to achieve effective blood levels of said opioid analgesic over the desired delivery period.

3.6.3 In addition to the specific examples, the skilled person is given in the cited state of the art precise directions - should he need them - as to how he can by means of simple tests control and regulate the release rates of the active agent, ie the opioid analgesic:

- see (2), page 4, lines 37 to 42:

"In order to obtain a controlled release formulation, it is usually necessary to overcoat the substrate comprising the therapeutically active agent with a sufficient amount of the aqueous dispersion of ethylcellulose to obtain a weight gain level from about 5 to about 15 percent, although the overcoat

may be lesser or greater depending upon the physical properties of the therapeutically active agent and the desired release rate, the inclusion of plasticizer in the aqueous dispersion of ethylcellulose and the manner incorporation of the same, for example."

- see (2), page 6, lines 2 to 8:

"The stabilized controlled release formulations of the present invention slowly release the therapeutically active agent, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of ethylcellulose, altering the manner in which the plasticizer is added to the aqueous dispersion of ethylcellulose, by varying the amount of plasticizer relative to ethylcellulose, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc."

- see (12), page 4, lines 6 to 16:

"In certain preferred embodiments of the present invention, the acrylic polymer comprising the controlled release coating is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. In order to obtain a controlled release formulation

it is usually necessary to overcoat the substrate comprising the therapeutically active agent with a sufficient amount of the aqueous dispersion of acrylic polymer to obtain a weight gain level from about 5 to about 15 percent, although the overcoat may be lesser or greater depending upon the physical properties of the therapeutically active agent and the desired release rate, the inclusion of plasticizer in the aqueous dispersion of ethylcellulose and the manner incorporation of the same, for example."

- see (12), page 5, lines 34 to 38

"The stabilized controlled release formulations of the present invention slowly release the therapeutically active agent, e.g., when ingested and exposed to gastric fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating, altering the manner in which the plasticizer is added, by varying the amount of plasticizer relative to acrylic resin, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc."

3.6.3.1 The technical teaching in the above-cited prior art documents (2) and (12) is **repeated in the present application**, for example, as follows:

- see application, page 13, lines 20 to 29

"In order to obtain a sustained—release of the opioid **sufficient to provide an analgesic effect for the**

extended durations set forth in the present invention, the substrate comprising the therapeutically active agent may be coated with a sufficient amount of hydrophobic material to obtain a weight gain level from about **2 to about 30 percent**, although the overcoat may be greater depending upon the physical properties of the particular opioid analgesic compound utilized and the desired release rate, among other things."

- see application, page 17, lines 4 to 14

"The sustained—release profile of the formulations of the invention can be altered, for example, by varying the thickness of the hydrophobic coating [ethylcellulose, acrylic polymer] changing the particular hydrophobic material used, or altering the relative amounts of, e.g., different acrylic resin lacquers, altering the manner in which the plasticizer is added (e.g., when the sustained—release coating is derived from an aqueous dispersion of hydrophobic polymer), by varying the amount of plasticizer relative to hydrophobic polymer, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc."

3.6.3.2 Moreover, citation (2) gives those skilled in the art sufficient specific instructions as to how to obtain oral dosage forms **which contain a plurality of substrates** including the opioid analgesic and having a **retardant overcoating** derived from an aqueous suspension of **ethylcellulose** in order to provide sustained-release products which provide effective

blood levels of said opioid analgesic over the desired delivery period:

- see (2), page 4, line 54 to page 6, line 1

"Because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is necessary to plasticize the ethylcellulose before using the same as a coating material. One commercially-available aqueous dispersion of ethylcellulose is ***Aquacoat®*** *(FMC Corp., Philadelphia, Pennsylvania, U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.*

Another aqueous dispersion of ethylcellulose is commercially available as ***Surelease®*** *(Colorcon, Inc., West Point, Pennsylvania, U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates. The*

coating formulations of the present invention should be capable of producing a ***strong, continuous film*** *that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.*

It is preferred that the aqueous dispersion of ethylcellulose used in the present invention include an effective amount of a suitable plasticizing agent, as it has been found that the use of a plasticizer will further improve the physical properties of the ***film****. The plasticization of the ethylcellulose may be accomplished either by so-called "internal plasticization" and "external plasticization.*

Internal plasticization usually pertains directly to molecular modifications of the polymer during its manufacture, e.g., by copolymerization, such as altering and/or substituting functional groups, controlling the number of side chains, or controlling the length of the polymer. Such techniques are usually not performed by the formulator of the coating solution.

External plasticization involves the addition of a material to a film solution so that the requisite changes in film properties of the dry film can be achieved. The suitability of a plasticizer depends on its affinity or solvating power for the polymer and its effectiveness at interfering with polymer-polymer attachments. Such activity imparts the desired flexibility by relieving molecular rigidity. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the

film-former, e.g., most often from about 1 to about 50 percent by weight of the ***film-former****. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.*

An important parameter in the determination of a suitable plasticizer for a polymer is related to the glass transition temperature (Tg) of the polymer. The glass transition temperature is related to the temperature or temperature range where there is a fundamental change in the physical properties of the polymer. This change does not reflect a change in state, but rather a change in the macromolecular mobility of the polymer. Below the Tg, the polymer chain mobility is severely restricted. Thus, for a given polymer, if its Tg is above room temperature, the polymer will behave as a glass, being hard, non-pliable and rather brittle, properties which could be somewhat restrictive in film coating since the coated dosage form may be subjected to a certain amount of external stress.

Incorporation of suitable plasticizers into the polymer matrix effectively reduces the Tg, so that under ambient conditions the films are softer, more pliable and often stronger, and thus better able to resist mechanical stress. Other aspects of suitable plasticizers include the ability of the plasticizer to act as a good "swelling agent" for the ethylcellulose, and the insolubility of the plasticizer in water.

Examples of suitable plasticizers include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tibutyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention."

3.6.3.3 The above teaching and instructions as **transferred into the present application** read as follows:

- see application, page 5, line 13 to page 16, line 29

"In other preferred embodiments the hydrophobic polymer which may be used for coating the substrates of the present invention is a hydrophobic cellulosic material such as **ethylcellulose**. Those skilled in the art will appreciate that other cellulosic polymers, including other alkyl cellulosic polymers, may be substituted for part or all of the ethylcellulose included in the hydrophobic polymer coatings of the present invention.

One commercially—available aqueous dispersion of ethylcellulose is **Aquacoat**® (FMC Corp., Philadelphia, Pennsylvania, U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated

under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as **Surelease**® (Colorcon, Inc., West 35 Point, Pennsylvania, U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic polymer, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic polymer will further improve the physical properties of the film. For example, because **ethylcellulose has a relatively high glass transition temperature** and does not form flexible **films** under normal coating conditions, it is necessary to plasticize the ethylcellulose before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the **film-former**, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating

solution and method of application. Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tibutyl citrate, and triacetin, although it is possible that other water—insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is especially preferred."

3.6.3.4 Comparable precise instructions are given in (12) for preparing sustained release dosage forms in accordance with the application having acrylic polymer coating:

- see (12), page 4, line 28 to page 5, line 30

"In a preferred embodiment of the present invention, the acrylic coating is derived from a mixture of two acrylic resin lacquers used in the form of aqueous dispersions, commercially available from Rohm Pharma under the Tradename ***Eudragit® RL 30 D and Eudragit® RS 30 D****, respectively. Eudragit® RL 30 D and Eudragit® RS 30 D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being in Eudragit® RL 30 D and 1:40 in Eudragit® RS 30 D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in*

aqueous solutions and digestive fluids. The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a controlled release formulation having a desirable dissolution profile.

Desirable controlled release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® AS, and 10% Eudragit® RL:Eudragit® 90% RS.

In addition to modifying the dissolution profile by altering the relative amounts of different acrylic resin lacquers, the dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

The aqueous dispersions of acrylic polymers used as coatings in the present invention may be used in conjunction with tablets, spheroids (or beads), microspheres, seeds, pellets or ion exchange resin beads and other multi-particulate systems in order to obtain a desired controlled release of the therapeutically active agent. Granules, spheroids, or pellets, etc., prepared in accordance with the present invention can be presented in a capsule or in any other suitable dosage form.

The coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-

toxic, inert, and tack-free. It is preferred that the acrylic coatings used in the present invention include an effective amount of a suitable plasticizing agent, as it has been found that the use of a plasticizer will further improve the physical properties of the ***film****. For example, the use of a plasticizer may improve the film elasticity and lower the film-forming temperature of the dispersion. The plasticization of the acrylic resin may be accomplished either by so-called "internal plasticization" and "external plasticization". Internal plasticization usually pertains directly to molecular modifications of the polymer during its manufacture, e.g., by copolymerization, such as altering and/or substituting functional groups, controlling the number of side chains, or controlling the length of the polymer. Such techniques are usually not performed by the formulator of the coating solution.*

External plasticization involves the addition of a material to a film solution so that the requisite changes in film properties of the dry film can be achieved. The suitability of a plasticizer depends on its affinity or solvating power for the polymer and its effectiveness at interfering with polymer-polymer attachments. Such activity imparts the desired flexibility by relieving molecular rigidity.

Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only

be properly determined after careful experimentation with the particular coating solution and method of application.

Most preferably, about 20% plasticizer is included in the aqueous dispersion of acrylic polymer. An important parameter in the determination of a suitable plasticizer for a polymer is related to the glass transition temperature (Tg) of the polymer. The glass transition temperature is related to the temperature or temperature range where there is a fundamental change in the physical properties of the polymer. This change does not reflect a change in state, but rather a change in the macromolecular mobility of the polymer. Below the Tg, the polymer chain mobility is severely restricted. Thus, for a given polymer, if its Tg is above room temperature, the polymer will behave as a glass, being hard, non-pliable and rather brittle, properties which could be somewhat restrictive in film coating since the coated dosage form may be subjected to a certain amount of external stress.

Incorporation of suitable plasticizers into the polymer matrix effectively reduces the IG, so that under ambient conditions the films are softer, more pliable and often stronger, and thus better able to resist mechanical stress. Other aspects of suitable plasticizers include the ability of the plasticizer to act as a good "swelling agent" for the ethylcellulose, and the insolubility of the plasticizer in water.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin."

3.6.3.5 The above teaching and instructions as transferred into the present application read as follows:

- see application, page 14 line 1 to page 15, line 12 and page 16, line 30 to page 17, line 3

"In certain preferred embodiments of the present invention, the hydrophobic polymer comprising the sustained release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(ethyl methacrylate), polymethacrylate, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well

known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In one preferred embodiment, the acrylic coating is an acrylic resin lacquers used in the form of an aqueous dispersion, such as that which is commercially available from Rohm Pharma under the Tradename **Eudragit®**. In further preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames **Eudragit® RL 30** and **Eudragit® RS 30 D**, respectively. Eudragit® RL 30 D and Eudragit® RS 30 D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL 30 and 1:40 in Eudragit® RS 30 D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids. The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained–release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL:Eudragit® 90% RS. Of course, one

skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L."

"Examples of suitable plasticizers for the acrylic polymers of the present invention include citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol, polyethylene glycols, propylene glycol, diethyl phthalate, 35 castor oil, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phtalate esters, castor oil etc.) may be used. Triethyl citrate is especially preferred".

3.6.4 The comparison above between the technical teaching of citations (2) and (12) and that of the present application specifically concerns embodiments and modifications of the retardant overcoating, which is the most relevant technical detail of the claimed dosage forms, but **serves only as an example to demonstrate** that the technical teaching of the state of the art according to citations (2) and (12) in its entirety is almost identical with that in the present application.

3.6.5 At the hearing before the board, the appellant also argued that at least the addition of pore-formers comprising one or more hydrophilic polymers, such as hydroxypropylmethylcellulose, to the hydrophobic polymer forming the retardant coating of the claimed dosage forms was a technical teaching in the present application not disclosed in citation (2) or (12). It further argued that precisely this technical feature

was essential in order to obtain dosage forms providing effective blood levels of the opioid analgesic over the desired delivery period of 24 hours.

3.6.5.1 In this respect, at a preliminary remark it is to be noted that **feature (h)** ("further comprising release-modifying agents, said release-modifying agents comprising one or more hydrophilic polymers such as hydroxypropylmethylcellulose" - see XI above), which has been introduced in claim 1 during oral proceedings, does not necessarily reflect the technical teaching considered by the appellant to be essential. This feature ("further comprising" does not stipulate that hydroxypropylmethylcellullose be present in the hydrophobic polymer forming the retardant coating but would also be satisfied by the presence of hydroxypropylmethylcellullose elsewhere in the claimed dosage form.

3.6.5.2 Moreover, feature (h) could not in any case contribute to the acknowledgment of an inventive step because this feature as such **and** its technical function is also already known from citation (2).

Thus, citation 2 states at page 4, lines 24 to 29:

"Ethylcellulose [ie the retardant coating in (2)], which is a cellulose ether that is formed by the reaction of ethyl chloride with alkaline cellulose, is completely insoluble in water and gastrointestinal juices, and therefore to date has been considered not to be suitable by itself for tablet coating. ***It [ethylcellulose]*** *has, however, been commonly used in*

combination with hydroxypropylmethylcellulose [HPMC] and other film-formers ***to toughen or influence the dissolution rate of the film*** *[contrary to the appellant's assertions at the hearing, the ethylcellulose retardant coating is also designated* ***film*** *throughout the description - see as an example only, page 16, lines 11 and 14 in the present application] Due to the stability characteristics of* ***ethylcellulose****, this polymer has mainly applied to the above-mentioned formulations from organic solutions".*

3.6.6 Citation (2) - see page 6, lines 9 and 14 - and citation (12) - see page 5, lines 39 and 44 - disclose that in addition to the preferred opioid analgesics a wide variety of other therapeutic agents, including anti-inflammatory agents, can advantageously be used as active ingredients for the sustained-release oral solid dosage forms described in the cited documents.

Citation (13) which was referred to in the search report as particularly relevant if taken alone (X document) and is thus citable in the present decision discloses already that the combination of the opioid analgesic codeine and the non-steroidal anti-inflammatory agent ibuprofen is particularly advantageous in the treatment of the pain of chronic medical conditions (see page 2, lines 28 to 29). The cited document also already suggests providing the combination of these two medicaments in sustained release form, for example, by inclusion in a suitable matrix such as e.g. cellulose esters or acrylic resins.

3.6.7 For the foregoing reasons it is clear that the proposed combination of active ingredients in the present application is thus also obviously derivable from the cited state of the art. Accordingly a skilled person being guided by the problem posed and following the technical teaching of citations (2) and (12) in combination with that of citation (13) would readily arrive at the claimed solution of the problem without application of inventive skill or undue experimentation.

It follows that the appellant's third auxiliary request must also fail since the claimed invention does not comply with the requirements of Articles 52(1) and 56 EPC, and that, therefore, the appeal has to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Townend U. Oswald