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(54) Benævnelse: **Oral farmaceutisk sammensætning med langvarig frigivelse omfattende hydromorphon og naloxon til anvendelse ved behandling af moderate til svære smerter.**

(56) Fremdragne publikationer:

US 2007/0014732 A1
WO 03/013525 A1

US 2006/0039970 A1
US 4457933 A
WO 2010/140007 A2

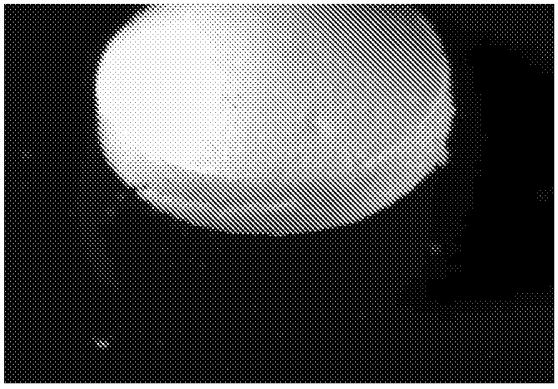
Fortsættes ...

(57) Sammendrag:
The present invention relates to prolonged release pharmaceutical dosage forms, the manufacture thereof as well as their use for administration to human beings.

Fortsættes ...

Figure 1

a)



Untreated tablet core

ORAL PROLONGED RELEASE PHARMACEUTICAL COMPOSITIONS COMPRISING HYDROMORPHONE AND NALOXONE FOR USE IN THE TREATMENT OF MODERATE TO SEVERE PAIN

FIELD OF THE INVENTION

The present invention relates to oral prolonged release pharmaceutical dosage forms comprising hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio range of 2:1 to 1:3 for use in the treatment of moderate to severe pain, thereby beneficially influencing hydromorphone-induced constipation.

BACKGROUND OF THE INVENTION

Prolonged release pharmaceutical dosage forms represent an important tool in a medical practioner's armoury for treating diseases. One of the general benefits generally attributed to prolonged release pharmaceutical dosage forms versus immediate release pharmaceutical dosage forms includes increased patient compliance as a consequence of reduced administration frequency.

There are various technologies available for obtaining prolonged release dosage forms. Prolonged release properties may be conveyed by so-called prolonged release matrix systems, prolonged release coatings, osmotic dosage forms, multi-layered dosage forms etc.

When developing a prolonged release formulation, it is generally necessary to choose the respective formulation technology with respect to the physico-chemical and physiological properties of the pharmaceutically active agent(s) in question. This means a substantial amount of work for the formulation specialist. This will be even more so where the dosage form comprises pharmaceutically active agents such opioid agonists which theoretically can be abused, i.e. are not used for medicinal purposes.

There is thus a continuing interest in pharmaceutical dosage forms which comprise opioid analgesic as pharmaceutically active agents, which provide prolonged release properties and account for opioids' potential of being abused.

US 2006/039970 A1 describes pharmaceutical dosage forms comprising an opioid agonist and an opioid antagonist. Preferred opioid agonists include oxycodone and hydrocodone. A preferred opioid antagonist is naltrexone. As preferred weight ratios, weight ratios of 40:1 to 50:1, preferably 20:1 are disclosed. However, US 2006/039970 A1 does not disclose the combination of hydromorphone and naloxone or suitable weight ratios of these active agents for providing a beneficial influence on hydromorphone-induced constipation.

US 2007/014732 A1 refers to abuse resistant dosage forms comprising an opioid agonist and an opioid antagonist. However, the issue of reducing constipation is not addressed. Furthermore, US 2007/014732 A1 does not disclose the active agent combination of hydromorphone and naloxone in a weight ratio range of 2:1 to 1:3.

WO 03/013525 A1 discloses oral dosage forms of an opioid agonist that are useful for decreasing the potential of abuse of the opioid agonist. However, the issue of reducing constipation is not addressed. Furthermore, WO 03/013525 A1 does not disclose the active agent combination of hydromorphone and naloxone in a weight ratio range of 2:1 to 1:3.

SUMMARY OF THE INVENTION

It is an objective of the present invention to provide prolonged release pharmaceutical dosage forms.

These and other objectives as they will become apparent from the ensuing description are attained by the subject matter of the independent claims. Some of the preferred embodiments are referred to by the dependent claims.

To some extent, the present invention is based on the finding that one can produce prolonged release pharmaceutical dosage forms comprising hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof combining various beneficial aspects. These include stability, alcohol tolerance, tamper resistance and the like.

The present invention relates to an oral prolonged release pharmaceutical composition comprising at least:

a) at least one prolonged release material;
b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof with hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof being present in the pharmaceutical composition in a weight ratio range of 2:1 to 1:3;

for use in the treatment of moderate to severe pain, thereby beneficially influencing hydromorphone-induced constipation.

In a first embodiment, hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are present in the pharmaceutical composition in a weight ratio of about 2:1, about 1:1, about 1:2 or about 1:3.

Further preferred embodiments are defined in the claims.

The pharmaceutical compositions are for use for treating moderate to severe pain, in particular cancer pain, neuropathic pain, visceral pain or bone pain. When used for treating these types of pain, the pharmaceutical compositions beneficially influence hydromorphone-induced constipation. In addition, they may beneficially influence side effects such as urinary retention, breath depression and bowel function as they may occur when using only hydromorphone or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention as illustratively described in the following may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein.

The present invention will be described with respect to particular embodiments and with reference to certain figures but the invention is not limited thereto but only by the claims. Terms as set forth hereinafter are generally to be understood in their common sense unless indicated otherwise.

Where the term "comprising" is used in the present description and claims, it does not exclude other elements. For the purposes of the present invention, the term "consisting of" is considered to be a preferred embodiment of the term "comprising of". If hereinafter a group is defined to comprise at least a certain number of embodiments, this is also to be understood to disclose a group which preferably consists only of these embodiments.

Where an indefinite or definite article is used when referring to a singular noun, e.g. "a", "an" or "the", this includes a plural of that noun unless something else is specifically stated.

In the context of the present invention the terms "about" or "approximately" denote an interval of accuracy that the person skilled in the art will understand to still ensure the technical effect of the feature in question. The term typically indicates deviation from the indicated numerical value of ±10%, and preferably of ±5%.

The term "*in vitro* release" and its grammatical variations as well as similar expression refers to the release rate by which a pharmaceutically active agent, e.g. hydromorphone HCl is released from the pharmaceutical composition when the in vitro release rate is tested by the paddle method according to the European Pharmacopeia as described in the Ph. Eur. 2.9.3 6th edition. The paddle speed is typically set at 75 or 100 rpm in 500 ml or 900 ml simulated gastric fluid (SGF) dissolution medium with pH 1.2. Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC with a C18 column, eluted with 30mM phosphate buffer in acetonitrile (70:70; pH 2.9) with a flow rate of 1.0 ml/min and detected at 220 nm. It is specifically indicated if in the context of the present invention *in vitro* release rates are determined using a different test method (such as SGF with 40% (v/v) of ethanol).

The amount of dissolution liquid and the rotational speed of the paddle apparatus may depend on the amount of active agent tested. For example, pharmaceutical compositions comprising up to 16 mg hydromorphone HCl may be tested at 75 rpm in 500 ml dissolution liquid while higher dosage strengths may be tested at 100 rpm in 900 ml dissolution liquid.

The term "Simulated Gastric Fluid, pH 1.2" refers to 0.1 N HCl, pH 1.2.

In the context of the present invention, the terms "immediate release" or "conventional release" refer to pharmaceutical compositions showing a release of the active substance(s) which is not deliberately modified by a special formulation design and/or manufacturing methods. For oral dosage forms this means that the

dissolution profile of the active substance(s) depends essentially on its (their) intrinsic properties. Typically, the terms "immediate release" or "conventional release" refer to pharmaceutical compositions which release *in vitro* >75% (by weight) of the pharmaceutically active agent(s) at 45 min.

In the context of the present, the terms "prolonged release" and "controlled release" are used interchangeably and refer to pharmaceutical compositions showing a slower release of the active agent(s) than that of a conventional release pharmaceutical composition administered by the same route. Prolonged or controlled release is achieved by a special formulation design and/or manufacturing method. Typically, the terms "prolonged release" and "controlled release refer to pharmaceutical compositions which release *in vitro* ≤75% (by weight) of the pharmaceutically active agent at 45 min.

Prolonged release properties may be obtained by different means such as by a coating which is then designated as a prolonged release coating, a matrix which is then designated by as a prolonged release matrix or e.g. by an osmotic structure of the pharmaceutical composition.

In order to obtain "prolonged or controlled release" properties, one typically uses materials which are known to prolong the release from a dosage form comprising e.g. a prolonged release matrix and/or prolonged release coating. Typical examples of such "prolonged or controlled release materials" are hydrophobic polymers such as ethyl cellulose or hydrophilic polymers such as hydroxypropyl cellulose. The nature of the "prolonged or controlled release material" may depend on whether the release properties are attained by a "prolonged release matrix" or a "prolonged release coating". The term "prolonged release materials" thus describes both types of materials. The term "prolonged release matrix material" indicates that a material is used for obtaining a prolonged release matrix. Likewise, the term "prolonged release

coating material" indicate that a material is used for obtaining a prolonged release coating.

The terms "prolonged release matrix formulation" or "controlled release matrix formulation" refer to a pharmaceutical composition including at least one prolonged release material or controlled release material, and at least hydromorphone and naloxone or the pharmaceutically acceptable salts thereof. The terms "prolonged release material" and "controlled release material" can be used interchangeably. In a "prolonged release matrix formulation" or "controlled release matrix formulation", the "prolonged release material" or "controlled release material" are combined with the pharmaceutically active agents to form a mixture from which the pharmaceutically active agent is released over prolonged periods of time, such as e.g. 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours.

It is to be understood that a material will be considered to act as prolonged or controlled release material if the dissolution profile of the pharmaceutically active agent(s) is slowed down compared to an immediate or conventional release formulation. If a prolonged or controlled release material can be used for manufacturing a prolonged or controlled release matrix, it will be considered as a prolonged or controlled release matrix material.

Pharmaceutically acceptable excipients which are used to adjust an already prolonged or controlled release to a specific profile are not necessarily considered to be prolonged or controlled release materials.

It is to be understood that a prolonged release matrix or a controlled release matrix does not necessarily consist only of the pharmaceutically active agent(s) and the prolonged or controlled release material. The prolonged or controlled release matrix may comprise additional pharmaceutically acceptable excipients such as fillers, lubricants and glidants.

The terms "prolonged release coating formulation" or "controlled release coating formulation" refer to a pharmaceutical composition including at least one prolonged release material or controlled release material, and at least hydromorphone and naloxone or the pharmaceutically acceptable salts thereof. The terms "prolonged release material" and "controlled release material" can be used interchangeably. In a "prolonged release coating formulation" or "controlled release coating formulation", the "prolonged release material" or "controlled release material" are disposed on the pharmaceutically active agents to form a diffusion barrier. Other than in prolonged release matrix formulation, the actives are not intimately mixed with the prolonged release material and the prolonged release coating does not form a three dimensional structure within which the actives are distributed. As the term implies, the prolonged release material forms a layer above the actives. The pharmaceutically active agent is released from a prolonged release coating formulation over prolonged periods of time, such as e.g. 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours.

It is to be understood that a material will be considered to act as prolonged or controlled release material if the dissolution profile of the pharmaceutically active agent(s) is slowed down compared to an immediate or conventional release formulation. If a prolonged or controlled release material can be used for manufacturing a prolonged or controlled release coating, it will be considered as a prolonged or controlled release coating material.

Pharmaceutically acceptable excipients which are used to adjust an already prolonged or controlled release to a specific profile are not necessarily considered to be prolonged or controlled release materials.

When it is mentioned that a prolonged release coating is disposed on pharmaceutically active agents, this is not to be construed as meaning that such a coating will necessarily be directly layered on such active pharmaceutically agents.

Of course, if pharmaceutically active agents are layered on a carriers such as nu-pareil beads, the coating may be disposed directly thereon. However, the pharmaceutically active agents may also be first embedded in a polymer layer or e.g. a prolonged release matrix. Subsequently the prolonged release coating may be disposed e.g. on granules which comprise a prolonged release matrix or on tablets which are made from such granules by compression for example.

A pharmaceutical composition with a controlled or prolonged release coating may be obtained by combining the pharmaceutically active agents with a carrier such as non-pareil beads and disposing a prolonged release coating on said combinations. Such coating may be made from polymers such cellulose ethers with ethyl cellulose being preferred, acrylic resins, other polymers and mixtures thereof. Such controlled or prolonged release coatings may comprise additional excipients such as pore-formers or binders..

It is further to be understood, that the term "prolonged release matrix formulation" or "controlled release matrix formulation" does not exclude pharmaceutical compositions with a prolonged or controlled release matrix and an additional prolonged or controlled release coating being disposed on the matrix. Likewise the term "prolonged release coating formulation" or "controlled release coating formulation" does not exclude pharmaceutical compositions with a prolonged or controlled release coating which is disposed on a prolonged release matrix or a controlled release matrix.

In fact, the invention in various embodiments considers prolonged release matrix formulations which also comprise a prolonged release coating.

The terms "prolonged release dosage form" and "controlled release dosage form" can be used interchangeably and refer to the administration form of a pharmaceutical composition for use according to the present invention comprising the at least one

pharmaceutically active agent in prolonged release form as e.g. in form of a "prolonged release matrix formulation", in the form of a "prolonged release coating formulation, combinations thereof or in other prolonged release formulations such as osmotic formulations. The terms "prolonged release matrix formulation" and "prolonged release dosage form" can be used interchangeably if the prolonged release dosage form consists essentially of the prolonged release matrix formulation. This means that a prolonged release dosage form can comprise in addition to the prolonged release matrix e.g. cosmetic coatings and pharmaceutically acceptable excipients such as fillers and lubricants.

For some embodiments, the term "prolonged release matrix dosage form" may indicate that the dosage form comprises a prolonged release matrix as the sole structure being responsible for prolonging the release. This, however, does not exclude that the dosage form may comprise an immediate release portion as described hereinafter.

For some embodiments, the term "prolonged release coating dosage form" may indicate that the dosage form comprises a prolonged release coating as the sole structure being responsible for prolonging the release. This, however, does not exclude that the dosage form may comprise an immediate release portion as described hereinafter.

The release rates indicated always refer to the formulation such as a monolithic tablet or multi-particulates. The release rates will be chosen such that a pharmaceutical composition can be administered e.g. on a twice a day or once a day basis, i.e. every 12 hours or every 24 hours. Typically, the release will occur by diffusion through the prolonged or controlled release matrix and/or coating, erosion of the prolonged or controlled matrix and/or coating or combinations thereof.

Oral solid dosage forms may take the form of tablets, granules, multiparticulates or mini-tablets. Mini-tablets are dosage forms wich comprise pharmaceutically active agents in a prolonged release matrix with optionally a prolonged release coating disposed thereon. They take a round form with a thickness of about 1 to about 5 mm and a diameter of about 1 to 5 mm. A thickenss and diameter of about 1 to about 4 mm, of about 1 to about 3 mm and of anout 2 mm is also considered. Multiparticulate and/or mini-tablets may be filled into e.g. capsules are embedded in other excipients to form e.g. a tablet or to be filled into capsules.

In a preferred embodiment, the dosage forms for use in accordance with the invention comprise a prolonged release matrix with a controlled release coating.

The term "heat treatment" is used in the context of heat treating a prolonged release matrix formulation. The term "curing" is used in the context of heat treating a prolonged release coating formulation and relates to the effects of heat on the coalescence of the coating. If a composition comprises a prolonged release matrix and a prolonged release coating, the term "heat treatment" or "heat treated" denotes that the prolonged release matrix has been heat treated before the prolonged release coating was applied.

Pharmaceutical compositions for use in accordance with the invention, and in particular those which are oral dosage forms, may be alcohol resistant.

The term "alcohol resistance" and its grammatical variations refer to the property of pharmaceutical compositions for use according to the invention to release about the same or less amount of the pharmaceutically active agents *in vitro,* the *in vitro* release rate being tested in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 with up to 40% (v/v) ethanol using the Ph. Eur. Paddle method at 100 rpm at 37° C compared to the *in vitro* release rate being tested in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 with up to 0% (v/v) ethanol using the Ph. Eur. Paddle method at 75 or 100

rpm at 37° C. The amount of dissolution liquid and the rotational speed of the paddle apparatus may depend on the amount of active agent tested. For example, pharmaceutical compositions comprising up to 16 mg hydromorphone HCl may be tested at 75 rpm in 500 ml dissolution liquid while higher dosage strengths may be tested at 100 rpm in 900 ml dissolution liquid.

Resistance to alcohol extraction can e.g. be tested by subjecting the formulation to Simulated Gastric Fluid (SGF), pH 1.2 with 40% ethanol. A typical manner in order to obtain "500 ml of Simulated Gastric Fluid (SGF), pH 1.2 with 40% ethanol" is by mixing 600 ml of SGF with 420 ml of 95% ethanol/water (which provides 400 ml of 100% ethanol) and taking 500 ml of the mixture. The effect of the additional 20 ml of water from the 95% ethanol will be minimal in the percentages of SGF and ethanol in the 500 ml mixture.

A typical manner in order to obtain 900 ml of Simulated Gastric Fluid (SGF), pH 1.2 with 40% ethanol" is by mixing 600 ml of SGF with 420 ml of 95% ethanol/water (which provides 400 ml of 100% ethanol) and taking 900 ml of the mixture. The effect of the additional 20 ml of water from the 95% ethanol will be minimal in the percentages of SGF and ethanol in the 100 ml mixture.

In certain embodiments, the prolonged release pharmaceutical composition for use according to the present invention comprises at least two pharmaceutically active agents, namely hydromorphone and naloxone or their pharmaceutically acceptable salts and at least one prolonged release material being combined to form a prolonged release matrix; wherein the ratio of the amount of hydromorphone or a pharmaceutically acceptable salt thereof released after 0.5, 1 or 2 hours of *in vitro* dissolution of the dosage form in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 with up to 40% ethanol using the Ph. Eur. paddle method at 75 or 100 rpm at 37 C compared to the amount of hydromorphone or a pharmaceutically acceptable salt thereof released after 0.5, 1 or 2 hours *in vitro* dissolution of the dosage form in 500

or 900 ml of Simulated Gastric Fluid, pH 1.2 with 0% ethanol using the Ph. Eur. paddle method at 75 or 100 rpm at 37° C is about 2:1 or less, about 1.5:1 or less, about 1:1 or less, about 1:1.2 or less, about 1:1.4 or less, about 1:1.6 or less, about 1:1.8 or less, about 1:2 or less, about 1:2.5 or less about 1:3 or less or about 1:5 or less, and wherein the ratio of the amount of naloxone or a pharmaceutically acceptable salt thereof released after 0.5, 1 or 2 hours of *in vitro* dissolution of the dosage form in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 with up to 40% ethanol using the Ph. Eur. paddle method at 75 or 100 rpm at 37° C compared to the amount of naloxone or a pharmaceutically acceptable salt thereof after 0.5, 1 or 2 hours *in vitro* dissolution of the dosage form in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 with 0% ethanol using the Ph. Eur. paddle method at 75 or 100 rpm at 37° C is about 2:1 or less, about 1.5:1 or less, about 1:1 or less, about 1:1.2 or less, about 1:1.4 or less, about 1:1.6 or less, about 1:1.8 or less, about 1:2 or less, about 1:2.5 or less about 1:3 or less or about 1:5 or less. Preferably, the ratio is about 1:1 or less such as 1:1.5 or 1:2 for hydromorphone and/or naloxone.

The present invention as disclosed herein with respect to all embodiments is meant to encompass the use of any pharmaceutically acceptable salt of hydromorphone and naloxone. Any embodiment of the invention referring to hydromorphone and naloxone is also meant to refer to salts and preferably the hydrochloride salts thereof unless indicated otherwise.

Pharmaceutically acceptable salts include, but are not limited to, inorganic acid salts such as hydrochloride, hydrobromide, sulfate or phosphate; organic acid salts such as formate, acetate, trifluoroacetate, maleate or tartrate; sulfonates such as methanesulfonate, benzenesulfonate or p-toluenesulfonate; amino acid salts such as arginate, asparginate or glutamate, and metal salts such as sodium salt, potassium salt or cesium salt; alkaline earth metals such as calcium salt or magnesium salt; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt or N,N'-dibenzylethylenediamine salt.

If in the following reference is made to a pharmaceutically active agent such as hydromorphone, this always also includes the reference to a pharmaceutically acceptable salt of the free base of this pharmaceutically active agent unless it is specifically indicated that the reference to the pharmaceutically active agent, such as use of the term "hydromorphone" should only refer to the free base.

The use of the hydrochloride salts of both hydromorphone and naloxone can be preferred.

In a preferred embodiment, the pharmaceutical dosage forms comprise hydromorphone or a pharmaceutically acceptable salt thereof or naloxone or a pharmaceutically acceptable salt thereof as the sole pharmaceutically active agents.

The pharmaceutical compositions may comprise about 1 to about 64 mg such as about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 12 mg, about 16 mg, about 24 mg, about 32 mg, about 40 mg, about 48 mg or about 64 mg hydromorphone hydrochloride or equimolar amounts of any other pharmaceutically acceptable salt or hydrates and solvates or of the free base. Where reference is made to amounts of hydromorphone hydrochloride this relates to anhydrous hydromorphone hydrochloride. If a hydrated version of hydromorphone hydrochloride is used, this will be used in an amount equivalent to the afore-mentioned amounts of anhydrous hydromorphone hydrochloride.

The pharmaceutical compositions may comprise about 1 to about 256 mg, such as about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 12 mg, about 16 mg, about 24 mg, about 32 mg, about 48 mg, about 64 mg, about 96 mg, about 128 or about 256 mg of naloxone hydrochloride or equimolar amounts of any other pharmaceutically acceptable salt or hydrates and solvates or of the free base. Where reference is made to amounts of naloxone hydrochloride this relates to anhydrous

naloxone hydrochloride. If a hydrated version of naloxone hydrochloride is used, this will be used in an amount equivalent to the afore-mentioned amounts of anhydrous naloxone hydrochloride.

In some embodiments, the prolonged release pharmaceutical composition for use according to the present invention comprises at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof and at least one prolonged release material which is preferably combined with these pharmaceutically active agents to form a prolonged release matrix; wherein the amount of hydromorphone or a pharmaceutically acceptable salt thereof and/or naloxone or a pharmaceutically acceptable salt thereof released *in vitro* in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 using the Ph. Eur. paddle method at 100 rpm at 37° C is:

at 1 h:	25 to 55% by weight of the pharmaceutically active agents,
at 2 h:	45 to 75% by weight of the pharmaceutically active agents,
at 3 h:	55 to 85% by weight of the pharmaceutically active agents,
at 4 h:	60 to 90% by weight of the pharmaceutically active agents,
at 6 h:	70 to 100% by weight of the pharmaceutically active agents,
at 8 h:	more than 85% by weight of the pharmaceutically active agents,
at 10 h:	more than 90% by weight of the pharmaceutically active agents.

The pharmaceutically active agents may preferably be hydromorphone HCl and naloxone HCl. The prolonged release pharmaceutical composition may comprise these actives in the above indicated amounts and weight ratio of about 2:1, about 1:1, about 1:2 or about 1:3. The composition may be alcohol resistant as described hereinafter.

In some embodiments, the prolonged release pharmaceutical composition for use according to the present invention comprises at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof and at least one prolonged release material which is preferably combined with these pharmaceutically active agents to form a prolonged release matrix; wherein the amount of hydromorphone and/or a pharmaceutically acceptable salt thereof or naloxone or a pharmaceutically acceptable salt thereof released *in vitro* in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 using the Ph. Eur. paddle method at 100 rpm at 37° C is:

at 1 h:	30 to 50% by weight of the pharmaceutically active agents,
at 2 h:	50 to 70% by weight of the pharmaceutically active agents,
at 3 h:	60 to 80% by weight of the pharmaceutically active agents,
at 4 h:	65 to 85% by weight of the pharmaceutically active agents,
at 6 h:	75 to 95% by weight of the pharmaceutically active agents,
at 8 h:	more than 90% by weight of the pharmaceutically active agents,
at 10 h:	more than 95% by weight of the pharmaceutically active agents.

The pharmaceutically active agents may preferably be hydromorphone HCl and naloxone HCl. The prolonged release pharmaceutical composition may comprise these actives in the above indicated amounts and weight ratio of about 2:1, about 1:1, about 1:2 or about 1:3. The composition may be alcohol resistant as described hereinafter.

In some embodiments, the prolonged release pharmaceutical composition for use according to the present invention comprises at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof and at least one prolonged release material which is preferably

combined with these pharmaceutically active agents to form a prolonged release matrix; wherein the amount of hydromorphone or a pharmaceutically acceptable salt thereof and/or naloxone or a pharmaceutically acceptable salt thereof released *in vitro* in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 using the Ph. Eur. paddle method at 100 rpm at 37° C is:

at 1 h:	10 to 30% by weight of the pharmaceutically active agents,
at 2 h:	34 to 54% by weight of the pharmaceutically active agents,
at 3 h:	53 to 73% by weight of the pharmaceutically active agents,
at 4 h:	65 to 85% by weight of the pharmaceutically active agents,
at 6 h:	75 to 95% by weight of the pharmaceutically active agents,
at 8 h:	80 to 100% by weight of the pharmaceutically active agents,
at 10 h:	more than 90% by weight of the pharmaceutically active agents.

The pharmaceutically active agents may preferably be hydromorphone HCl and naloxone HCl. The prolonged release pharmaceutical composition may comprise these actives in the above indicated amounts and weight ratio of about 2:1, about 1:1, about 1:2 or about 1:3. The composition may be alcohol resistant as described hereinafter.

In some embodiments, the prolonged release pharmaceutical composition for use according to the present invention comprises at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof and at least one prolonged release material which is preferably combined with these pharmaceutically active agents to form a prolonged release matrix; wherein the amount of hydromorphone or a pharmaceutically acceptable salt thereof and/or naloxone or a pharmaceutically acceptable salt thereof released *in vitro* in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 using the Ph. Eur. paddle method at 100 rpm at 37° C is:

at 1 h:	5 to 45% by weight of the pharmaceutically active agents,

at 2 h:	15 to 55% by weight of the pharmaceutically active agents,
at 3 h:	30 to 70% by weight of the pharmaceutically active agents,
at 4 h:	35 to 75% by weight of the pharmaceutically active agents,
at 6 h:	40 to 80% by weight of the pharmaceutically active agents,
at 8 h:	50 to 90% by weight of the pharmaceutically active agents,
at 10 h:	60 to 100% by weight of the pharmaceutically active agents,
at 12 h:	65 to 100% by weight of the pharmaceutically active agents.

The pharmaceutically active agents may preferably be hydromorphone HCl and naloxone HCl. The prolonged release pharmaceutical composition may comprise these actives in the above indicated amounts and weight ratio of about 2:1, about 1:1, about 1:2 or about 1:3. The composition may be alcohol resistant as described hereinafter.

Preferably, the amount of the pharmaceutically active agents released *in vitro* in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 using the Ph. Eur. paddle method at 100 rpm at 37° C is:

at 1 h:	8 to 42% by weight of the pharmaceutically active agents,
at 2 h:	18 to 52% by weight of the pharmaceutically active agents,
at 3 h:	33 to 67% by weight of the pharmaceutically active agents,
at 4 h:	38 to 72% by weight of the pharmaceutically active agents,
at 6 h:	43 to 77% by weight of the pharmaceutically active agents,
at 8 h:	53 to 87% by weight of the pharmaceutically active agents,
at 10 h:	63 to 97% by weight of the pharmaceutically active agents,
at 12 h:	73 to 100% by weight of the pharmaceutically active agents.

The pharmaceutically active agents may preferably be hydromorphone HCl and naloxone HCl. The prolonged release pharmaceutical composition may comprise these actives in the above indicated amounts and weight ratio of about 2:1, about 1:1,

about 1:2 or about 1:3. The composition may be alcohol resistant as described hereinafter.

More preferably, the amount of the pharmaceutically active agents released *in vitro* in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 using the Ph. Eur. paddle method at 100 rpm at 37° C is:

at 1 h:	15 to 37% by weight of the pharmaceutically active agents,
at 2 h:	25 to 47% by weight of the pharmaceutically active agents,
at 3 h:	38 to 62% by weight of the pharmaceutically active agents,
at 4 h:	42 to 66% by weight of the pharmaceutically active agents,
at 6 h:	50 to 74% by weight of the pharmaceutically active agents,
at 8 h:	60 to 84% by weight of the pharmaceutically active agents,
at 10 h:	68 to 92% by weight of the pharmaceutically active agents,
at 12 h:	78 to 100% by weight of the pharmaceutically active agents.

The pharmaceutically active agents may preferably be hydromorphone HCl and naloxone HCl. The prolonged release pharmaceutical composition may comprise these actives in the above indicated amounts and weight ratio of about 2:1, about 1:1, about 1:2 or about 1:3. The composition may be alcohol resistant as described hereinafter.

Even more preferably, the amount of the pharmaceutically active agents released *in vitro* in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 using the Ph. Eur. paddle method at 100 rpm at 37° C is:

at 1 h:	19 to 33% by weight of the pharmaceutically active agents,
at 2 h:	29 to 43% by weight of the pharmaceutically active agents,
at 3 h:	43 to 47% by weight of the pharmaceutically active agents,
at 4 h:	47 to 61% by weight of the pharmaceutically active agents,
at 6 h:	55 to 69% by weight of the pharmaceutically active agents,
at 8 h:	65 to 79% by weight of the pharmaceutically active agents,

at 10 h:	73 to 87% by weight of the pharmaceutically active agents,
at 12 h:	83 to 100% by weight of the pharmaceutically active agents.

The pharmaceutically active agents may preferably be hydromorphone HCl and naloxone HCl. The prolonged release pharmaceutical composition may comprise these actives in the above indicated amounts and weight ratio of about 2:1, about 1:1, about 1:2 or about 1:3. The composition may be alcohol resistant as described hereinafter.

As mentioned above, the present invention relates to an oral prolonged release pharmaceutical composition comprising at least:

a) at least one prolonged release material;

b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof with hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof being present in the pharmaceutical composition in a weight ratio range of 2:1 to 1:3;

for use in the treatment of moderate to severe pain, thereby beneficially influencing hydromorphone-induced constipation.

Storage under stressed conditions means that a pharmaceutical composition is subjected to increased temperature and/or relative humidity (RH) for prolonged periods of time. For example, typical stressed conditions refer to storage over at least one, two, three, four, five, six, twelth or eigtheen months at 25°C and 60% RH. Other stressed conditions refer to storage over at least one, two, three, four, five, six or twelth months at 30°C and 65% RH Other stressed conditions refer to storage over at least one, two, three, four, five or six months at 40°C and 75% RH.

Such stressed storage conditions are used to determine whether a pharmaceutical composition has a shelf life sufficient for long time storage under conditions as they are common in patients' households without negative effects on its safety and efficacy. Such negative effects may include that the in-vitro release rates change over time so that the efficacy of the composition is affected as different amounts of actives are released after administration. Similarly, negative effects may also result from degradation of the pharmaceutically active agents which may either decrease the overall amount of functional pharmaceutically active agent or lead to formation of toxic by-products.

If changes in the in vitro release profile or with respect to the amount of the active agent(s) of a pharmaceutical composition are observed after storage under stressed conditions, this may be indicative of stability problems. If such changes are not observed, this means vice versa that the pharmaceutical composition is storage stable.

The above mentioned stressed storage conditions can be used to estimate whether a pharmaceutical dosage will have a shelf life of at least about 12 months, at least about 18 months, at least about 24 months or at least about 36 months. Usually a shelf life of 18 months or more may be desirable as this is usually better compatible with e.g. supply of excipients, actives etc. for manufacturing purposes. If a pharmaceutical composition is storage stable, i.e. has essentially the same release rate after storage over at least one, two, three, four, five or more months at 25°C and 60% RH, this will be usually indicative of shelf life of at least about 12 months. If a pharmaceutical composition is storage stable, i.e. has essentially the same release rate after storage over at least one, two, three, four, five or more months at 30°C and 65% RH, this will be usually indicative of shelf life of at least about 18 months. If a pharmaceutical composition is storage stable, i.e. has essentially the same release rate after storage over at least one, two, three, four, five or more months at 40°C and

75% RH, this will be usually indicative of a shelf life of at least about 24 months such as 36 months.

The term "substantially the same release rate" refers to the situation where the in vitro release rate for a pharmaceutical composition which has been subjected to stressed conditions is compared to a reference composition. The reference composition is an identical pharmaceutical composition which, however, has not been subjected to stressed conditions. If the in vitro release profile of the composition subjected to stressed conditions does not deviate by more than about 20%, preferably by no more than about 15%, more preferably by no more than 10% and even more preferably by no more than about 5% from the in vitro release profile of the reference composition, the in-vitro release rate is considered to be substantially the same.

The term "hydromorphone and/or naloxone related substances" or the like refers to substances that arise from chemical reactions of hydromorphone or naloxone, pharmaceutically acceptable salts thereof such as e.g. degradation. These substances can be distinguished as known hydromorphone-related substances where the identity of the substance and its origin is known, as known naloxone-related substances where the identity of the substance and its origin is known, and as unknown substances. For unknown substances, their identity is not known. However, it is assumed that they arise from hydromorphone and/or naloxone, pharmaceutically acceptable salts thereof. It is to be understood that the term "hydromorphone and naloxone related substances" includes the sum of known hydromorphone related substances, known naloxone related substances and unknown substances and is thus equivalent to the term "total hydromorphone and naloxone related substances".

Terms like "less than about 4 % of substances related to hydromorphone and naloxone, or to pharmaceutically acceptable salts thereof " or "less than about 3 % of substances related to hydromorphone and naloxone or to pharmaceutically acceptable

salts thereof" etc. indicate that the amount of total substances as described in the preceding paragraph is less than e.g. 4% or 3% by weight based on the total amount of the active ingredient which is present in lower amounts (i.e. hydromorphone or naloxone), or a pharmaceutically acceptable salt thereof which is present in the pharmaceutical composition in the lower amount. Thus, if a pharmaceutical composition comprises hydromorphone HCl and naloxone HCl in 1:2 ratio by weight, the amount of total substances is calculated from the sum of known hydromorphone HCl related substances, known naloxone HCl related substances and unknown substances which is then referenced to the amount of hydromorphone HCl. If a pharmaceutical composition comprises hydromorphone HCl and naloxone HCl in 2:1 ratio by weight, the amount of total substances is calculated from the sum of known hydromorphone HCl related substances, known naloxone HCl related substances and unknown substances which is then referenced to the amount of naloxone HCl.

"Known hydromorphone related substances" include hydromorphone n-oxide, noroxymorphone and pseudohydromorphone.

"Known naloxone related substances" include noroxymorphon, 10a-hydroxynaloxon, 7,8-didehydronaloxon, pseudonaloxon and 3-o-allylnaloxon.

Terms like "less than 4 % of known substances related to hydromorphone, or to pharmaceutically acceptable salts thereof " or "less than 3 % of known substances related to hydromorphone, or to pharmaceutically acceptable salts thereof" etc. indicate that the amount of known hydromorphone related substances is less than e.g. 4% or 3% of known hydromorphone related substance by weight based on the total amount of hydromorphone, or a pharmaceutically acceptable salt thereof in the composition.

Terms like "less than 4 % of known substances related to naloxone, or to pharmaceutically acceptable salts thereof" or "less than 3 % of known substances related to naloxone, or to pharmaceutically acceptable salts thereof" etc. indicate that the amount of known naloxone related substances is less than e.g. 4% or 3.0% of known naloxone related substance by weight based on the total amount of naloxone, or a pharmaceutically acceptable salt thereof in the composition.

In order to assess stability one may subject a pharmaceutical composition to stressed conditions as mentioned above and determine the amount of total hydromorphone and/or naloxone related substances. One then determines the amount of total hydromorphone and/or naloxone related substances for an identical pharmaceutical composition which has not been subjected to stressed conditions. This composition is considered to be a reference composition. The detection of " total hydromorphone related and/or naloxone substances" is typically performed by HPLC analysis using e.g. CAT columns. The amount of the substances including the amount of unknown substances is then determined by calculating the area under the respective peaks in the chromatogram. The identity of substances can be determined by doing the same analysis with pure known reference substances. Preferably, the pharmaceutical compositions for use according to the present invention after storage under stressed conditions have less than 4 %, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.2% or even less than 0.1% of total substances related to hydromorphone or a pharmaceutically acceptable salt thereof and/or related to naloxone or a pharmaceutically acceptable salt thereof.

Preferably, the pharmaceutical compositions for use according to the present invention after storage under stressed conditions have less than 1 % such as less than 0.5%, less than 0.4%, less than 0.3%, less than 0.2%, less than 0.1% or even less than 0.05% of known substances related to hydromorphone or a pharmaceutically acceptable salt thereof and less than 1% such as less than 0.5% of known substances related to naloxone or a pharmaceutically acceptable salt thereof.

Stressed storage conditions may be the same as mentioned above. Thus typical stressed conditions may refer to storage over at least one, two, three, four, five or six months at 25°C and 60% RH, at 30°C and 65% RH or at 40°C and 75% RH.

A pharmaceutical composition will thus be considered to be stable if after subjecting it to stressed conditions, it has no more than about 4% such as no more than about 3%, preferably no more than about 2%, more preferably no more than about 1% and even more preferably no more than about 0.5% of hydromorphone and/or naloxone related substances.

It will be described below how stable prolonged release pharmaceutical compositions of hydromorphone and naloxone for use according to the present invention can be manufactured. It will be apparent from this description that selection of anhydrous diluents and the choice of lubricant may be a means to positively influence stability. Heat treatment may improve physical stability such as robustness and hardness.

The prolonged release coating may either be disposed on each prolonged release matrix if the prolonged release matrix is manufactured in the form of multi-particulates such as granules or it may be disposed on the formulation comprising the prolonged release matrix if e.g. prolonged release matrix multi-particulates such as granules are compressed into a tablet. The coating will then be disposed on the monolithic formulation.

The above heat treated pharmaceutical compositions may be preferably provided in the form of multiparticulates or mini-tablets that are filled into capsules.

Heat treatment may be performed such that the hardness/breaking strength of the pharmaceutical composition is increased for the heat treated versus the non heat treated composition. By heat treating pharmaceutical compositions for use in

accordance with the invention, one may thus obtain compositions with improved hardness/breaking strength proportional to the tablet weight, size and shape. Heat treatment may improve physical stability such as robustness and hardness and in some although not all cases also positively influence chemical stability As will be shown below, heat treatment may have an effect on *in vitro* release properties. Thus, heat treatment may further decrease the *in vitro* release compared to a non-heat treated composition. However, after heat treatment for relatively short periods of time (e.g. 30 min at 55°C) the *in vitro* release rate will not change any further upon further heat treatment, i.e. remains substantially the same. It is further observed that such heat treated compositions when being subjected to stressed conditions will have substantially the same *in vitro* release rate as the same heat treated composition which has not been subjected to stressed conditions. Similarly such heat treated compositions will have less than about 4% of total hydromorphone and/or naloxone related substances and less than about 1% of known hydromorphone or known naloxone-related substance upon storage under stressed conditions.

Heat treatment will positively effect physical stability as can be deduced from a reduced occurrence of e.g. cracks and improved intactness of the formulation. This should help to ensure a reproducible release behavior also in vivo settings as changes due to e.g. an altered surface which occure as a consequence of cracks will be minimized. Further, heat treatment in general improves the hardness of the formulation in case of a prolonged release matrix formulation by usually about 3 to about 7 kP such as about 6 kP to an overall value of about 10 to 15 about kP such as about 11 kP. Hardness is usually tested using a mechanical strength tester such as a Holland C50 tablet hardness tester. 10 tablets are tested to provide a mean value every 15-20 mins during the compression run.

The term "heat treatment" refers to a thermal treatment under either or both increased temperature for a prolonged period of time. Typically, heat treatment takes place at a temperature in the range of about 30°C to about 95°C and for a time in the range of

about 10 min to about 3 hours. Typically heat treatment conditions may thus be treatment for at least about 15 min, at least about 30 min, at least about 45 min, at least about 60 min, at least about 75 min, at least about 90 min, at least about 120 min, at least about 150 min, at least about 180 min or at least about 240 min at about at least 30°C, at about at least 40°C, at about at least 50°C, at about at least 60°C or at about at least 80°C at ambient humidity. Heat treatment conditions may be selected according to the specific prolonged release matrix materials being used. In general the temperature will be around the melting and/or softening temperature of the prolonged release matrix materials being used. Such conditions may thus ensure that the prolonged release matrix materials are sufficiently soft to mobilise and to fill pores in the prolonged release matrix and/or e.g. compressed granules. In case of formulations using e.g. hydrophobic polymers such as ethyl cellulose and fatty alcohols such as stearyl or cetostearyl alcohol, a temperature of about 55°C may be appropriate. In general, heat treatment for at least 30 min at 55°C may be sufficient to ensure physical stability.

Heat treatment can be performed in a convection oven, in an open oven, under vacuum, or in a coating drum using conventional heat, microwave and any other sources of heat. Heat treatment in a coating drum can be preferred. If the pharmaceutical compositions comprise a prolonged release coating either alone or in addition to a controlled release matrix, heat treatment of such prolonged release coatings is also designated as curing which helps coalescence of e.g. polymer coatings.

Prolonged release pharmaceutical compositions for use in accordance with the invention may comprise a prolonged release matrix and/or coating which ensures prolonged release of the active ingredients and/or they may alternatively rely on a coating for imparting controlled release properties. In case of a prolonged release coating, the actives may be disposed on bead-like structures such as non pareil beads or granules or they may be incorporated into extruded granules or spheroids which as

such do not provide prolonged release. The prolonged release coating is then layered thereon.

If a prolonged release coating is used it may be layered on individual prolonged release matrices such as granules or mini-tablets or it may layered on a monolithic formulation such as tablets or mini-tablets which are obtained by compressing prolonged release matrix granules.

If a prolonged release coating is used the prolonged release composition may be optionally cured in order to enhance coalescence of the coating and thus to improve stability and intactness of the coating. The curing conditions may be the same as described above for coatings. Curing can further slow down the release properties. A curing step of about 20 minutes to 30 minutes at about 50° to 100° may be sufficient to slow down the release such that it won`t substantially changes after storage under stressed conditions as the coating's properties will not substantially change anymore.

Pharmaceutical compositions for use in accordance with the invention may also comprise a prolonged release matrix with one or more prolonged release coatings thereon.

In addition prolonged release compositions comprising a prolonged release matrix or prolonged release coating may comprise e.g. a fraction of at least one or both of the pharmaceutically active agents in immediate release form. Such an immediate release phase which may account for up to 30% of the overall amount of the pharmaceutically active agent(s) being present in the composition can ensure an early onset of therapeutic efficacy.

The prolonged release compositions for use in accordance with the invention may be formulated into different dosage forms. For example, prolonged release compositions

may take the form of tablets or mini-tablets. Tablets may be a monolithic tablet comprising e.g. a continuous prolonged release matrix. However, tablets or mini-tablets may be also be made from multiparticulates which are compressed into tablets. Such multiparticulates may e.g. comprise a prolonged release matrix optionally with an immediate release phase or active loaded beads with a prolonged release coating and optionally an immediate release phase thereon. The dosage form may also take the form of such multiparticulates, e.g. granules or mini-tablets which may be filled into a capsule.

The *in vitro* release rates of the prolonged release pharmaceutical compositions will be chosen such that a therapeutic efficacy in vivo is achieved over preferably at least twelve hours and in some instance even up to twenty four hours. Such compositions may be described as "twice a day" or "once a day" formulations as they may be administered on such a regimen.

A preferred embodiment of all embodiments as described above, the pharmaceutical compositions for use according to the invention may comprise a prolonged release matrix and a prolonged release coating. These pharmaceutical compositions may comprise hydromorphone and naloxone or the pharmaceutically acceptable salts thereof in the above mentioned ratios and amounts. In the embodiments described above, hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof may thus be combined with a prolonged release material such that a prolonged release matrix is formed on which a prolonged release coating is then disposed. The prolonged release coating may be disposed on individual prolonged release matrix formulations so that a multiparticulate formulation is obtained. These multi-particulates may be directly filled into capsules or blended with other excipients to obtain a dosage form. In other embodiments, the prolonged release matrix formulation may take the form of e.g. granules which are compressed into mini-tablets or a monolithic dosage from such as tablets on which the prolonged release coating is then disposed. The manufacture of the prolonged

release matrix may preferably be undertaken using an anhydrous method as described below. Manufacturing a prolonged release matrix in an anhydrous manner will have a beneficial effect on chemical stability as expressed e.g. by a substantially same in vitro release profile after storage under stressed conditions. Heat treatment will beneficially influence physical stability. A multiparticulate nature may have positive effects of food effects upon administration.

The prolonged release material may be any material that is known to be capable of imparting controlled release properties on the active agent when being formulated into a prolonged release matrix.

Such materials may be hydrophilic and/or hydrophobic materials such as gums, cellulose ethers, acrylic polymers, or protein-derived materials.

Prolonged materials may also include fatty acids, fatty alcohols, glyceryl esters of fatty acids, polyethylene glycols, mineral and oils and waxes. Fatty acids and fatty alcohols preferable are those with a C_{10} to C_{30} chain, preferably with a C_{12} to C_{24} chain and more preferably with a C_{14} to C_{20} chain or a C_{16} to C_{20} chain. Materials such as stearyl alcohol, cetostearyl alcohol, cetyl alcohol, myristyl alcohol and polyalkylene glycols may be preferred. Waxes may be selected from natural and synthetic waxes such as beeswax, carnauba wax. Oils may be vegetable oils and include for example castor oil.

The prolonged release matrix materials which may be considered in the context of the present invention may also be selected from cellulose ethers.

The term "cellulose ethers" comprises cellulose-derived polymers derivatized with at least alkyl and/or hydroxyalkyl groups which may be hydrophilic or hydrophobic.

For example, the prolonged release matrix material may be a hydrophilic hydroxy alkyl cellulose such as a hydroxy (C1 – C6) alkyl celluloses such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose and particularly preferably hydroxyethyl cellulose.

Examples of hydrophobic cellulose ethers include e.g. ethyl cellulose. The use of ethyl cellulose may be preferred. Hydrophobic cellulose ethers such as ethyl cellulose may be particularly suitable for imparting alcohol resistance to pharmaceutical compositions.

A particularly suitable material for prolonged release matrix formulations in accordance with the present invention may be selected from the group of acrylic resins. Such acrylic resins may be made from (meth)acrylic acid (co) polymers.

There are various types of (meth)acrylic acid (co)polymers available which may be characterised according to the nature of their residues such as neutral (meth)acrylic acid (co)polymers, (meth)acrylic acid (co)polymers with anionic residues or (meth)acrylic acid ester copolymers with cationic residues.

Neutral (meth)acrylic acid (co)polymers include polymers having 95 to 100% by weight of polymerised monomers having neutral residues. Monomers with neutral residues can be C_1-C_4 alkyl esters of acrylic or methacrylic acid such as methylmethacrylate, ethylmethacrylate, butylmethacrylate, methylacrylate, ethylacrylate and butylacrylate. For example, neutral (meth)acrylic acid (co)polymers may comprise 20 to 40 % by weight ethylacrylate and 60 to 80 % by weight methylmethacrylate. Such polymers are e.g. available under the trade name Eudragit® NE which is a copolymer of 30 % by weight ethylacrylate and 70 % by weight methylmethacrylate. This polymer is usually provided in the form of a 30 % or 40% aqueous dispersion (Eudragit® NE 30 D, Eudragit® NE 40 D or Eudragit® NM 30 D).

(Meth)acrylic acid (co)polymers with functional anionic residues may be (meth)acrylic acid (co)polymers having 25 to 95 % by weight of radically polymerised C_1 to C_4 alkyl esters of acrylic or methacrylic acid and 5 to 75 % by weight of methacrylate monomers with an anionic group in the alkyl residue. C_1 to C_4 alkyl esters of acrylic or methacrylic acid are again methylmethacrylate, ethyl methacrylate, butylmethacrylate, methylacrylate, ethylacrylate and butylacrylate. A (meth)acrylate monomer with an anionic group in the alkyl residue may be for example acrylic acid and preferably methacrylic acid. Such methacrylic acid copolymers with an anionic functional group may comprise e.g. 40 to 60 % by weight methacrylic acid and 60 to 40 % by weight methylmethacrylate or 60 to 40 % by weight ethyl acrylate. These types of polymers are available as Eudragit® L100 / Eudragit® L 12.5 or Eudragit® L 100-55 / Eudragit® L 30 D-55, respectively.

For example, Eudragit® L 100 is a copolymer of 50 % by weight methylmethacrylate and 50 % by weight methacrylic acid. It is also provided as a 12.5% solution (Eudragit® L 12.5). Eudragit® L 100-55 is a copolymer of 50 % by weight ethylacrylate and 50 % by weight methacrylic acid. It is also provided as 30 % dispersion (Eudragit® L 30 D-55).

(Meth)acrylic acid (co)polymers with an anionic functional group may also comprise 20 to 40 % by weight methacrylic acid and 80 to 60 % by weight methylmethacrylate. These types of polymers are usually available under the trade name Eudragit® S. It is also provided as a 12.5 % solution (Eudragit® S 12.5). Another type of methacrylic acid copolymers with an anionic functional group is available under the trade name Eudragit® FS which typically comprises 10 to 30 % by weight methylmethacrylate, 50 to 70 % by weight methylacrylate and 5 to 15 % by weight methacrylic acid. Thus, Eudragit®FS may be a polymer of 25 % by weight methylmethacrylate, 65 % by weight methylacrylate and 10 % by weight methacrylic acid. It is usually provided as 30 % dispersion (Eudragit® FS 30 D).

(Meth)acrylic acid (co)polymers with functional cationic groups may be methacrylic acid copolymers with tertiary amino groups. Such polymers may comprise 30 % to 80 % by weight of radically polymerised C_1-C_4 alkyl esters of acrylic acid or methacrylic acid and 70 to 20 % by weight methacrylate monomers with a tertiary amino group in the alkyl rest.

Suitable monomers with a functional tertiary amino group are disclosed e.g. in US 4,705,695, column 3, line 64 to column 4, line 13. They include for example dimethylaminoethyl acrylate, 2-dimethylaminopropyl acrylate, dimethylaminopropyl methacrylate, dimethylaminobenzyl acrylate, dimethylaminobenzyl methacrylate, (3-dimethylamino-2,2-dimethyl)propyl acrylate, dimethylamino-2,2-dimethylpropylmethacrylate, (3-diethylamino-2,2-dimethyl)propyl acrylate and diethylamino-2,2-dimethylpropylmethacrylate. Particularly suitable is dimethylaminoethyl methacrylate. The amount of monomers with a tertiary amino group in the copolymer may vary between 20 to 70 %, between 40 to 60 %. The amount of C_1 to C_4 alkyl esters of acrylic or methacrylic acid may be within 70 to 30 % by weight. C_1 to C_4 alcohol esters of acrylic or methacrylic acid include methylmethacrylate, ethylmethacrylate, butylmethacrylate, methylacrylate, ethylacrylate and butylacrylate. A common (meth)acrylic acid (co)polymer with a tertiary amino group may comprise 20 to 30 % by weight methylmethacrylate, 20 to 30 % by weight butylmethacrylate and 60 to 40 % by weight dimethylaminoethyl methacrylate. For example the commercially available Eudragit® E 100 comprises 25 % by weight methylmethacrylate, 25 % by weight butylmethacrylate and 50 % by weight dimethylaminoethyl methacrylate. Another common commercially available polymer, Eudragit®E PO comprises copolymers of methylmethacrylate, butylmethacrylate and dimethylaminoethyl methacrylate in a ratio of 25:25:50.

Another type of (meth)acrylic acid (co)polymers with functional cationic groups is (meth)acrylic acid (co)polymers with a quaternary amino group. This type of

(meth)acrylic acid (co)polymers typically comprises 50 to 70 % of radically polymerised methylmethacrylate, 20 to 40 % by weight of ethylacrylate and 12 to 2 % by weight of 2-trimethylammoniumethyl methacrylate chloride. Such polymers are e.g. available under the trade names Eudragit®RS or Eudragit®RL.

For example, Eudragit®RS comprises radically polymerised units of 65 % by weight methylmethacrylate, 30 % by weight ethylacrylate and 5 % by weight 2-trimethylamoniumethyl methacrylate chloride. Eudragit®RL comprises radically polymerised units of 60 % by weight methylmethacrylate, 30 % by weight ethylacrylate and 10 % by weight 2-trimethylamoniumethyl methacrylate chloride.

Prolonged release matrix materials which are particularly suitable for the present invention are e.g. the neutral (meth)acrylic acid (co)polymers or the (meth)acrylic acid (co)polymers with anionic functional groups. One may for example use mixtures of these types of polymers.

For example, one may use Eudragit®NE as a neutral (meth)acrylic acid (co)polymer and Eudragit®RSPO as a (meth)acrylic acid (co)polymer with an anionic functional group. One may also use a mixture of these types of polymers.

However, one may also use a mixture of (meth)acrylic acid (co)polymers and other prolonged release matrix materials such as cellulose ethers. For example, one may use a mixture of a neutral (meth)acrylic acid (co)polymer and a hydrophobic cellulose ether. A particularly suitable example is the combination of a Eudragit®NE together with ethyl cellulose. Another prolonged release material which may be used for the present invention may be polymers such as polyethylene oxide.

As regards polyethylene oxides, particularly those polyethylene oxides with a molecular weight in the range of 1×10^5 - 5×10^5 may be used.

Prolonged release materials which are particularly suitable for the present invention are e.g. the neutral (meth)acrylic acid (co)polymers or the (meth)acrylic acid (co)polymers with anionic functional groups. One may for example use mixtures of these types of polymers.

For example, one may use Eudragit®NE as a neutral (meth)acrylic acid (co)polymer and Eudragit®RSPO as a (meth)acrylic acid (co)polymer with an anionic functional group. One may also use a mixture of these types of polymers.

The use of (meth)acrylic acid (co)polymers can be particularly suitable for increasing hardness/breaking strength upon heat treatment.

However, one may also use a mixture of (meth)acrylic acid (co)polymers and other prolonged release matrix materials such as cellulose ethers. For example, one may use a mixture of a neutral (meth)acrylic acid (co)polymer and a hydrophobic cellulose ether. A particularly suitable example is the combination of a Eudragit®NE together with ethyl cellulose. Another example is a mixture of cellulose ether such as hydrophobic cellulose ethers (e.g. ethyl cellulose) with a fatty alcohol (e.g. stearyl alcohol). A mixture of (meth)acrylic acid (co)polymers such as neutral (meth)acrylic acid (co)polymer (e.g. Eudragit®NE) and cellulose ethers such as hydrophobic cellulose ethers (e.g. ethyl cellulose) may also comprise a fatty alcohol (such as stearyl or cetostearyl alcohol) as a further prolonged release matrix material. Such mixtures may allow combining beneficial characteristics such as alcohol resistance and increased hardness and improved stability upon heat treatment.

The amount of prolonged release material(s) in the prolonged release formulation may be of about 5 to 90 % by weight, of about 10 to 70% by weight, of about 20 to 60 % by weight, of about 20% to about 55% by weight, of about 25% to about 50% by weight, of about 25% to about 45% by weight and preferably of about 30 to about

40% by weight based on the weight of the pharmaceutical composition. The amount of prolonged release material that is incorporated into the composition can be one way of adjusting the prolonged release properties. For example, if the amount of prolonged release material is increased, the release can be further prolonged. The aforementioned amounts refer to the overall content of prolonged release materials in a pharmaceutical composition. These amounts may thus refer to a mixture of various prolonged release materials such as a neutral (meth)acrylic acid (co)polymer, a hydrophobic cellulose ether and/or a fatty alcohol.

If cellulose ether is among the prolonged release materials, it will typically be present in an amount of about 5% to about 50% by weight, of about 5% to about 45% by weight, of about 5% to about 40% by weight, of about 5% to about 35% by weight, of about 5% to about 30% by weight, of about 5% to about 25% by weight, of about 5% to about 20% by weight such as of about 5% by weight, of about 7% by weight, of about 10% by weight, of about 15% by weight, of about 18% by weight or of about 20% by weight based on the weight of the pharmaceutical composition.

If fatty alcohol is among the prolonged release materials, it will typically be present in an amount of about 5% to about 50% by weight, of about 5% to about 45% by weight, of about 5% to about 40% by weight, of about 5% to about 35% by weight, of about 10% to about 30% by weight, of about 10% to about 25% by weight such as of about 10% by weight, of about 15% by weight, of about 20% by weight or about 25% by weight based on the weight of the pharmaceutical composition.

If (meth)acrylic acid (co)polymer is among the prolonged release materials, it will typically be present in an amount of about 5% to about 50% by weight, of about 5% to about 45% by weight, of about 5% to about 40% by weight, of about 5% to about 35% by weight, of about 10% to about 30% by weight, of about 10% to about 25% by weight such as of about 10% by weight, of about 15% by weight, of about 20% by

weight or about 25% by weight based on the weight of the pharmaceutical composition.

The pharmaceutical compositions in accordance with the invention may also include pharmaceutically acceptable excipients such fillers, lubricants, binders, release rate modifiers, or anti-tacking agents.

Fillers which may also be designated as diluents may include e.g. lactose, preferably anhydrous lactose, glucose or saccharose, starches, their hydrolysates, microcrystalline cellulose, cellatose, sugar alcohols such as sorbitol or mannitol, polysoluble calcium salts like calcium hydrogen phosphate, dicalcium- or tricalcium phosphate and combinations of two or more of the above fillers.

It has been observed that the combination of hydromorphone and naloxone can be moisture sensitive in particular if cellulose ethers are used as prolonged release material. In view of this situation it can be preferred to use fillers which do not import moisture e.g. in the form of water. In preferred embodiments one may thus use anhydrous fillers such as anhydrous lactose.

Lubricants can include highly dispersed silica, talcum, corn starch, magnesium oxide and magnesium- or calcium stearate, fats like hydrated castor oil, sodium stearyl fumarate and combinations of two or more of the above lubricants.

It can be preferred to use a combination of magnesium stearate and talcum as lubricants. It has been found that if appropriate amounts of these lubricants are chosen, one can e.g. improve flow properties of granules used for compressing.

It thus can be preferred to use a lubricant amount of about 0.5% to about 4% by weight, of about 0.7% to about 3% by weight, of about 1% to about 2% by weight such as of about 1.0 % by weight, of about 1.1 % by weight, of about 1.2 % by

weight, of about 1.3 % by weight, of about 1.4 % by weight, of about 1.5 % by weight, of about 1.6% by weight, of about 1.7 % by weight, of about 1.8 % by weight, of about 1.9 % by weight or of about 2.0 % by weight based on the weight of the pharmaceutical composition. An amount of about 0.75% to about 1.25% by weight based on the weight of the pharmaceutical composition can be preferred, particularly if magnesium stearate and talc are used. The aforementioned amounts refer to the amount of all lubricants (i.e. including mixtures) in the composition.

Binders can include hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose, polyvinyl pyrollidone, carbopol, and combinations thereof.

It can be preferred to use HPC as a binder as this may positively influence the hardness of the tablets.

It thus can be preferred to use a binder amount of about 1% to about 10% by weight, of about 2% to about 9% by weight, of about 3% to about 7% by weight, of about 3% to about 6% by weight, of about 4% to about 5% by weight such as of about 4.0 % by weight, of about 4.1 % by weight, of about 4.2 % by weight, of about 4.3 % by weight, of about 4.4 % by weight, of about 4.5 % by weight, of about 4.6% by weight, of about 4.7 % by weight, of about 4.8 % by weight, of about 4.9 % by weight or of about 5.0 % by weight based on the weight of the pharmaceutical composition. An amount of about 4.4% to about 5.0% by weight based on the weight of the pharmaceutical composition can be preferred, particularly of HPC is used as binder. The aforementioned amounts refer to the amount of all binders (i.e. including mixtures) in the composition.

It can be preferred to not use povidone as a binder.

Release rate modifiers are pharmaceutically acceptable excipients which may be used to tune the release which otherwise would be obtained using the prolonged

release materials, e.g. to accelerate the release or to further slow it down. Such release modifiers may be hydrophilic substances such as polyethylenglycols, hydroxypropylmethlycellulose, hydroxyethylcellulose, and the like or hydrophobic substances such as oils, waxes and the like. Other release modifiers may include some the aforementioned (meth)aycrylic acid(co)polymers such as polymers of the Eudragit® RLPO type or gums such as xanthan gum.

Release rate modifiers such as polymers of the Eudragit/®RLPO type, low molecular weight hydroxypropylmethlycellulose such as Hypromellose K100M or xanthan gum may be preferred.

Such release rate modifiers may be present in an amount of about 1% to about 20% by weight, of about 2% to about 19% by weight, of about 3% to about 18% by weight, of about 4% to about 17% by weight, of about 5% to about 15% by weight such as of about 5 % by weight, of about 6% by weight, of about 7% by weight, of about 8% by weight, of about 9% by weight, of about 10% by weight, of about 11% by weight, of about 12% by weight, of about 13% by weight, of about 14% by weight or of about 15% by weight based on the weight of the pharmaceutical composition. The aforementioned amounts refer to the amount of all release rate modifiers (i.e. including mixtures) in the composition.

It is to be understood that the functions of pharmaceutically acceptable excipients may be overlapping. For example, a spheronising agent such as microcrystalline cellulose can also be used as filler if appropriate amounts are chosen. Further, HPMC may not only act as release rate modifying agent but also as binder if e.g. used in prolonged release formulation with a coating.

Prolonged release coatings may be made from materials which are common in the art.

They may thus be selected from e.g. prolonged release materials selected e.g. from (i) an alkylcellulose; (ii) an acrylic polymer; (iii) polyvinylalcohol or (iv) mixtures thereof. Hydrophobic representatives of the afore-mentioned groups can be preferred. The coating may be applied in the form of an organic or aqueous solution or dispersion.

In some embodiments, the controlled release coating is derived from an aqueous dispersion of the hydrophobic controlled release material. The coated composition can then be cured.

In preferred embodiments, the controlled release coatings include a plasticizer such as those described herein below.

In certain embodiments, one may coat with an amount of coating material which is sufficient to obtain a weight gain level from about 2 to about 20%, e.g., about 2 to about 15% and preferably about 5 to about 10% such as 6%, 7%, 8% or 9% in order to obtain sufficiently prolong the release from the formulation.

Cellulosic materials and polymers, including alkyl celluloses are prolonged release materials well suited for coating substrates, e.g. beads, granules, or tablets according to the invention. Simply by way of example, one preferred alkyl cellulosic polymer is ethyl cellulose

One commercially available aqueous dispersion of ethyl cellulose is Aquacoat® such as Aquacoat® ECD30 (FMC Corp., Philadelphia, Pennsylvania, U.S.A.). Aquacoat is prepared by dissolving the ethyl cellulose 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 pseudo latex.

Another aqueous dispersion of ethyl cellulose 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.

In embodiments of the present invention, the prolonged release coating material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, 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 ammonium methacrylate copolymers. Ammonium methacrylate copolymers are well known in the art, and are described as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. Typical examples include Eudragit® RS30D which is a low permeability ammonium methacrylate polymer and Eudragit®RL30D which is a high permeability ammonium methacrylate polymer. Eudragit RL and Eudragit RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit RL and RS are pH-independent.

The acrylic coatings may comprise a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Trade names Eudragit®RL30D and Eudragit®RS30D, respectively. The Eudragit®RL/RS

dispersions of the present invention may be mixed together in any desired ration in order to ultimately obtain a prolonged-release formulation having a desirable dissolution profile.

Other polymers which can be used as a prolonged release coating materials if they are applied at sufficient amounts are e.g. hydrophilic polymers such as hyrdoxypropylmethylcellulose.

The above mentioned coatings may also be applied in combination. Further it is possible to influence the release properties of a dosage form by increasing the amount of the coating material and thus the thickness of the coating.

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic controlled release material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material may further improve the physical properties of the prolonged release coating. For example, because ethyl cellulose has a relatively high glass transition temperature and may not form flexible films under normal coating conditions, it can be preferred to incorporate a plasticizer into an ethyl cellulose coating containing prolonged release coating 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 % by weight of the film-former.

Examples of suitable plasticizers for ethyl cellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl 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.

Examples of suitable plasticizers for the acrylic polymers 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.

In the following it is described how prolonged release matrices which may be used in the pharmaceutical compositions for use according to the invention may be composed.

A first option comprises an oral prolonged release pharmaceutical composition comprising at least:

a) at least one (meth)acrylic acid (co)polymer, preferably at least one neutral (meth)acrylic acid (co)polymer such as Eudragit®NE as prolonged release material;
b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein
c) the hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof is combined with said prolonged release material to form a prolonged release matrix.

A second option comprises an oral prolonged release pharmaceutical composition comprising at least:

a) at least one cellulose ether, preferably at least one hydrophobic cellulose ether such as ethyl cellulose as prolonged release material;
b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein

c) the hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof is combined with said prolonged release material to form a prolonged release matrix.

A third option comprises an oral prolonged release pharmaceutical composition comprising at least:

a) at least one fatty alcohol as prolonged release material;
b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein
c) the hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release material to form a prolonged release matrix.

A fourth option comprises an oral prolonged release pharmaceutical composition comprising at least:

a) at least one (meth)acrylic acid (co)polymer, preferably at least one neutral (meth)acrylic acid (co)polymer such as Eudragit®NE and at least one cellulose ether, preferably at least one hydrophobic cellulose ether such as ethyl cellulose as prolonged release materials;
b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein
c) the hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release materials to form a prolonged release matrix.

A fifth option comprises an oral prolonged release pharmaceutical composition comprising at least:

a) at least one (meth)acrylic acid (co)polymer, preferably at least one neutral (meth)acrylic acid (co)polymer such as Eudragit®NE and at least one fatty alcohol as prolonged release materials;
b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein
c) the hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release materials to form a prolonged release matrix.

A sixth option which may be particularly preferred, comprises an oral prolonged release pharmaceutical composition comprising at least:

a) at least one cellulose ether, preferably at least one hydrophobic cellulose ether such as ethyl cellulose and at least one fatty alcohol as prolonged release materials;
b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein
c) the hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release materials to form a prolonged release matrix.

A seventh option comprises an oral prolonged release pharmaceutical composition comprising at least:

a) at least one (meth)acrylic acid (co)polymer, preferably at least one neutral (meth)acrylic acid (co)polymer such as Eudragit®NE, at least one cellulose ether, preferably at least one hydrophobic cellulose ether such as ethyl cellulose and at least one fatty alcohol as prolonged release materials;

b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein

c) the hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release materials to form a prolonged release matrix.

The prolonged release materials may be used in the amounts mentioned above.

In a first embodiment of the first to seventh option, the pharmaceutical composition is heat treated as described above.

In addition or alternatively to this first embodiment of the first to seventh option, the pharmaceutical composition may comprise an anhydrous filler such as anhydrous lactose.

In addition or alternatively to this first and second embodiment of the first to seventh option, the pharmaceutical composition may comprise magnesium stearate and/or talc in the above mentioned amounts.

In addition or alternatively to this first, second and third embodiment of the first to seventh option, the pharmaceutical composition may comprise HPC in the above mentioned amounts.

In addition or alternatively to this first, second, third and fourth embodiment of the first to seventh option, the pharmaceutical composition may comprise HPC in the above mentioned amounts.

In addition or alternatively to this first, second, third, fourth and fifth embodiment of the first to seventh option, the pharmaceutical composition may comprise an

additional prolonged release coating. Such a coating may comprise preferably ethyl cellulose as prolonged release coating material.

These pharmaceutical compositions according to the first to seventh option comprise hydromorphone and naloxone or a pharmaceutically acceptable salt thereof in the above mentioned ratios and amounts. They may further provide the above mentioned *in* vitro release data and alcohol resistance as described above. Further, these compositions may provide storage stability. They may also be of a multiparticulate nature. They may further provide the pharmacokinetic parameters as mentioned herein.

If one attempts to realize specific in vitro release rates, one can use combinations of the above mentioned measures. For example, if the release from a prolonged release matrix is deemed too fast one may apply a prolonged release coating in addition. In addition or alternatively, one may add additional prolonged release matrix materials such as hydrophobic polymers, with ethyl cellulose being preferred and/or fatty alcohols to granules which already comprise a prolonged release matrix and to then compress these granules together with the additional prolonged release matrix materials into e.g. tablets. In a preferred embodiment, such prolonged release matrix formulations which are coated with such prolonged release matrix formulations and then are used as a multiparticulate formulation.

The pharmaceutical compositions for use in accordance with the invention as described herein may be formulated to provide a mean AUCt of about 1162 h*pg/ml to about 2241 h*pg/ml and preferably of about 1328 to about 2075 h*pg/ml per mg administered amount of hydromorphone and a mean Cmax of about 122 pg/ml to about 234 pg/ml and preferably of about 139 to about 218 pg/ml per mg administered amount of hydromorphone and mean tmax of about 1h to about 4.5h, preferably of about 1.5h to about 4h and more preferably of about 1.5h to about 3h. These values refer preferably to single dose administration to healthy subjects. Preferably,

administration is in the fasted state. The mean values of Cmax, AUCt and tmax refer to the geometric mean.

The "Cmax value" indicates the maximum blood plasma concentration of the active agent hydromorphone.

The "tmax value" indicates the time point at which the Cmax value is reached. In other words, tmax is the time point of the maximum observed plasma concentration.

The "AUC (Area Under the Curve)" value corresponds to the area of the concentration curve. The AUC value is proportional to the amount of the active agent absorbed into the blood circulation in total and is hence a measure for the bioavailability.

The "AUCt value" is the value for the area under the plasma concentration-time curve from the time of administration to the last measurable concentration. AUCt values are usually calculated using the linear trapezoidal method.

If pharmacokinetic parameters such as mean t_{max}, c_{max} and AUCt are measured for healthy subjects which may be healthy human, they are typically obtained by measuring the development of blood plasma values over time in a test population of approximately 16 to 24 healthy human subjects. Regulatory bodies such as the European Agency for the Evaluation of Medicinal Products (EMEA) or the Food and Drug Administration (FDA) will usually accept data obtained from e.g. 16 or 24 test persons. However, initial trials involving fewer participants such as 8 to 16 participants may also be acceptable.

The term "healthy" subjects in this context refers to a typical male or female of usually Caucasian origin with average values as regards height, weight and physiological parameters such as blood pressure etc. Healthy human subjects for the

purposes of the present invention are selected according to inclusion and exclusion criteria which are based on and in accordance with recommendations of the International Conference for Harmonization of Clinical Trials (ICH). For the purposes of the present invention, healthy subjects may be identified according to the inclusion and exclusion criteria as outlaid in Example 7.

Thus, inclusion criteria comprise e.g. an age between ≥18 and ≤45 years; a BMI within the range 19 - 29 kg/m^2, and within the weight range 60 - 100 kg for males and 55 - 90 kg for females; that females must be non-nursing, non-pregnant, and provide a negative urine ß-hCG pregnancy test within 24 hours before receiving the study medication; generally good health, evidenced by a lack of significantly abnormal findings on medical history, physical examination, clinical laboratory tests, vital signs, and ECG etc.

Exclusion criteria comprise e.g. exposure to any investigational drug or placebo within 3 months of the first dose of study medication, any significant illness within the 30 days before the first dose of study medication, any clinically significant abnormalities identified at prestudy screening for medical history, physical examination or laboratory analyses, use of any prescription medication (except HRT for postmenopausal females and contraceptive medication) in the 21 days, or over the counter medication including acid controllers, vitamins, herbal products and/or mineral supplements in the 7 days, before first dose of study medication, concurrent medical condition known to interfere with gastrointestinal drug absorption (e.g. delayed gastric emptying, mal absorption syndromes), distribution (e.g. obesity), metabolism or excretion (e.g. hepatitis, glomerulonephritis), history of or concurrent medical condition, which in the opinion of the investigator would compromise the ability of the subject to safely complete the study, history of seizure disorders for which subjects required pharmacologic treatment, current history of smoking more than 5 cigarettes a day, subjects with evidence of active or past history of substance or alcohol abuse according to DSM-IV criteria, subjects who reported regular

consumption of 2 or more alcoholic drinks per day or have blood alcohol levels of ≥0.5% at screening, donation of more than 500 mL of blood or blood products or other major blood loss in the 3 months before first dose of study medication, any positive results in the prestudy screen for ethanol, opiates, barbiturates, amphetamines, cocaine metabolites, methadone, propoxyphene, phencyclidine, benzodiazepines, and cannabinoids in the specimen of urine collected at screening, known sensitivity to hydromorphone, naloxone, or related compounds etc.

The afore-mentioned pharmacokinetic data may preferably be obtainable with a prolonged release pharmaceutical composition for use according to the invention comprising at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof and at least one prolonged release material which is preferably combined with these pharmaceutically active agents to form a prolonged release matrix; wherein the amount of hydromorphone or a pharmaceutically acceptable salt thereof or naloxone or a pharmaceutically acceptable salt thereof released *in vitro* in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 using the Ph. Eur. paddle method at 100 rpm at 37° C is:

at 1 h:	25 to 55% by weight of the pharmaceutically active agents,
at 2 h:	45 to 75% by weight of the pharmaceutically active agents,
at 3 h:	55 to 85% by weight of the pharmaceutically active agents,
at 4 h:	60 to 90% by weight of the pharmaceutically active agents,
at 6 h:	70 to 100% by weight of the pharmaceutically active agents,
at 8 h:	more than 85% by weight of the pharmaceutically active agents,
at 10 h:	more than 90% by weight of the pharmaceutically active agents.

The pharmaceutically active agents may preferably be hydromorphone HCl and naloxone HCl. The prolonged release pharmaceutical composition may comprise these actives in the above indicated amounts and weight ratio of about 2:1, about 1:1,

about 1:2 or about 1:3. The composition may be alcohol resistant as described hereinafter.

The afore-mentioned pharmacokinetic data may even more preferably be obtainable with a prolonged release pharmaceutical composition for use according to the invention comprising at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof and at least one prolonged release material which is preferably combined with these pharmaceutically active agents to form a prolonged release matrix; wherein the amount of hydromorphone or a pharmaceutically acceptable salt thereof or naloxone or a pharmaceutically acceptable salt thereof released *in vitro* in 500 or 900 ml of Simulated Gastric Fluid, pH 1.2 using the Ph. Eur. paddle method at 100 rpm at 37° C is:

at 1 h:	30 to 50% by weight of the pharmaceutically active agents,
at 2 h:	50 to 70% by weight of the pharmaceutically active agents,
at 3 h:	60 to 80% by weight of the pharmaceutically active agents,
at 4 h:	65 to 85% by weight of the pharmaceutically active agents,
at 6 h:	75 to 95% by weight of the pharmaceutically active agents,
at 8 h:	more than 90% by weight of the pharmaceutically active agents,
at 10 h:	more than 100% by weight of the pharmaceutically active agents.

The pharmaceutically active agents may preferably be hydromorphone HCl and naloxone HCl. The prolonged release pharmaceutical composition may comprise these actives in the above indicated amounts and weight ratio of about 2:1, about 1:1, about 1:2 or about 1:3. The composition may be alcohol resistant as described hereinafter.

Prolonged release pharmaceutical compositions as mentioned hereinafter can be obtained using a method of manufacturing comprising at least the steps of:

a) producing granules comprising at least one prolonged release material, at least hydromorphone or a pharmaceutically acceptable salt thereof and at least naloxone or a pharmaceutically acceptable salt thereof,
b) optionally selecting granules of step a) of substantially uniform size;
c) optionally adding additional prolonged release materials;
d) compressing said granules of step a), step b) or step c) to obtain an oral prolonged release pharmaceutical composition in the form of a tablet,
e) optionally heat treating said compressed granules of step d);
f) optionally disposing a prolonged release coatings either on the granules of step a), b) or c) or on the monolithic composition obtained in step d) or e);
g) optionally curing the obtained composition.

It is to be understood that at least the compression step c) produces an oral prolonged release pharmaceutical composition in the form of a tablet which comprises a prolonged release matrix. However, the granules obtained in step a) may also already comprise a prolonged release matrix.

Prolonged release pharmaceutical compositions as mentioned hereinafter can also be obtained using a method of manufacturing comprising at least the steps of:

a) producing granules comprising at least one prolonged release material, at least hydromorphone or a pharmaceutically acceptable salt thereof and at least naloxone or a pharmaceutically acceptable salt thereof,
b) optionally selecting granules of step a) of substantially uniform size;
c) optionally heat treating said granules of step a) or step);
d) optionally disposing a prolonged release coatings either on the granules of step a), b) or or c);
e) optionally curing the obtained composition.

The person skilled in the art is aware of different means and methods for producing granules according to step a).

Such granules may be produced by wet or dry granulation. Thus, for producing granules, step a) may comprise the following steps:

aa) blending a prolonged release material with at least hydromorphone or a pharmaceutically acceptable salt thereof and at least naloxone or a pharmaceutically acceptable salt thereof and optionally with a pharmaceutically acceptable excipient,

ab) wet or dry granulating said blend of step aa) to obtain granules, and optionally spheronising them,

ac) drying said granules of step ab).

The pharmaceutically acceptable excipients may include the fillers, binders, lubricants, release rate modifiers, spheronising agents, anti-tacking agents, etc. as mentioned above. However, some of these excipients such as e.g. lubricants may be added at a later stage (see below).

Different technology is available to obtain such granules. One may use e.g. drum granulation or fluidized bed granulation.

Alternatively and/or additionally granules according to step a) may be produced comprising the steps of:

aa) blending a prolonged release matrix material with at least hydromorphone or a pharmaceutically acceptable salt thereof and at least naloxone or a pharmaceutically acceptable salt thereof and optionally with a pharmaceutically acceptable excipient,

ab) extruding said blend of step aa) to obtain granules,

ac) drying said granules of step ab).

The pharmaceutically acceptable excipients may include the fillers, binders, lubricants, release rate modifiers, spheronising agents, anti-tacking agents, etc. as mentioned above. However, some of these excipients such as e.g. lubricants may be added at a later stage (see below).

Different extruder technology is available to obtain extruded granules. For example, one may use a single screw or twin screw extruder. For twin screw extruders, one may use counter-rotating or co-rotating screws having optionally paddle means.

As mentioned above, the granules which may be produced by wet granulation extrusion may be dried before being mixed with the at least one pharmaceutically active agent.

Typically, drying takes place at humidity in the range of about 0.5 % to about 5.0 % at a temperature in the range of about 20°C to about 90°C and for a time in the range of about 10 min to about 3 hours. Drying at ambient humidity at a temperature in the range of about 40°C to about 90°C and for a time in the range of about 15 min to about 2 hours can be preferred.

The granules may then be optionally screened in order to select granules of substantially uniform size. Selecting granules of substantially uniform size before compressing them may improve the prolonged release properties of the final prolonged release pharmaceutical composition as the active and the granules are then assumed to be more uniformly distributed which may prevent irregularities in the release profile. Granules for which at least about 70%, preferably at least about 80%, more preferably at least about 90% are of about the same mean size will typically be considered as being of substantially uniform size.

Preferably, granules are selected of a mean size in the range of about 100 μm to about 2 mm, more preferably in the range of about 100 μm to about 1 mm, and even

more preferably in the range of about 100 µm to about 600 µm. Selection may be performed using a sieve with an appropriate mesh size.

The granules may be milled before selecting them for their size. Milling may both increase the yield of the selection step and improve the granules' suitability for the subsequent compression step. For milling one may use for example a rotary hammer mill or top/bottom driven conical mill.

Even though granules may be produced by wet granulation, anyhdrous manufacturing steps and methods such as anhydrous extrusion may be preferred, at least where hydromorphone and naloxone or its pharmaceutically acceptable salts thereof are to be included in a prolonged release matrix. The preference for anhydrous manufacturing steps and methods when making a prolonged release matrix is that this has a beneficial impact on the chemical stability of hydromorphone or naloxone or its pharmaceutically acceptable salts. Once the active agents have been included in such a prolonged release matrux, the optional additional application of e.g. a prolonged release coating does not have be in an anhydrous manner. It is to be understood that the term "anhydrous manufacturing" indicates that the process that leads to a prolonged release matrix may be performed in the absence of substantial amounts of water. This does not mean that the components which are used do not comprise molecular bound water. Thus, even where the process is performed in an anhydrous manner such as extrusion, naloxone hydrochloride may e.g. be provided as a dihydrate and fillers such as lactose may be provided as lactose monohydrate even though anhydrous lactose can be preferred.
For compressing the pharmaceutically active agent(s) with the granules, one may use typical tabletting equipment such as Example Fette or Kilian press.

When compressing granules and active(s), one may also include pharmaceutically acceptable excipients as they are commonly used in the art. For example, one may

add lubricants, anti-tacking agents, binders and the like. For lubricants, the use of magnesium stearate and/or talc in the aforementioned amounts can be of advantage.

As mentioned above, prolonged release pharmaceutical dosage forms for use in accordance with the invention may be additionally subjected to a heat treatment step as has been described above.

The prolonged release coating may be produced by methods common in the art such a fluidized bed spraying.

As described above, the invention relates to oral prolonged release pharmaceutical compositions for use as defined above comprising hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in weight ratios in a range of 2:1 to 1:3, preferably of about 2:1, 1:1, 1:2 or 1:3.

The invention is now illustrated with respect to specific examples. These examples are, however, not to be construed as limiting.

EXAMPLES

Example 1:

Tablets of the composition as shown in **Table 1** were manufactured.

Tablets	F880/99	F880/105	F893/31
Ingredient	Amount (mg)	Amount (mg)	Amount (mg)
Hydromorphone HCl	2.0	2.0	2.0
Naloxone HCl	4.0	4.0	4.0
Stearyl alcohol	25.0	25.0	25.0
Ethyl cellulose N45	20.0	20.0	---
Lactose anhydrous	76.4	76.4	76.4
Eudragit RSPO*	---	---	20.0
Sodium stearyl fumarate	2.6	2.6	2.6
Hypromellose K100M	20.0	---	20.0
Xanthan Gum 'extra'	---	12.0	---
Total	150.0	142.0	150

*The amount indicated refers to the amount of solids used.

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol and either ethyl cellulose N45 or Eudragit RSPO as a prolonged release polymer in a double cone mixer for 10 min.

Subsequently the blend was melt extruded using a heated twin screw extruder..

The temperature profile for the extruder was as follows:

Extruder type	twin screw
Heating zone 1 (feeding zone)	25°C
Heating zone 2	50-55°C
Heating zone 3	73-83°C
Heating zones 5-10	70-80°C
Die head	50-55

The feeder rate was 10-15 kg/h. The screw speed was set at 150-250 rpm. The die plate design allowed for multiple strand extrusion. Compressed air was used to cool the extruded strands on conveyor belt.

Subsequently, the strands were milled to obtain granules. For milling, a Retsch mill with a 1.25 mm screen was used. This gave a substantially unimodal size distribution of the granules mainly in the range 100 to 600 µm.

The granules were then blended with sodium stearyl fumarate which was included as a lubricant. In addition, Hypromellose K100M was included as a release modifier. These components were blended for an additional 5 min. The granules were then compressed into tablets using a Kilian press.

Tablets F880/99, F880/105 and F893/31 were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release are indicated as percentage (based on the label content of active tested) in table 2.

Table 2

Tablets	F880/99		F880/105		F893/31	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
0.5h	25	24	29	28	25	23
1h	37	35	41	40	36	33
2h	55	53	59	56	53	49
3h	68	66	71	68	65	62
4h	78	77	79	77	75	71
5h	88	86	86	83	83	79
6h	94	92	91	88	89	85
7h	97	96	93	91	92	89
8h	99	97	96	94	95	92
9h	99	98	97	96	97	95
10h	99	98	98	97	97	96
11h	99	98	99	98	97	96
12h	99	98	99	98	97	96

Hm = hydromorphone HCl, Nal = naloxone HCl, 0.1 N HCl w/o 40% EtOH = 0.1 N HCl pH 1.2 without 40% ethanol; Values are averages of 6 measurements.

The tablets were further evaluated with respect to their alcohol resistance. To this end in vitro release rates were determined using the Ph. European paddle method at 75 rpm in 500 simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2) with 40% EtOH. Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release rates are indicated as percentage (based on the label content of active tested) in table 3.

Table 3

Tablet	F880/99		F880/105		F893/31	
Dissolution medium	0.1 N HCl w 40% EtOH		0.1 N HCl w 40% EtOH		0.1 N HCl w 40% EtOH	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
15min	0	0	0	0	0	0
30 min	12	11	9	9	12	11
45 min	16	16	23	21	17	16
60 min	21	20	39	36	21	20
90 min	25	24	63	59	25	23
120min	31	30	83	77	31	29

Hm = hydromorphone HCl, Nal = naloxone HCl, 0.1 N HCl w 40% EtOH = 0.1 N HCl pH 1.2 with 40% ethanol, Values are averages of 6 measurements.

Example 2

Tablets of the composition as shown in Table 4 were manufactured.

Table 4

Tablets	F880/77	F880/83	F893/89
Ingredient	Amount (mg)	Amount (mg)	Amount (mg)
Hydromorphone HCl	2.0	2.0	2.0
Naloxone HCl	4.0	4.0	4.0
Stearyl alcohol	25.0	25.0	15.0
Ethyl cellulose N45	20.0	20.0	20
Lactose anhydrous	76.4	76.4	76.4
Sodium stearyl fumarate	2.6	2.6	2.6
Hypromellose K100M"Extra"	20.0	7.5	12.5
Total	150	142.5	137.5

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol and ethyl cellulose as a prolonged release polymer in a double cone mixer for 10 min.

Subsequently the blend was melt extruded using a heated twin screw extruder.

The temperature profile for the extruder was as follows:

Extruder type	twin screw
Heating zone 1 (feeding zone)	25°C
Heating zone 2	50-55°C
Heating zone 3	73-83°C
Heating zones 5-10	70-80°C
Die head	50-55

The feeder rate was 10-15 kg/hr. The screw speed was set at 150-250 rpm. The die plate design allowed for multiple strand extrusion. Compressed air was used to cool the extruded strands on a conveyor belt.

Subsequently, the strands were milled to obtain granules. For milling, a Retsch mill with a 1.25 mm screen was used. This gave a substantially unimodal size distribution of the granules mainly in the range 100 to 600 µm.

The granules were then blended with sodium stearyl fumarate which was included as a lubricant. In addition, Hypromellose K100M was included as a release modifier. These components were blended for an additional 5 min. The granules were then compressed into tablets using a Kilian press.

Tablets F880/77, F880/83 and F880/89 were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated

gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

Tablets F880/77, F880/83 and F880/89 were further evaluated with respect to their alcohol resistance. To this end in vitro release rates were determined using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2) with 40% EtOH. Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in tables 5 to 6.

Table 5

Tablets	F880/77		F880/83		F880/89	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
0.5h	16	14	25	24	23	20
1h	24	22	40	39	35	33
2h	38	35	68	67	51	49
3h	50	45	87	86	65	63
4h	59	54	96	96	78	76
5h	68	62	99	99	87	86
6h	76	70	100	100	95	93
7h	82	77	100	100	96	95
8h	87	82	101	100	96	95
9h	92	86	101	101	97	96
10h	95	90	101	100	96	96
11h	97	93	101	101	97	96
12h	99	94	102	101	97	96

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Table 6

Tablets	F880/77		F880/83		F880/89	
Dissolution medium	0.1 N HCl w 40% EtOH		0.1 N HCl w 40% EtOH		0.1 N HCl w 40% EtOH	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
15 min	15	14	12	10	10	8
30 min	25	22	19	17	16	14
45 min	37	34	24	23	21	20
60 min	n.d.	n.d.	29	28	25	23
90 min	n.d.	n.d.	37	35	32	30
120 min	n.d.	n.d.	43	42	38	36

Hm = hydromorphone HCl, Nal = naloxone HCl, 0.1 N HCl w 40% EtOH = 0.1 N HCl pH 1.2 with 40% ethanol, n.d. = not determined; Values are averages of 6 measurements.

Example 3:

Granules of the composition as shown in table 7 were manufactured.

Table 7

Tablets	PN3450	PN3451	PN3452
Ingredient	Amount (mg)	Amount (mg)	Amount (mg)
Hydromorphone HCl	4.0	4.0	4.0
Naloxone HCl	8.0	8.0	8.0
Hydroxypropyl cellulose	5.0	5.0	5.0
Stearyl alcohol	17.5	25.0	25.0
Ethyl cellulose N45	7.5	10.0	15.0
Lactose anhydrous	46.0	46.0	46.0
Magnesium stearate	1.25	1.25	1.25
Talc	0.75	0.75	0.75
Total	90	100	105

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol, hydroxypropyl cellulose and ethyl cellulose N45 as a prolonged release polymer. These components were blended in a double cone mixer for 10 min.

Subsequently the blend was melt extruded using a heated twin screw extruder.

The temperature profile was as follows:

Extruder type	twin screw
Heating zone 1 (feeding zone)	25°C
Heating zone 2	50-55°C
Heating zone 3	73-83°C
Heating zones 5-10	70-80°C
Die head	50-55

The feeder rate was 10-15 kg/hr. The screw speed was set at 150-250 rpm. The die plate design allowed for multiple strand extrusion. Compressed air was used to cool the extruded strands on a conveyor belt.

The granules were milled and the milled granules were blended with magnesium stearate and talc in a tumbler mixer. Subsequently, the blended granules were compressed into tablets and heat treated for 30 minutes at 55°C.

Figure 1 shows for e.g. for the case of PN3450 that heat treatment of the prolonged matrix improves the physical stability of the formulation, e.g. in that the appearance of cracks is reduced and the intactness of the tablet is improved. Similar observations were made for the other heat treated tablets mentioned herein. This may positvely influence the in vitro release properties of the formulation, particularly in an in vivo setting as cracks may e.g. affect the release properties in an unpredictable manner due to e.g. a sudden change in the surface of the tablet. Furthermore, the hardness of the tablets is increase by usually 6 kP to 10 to 11 kP.

Tablets PN3450, PN3451 and PN3452 were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 9.

Table 9

Tablets	PN3450		PN3451		PN3452	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
1h	51,50	50,80	40,54	39,69	33,22	32,31
2h	68,10	67,60	54,82	53,92	45,89	45,04
3h	78,50	78,30	64,22	63,54	54,80	54,05
4h	85,50	85,60	71,72	71,11	61,85	61,21
5h	90,50	90,70	77,74	77,28	67,57	67,06
6h	93,90	94,30	82,11	81,72	72,22	71,97
7h	95,90	96,60	85,82	85,65	76,29	75,94
8h	96,90	97,90	89,19	89,24	79,75	79,63
9h	97,50	98,50	91,82	91,93	82,81	82,73
10h	97,50	98,60	93,71	94,04	85,24	85,59
11h	97,00	98,30	95,19	95,72	87,60	87,83
12h	97,20	98,40	96,54	97,26	89,43	89,91

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Subsequently, tablets PN350, PN3451 and PN3452 were placed in PVC blisters and stored for 3 months at 25°C and 60% RH or for 1, 2 and 3 months at 40°C and 75% RH.

All tablets were tested either initially or after storage for total related substances.

The results are shown in table 10.

Table 10

Tablets	PN3450	PN3450	PN3451	PN3451	PN3452	PN3452
Container	PVC	PVC	PVC	PVC	PVC	PVC
Storage	25°C/60 % RH	40°C/75 % RH	25°C/60 % RH	40°C/75 % RH	25°C/60 % RH	40°C/75% RH
Initial	0,15%	0.15%	0.15%	0.15%	0.16%	0.16%
1 month	---	0.26%	---	0.31%	---	0.33%
2 months	---	0.28%	---	0.39%	---	0.29%
3 months	0.33%	0.24%	0.34%	0.24%	0.36%	0.32%

Example 4:

Granules of the composition as shown in Table 11 were manufactured.

Table 11

Tablets	F923/16
Ingredient	Amount (mg)
Hydromorphone HCl	4.0
Naloxone HCl	8.0
Hydroxypropyl cellulose	5.0
Stearyl alcohol	25.0
Ethyl cellulose N45	10.0
Lactose anhydrous	46.0
Total	98

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol, hydroxypropyl cellulose and ethyl cellulose N45 as a prolonged release polymer. These components were blended in a double cone mixer for 10 min.

Subsequently the blend was melt extruded using a heated twin screw extruder. The granules were milled and the milled granules were blended with magnesium stearate and talc in a tumbler mixer. Subsequently, the blended granules were compressed into tablets.

Tablets F923/16 were heat treated for 15 min at 55°C. The heat treated tablets were labeled F922/58A.

Tablets F923/16 were heat treated for 30 min at 55°C. The heat treated tablets were labeled F922/58B.

Tablets F923/16 were heat treated for 45 min at 55°C. The heat treated tablets were labeled F922/58C.

Tablets F923/16 as well as their heat treated counterparts were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 12.

Table 12

Tablets	F923/16		F923/58A		F923/58B		F923/58C	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal	Hm	Nal
1h	48	47	40,06	39,10	39,12	38,17	38,31	37,54
2h	64	64	53,93	52,15	53,47	52,68	52,43	51,04
3h	75	74	63,75	62,68	63,79	62,34	62,19	61,07
4h	82	82	71,05	70,47	70,74	69,86	69,53	68,41
5h	86	87	78,03	77,01	76,58	75,71	75,37	76,35
6h	91	92	81,42	81,27	81,27	80,61	79,94	79,05
7h	94	94	84,75	84,56	85,59	82,89	83,97	83,26
8h	95	96	87,70	87,62	88,74	88,42	87,17	86,71
9h	96	97	91,27	90,97	90,86	90,71	89,67	88,92
10h	96	97	92,80	92,86	92,88	92,73	92,80	92,34
11h	96	97	94,14	94,45	94,32	94,42	93,73	91,82
12h	98	97	95,16	95,46	96,33	95,58	94,60	94,55

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Example 5:

Tablets with a prolonged release matrix and of comparable composition as in example 3 but comprising 20 mg ethyl cellulose were prepared. These tablets were then subjected to different heat treatments.

F922/70C: heat treated for 45 min at 55°C

F922/70D: heat treated for 60 min at 55°C

F922/70E: heat treated for 75 min at 55°C

Tablets F922/70C, F922/70D and F922/70E were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 13.

Table 13

Tablets	F922/70C		F922/70BD		F922/70E	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
1h	23,09	21,44	22,56	20,95	21,89	20,37
2h	33,32	31,48	31,65	29,87	31,24	29,27
3h	41,16	38,85	38,90	36,71	38,24	36,14
4h	47,38	45,14	44,50	42,18	44,05	41,80
5h	52,37	49,95	49,65	47,36	49,11	46,87
6h	57,11	54,79	53,72	51,77	53,39	51,11
7h	60,75	59,23	57,67	55,57	57,25	55,11
8h	65,12	62,84	61,13	59,31	60,78	58,65
9h	68,15	66,50	64,27	62,44	63,93	61,81
10h	71,75	69,40	67,47	65,21	66,76	64,95
11h	74,02	72,26	70,10	68,42	69,53	67,72
12h	76,49	75,01	72,82	70,86	71,83	70,16

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Example 6

Tablets F906/46 with a prolonged release matrix and of comparable composition as in example 3 but comprising 20 mg ethyl cellulose were prepared. These tablets were then subjected to different heat treatments.

F906/95B: F906/46 heat treated for 15 min at 55°C

F906/95C: F906/46 heat treated for 45 min at 55°C

Tablets F906/46, F906/95B and F906/95C were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml

simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 14.

Table 14

Tablets	F906/46		F9906/95B		F906/95C	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
1h	42,23	41,72	35,2	34,1	35,9	34,8
2h	57,26	57,35	48,8	47,8	49,8	48,9
3h	68,41	69,12	58,1	57,4	59,4	58,7
4h	89,71	89,87	64,5	64,0	65,4	65,0
5h	95,66	96,01	71,6	71,4	71,4	71,3
6h	96,21	96,69	77,2	77,3	77,8	77,8
7h	96,24	96,80	80,6	80,7	82,6	82,5
8h	96,29	96,70	85,6	85,7	85,6	85,5
9h	96,24	96,75	88,1	88,2	89,7	89,6
10h	96,27	96,88	91,6	91,7	90,6	90,4
11h	96,38	96,87	93,4	93,7	93,1	93,4
12h	96,26	96,85	94,7	95,2	93,9	94,3

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Example 7

Tablets of the composition as shown in table 15 were manufactured.

Table 15

Tablets	933/67	F933/69	F933/71	F933/73
Ingredient	Amount (mg)	Amount (mg)	Amount (mg)	Amount (mg)

Hydromorphone HCl	2.0	4.0	4.0	4.0
Naloxone HCl	4.0	2.0	4.0	12.0
Hydroxypropyl cellulose	5.0	5.0	5.0	5.0
Stearyl alcohol	25.0	25.0	25.0	25.0
Ethyl cellulose N45	10.0	10.0	10.0	10.0
Lactose anhydrous	52.0	52.0	50.0	42.0
Talc	1.25	1.25	1.25	1.25
Magnesium Stearate	0.75	0.75	0.75	0.75
Total	100	100	100	100

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol, hydroxypropyl cellulose and ethyl cellulose N45 as a prolonged release polymer. These components were blended in a double cone mixer for 10 min. Subsequently the blend was melt extruded using a heated twin screw extruder as described above.

The granules were milled and the milled granules were blended with magnesium stearate and talc in a tumbler mixer. Subsequently, the blended granules were compressed into tablets. The tablets were then heat treated for 30 min at 55°C.

Tablets F933/67, F933/69, F933/71 and F933/73 were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 16.

Table 16

Tablets	F933/67		F933/69		F933/71		F933/73	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal	Hm	Nal
1h	38,16	37,43	38,24	37,75	39,15	38,22	42,14	40,53
2h	52,62	51,72	53,18	52,23	53,69	52,54	57,09	55,52
3h	62,53	61,83	63,45	62,35	63,42	62,60	67,91	66,23
4h	70,09	69,43	71,23	70,26	70,94	70,02	75,35	73,88
5h	76,18	75,56	77,48	76,50	76,89	75,93	81,10	79,68
6h	81,03	80,48	82,50	81,63	81,66	80,68	85,90	84,79
7h	84,93	84,74	86,70	85,77	85,49	84,77	89,59	88,81
8h	88,38	88,30	89,90	88,98	88,63	87,76	92,33	91,74
9h	91,30	91,17	92,81	91,81	91,11	90,31	94,21	93,78
10h	93,48	93,63	94,97	94,13	93,16	92,53	96,13	95,87
11h	95,36	95,66	96,71	96,03	94,67	93,84	97,31	97,29
12h	96,88	97,32	98,06	97,47	95,98	95,37	98,78	99,08

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Example 8

Tablets F918/109 with a similar composition as in examples 1 to 7 were manufactured and cured for 60 minutes at 55°C. They were stored for 1 month at 25°C and 60° relative humidity (RH) or for 1 month at 40°C and 75% RH.

Tablets F919/77 with a similar composition as in examples 1 to 7 were manufactured cured for 30 minutes at 55°C. They were stored for 1 or 2 months at 40°C and 75% RH.

Tablets F918/109 and F919/77 were then analyzed either initially or after storage as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in tables 17 and 18.

Table 17

Tablets	F918/109		F918/109		F918/109	
Storage	---		1 month, 25°C, 60% RH		1 month, 40°C, 75% RH	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH 1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
1h	32,11	31,09	32,85	31,47	35,03	33,83
2h	44,68	43,47	45,64	44,07	47,77	46,49
3h	53,86	52,54	54,62	52,89	56,80	55,47
4h	60,84	59,48	61,71	59,87	63,65	62,30
5h	66,90	65,53	67,71	65,84	69,30	67,88
6h	71,81	70,44	72,41	70,53	74,05	72,68
7h	75,90	74,65	76,58	74,83	78,18	76,77
8h	79,41	78,30	80,24	78,49	81,63	80,26
9h	82,63	81,70	83,33	81,67	84,72	83,36
10h	85,28	84,41	85,86	84,19	87,31	86,03
11h	87,67	86,88	88,37	86,72	89,39	88,21
12h	89,71	89,22	90,14	88,69	91,13	90,18

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Table 18

Tablets	F919/77		F919/77		F919/77	
Storage	---		1 month, 40°C, 75% RH		1 month, 40°C, 75% RH	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH 1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
1h	30,29	29,36	30,49	29,50	31,07	30,12
2h	42,41	41,49	41,88	40,81	42,69	41,64
3h	51,14	50,30	50,08	48,95	50,93	49,78
4h	58,01	57,25	56,59	55,39	57,40	56,41

5h	63,64	63,05	61,98	60,72	62,60	61,78
6h	68,66	68,05	66,43	65,29	67,16	66,22
7h	72,77	72,37	70,28	69,16	71,10	70,16
8h	76,30	76,10	73,60	72,66	74,52	73,49
9h	79,47	79,32	76,55	75,72	77,38	76,63
10h	82,27	82,18	79,24	78,34	79,95	79,19
11h	84,62	84,57	81,50	80,82	82,36	81,72
12h	86,68	86,83	83,43	82,82	84,36	84,07

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Example 9

Tablets F899/29, F899/39 and F908/93 were produced similarly to examples 1 to 8.

Subsequently, tablets F899/29 and F899/39 were placed in Duma fos containers and stored for 1, 2 or 5 months at 25°C and 60% RH or at 40°C and 75% RH. Tablets F908/93 were placed either in PVC containers or in PVC coated PVdC blisters and stored for 1, 2 or 5 months at 25°C and 60% RH or at 40°C and 75% RH.

All tablets were tested either initially or after storage for total related substances.

The results are shown in tables 19 and 20.

Table 19

Tablets	F899/29	F899/29	F899/39	F899/29
Container	Duma fos	Duma fos	Duma fos	Duma fos
Storage	25°C/60% RH	40°C/75% RH	25°C/60% RH	40°C/75% RH
Initial	0,05%	0.05%	0.16%	0.16%
1 month	---	0.09%	---	0.17%
2 months	---	0.26%	---	0.24%
5 months	0.17%	0.30%	0.10%	0.24%

Table 20

Tablet	F908/93	F908/93	F908/93	F908/93
Container	PVC	PVC	PVS/PVdC	PVC/PVdC
Storage	25°C/60% RH	40°C/75% RH	25°C/60% RH	40°C/75% RH
Initial	0,10%	0.10%	0.10%	0.10%
1 month	0.21%	0.24%	0.40%	0.31%
2 months	0.25%	0.30%	0.65%	0.46%
5 months	---	0.49%	---	0.64%

Example 10

Tablets of the composition as shown in Table 21 were manufactured.

Table 21

Tablets	933/107B	F929/73B	F929/85B	F929/79B
Ingredient	Amount (mg)	Amount (mg)	Amount (mg)	Amount (mg)
Hydromorphone HCl	4.00	4.00	4.00	4.00
Naloxone HCl	8.00	8.00	8.00	8.00
Hydroxypropyl cellulose	5.00	5.00	5.00	5.00
Ethyl cellulose N45	15.0	15.0	15.0	15.0
Stearyl alcohol	25.0	25.0	25.0	25.0
Lactose anhydrous	46.0	46.0	46.0	46.0
Magnesium Stearate	1.25	1.25	1.25	1.25
Talcum	0.75	0.75	0.75	0.75
Total	105	105	105	105
Surelease E7-7050*		7.00	5.00	3.75
Opadry II brown*		2.30	2.50	3.75
Purified water**		28.0	20.0	15.0
Total	105	114.3	112.5	112.5

*The amount indicated refers to the amount of solids used.
** Evaporated during coating

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol, hydroxypropyl cellulose and ethyl cellulose N45 as a prolonged release polymer. These components were blended in a double cone mixer for 10 min. Subsequently the blend was melt extruded using a heated twin screw extruder as described above. The milled granules were blended with magnesium stearate and talc in a tumbler mixer. Subsequently, the blended granules were compressed into tablets. The tablets were then heat treated for 45 min at 55°C. Subsequently the coatings were applied.

Tablets F933/107B, F929/73B, F929/85B and F929/79B were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 22.

Table 22

Tablets	F933/107B		F929/73B		F929/85B		F929/79B	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal	Hm	Nal
1h	41,11	40,19	0,13	0,19	8,61	7,26	29,21	27,74
2h	56,10	55,15	0,81	0,65	17,89	15,80	43,70	41,98
3h	66,02	64,99	1,58	1,27	25,06	22,59	54,21	52,41
4h	73,90	73,07	2,55	1,97	31,14	28,42	62,18	60,40
5h	79,71	79,18	3,45	2,65	36,34	33,38	68,94	67,27
6h	84,28	83,60	5,08	3,95	41,15	38,09	74,37	72,63
7h	88,19	87,84	6,76	5,45	45,75	42,60	78,62	77,05
8h	91,29	91,03	8,56	7,05	50,55	47,25	82,91	81,37
9h	93,91	93,62	10,18	8,51	54,51	51,28	86,11	84,57
10h	95,95	95,91	11,92	10,05	58,50	55,34	88,67	87,31
11h	97,67	98,06	13,56	11,62	61,91	58,80	91,23	90,11
12h	98,57	98,74	15,37	13,27	65,24	62,11	92,91	91,70

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Example 11

Tablets of the composition as shown in Table 23 were manufactured.

Table 23

Tablets	F941/07B	F929/91C	F929/97C
Ingredient	Amount (mg)	Amount (mg)	Amount (mg)
Hydromorphone HCl	4.00	4.00	4.00
Naloxone HCl	4.00	4.00	4.00
Hydroxypropyl cellulose	5.00	5.00	5.00
Ethyl cellulose N45*	7.50	7.50	7.50
Stearyl alcohol	17.5	17.5	17.5
Lactose anhydrous	50.0	50.0	50.0
Magnesium Stearate	1.25	1.25	1.25
Talcum	0.75	0.75	0.75
Total	90	90	90
Surelease E7-7050*		7.50	10.0
Opadry II brown*		5.00	5.00
Purified water**		30.0	40.0
Total	90	102.5	105

*The amount indicated refers to the amount of solids used.
** Evaporated during coating

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol, hydroxypropyl cellulose and ethyl cellulose N45 as a prolonged release polymer. These components were blended in a double cone mixer for 10 min. Subsequently the blend was melt extruded using a heated twin screw extruder as described above. The milled granules were blended with magnesium stearate and talc in a tumbler mixer. Subsequently, the blended granules were compressed into tablets. The tablets were then heat treated for 45 min at 55°C. Subsequently the coatings were applied.

Tablets F941/07B, F929/91C and F929/97C were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 24.

Table 24

Tablets	F941/07B,		F929/91C		F929/97C	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
1h	48,75	47,97	12,07	11,02	1,30	0,97
2h	65,20	64,34	25,71	24,46	4,46	3,51
3h	75,96	75,05	35,83	34,48	7,82	6,46
4h	83,03	82,25	44,13	42,68	11,81	10,09
5h	88,29	87,64	51,32	49,85	18,08	16,14
6h	92,21	91,60	57,86	56,41	28,52	26,46
7h	94,81	94,48	63,60	62,18	35,81	33,71
8h	96,53	96,01	68,42	66,99	41,92	39,79
9h	97,31	97,11	72,85	71,44	47,04	44,85
10h	97,54	97,46	76,94	75,72	51,46	49,24
11h	97,75	97,82	79,73	78,48	55,40	53,22
12h	97,70	97,71	82,77	81,59	58,87	56,65

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Tablets F929/91C and F929/97C were further evaluated with respect to their alcohol resistance. To this end in vitro release rates were determined using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2) with 40% EtOH. Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 25.

Table 25

Tablets	F929/91C		F929/97C	
Dissolution medium	0.1 N HCl w 40% EtOH		0.1 N HCl w 40% EtOH	
Active tested	Hm	Nal	Hm	Nal
15 min	1,16	0,78	0,00	0,00
30 min	n.d.	n.d.	n.d.	n.d.
45 min	n.d.	n.d.	n.d.	n.d.
60 min	12,07	11,02	1,30	0,97
90 min	n.d.	n.d.	n.d.	n.d.
120 min	25,71	24,46	4,46	3,51

Hm = hydromorphone HCl, Nal = naloxone HCl, 0.1 N HCl w 40% EtOH = 0.1 N HCl pH 1.2 with 40% ethanol, n.d. = not determined

Example 12

Tablets of the composition as shown in Table 26 were manufactured.

Table 26

Tablets	F941/60B	F945/06	F944/86	F945/30
Ingredient	Amount (mg)	Amount (mg)	Amount (mg)	Amount (mg)
Hydromorphone HCl	4.00	4.00	4.00	4.00
Naloxone HCl	2.00	2.00	8.00	8.00
Hydroxypropyl cellulose	5.00	5.00	5.00	5.00
Ethyl cellulose N45	15.0	15.0	10.00	10.00
Stearyl alcohol	25.0	25.0	25.0	25.0
Lactose anhydrous	52.0	52.0	46.0	46.0
Magnesium Stearate	1.25	1.25	1.25	1.25
Talcum	0.75	0.75	0.75	0.75
Total	105	105	100	100
Surelease E7-7050*		12.0		7.50
Opadry II brown*		0.0		5.00
Purified water**		48.0		30.0
Total	105	117	100	112.5

*The amount indicated refers to the amount of solids used.
** Evaporated during coating

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol, hydroxypropyl cellulose and ethyl cellulose N45 as a prolonged release polymer. These components were blended in a double cone mixer for 10 min. Subsequently the blend was melt extruded using a heated twin screw extruder as described above. The milled granules were blended with magnesium stearate and talc in a tumbler mixer. Subsequently, the blended granules were compressed into tablets. Tablets F941/60B were heat treated for 45 min at 55°C. Tablets F944/86 were heat treated for 30 min at 55°C. Subsequently the coatings were applied.

Tablets F941/60B, F945/06, F944/86 and F945/30 were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 27.

Table 27

Tablets	F941/60B		F945/06		F944/86		F945/30	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal	Hm	Nal
1h	31,91	31,30	0,07	0,24	42,34	41,05	10,12	8,50
2h	44,71	44,11	0,00	0,00	57,27	55,66	22,45	20,08
3h	53,54	52,76	0,00	0,15	67,40	65,71	31,05	28,40
4h	60,84	59,92	0,00	0,00	75,13	73,49	37,72	34,87
5h	66,54	65,73	0,00	0,00	80,39	79,05	43,69	40,70
6h	71,65	70,74	0,00	0,45	85,16	83,78	49,07	45,90
7h	75,81	74,88	0,00	0,86	88,91	87,48	53,65	50,47
8h	79,32	78,62	0,00	1,15	91,74	90,58	58,14	54,82
9h	82,63	81,74	0,00	1,31	94,30	93,04	61,81	58,69
10h	85,47	84,67	0,00	1,50	96,59	95,76	65,50	62,36
11h	87,92	87,17	0,00	1,68	97,14	96,57	69,01	65,70
12h	89,64	88,92	0,00	1,87	97,82	97,39	72,00	68,89

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Example 13

Tablets of the composition as shown in Table 28 were manufactured.

Table 28

Tablets	F941/07B	F944/49	F929/103
Ingredient	Amount (mg)	Amount (mg)	Amount (mg)
Hydromorphone HCl	4.00	4.00	4.00
Naloxone HCl	4.00	4.00	4.00
Hydroxypropyl cellulose	5.00	5.00	5.00
Ethyl cellulose N45	7.50	7.50	7.50
Stearyl alcohol	17.5	17.5	17.5
Lactose anhydrous	50.0	50.0	50.0
Magnesium Stearate	1.25	1.25	1.25
Talcum	0.75	0.75	0.75
Total	90	90	90
Eudragit RL30D*		5.00	14.0
Eudragit RS30D*		5.00	0.00
Talc		5.00	7.00
Triethyl citrate		2.00	2.80
Purified water**		44.8	62.6
Total	90	107	113.8

*The amount indicated refers to the amount of solids used.
** Evaporated during coating

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol, hydroxypropyl cellulose and ethyl cellulose N45 as a prolonged release polymer. These components were blended in a double cone mixer for 10 min. Subsequently the blend was melt extruded using a heated twin screw extruder as described above. The milled granules were blended with magnesium stearate and talc in a tumbler mixer. Subsequently, the blended granules were compressed into tablets.

Tablets were then heat treated for 45 min at 55°C. Subsequently the coatings were applied.

Tablets F941/07B, F944/49 and F929/103 were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 29.

Table 29

Tablets	F941/07B		F944/49		F929/103	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
1h	48,75	47,97	6,04	4,60	14,54	12,42
2h	65,20	64,34	24,83	21,75	39,00	35,75
3h	75,96	75,05	49,18	46,69	57,55	54,52
4h	83,03	82,25	61,94	59,94	70,09	67,76
5h	88,29	87,64	71,03	69,11	78,89	77,01
6h	92,21	91,60	78,22	76,31	85,20	83,57
7h	94,81	94,48	83,60	81,83	89,78	88,43
8h	96,53	96,01	87,96	86,66	93,23	92,16
9h	97,31	97,11	91,56	90,05	95,60	94,58
10h	97,54	97,46	93,89	92,84	97,08	96,33
11h	97,75	97,82	95,84	95,06	98,16	97,36
12h	97,70	97,71	97,07	96,61	98,46	98,01

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Example 14

Tablets of the composition as shown in Table 30 were manufactured.

Table 30

Tablets Ingredient	F944/90 Amount (mg)	F944/101D Amount (mg)
Hydromorphone HCl	4.00	4.00
Naloxone HCl	8.00	8.00
Hydroxypropyl cellulose	5.00	5.00
Ethyl cellulose N45	7.50	7.50
Stearyl alcohol	17.5	17.5
Lactose anhydrous	46.0	46.0
Magnesium Stearate	1.25	1.25
Talcum	0.75	0.75
Total	90	90
Surelease E7-7050*		7.50
Advantia Preferred* (Aquarius HPMC)		5.00
Purified water**		30.0
Total	90	102.5

*The amount indicated refers to the amount of solids used.
** Evaporated during coating

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol, hydroxypropyl cellulose and ethyl cellulose N45 as a prolonged release polymer. These components were blended in a double cone mixer for 10 min. Subsequently the blend was melt extruded using a heated twin screw extruder as described above. The milled granules were blended with magnesium stearate and talc in a tumbler mixer. Subsequently, the blended granules were compressed into tablets. Tablets were then heat treated for 30 min at 55°C. Subsequently the coatings were applied.

Tablets F944/90 and F944/101D were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 31.

Table 31

Tablets	F944/90		F944/101D	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal
1h	51,08	49,95	21,88	20,12
2h	68,55	67,18	38,23	36,15
3h	79,32	77,97	50,93	48,65
4h	86,47	85,26	60,36	58,15
5h	91,63	90,53	67,82	65,77
6h	94,86	94,04	74,74	72,72
7h	96,95	96,34	79,32	77,41
8h	97,90	97,48	83,90	82,14
9h	98,56	98,27	87,03	85,47
10h	98,97	98,72	90,14	88,73
11h	98,86	98,71	92,32	91,10
12h	98,87	98,76	94,09	93,11

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Tablets similar to F994/101D were manufactured. In tablets F994/101B, the weight gain by coating was about 5 mg. Tablets F994/101E were the same as tablets F994/101D except that they had been cured 30 minutes at 55°C after the coating had been applied. These tablets were also tested for their in vitro release.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 32.

Table 32

Tablets	F944/101B		F944/101D		F944/101E	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal
1h	33,91	32,23	21,88	20,12	15,55	13,05
2h	50,66	48,53	38,23	36,15	31,17	28,20
3h	62,06	59,71	50,93	48,65	42,66	39,67
4h	70,64	68,21	60,36	58,15	52,68	49,67
5h	77,57	75,20	67,82	65,77	60,06	56,91
6h	82,52	80,46	74,74	72,72	67,14	64,15
7h	86,96	84,87	79,32	77,41	72,70	69,83
8h	90,51	88,57	83,90	82,14	77,78	75,03
9h	92,75	90,85	87,03	85,47	82,36	79,77
10h	94,99	93,44	90,14	88,73	85,18	82,76
11h	95,81	94,56	92,32	91,10	87,84	85,55
12h	97,02	95,83	94,09	93,11	90,58	88,36

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Example 15

Tablets of the composition as shown in Table 33 were manufactured.

Table 33

Tablets	PN3450	F944/78	PN3451	F944/82	F945/69
Ingredient	Amount (mg)	Amount (mg)	Amount (mg)	Amount (mg)	Amount (mg)
Hydromorphone HCl	4.0	4.00	4.0	4.00	4.00
Naloxone HCl	8.0	8.00	8.0	8.00	8.00
Hydroxypropyl cellulose	5.0	5.00	5.0	5.00	5.00
Stearyl alcohol	17.5	17.5	25.0	25.0	25.0
Ethyl cellulose N45	7.5	7.5	10.0	10.0	10.0
Lactose anhydrous	46.0	46.0	46.0	46.0	46.0
Talc	1.25	1.25	1.25	1.25	1.25
Magnesium Stearate	0.75	0.75	0.75	0.75	0.75
Total	90	90	100	100	100
Stearyl alcohol (extragranular)		15.00		15.00	0.00
Ethylcellulose N45 (extragranular)		0.00		0.00	15.00
Total	90	105	100	115	115

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol, hydroxypropyl cellulose and ethyl cellulose N45 as a prolonged release polymer. These components were blended in a double cone mixer for 10 min. Subsequently the blend was melt extruded using a heated twin screw extruder as described above.

The milled granules were blended with magnesium stearate and talc and the additional amount of extragranular stearyl alcohol or ethyl cellulose in a tumbler mixer. Subsequently, the blended granules were compressed into tablets. The tablets were then heat treated for 30 min at 55°C.

Tablets PN3450, PN3451, F944/78, F944/82 and F945/69 were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 34.

Table 34

Tablets	PN3450		F944/78		PN3451		F944/82		F945/69	
Disso-lution me-dium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal	Hm	Nal	Hm	Nal
1h	51,50	50,80	43,94	42,52	40,54	39,69	30,89	29,56	38,94	37,56
2h	68,10	67,60	59,69	57,94	54,82	53,92	42,72	41,12	53,24	55,65
3h	78,50	78,30	70,31	68,46	64,22	63,54	51,12	49,36	62,95	61,61
4h	85,50	85,60	77,61	75,77	71,72	71,11	57,95	56,13	70,34	68,94
5h	90,50	90,70	83,81	82,16	77,74	77,28	63,21	61,38	76,28	75,05
6h	93,90	94,30	88,25	86,65	82,11	81,72	67,88	65,91	81,31	80,03
7h	95,90	96,60	91,83	90,29	85,82	85,65	71,76	69,85	85,10	84,05
8h	96,90	97,90	94,57	93,06	89,19	89,24	75,34	73,46	88,53	87,47
9h	97,50	98,50	96,50	95,28	91,82	91,93	78,37	76,52	91,35	90,32
10h	97,50	98,60	98,34	97,37	93,71	94,04	81,07	79,29	93,67	92,44
11h	97,00	98,30	99,36	98,52	95,19	95,72	83,52	81,76	95,31	94,47
12h	97,20	98,40	99,58	98,93	96,54	97,26	85,64	83,97	96,61	95,71

Hm = hydromorphone HCl, Nal = naloxone HCl; Values are averages of 6 measurements.

Example 16

Tablets of the composition as shown in Table 35 were manufactured.

Table 35

Tablets	PN3642	PN3643	PN3644	PN3645
Ingredient	Amount (mg)	Amount (mg)	Amount (mg)	Amount (mg)
Hydromorphone HCl	4.00	4.00	4.00	4.00
Naloxone HCl	8.00	8.00	8.00	8.00
Hydroxypropyl cellulose	5.00	5.00	5.00	5.00
Ethyl cellulose N45	7.50	7.50	15.0	15.0
Stearyl alcohol	17.5	17.5	25.0	25.0
Lactose anhydrous	52.0	52.0	46.0	46.0
Magnesium Stearate	0.75	0.75	0.75	0.75
Talcum	1.25	1.25	1.25	1.25
Total	90	90	105	105
Surelease E7-19030*	5.00	6.00	5.00	9.00
Opadry II brown*	5.00	4.00	5.00	6.00
Purified water**	20.0	24.0	20.0	36.0
Total	100	100	115	120

*The amount indicated refers to the amount of solids used.
** Evaporated during coating

Hydromorphone HCl and naloxone HCl were mixed with lactose anhydrous, stearyl alcohol, hydroxypropyl cellulose and ethyl cellulose N45 as a prolonged release polymer. These components were blended in a double cone mixer for 10 min. Subsequently the blend was melt extruded using a heated twin screw extruder as described above. The milled granules were blended with magnesium stearate and talc in a tumbler mixer. Subsequently, the blended granules were compressed into tablets. The tablets were then heat treated for 60 min at 55°C. Subsequently the coatings were applied with Manesty air atomised spray fitted with a 1.2 mm nozzle adjusted to give an even spray pattern and located approximately 15 cm from tablet bed.

Atomising air pressure 1.8 bar

Fan width air pressure 2.0 bar

Inlet air temperature 52° C

Outlet air temperature 40-45°C
Air flow 350 m3/hr
Drum speed 20 rpm
Spray rate ca. 6-10 g/min
Cabinet depression -50
Wall thickness of silicon tubing 1.6mm
Bore of silicon tubing 4.8mm

Tablets PN3642, PN3643, PN 3644 and PN3645 were then analyzed as regards in vitro release behavior using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2). Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 36.

Table 36

Tablets	PN3642		PN3643		PN3644		PN3645	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal	Hm	Nal
1h	30,14	28,16	16,15	13,62	23,29	21,81	12,70	10,75
2h	49,65	47,91	35,51	32,66	38,00	36,72	26,59	24,45
3h	63,09	61,54	48,58	45,95	48,11	46,87	36,40	34,25
4h	72,95	71,53	58,85	56,36	55,98	54,76	44,48	42,37
5h	80,56	79,42	67,19	64,83	62,40	61,34	51,12	49,13
6h	86,32	85,32	74,14	71,99	68,00	67,04	56,94	54,86
7h	90,74	89,90	79,91	77,93	72,67	71,84	62,26	60,16
8h	93,79	93,27	84,68	82,84	76,69	76,04	66,72	64,85
9h	95,94	95,81	88,57	87,10	80,26	79,73	70,73	68,92
10h	97,59	97,63	91,68	90,47	83,28	82,73	74,08	72,62
11h	98,31	98,63	94,10	93,30	86,00	85,59	77,48	75,82
12h	98,77	99,28	96,05	95,31	88,08	87,94	80,30	78,70

Hm = hydromorphone HCl, Nal = naloxone HCl. Values are averages of 6 measurements.

Tablets PN3642, PN3643, PN3644, PN3645 were further evaluated with respect to their alcohol resistance. To this end in vitro release rates were determined using the Ph. European paddle method at 75 rpm in 500 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2) with 40% EtOH. Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC at 220 nm.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 37.

Table 37

Tablets	PN3642		PN3643		PN3644		PN3645	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal	Hm	Nal	Hm	Nal
15 min	3.8	2.7	1.8	1.4	4.0	2.7	1.4	0.7
30 min	10.2	8.6	5.6	4.5	9.5	8.2	2.1	1.9
45 min	16.7	14.6	9.9	8.3	15.3	13.8	4.6	3.8
60 mi	22.4	20.1	14.1	10.7	20.3	18.5	7.3	6.1
90 min	31.8	29.3	21.9	17.6	27.9	26.1	12.8	11.0
120 min	39.5	36.8	29.4	25.6	34.1	32.4	18.0	15.8

Hm = hydromorphone HCl, Nal = naloxone HCl, 0.1 N HCl w 40% EtOH = 0.1 N HCl pH 1.2 with 40% ethanol, n.d. = not determined; Values are averages of 6 measurements.

Subsequently, tablets PN3642, PN3643, PN3644 and PN3645 were placed in PVC blisters and stored for 1, 2 and 3 months at 40°C and 75% RH.

All tablets were tested either initially or after storage for total related substances.

The results are shown in table 38.

Table 38

Tablets	PN3642	PN3643	PN3644	PN3645
Container	PVC	PVC	PVC	PVC
Storage	40°C/75 % RH	40°C/75 % RH	40°C/75 % RH	40°C/75 % RH
Initial	0.00%	0.00%	0.00%	0.08%
1 month	0.00%	0.05%	0.05%	0.00%
2 months	0.05%	0.00%	0.00%	0.00%
3 months	0.05%	0.05%	0.00%	0.05%

All tablets were tested either initially or after storage also for known related substances. These were noroxymorphone, hydromorphone N-oxide,

pseudohydromorphone, naloxone N-oxide, pseudonaloxone. All known substances were either less than limit of detection or less than limit of quantification.

Example 17

Tablets corresponding to tablets of PN3462 were tested in an open label, single-dose study in 15 healthy subjects in the fasted state. The mean AUCt /h*pg/ml was 7675.9, the mean Cmax (pg/ml) was 664.6, the mean tmax was 1.9h.

Example 18

Formulations with a prolonged release coating were produced having the composition of Table 39.

Table 39

Formulation	A	B
Ingredient	amount per capsule (mg)	amount per capsule (mg)
Microcrystalline cellulose (MCC) spheres	44.89	44.83
Hydromorphone hydrochloride	3.00	3.00
Naloxone hydrochloride dihydrate	1.65	1.65
Hydroxypropyl methylcellulose, polyethylene glycol film coating concentrate (Opadry YS-1-7006, Clear) HS	1.63	1.68
Aqueous ethylcellulose dispersion (Surelease)	4.66	6.04
Polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat IR) HS	0.34	0.45

Silicon dioxide NF (Syloid 244FP) NF	0.00	0.29
Purified Water USP	q.s.	q.s.
Total	~56	~58

For Formulation A, a solution is produced from hydromorphone and naloxone dissolved in water, Opadry Clear ® YS-1-7006. This solution is then sprayed on to a microcrystalline cellulose (MXX) beads in a fluid bed dryer with a Wurster column. This produces an immediate-release (IR) bead. The IR bead is then sprayed with Surelease dispersion and Kollicoat IR in a fluid bed dryer with a Wurster column, a prolonged release bead is thus formed. The prolonged release beads are then sprayed with Opadry Clear ® YS-1-7006 aqueous solution. Opadry protects the beads from agglomeration. The beads are then encapsulated.

For Formulation B, a solution is produced from hydromorphone and naloxone dissolved in water, Opadry Clear ® YS-1-7006. This solution is then sprayed on to a microcrystalline cellulose (MXX) beads in a fluid bed dryer with a Wurster column. This produces an immediate-release (IR) bead. The IR bead is then sprayed with Surelease dispersion and Kollicoat IR in a fluid bed dryer with a Wurster column, a prolonged release bead is thus formed. The prolonged release beads are then sprayed with Opadry Clear ® YS-1-7006 aqueous solution. Opadry protects the beads from agglomeration. The beads are then cured in a fluid bed dryer at 60°C outlet temperature with water spraying for 2 hours. The cured beads are then coated with Opadry Clear coating and mixed with silicon dioxide before encapsulation.

Formulations A and B were then analyzed as regards in vitro release behavior using the USP basket method at 100 rpm in 000 ml simulated gastric fluid (SGF) dissolution medium (0.1 N HCl with pH 1.2) without enzyme. Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC/UV.

The in vitro release data is indicated as percentage (based on the label content of active tested) in table 40. The values in the brackets indicate the range observed when measuring six tablets.

Table 40

Formulation	A		B	
Dissolution medium	0.1 N HCl pH1.2		0.1 N HCl pH1.2	
Active tested	Hm	Nal	Hm	Nal
1h	3 (2-3)	4 (3-5)	14 (13-15)	15 (14-17)
2h	6 (5-7)	7 (7-8)	40 (39-42)	42 (41-43)
4h	20 (19-22)	12 (12-14)	68 (68-69)	69 (68-69)
8h	67 (65-68)	65 (63-66)	90 (89-90)	89 (88-90)
12h	87 (87-88)	85 (84-86)	97 (97-98)	97 (96-97)
16h	96 (95-96)	94 (93-95)	100 (99-101)	100 (99-101)
24h	102 (101-102)	101 (100-101)	103 (101-104)	103 (101-104)

Hm = hydromorphone HCl, Nal = naloxone HCl; values are the average of 6 measurements, values in the brackest indicate the observed ranges.

The controlled release bead dosage forms form Formulation A and Formulation B were tested against Hydromorph Contin™ in single-dose pK study conducted under fasted conditions. A summary of the results is shown in Figure 2.

The results showed that all three formulations are bioequivalent. Formulation A is preferred since it resulted in a tmax closest to that of the reference formulation. Thus, when the dosage form according to the invention is in the form of a controlled release bead dosage form, it can be preferred that: (i) it is not subjected to a curing step during manufacture, and (ii) it contains a weight ratio of hydromorphone to naloxone of 2:1 (this was confirmed in a randomized, double-blind, placebo-controlled, dose-ranging crossover study evaluating the effect of naloxone on intravenous hydromorphone abuse potential in healthy, non-dependent, opioid-experienced recreational drug users).

Example 19

This example shows an aqueous method of manufacturing. Granules of the composition as shown in Table 41 were manufactured.

Table 41

Granules Ingredient	F888/49 Amount (mg)	F888/55 Amount (mg)
Hydromorphone HCl	2.0	
Naloxone HCl		4.0
Ethyl cellulose	32.0	32.0
Eudragit NE 40 D*	23.0	23.0
Lactose Anhydrous	29.7	29.7
Purified Water**	11.5	11.5
Glycerol Monostearate 40-55%	2.3	2.3
Hypromellose 5.2 mPas***	0.23	0.23
Talc	5.8	5.8
Total***	95.0	97.0

*The amount indicated refers to the amount of solids used
**Water was removed from the granules by drying
***The amount refers to the weight of the granules without water
The amounts refer to Hydromorphone HCl and Naloxone HCl.

To obtain granules, Hypromellose 5.2 mPas was mixed with purified water until fully dissolved using a Silverson high shear mixer. Then, whilst heating to 60°C and maintaining mixing, glycerol monostearate 40-55% was added. When the mixture reached 60°C, heating was discontinued the mixture was cooled to <54°C with mixing being continued. Talc was added to the Eudragit NE 40 D dispersion while stirring with a Heidolph paddle stirrer until fully dispersed. Then the hypromellose/glycerol monostearate dispersion was added to the Eudragit NE 40 D /

talc dispersion with paddle stirring until a homogenous mixture was obtained. Stirring was maintained.

Ethyl cellulose, lactose, and hydromorphone hydrochloride or naloxone hydrochloride were placed into an Aeromatic Fielder S2 fluid bed granulator.

The conditions for fluidised bed granulation were as follows:

Apparatus:	Aeromatic-Fielder S2 fluid bed granulator
Nozzle diameter:	1.8mm
Spraying pressure:	filter chamber
Air velocity (m/s):	4-6
Inlet Air temperature (°C):	30-40
Spray rate (g/minxkg):	30-50
Spray time (min):	120
Product temperature (°C):	24-26

The granules were then dried in the fluidized bed granulator at <28°C for 20-30 minutes until the moisture content was below 2% w/w. The granules were then sieved using a Demi Finex sieve shakerwith a mesh size of 1mm. Subsequently the granules were milled using a Quadro Comil 197S.

Granules were then pressed into tablets (see Table 42).

Table 42

Tablets	F888/72	F888/83
Ingredient	Amount (mg)	Amount (mg)
Hydromorphone HCl Granules	95.0	

F888/49		
Naloxone HCl Granules F888/55		97.0
Hydromorphone HCl		2.0
Naloxone HCl	4.0	
Magnesium stearate	1.0	1.0
Total	100	100

The amounts refer to Hydromorphone HCl and Naloxone HCl.

For obtaining the tablets, granules were blended with hydromorphone HCl, or naloxone HCl and magnesium stearate using an Apex cone blender. Tablets were obtained by compressing the blend using a Kilian rotary tablet press at a tablet speed of up to 50,000 tablets/hr.

Tablet F888/72 was cured in a convection oven at 60°C for 1 h. The cured tablet was labeled F892/15.

Tablet F888/83 was cured at 60°C for 1 h. The cured tablet was labeled F892/16.

Tablets F892/15 and F892/16 were further subjected to prolonged storage under ICH stressed conditions, namely storage at 25°C/60%RH for 7 months.

For F892/15 the amount of total related substances was 0.28%. The amount of hydromorphone N-oxide was 0.18%.

For F892/16 the amount of total related substances was 0.56%. The amount of hydromorphone N-oxide was 0.14%. The amount of noroxymorphone was 0.10%. The amount of naloxone N-oxide was 0.06%.

Embodiments of the invention relate to the following pharmaceutical compositions for use in the treatment of moderate to severe pain, thereby beneficially influencing hydromorphone-induced constipation:

1. An oral prolonged release pharmaceutical composition comprising at least:
   a) at least one prolonged release material;
   b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof with hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof being present in the pharmaceutical composition in a weight ratio range of 2:1 to 1:3, preferably of about 2:1, about 1:1, about 1:2 or about 1:3;

for use in the treatment of moderate to severe pain, thereby beneficially influencing hydrmorphone-induced constipation.

2. Pharmaceutical composition according to 1, wherein the prolonged release pharmaceutical composition is heat treated.

3. Pharmaceutical composition according to 1 or 2, wherein the at least one prolonged release material and hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined such that a prolonged release matrix is formed.

4. Pharmaceutical composition according to 1, 2 or 3, wherein a prolonged release coating is disposed on the active ingredients hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof.

5. Pharmaceutical composition according to 1, 2, 3 or 4, wherein the prolonged release material is selected from the group comprising hydrophobic or hydrophilic polymers, protein-derived material, gums, substituted or unsubstituted hydrocarbons, digestible carbohydrates, fatty acids, fatty alcohols, glyceryl esters of fatty acids, natural and synthetic oil and waxes.

6. Pharmaceutical composition according to 5, wherein the prolonged release material is a cellulose ether, a (meth)acrylic based (co)polymer and/or a fatty alcohol.

7. Pharmaceutical composition according to 6, wherein prolonged release material is a neutral (meth)acrylic based (co)polymer, a hydrophobic cellulose ether and/or a fatty alcohol.

8. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6 or 7, comprising at least:

a) at least one (meth)acrylic acid (co)polymer, preferably at least one neutral (meth)acrylic acid (co)polymer such as Eudragit®NE as prolonged release material;

b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, and wherein

c) hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release material to form a prolonged release matrix.

9. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6 or 7, comprising at least:

a) at least one cellulose ether, preferably at least one hydrophobic cellulose ether such as ethyl cellulose as prolonged release material;
b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein
c) hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release material to form a prolonged release matrix.

10. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6 or 7, comprising at least:

a) at least one fatty alcohol as prolonged release material;
b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein
c) hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release material to form a prolonged release matrix.

11. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6 or 7, comprising at least:

a) at least one (meth)acrylic acid (co)polymer, preferably at least one neutral (meth)acrylic acid (co)polymer such as Eudragit®NE and at least one cellulose ether, preferably at least one hydrophobic cellulose ether such as ethyl cellulose as prolonged release materials;
b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein
c) hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined

with said prolonged release materials to form a prolonged release matrix.

12. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6 or 7, comprising at least:

a) at least one (meth)acrylic acid (co)polymer, preferably at least one neutral (meth)acrylic acid (co)polymer such as Eudragit®NE and at least one fatty alcohol as prolonged release materials;

b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein

c) hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release materials to form a prolonged release matrix.

13. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6 or 7, comprising at least:

a) at least one cellulose ether, preferably at least one hydrophobic cellulose ether such as ethyl cellulose and at least one fatty alcohol as prolonged release materials;

b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein

c) hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release materials to form a prolonged release matrix.

14. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6 or 7, comprising at least:

a) at least one (meth)acrylic acid (co)polymer, preferably at least one neutral (meth)acrylic acid (co)polymer such as Eudragit®NE, at least one cellulose ether, preferably at least one hydrophobic cellulose ether such as ethyl cellulose and at least one fatty alcohol as prolonged release materials;

b) at least hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, wherein

c) hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are combined with said prolonged release materials to form a prolonged release matrix.

15. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14, wherein the pharmaceutical composition comprises additionally at least one filler, at least one lubricant, at least one binder, at least one release rate modifiers, at least one spheronising agent and/or at least one anti-tacking agent

16. Pharmaceutical composition according to 15, wherein said filler is anhydrous lactose.

17. Pharmaceutical composition according to 15 or 16, wherein magnesium stearate and/or talc are used as lubricants.

18. Pharmaceutical composition according to 15, 16 or 17, wherein hydroxypropyl cellulose is used as binder.

19. Pharmaceutical composition according to 15, 16, 17 or 18, wherein hydroxypropylmethyl cellulose, an anionic (meth)acrylic acid (co)polymer such as Eudragit RSPO and/or Xanthan gum are used release rate modifiers.

20. Pharmaceutical composition according to 15, 16, 17, 18 or 19, wherein microcrystalline cellulose is used as spheronising agent.

21. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, wherein heat treatment takes place at a temperature in the range of about 30°C to about 95°C and for a time in the range of about 10 min to about 3 hours.

22. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21, wherein the composition releases the pharmaceutically active agents with the following in vitro release rate when measured using the Ph. Eur. paddle method in 500 or 900 ml of Simulated Gastric Fluid at 75 or 100 rpm at 37 degrees °C:

at 1 h:	5 to 45% by weight of the pharmaceutically active agents,
at 2 h:	15 to 55% by weight of the pharmaceutically active agents,
at 3 h:	30 to 70% by weight of the pharmaceutically active agents,
at 4 h:	35 to 75% by weight of the pharmaceutically active agents,
at 6 h:	40 to 80% by weight of the pharmaceutically active agents,
at 8 h:	50 to 90% by weight of the pharmaceutically active agents,
at 10 h:	60 to 100% by weight of the pharmaceutically active agents,
at 12 h:	65 to 100% by weight of the pharmaceutically active agents.

23. Pharmaceutical composition according to any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 22, wherein the ratio of the amount of the pharmaceutically active agents released after 0.5, 1 or 2 hours of in vitro dissolution of the dosage form in 500 or 900 ml of Simulated Gastric Fluid with up to 40% ethanol using the Ph. Eur. paddle method at 75 or 100 rpm at 37 degrees °C compared to the amount of the active agents released after 0.5, 1 or 2 hours of in vitro dissolution of the dosage form in 500 or 900 ml of Simulated Gastric Fluid with 0% ethanol using the Ph. Eur. paddle method at 75 or 100 rpm at 37 degrees °C is

about 2:1 or less, is about 1.5:1 or less, is about 1:1 or less, about 1:1.2 or less, about 1:1.4 or less, about 1:1.6 or less, about 1:1.8 or less, about 1:2 or less, about 1:2.5 or less about 1:3 or less or about 1:5 or less.

24. Pharmaceutical dosage form according to any of 1 to 23, wherein hydromorphone hydrochloride and naloxone hydrochloride are used.

25. Pharmaceutical dosage form according to any of 1 to 24, wherein about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 12 mg, about 16 mg, about 24 mg, about 32 mg, about 40 mg, about 48 mg or about 64 mg hydromorphone hydrochloride are used.

26. Pharmaceutical dosage form according to any of 1 to 25, wherein about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 12 mg, about 16 mg, about 24 mg, about 32 mg, about 48 mg, about 64 mg, about 96 mg, about 128 or about 256 mg of naloxone hydrochloride are used.

Patentkrav

1. Oral farmaceutisk sammensætning med langvarig frigivelse, omfattende mindst:
   a) mindst et materiale med langvarig frigivelse;
   b) mindst hydromorphon eller et farmaceutisk acceptabelt salt deraf og naloxon eller et farmaceutisk acceptabelt salt deraf, idet hydromorphon eller et farmaceutisk acceptabelt salt deraf og naloxon eller et farmaceutisk acceptabelt salt deraf er til stede i den farmaceutiske sammensætning i et vægtforhold på 2:1 til 1:3;

til anvendelse ved behandling af moderate til svære smerter, hvorved der sker en gavnlig påvirkning af hydromorphon-induceret obstipation.

2. Farmaceutisk sammensætning ifølge krav 1, hvor hydromorphon eller et farmaceutisk acceptabelt salt deraf og naloxon eller et farmaceutisk acceptabelt salt deraf er til stede i den farmaceutiske sammensætning i et vægtforhold på ca. 2:1, ca. 1:1, ca. 1:2 eller ca. 1:3.

3. Farmaceutisk sammensætning ifølge krav 1 eller 2, hvor det mindst ene materiale med langvarig frigivelse og hydromorphon eller et farmaceutisk acceptabelt salt deraf og naloxon eller et farmaceutisk acceptabelt salt deraf er kombineret således, at der er dannet en matrix med langvarig frigivelse.

4. Farmaceutisk sammensætning ifølge krav 3, hvor materialet med langvarig frigivelse er udvalgt fra gruppen omfattende hydrofobiske eller hydrofile polymerer, proteinafledt materiale, gummier, substituerede eller usubstituerede kulbrinter, fordøjelige kulhydrater, fedtsyrer, fedtalkoholer, glycerylestere af fedtsyrer, naturlige og syntetiske olier og naturlige og syntetiske vokser.

5. Farmaceutisk sammensætning ifølge krav 4, hvor materialet med langvarig frigivelse er en celluloseether, en (meth)acrylbaseret (co)polymer og/eller en fedtalkohol.

6. Farmaceutisk sammensætning ifølge krav 5, hvor materialet med langvarig frigivelse er en neutral (meth)acrylbaseret (co)polymer, en hydrofobisk celluloseether og/eller en fedtalkohol.

7. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 3, 4, 5 eller 6, hvor den farmaceutiske sammensætning endvidere omfatter mindst et fyldstof, mindst et smøremiddel, mindst et bindingsmiddel, mindst en frigivelseshastighedsmodifikator, mindst et sfæroniseringsmiddel og/eller mindst et antiklæbemiddel.

8. Farmaceutisk sammensætning ifølge krav 7, hvor fyldstoffet er vandfri lactose.

9. Farmaceutisk sammensætning ifølge krav 7 eller 8, hvor magnesiumstearat og/eller talkum er anvendt som smøremidler.

10. Farmaceutisk sammensætning ifølge krav 7, 8 eller 9, hvor hydroxypropylcellulose er anvendt som bindingsmiddel.

11. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 3, 4, 5, 6, 7, 8, 9 eller 10, hvor matrixen med langvarig frigivelse er varmebehandlet.

12. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 3, 4, 5, 6, 7, 8, 9, 10 eller 11, hvor varmebehandling finder sted ved en temperatur i området ca. 30 °C til ca. 95 °C og i et tidsrum i området ca. 10 minutter til ca. 3 timer.

13. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 3, 4, 5, 6, 7, 8, 9, 10, 11 eller 12, hvor en coating med langvarig frigivelse er anbragt på matrixen med langvarig frigivelse.

14. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 eller 13, hvor sammensætningen frigiver de farmaceutisk virksomme midler med følgende in vitro-frigivelseshastighed ved måling under anvendelse af Ph. Eur.- paddle-fremgangsmåden i 500 eller 900 ml af simuleret mavevæske ved 75 eller 100 omdr./min ved 37 °C:

ved 1 t:	25 til 55 vægt-% af de farmaceutisk virksomme midler,
ved 2 t:	45 til 75 vægt-% af de farmaceutisk virksomme midler,
ved 3 t:	55 til 85 vægt-% af de farmaceutisk virksomme midler,
ved 4 t:	60 til 90 vægt-% af de farmaceutisk virksomme midler,
ved 6 t:	70 til 100 vægt-% af de farmaceutisk virksomme midler,
ved 8 t:	mere end 85 vægt-% af de farmaceutisk virksomme midler,
ved 10 t:	mere end 90 vægt-% af de farmaceutisk virksomme midler.

15. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 eller 14, hvor forholdet mellem mængden af de farmaceutisk virksomme midler, der frigives efter 0.5, 1 eller 2 timers in vitro-opløsning af doseringsformen i 500 eller 900 ml af simuleret mavevæske med op til 40 % ethanol under anvendelse af Ph. Eur. paddle-fremgangsmåden ved 75 eller 100 omdr./min ved 37 °C, og mængden af de virksomme midler, der frigives efter 0.5, 1 eller 2 timers in vitro-opløsning af doseringsformen i 500 eller 900 ml af simuleret mavevæske med 0 % ethanol under anvendelse af Ph. Eur. paddle-fremgangsmåden ved 75 eller 100 omdr./min ved 37 °C, er ca. 2:1 eller derunder, er ca. 1.5:1 eller derunder, er ca. 1:1 eller derunder, ca. 1:1.2 eller derunder, ca. 1:1.4 eller derunder, ca. 1:1.6 eller derunder, ca. 1:1.8 eller derunder, ca. 1:2 eller derunder, ca. 1:2.5 eller derunder, ca. 1:3 eller derunder eller ca. 1:5 eller derunder.

16. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 eller 15, hvor den farmaceutiske sammensætning er en multipartikelformulering.

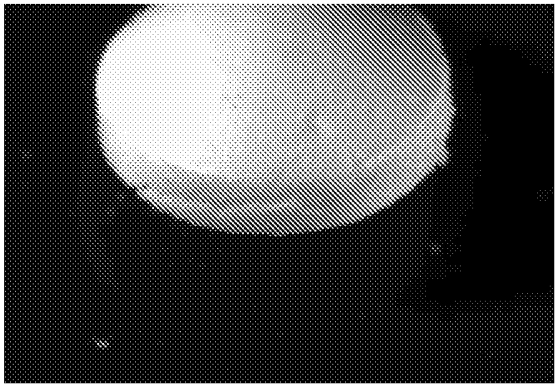
17. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 eller 16, hvor der er anvendt hydromorphonhydrochlorid og naloxonhydrochlorid.

18. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 eller 17, hvor den farmaceutiske sammensætning er formuleret i en doseringsform og omfatter hydromorphonhydrochlorid i mængder svarende til ca. 1 mg, ca. 2 mg, ca. 4 mg, ca. 8 mg, ca. 12 mg, ca. 16 mg, ca. 24 mg, ca. 32 mg, ca. 40 mg, ca. 48 mg eller ca. 64 mg vandfri hydromorphonhydrochlorid.

19. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 eller 18, hvor den farmaceutiske sammensætning er formuleret i en doseringsform og omfatter naloxonhydrochlorid i mængder svarende til ca. 1 mg, ca. 2 mg, ca. 4 mg, ca. 8 mg, ca. 12 mg, ca. 16 mg, ca. 24 mg, ca. 32 mg, ca. 48 mg, ca. 64 mg, ca. 96 mg, ca. 128 eller ca. 256 mg vandfri naloxonhydrochlorid.

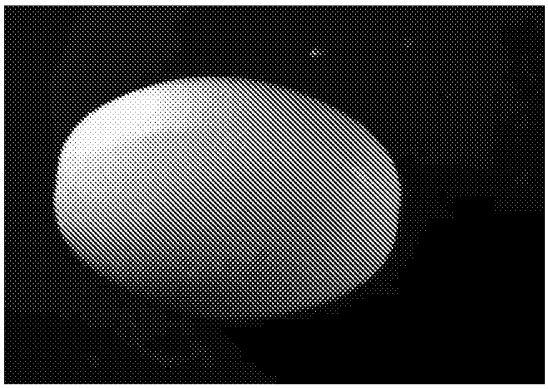
Figure 1

a)



Untreated tablet core

b)



Tablet core, heat treated at 55°C for 30 minutes

Figure 2

SUMMARY OF RESULTS
HYDROMORPHONE
N = 11

Parameters		Test (Hydromorphone-Naloxone)						Reference (Hydromorph Contin (C))		
		Test-1 (A) N = 11			Test-2 (B) N = 10			N = 11		
		Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC_{0-t}	(pg·h/mL)	6927.10	1602.27	26.58	5721.45	1850.89	32.35	5905.86	1749.06	29.62
$AUC_{0-\infty}$	(pg·h/mL)	7762.05	2923.79	37.67	7440.23	2831.42	38.06	7131.66	1723.95	24.17
AUC_{ext}	(%)	81.49	14.83	18.20	80.08	15.39	19.22	82.63	10.76	13.02
AUC_{0-12h}	(pg·h/mL)	2808.57	654.85	23.32	2818.37	1056.88	37.50	2782.87	1018.48	36.60
AUC_{ext}	(%)	38.72	9.74	25.16	39.36	9.31	23.65	38.72	8.09	20.89
C_{max}	(pg/mL)	454.34	159.24	35.05	568.34	257.83	45.36	392.47	124.09	31.62
T_{max}	(h)	4.23	1.91	45.26	1.66	0.34	20.24	5.27	2.53	48.00
T_{max} *	(h)	5.00	2.49	-	1.51	0.50	-	5.00	0.99	-
K_{el}	(h^{-1})	0.0594	0.0262	44.06	0.0530	0.0205	38.76	0.0587	0.0218	37.11
$T_{1/2}$	(h)	14.92	9.60	64.37	16.78	12.41	73.93	13.60	5.73	42.11

* Medians and interquartile ranges are presented.

DANISH PATENT AND TRADEMARK OFFICE

SEARCH REPORT - PATENT	Application No. PA 2012 70677

1. ☐ Certain claims were found unsearchable (See Box No. I).

2. ☐ Unity of invention is lacking prior to search (See Box No. II).

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 9/22 (2006.01); A 61 K 9/30 (2006.01); A 61 K 31/485 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

DK, NO, SE, FI: IPC-classes as above.

Electronic database consulted during the search (name of database and, where practicable, search terms used)

Search Report for WO 2011/141488 A2 has been used, see this for details

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant for claim No.
X, P	WO 2010/140007 A2 (EUROCELTIQUE S.A. (LU)) 09/12/2010 See page 40, lines 9-10; Figures 2 and 5 and examples 2-6.	1-8, 10-11, 14, 18 and 21-24
A, P		9, 12-13, 15-17 and 19-20
X	US 2006/0039970 A1 (OSHLACK, B. et al.) 23/02/2006 See entire document, in particular abstract; paragraphs [0011], [0015]-[0016], [0025], [0092]-[0094], [0101], [0105]-[0106], [0109]-[0110] and [0115] and examples 1-4.	1-24

☒ Further documents are listed in the continuation of Box C.

*	Special categories of cited documents:	"P"	Document published prior to the filing date but later than the priority date claimed.
"A"	Document defining the general state of the art which is not considered to be of particular relevance.	"T"	Document not in conflict with the application but cited to understand the principle or theory underlying the invention.
"D"	Document cited in the application.	"X"	Document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone.
"E"	Earlier application or patent but published on or after the filing date.	"Y"	Document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"L"	Document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).	"&"	Document member of the same patent family.
"O"	Document referring to an oral disclosure, use, exhibition or other means.		

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12 February 2014

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SEARCH REPORT - PATENT		Application No. PA 2012 70677
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant for claim No.
X	US 2007/0014732 A1 (SACKLER, R.) 18/01/2007 See entire document, in particular paragraphs [0028], [0058]-[0059], [0070], [0075], [0081], [0100]-[0104], [0136]-[0146], [0153]-[0164] and [0167] and examples 1-4, 15 and 16.	1-24
X	WO 03/013525 A1 (EUROCELTIQUE S.A. (LU)) 20/02/2003 See entire document, in particular page 2, lines 22-26; page 8, lines 24-25; page 23, lines 8-24; page 30, lines 19-24; page 32, line 19 - page 34, line 16 and examples 8, 13 and 21.	1-24
A	US 4457933 A (GORDON, M et al.) 03/07/1984 See column 2, lines 5-10 and 45-65.	1-24
A	OLIVETO, A.H. et al.: "Hydromorphone-Naloxone Combinations in Opioid-Dependent Humans Under a Naloxone Novel-Response Discrimination Procedure", EXPERIMENTAL AND CLINICAL PSYCHOPHARMACOLOGY, 1998, Vol. 6, No. 2, pages 169-178. See entire document.	1-24

SEARCH REPORT - PATENT	Application No. PA 2012 70677

Box No. I Observations where certain claims were found unsearchable

This search report has not been established in respect of certain claims for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched, namely:

2. ☐ Claims Nos.:
because they relate to parts of the patent application that do not comply with the prescribed requirements to such an extent that no meaningful search can be carried out, specifically:

3. ☐ Claims Nos.:
because of other matters.

Box No. II Observations where unity of invention is lacking prior to the search

The Danish Patent and Trademark Office found multiple inventions in this patent application, as follows:

SEARCH REPORT - PATENT	Application No. PA 2012 70677

SUPPLEMENTAL BOX

Continuation of Box [.]