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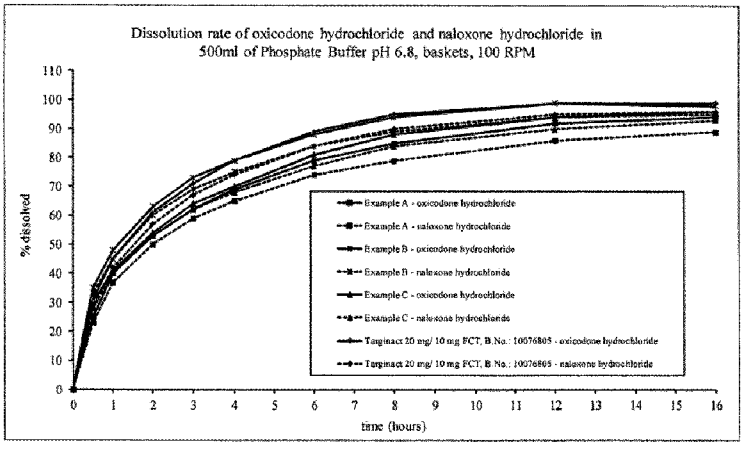
(54) Title: PHARMACEUTICAL FORMULATION COMPRISING AN OPIOID AGONIST AND AN OPIOID ANTAGONIST PREPARED BY MELT GRANULATION USING LIPID ESTERS

Figure 1



(57) Abstract: The present invention provides pharmaceutical formulations containing opioid agonist such as oxycodone and opioid antagonist such as naloxone. These pharmaceutical formulations exhibit satisfactory release properties for both drugs.

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Pharmaceutical formulation comprising an opioid agonist and an opioid antagonist prepared by melt granulation using lipid esters

1. Technical field of the invention

The present invention pertains to new pharmaceutical formulations containing an opioid agonist and an opioid antagonist, such as oxycodone and naloxone or any pharmaceutically acceptable salts and/or hydrates or solvates thereof. In particular, the present invention provides pharmaceutical formulations containing these active ingredients, which are sustained release formulations exhibiting excellent release properties and have abuse deterrent properties. The present invention further provides methods for making the same.

2. Background of the invention

Pharmaceutical formulations containing oxycodone and naloxone as active ingredients are disclosed *inter alia* in WO 03/084520 A2 and WO 03/084504 A2 and prior art cited therein. In particular, WO 03/084520 A2 and WO 03/084504 A2 teach pharmaceutical formulations, which are said to release the two active compounds from a non-swellable diffusion matrix in a sustained, invariant and independent manner. Preferably such matrices comprise polymers based on ethylcellulose and at least one fatty alcohol, preferably stearyl alcohol, as the components that essentially influence the release characteristics of the matrix. Fatty alcohols do not regularly occur in human body. They can originate from natural or synthetic sources, but are not of human origin.

EP2277521 discloses an oral dosage form comprising an opioid agonist and an opioid antagonist which is dispersed in a matrix comprising one or more hydrophobic material. Said matrix renders the antagonist substantially non-releasable when the dosage form is administered orally intact while in EP2283842 the opioid antagonist is in a substantially non-releasable form by coating the particles with a coating that substantially prevents release of the antagonist.

WO2002092060 discloses a controlled release tablet comprising an opioid agonist in a controlled release matrix and an opioid antagonist having an

oral:parenteral potency ratio > 1 contained in a controlled release matrix; wherein ammonium methacrylate polymer is present in the controlled release matrix.

WO2003013476 and WO2003013479 disclose a controlled release oral dosage form comprising oxycodone hydrochloride and a gelling agent comprising polyethylene oxide.

In WO2003013538 the composition comprising an opioid agonist and antagonist coated with inner-acid soluble layer and an outer base-soluble layer is disclosed.

WO2004026283 discloses a composition comprising a sequestering unit and an opioid agonist wherein opioid antagonist is over-coated with opioid agonist.

WO2005079760 and WO2006079550 disclose the use of sparingly water permeable thermoplastic polymer or hydrophilic polymer in an opioid controlled release matrix to impart resistance to alcohol extraction of the opioid.

WO2007085637 discloses the controlled release dosage form of oxycodone hydrochloride and naloxone hydrochloride comprising a homogenous controlled release matrix comprising a hydrophobic material and at least one fatty alcohol or fatty acid selected from C12 to C36 aliphatic alcohols or acids.

WO2012020097 discloses the use of hydroxypropyl cellulose for the manufacturing of a prolonged release pharmaceutical composition comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof.

However, for various reasons, there remains a need for alternative pharmaceutical formulations exhibiting a comparable release profile.

3. Summary of the invention

The present invention provides further pharmaceutical formulations containing oxycodone and naloxone, which exhibit such favorable release profiles. The essential features of such inventive formulations are characterized in appended claims 1 and 14. Preferred embodiments

thereof are described in subsequent dependent claims 2 to 9. Methods for making such formulations are also described in appended claims 10 to 13.

4. Short description of Figures

Figures 1 and 2 show the release characteristics of several exemplified compositions of the present invention.

5. Detailed description

The pharmaceutical formulation of the present invention comprises an opioid agonist and an opioid antagonist, such as oxycodone and naloxone or any pharmaceutically acceptable salts and/or hydrates or solvates thereof, one or more binder, one or more diluent, one or more lubricant, one or more flow enhancing agent and optionally other pharmaceutical acceptable excipients selected from the group but not limited to glidants, pH modifiers, antioxidants and surfactants. The pharmaceutical formulation of the present invention may comprise in addition to the opioid agonist and antagonist at least one other active substance. The pharmaceutical formulation of the present invention can be in the form of a tablet or capsule wherein they can be uncoated or coated. In case the coating is applied onto the solid pharmaceutical formulation it is composed of at least one polymer for coating and at least one further pharmaceutically acceptable excipient, which can be selected but not limited from plasticizers, anti-tacking agents, pigments and coloring agents, pore formers. The thickness of the coating can be in the range from 5 to 80 μm, preferably 10-50 μm and most preferably 10-40 μm. The coating can optionally decrease permeability for gases such as oxygen and/or for moisture. Such decreased permeability can be achieved by the use of functional polymers which in combination with selected further excipients in the coating give the desired properties of the coating.

5.1. Definitions

In the context of the present invention and unless specified otherwise, the melting point of substances is to be determined according to Ph.Eur. 2.2.14.

The softening point is defined as the temperature at which the sample softens on heating but does not form a melt of low viscosity. Softening point can be determined according to Ph.Eur. 2.2.17 (preferably METHOD B). The measuring principle of softening point differs from that of the drop point in respect to the sample cup: it has an opening of 6,35 mm. Sample is loaded in a standard softening point sample cup and it should flow 20mm out of the 6,35mm sample cup opening. (Instrument Mettler Toledo FP900, FP83HT cell)

In the context of the present invention and unless specified otherwise, the mean particle size of particulate substances is to be determined by laser diffraction method, using Malvern Mastersizer 2000 equipped with Hydro 2000S dispersion unit, vegetable oil (sunflower oil) is used as dispersant.

According to the present invention and unless specified otherwise, the term "pharmaceutically acceptable salts" refers to all salts formed with organic and/or inorganic counter ions in any possible physical state including crystalline and amorphous forms of anhydrous, hydrated or solvated forms of the respective pharmaceutically active ingredient, which are safe for administration to human patients.

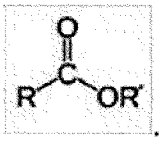
According to the present invention and unless specified, all amount indications are provided on a weight basis or weight/weight basis, as appropriate. If the active pharmaceutical ingredient is used in the form of a pharmaceutically acceptable salt, the weight of the entire salt is to be considered, including the weight component of the counter ion. If the active pharmaceutical ingredient is used in the form of a solvate or hydrate, the additional weight associated with solvent or water components in the substance is to be disregarded. That is, a theoretical weight of the anhydrous pure substance (or its pharmaceutically acceptable salt and/or hydrate or solvate, if appropriate) is to be calculated and considered in connection with the present invention.

According to certain preferred aspects of the present invention and unless specified otherwise, the term „opioid agonist" and the term „opioid antagonist" relate to active pharmaceutical ingredients which are in a form of salts with organic and inorganic acids belonging to a group of water soluble or water freely soluble compounds as defined by European Pharmacopeia (Ph. Eur 3rd Ed.), i.e that 1 g of opioid agonist and/or opioid antagonist in the form of approriate salt is soluble in 10 to 30 ml of water (water soluble according European

Pharmacopeia) and/or that 1 g of opioid agonist and/or opioid antagonist in the form of approriate salt is soluble in 1 to 10 ml of water (freely soluble according to European Pharmacopeia).

According to certain preferred aspects of the present invention and unless specified otherwise, the term "hydrophilic " is defined as a pharmaceutically acceptable excipient which is soluble in water at 25°C in concentration of at least 0.1 weight/vol%, preferably of at least 0.5 weight/vol% and most preferably of at least 1.0 weight/vol%, wherein volume indications refer to the volume of the formed solution. It is typically capable of forming highly viscous and sticky solutions at higher concentrations.

According to certain preferred aspects of the present invention and unless specified otherwise, the term "hydrophobic (molten) binder" is defined as a pharmaceutically acceptable excipient which is insoluble or slightly soluble in water at 25°C. This means, in accordance with USP30/NF25, that the excipient has a solubility in water at 25°C of 10 mg/mL or less. It is typically designated with melting and/or softening point in the range of 35 to 160°C, preferably 40 to 130°C, more preferably between 42 and 85°C and even more preferably between 45 and 80°C. It is specially preferred that the hydrophobic binder is selected from the chemical group of esters with the following general formula:



Commercially available excipients used for manufacturing the pharmaceutical formulation according to present invention can be used in an "as is form" or can be mechanically pretreated in order to optimize particle size and particle size distribution by milling and/or sieving.

5.2. Overview

The present invention provides pharmaceutical formulations containing an opioid agonist and an opioid antagonist, such as oxycodone and naloxone, which are derived from WO 03/084520 and WO 03/08440. In particular, these prior art patent applications teach the use of ethylcellulose and a fatty alcohol such as stearyl alcohol as essential components of a non-swellable diffusion matrix, which gives rise to the desired release characteristics. The present inventors have surprisingly found that ethylcellulose and/or fatty alcohol may be

replaced by the alternative components without compromising the release characteristics. The present invention has been completed based on these findings.

5.3. Active pharmaceutical ingredients

A first active pharmaceutical ingredient is an opioid agonist (or opioid analgesic). Suitable for use in the present invention are all opioid analgesics described on pages 25 and 26 of WO 03/084504 A2. Oxycodone or any pharmaceutically acceptable salt and/or solvate or hydrate thereof is the preferred opioid analgesic.

Oxycodone or a pharmaceutically acceptable salt and/or solvate or hydrate thereof is a narcotic analgesic which is used to help relieve moderate to severe pain of different origin, as for example injuries, arthritis, cancer, to treat pain after a surgical operation. It belongs to a class of drugs known as narcotic (opiate) analgesics. Oxycodone or pharmaceutically acceptable salts thereof is a type of a strong opioid. It works on nervous system and brain to reduce the way a human feels pain.

Oxycodone or any pharmaceutically acceptable salts and/or hydrates or solvates thereof can be used in anhydrous or solvated or hydrated form. Additionally, they may be used in amorphous form or in any crystalline form as for example disclosed in WO 2004/016618, US 2007/0197572, including solvate and hydrate crystals.

Oxycodone hydrochloride used in the pharmaceutical formulation according to the present invention may be prepared according to any manufacturing process known from the state art such as for example WO 99/02529, WO 2004/108090, US7071336, WO 2005/097801, WO2006019364, US7153966, WO 2006/094672, WO 2006/138020, WO 2007/062184, WO 2007/103105, WO 2007/137785, WO 2007/124114, WO 2007/ 137785, WO 2008/070656, WO 2008/070658, WO 2008/130553, WO 2009/004491, EP 2062896B1, WO 2010/144641, WO 2011/021029, WO 2011/032214, WO 2011/034747, WO 2011/117172, WO 2011/154827, WO 2012/003468, WO 2012/14963, WO 2013/085937, WO 2013/119886, US 8846923, WO 2014/013311, WO2014/013313.

According to one embodiment oxycodone hydrochloride used in the pharmaceutical formulation according to the present invention may have an average particle size less than

100 μm, preferably less than 75 μm and more preferably less than 50 μm or d_{90} less than 250 μm, preferably less than 200 μm and more preferably less than 110 μm. According to one aspect of this embodiment, the average particle size is the average particle size according to a D [4,3]-volume distribution. In another embodiment oxycodone hydrochloride used in the pharmaceutical formulation according to the present invention may have an average particle size (D [4,3]-volume distribution) less than 100 μm, preferably less than 75 μm and more preferably between 5 - 70 μm and/or d_{90} less than 250 μm, preferably less than 200 μm and more preferably between 10 and 150 μm.

The second active pharmaceutical ingredient is an opioid antagonist. Suitable for use in the present invention are all opioid antagonists described on page 26 of WO 03/084504 A2. The preferred opioid antagonist is naloxone or any pharmaceutically acceptable salts and/or hydrates or solvates thereof.

Naloxone or pharmaceutically acceptable salt and/or solvate or hydrate thereof is an opioid antagonist that is added to the pharmaceutical formulation of the present invention to counteract opioid induced side effects, as for example constipation by blocking the action of oxycodone at opioid receptors locally in the gut, nausea, vomiting, pruritis, urinary retention, respiratory depression, physical dependence, tolerance, hyperexcitability, and hyperalgeia. Pharmacologically, opioid antagonists block or reverse all of the effect of opioid agonists.

Naloxone or any pharmaceutically acceptable salts and/or hydrates or solvates thereof can be used in anhydrous forms or in the form of solvates or hydrates, wherein the dihydrate is preferred. Additionally, they may be used in amorphous form or in any crystalline form, including solvate and hydrate crystals. This component is incorporated into the pharmaceutical formulation to prevent or discourage abuse, tampering, misuse or diversion of the pharmaceutical formulation and to reduce side-effects of opioid agonist such as for example obstipation, breath depression, danger of the development of dependency and addiction.

Naloxone hydrochloride dihydrate, which is preferably used in the pharmaceutical formulation according to the present invention, may be prepared according to any manufacturing process known from the state of the art such as for example WO 2006/084389, CN 101033228, WO 2007/103105, WO 2007/137785, WO 2007/124114, WO 2007/137785,

WO 2009/092912, WO 2009/079013, WO 2009/111162, WO 2009/155259, WO 2010/039222, WO 2010/144641, CN 101768164, WO 2011/021029, WO 2011/154826, CN 102174049, WO 2012/151669, WO 2013/085937, WO 2013/113120, IN 2012MU00409, CN 103304570.

According to one embodiment naloxone hydrochloride dihydrate may have an average particle size less than 100 μm, preferably less than 60 μm and more preferably less than 40 μm or d_{90} less than 250 μm, preferably less than 200 μm and more preferably less than 80 μm. According to one aspect of this embodiment, the average particle size is the average particle size according to a D [4,3]-volume distribution. According to another embodiment naloxone hydrochloride dihydrate may have an average particle size (D [4,3]-volume distribution) less than 100 μm, preferably less than 60 μm and more preferably between 5-50 μm and/or d_{90} less than 250 μm, preferably less than 200 μm and more preferably between 15 and 150 μm.

In case that active ingredients do not correspond to the above disclosed requirements for particulate properties, i.e. particle size and/or particle size distribution, they can be adjusted by optional milling and/or sieving. Standard state of the art milling/micronizing and sieving techniques and equipment can be used for achieving the desired particulate properties. Preferably a micronizing mill such as an air jet mill can be used. The invention is however not limited to the use of this device.

Oxycodone hydrochloride and naloxone hydrochloride dihydrate as used in the examples described below can be prepared by any above mentioned processes and can have any characteristics as defined above.

In one aspect the pharmaceutical formulation according to the present invention may comprise other active ingredients suitable to be incorporated into the same formulation.

5.4. Hydrophilic binder/Hydrophobic - molten binder

The pharmaceutical formulation of the present invention is in one aspect designated by the use of combination of two types of binders, wherein one is hydrophilic and the other one is hydrophobic and is used in a molten state during the manufacturing of the pharmaceutical formulation. The pharmaceutical formulation of the present invention thus comprises at least

one hydrophilic binder and at least one hydrophobic binder. The present specification refers to the hydrophobic binder also as molten binder.

The pharmaceutical formulations of the present invention thus comprise two types of binders, one of which is a hydrophilic binder such as for example polyvinylpyrrolidone (povidone), polyvinylpyrrolidone-vinyl acetate copolymer (copovidone), hydroxypropyl methylcellulose (hypromellose), hydroxypropylcellulose (hyprollose), hydroxyethyl cellulose, polyvinyl alcohol and its derivatives and the other one is a hydrophobic binder which is molten during the agglomeration process. In one embodiment the hydrophilic binder is selected from the group consisting of povidone types with K value in the range of 12 to 100, preferably 20 to 35 and/or having a weight average molecular weight Mw preferably in the range of 18,000-55,000.

In an another embodiment of the present invention, hydrophilic binders can be selected from cellulose ether derivatives such as hydroxypropyl cellulose (HPC, hyprollose), methyl cellulose (MC) and or, hydroxypropyl methyl cellulose (HPMC, hypromellose). A wide span of cellulose ethers of molecular weights and resulting viscosities of 2% aqueous solutions measured with rotating viscosimeter such as Brookfield at 20°C is available on the market. As hydrophilic binders are typically used those having viscosities below 100 mPas, preferably below 50mPas and most preferably below 30mPas. Cellulose ethers typically used as binders have in some embodiments viscosities in the range from 2 to 20 mPas, preferably from 3 to 15 mPas.

The pharmaceutical formulation of the present invention may comprise more than one hydrophilic binder i.e a mixture of two or more hydrophilic binders can be used.

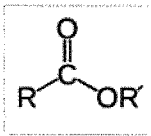
The term molten binder includes in one embodiment one or more substances having hydrophobic nature which are in order to exhibit their binding function in the formulation transformed to liquid melt. In an another embodiment of present invention the molten binder includes one or more substances which are prior and/or during the formulation process softened by heating and/or increased pressure and/or torque, i.e. kneading and/or shearing forces, into a softened mass which is capable of binding solid particles of the composition into the granules.

In one embodiment the molten binder to be used in the present invention is characterized by having a melting or softening point below 160°C, preferably below 130°C and most preferably below 95°C.

In still another embodiment the molten binder is melted or softened at temperatures above 40°C and is in solid form at room temperature. Preferably it is melted or softened at temperatures between 40 and 95°C, more preferably between 42 and 85°C and even more preferably between 45 and 80°C.

The hydrophobic binder can be added in a molten form preferably by spraying to the powder mixture or can be admixed with the rest of the ingredients of the powder mixture for agglomeration and is then molten during the agglomeration process by the heat formed by the friction or pressure and by the additional heat applied to the mixture by external heating such as by the use of a heated double jacket of the mixing bowl or the extruder tube.

The molten binder can be selected from pharmaceutically acceptable esters with a general formula:



where the acyl residue (R-COO) is derived from organic acids having at least 8 carbon atoms in the molecule, preferably at least 10 carbon atoms and most preferably at least 12 carbon atoms and preferably no more than 30 carbon atoms, more preferably no more than 26 carbon atoms and most preferably no more than 23 carbon atoms. Residue (R′) is a residue that may be derived from an alcohol, which can be selected from monohydroxylic alcohols, which can be selected but not limited from dodecanoic, tetradecanoic, hexadecanoic; octadecanoic or eiconoic alcohols; dihydroxylic alcohols such as ethyleneglycol or oligohydroxylic alcohols having 3 to 30, preferably 3 to 20 and most preferably 3 to 10 hydroxylic groups in their molecule such as glycerol, saccharose, sorbitan. In case dihydroxylic or oligohydrohylic alcoholic residues are used as R′ total or partial esters can be used. The expression total ester means that all hydroxylic groups in the alcohol are esterified by organic acids and the expression partial ester means that only a part of the hydroxylic groups in the alcohol is esterified by organic acids. Residue R' may thus include one or more hydroxyl groups and/or

one or more acyl ester groups R-COO in addition to the core moiety of the alcohol. If more than one acyl ester group is present, the acyl ester groups may be the same or different from each other. Exemplified compounds are glycerol monostearate, glycerol distearate, glycerol palmitostearate, partial fatty acid esters of saccharose, sorbitan mono, di or tri acyl esters such as sorbitan monostearate, sorbitan dilaurate, sorbitan trilaurate or the like. Pharmaceutically acceptable esters used in the present invention are further characterized by having a melting or softening point below 160°C, preferably below 130°C and most preferably below 95°C.

In one further embodiment the molten binder is selected from the group consisting of glycerol distearate, glycerol dibehenate and sucrose stearate that may have HLB (hydrophilic lipophilic balance) value (defined by Griffin WC: "Classification of Surface-Active Agents by 'HLB,'" Journal of the Society of Cosmetic Chemists 1 (1949): 311. and "Calculation of HLB Values of Non-Ionic Surfactants," Journal of the Society of Cosmetic Chemists 5 (1954): 259) below 12, preferably below 10 and most preferably below 8.

In still one further embodiment the molten binder is selected from the group consisting of glycerol distearate having the melting or softening point of 45 – 65°C and preferably 50-60°C, glycerol dibehenate having the melting or softening point of 60 - 80 °C and preferably 65-77°C and sucrose stearate having the melting or softening point of 45 – 65 °C and preferably 51-58°C.

In a special embodiment the molten binder includes polymers, which are at room temperature mainly in amorphous state and have a glass transition temperature (Tg) below 200°C, preferably below 180°C and most preferably below 160°C. Tg can be further decreased by using a pharmaceutically acceptable plasticizer whereas the weight ratio between the amorphous polymer and the plasticizer is in the range 20:1 to 1:1, preferably 11:1 to 4:1 and most preferably 10:1 to 5:1. Plasticizer is preferably selected from substances having a molecular weight of less than 25,000, preferably of less than 20,000 and most preferably of less than 10,000.

The pharmaceutical formulation of the present invention may comprise more than one molten binders, i.e a mixture of two or more molten binders can be used.

The pharmaceutical formulation of the present invention is in another special aspect characterized by the use of at least one molten binder and by the absence of hydrophilic binder in said formulation.

5.5. Matrix former

The state of the art teaches ethylcellulose as an essential component to form the matrix. In one aspect of the present invention the inventors surprisingly found that this matrix former may be replaced by any kind of water insoluble or very low water soluble pharmaceutically acceptable ingredient, which may either be of organic or inorganic nature. Organic insoluble matrix formers can be selected from the group consisting of polymers such as cellulose derivatives including ethylcellulose and cellulose-based polymers other than ethylcellulose like cellulose acetate, cellulose acetate propionate, cellulose acetate butyrate, methacrylic acid derivatives such as Eudragit® RS, polyvinyl esters such as polyvinyl acetate, derivatives of alkyl siloxanes such as polydimethylsiloxane, urethane derivatives such as polyether urethane, where cellulose acetate is being preferred. Cellulose acetate can be partly or completely *O*-acetylated cellulose. It contains not less than 29.0 per cent and not more than 44.8 per cent by weight of acetyl groups (C_2H_3O), calculated with reference to the dried substance. The acetyl content is preferably not less than 90.0 per cent and not more than 110.0 per cent of that stated on the label. The acetyl content is calculated with reference to the dried substance (as described in Ph Eur. Monograph 0887, retrievable under the following URL: http://www.newdruginfo.com/pharmacopeia/bp2003/British%20Pharmacopoeia%20Volume%20I%20and%20II%5CMonographs%20Medicinal%20and%20Pharmaceutical%20substances%5CC%5CCellulose%20Acetate.htm). A particularly preferred matrix former is the product Eastman® Cellulose Acetate which is commercially available from Eastman or methacrylic acid derivatives such as Eudragit® RS which is commercially available from Evonic Industries.

Inorganic matrix formers can be selected from water insoluble inorganic materials which do not change the pH of the aqueous dispersion (measured as 10 weight/volume%) by more than 2 pH units, preferably by more than 1.5 pH units and most preferably by 1 pH unit in relation to pure deionized water from which the dispersions are prepared. Typical examples of such insoluble inorganic materials are calcium salts of carbonic, phosphoric or sulphonic acid such as calcium hydrogen phosphate in anhydrous or hydrated form.

Matrix former used in the pharmaceutical formulation according to the present invention may have an average particle size (D [4,3]-volume distribution) less than 700 μm, preferably less than 600 μm and more preferably between 200 and 500 μm and/or d_{90} less than 1300 μm, preferably less than 900 μm and more preferably between 300 and 800 μm.

Matrix former obtained in standard pharmaceutical quality and particle size distribution can be in a special embodiment of present invention mechanically pre-treated by milling and/or sieving to achieve desired particle size and particle size distribution. Mechanical pre-treatment of the matrix former can be executed by the state of the art milling equipment such as pin mills and/or sieving equipment such as vibrational mill. Mechanical treatment of matrix former by sieving is being preferred option.

The weight ratio between molten binder and matrix former is advantageously selected to regulate the release kinetics and profile of active ingredient(s) from solid dosage form and the desired processability. If the content of molten binder is kept within appropriate limits, it is possible to avoid that the formulation is compromised by the stickiness during the agglomeration process and/or compression of the tablets or clogging of the sieve openings during sieving may occur. On the other hand, when the concentration of the molten binder is too low, incomplete formation of granules due to insufficient binding capacity could result on one hand and on the other hand too fast release in vivo and in vitro of incorporated active ingredients could result.

Therefore, according to one embodiment of the present invention, the weight ratio between molten binder and matrix former is from 0.8 : 0.2 to 0.2 : 0.8, preferably from 0.7 : 0.3 to 0.3 : 0.7 and more preferably from 0.6 : 0.4 to 0.4 : 0.6.

According to another embodiment of the present invention, ethylcellulose may be used as the matrix former. The resulting pharmaceutical formulations of the present invention nevertheless differ from those known from the above-mentioned prior art due to the combination of hydrophilic binder and molten binder and particularly due to the presence of the component "molten binder" described above.

If ethylcellulose is used in the context of the present invention, its ethoxylation degree may be from 45 to 52.5%, preferably 47.2 to 51.5% and most preferably from 48 to 51.0% (N-type). The weight average molecular weight of the ethylcellulose may range from 75,000 to 215,000. The ethylcellulose preferably has a viscosity of from 6 to 130 mPas, more preferably from 9 to 85 mPas and most preferably 18 to 60 mPas, when measured as a 5% solution in a mixture of methylbenzene (80%) and isopropanol (20%) by a Brookfield LV rotation viscosimeter at 25°C. A preferred commercially available ethylcellulose product is Ethocel Standard 45 Premium Ethylcellulose which is supplied by Dow Chemicals.

According to one embodiment of the present invention the weight ratio between molten binder and ethylcellulose is from 0.8 : 0.2 to 0.2 : 0.8, preferably from 0.7 : 0.3 to 0.3 : 0.7 and more preferably from 0.6 : 0.4 to 0.4 : 0.6.

According to another embodiment of the present invention the weight ratio between glyceryl distearate and ethylcellulose is from 0.8 : 0.2 to 0.2 : 0.8, preferably from 0.7 : 0.3 to 0.3 : 0.7 and more preferably from 0.6 : 0.4 to 0.4 : 0.6.

According to still another embodiment of the present invention ethylcellulose used in the pharmaceutical formulation according to the present invention may have an average particle size (D [4,3]-volume distribution) less than 700 μm, preferably less than 600 μm and more preferably between 200 and 500 μm and/or d_{90} less than 1300 μm, preferably less than 900 μm and more preferably between 300 and 800 μm.

Matrix former used in the examples of the present invention can have any characteristics as defined above. The pharmaceutical formulation of the present invention may comprise a single matrix former or a combination of more than one matrix formers, i.e a mixture of two or more matrix formers can be used.

5.6. Diluent

The diluent present in the pharmaceutical formulation according to the present invention can be selected among any known state of the art pharmaceutical diluents for solid dosage forms, as described e.g. in Avis K. E, Pharmaceutical Dosage Forms: Tablets, Third Edition, 2008 Particularly useful for the present invention are diluents selected from the group consisting of

soluble carbohydrates such as oligosaccharides such as dextrin, cyclodextrins, disaccharides such as lactose, mannose, sucrose, monosacharides such as glucose or fructose or derivatives thereof such as for example sugar alcohols such as mannitol, sorbitol, inositol, maltitol, and lactitol. Optionally the diluent can be selected form water insoluble excipients selected from the group consisting of calcium hydrogen phosphate in anhydrous or hydrated form, powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose or the like. Different grades of individual diluents can be used such as granulated, spray dryed co-processed grades, or the like.

The diluent to be used according to a preferred embodiment of the present invention is lactose. Lactose may be used in its anhydrous form or in the form of a hydrate. There are no particular limitations concerning the type of lactose to be used in the present invention. The use of lactose monohydrate is particularly preferred.

5.7. Flow enhancing agent

Talc and/or colloidal silicone dioxide can be used as a flow enhancing agent in the pharmaceutical formulation according to the present invention; talc is the preferred option by the present invention. There are no particular limitations concerning the type of talc to be used in the present invention.

5.8. Lubricant

The lubricant present in the pharmaceutical formulation according to the present invention may be selected from the group consisting of metal salts of fatty acids such as for example magnesium or calcium stearate, stearic acid, sodium stearyl fumarate, sodium starch glycolate or the like. Magnesium stearate is the preferred lubricant.

5.9. Other pharmaceutically acceptable excipients

Other pharmaceutically acceptable excipients present in the pharmaceutical formulation according to the present invention can be selected among any known state of the art pharmaceutical diluents for solid dosage forms, as described e.g. in Remington: The Science

and Practice of Pharmacy, Edited by Loyd V. Allen, Jr, Pharmaceutical Press, 22nd Edition, 2012.

5.10. Relative amounts of components

The above-mentioned components may be present in relative amounts as shown in the following tables. Amount indications in the following tables may be understood as indications in parts by weight.

Core	Amount	Preferred Amount	More preferred Amount	Most preferred Amount
Opioid agonist	1.00-150.00	1.00 – 80.00	1.50-40.00	1.50-40.00
Opioid antagonist	1.00-50.00	1.00-40.00	1.25-20.00	1.25-20.00
Binder	1.00 – 100.00	2.50 – 75.00	5.00 – 50.00	5.00 – 25.00
Matrix former	1.00 – 500.00	2.00 – 400.00	5.00 – 200.00	5.00 – 80.00
Molten binder	5.00 – 600.000	10.00 – 500.00	15.00 – 400.00	20.00 – 50.00
Diluent	10.00 – 800.00	20.00 – 600.00	40.00 – 400.00	40.00 – 200.00
Flow enhancing agent	1.00 – 50.00	1.00 – 35.00	1.00 – 25.00	1.00 – 10.00
Lubricant	1.00 – 50.00	1.00 – 30.00	1.00 – 15.00	1.00 – 7.50

For the preferred active agents oxycodone hydrochloride and naloxone hydrochloride dihydrate, the following specific compositions are of interest.

Core	Amount	Preferred Amount	More preferred amount	Most preferred Amount
Oxycodone hydrochloride	1.00-150.00	1.00 – 80.00	1.50-40.00	1.50-40.00
Naloxone hydrochloride dihydrate	1.00-50.00	1.00-40.00	1.25-30.00	1.25-25.00
Hydrophilic binder	1.00 – 100.00	2.50 – 75.00	5.00 – 50.00	5.00 – 25.00
Matrix former	1.00 – 500.00	2.00 – 400.00	5.00 – 200.00	5.00 – 80.00
Molten binder	5.00 – 600.000	10.00 – 500.00	15.00 – 400.00	16.00 – 50.00
Diluent	10.00 – 800.00	20.00 – 600.00	40.00 – 400.00	40.00 – 200.00
Flow enhancing agent	1.00 – 50.00	1.00 – 35.00	1.00 – 25.00	1.00 – 10.00
Lubricant	1.00 – 50.00	1.00 – 30.00	1.00 – 15.00	1.00 – 7.50

Yet further preferred formulations of the present invention are characterized in the following table.

Core	Amount	Preferred Amount	More preferred amount	Most preferred Amount
Oxycodone hydrochloride	1.00-40.00	1.00-40.00	1.00-40.00	1.00-40.00
naloxone hydrochloride dihydrate	1.25-25.00	1.25-25.00	1.25-25.00	1.25-25.00
Hydrophilic binder	5.00 – 10.00	5.00 – 10.00	5.00 – 10.00	5.00 – 10.00
Matrix former	5.00 – 80.00	5.00 – 80.00	5.00 – 80.00	5.00 – 80.00
Molten binder	16.00 – 50.00	16.00 – 50.00	16.00 – 50.00	16.00 – 50.00
Diluent	20.00 – 100.00	20.00 – 100.00	20.00 – 100.00	20.00 – 100.00
Flow enhancing agent	1.00 – 5.00	1.00 – 5.00	1.00 – 5.00	1.00 – 5.00
Lubricant	1.00 – 2.50	1.00 – 2.50	1.00 – 2.50	1.00 – 2.50

It is particularly preferred to use formulations according to the above tables, wherein the weight ratio between molten binder and matrix former is from 0.6 : 0.4 to 0.4 : 0.6. It is even more preferred to use oxycodone hydrochloride, which has an average particle size less than 50 µm and/or d90 between 10 and 150 µm and/or a D [4,3]-volume distribution between 5 - 70 µm and/or wherein naloxone hydrochloride dihydrate has an average particle size less than 40 µm and/or d90 between 15 and 150 µm and/or a D [4,3]-volume distribution between 5-50 µm.

According to a preferred embodiment, amount indications in the above tables are to be understood as indications of absolute weight, the unit being milligrams.

In another embodiment of the present invention the amount of opioid agonist and opioid antagonist used in the pharmaceutical formulation for the pediatric use or for patients with severe renal and/or hepatic disfunction can be downsized below the minimal amount as for example given in the above table.

Other dosages, such as dosages of 2.5mg, 5mg, 10mg, 15mg, 20mg, 30mg and 40mg of oxycodone hydrochloride and 1.25mg, 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg of naloxone hydrochloride dihydrate are available by up- or down-scaling based on the above parts-by-weight indications.

In another embodiment the pharmaceutical formulation according to the present invention may comprise 2.5mg, 5mg, 10mg, 15mg, 20mg, 30mg and 40mg of oxycodone hydrochloride

and naloxone hydrochloride dihydrate equivalent to 1.25mg, 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg of naloxone hydrochloride.

The amount of naloxone hydrochloride dihydrate present in the pharmaceutical formulation of the present invention does not reduce the level of analgesic effect of oxycodone hydrochloride upon oral administration.

The dosage is advantageously adjusted to the intensity of pain and the sensitivity of the individual patient. Usually, the pharmaceutical formulation of the present invention may be administered once, twice, three times or even more times per day, preferably once, twice or three times, more preferably twice per day.

5.11. Manufacturing method

Solid dosage forms of the present invention, preferably tablets containing oxycodone and naloxone in the form of free base or preferably pharmaceutically acceptable salts and/or hydrates or solvates thereof with organic and/or inorganic pharmaceutically acceptable acids, where salts with inorganic acids such as hydrochloric acid are preferred, can be prepared by state of the art processes that allow melting of the molten binder component, wherein processes which include granulation of at least one active ingredient are preferred. Granulation of one or both active ingredients can be performed by wet, dry or melt granulation methods, where direct mixtures or granulating methods in the absence of solvents such as dry granulation, roller compaction, melt granulation, thermoplastic granulation and melt extrusion are preferred.

The pharmaceutical formulations of the present invention can be manufactured by means of the following processes. In particular, the processes of the present invention comprise the following steps:

(a) Providing a mixture comprising at least the following ingredients: opioid agonist, opioid antagonist, hydrophilic binder, matrix former, molten binder and diluent;

(b) Granulating the obtained mixture at elevated temperatures; and

(c) Filling the granules, optionally after mixing them with other excipients, into capsules or compressing the granules in tablet form.

Step c) can include also mixing of granulate obtained under step b) with extragranular excipients to obtain a compression mixture, which is further compressed into tablets of desired weight, shape and dimensions. Extragranular excipients can be selected from but are not limited to lubricants, glidants, flow enhancing agents, diluents. The tablet weight may be 50-1,000 mg, preferably 75-500 mg, more preferably 100-300 mg and is adjusted by the quantity of the diluent.

Step (a) may comprise the sub-steps of

(i) mixing;

(ii) grinding; and

(iii) sieving.

The above-mentioned sub-steps (ii) and (iii) are optional and may be applied as desired, depending on the particle size of the starting materials. According to the present invention, it is preferable to use particles having a particle size distribution with a mean particle size in the range of from 5μm to 800μm. Hence, if starting materials with a larger particle size are used, it is preferable to reduce the particle size and average particle size to the preferred range specified above. Any available means for reducing the particle size e.g. grinding and/or screening may be employed.

Moreover, the relative order of the above-mentioned mixing, grinding and/or sieving steps is not particularly limited. The type of mixing employed in the present invention is also not particularly limited. Hence, any conventionally employed method for mixing particulate compositions in the field of pharmaceutical sciences and manufacturing may be employed. For instance, the particles may be mixed by simple shaking in a PE bag or by using state of the art pharmaceutical mixers such as container mixers of different shape (uniconical, biconical, V-blender), turbula mixers, share mixers such as high and low share mixers, fluid bed mixers. The present invention is however not limited to this embodiment.

The granulation of step (b) may be carried out in an extruder, a roller compactor, in a slugging device, or in a high or low shear mixer, which allows granulation of the mixture at the selected elevated temperature. In a special embodiment of the present invention fluid bed

granulation using a modified fluid bed apparatus can performed by either spraying of molten binder onto the fluidized powder bed or by "in situ" melt granulation of a mixture of all intragranular ingredients including at least one binder having a low melting point according to the definition of present invention in the fluidized air heated to the temperature of the melting point of such binder. The heat of fluidized air melts or softens the binder and the resulting melted/softened material binds the powder particles into agglomerates. When the appropriate particle size is achieved the temperature of fluidized air is decreased allowing the granulation mass to cool down to at least room temperature. The obtained granulate can be optionally sieved and/or, if needed, milled to the desired particle size. It is essential to choose a granulation temperature (or peak temperature in a temperature profile), which ensures that the molten binder component actually melts or softens during granulation.

It is furthermore advisable to select the granulation temperature such that it does not reach temperature ranges that could lead to thermal decomposition of the components of the formulation. Hence, it is preferred to select processing conditions such that the internal temperature during granulation is in the temperature range of from Tm to Tm+10°C and preferably from Tm to Tm+5°C, wherein Tm represents the melting or softening point of the molten binder component.

Subsequently, especially if the granulation involves compaction of the mixture, the granulated (compacted) mass may be screened to yield granules of the desired particle size. A preferred mean particle size of the granules is from 0.05 mm to 1 mm.

The granules obtained in step (b) may be mixed with further components such as flow enhancing agent and lubricant. The resultant granules or composition may then either be filled into capsules or be further compressed to yield tablets. Any conventionally used tableting method may be suitable in this connection.

Granulate or granules of step (b) can be manufactured by any state of the art agglomeration technique and equipment capable of performing agglomeration at elevated temperatures, i.e temperatures required for melting and/or softening of hydrophobic binder. Suitable granulation techniques can be selected from, but are not limited to, hot melt granulation or thermoplastic granulation in high shear mixers/granulators such as those produced by Collete Grall, Glatt or similar, hot melt granulation in fluid bed granulators and/or hot melt extrusion

using single screw or preferably twin screw extruders. In case granulation in high shear and/or fluid bed granulators is selected, molten binder is added in one embodiment of the present invention to the powder mixture comprising both active ingredients and the agglomeration of powder mixture particles, i.e. granulation is achieved by the heat produced due to friction and torque and/or external heating of the product bowl in case of high shear mixers or by heated inlet air in case of fluid bed granulators. In second embodiment agglomeration i.e granulation in case of using high shear or fluid bed granulators is achieved by spraying molten binder into the powder mixture while mixing. In case of using hot melt extrusion, molten binder is admixed with both active ingredients and the rest of the intragranular excipients and conveyed to single or twin screw extruder, where extrudates are formed by melting or softening of molten binder by the heat formed by friction and torque and optionally by additional external heating of the extruder barrel.

When granules of step (b) are obtained by hot melt extrusion (HME) in a special embodiment of the present invention, binding of the powder mixture which comprises both active ingredients can be performed with amorphous polymers which are softened by external heating of the extrusion barrel or by heat produced "in process" by friction and torque. In order to decrease the Tg of the amorphous polymer a suitable plasticizer can be used.

The plasticizer is preferably selected from substances having a molecular weight of less than 25,000, preferably of less than 20,000 and most preferably of less than 10,000. In case of use of polymeric molten binders with a melting/softening temperature above 60°C are used plasticizers can be used to decrease the glass transition temperature of the polymer and increase plasticity of the material. The plasticizer can be selected from hydrophilic and /or hydrophobic ones, whereas the hydrophobic ones are preferred according to present invention. Plasticizers are preferably selected from, but are not limited to, triethyl citrate (TEC), tributyl citrate (TBC), acetyl triethyl citrate (ATEC), dibutyl sebacate (DBS) diethyl phthalate (DEP), dibutyl phthalate (DBP), diesters and triesters of alcohols that are preferably selected from, but are not limited to, triacetin (TA), vegetable oils, fractioned coconut oil, acetylated monoglycerides.

Melt granulation using high share granulators is the preferred manufacturing process by the present invention due to its robustness and availability of the equipment.

The granulate obtained in step (b) is further processed into single unit solid dosage forms such as capsules and/or tablets in step (c).

The obtained tablets may be further provided with a water soluble film coating. Film coating is used in one aspect of the present invention for smoothing the surface of the tablet and to enable coloring them to permit easier swallowing of the tablets and better differentiation among different strengths. In another aspect of the present invention film coating is used to decrease the ability of the tablet cores to absorb moisture, i.e. to decrease the moisture permeability. In such cases polymers forming low moisture films are used such as polyvinyl alcohol, polymethacrylic acid derivatives e.g. as commercially available under trade names Eudragit® E and/or Eudragit® L, block copolymers of polyvinyl alcohol and polyethylene glycol e.g. as commercially available under trade names Kollicoat® IR and Kollicoat® Protect.

5.12. Abuse deterrent properties

It is known that opioids, which are very effective in controlling pain, are frequently abused to induce euphoric states in a number of ways. The pharmaceutical formulations containing an opioid and being originally prepared to relief pain, can be crushed, the opioid is extracted from the obtained powder and administered in very different ways, as for example parenteral, oral, nasal, smoking, swallowing, sublingual or buccal administration. A potential abuse and safety problem also presents alcohol-induced dose dumping of opioid drug.

Another embodiment of the present invention is reduced risk of abusing the pharmaceutical formulation of the present invention via alternative, i.e. non–oral, use of whole, tampered and/or crushed and or dissolved present solid composition, such as parenteral, inhalation and/or transdermal use.

The fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must in the end be able to deliver the opioid to the patient, there may always be some abuse of these products.

5.13. Release characteristics

The present invention is inter alia directed to sustained release formulations providing sustained release of an opioid agonist and an opioid antagonist. In an embodiment, the release rate of the opioid agonist and the antagonist from the pharmaceutical formulation of the present invention is controlled to maintain an analgesically effective amount of the agonist in the blood throughout the dosing period and to maintain the concentration of the opioid antagonist throughout the dosing period sufficient for decreasing the side effects associated with the opioid agonist but not sufficient to negate the analgesic efficacy of the agonist.

In a preferred embodiment, the pharmaceutical formulation of the present invention releases the opioid agonist and the antagonist at substantially proportionate rates. Unless defined otherwise, the term "substantially proportionate" is used in the context of the present specification to indicate that variation of ±20% is permissible at any point in time. Preferably, the release rates of the opioid agonist and antagonist are approximately proportionate over time, more preferably over a dosing period.

In another preferred embodiment, the pharmaceutical formulation of the present invention releases oxycodone hydrochloride between 1-60%, preferably between 5-55%, more preferably between 10-50% and even more preferably between 20-45% after 0.5 hour and/or naloxone hydrochloride between 1-60%, preferably between 5-55%, more preferably between 10-50% and even more preferably between 20-45% after 0.5 hour.

In another preferred embodiment, the pharmaceutical formulation of the present invention releases oxycodone hydrochloride between 30-90%, preferably between 40-80%, more preferably between % and even more preferably between 50-75% after 2 hours and/or naloxone hydrochloride between 30-90%, preferably between 40-80%, more preferably between % and even more preferably between 50-75% after 2 hours.

In another preferred embodiment, the pharmaceutical formulation of the present invention releases oxycodone hydrochloride between 60-100%, preferably between 65-100%, more preferably between 68-98% and even more preferably between 65-95% after 4 hours and/or naloxone hydrochloride between 60-100%, preferably between 65-100%, more preferably between 68-98% and even more preferably between 65-95% after 4 hours.

In another preferred embodiment, the pharmaceutical formulation of the present invention releases not less than 75%, preferably not less than 78% and more preferably not less than 80% of oxycodone hydrochloride after 12 hours and/or the pharmaceutical formulation of the present invention releases not less than 75%, preferably not less than 78% and more preferably not less than 80% of naloxone hydrochloride after 12 hours.

Indications of release characteristics in % characterize the released dose of the active agent (on a weight basis) in relation to the total amount of this active agent contained in the dosage form (on a weight basis).

The release characteristics of some exemplified pharmaceutical formulation of the present invention are presented in Figures 1 and 2.

6. Examples

Preferred specific embodiments of the present invention are describes in the following examples. It is, however, to be understood that the present invention is not limited to these examples.

Description of method for particle size determination:

a) OXCODONE HYDROCHLORIDE AND/OR NALOXONE HYDROCHLORIDE

Method: Laser diffraction (wet dispersion)
Instrument: Malvern Mastersizer 2000
Dispersant cell: Hydro 2000S
Dispersion medium: Sunflower oil
Dispersant RI: 1,469
Particle RI: 1,66 (Oxycodone) or 1,69 (Naloxone)
Absorption: 1
Obscuration: 10-25%
Stirrer/Pump speed: 2200rpm
Sonication (Time, Power): 30s, 75%
Sample preparation

A small amount of the sample, which was taken from a representative packaging unit, is placed in a test tube. Add a few drops of sunflower oil and shake it (vortex) until homogenous dense suspension is formed. Then dilute with a few milliliters of sunflower oil and shake again.

Procedure

1. Run the program, set prescribed conditions and enter data of sample.
2. Rinse a clean dispersion cell with sunflower oil at least twice, then re-fill with sunflower oil and let it circulate through the system at the specified stirrer/pump speed.
3. Measure a background.
4. Into the dispersion cell during circulation/homogenization add with a pipette representative suspension until you get the appropriate obscuration value.
5. Perform the first measurement set for information only, then sonicate the sample using the above specified settings, wait that the system stabilizes and perform another measurement set.
6. As the final result the average value of five consecutive measurements after sonication (one measurement set) is considered. If primary particles are damaged during sonication the average value from the first set of measurement is considered.

b) MATRIX FORMER

Method: Laser diffraction (dry dispersion)
Instrument: Malvern Mastersizer 2000
Dispersant cell: Scirocco
Particle refractive index: calculated according to structure
Absorption: chosen according to the best data fit
Obscuration range: 0,5-6,0%
Vibration feed rate: 50%
Dispersive air pressure: 1bar (or higher if the powder is cohesive)
Tray gates aperture: 5mm or more if necessary
Sieve: large (apertures ca. 2mm) with balls

Procedure

1. Run the program, set prescribed conditions and enter data of sample.

2. If necessary, clean the measuring system with a quartz sands, replace the bag in the vacuum cleaner, etc.
3. Place about 4g of the representative sample onto the tray a few millimeters behind the gates and close the tray lid.
4. Measure a background and perform the measurement.
5. As a result, the average value (manual calculation according to the measurements) of five measurements which are performed individually (measurements cycles: 1) is considered.

6.1. Example 1

Manufacture of tablets having the following formulation:

Core-component	Amount	Function
Oxycodone hydrochloride	20.00	Active ingredient
Naloxone hydrochloride dihydrate	10.90	Active ingredient
Povidone K 30	7.25	Hydrophilic binder
Ethylcellulose*	12.00	Matrix former
Glyceryl distearate	29.50	Molten binder
Lactose monohydrate	54.50	Diluent
Talcum	2.50	Flow enhancing agent
Magnesium stearate	1.25	Lubricant

*in all examples Ethylcellulose 45 mPas was used

Tablet manufacture took place using the following procedure: Oxycodone hydrochloride, Naloxone hydrochloride dihydrate, Povidone K 30, Glyceryl distearate, Ethylcellulose, and Lactose monohydrate were homogenized in PE bag. The resulting mixture was granulated in a heated double-wall high shear mixer Collette 10. The set temperature of the heated wall was 80°C and the granulation end point was within a range of Tm ± 5°C wherein Tm represents the melting or softening point of the molten binder. Granulate was sieved through Erweka mesh 18 (1.0) mm. The sieved granulate was mixed with talcum and magnesium stearate and subsequently pressed into tablets. All produced tablet cores had a mass of 137.9 mg. The cores were subsequently film coated with a polyvinyl alcohol (PVA) based film coating.

6.2. Examples 2 to 6

Further formulations were made according to the present invention using the same procedure as described above with respect to example 1. In these examples, the compositions were employed as shown in Table 1 below (the composition of Example 1 is also included to facilitate comparison):

Table 1

Core-component	**Example**				
	1	**2**	**3**	**4**	**5**
Oxycodone hydrochloride	20.00	20.00	20.00	20.00	20.00
Naloxone hydrochloride dihydrate	10.90	10.90	10.90	10.90	10.90
Povidone K 30	7.25	7.25	7.25	7.25	7.25
Ethylcellulose	12.00	16.60		12.00	12.00
Cellulose acetate			12.00		
Glyceryl distearate	29.50	24.90	29.50		
Glyceryl dibehenate				29.50	
Sucrose stearate					29.50
Lactose monohydrate	54.50	54.50	54.50	54.50	54.50
Talcum	2.50	2.50	2.50	2.50	2.50
Magnesium stearate	1.25	1.25	1.25	1.25	1.25
Tablet ID in Figure 1	**A**	**B**	**C**		

The release characteristics of the above-mentioned exemplified tablets were tested under the following conditions: 500ml of phosphate buffer pH 6.8, baskets, 100rpm.

The results of these experiments are summarized in Figure 1. It may be derived from Figure 1 that all tablets according to the present invention exhibit excellent release characteristics, which are comparable to the release characteristics the originator's commercial product Targinact® (also shown in Figure 1).

6.3. Examples 7 to 17

Further formulations were made according to the present invention using the same procedure as described above with respect to example 1. In these examples, the compositions were employed as shown in Table 2 below:

Table 2

Core-component	Example											Function
	7	8	9	10	11	12	13	14	15	16	17	
Oxycodone hydrochloride	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	Active ingredient
Naloxone hydrochloride dihydrate	10.90	10.90	10.90	10.90	10.90	10.90	10.90	10.90	10.90	10.90	10.90	Active ingredient
Hydroxypropyl cellulose	7.25	7.25	10.00	12.00	7.25	10.00	7.25	10.00	12.00	12.00	7.25	Hydrophilic binder
Ethylcellulose	13.00	14.52	18.50	22.20	27.70	13.82	18.44	17.02	13.00	17.91	16.60	Matrix former
Glyceryl distearate	/	26.98	/	/	/	/	23.06	/	17.13	/	24.90	Molten binder
Glyceryl dibehenate	23.38	/	/	18.55	23.90	/	/	/	/	/	/	Molten binder
Sucrose stearate	/	/	28.85	/	/	28.78	/	24.23	/	19.90	/	Molten binder
Lactose monohydrate	59.62	54.50	45.90	50.50	44.40	50.65	54.50	44.40	59.62	53.44	54.50	Diluent
Talcum	2.50	2.50	2.50	2.50	2.50	2.50	2.50	4.00	4.00	2.50	2.50	Flow enhancing agent
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	Lubricant
Tablet ID in Figure 2		**F**					**E**				**D**	

The release characteristics of the above-mentioned exemplified tablets were tested under the following conditions: 500ml of phosphate buffer pH 6.8, baskets, 100 rpm

Particle size of oxycodone hydrochloride used in examples 8, 13 and 17 was (D [4,3]-volume distribution) 49µm and d_{90} 102µm, and particle size of naloxone hydrochloride dihydrate was (D [4,3]-volume distribution) 31µm and d_{90} 78µm.

Particle size of oxycodone hydrochloride used in examples 10, 14 and 15 was (D [4,3]-volume distribution) 14µm and d_{90} 33µm and particle size of naloxone hydrochloride dihydrate was (D [4,3]-volume distribution) 13µm and d_{90} 29µm.

The results of these experiments are summarized in Figure 2. It may be derived from Figure 2 that all tablets according to the present invention exhibit excellent release characteristics, which are comparable to the release characteristics the originator's commercial product Targinact® (same product as in Figure 1).

6.4. Examples 18 to 28

Further formulations were made according to the present invention using the same procedure as described above with respect to example 1. In these examples, the compositions were employed as shown in Table 3 below:

Table 3

Core-component	Example											Function
	18	19	20	21	22	23	24	25	26	27	28	
Oxycodone hydrochloride	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	Active ingredient
Naloxone hydrochloride dihydrate	10.90	10.90	10.90	10.90	10.90	10.90	10.90	10.90	10.90	10.90	10.90	Active ingredient
Hydroxypropylcellulose	7.25	7.25	7.25	7.25	7.25	10.00	10.00	10.00	12.00	12.00	12.00	Hydrophilic binder
Cellulose acetate	13.00	14.52	16.60	18.44	27.70	13.82	17.02	18.50	13.00	17.91	22.20	Matrix former
Glyceryl distearate	23.38	/	/	23.06	/	/	/	28.85	/	19.90	/	Molten binder
Glyceryl dibehenate	/	26.98	/	/	23.90	/	/	/	/	/	18.55	Molten binder
Sucrose stearate	/	/	24.90	/	/	28.78	24.23	/	17.13	/	/	Molten binder
Lactose monohydrate	59.62	54.50	54.50	54.50	44.40	50.65	50.50	44.40	59.62	53.44	50.50	Diluent
Talcum	2.50	2.50	2.50	2.50	2.50	2.50	4.00	4.00	4.00	2.50	2.50	Flow enhancing agent
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	Lubricant

6.5. Examples 29 to 33

Manufacture of tablets having the following formulation:

Table 4

Core-component	Example					Function
	29	30	31	32	33	
Oxycodone hydrochloride	20.00	20.00	20.00	20.00	20.00	Active ingredient
Hydroxypropylcellulose	7.25	7.25	7.25	12.00	12.00	Hydrophilic binder
Ethylcellulose*	13.00	16.60	27.70	13.00	22.20	Matrix former
Glyceryl distearate	23.38	24.90	23.90	17.13	18.55	Molten binder
Lactose monohydrate	70.52	65.40	55.30	70.22	61.40	Diluent
Talcum	2.50	2.50	2.50	4.00	2.50	Flow enhancing agent
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	Lubricant

*in all examples Ethylcellulose 45 mPas was used

Tablet manufacture took place using the following procedure: Oxycodone hydrochloride, Ethylcellulose, Glyceryl distearate and Lactose monohydrate were homogenized in PE bag.

The resulting mixture was granulated in a heated double-wall high shear mixer Collette 10. The set temperature of the heated wall was 80°C and the granulation end point was within a range of Tm ± 5°C wherein Tm represents the melting or softening point of the molten binder. Granulate was sieved through Erweka mesh 18 (1.0) mm. The sieved granulate was mixed with talcum and magnesium stearate. All produced tablet cores had a mass of 137.9 mg. The cores were subsequently film coated with a polyvinyl alcohol (PVA) based film coating.

6.6. Examples 34 to 42

Further formulations were made according to the present invention using the same procedure as described above with respect to example 1. In these examples, the compositions were employed as shown in Table 5 below:

Table 5

Core-component	Example									Function
	34	35	36	37	38	39	40	41	42	
Oxycodone hydrochloride	5.00	5.00	10.00	10.00	10.00	10.00	10.00	40.00	40.00	Active ingredient
Naloxone hydrochloride dihydrate	2.74	2.74	5.48	5.48	5.48	5.48	5.48	21.92	21.92	Active ingredient
Hydroxypropylcellulose	5.00	7.25	5.00	7.25	7.25	5.00	5.00	14.50	14.50	Hydrophilic binder
Ethylcellulose	20.00	16.60	10.00	18.44	18.44	12.25	14.00	36.88	33.20	Matrix former
Glyceryl distearate	25.00	24.90	25.00	23.06	23.06	22.75	21.00	46.12	49.80	Molten binder
Lactose monohydrate	71.74	54.74	64.22	69.92	55.47	64.22	64.22	108.88	108.88	Diluent
Talcum	2.50	2.50	2.50	2.50	2.50	2.50	2.50	5.00	5.00	Flow enhancing agent
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	2.50	2.50	Lubricant

Particle size of oxycodone hydrochloride used in examples 35, 38 and 42 was (D [4,3]-volume distribution) 28µm and d_{90} 56µm, and particle size of naloxone hydrochloride dihydrate was (D [4,3]-volume distribution) 21µm and d_{90} 46µm.

6.7. Example 43

A further formulation was made according to the present invention using the same procedure as described above with respect to example 1. In this example, the composition was employed as shown in Table 6 below:

Table 6

Core-component	Example 43	Function
Oxycodone hydrochloride	20.00	Active ingredient
Naloxone hydrochloride dihydrate	10.90	Active ingredient
Hydroxypropylcellulose	7.25	Hydrophilic binder
Eudragit RS	18.44	Matrix former
Glyceryl distearate	23.06	Molten binder
Lactose monohydrate	54.50	Diluent
Talcum	2.50	Flow enhancing agent
Magnesium stearate	1.25	Lubricant

6.8. Examples 44 to 48

Tablet manufacture took place using the following procedure: Oxycodone hydrochloride, Naloxone hydrochloride dihydrate, Hydroxypropylcellulose, Glyceryl Distearate, Ethylcellulose and Lactose monohydrate were homogenized in biconical container. The resulting mixture was subsequently extruded with co-rotating twin screw extruder of type ZSE18 (Leistritz AG, Nürnberg, Germany). Temperature of heating zone 1 was 20°C, of heating zone 2 40°C, of heating zone 3 60°C, of heating zone 4 90°C, of heating zones 5-7 110-130°C and of heating zone 8 120-130°C. The screw rotating speed was 150-200 revolutions per minute; the resulting melt temperature was 125-136°C. Fed rate was app. 1 kg/h and the diameter of nozzle opening was 2 mm. Granulate was sieved in two stages through conical sieve Comill U10 (Quadro, Waterloo, Canada) using screen 040 G, followed by sieving through screen 032R. Sieved granulate was mixed with talcum and magnesium stearate and subsequently pressed into tablets. All produced tablet cores had a mass of 137.9 mg. The cores were subsequently film coated with a polyvinyl alcohol (PVA) based film coating.

Table 7

Core-component		**Example**			
	44	**45**	**46**	**47**	**48**
Oxycodone hydrochloride	20.00	20.00	20.00	20.00	20.00
Naloxone hydrochloride dihydrate	10.90	10.90	10.90	10.90	10.90

Povidone K 30	7.25	7.25	7.25	7.25	7.25
Ethylcellulose	12.00	16.60		12.00	12.00
Cellulose acetate			12.00		
Glyceryl distearate	29.50	24.90	29.50		
Glyceryl dibehenate				29.50	
Sucrose stearate					29.50
Lactose monohydrate	54.50	54.50	54.50	54.50	54.50
Talcum	2.50	2.50	2.50	2.50	2.50
Magnesium stearate	1.25	1.25	1.25	1.25	1.25

6.9. Examples 49 to 51

Further formulations of examples 49-50 were made according to the present invention using the same procedure as described above with respect to examples 44-48. Moreover, formulation of example 51 was made according to the present invention using the same procedure as described above with respect to example 1. In these examples, the compositions were employed as shown in Table 8 below:

Table 8

Core-component	Example			Function
	49	50	51	
Oxycodone hydrochloride	5.00	10.00	20.00	Active ingredient
Naloxone hydrochloride dihydrate	2.74	5.48	10.90	Active ingredient
Ethylcellulose	16.60	12.25	18.44	Matrix former
Glyceryl distearate	24.90	22.75	23.06	Molten binder
Lactose monohydrate	61.99	69.22	61.75	Diluent
Talcum	2.50	2.50	2.50	Flow enhancing agent
Magnesium stearate	1.25	1.25	1.25	Lubricant

Claims

1. Pharmaceutical formulation comprising opioid agonist or a pharmaceutically acceptable salt and/or solvate or hydrate thereof in an amount of from 1.00 to 150.00 parts by weight, opioid antagonist or a pharmaceutically acceptable salt and/or solvate or hydrate thereof in an amount of from 1.00 to 50.00 parts by weight, hydrophilic binder in an amount of from 1.00 to 100.00 parts by weight, diluent in an amount of from 10.00 to 800.00 parts by weight, flow enhancing agent in an amount of from 1.00 to 50.00 parts by weight, lubricant in amount of from 1.00 to 50.00 parts by weight,

   characterized in that the pharmaceutical formulation further contains 1.00 to 500.00 parts by weight of a matrix former, as well as 5.00 to 600.00 parts by weight of a hydrophobic binder wherein the melting point or softening point of the hydrophobic binder is below 160°C.

2. The pharmaceutical formulation according to Claim 1, wherein the hydrophobic binder is a carboxylic ester of a polyol selected from glycerol and saccharose.

3. Pharmaceutical formulation according to Claim 1 or 2, wherein the acyl moiety in the carboxylic ester is derived from a fatty acid selected from stearic acid and behenic acid.

4. Pharmaceutical formulation according to Claim 3, wherein the hydrophobic binder is selected from glycerol distearate, glycerol dibehenate and sucrose stearate.

5. Pharmaceutical formulation according to anyone of the preceding claims 1 to 4, wherein the opioid agonist is oxycodone or a pharmaceutically acceptable salt and/or solvate or hydrate thereof and the opioid antagonist is naloxone or a pharmaceutically acceptable salt and/or solvate or hydrate thereof.

6. Pharmaceutical formulation according to anyone of the preceding claims 1 to 5, wherein the components are present in the following relative amounts, in parts by weight:

Core	**Amount**
Opioid agonist	1.00 – 80.00
Opioid antagonist	1.00 – 40.00
Hydrophilic binder	2.50 – 75.00

Matrix former	2.00 – 400.00
Hydrophobic binder	10.00 – 500.00
Diluent	20.00 – 600.00
Flow enhancing agent	1.00 – 35.00
Lubricant	1.00 – 30.00

7. Pharmaceutical formulation according to anyone of the preceding claims 1 to 6, wherein oxycodone is present in the form of its hydrochloride salt.

8. Pharmaceutical formulation according to anyone of the preceding claims 1 to 7, wherein naloxone is present in the form of naloxone hydrochloride dihydrate.

9. Pharmaceutical formulation according to anyone of preceding claims 1 to 8 for use in the treatment of pain.

10. Method for manufacturing a pharmaceutical formulation according to anyone of claims 1 to 9, which comprises the following steps:
    (a) providing a mixture of components comprising opioid agonist, opioid antagonist, hydrophilic binder, matrix former, hydrophobic binder and diluent;
    (b) granulating the mixture of step (a) such that the hydrophobic binder material melts or softens; and
    (c) filling the granules of step (b) into capsules or compressing the granules of step (b) to form tablets.

11. Method according to claim 10, wherein granulation is carried out in step (b) at a temperature of from Tm to Tm+10° Celsius, wherein Tm represents the melting point or softening point of the hydrophobic binder component.

12. Method according to claim 10 or 11, wherein granulation is carried out in an extruder, a chilsonator, a high shear mixer or in a slugging device.

13. Method according to anyone of claims 10 to 12, wherein the components flow enhancing agent and lubricant are added to the granules after granulation step (b) but before step (c).

14. Pharmaceutical formulation according to anyone of preceeding claims 1 to 9, wherein no hydrophilic binder is present in the formulation.

Figure 1

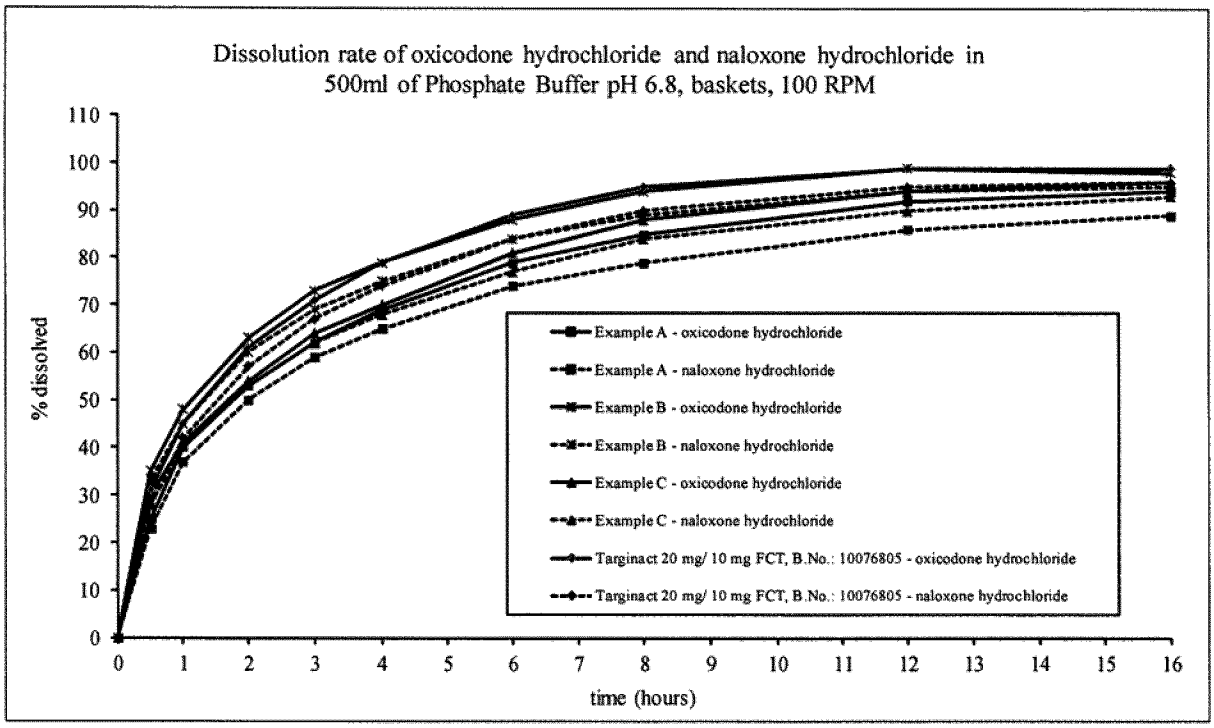
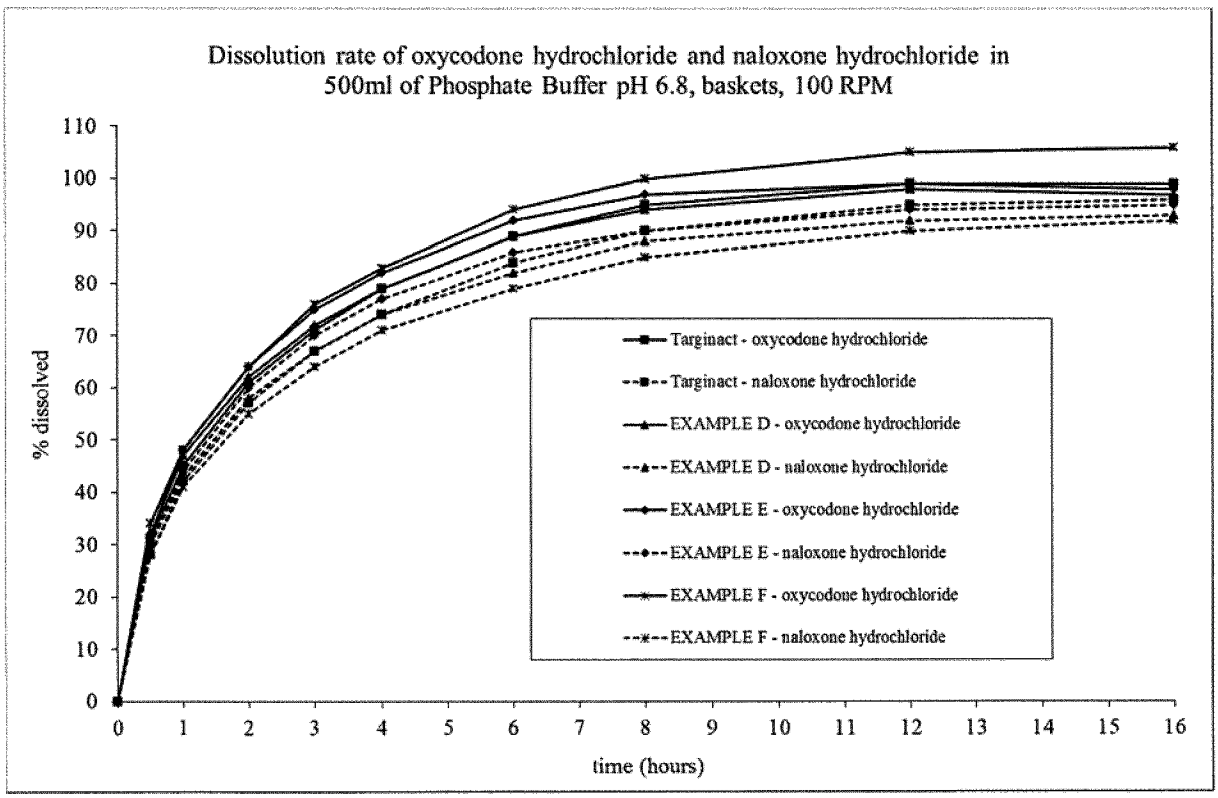


Figure 2



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067670

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/28 A61K31/485
ADD.

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2015	09/09/2015

Name and mailing address of the ISA/	Authorized officer
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