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(54) Titre : FORMULATIONS DE MEDICAMENTS CONTENANT UN OPIOIDE ET UN α-AGONISTE
(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING AN OPIOID AND AN α-AGONIST

(57) Abrégé/Abstract:
The invention relates to medicinal formulations containing an opioid, an α-antagonist and/or their physiologically compatible salts, from which at least one medicinal active ingredient is released in a sustained manner.

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(54) **Title:** MEDICINAL FORMULATIONS CONTAINING AN OPIOID AND AN α-ANTAGONIST

(54) **Bezeichnung:** ARZNEIFORMULIERUNGEN ENTHALTEND EIN OPIOID UND EINEN α-AGONISTEN

(57) **Abstract:** The invention relates to medicinal formulations containing an opioid, an α-antagonist and/or their physiologically compatible salts, from which at least one medicinal active ingredient is released in a sustained manner.

(57) **Zusammenfassung:** Die Erfindung betrifft Arzneiformulierungen enthaltend ein Opioid, einen α-Agonisten und/oder jeweils dessen physiologisch verträgliches Salz, aus denen wenigstens ein Arzneimittelwirkstoff verzögert freigesetzt wird.

# Pharmaceutical formulations containing an opioid and an α-agonist

This invention relates to pharmaceutical formulations containing an opioid, an α-agonist and/or in each case the physiologically compatible salt thereof, from which formulations at least one pharmaceutical active substance is released in delayed manner.

Due to their strong analgesic action, opioids are used for alleviating moderately severe and severe acute pain. One major disadvantage of using opioids, however, resides in the severe side-effects associated therewith. Side-effects on the gastrointestinal tract, such as for example severe constipation, thus frequently occur. They moreover cause respiratory depression and, on repeated administration, dependency, which may result in abuse. A further disadvantage is the rapid development of tolerance.

It is known to administer opioids and α-agonists as single preparations using various pharmaceutical formulations. In addition to known non-controlled release systems, there are also controlled release systems with opioids, such as described in WO 95/14460 or EP-A-0 647 448, in which, *inter alia*, butyrates, ketobemidone, codeine and the like are used. EP-B-0 271 193 discloses a controlled release system using solely hydromorphone. Controlled release systems with α-agonists are disclosed in EP-A-0 805 677 or US 5,484,607. In both cases, clonidine is used as the only α-agonist.

The object of the present invention was accordingly to provide a pharmaceutical formulation which is suitable for

treating severe to very severe pain and which does not exhibit the typical side-effects of opioids and which in particular very considerably delays or completely prevents the development of opioid tolerance.

This object is achieved according to the invention by the provision of pharmaceutical formulations which contain an opioid, an α-agonist and/or in each case physiologically compatible salts thereof, from which formulations at least one pharmaceutical active substance is released in delayed manner.

It is preferably the opioid which is released from the pharmaceutical formulation according to the invention in delayed manner.

Delayed release of the opioid preferably proceeds over a period of 8 hours, particularly preferably of 12 hours and very particularly preferably over 24 hours.

It is likewise preferred for both the pharmaceutical active substances to be released from the pharmaceutical formulation according to the invention in delayed manner.

The pharmaceutical formulation according to the invention preferably contains morphine, hydromorphone, codeine, oxycodone, dihydrocodeine, dextropropoxyphene, buprenorphine, levomethadone, fentanyl, sufentanil, etorphine, pentazocine, tilidine, tramadol, levorphanol, methadone, dihydromorphine, pethidine, piritramide or a physiologically compatible salt of the stated opioids as the opioid.

The pharmaceutical formulation according to the invention particularly preferably contains morphine, tramadol and/or a physiologically compatible salt thereof as the opioids.

The pharmaceutical formulation according to the invention preferably contains clonidine, guanfacine, guanabenz, lofexidine, adrenaline, methyldopa, noradrenaline, methoxamine, oxymetazoline, xylometazoline, teryzoline, ST-91, medetomidine, dexmedetomidine, agmatine, UK14,304, para-aminoclonidine, U-47,476A, DJ-741, ICI-106270, xylazine, talipexole (BHT-920), naphazoline, tizanidine and/or a physiologically compatible salt of the stated α-agonists as the α-agonist.

The pharmaceutical formulation according to the invention particularly preferably contains clonidine, guanfacine and/or a physiologically compatible salt thereof as the α-agonist.

Very particularly preferably, the pharmaceutical formulation according to the invention contains morphine and/or tramadol as the opioid and clonidine as the α-agonist and/or in each case the physiologically compatible salt thereof.

Physiologically compatible salts of the active substances which are preferably used are acetates, tartrates, sulfates, hydrochlorides, phosphates and additionally salicylates and acetylsalicylates for the group of opioids.

The weight ratio of the opioid to the α-agonist in the pharmaceutical formulations according to the invention is preferably 200:1 to 10:1. In a particularly preferred embodiment, the weight ratio of the opioid to the α-agonist is 100:1 to 10:1.

The pharmaceutical formulation according to the invention is preferably administered orally. Preferred oral pharmaceutical formulations are tablets, sugar-coated tablets or capsules, particularly preferably tablets, very particularly preferably multilayer tablets.

The pharmaceutical formulation according to the invention may also be in multiparticulate form, such as for example in the form of microtablets, microcapsules, ion exchange resinates, granules, active substance crystals or pellets. The pharmaceutical formulation according to the invention may preferably also assume the form of a pellet tablet which disintegrates particularly quickly.

Controlled release of the particular active substances may preferably be achieved by a controlled release coating, immobilisation on an ion exchange resin, embedding in a controlled release matrix or a combination thereof.

Controlled release is preferably achieved by means of controlled release coatings. Suitable controlled release coatings include water-insoluble waxes or polymers, such as for example acrylic resins, preferably poly(meth)acrylates, or water-insoluble celluloses, preferably ethylcellulose. These materials are known from the prior art, for example Bauer, Lehmann, Osterwald, Rothgang, *"Überzogene*

*Arzneiformen*", Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1988, pp. 69 *et seq*.. They are hereby included by reference.

In addition to the water-insoluble polymers, the controlled release coatings may, in order to establish the rate of release of the active substance, also contain polymers, preferably water-soluble polymers, which do not delay release in quantities of up to 30 wt.%, such as polyvinyl-pyrrolidone or water-soluble celluloses, preferably hydroxypropylmethylcellulose or hydroxypropylcellulose, and/or hydrophilic pore formers, such as sucrose, sodium chloride or mannitol and/or known plasticisers.

Another conventional method for achieving controlled release is immobilisation of the active substances on ion exchange resins. Colestyramine is preferably used as an anionic ion exchange resin, while polystyrene sulfonates are preferably used as cationic ionic exchange resins.

For the purposes of controlled release, the active substances may also be present in a controlled release matrix, preferably uniformly distributed therein.

Physiologically compatible, hydrophilic materials, which are known to the person skilled in the art, may be used as matrix materials. Hydrophilic matrix materials which are used are preferably polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins. Very particularly preferably used matrix materials are ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose,

poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof.

Matrix materials prepared from hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof are also preferred. Particularly preferably used hydrophobic materials are mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof.

It is also possible to use mixtures of the stated hydrophilic and hydrophobic materials as a controlled release matrix material.

In another preferred embodiment, the controlled release pharmaceutical formulations may also contain both active substances in controlled release form.

The pharmaceutical formulation according to the invention may also contain at least one of the active substances in controlled release form as well as in non-controlled release form. Combination with the immediately released active substance means that it is possible to achieve an elevated initial dose to alleviate pain rapidly. Slow release from the controlled release form then prevents the analgesic action from declining. Release of the active substances should particularly preferably be adjusted such that the controlled release pharmaceutical formulation need be administered at most twice, preferably just once daily. The person skilled in the art knows, on the basis of the action of the analgesics, the mixing ratios in which they

should be used in order to achieve the desired release of the active substances.

The pharmaceutical formulations according to the invention may moreover comprise still further coatings. Further coatings which may be present are those with pH-dependent dissolution behaviour. It is thus possible to ensure that the sub-units pass through the stomach in undissolved form and are released only once they reach the intestine. Coatings which serve to improve taste may also be used.

The pharmaceutical formulations according to the invention may be produced in accordance with various methods known to the person skilled in the art, tablets, for example, being produced by conventional processes such as for example by extrusion, accretion agglomeration, wet granulation, fluidised bed processes, dry mixing or compression moulding processes. In the event that the pharmaceutical formulation according to the invention, such as for example tablets, comprises coatings, these may be applied by conventional processes, such as for example sugar-coating, spray-application of solutions, dispersions or suspensions, by melt processes of by powder application processes.

The quantity of active substance to be administered depends upon the active substances to be used and upon the route of administration. For oral administration, clonidine, for example, is preferably used in a quantity of between 1 μg and 500 μg, particularly preferably between 10 μg and 50 μg, in each case relative to the base, and guanfacine is preferably used in a quantity of between 5 μg and 900 μg, particularly preferably between 100 μg and 500 μg, in each case relative to the base.

In the case of oral administration of the combination to be used, morphine, for example, is preferably used in a quantity of between 0.1 mg and 20 mg, particularly preferably in a quantity of between 0.5 mg and 5 mg, in each case relative to the base, and tramadol is preferably used in a quantity of between 1 mg and 50 mg, particularly preferably in a quantity of between 1 mg and 20 mg, in each case relative to the base.

The pharmaceutical formulations according to the invention are preferably administered orally, parenterally or transdermally, particularly preferably orally.

Transdermal controlled release formulations may, for example, be produced in the form of dressings having one or more active substance matrices or one or more active substance reservoirs and a control membrane.

Apart from an opioid, an α-agonist and/or in each case the physiologically compatible salt thereof, the pharmaceutical formulations according to the invention may contain further pharmaceutical active substances and/or auxiliary substances. The pharmaceutical auxiliary substances preferably comprise binders, extenders, lubricants, excipients, disintegration promoters, solvents, diluents, dyes, controlled release auxiliary substances and/or mixtures thereof. Selection of the auxiliary substances and the quantities thereof to be used are determined by whether the controlled release dosage forms according to the invention are used orally, parenterally or transdermally.

The term "extenders" is taken to mean, *inter alia*, starch, microcrystalline cellulose, dextrose, mannitol or mixtures thereof.

Binders which may preferably be used are hydroxypropyl-methylcelluloses, polyvinylpyrrolidines, hydroxypropyl-celluloses, starch paste or mixtures thereof.

Disintegration promoters which are preferably used are hydroxypropylcelluloses having a low degree of substitution, crosspovidones, crosscarmelloses, starches, pectins, alginates, surfactants or mixtures thereof.

Examples from the group of usable lubricants which may be mentioned are magnesium stearate, stearic acid, calcium stearate, fatty alcohols or mixtures thereof.

The present invention also provides the use of the pharmaceutical formulations according to the invention for combating moderately severe to very severe pain.

In comparison with using an opioid alone, the pharmaceutical formulations according to the invention exhibit a marked enhancement of analgesic action. This means that the quantity of opioid used may be distinctly reduced while the same analgesic action is achieved.

Furthermore, the potential for opioid dependency and the constipating action of opioids may be distinctly reduced in comparison with using an opioid alone.

This reduction in side-effects is still further enhanced because, due to the delayed release, only a relatively

small quantity of the active substances is released at any one time.

One particular advantage of the controlled release pharmaceutical formulations according to the invention is that the development of tolerance to the opioid is greatly delayed or completely avoided.

The following Examples are intended to illustrate the invention, but do not restrict the general concept of the invention.

**Examples**

Granulation was performed in a Lödiger FM 5 high-speed mixer and tablets were produced using a Fette eccentric press.

For the purposes of the present invention, the term "PVP" should be taken to mean polyvinylpyrrolidones.

For the purposes of the present invention, the term "morphine HCl" means morphine HCl trihydrate.

For the purposes of the present invention, the term "tramadol HCl" means tramadol HCl trihydrate.

The term "min" means minutes.

The term "rpm" means revolutions per minute.

**Example 1**

Production of two-layer tablets with controlled release opioid and non-controlled release α-agonist

| Constituent | Quantity per tablet in mg |
|---|---|
| Morphine HCl | 5.00 |
| Clonidine HCl | 0.30 |
| Lactose | 72.70 |
| Hydroxyethylcellulose | 11.00 |
| Cetostearyl alcohol | 33.00 |
| Talcum | 1.00 |
| Maize starch | 7.50 |
| PVP 30 | 2.00 |
| PVP Cl | 2.00 |
| Magnesium stearate | 0.88 |
| Total | 135.88 |

The two-layer tablets produced consisted of a controlled release layer containing the active substance morphine HCl and a non-controlled release layer containing the active substance clonidine. The controlled release granules were produced by processing morphine HCl, a proportion of the lactose, hydroxyethylcellulose and cetostearyl alcohol in a suitable mixer. The mixture was heated to 80°C and granulated. After cooling, the granules were screened and mixed with magnesium stearate and talcum.

The non-controlled release granules were produced by granulating the remaining lactose and maize starch with a solution of clonidine HCl, PVP 30 and purified water in a suitable mixer. Magnesium stearate and PVP Cl were mixed into the dried granules. Both types of granules were compression moulded to form the two-layer tablets.

*In vitro* release testing was performed in a paddle stirrer apparatus with a volume of 600 ml of dilute hydrochloric

acid, at a pH of 1.2 and a speed of 75 rpm. Testing of the two layer tablet provided the following release profile over a period of 480 min (mean, n = 6).

- Release of morphine HCl

| Time in min | Quantity released in % |
|---|---|
| 0 | 0 |
| 30 | 31.5 |
| 60 | 44.9 |
| 180 | 80.1 |
| 300 | 97.4 |
| 480 | 100 |

- Release of clonidine HCl

| Time in min | Quantity released in % |
|---|---|
| 0 | 0 |
| 5 | 53.3 |
| 10 | 94.9 |
| 15 | 100 |
| 30 | 100 |
| 60 | 100 |

**Example 2**

Production of two-layer tablets with controlled release opioid and non-controlled release α-agonist

| **Constituent** | **Quantity per tablet in mg** |
|---|---|
| Morphine HCl | 5.00 |
| Clonidine HCl | 0.10 |
| Lactose | 72.90 |
| Hydroxyethylcellulose | 11.00 |
| Cetostearyl alcohol | 33.00 |
| Talcum | 1.00 |
| Maize starch | 7.50 |
| PVP 30 | 2.00 |
| PVP Cl | 2.00 |
| Magnesium stearate | 0.88 |
| Total | 135.88 |

The two-layer tablets produced consisted of a controlled release layer containing the active substance morphine HCl and a non-controlled release layer containing the active substance clonidine.

The controlled release granules were produced by processing morphine HCl, a proportion of the lactose, hydroxyethyl-cellulose and cetostearyl alcohol in a suitable mixer. The mixture was heated to 80°C and granulated. After cooling, the granules were screened and mixed with magnesium stearate and talcum.

The non-controlled release granules were produced by granulating the remaining lactose and maize starch with a

solution of clonidine HCl, PVP 30 and purified water in a suitable mixer. Magnesium stearate and PVP Cl were mixed into the dried granules. Both types of granules were compression moulded to form the two-layer tablets.

*In vitro* release testing was performed in a paddle stirrer apparatus with a volume of 600 ml of dilute hydrochloric acid, at a pH of 1.2 and a speed of 75 rpm. Testing of the two layer tablet provided the following release profile over a period of 480 min (mean, n = 6).

- Release of morphine HCl

| **Time in min** | **Quantity released in %** |
|---|---|
| 0 | 0 |
| 30 | 30.5 |
| 60 | 46.3 |
| 180 | 79.4 |
| 300 | 95.2 |
| 480 | 100 |

- Release of clonidine HCl

| **Time in min** | **Quantity released in %** |
|---|---|
| 0 | 0 |
| 5 | 62.7 |
| 10 | 93.4 |
| 15 | 100 |
| 30 | 100 |
| 60 | 100 |

**Example 3**

Production of two-layer tablets with controlled release opioid and controlled release α-agonist

The two-layer tablets produced consisted of a controlled release layer with the active substance tramadol HCl and another controlled release layer containing the active substance clonidine HCl.

- Production of the first layer with tramadol HCl.

| **Constituent** | **Quantity per tablet in mg** |
|---|---|
| Tramadol HCl | 50.00 |
| Methylhydroxypropylcellulose 100000 mPa*s | 80.00 |
| Highly disperse silicon dioxide | 3.00 |
| Microcrystalline cellulose | 124.00 |
| Magnesium stearate | 3.00 |
| Total | 260.00 |

Tramadol HCl was mixed with microcrystalline cellulose, methylhydroxypropylcellulose, a proportion of the highly disperse silicon dioxide and magnesium stearate and precompressed to form tablets. The broken tablets were then screened, mixed with the remaining magnesium stearate and highly disperse silicon dioxide.

- Production of the second layer with clonidine HCl.

| **Constituent** | **Quantity per tablet in mg** |
|---|---|
| Clonidine HCl | 0.30 |
| Lactose | 20.00 |
| Hydroxyethylcellulose | 11.00 |
| Cetostearyl alcohol | 33.00 |
| Talcum | 1.00 |
| Magnesium stearate | 0.70 |
| Total | 71.00 |

The lactose and hydroxyethylcellulose were initially introduced into a suitable mixer and mixed. The mixture was thoroughly moistened with a solution of clonidine HCl in water. After drying, the mixture was mixed with cetostearyl alcohol, heated to 80°C and then granulated. The cooled granules were screened, combined with talcum and magnesium stearate and the two types of granules were compression moulded to form two-layer tablets.

*In vitro* release testing was performed in a paddle stirrer apparatus with a volume of 600 ml of dilute hydrochloric acid, at a pH of 1.2 and a speed of 75 rpm. Testing of the two layer tablet provided the following release profile over a period of 600 min (mean, n = 6).

- Release of tramadol HCl

| Time in min | Quantity released in % |
|---|---|
| 0 | 0 |
| 30 | 19.44 |
| 60 | 30.20 |
| 180 | 56.51 |
| 300 | 73.29 |
| 480 | 89.45 |
| 600 | 96.70 |

- Release of clonidine HCl

| Time in min | Quantity released in % |
|---|---|
| 0 | 0 |
| 30 | 32.7 |
| 60 | 44.4 |
| 180 | 78.4 |
| 300 | 90.8 |
| 480 | 100 |
| 600 | 100 |

**Example 4**

Production of a two-layer tablet with controlled release opioid and α-agonist

The two-layer tablets produced consisted of a controlled release layer with the active substance tramadol HCl and another controlled release layer containing the active substance clonidine HCl.

- Production of the first layer with tramadol HCl.

| **Constituent** | **Quantity per tablet in mg** |
|---|---|
| Tramadol HCl | 50.00 |
| Methylhydroxypropylcellulose 100000 mPa*s | 80.00 |
| Highly disperse silicon dioxide | 3.00 |
| Microcrystalline cellulose | 124.00 |
| Magnesium stearate | 3.00 |
| Total | 260.00 |

Tramadol HCl was mixed with microcrystalline cellulose, methylhydroxypropylcellulose, a proportion of the highly disperse silicon dioxide and magnesium stearate and precompressed to form tablets. The broken tablets were then screened, mixed with the remaining magnesium stearate and highly disperse silicon dioxide.

- Production of the second layer with clonidine HCl.

| **Constituent** | **Quantity per tablet in mg** |
|---|---|
| Clonidine HCl | 0.15 |
| Lactose | 20.15 |
| Hydroxyethylcellulose | 11.00 |
| Cetostearylcellulose | 33.00 |
| Talcum | 1.00 |
| Magnesium stearate | 0.70 |
| Total | 71.00 |

The lactose and hydroxyethylcellulose were initially introduced into a suitable mixer and mixed. The mixture was thoroughly moistened with an aqueous solution of clonidine

HCl. After drying, the mixture was mixed with cetostearyl-cellulose, heated to 80°C and then granulated. The cooled granules were screened, mixed with talcum and magnesium stearate and the two types of granules were compression moulded to form two-layer tablets.

*In vitro* release testing was performed in a paddle stirrer apparatus with a volume of 600 ml of dilute hydrochloric acid, at a pH of 1.2 and a speed of 75 rpm. Testing of the two layer tablet provided the following release profile over a period of 600 min (mean, n = 6).

- Release of tramadol HCl

| **Time in min** | **Quantity released in %** |
|---|---|
| 0 | 0 |
| 30 | 20.3 |
| 60 | 30.8 |
| 180 | 57.3 |
| 300 | 74.7 |
| 480 | 90.2 |
| 600 | 98.1 |

- Release of clonidine HCl

| **Time in min** | **Quantity released in %** |
|---|---|
| 0 | 0 |
| 30 | 33.4 |
| 60 | 46.1 |
| 180 | 80.2 |
| 300 | 92.7 |
| 480 | 100 |
| 600 | 100 |

**Example 5**

Production of various pellet pharmaceutical formulations

5.1 Rapid release active substance absorbed on a controlled release pellet

The active substance clonidine was applied as the α-agonist onto a controlled release morphine pellet using a suitable lacquer coating unit. The pellets produced were packaged in capsules or compression moulded to form tablets.

The constituents of the controlled release pellets contained:

| **Constituent** | **Quantity per capsule in mg** |
|---|---|
| Morphine sulfate | 10.00 |
| Lactose | 2.00 |
| Sucrose and maize starch microgranules USP 23-NF18 | 10.00 |
| Polyethylene glycol 4000 | 2.50 |
| Ethylcellulose | 3.00 |
| Talcum | 0.15 |
| Dibutyl sebacate | 0.70 |
| Total | 26.35 |

Neutral starter nuclei were placed in the lacquer coating unit and moistened with an ethanolic polyethylene glycol 4000 solution. A mixture of morphine sulfate and lactose was repeatedly applied onto the moist nuclei and the nuclei dried. This operation was repeated until the morphine sulfate/lactose mixture had been completely applied.

A suspension of clonidine HCl, hydroxypropylmethylcellulose, polyethylene glycol 4000 and propylene glycol was applied onto the morphine pellets produced in this manner in a lacquer coating unit. The material applied was of the following composition:

| **Constituent** | **Quantity per capsule in mg** |
|---|---|
| Clonidine HCl | 0.30 |
| Hydroxypropylmethylcellulose | 4.000 |
| Polyethylene glycol 4000 | 1.00 |
| Propylene glycol | 0.33 |
| Total | 26.35 |

The total quantity per capsule was 31.98 mg.

*In vitro* release testing was performed in a rotating basket apparatus with a volume of 600 ml of dilute hydrochloric acid and at a pH of 1.2 and a speed of 100 rpm. Testing of the formulation provided the following release profile over the period (mean, n = 6).

- Release of morphine sulfate

| **Time in min** | **Quantity released in %** |
|---|---|
| 0 | 0 |
| 60 | 28.5 |
| 180 | 34.3 |
| 240 | 46.2 |
| 480 | 64.4 |
| 600 | 81.1 |
| 720 | 98.5 |

- Release of clonidine HCl

| Time in min | Quantity released in % |
|---|---|
| 0 | 0 |
| 5 | 50.3 |
| 10 | 93.9 |
| 15 | 100 |
| 30 | 100 |
| 60 | 100 |

5.2 Mixed pellets in capsules

- Production of tramadol pellets

| Constituent | Quantity per capsule in mg |
|---|---|
| Tramadol HCl | 50.00 |
| Hydroxypropylcellulose with a low degree of substitution | 20.00 |
| Microcrystalline cellulose | 106.00 |
| Calcium hydrogen phosphate | 20.00 |
| Hydroxypropylmethylcellulose | 4.00 |
| Aquacoat (ethylcellulose) | 20.00 |
| Dibutyl sebacate | 5.00 |
| Total | 225.00 |

Tramadol hydrochloride, microcrystalline cellulose, calcium hydrogen phosphate and the hydroxypropylcellulose with a low degree of substitution were thoroughly moistened with an aqueous solution of hydroxypropylmethylcellulose and extruded through a 0.5 mm perforated disk in a Pharmatex 35 T extruder. The extrudate was rounded in a Spheromat, dried in a fluidised bed and then provided with a

controlled release coating of an aqueous dispersion of ethylcellulose and dibutyl sebacate.

- Production of clonidine pellets

| Constituent | Quantity per capsule in mg |
|---|---|
| Clonidine HCl | 0.30 |
| Microcrystalline cellulose | 120.00 |
| Hydroxypropylcellulose with a low degree of substitution | 20.00 |
| Hydroxypropylmethylcellulose | 4.00 |
| Total | 144.30 |

Microcrystalline cellulose and hydroxypropylcellulose with a low degree of substitution were thoroughly moistened with an aqueous solution of hydroxypropylmethylcellulose and clonidine HCl. The mixture was extruded through a 0.5 mm perforated disk in a Pharmatex 35 T extruder, rounded in a Spheromat and dried in a fluidised bed. The coated tramadol and clonidine pellets were packaged in capsules and compression moulded to form tablets.

*In vitro* release testing was performed in a rotating basket apparatus with a volume of 600 ml of dilute hydrochloric acid, at a pH of 1.2 and a speed of 100 rpm. Testing of the capsules provided the following release profile over the period (mean, n = 6).

- Release of tramadol HCl

| Time in min | Quantity released in % |
|---|---|
| 0 | 0 |
| 120 | 13.0 |
| 240 | 31.0 |
| 480 | 57.0 |
| 600 | 71.0 |
| 720 | 100 |

- Release of clonidine HCl

| Time in min | Quantity released in % |
|---|---|
| 0 | 0 |
| 5 | 75.1 |
| 10 | 96.3 |
| 15 | 96.8 |
| 30 | 96.9 |
| 60 | 97.0 |

**Example 6**

The matrix tablet contained the following composition:

| Constituent | Quantity per tablet in mg |
|---|---|
| Morphine HCl | 5.00 |
| Clonidine HCl | 0.30 |
| Lactose | 20.00 |
| Hydroxyethylcellulose | 11.00 |
| Cetostearyl alcohol | 33.00 |
| Talcum | 1.00 |
| Magnesium stearate | 0.70 |
| Total | 71.00 |

Morphine HCl, lactose, hydroxyethylcellulose and cetostearyl alcohol were mixed. The mixture was thoroughly moistened with aqueous clonidine HCl. The resultant mixture was dried, then heated to 80°C and granulated. After cooling, the granules were screened, mixed with magnesium stearate and tabletted.

*In vitro* release testing was performed in a paddle stirrer apparatus with a volume of 600 ml of dilute hydrochloric acid, at a pH of 1.2 and a speed of 75 rpm. Testing of the matrix tablet provided the following release profile over a period of 480 min (mean, n = 6).

- Release of morphine HCl

| **Time in min** | **Quantity released in %** |
|---|---|
| 0 | 0 |
| 30 | 31.5 |
| 60 | 44.9 |
| 180 | 80.1 |
| 300 | 97.4 |
| 480 | 100 |

- Release of clonidine HCl

| **Time in min** | **Quantity released in %** |
|---|---|
| 0 | 0 |
| 30 | 32.7 |
| 60 | 44.4 |
| 180 | 78.4 |
| 300 | 90.8 |
| 480 | 100 |

**Example 7**

Production of a matrix tablet with the following composition:

| **Constituent** | **Quantity per tablet in mg** |
|---|---|
| Tramadol HCl | 50.00 |
| Clonidine HCl | 0.20 |
| Methylhydroxypropylcellulose, type 2208, 100000 mPa*s | 85.00 |
| Highly disperse silicon dioxide | 5.00 |
| Calcium hydrogen phosphate | 155.80 |
| Magnesium stearate | 4.00 |
| Total | 300.00 |

The total quantity of starting materials was 200 g. The constituents were screened (0.63 mm), then mixed for 10 minutes in a small cube mixer and compression moulded in a Korsch EK 0 eccentric tablet press to form tablets of a diameter of 10 mm with a radius of curvature of 8.5 mm and an average weight of 300 mg.

*In vitro* release testing was performed in a paddle stirrer apparatus with a volume of 600 ml of dilute hydrochloric acid, at a pH of 1.2 and a speed of 75 rpm. Testing of the matrix tablet provided the following release profile over a period of 480 min (mean, n = 6).

- Release of tramadol HCl

| Time in min | Quantity released in % |
|---|---|
| 0 | 0 |
| 30 | 22.6 |
| 60 | 35.2 |
| 180 | 52.4 |
| 300 | 78.2 |
| 480 | 86.3 |

- Release of clonidine HCl

| Time in min | Quantity released in % |
|---|---|
| 0 | 0 |
| 30 | 23.2 |
| 60 | 36.8 |
| 180 | 51.3 |
| 300 | 79.2 |
| 480 | 87.7 |

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**Patent Claims**

1. A pharmaceutical formulation containing an opioid, an α-agonist and/or in each case the physiologically compatible salt thereof, from which formulation at least one pharmaceutical active substance is released in delayed manner.

2. A pharmaceutical formulation as claimed in claim 1, wherein the opioid is released in delayed manner.

3. A pharmaceutical formulation as claimed in claim 1 or 2, wherein the opioid is released over a period of 8 hours, preferably of 12 hours, particularly preferably of 24 hours.

4. A pharmaceutical formulation as claimed in one of claims 1 to 3, wherein both active substances are released in delayed manner.

5. A pharmaceutical formulation as claimed in one of claims 1 to 4, wherein morphine, hydromorphone, codeine, oxycodone, dihydrocodeine, dextropropoxyphene, buprenorphine, levomethadone, fentanyl, sufentanil, etorphine, pentazocine, tilidine, tramadol, levorphanol, methadone, dihydromorphine, pethidine, piritramide and/or a physiologically compatible salt thereof is present as the opioid.

6. A pharmaceutical formulation as claimed in claim 5, wherein morphine, tramadol and/or a physiologically compatible salt thereof is present as the opioid.

7. A pharmaceutical formulation as claimed in one of claims 1 to 6, wherein clonidine, guanfacine, guanabenz, lofexidine, adrenaline, methyldopa, noradrenaline, methoxamine, oxymetazoline, xylometazoline, teryzoline, ST-91, medetomidine, dexmedetomidine, agmatine, UK14,304, para-aminoclonidine, U-47,476A, DJ-741, ICI-106270, xylazine, talipexole (BHT-920), naphazoline, tizanidine and/or a physiologically compatible salt thereof is present as the α-agonist.

8. ~~A pharmaceutical formulation as claimed in one~~ of claim 7, wherein clonidine, guanfacine and/or a physiologically compatible salt thereof is present as ~~the α-agonist.~~

9. A pharmaceutical formulation as claimed in one of claims 1 to 8, wherein the weight ratio of opioid to α-agonist is 200:1 to 10:1, preferably 100:1 to 10:1.

10. A pharmaceutical formulation as claimed in one of claims 1 to 9, wherein it assumes the form of a tablet, capsule or sugar-coated tablet, preferably of a multilayer tablet.

11. A pharmaceutical formulation as claimed in one of claims 1 to 9, wherein it assumes multiparticulate form, preferably the form of microtablets, micro-capsules, ion exchange resinates, granules, active substance crystals or pellets.

12. A pharmaceutical formulation as claimed in one of claims 1 to 11, wherein controlled release is achieved by a controlled release coating, immobilisation on an ion exchange resin, embedding in a controlled release matrix or a combination thereof.

13. A pharmaceutical formulation as claimed in claim 12, wherein the coating is based on a water-insoluble polymer or wax.

~~14. A pharmaceutical formulation as claimed in claim 13,~~ wherein a polyacrylic resin or cellulose derivative, preferably alkylcellulose, is used as the water-insoluble polymer.

15. A pharmaceutical formulation as claimed in claim 14, wherein ethylcellulose and/or a poly(meth)acrylate is used as the polymer.

16. A pharmaceutical formulation as claimed in claim 12, wherein the matrix comprises at least a polymer, a wax, a fat, a fatty acid, a fatty alcohol or a corresponding ester ~~or ether~~.

17. A pharmaceutical formulation as claimed in claim 16, wherein cellulose ethers, cellulose esters and/or acrylic resins are used as the polymers.

18. A pharmaceutical formulation as claimed in claim 12, wherein ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, mono- and diglycerides of C12 to C30 fatty acids

and/or C12-C30 fatty alcohols or the mixtures thereof are used as the matrix material.

19. A pharmaceutical formulation as claimed in one of claims 1 to 18, wherein at least one of the pharmaceutical active substances is present in controlled release form and in non-controlled release form.

20. A pharmaceutical formulation as claimed in one of claims 1 to 19, wherein it is administered orally, parenterally or transdermally, preferably orally.

~~21. Use of the pharmaceutical formulation as claimed~~ in one of claims 1 to 20 ~~for~~ the treatment of moderately ~~severe to severe acute or chronic pain states~~.

8. A pharmaceutical formulation as claimed in claim 7, wherein clonidine, guanfacine and/or a physiologically compatible salt thereof is present as the α-agonist.

14. A pharmaceutical formulation as claimed in claim 13, wherein a polyacrylic resin or cellulose derivative, preferably alkylcellulose, is used as the water-insoluble polymer.

15. A pharmaceutical formulation as claimed in claim 14, wherein ethylcellulose and/or a poly(meth)acrylate is used as the polymer.

16. A pharmaceutical formulation as claimed in claim 12, wherein the matrix comprises at least a polymer, a wax, a fat, a fatty acid, a fatty alcohol or a corresponding ester or ether.

21. A pharmaceutical formulation as claimed in one of claims 1 to 20 for the treatment of moderately severe to severe acute or chronic pain states.

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