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<td>Acino Pharma AG</td>
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(54) Title: MEDICINAL PRODUCT COMPRISING HYDROMORPHONE, WITH IMPROVED SHELF-LIFE

(54) Bezeichnung: ARZNEIMITTEL ENTHALTEND HYDROMORPHON MIT VERBESSERTER LAGERSTABILITÄT

(57) Abstract: The invention relates to an active ingredient-containing particle with delayed release of active ingredient, comprising a core which contains the active ingredient, and a delayed-release coating that delays the release of the active ingredient, this active ingredient comprising hydromorphone or a salt or solvate thereof, where the core comprises the hydromorphone or the pharmaceutically tolerated salt or the solvate thereof in a mixture with an antioxidant.

(57) Zusammenfassung: Die Erfindung betrifft ein wirkstoffhaltiges Teilchen mit retardiertem Wirkstoffaustritt, umfassend einen Kern, der den Wirkstoff enthält und eine Retardierung, die die Freisetzung des Wirkstoffs retardierte, wobei es sich bei dem Wirkstoff um Hydromorphon oder ein Salz oder Solvat davon handelt und wobei der Kern das Hydromorphon oder das pharmazeutisch verträgliche Salz oder das Solvat davon im Gemisch mit einem Antioxidationsmittel enthält.
The present invention relates to medicinal products with one or more active ingredient-containing particles for the administration of the active ingredient hydromorphone. The particles retard the release of active ingredient. The medicinal products and particles according to the invention have an outstanding shelf-life.

Medicinal products having the active ingredient hydromorphone have long been known. It is also known to administer hydromorphone via retarded-release formulations wherein the active ingredient is slowly released over a prolonged period with a certain release profile. Such medicinal products are already described in EP-A 0 271 193, for example. This printed matter in an exemplary manner discloses tablets wherein hydromorphone hydrochloride is formulated in a retarding matrix. The printed matter also generally discloses that the medicinal product may be present as a particle that is provided with a release-controlling film coating. The film coating is selected such that a particular *in vitro* release profile is achieved. The printed matter does not disclose any stability problems for the active ingredient hydromorphone hydrochloride; antioxidants are not mentioned.

EP-A 0 548 448 generally discloses that there can arise stability problems with retarded-release formulations wherein the active ingredient is present as a coating on an inert core if the coating is applied from an aqueous system. As examples for such retarded-release formulations there are also mentioned formulations with the active ingredient hydromorphone and most of the examples of the printed matter relate to hydromorphone. In order to solve these stability problems the printed matter suggests subjecting the coated cores to a particular curing reaction. Antioxidants are not mentioned.

US 5,866,164 discloses medicinal products having an opioid and an opioid antagonist. The medicinal products have two layers, one layer in which the hydromorphone is present and one layer containing the opioid antagonist. Together with the opioid antagonist an antioxidant can be formulated. Stability problems with the hydromorphone are not reported in the printed matter, also the hydromorphone is not formulated with an antioxidant.
US 2008/0020032 discloses a method to safeguard medicinal products with opioids, inter alia also hydromorphone, against abuse. Stability problems with hydromorphone in the medicinal products are not reported. In none of the examples of the printed matter hydromorphone is formulated together with an antioxidant.

A similar disclosure may also be found in the printed matters US 2007/0104789 and US 2010/0047345. In none of these printed matters there are reported stability problems with the hydromorphone during storage of a medicinal product and in none of these printed matters hydromorphone is formulated with an antioxidant.

US 5,914,131 and US 2010/0028389 relate to medicinal products with the active ingredient hydromorphone which are osmotic systems. As can be seen from figure 3 of these printed matters the active ingredient compositions and an expanding composition are in a bilayer arrangement. The expanding composition contains an osmopolymer, an osmotic agent (osmagent), and optionally an antioxidant. Stability problems with the hydromorphone in storage of the medicinal product are not reported, and also hydromorphone is not formulated in a mixture with an antioxidant.

WO 2009/059701 discloses retarded-release tablets with the active ingredient hydromorphone. The retarded-release tablets contain pellets wherein an inert core is coated with an active ingredient layer containing the hydromorphone. A retarded-releasing coating is applied to said coating and in this way, an intermediate for the production of the final product is prepared. The final product is prepared from the intermediate in that a rapidly releasing coating with the active ingredient hydromorphone again is applied to the retarded-releasing coating. In particular, the thus prepared pellets can be compressed to the so-called “MUPS” tablets. Also, in WO 2009/059701 there is no indication regarding a possible instability of the hydromorphone during storage, and the hydromorphone is not formulated together with an antioxidant.

The inventors of the present application now have found that with the medicinal products described in the prior art having the active ingredient hydromorphone in the core and a retarded-release coating applied thereon a stability problem during storage occurs. In particular, especially in the first weeks after the production of the corresponding medicinal products, no undesired decomposition of the active ingredient does occur.
The problem of the invention was to provide a medicinal product having a substantially improved shelf-life and in which, in particular also in the first weeks of storage, no decomposition of the active ingredient does occur.

This problem is solved by the object of the claims.

The solution of the problem is based on the surprising finding that unlike assumed in the prior art hydromorphone as well as the salts thereof and solvates thereof in retarded-release formulations containing coated particles with an active ingredient-containing core are oxidation-sensitive. After it has surprisingly been found that the low shelf-life of the hydromorphone in the known formulations is attributable to a sensitivity of the hydromorphone to atmospheric oxygen the stability problem could be solved by providing formulations wherein the hydromorphone is present mixed with an antioxidant in the core of a particle having a retarded-release coating. In this way, medicinal products with an outstanding shelf-life are provided.

The present invention in a preferred embodiment provides an active ingredient-containing particle with retarded release of active ingredient which has the following structure:

a) an inert pellet,
b) an active ingredient layer applied to the inert pellet which contains the active ingredient in a mixture with the antioxidant, and
c) a retarded-release coating applied to the active ingredient layer which retards the release of the active ingredient and which is preferably directly present on the active ingredient layer,

wherein the active ingredient layer contains the hydromorphone or the pharmaceutically acceptable salt thereof or the solvate thereof in a mixture with an antioxidant.

In an alternative preferred embodiment the active ingredient-containing particle has a core which is an extrusion pellet, wherein the active ingredient is present in a mixture with a spheronizing agent and an antioxidant. The core is coated with a retarded-release coating which retards the release of the active ingredient.
The invention also provides a medicinal product for the oral administration with at least one, preferably several of such active ingredient-containing particles as well as a method for the production of the particles and the use of the medicinal products for the treatment of chronic pain.

The particles according to the invention and thus, also the medicinal product according to the invention, contain hydromorphone as the active ingredient. Preferably, the hydromorphone is the only active ingredient that is present in the particles according to the invention and the medicinal product according to the invention. The active ingredient is contained in the medicinal product according to the invention preferably in a concentration in the range of 0.5% by weight to 20% by weight, in particular in the range of 1% by weight to 10% by weight, based on the total weight of the medicinal product, particularly preferred in the range of 1.5% by weight to 5.0% by weight. Preferably, the medicinal product according to the invention contains hydromorphone or the salt or solvate thereof, respectively, in the range of 1 to 100mg, in particular in the range of 2 to 50mg, more preferably in the range of 2 to 40mg, for example in the range of 2mg to 30mg, most preferably in the range of 2mg to 24mg.

It is preferred according to the invention that an active ingredient-containing particle has a content of active ingredient in the range of 1% by weight to 40% by weight, more preferably in the range of 2% by weight to 30% by weight, in particular in the range of 2% by weight to 10% by weight, based on the weight of the core containing the active ingredient (e.g., inert pellet + active ingredient layer or extrusion pellet, respectively).

Preferably, the active ingredient is present as a hydrochloride, but it may also be present as another salt or as solvate, or as solvate of a salt, or as a free base. If in the context of this application it is spoken about the active ingredient content this always relates to the weight of the salt or the solvate, if a salt or solvate is used. A solvate of the active ingredient is also meant to be a solvate of the salt of the active ingredient.

According to the invention there can be used any of the known pharmaceutically acceptable antioxidants as the antioxidant, e.g. ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, vitamin E, sorbic acid, isoascorbic acid, citric acid, etc. According to the invention the antioxidant is preferably water-soluble. The antioxidant that is particularly preferred according to the invention is ascorbic acid, in particular naturally occurring L-(+)-
ascorbic acid (vitamin C). According to the invention, also salts of the ascorbic acid, for example calcium ascorbate, or also esters of the ascorbic acid such as ascorbyl palmitate are preferred as the antioxidant.

It is preferred according to the invention that the medicinal product has a content of antioxidant in the range of 0.1 to 5mg, more preferably in the range of 0.1 to 3mg, in particular in the range of 0.1 to 2mg.

It is preferred according to the invention that an active ingredient-containing particle has a content of antioxidant in the range of 0.01% by weight to 30% by weight, more preferably in the range of 0.05% by weight to 20% by weight, in particular in the range of 0.05% by weight to 10% by weight, such as for example in the range of 0.05% by weight to 0.5% by weight, based on the weight of the core (e.g. inert pellet + active ingredient layer or extrusion pellet, respectively).

The preceding quantities for the antioxidant refer to the amount of antioxidant in the particle.

According to the invention it is preferred that in the medicinal product and thus, also in the active ingredient-containing particle the weight ratio of hydromorphone or the salt or solvate thereof, respectively, to antioxidant is in the range of 100:1 to 1:1, more preferably in the range of 70:1 to 5:1, even more preferably in the range of 40:1 to 5:1.

In an embodiment that is preferred according to the invention the core of the particle is an inert pellet having an active ingredient layer.

In this embodiment, the active ingredient-containing cores according to the invention have an inert pellet. Such inert pellets are known in the prior art and are sold for example as Non-Pareil in different sizes. As an example here, the product Non-Pareil 18-20 (mesh) can be mentioned. In general, such inert pellets have a diameter in the range of 0.2mm to 2.5mm, in particular in the range of 0.2mm to 1.5mm. They are also known under the designation "Neutral Cores". Frequently, sugar cores or cores of microcrystalline cellulose are used as neutral cores, but other neutral cores are also known among the experts.

According to the invention an active ingredient layer is present on the inert pellets in which the active ingredient, that is the hydromorphone or the salt or solvate thereof, respectively,
in a mixture with an antioxidant and one or more binders is applied as a coating to the inert core. This coating preferably is non-retarding, that is the active ingredient is rapidly released from it, that is at least 90% within 15 minutes, determined according to the Paddle method of the US pharmacopoeia (100 rpm in 900 ml aqueous buffer, pH in the range of 1.6 and 7.2 at 37°C). Unless stated otherwise all releasing data mentioned in this application refer to in vitro releases that are obtained according to the method of the US pharmacopoeia.

Said active ingredient-containing layer that is present on the inert pellet in the context of this application is referred to as active ingredient layer. In general, the active ingredient layer contains a binder, the active ingredient in a mixture with an antioxidant, and may also contain further common pharmaceutically acceptable excipients and additives. Such substances are known to the skilled person.

Suitable binders are for example water-soluble low-viscosity polymers, in particular water-soluble hydroxy lower alkyl celluloses such as hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, hydroxypropyl methylcellulose, etc. Further suitable binders are aminoalkyl methacrylate copolymers, gelatin, arabic gum, guar gum, methylcellulose, carboxy methylcellulose, ethylhydroxy ethylcellulose, hydroxyethyl methylcellulose, hydroxyethyl cellulose, gum tragacanth, polyvinylpyrrolidone, polyvinylacetate, polyvinylalcohol as well as inorganic gels, but also dextrin, sodium alginate, pectin, etc. According to the invention the binder is preferably hydroxypropyl cellulose or hydroxypropyl methylcellulose.

Moreover, the active ingredient layer may contain for example colorants, plastizisers such as triethylcitrate, polyethylene glycol or further excipients and additives.

In a second embodiment that is preferred according to the invention the core of the particle according to the invention is an extrusion pellet. The extrusion pellet contains the active ingredient, an antioxidant, a spheronizing agent, and optionally further pharmaceutically acceptable excipients and additives. Such extrusion pellets are known to those with skill in the art. They contain a spheronizing agent since the extrusion pellets after extrusion are just made round before they are provided with a retarded-release coating. The spheronizing agent gives the extrusion pellet the required plasticity so that during rounding it does not break or is otherwise destroyed. The preferred spheronizing agent is microcrystalline cellulose. The extrusion pellets are also referred to as spheroides.
The content of spheronizing agent, in particular of microcrystalline cellulose in the extrusion pellet is preferably in the range of 40-90\% by weight, in particular 60-85\% by weight, more preferably 65-80\% by weight.

In addition to the spheronizing agent the extrusion pellet may also have further common excipients and additives as is known in the prior art, in particular one or more binders such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, and povidone and optionally fillers such as mannitol, sucrose, Kollidon, etc. The binders and fillers are typically water-soluble.

The extrusion pellets preferably have a form factor of $\leq 1.4$. The form factor reflects the deviation of a particle from a sphericity. It is defined as circumference x circumference / (4 $\pi$ x face) wherein circumference and face refer to a cross section of the particle. Preferably, the form factor is $\leq 1.3$, more preferably $\leq 1.2$, in particular $\leq 1.1$. With an ideal sphere the form factor is 1.

According to the invention on the core of the particle there is the retarded-release coating that controls the release of the active ingredient. Such retarded-release coatings are known in the prior art, and again reference can be made to EP-A 0 271 193, EP-A 0 553 392 or WO 2009/059701, for example. Said retarded-release coating may for example consist of a water-insoluble polymer or a mixture of several water-insoluble polymers, e.g., a mixture of the products Eudragit RL and RS.

However, generally the retarded-release coating has a mixture of water-insoluble and water-soluble components. As suitable water-soluble components basically all the watersoluble polymers may be considered which above have been mentioned as binders for the inner active ingredient layer. For example, hydroxypropyl methylcellulose or another water-soluble cellulose or polyvinylpyrrolidone or a similar material is particularly preferred as the water-soluble component. As the water-insoluble component, for example a wax alone or in a mixture with a fatty alcohol, water-insoluble cellulose, in particular ethylcellulose, or a suitable polymethacrylate, for example a product of the Eudragit® series may be used. Such materials are known and in addition to the above-mentioned printed matters also described in EP-A 0 722 730, for example. Also mixing the water-insoluble component with the watersoluble component is done as known in the prior art. The retarded-release coating applied
to the active ingredient layer can contain further common pharmaceutically acceptable excipients and additives, such as colorants, plasticizers such as dibutylsebacate, etc.

By the use of the particles according to the invention an advantageous release profile and an advantageous release of the hydromorphone is achieved.

Preferably, the active ingredient layer has a thickness in the range of 5\(\mu\)m to 200\(\mu\)m, more preferably in the range of 5\(\mu\)m to 100\(\mu\)m.

Preferably, the extrusion pellets have a diameter in the range of 0.2mm to 2.6mm, in particular in the range of 0.4mm to 1.8mm.

Preferably, the retarded-release coating has a thickness in the range of 5\(\mu\)m to 200\(\mu\)m, more preferably in the range of 5\(\mu\)m to 100\(\mu\)m.

Preferably, the particles according to the invention have a diameter in the range of 200\(\mu\)m to 3000\(\mu\)m, more preferably in the range of 500\(\mu\)m to 2000\(\mu\)m.

According to the invention it is possible that the particles in addition to the described layers still have further layers. For example, the inert pellet and the active ingredient layer, the active ingredient layer and the retarded-release coating, or also the extrusion pellet and the retarded-release coating each can be separated by an intermediate layer. Further, on the retarded-release coating further coatings may be present. The composition of such intermediate layers or outer coatings, respectively, is known to the skilled person, for example they consist of a binder, such as in particular a water-soluble cellulose polymer and optionally common pharmaceutically safe excipients and additives. It is important that these additional layers do not adversely affect the release properties of the particles according to the invention. However, according to the invention it is preferred that the active ingredient-containing particles do not contain any further layers and e.g. consist of the inert pellet, the active ingredient layer, and the retarded-release coating, or of the extrusion pellet and the retarded-release coating, respectively.

According to the invention it is also possible, although not preferred, that the particles also have an outer active ingredient layer, as is described in WO 2009/059701.
The particles according to the invention may be directly or with a common pharmaceutically acceptable excipient and additive made into a medicinal product for the oral administration. Preferably, the medicinal product according to the invention is at first converted into a unit dosage form suitable and common for the oral administration. Suitable unit dosage forms are for example sachets, stickpacks, capsules, or tablets. According to the invention capsules are preferred wherein capsules in particular are hypromellose capsules. Preferably, a capsule contains 10 to 1200mg of particles, more preferably 20 to 750mg of the particles according to the invention.

For this, the particles according to the invention may for example directly and without further excipients and additives be transferred for example into a sachet or a capsule, or they may be at first mixed with suitable excipients and additives and subsequently filled for example into a sachet or capsule, or compressed into a tablet. Suitable excipients and additives are known to the skilled person, and are for example described in the European Pharmacopoeia. Possible excipients are for example blasting agents, release agents, fillers, binders, additives for improving the flowability, lubricants, flow control agents, and/or tensides.

Of course, also flavorings, colorants, and further excipients may be present in the medicinal product according to the invention. Preferably, the medicinal products according to the invention, if they are tablets, in addition to active ingredient-containing particles according to the invention still contain at least one filler, more preferably at least one filler and at least one blasting agent, even more preferably at least one filler, at least one blasting agent, and at least one binder. Preferably, there are also present lubricants and slip additives.

As binders, the same binders may be mentioned as previously disclosed in connection with the inner active ingredient-containing layer.

Suitable fillers are for example lactose, wherein modified lactose or anhydrous (NF) lactose may be mentioned, starch, in particular modified (pregelatinized) starch, native starch, or mixtures of both, calcium phosphate, in particular dibasic, unground dibasic, and anhydrous dibasic calcium phosphate, cellulose derivatives, cellulose, in particular microcrystalline cellulose, mannitol, sorbitol, etc.

Of course, mixtures of various fillers can be used.
Suitable blasting agents are for example polyvinylpolypyrrolidone (PVPP), agar, potato starch, formaldehyde casein, sodium carboxymethyl amylopectin, bentonite, sodium alginate, sodium carboxymethyl cellulose, cross-linked PVP, highly-dispersed silica or also dry pectin. As with binders and the fillers, of course also with the blasting agents mixtures of various blasting agents can be used.

Suitable flow control agents are known according to the invention, these may be for example “Gleitol”, talcum, colloidal silica, precipitated silica, calcium stearate, magnesium stearate, stearic acid, lauric acid, stearyl alcohol, palmitic acid, behenic acid, capric acid, Carbowax® or Aerosil®.

Suitable lubricants are also known to the skilled person, wherein many compounds that are suitable as flow control agents can also be used as lubricants. Suitable lubricants are for example calcium stearate, behenic acid, stearic acid, aluminum stearate, stearyl alcohol, sodium stearyl fumarate, hydrogenated castor oil, palmitic acid, cetylalcohol, talcum, magnesium stearate, tetradecanoic acid, Lanette® O, lauric acid, defatted milk powder, Gleitol, Talkumin, capric acid, bolus alba, starch, and polyethylene glycols, such as Carbowax® 6000.

The production of the particles according to the invention is done in a conventional manner.

In the production of the embodiment in which an inert pellet is provided with an active ingredient layer and a retarded-release layer at first the constituents of the active ingredient layer, e.g. hydromorphone or a pharmaceutically acceptable salt or solvate thereof, an antioxidant, a binder and optionally further pharmaceutically acceptable excipients and additives are introduced into a suitable solvent. Here, at first the hydromorphone or the pharmaceutically acceptable salt in a mixture with an antioxidant can be added to the solvent and subsequently the binder and optionally further pharmaceutically acceptable excipients and additives can be added. Alternatively, at first the binder and optionally further pharmaceutically acceptable excipients and additives can be fed into a solvent, followed by the addition of hydromorphone and an antioxidant. Moreover, hydromorphone, an antioxidant, a binder, and optionally further pharmaceutically acceptable excipients and additives may be simultaneously added to the solvent. Subsequently, the mixture is homogenized. Here, the solvent is preferably present in excess.
Preferably, all constituents are dissolved in the solvent so that a solution is formed that is used as spraying solution. However, it is also possible that one or more constituents are not or not completely soluble in the solvent. In this case, a suspension is formed that is used as spraying suspension.

Subsequently, the pH value of the obtained spraying solution or the spraying suspension, respectively, can optionally be decreased to pH 1.5 to pH 5.5 by a suitable addition of acid. For that, a suitable acid can be any pharmaceutically acceptable acid or any acid, respectively, that gives a pharmaceutically acceptable salt in the neutralization of the hydromorphone. For that, hydrochloric acid, citric acid, and acetic acid are suitable, for example.

As suitable solvents for the production of the spraying solution or the spraying suspension, respectively, all pharmaceutically acceptable and sufficiently volatile solvents that solve the hydromorphone or a pharmaceutically acceptable salt thereof to a sufficient extent are suitable. As a solvent that is particularly preferred for this purpose there is used water, in particular demineralized water.

In a separate step, the spraying solution or the spraying suspension, respectively, is sprayed onto the inert pellets in a fluidized bed apparatus. The preferred process temperature in this step is between 30°C and 60°C, particularly preferred between 35°C and 50°C.

Coating of the neutral pellets with the active ingredient layer may be done in conventional fluidized bed apparatuses, e.g. with a spray nozzle disposed in the lower part, e.g. in a Ventilus®, Innojet. The obtained active ingredient-containing cores are preferably sieved out to the desired particle size.

Separation of the active ingredient-containing cores of the desired particle size is done in conventional vibrating screens, e.g. in JEL-FIX 50, J. Engelsmann AG. Preferably, sieving is done such that the obtained active ingredient-containing cores have a particle size (D50 value) in the range of 100 to 3000μm, more preferably in the range of 500 to 2000μm. For that, for example a set of sieves having a mesh size of 1.250mm may be used.
The particle size of the active ingredient-containing cores can be determined for example by means of sieve analysis for example using a Retsch® AS 2000 device, wherein an amplitude of 1.5mm, an interval of 3 minutes, and a sample weighted portion of 50g may be given as exemplary measurement conditions.

The active ingredient-containing cores are provided with a retarded-release coating. This is preferably done in the same device and substantially under the same conditions as the application of the active ingredient layer to the inert pellets. Preferably, a mixture of a water-insoluble polymer and a water-soluble polymer as well as optionally plasticizers, and optionally further pharmaceutically acceptable excipients and additives is introduced into a suitable solvent. A suitable solvent may be a conventional pharmaceutically acceptable and sufficiently volatile solvent that can dissolve or suspend these compounds to a sufficient extent. As a solvent that is particularly preferred for this purpose there is used ethanol.

The obtained active ingredient-containing cores with the retarded-release coating are preferably sieved to the desired particle size. This sieving is preferably done in the same device and substantially under the same conditions as the separation of the active ingredient-containing cores without a retarded-release coating.

In the embodiment according to the invention wherein the core of the particle is an extrusion pellet the particles may be prepared in a manner per se known in the prior art. For example, the constituents of the extrusion pellet are added to an intensive mixer and mixed. Subsequently, the mass is grained with the addition of a suitable granulating fluid, e.g. demineralized water, and then extruded. Alternatively, the constituents of the extrusion pellet may also be mixed e.g. in a tumbling mixer and subsequently, the mixture can directly be moistened and extruded in an extruder. In both cases, the still moist extract strains have been made round in a suitable spheronizer to the desired form factor of \( \leq 1.4 \).

The obtained extrusion pellets may be sieved and provided with a retarded-release coating, as it was basically described above in the embodiment with the coated neutral pellet. The corresponding statements also apply to the extrusion pellets.

In an embodiment that is preferred according to the invention the particles according to the invention are then filled into hypromellose capsules, e.g. of size 4. Filling can be done with
filling machines known in the prior art, for example with Bosch GKF 701, Robert Bosch GmbH.

According to the invention it is particularly preferred that the medicinal products according to the invention and in particular the capsules according to the invention have an outstanding uniformity of mass being in the range of 95-105% of the average content, preferably in the range of 98-102% of the average content, particularly preferred in the range of 99-101% of the average content. The uniformity of mass is determined according to PH Eur. 6.0 section 2.9.5.

For the package of the medicinal products according to the invention there may be used for example blister packs of PVC-PVDC, childproofed blister packs of aluminum or Rexam bottles.

The following examples explain the invention.

Example 1

400g hydromorphone hydrochloride, 20g ascorbic acid, and 75g hypromellose (Pharmacoat 606, Shin-Etsu, apparent viscosity 4.8-7.2mPas) are dissolved in 1.7kg demineralized water and placed in a fluidized bed apparatus of Innojet which has a lower spray nozzle. 7.4kg sugar beads, 850-1000μm (Pharm-a-spheres, Werner, 90% within 850-1000μm) are added to the fluidized bed apparatus and pre-heated to a temperature of 40 to 50°C. In the apparatus, the spraying solution is sprayed onto the pre-heated sugar beads wherein the temperature is maintained in the range of 35 to 50°C until the desired coating amount was achieved. If necessary, one can work in the batch mode. The obtained cores are sieved (1.250mm).

Subsequently, the solution for the retarded-release coating of the cores is prepared. For that, 128g dibutyl sebacate, 192g hydroxypropyl cellulose (Klucel® EF Pharm, Hercules) and 640g ethylcellulose (Aqualon® N 14, Hercules, apparent viscosity 11.2-16.8mPas) are sequentially dissolved in 8.6kg absolute alcohol. The cores coated with the active ingredient layer are pre-heated in the fluidized bed apparatus to a temperature of 40 to 45°C. The solution for the retarded-release coating is subsequently sprayed onto the pre-heated cores with the temperature being held in the range of 35 to 50°C. Here, the particles according to
the invention are formed. The release profile of the particles can be adjusted by the layer thickness.

The particles thus coated with ethylcellulose are sieved through a 1.250mm sieve and filled into hypromellose capsules.

The particles listed in the following table 1 have been prepared in this manner (all figures refer to mg, unless explicitly stated otherwise).

<table>
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<th>Constituent</th>
<th>Function</th>
<th>1(a)</th>
<th>1(b)</th>
<th>1(c)</th>
<th>1(d)</th>
<th>1(e)</th>
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<td>133.65</td>
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<td>Hydromorphone HCl [mg]</td>
<td>Active Ingredient</td>
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<td>Pharmacoat 606 (Hypermellose) [mg]</td>
<td>Binder</td>
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<td>11.52</td>
<td>16.00</td>
<td>6.40</td>
<td>25.60</td>
</tr>
<tr>
<td>Klucel® EF (Hydroxypropyl Cellulose) [mg]</td>
<td>Pore Former</td>
<td>3.46</td>
<td>3.46</td>
<td>4.80</td>
<td>1.92</td>
<td>7.88</td>
</tr>
<tr>
<td>Dibutyl Sebacate [mg]</td>
<td>Plasticizer</td>
<td>2.30</td>
<td>2.30</td>
<td>3.20</td>
<td>1.28</td>
<td>5.12</td>
</tr>
<tr>
<td>Gelatin</td>
<td>Capsule</td>
<td>1 Piece</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMC</td>
<td>Capsule</td>
<td>1 Piece</td>
<td>1 Piece</td>
<td>1 Piece</td>
<td>1 Piece</td>
<td>1 Piece</td>
</tr>
<tr>
<td>Total Amount per Capsule [mg]</td>
<td></td>
<td>197.5</td>
<td>197.5</td>
<td>283.5</td>
<td>126.6</td>
<td>556.4</td>
</tr>
</tbody>
</table>

Examples 1(a) and 1(b) are comparative examples.
Example 2

The capsules of example 1 were filled either into blister packs (Alu/PVC/PVDC blisters or double blisters, respectively) or into a Rexam bottle with desiccant and subjected to a storage test under stress conditions. The results are summarized in the following table 2. All figures are in percent of active ingredient based on 100% active ingredient content.

Table 2

<table>
<thead>
<tr>
<th>Example</th>
<th>Package</th>
<th>T/rH</th>
<th>T/rH</th>
<th>T/rH</th>
<th>Storage Time</th>
<th>Initial Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>25°C/60%</td>
<td>30°C/65%</td>
<td>40°C/75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(a)</td>
<td>Double Blister</td>
<td>96.99</td>
<td>96.37</td>
<td>95.07</td>
<td>1 Month</td>
<td>99.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>98.20</td>
<td>97.60</td>
<td>95.66</td>
<td>3 Months</td>
<td></td>
</tr>
<tr>
<td>1(a)</td>
<td>Rexam Bottle</td>
<td>98.16</td>
<td>97.82</td>
<td>98.05</td>
<td>1 Month</td>
<td>99.69</td>
</tr>
<tr>
<td>1(a)</td>
<td>Alu/PVC/PVDC Blister</td>
<td>96.76</td>
<td>97.48</td>
<td>94.79</td>
<td>1 Month</td>
<td>99.69</td>
</tr>
<tr>
<td>1(b)</td>
<td>Rexam Bottle</td>
<td>98.02</td>
<td>97.93</td>
<td>93.38</td>
<td>1 Month</td>
<td>99.69</td>
</tr>
<tr>
<td>1(b)</td>
<td>Alu/PVC/PVDC Blister</td>
<td>98.30</td>
<td>97.31</td>
<td>95.55</td>
<td>1 Month</td>
<td>99.69</td>
</tr>
<tr>
<td>1(c)</td>
<td>Double Blister</td>
<td>102.56</td>
<td>104.27</td>
<td>101.89</td>
<td>1 Month</td>
<td>103.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>102.85</td>
<td>104.28</td>
<td>103.41</td>
<td>3 Months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>105.43</td>
<td>103.20</td>
<td>100.85</td>
<td>6 Months</td>
<td></td>
</tr>
<tr>
<td>1(d)</td>
<td>Rexam Bottle</td>
<td>101.7</td>
<td>102.3</td>
<td>99.6</td>
<td>6 Months</td>
<td>102.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100.6</td>
<td>101.1</td>
<td>100.2</td>
<td>9 Months</td>
<td></td>
</tr>
<tr>
<td>1(d)</td>
<td>Alu/PVC/PVDC Blister</td>
<td>98.4</td>
<td>-</td>
<td>100.6</td>
<td>3 Months</td>
<td>98.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100.7</td>
<td>-</td>
<td>101.1</td>
<td>18 Months</td>
<td></td>
</tr>
</tbody>
</table>

Further it has been shown that the samples in which the active ingredient was not formulated with an antioxidant after storage over 1 month already had a content of unknown impurities that is classified by many national Food and Drug Administrations as critical, namely in particular during storage above 40°C and 75% air humidity. Moreover, in the samples without antioxidant with prolonged storage frequently slight yellowing of the medicinal product occurred.
Altogether, it can be seen from the data above that the medicinal products according to the invention in which the active ingredient layer of the active ingredient-containing cores contains the active ingredient in a mixture with an antioxidant have a substantially improved shelf-life, namely over a period of up to 18 months also under stress conditions. In contrast, with medicinal products not containing an antioxidant a considerable degradation of the active ingredient occurs generally already after one month. This is in particular surprising, because in the prior art with solid dosage forms there is no indication of a possible sensitivity of the hydromorphone over atmospheric oxygen or of the use of antioxidants for stabilizing the hydromorphone.

**Example 3**

The constituents for the extrusion pellets, as given in table 3, were placed in an intensive mixer and mixed for 5 minutes until a homogeneous mixture has formed. The mixtures were grained with sufficiently demineralized water and subsequently extruded. The still moist extrudate strains were added to a spheronizer and made round to a form factor of \( \leq 1.4 \).

From the constituents for the retarded-release layer given in table 3 a coating solution was prepared according to example 1 and the extrusion pellets were coated therewith in analogy to the specification of example 1. The obtained particles were dried, filled into the HPMC capsules, and packed as given in table 3.
Example 3(e) is a comparative example.

The particles according to the invention showed an outstanding shelf-life.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An active ingredient-containing particle with retarded release of active ingredient, comprising a core which contains the active ingredient, and a retarded-release coating that retards the release of the active ingredient, wherein said active ingredient is hydromorphone or a salt or solvate thereof, and wherein the core contains the hydromorphone or the pharmaceutically acceptable salt or the solvate thereof in a mixture with ascorbic acid or a salt or an ester thereof.

2. The active ingredient-containing particle according to claim 1, wherein the particle has a content of hydromorphone or a pharmaceutically acceptable salt thereof or a solvate thereof in the range of 2% by weight to 20% by weight based on the weight of the particle.

3. The active ingredient-containing particle according to claim 1 or claim 2, wherein the particle does not contain an opioid antagonist.

4. The active ingredient-containing particle according to any one of claims 1 to 3, wherein the retarded-release coating contains ethyl cellulose.

5. The active ingredient-containing particle according to any one of claims 1 to 4, wherein the weight ratio of hydromorphone or the salt or the solvate thereof, respectively, to the antioxidant is in the range of 40:1 to 5:1.

6. The active ingredient-containing particle according to any one of claims 1 to 5, wherein the core containing the active ingredient comprises

   a) an inert pellet and
   b) an active ingredient layer applied to the inert pellet which has the active ingredient in a mixture with the antioxidant.

7. The active ingredient-containing particle according to claim 6, wherein the retarded-release coating is directly applied to the active ingredient layer.
8. The active ingredient-containing particle according to claim 6 or claim 7, wherein the active ingredient layer consists of hydromorphone hydrochloride, hydroxypropyl methylcellulose, and ascorbic acid.

9. The active ingredient-containing particle according to any one of claims 6 to 8, wherein the content of antioxidant in the active ingredient layer applied to the inert pellet is in the range of 0.01% by weight to 30% by weight based on the weight of the particle.

10. The active ingredient-containing particle according to any one of claims 1 to 9, wherein the core containing the active ingredient is an extrusion pellet in which the active ingredient is present in a mixture with a spheronizing agent and the antioxidant.

11. The active ingredient-containing particle according to claim 10, wherein the spheronizing agent is microcrystalline cellulose.

12. The active ingredient-containing particle according to claim 10 or claim 11 which has a form factor of ≤ 1.4.

13. A medicinal product for the oral administration with at least one active ingredient-containing particle according to any one of claims 1 to 12.

14. The medicinal product according to claim 13 with a content of hydromorphone or the salt or solvate thereof in the range of 2mg to 40mg.

15. A method for the production of an active ingredient-containing particle according to any one of claims 6 to 9, wherein

   (i) an inert pellet is coated with an active ingredient-containing layer,
   (ii) the thus obtained product is dried; and
   (iii) the dried product is coated with a retarded-release coating.

16. The method for the production of an active ingredient-containing particle according to any one of claims 10 to 12, wherein
(i) a mixture comprising the active ingredient, the spheronizing agent, and the antioxidant is extruded,
(ii) made round in a spheronizer and subsequently
(iii) coated with a retarded-release coating.

17. A method for treating chronic pain, the method comprising the step of administering to an animal in need thereof an effective amount of the medicinal product according to claim 13 or claim 14.