(12) STANDARD PATENT (11) Application No. AU 2010275754 B2
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Tamper-resistant dosage form for oxidation-sensitive opioids

(51) International Patent Classification(s)
A61K 9/20 (2006.01) ***A61K 31/485*** (2006.01)
A61K 9/28 (2006.01)

(21) Application No: **2010275754** (22) Date of Filing: **2010.07.21**

(87) WIPO No: **WO11/009603**

(30) Priority Data

(31) Number	(32) Date	(33) Country
09009480.6	**2009.07.22**	**EP**

(43) Publication Date: **2011.01.27**
(44) Accepted Journal Date: **2014.05.15**

(71) Applicant(s)
Grunenthal GmbH

(72) Inventor(s)
Bartholomaus, Johannes;Geissler, Anja;Bertram, Ulrike;Griessmann, Kornelia

(74) Agent / Attorney
Spruson & Ferguson, L 35 St Martins Tower 31 Market St, Sydney, NSW, 2000

(56) Related Art
WO 2008/086804 A (EGALET AS ET AL) 24 July 2008
WO 2008/148798 A (EGALET AS ET AL) 11 December 2008

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 January 2011 (27.01.2011)

PCT

(10) International Publication Number
WO 2011/009603 A1

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 31/485* (2006.01)
A61K 9/28 (2006.01)

(21) International Application Number:
PCT/EP2010/004460

(22) International Filing Date:
21 July 2010 (21.07.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09009480.6 22 July 2009 (22.07.2009) EP

(71) Applicant *(for all designated States except US)*: **GRÜNENTHAL GMBH** [DE/DE]; Zieglerstrasse 6, 52078 Aachen (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BARTHOLOMÄUS, Johannes** [DE/DE]; Burghöhenweg 5, 52080 Aachen (DE). **GEISSLER, Anja** [DE/DE]; Leuwstrasse 56, 52224 Stolberg (DE). **BERTRAM, Ulrike** [DE/DE]; Flandrische Strasse 27, 52076 Aachen (DE). **GRIESSMANN, Kornelia** [DE/DE]; Bergdriesch 40a, 52062 Aachen (DE).

(74) Agents: **BÜLLE, Jan** et al.; Patentanwälte Kutzenberger & Wolff, Theodor-Heuss-Ring 23, 50668 Köln (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2011/009603 A1

(54) Title: TAMPER-RESISTANT DOSAGE FORM FOR OXIDATION-SENSITIVE OPLOIDS

(57) Abstract: The invention relates to a thermoformed pharmaceutical dosage form having a breaking strength of at least 300 N, said dosage form comprising - an opioid (A), - - a free physiologically acceptable acid (B) in an amount of from 0T001 to 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form, and - a polyalkylene oxide (C) having a weight average molecular weight M_w of at least 200,000 g/mol.

Tamper-Resistant Dosage Form for Oxidation-Sensitive Opioids

The invention relates to a pharmaceutical dosage form which contains an opioid with improved storage stability.

Many pharmacologically active compounds have a potential of being abused and thus, are advantageously provided in form of tamper resistant pharmaceutical dosage forms. Prominent examples of such pharmacologically active compounds are opioids.

It is known that abusers crush conventional tablets, which contain opioids, to defeat the time-release "micro-encapsulation" and then ingest the resulting powder orally, intra-nasally, rectally, or by injection.

Various concepts for the avoidance of drug abuse have been developed. One concept relies on the mechanical properties of the pharmaceutical dosage forms, particularly an increased breaking strength (resistance to crushing). The major advantage of such pharmaceutical dosage forms is that comminuting, particularly pulverization, by conventional means, such as grinding in a mortar or fracturing by means of a hammer, is impossible or at least substantially impeded.

Such pharmaceutical dosage forms are useful for avoiding drug abuse of the pharmacologically active compound contained therein, as they may not be powdered by conventional means and thus, cannot be administered in powdered from, e.g. nasally. The mechanical properties, particularly the high breaking strength of these pharmaceutical dosage forms renders them tamper resistant. In the context of such tamper resistant pharmaceutical dosage forms it can be referred to, e.g., WO 2005/016313, WO 2005/016314, WO 2005/063214, WO 2005/102286, WO 2006/002883, WO 2006/002884, WO 2006/002886, WO 2006/082097, WO 2006/082099, and WO 2008/107149.

A problem in the manufacture of pharmaceutical dosage forms that contain opioids, such as oxymorphone, hydromorphone, and oxycodone, is their sensitivity towards oxidative degradation and decomposition. Oxidation may be caused by molecular oxygen or by radicals or peroxides generated by compounds that come into close proximity with these oxidation-sensitive opioids. Pharmaceutical excipients as such, e.g. polyethylene glycols, may cause or catalyze oxidative degradation, for example in the course of the process for the manufacture the pharmaceutical dosage forms. Further, molecular oxygen may generate said radicals or peroxides.

Typically, decomposition is monitored in standard storage stability tests e.g. under accelerated storage conditions, such as 40 °C / 75 % rel. humidity. Under these conditions, degradation and decomposition proceeds faster than under ambient conditions. The drug approving authorities, such as CHMP and FDA, and international harmonization unions, such as ICH, have set standard storage stability thresholds which have to be met in order to get a pharmaceutical dosage form approved.

Particular problems arise when the oxidation-sensitive opioid needs to be exposed to elevated temperatures in the course of the manufacturing process, such as hot-melt extrusion, film coating and the like. Under these conditions the opioids are even more sensitive towards oxidation. For example, several known processes for the manufacture of pharmaceutical dosage forms having an increased breaking strength require that a pharmaceutical composition containing the active ingredient is subjected to a specific amount of pressure at a specific elevated temperature for a specific period of time. Depending on the constituents of the pharmaceutical composition and their amounts, temperature, pressure and time may be varied within certain limits. However, if the minimal requirements are not satisfied, the breaking strength of the resultant pharmaceutical dosage form is too low.

In consequence, some conventional processes for the manufacture of pharmaceutical dosage forms, particularly for pharmaceutical dosage forms having an increased breaking strength, require comparatively harsh process conditions and thus, are so far not applicable for oxidation-sensitive opioids. In particular, chain rupture of pharmaceutical excipients such as polyethylene oxide during hot melt extrusion risks the formation of free radicals thereby further increasing the oxidative stress.

Lower dosages of oxidation-sensitive opioids often show a higher percentage of oxidative degradation and decomposition than higher dosages. Thus, as far as storage stability is concerned, pharmaceutical dosage forms containing lower dosages of oxidation-sensitive opioids need particular attention.

The effect of oxidation mechanisms and chemical interactions on stability of polymeric systems for amorphous Δ^9-tetrahydrocannabinol (a non-opioid) produced by a hot-melt method is described in M. Munjal et al., J. Pharm. Sciences, 95(11), 2006, 2473-85. The study demonstrated for this highly unstable drug a complex nature of interactions including drug-excipient compatibility, use of antioxidants, cross-linking in polymeric matrixes, micro environment pH, and moisture effect.

K.C. Waterman et al., Pharm. Develop. Tech. 7(1), 2002, 1-32 reviews the stabilization of pharmaceuticals to oxidative degradation. Various methods for reducing oxidation are recommended. The authors conclude that in the end, every drug presents a unique situation.

WO 2008/107149 discloses oral dosage forms having an increased breaking strength that may contain redox stabilizers such as complexing agents, e.g. EDTA.

WO 2008/086804 relates to controlled release compositions containing a matrix composition comprising a) polymer or a mixture of polymers, b) an active drug substance and optionally c) one or more pharmaceutically acceptable excipients that is without alcohol induced dose dumping and have excellent properties with respect to avoiding drug abuse. Preferably, the composition is resistant to isolate and/or dissolve the active drug substance from the composition by crushing, melting and/or ethanol extraction, whereby the composition is resistant to drug abuse. Citric acid may be present as flavouring agent. Example 2 relates to a composition containing 7 wt.-% of citric acid.

WO 2008/148798 discloses an layered extended release composition for prolonged effect and a way to ensure prolonged effect e.g. once daily administration is to ensure optimal absorption of the active substance though the gastrointestinal tract i.e. from the stomach to rectum.

There is no general concept to successfully suppress oxidative degradation of oxidation-sensitive drugs in pharmaceutical dosage forms. The complex individual oxidation mechanisms that are relevant for a particular drug as well as the plurality of possible factors that have an influence on oxidation processes require extensive investigations in each particular case taking into account the particular circumstances.

It is further known that the other ingredients of the pharmaceutical dosage forms may show stability problems when being exposed to such harsh process conditions. For example, high molecular weight polyethylene oxide tends to degrade upon hot-melt extrusion. Polymer degradation, however, may result in an uncontrolled release profile, particularly when the active ingredient is embedded in a matrix of the polyethylene oxide, and this might be another cause for oxidative degradation of the active ingredient by radicals. When adding suitable excipients in order to stabilize the high molecular weight polyethylene oxide, such as α-tocopherol, it should be taken into considerations that said excipients in turn may have a detrimental effect on the stability of other ingredients of the pharmaceutical dosage, e.g. of the pharmacologically active compound.

It is an object of the present invention to provide tamper-resistant pharmaceutical dosage forms containing opioids, particularly oxidation-sensitive opioids, that have advantages over the pharmaceutical dosage forms of the prior art. The pharmaceutical dosage forms should have improved storage stability, so that they may contain oxidation-sensitive opioids even at comparatively low doses. Further, it should be possible to prepare the pharmaceutical dosage forms by conventional processes under conventional conditions such as elevated temperature and pressure (e.g. in the course of thermoforming by hot-melt extrusion).

This object has been solved by the subject-matter of the patent claims.

The invention relates to a thermoformed pharmaceutical dosage form having a breaking strength of at least 300 N and comprising

- an opioid (A),
- a free physiologically acceptable acid (B) in an amount of from 0.001 to 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form, and
- a polyalkylene oxide (C) having a weight average molecular weight Mw of at least 200,000 g/mol.

A first aspect of the present invention provides a thermoformed pharmaceutical dosage form having a breaking strength of at least 300 N and comprising

- an opioid (A),
- a free physiologically acceptable acid (B) in an amount of from 0.3 ± 0.18 wt.-%, based on the total weight of the pharmaceutical dosage form, and
- a polyalkylene oxide (C) having a weight average molecular weight M_w of at least 500,000 g/mol,

wherein the acid (B) is a multicarboxylic acid.

It has been surprisingly found that certain morphinan derivatives such as oxymorphone are oxidatively degraded to N-oxides (e.g., oxymorphone-N-oxide, N-oxides in general are often said to be toxic and possibly cancerogenic) upon manufacture and storage of the corres-ponding dosage forms and that the formation of said N-oxides and other decomposition

2010275754 11 Apr 2014

products can be suppressed by the presence of suitable amounts of acid (B) in the pharmaceutical dosage forms according to the invention.

While it is not intended to be bound to any theory, the stabilizing effect of acid (B) might correlate with the pKA-value of the oxidation-sensitive opioids. The pKA-value of oxymorphone is 8.3. Conventional formulations of oxymorphone, which are tamper resistant due to their increased breaking strength but which do not show the desired shelf life, give a pH value of about 7.5 when being dispersed in water. Under these conditions, a considerable amount of the oxymorphone is present as a free base (i.e., is not protonated), which might be more sensitive towards oxidation than the (protonated) salt form. This concept is further supported by the fact that in the absence of acid (B), the dosage forms tend to have a yellowish, beige color, while the presence of acid (B) leads to whiter, e.g. colorless tablets. Thus, the presence of acid (B) might decrease the pH value within the dosage form thereby improving drug resistance towards oxidative degradation.

It has been surprisingly found that pharmaceutical excipients which are conventionally used in order to improve drug resistance towards oxidative degradation, particularly certain anti-oxidants, e.g., α-tocopherol, can be contra-productive and rather deteriorate than improve drug resistance towards oxidative degradation.

Furthermore, there is experimental evidence that surprisingly, acid (B) is also capable of stabilizing high molecular weight polyalkylene oxides against degradation, such as polyalkylene oxides (C) having a weight average molecular weight M_w of at least 200,000 g/mol.

The pharmaceutical dosage form according to the invention is thermoformed, preferably by extrusion, although also other methods of thermoforming may be used in order to manufacture the pharmaceutical dosage form according to the invention such as press-molding at elevated temperature or heating of tablets that were manufactured by conventional compression in a first step and then heated above the softening temperature of the polymer in the tablet in a second step to form hard tablets. In this regards, thermoforming means the forming, or molding of a mass after the application of heat. In a preferred embodiment, the pharmaceutical dosage form is thermoformed by hot-melt extrusion.

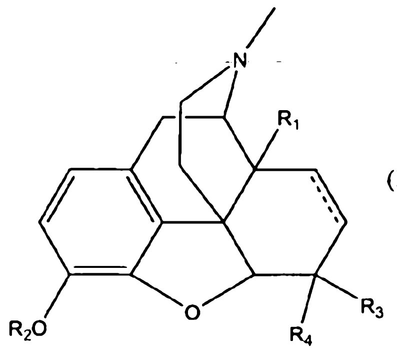
Preferably, the pharmaceutical dosage form is a monolithic mass. The pharmaceutical dosage form is preferably prepared by hot-melt extrusion. The melt extruded strands are preferably cut into monoliths, which are then preferably formed into tablets. In this regard, the term "tablets" is preferably not to be understood as dosage forms being made by compression of powder or granules (compressi) but rather, as shaped extrudates.

The pharmaceutical dosage form according to the invention contains, as component (A), an opioid (A), preferably an oxidation-sensitive opioid (A), most preferably oxymorphone or oxycodone. For the purpose of the specification, the term opioid (A) also includes the free base and the physiologically acceptable salts thereof.

According to the ATC index, opioids are divided into natural opium alkaloids, phenylpiperidine derivatives, diphenylpropylamine derivatives, benzomorphan derivatives, oripavine derivatives, morphinan derivatives and others. Examples of natural opium alkaloids are morphine, opium, hydromorphone, nicomorphine, oxycodone, dihydrocodeine, diamorphine, papaveretum, and codeine. Further opioids (A) are, for example, ethylmorphine, hydrocodone, oxymorphone, and the physiologically acceptable derivatives thereof or compounds, preferably the salts and solvates thereof, preferably the hydrochlorides thereof, physiologically acceptable enantiomers, stereoisomers, diastereomers and racemates and the physiologically acceptable derivatives thereof, preferably ethers, esters or amides.

Further preferred opioids (A) include N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluorobenzyloxy)-1-(m-methoxyphenyl)cyclohexanol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, (1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (2R,3R)-1-dimethylamino-3(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,-6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, preferably as racemate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(4-isobutyl-phenyl)propionate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, (RR-SS)-2-acetoxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-4-chloro-2-hydroxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-5-nitro-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2',4'-difluoro-3-hydroxy-biphenyl-4-carboxylic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, 1,1-(3-dimethylamino-3-phenyl-pentamethylen)-6-fluor-1,3,4,9-tetrahydropyrano[3,4-b]indole, in particular its hemicitrate; 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylen]-1,3,4,9-tetrahydropyrano[3,4-b]indole, in particular its citrate; and 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylen]-1,3,4,9-tetrahydropyrano[3,4-b]-6-fluoro-indole, in particular its hemicitrate, and corresponding stereoisomeric compounds, in each case the corresponding derivatives thereof, physiologically acceptable enantiomers, stereoisomers, diastereomers and racemates and the physiologically acceptable derivatives thereof, e.g. ethers, esters or amides, and in each case the physiologically acceptable compounds thereof, in particular the salts thereof and solvates, e.g. hydrochlorides.

Preferred opioids (A) are of general formula (I)



(I)

wherein

R_1 is -H, -OH or -OC_{1-6}-alkyl;

R_2 is -H or -C_{1-6}-alkyl;

R_3 is -H or -OH and R_4 is -H; or R_3 and R_4 together are =O; and

---- is an optional double bond;

or the physiologically acceptable salts thereof.

Particularly preferred opioids (A) include oxymorphone, oxycodone, hydromorphone, and the physiologically acceptable salts thereof.

The content of the opioid (A) in the pharmaceutical dosage form is not limited.

Preferably, its content is within the range of from 0.01 to 80 wt.-%, more preferably 0.1 to 50 wt.-%, still more preferably 1 to 25 wt.-%, based on the total weight of the pharmaceutical dosage form. In a preferred embodiment, the content of opioid (A) is within the range of from 7±6 wt.-%, more preferably 7±5 wt.-%, still more preferably 5±4 wt.-%, 7±4 wt.-% or 9±4 wt.-%, most preferably 5±3 wt.-%, 7±3 wt.-% or 9±3 wt.-%, and in particular 5±2 wt.-%, 7±2 wt.-% or 9±2 wt.-%, based on the total weight of the pharmaceutical dosage form. In another preferred embodiment, the content of opioid (A) is within the range of from 11±10 wt.-%, more preferably 11±9 wt.-%, still more preferably 9±6 wt.-%, 11±6 wt.-%, 13±6 wt.-% or 15±6 wt.-%, most preferably 11±4 wt.-%, 13±4 wt.-% or 15±4 wt.-%, and in particular 11±2 wt.-%, 13±2 wt.-% or 15±2 wt.-%, based on the total weight of the pharmaceutical dosage form. In a further preferred embodiment, the content of opioid (A) is within the range of from 20±6 wt.-%, more preferably 20±5 wt.-%, still more preferably 20±4 wt.-%, most preferably 20±3 wt.-%, and in particular 20±2 wt.-%, based on the total weight of the pharmaceutical dosage form.

Preferably, the total amount of the opioid (A) that is contained in the pharmaceutical dosage form is within the range of from 0.01 to 200 mg, more preferably 0.1 to 190 mg, still more preferably 1.0 to 180 mg, yet more preferably 1.5 to 160 mg, most preferably 2.0 to 100 mg and in particular 2.5 to 80 mg.

In a preferred embodiment, the opioid (A) is contained in the pharmaceutical dosage form in an amount of 7.5±5 mg, 10±5 mg, 20±5 mg, 30±5 mg, 40±5 mg, 50±5 mg, 60±5 mg, 70±5 mg, 80±5 mg, 90±5 mg, 100±5 mg, 110±5 mg, 120±5 mg, 130±5, 140±5 mg, 150±5 mg, or 160±5 mg. In another preferred embodiment, the opioid (A) is contained in the pharmaceutical dosage form in an amount of 5±2.5 mg, 7.5±2.5 mg, 10±2.5 mg, 15±2.5 mg, 20±2.5 mg, 25±2.5 mg, 30±2.5 mg, 35±2.5 mg, 40±2.5 mg, 45±2.5 mg, 50±2.5 mg, 55±2.5 mg, 60±2.5 mg, 65±2.5 mg, 70±2.5 mg, 75±2.5 mg, 80±2.5 mg, 85±2.5 mg, 90±2.5 mg, 95±2.5 mg, 100±2.5 mg, 105±2.5 mg, 110±2.5 mg, 115±2.5 mg, 120±2.5 mg, 125±2.5 mg, 130±2.5 mg, 135±2.5 mg, 140±2.5 mg, 145±2.5 mg, 150±2.5 mg, 155±2.5 mg, or 160±2.5 mg.

In a particularly preferred embodiment, opioid (A) is oxymorphone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration twice daily. In this embodiment, opioid (A) is preferably contained in the pharmaceutical dosage form in an amount of from 5 to 40 mg. In another particularly preferred embodiment, opioid (A) is oxymorphone, preferably its HCl, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, opioid (A) is preferably contained in the pharmaceutical dosage form in an amount of from 10 to 80 mg.

In another particularly preferred embodiment, opioid (A) is oxycodone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration twice daily. In this embodiment, opioid (A) is preferably contained in the pharmaceutical dosage form in an amount of from 5 to 80 mg. In another particularly preferred embodiment, opioid (A) is oxycodone, preferably its HCl, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, opioid (A) is preferably contained in the pharmaceutical dosage form in an amount of from 10 to 320 mg.

In still another particularly preferred embodiment, opioid (A) is hydromorphone, preferably its HCl, and the pharmaceutical dosage form is adapted for administration twice daily. In this embodiment, opioid (A) is preferably contained in the pharmaceutical dosage form in an amount of from 2 to 52 mg. In another particularly preferred embodiment, opioid (A) is hydromorphone, preferably its HCl, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, opioid (A) is preferably contained in the pharmaceutical dosage form in an amount of from 4 to 104 mg.

The pharmaceutical dosage form according to the invention is characterized by excellent storage stability. Preferably, after storage for 4 weeks at 40°C and 75% rel. humidity, the content of opioid (A) amounts to at least 98.0%, more preferably at least 98.5%, still more preferably at least 99.0%, yet more preferably at least 99.2%, most preferably at least 99.4% and in particular at least 99.6%, of its original content before storage. Suitable methods for measuring the content of the opioid (A) in the pharmaceutical dosage form are known to the skilled artisan. In this regard it is referred to the Eur. Ph. or the USP, especially to reversed phase HPLC analysis. Preferably, the pharmaceutical dosage form is stored in closed, preferably sealed containers, preferably as described in the experimental section, most preferably being equipped with an oxygen scavenger, in particular with an oxygen scavenger that is effective even at low relative humidity.

The pharmaceutical dosage form according to the invention contains, as component (B), a free physiologically acceptable acid in an amount of from 0.001 to 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form. The acid (B) may be organic or inorganic, liquid or solid. Solid acids are preferred, particularly crystalline organic or inorganic acids.

Acid (B) is free. This means that the acidic functional groups of the acid (B) are not all together constituents of a salt of the opioid (A). If the opioid (A) is present as a salt of an acid, e.g. as hydrochloride, the pharmaceutical dosage form according to the invention preferably contains as component (B) another, chemically different acid which is not present as a constituent of the salt of the opioid (A). In other words, monoacids that form a salt with opioid (A) are not to be considered as free acids (B) in the meaning of the present invention. When acid (B) has more than a single acidic functional group (e.g. phosphoric acid), the acid (B) may be present as a constituent of a salt of the opioid (A), provided that at least one of the acidic functional groups of the acid (B) is not involved in the formation of the salt, i.e. is free. Preferably, however, each and every acidic functional group of acid (B) is not involved in the formation of a salt with opioid (A). It is also possible, however, that free acid (B) and the acid forming a salt with opioid (A) are identical. Under these circumstances the acid (B) is preferably present in molar excess compared to opioid (A).

In a preferred embodiment, the acid (B) contains at least one acidic functional group (e.g. $-CO_2H$, $-SO_3H$, $-PO_3H_2$, -OH and the like) having a pK_A value within the range of 2.00±1.50, more preferably 2.00±1.25, still more preferably 2.00±1.00, yet more preferably 2.00±0.75, most preferably 2.00±0.50 and in particular 2.00±0.25. In another preferred embodiment, the acid (B) contains at least one acidic functional group having a pK_A value within the range of 2.25±1.50, more preferably 2.25±1.25, still more preferably 2.25±1.00, yet more preferably 2.25±0.75, most preferably 2.25±0.50 and in particular 2.25±0.25. In another preferred embodiment, the acid (B) contains at least one acidic functional group having a pK_A value within the range of 2.50±1.50, more preferably 2.50±1.25, still more preferably 2.50±1.00, yet more preferably 2.50±0.75, most preferably 2.50±0.50 and in particular 2.50±0.25. In another preferred embodiment, the acid (B) contains at least one acidic functional group having a pK_A value within the range of 2.75±1.50, more preferably 2.75±1.25, still more preferably 2.75±1.00, yet more preferably 2.75±0.75, most preferably 2.75±0.50 and in particular 2.75±0.25. In another preferred embodiment, the acid (B) contains at least one acidic functional group having a pK_A value within the range of 3.00±1.50, more preferably 3.00±1.25, still more preferably 3.00±1.00, yet more preferably 3.00±0.75, most preferably 3.00±0.50 and in particular 3.00±0.25. In still another preferred embodiment, the acid (B) contains at least one acidic functional group having a pK_A value within the range of 3.25±1.50, more preferably 3.25±1.25, still more preferably 3.25±1.00, yet more preferably 3.25±0.75, most preferably 3.25±0.50 and in particular 3.25±0.25.

In yet another preferred embodiment, the acid (B) contains at least one acidic functional group having a pK_A value within the range of 4.50±1.50, more preferably 4.50±1.25, still more preferably 4.50±1.00, yet more preferably 4.50±0.75, most preferably 4.50±0.50 and in particular 4.50±0.25. In yet another preferred embodiment, the acid (B) contains at least one acidic functional group having a pK_A value within the range of 4.75±1.50, more preferably 4.75±1.25, still more preferably 4.75±1.00, yet more preferably 4.75±0.75, most preferably 4.75±0.50 and in particular 4.75±0.25. In yet another preferred embodiment, the acid (B) contains at least one acidic functional group having a pK_A value within the range of 5.00±1.50, more preferably 5.00±1.25, still more preferably 5.00±1.00, yet more preferably 5.00±0.75, most preferably 5.00±0.50 and in particular 5.00±0.25.

Preferably, the acid (B) is an organic carboxylic or sulfonic acid, particularly a carboxylic acid. Multicarboxylic acids and/or hydroxy-carboxylic acids are especially preferred.

In case of multicarboxylic acids, the partial salts thereof are also to be regarded as multicarboxylic acids, e.g. the partial sodium, potassium or ammonium salts. For example, citric acid is a multicarboxylic acid having three carboxyl groups. As long as there remains at least one carboxyl group protonated (e.g. sodium dihydrogen citrate or disodium hydrogen citrate), the salt is to be regarded as a multicarboxylic acid. Preferably, however, all carboxyl groups of the multicarboxylic acid are protonated.

Preferably, the acid (B) is of low molecular weight, i.e., not polymerized. Typically, the molecular weight of the acid (B) is below 500 g/mol.

Examples of acids include saturated and unsaturated monocarboxylic acids, saturated and unsaturated bicarboxylic acids, tricarboxylic acids, α-hydroxyacids and β-hydroxylacids of monocarboxylic acids, α-hydroxyacids and β-hydroxyacids of bicarboxylic acids, α-hydroxy-acids and β-hydroxyacids of tricarboxylic acids, ketoacids, α-ketoacids, β-ketoacids, of the polycarboxylic acids, of the polyhydroxy monocarboxylic acids, of the polyhydroxy bicarboxylic acids, of the polyhydroxy tricarboxylic acids.

Preferably, the acid (B) is selected from the group consisting of benzenesulfonic acid, citric acid, α-glucoheptonic acid, D-gluconic acid, glycolic acid, lactic acid, malic acid, malonic acid, mandelic acid, propanoic acid, succinic acid, tartaric acid (d, l, or dl), tosic acid (toluenesulfonic acid), valeric acid, palmitic acid, pamoic acid, sebacic acid, stearic acid, lauric acid, acetic acid, adipic acid, glutaric acid, 4-chlorobenzenesulfonic acid, ethanedisulfonic acid, ethylsuccinic acid, fumaric acid, galactaric acid (mucic acid), D-glucuronic acid, 2-oxo-glutaric acid, glycerophosphoric acid, hippuric acid, isethionic acid (ethanolsulfonic acid), lactobionic acid, maleic acid, maleinic acid, 1,5-naphthalene-disulfonic acid, 2-naphthalene-sulfonic acid, pivalic acid, terephthalic acid, thiocyanic acid, cholic acid, n-dodecyl sulfate, 3-hydroxy-2-naphthoic acid, 1-hydroxy-2-naphthoic acid, oleic acid, undecylenic acid, ascorbic acid, (+)-camphoric acid, d-camphorsulfonic acid, dichloroacetic acid, ethanesulfonic acid, formic acid, methanesulfonic acid, nicotinic acid, orotic acid, oxalic acid, picric acid, L-pyroglutamic acid, saccharine, salicylic acid, gentisic acid, and/or 4-acetamidobenzoic acid.

The content of the acid (B) is within the range of from 0.001 to 5.0 wt.-%, preferably 0.005 to 2.5 wt.-%, more preferably 0.01 to 2.0 wt.-%, still more preferably 0.05 to 1.5 wt.-%, most preferably 0.1 to 1.0 wt.-% and in particular 0.2 to 0.9 wt.-%, based on the total weight of the pharmaceutical dosage form.

Preferably, the acid (B) is a multicarboxylic acid. More preferably, the multicarboxylic acid is selected from the group consisting of citric acid, maleic acid and fumaric acid.

Citric acid is particularly preferred.

The multicarboxylic acid, preferably citric acid, may be present in its anhydrous form or as a solvate and hydrate, respectively, e.g., as monohydrate.

In a preferred embodiment, the content of the acid (B), preferably citric acid, is within the range of 0.2±0.18 wt.-%, more preferably 0.2±0.15 wt.-%, still more preferably 0.2±0.12 wt.-%, yet more preferably 0.2±0.09 wt.-%, most preferably 0.2±0.06 wt.-%, and in particular 0.2±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

In another preferred embodiment, the content of the acid (B), preferably citric acid, is within the range of 0.3±0.18 wt.-%, more preferably 0.3±0.15 wt.-%, still more preferably 0.3±0.12 wt.-%, yet more preferably 0.3±0.09 wt.-%, most preferably 0.3±0.06 wt.-%, and in particular 0.3±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

In still another preferred embodiment, the content of the acid (B), preferably citric acid, is within the range of 0.4±0.18 wt.-%, more preferably 0.4±0.15 wt.-%, still more preferably 0.4±0.12 wt.-%, yet more preferably 0.4±0.09 wt.-%, most preferably 0.4±0.06 wt.-%, and in particular 0.4±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

In yet another preferred embodiment, the content of the acid (B), preferably citric acid, is within the range of 0.5±0.18 wt.-%, more preferably 0.5±0.15 wt.-%, still more preferably 0.5±0.12 wt.-%, yet more preferably 0.5±0.09 wt.-%, most preferably 0.5±0.06 wt.-%, and in particular 0.5±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

In yet another preferred embodiment, the content of the acid (B), preferably citric acid, is within the range of 0.6±0.18 wt.-%, more preferably 0.6±0.15 wt.-%, still more preferably 0.6±0.12 wt.-%, yet more preferably 0.6±0.09 wt.-%, most preferably 0.6±0.06 wt.-%, and in particular 0.6±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

In yet another preferred embodiment, the content of the acid (B), preferably citric acid, is within the range of 0.7±0.18 wt.-%, more preferably 0.7±0.15 wt.-%, still more preferably 0.7±0.12 wt.-%, yet more preferably 0.7±0.09 wt.-%, most preferably 0.7±0.06 wt.-%, and in particular 0.7±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

In yet another preferred embodiment, the content of acid (B), preferably citric acid, is within the range of 0.8±0.18 wt.-%, more preferably 0.8±0.15 wt.-%, still more preferably 0.8±0.12 wt.-%, yet more preferably 0.8±0.09 wt.-%, most preferably 0.8±0.06 wt.-%, and in particular 0.8±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

In yet another preferred embodiment, the content of the acid (B), preferably citric acid, is within the range of 0.85±0.18 wt.-%, more preferably 0.85±0.15 wt.-%, still more preferably 0.85±0.12 wt.-%, yet more preferably 0.85±0.09 wt.-%, most preferably 0.85±0.06 wt.-%, and in particular 0.85±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

In still another preferred embodiment, the content of the acid (B), preferably citric acid, is within the range of 0.9±0.18 wt.-%, more preferably 0.9±0.15 wt.-%, still more preferably 0.9±0.12 wt.-%, yet more preferably 0.9±0.09 wt.-%, most preferably 0.9±0.06 wt.-%, and in particular 0.9±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a further preferred embodiment, the content of the acid (B), preferably citric acid, is within the range of 1.0±0.18 wt.-%, more preferably 1.0±0.15 wt.-%, still more preferably 1.0±0.12 wt.-%, yet more preferably 1.0±0.09 wt.-%, most preferably 1.0±0.06 wt.-%, and in particular 1.0±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

The pharmaceutical dosage form according to the invention comprises, as component (C), a polyalkylene oxide (C) having a weight average molecular weight M_w of at least 200,000 g/mol, preferably at least 500,000 g/mol, more preferably at least 750,000 g/mol, still more preferably at least 1,000,000 g/mol, most preferably at least 2,000,000 g/mol and in particular within the range of from 500,000 to 15,000,000 g/mol.

Preferably, the polyalkylene oxide is selected from the group consisting of polymethylene oxide, polyethylene oxide and polypropylene oxide, the copolymers and mixtures thereof.

Polyalkylene oxide (C) may comprise a single polyalkylene oxide having a particular average molecular weight, or a mixture (blend) of different polymers, such as two, three, four or five polymers, e.g., polymers of the same chemical nature but different average molecular weight, polymers of different chemical nature but same average molecular weight, or polymers of different chemical nature as well as different molecular weight.

For the purpose of the specification, a polyalkylene glycol has a molecular weight of up to 20,000 g/mol whereas a polyalkylene oxide has a molecular weight of more than 20,000 g/mol. In a preferred embodiment, the weight average over all molecular weights of all polyalkylene oxides that are contained in the pharmaceutical dosage form is at least 200,000 g/mol. Thus, polyalkylene glycols, if any, are preferably not taken into consideration when determining the weight average molecular weight of polyalkylene oxide (C).

Preferably, the content of the polyalkylene oxide (C) is within the range of from 20 to 99 wt.-%, more preferably 25 to 95 wt.-%, still more preferably 30 to 90 wt.-%, yet more preferably 30 to 85 wt.-%, most preferably 30 to 80 wt.-% and in particular 30 to 75 wt.-%, based on the total weight of the pharmaceutical dosage form. In a preferred embodiment, the content of the polyalkylene oxide is at least 20 wt.-%, more preferably at least 25 wt.-%, still more preferably at least 30 wt.-%, yet more preferably at least 35 wt.-% and in particular at least 40 wt.-%.

In a preferred embodiment, the overall content of polyalkylene oxide (C) is within the range of 25±20 wt.-%, more preferably 25±15 wt.-%, most preferably 25±10 wt.-%, and in particular 25±5 wt.-%. In another preferred embodiment, the overall content of polyalkylene oxide (C) is within the range of 35±20 wt.-%, more preferably 35±15 wt.-%, most preferably 35±10 wt.-%, and in particular 35±5 wt.-%. In still another preferred embodiment, the overall content of polyalkylene oxide (C) is within the range of 45±20 wt.-%, more preferably 45±15 wt.-%, most preferably 45±10 wt.-%, and in particular 45±5 wt.-%. In yet another preferred embodiment, the overall content of polyalkylene oxide (C) is within the range of 55±20 wt.-%, more preferably 55±15 wt.-%, most preferably 55±10 wt.-%, and in particular 55±5 wt.-%. In a further preferred embodiment, the overall content of polyalkylene oxide (C) is within the range of 65±20 wt.-%, more preferably 65±15 wt.-%, most preferably 65±10 wt.-%, and in particular 65±5 wt.-%. In still a further a preferred embodiment, the overall content of polyalkylene oxide (C) is within the range of 75±20 wt.-%, more preferably 75±15 wt.-%, most preferably 75±10 wt.-%, and in particular 75±5 wt.-%. In a still further a preferred embodiment, the overall content of polyalkylene oxide (C) is within the range of 80±15 wt.-%, more preferably 80±10 wt.-%, and most preferably 80±5 wt.-%.

In a preferred embodiment, polyalkylene oxide (C) is homogeneously distributed in the pharmaceutical dosage form according to the invention. Preferably, polyalkylene oxide (C) forms a matrix in which the opioid (A) is embedded. In a particularly preferred embodiment, the opioid (A) and polyalkylene oxide (C) are intimately homogeneously distributed in the pharmaceutical dosage form so that the pharmaceutical dosage form does not contain any segments where either opioid (A) is present in the absence of polyalkylene oxide (C) or where polyalkylene oxide (C) is present in the absence of opioid (A).

When the pharmaceutical dosage form is film coated, the polyalkylene oxide (C) is preferably homogeneously distributed in the core of the pharmaceutical dosage form, i.e. the film coating preferably does not contain polyalkylene oxide (C). Nonetheless, the film coating as such may of course contain one or more polymers, which however, preferably differ from the polyalkylene oxide (C) contained in the core.

The polyalkylene oxide (C) may be combined with one or more different polymers selected from the group consisting of polyalkylene oxide, preferably polymethylene oxide, polyethylene oxide, polypropylene oxide; polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyvinylpyrrolidone, poly(alk)acrylate, poly(hydroxy fatty acids), such as for example poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (Biopol®), poly(hydroxyvaleric acid); polycaprolactone, polyvinyl alcohol, polyesteramide, polyethylene succinate, polylactone, polyglycolide, polyurethane, polyamide, polylactide, polyacetal (for example polysaccharides optionally with modified side chains), polylactide/glycolide, polylactone, polyglycolide, polyorthoester, polyanhydride, block polymers of polyethylene glycol and polybutylene terephthalate (Polyactive®), polyanhydride (Polifeprosan), copolymers thereof, block-copolymers thereof, and mixtures of at least two of the stated polymers, or other polymers with the above characteristics.

Preferably, the molecular weight dispersity M_w/M_n of polyalkylene oxide (C) is within the range of 2.5±2.0, more preferably 2.5±1.5, still more preferably 2.5±1.0, yet more preferably 2.5±0.8, most preferably 2.5±0.6, and in particular 2.5±0.4.

The polyalkylene oxide (C) preferably has a viscosity at 25°C of 30 to 17,600 cP, more preferably 55 to 17,600 cP, still more preferably 600 to 17,600 cP and most preferably 4,500 to 17,600 cP, measured in a 5 wt.-% aqueous solution using a model RVF Brookfield viscosimeter (spindle no. 2 / rotational speed 2 rpm); of 400 to 4,000 cP, more preferably 400 to 800 cP or 2,000 to 4,000 cP, measured on a 2 wt.-% aqueous solution using the stated viscosimeter (spindle no. 1 or 3 / rotational speed 10 rpm); or of 1,650 to 10,000 cP, more preferably 1,650 to 5,500 cP, 5,500 to 7,500 cP or 7,500 to 10,000 cP, measured on a 1 wt.-% aqueous solution using the stated viscosimeter (spindle no. 2 / rotational speed 2 rpm).

In a preferred embodiment according to the invention the polyalkylene oxide (C) having a weight average molecular weight of at least 200,000 g/mol is combined with at least one further polymer, preferably but not necessarily also having a weight average molecular weight (M_w) of at least 200,000 g/mol, selected from the group consisting of polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, poly(hydroxy fatty acids), polycaprolactone, polyvinyl alcohol, polyesteramide, polyethylene succinate, polylactone, polyglycolide, polyurethane, polyvinylpyrrolidone, polyamide, polylactide, polylactide/glycolide, polylactone, polyglycolide, polyorthoester, polyanhydride, block polymers of polyethylene glycol and polybutylene terephthalate, polyanhydride, polyacetal, cellulose esters, cellulose ethers and copolymers thereof. Cellulose esters and cellulose ethers are particularly preferred, e.g. methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose hydroxypropylmethylcellulose, carboxymethylcellulose, and the like.

In a preferred embodiment, said further polymer is neither a polyalkylene oxide nor a polyalkylene glycol. Nonetheless, the pharmaceutical dosage form may contain polyalkylene glycol, e.g. as plasticizer, but then, the pharmaceutical dosage form preferably is a ternary mixture of polymers: polyalkylene oxide (C) + further polymer + plasticizer.

In a particularly preferred embodiment, said further polymer is a hydrophilic cellulose ester or cellulose ether, preferably hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC) or hydroxyethylcellulose (HEC), preferably having an average viscosity (preferably measured by capillary viscosimetry or rotational viscosimetry) of 1,000 to 150,000 mPas, more preferably 3,000 to 150,000. In a preferred embodiment, the average viscosity is within the range of 110,000±50,000 mPas, more preferably 110,000±40,000 mPas, still more preferably 110,000±30,000 mPas, most preferably 110,000±20,000 mPas, and in particular 100,000±10,000 mPas.

In a preferred embodiment the relative weight ratio of said polyalkylene oxide (C) and said further polymer is within the range of from 20:1 to 1:20, more preferably 10:1 to 1:10, still more preferably 7:1 to 1:5, yet more preferably 5:1 to 1:1, most preferably 4:1 to 1,5:1 and in particular 3:1 to 2:1. In a preferred embodiment, the relative weight ratio of said polyalkylene oxide (C) and said further polymer is within the range of from 10:1 to 5:1, more preferably 8:1 to 5:1, most preferably 7:1 to 5:1.

Preferably, the content of said further polymer amounts to 0.5 to 25 wt.-%, more preferably 1.0 to 20 wt.-%, still more preferably 2.0 to 22.5 wt.-%, yet more preferably 3.0 to 20 wt.-% and most preferably 4.0 to 17.5 wt.-% and in particular 5.0 to 15 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the further polymer is a cellulose ester or cellulose ether, preferably HPMC, having a content within the range of 10±8 wt.-%, more preferably 10±6 wt.-%, still more preferably 10±5 wt.-%, yet more preferably 10±4 wt.-%, most preferably 10±3 wt.-%, and in particular 10±2 wt.-%, based on the total weight of the pharmaceutical dosage form.

In another preferred embodiment, the further polymer is a cellulose ester or cellulose ether, preferably HPMC, having a content within the range of 14±8 wt.-%, more preferably 14±6 wt.-%, still more preferably 14±5 wt.-%, yet more preferably 14±4 wt.-%, most preferably 14±3 wt.-%, and in particular 14±2 wt.-%, based on the total weight of the pharmaceutical dosage form.

All polymers are preferably employed as powders. They can be soluble in water.

Besides the opioid (A), the acid (B) and polyalkylene oxide (C) the pharmaceutical dosage form according to the invention may contain further constituents, such as conventional pharmaceutical excipients.

Preferably, the pharmaceutical dosage form comprises an antioxidant. Suitable antioxidants include ascorbic acid, α-tocopherol (vitamin E), butylhydroxyanisol, butylhydroxytoluene, salts of ascorbic acid (vitamin C), ascorbylic palmitate, monothioglycerine, coniferyl benzoate, nordihydroguajaretic acid, gallus acid esters, phosphoric acid, and the derivatives thereof, such as vitamin E-succinate or vitamin E-palmitate and/or sodium bisulphite, more preferably butylhydroxytoluene (BHT) or butylhydroxyanisol (BHA) and/or α-tocopherol.

Preferably, the content of the antioxidant is within the range of from 0.001 to 5.0 wt.-%, more preferably 0.002 to 2.5 wt.-%, more preferably 0.003 to 1.5 wt.-%, still more preferably 0.005 to 1.0 wt.-%, yet more preferably 0.01 to 0.5 wt.-%, most preferably 0.05 to 0.4 wt.-% and in particular 0.1 to 0.3 wt.-%, based on the total weight of the pharmaceutical dosage form.

A particularly preferred antioxidant is α-tocopherol. It has been surprisingly found that α-tocopherol stabilizes polyalkylene oxide and simultaneously destabilizes certain opioids (A), such as oxymorphone. Thus, in a preferred embodiment, the content of α-tocopherol is balanced between a sufficient stability of the polyalkylene oxide on the one hand and a sufficient stability of the opioid (A) on the other hand.

In a preferred embodiment, the content of α-tocopherol is within the range of 0.2±0.18 wt.-%, more preferably 0.2±0.15 wt.-%, still more preferably 0.2±0.12 wt.-%, yet more preferably 0.2±0.09 wt.-%, most preferably 0.2±0.06 wt.-%, and in particular 0.2±0.03 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the relative weight ratio of the acid (B), preferably citric acid, and the antioxidant, preferably α-tocopherol, is within the range of from 10:1 to 1:10, more preferably 8:1 to 1:8, still more preferably 6:1 to 1:6, yet more preferably 5:1 to 1:4, most preferably 4:1 to 1:3 and in particular 3:1 to 1:2.

The pharmaceutical dosage form according to the invention may also contain a natural, semi-synthetic or synthetic wax. Waxes with a softening point of at least 50 °C, more preferably 60 °C are preferred. Carnauba wax and beeswax are particularly preferred, especially carnauba wax.

Preferably, the release profile of the opioid (A) is matrix-retarded. Preferably, the opioid (A) is embedded in a matrix comprising the polyalkylene oxide, said matrix controlling the release of the opioid (A) from the pharmaceutical dosage form.

Physiologically acceptable materials which are known to the person skilled in the art may be used as supplementary matrix materials. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are very particularly preferably used as matrix materials. 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. Mono- or diglycerides of C_{12}-C_{30} fatty acids and/or C_{12}-C_{30} fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic materials. It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic materials as matrix materials.

Preferably, the relative weight ratio of the polyalkylene oxide to the opioid (A) is at least 0.5:1, more preferably at least 1:1, at least 2:1, at least 3:1, at least 4:1, at least 5:1, at least 6:1, at least 7:1, at least 8:1 or at least 9:1; still more preferably at least 10:1 or at least 15:1, yet more preferably at least 20:1, most preferably at least 30:1 and in particular at least 40:1. In a preferred embodiment, the relative weight ratio of the polyalkylene oxide to the opioid (A) is within the range of from 3:1 to 50:1, more preferably 3:1 to 40:1 and in particular 3:1 to 30:1.

The pharmaceutical dosage form according to the invention preferably contains a plasticizer. The plasticizer improves the processability of the polyalkylene oxide. A preferred plasticizer is polyalkylene glycol, like polyethylene glycol, triacetin, fatty acids, fatty acid esters, waxes and/or microcrystalline waxes. Particularly preferred plasticizers are polyethylene glycols, such as PEG 6000.

Preferably, the content of the plasticizer is within the range of from 0.1 to 25 wt.-%, more preferably 0.5 to 22.5 wt.-%, still more preferably 1.0 to 20 wt.-%, yet more preferably 2.5 to 17.5 wt.-%, most preferably 5.0 to 15 wt.-% and in particular 7.5 to 12.5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the plasticizer is a polyalkylene glycol having a content within the range of 10±8 wt.-%, more preferably 10±6 wt.-%, still more preferably 10±5 wt.-%, yet more preferably 10±4 wt.-%, most preferably 10±3 wt.-%, and in particular 10±2 wt.-%, based on the total weight of the pharmaceutical dosage form.

In another preferred embodiment, the plasticizer is a polyalkylene glycol having a content within the range of 15±8 wt.-%, more preferably 15±6 wt.-%, still more preferably 15±5 wt.-%, yet more preferably 15±4 wt.-%, most preferably 15±3 wt.-%, and in particular 15±2 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the relative weight ratio of the polyalkylene oxide to the polyalkylene glycol is within the range of 4.2±2 : 1, more preferably 4.2±1.5 : 1, still more preferably 4.2±1 : 1, yet more preferably 4.2±0.5 : 1, most preferably 4.2±0.2 : 1, and in particular 4.2±0.1 : 1. This ratio satisfies the requirements of relative high polyalkylene oxide content and good extrudability.

When manufacturing the dosage forms from slices that are obtained by cutting the extrudate strand, the weight of the slices determines the weight of the resulting dosage form. Pronounced variation in weight of these slices results in an accordant weight deviation of dosage forms from the target weight. The weight variation of slices depends strongly on the surface properties of the extrudate strand. A strand with a thoroughly smooth surface allows the generation of slices exhibiting a low weight variation. In contrast, a wavy or shark skinning strand results in slices exhibiting a higher weight variation thereby increasing the number of rejects.

It has now been surprisingly found that the surface properties of the extrudate strand can be triggered by the polyalkylene oxide : polyalkylene glycol weight ratio.

Preferred compositions X_1 to X_{32} of the pharmaceutical dosage form according to the invention are summarized in the tables here below:

wt.-%	X_1	X_2	X_3	X_4
opioid (A) (e.g. oxymorphone HCl)	1.50±1.25	1.50±1.00	1.50±0.75	1.50±0.50
acid (B) (e.g. citric acid)	0.5±0.30	0.5±0.25	0.5±0.20	0.5±0.15
polyalkylene oxide (C)	77±22	77±20	77±15	77±10
cellulose ester or ether (e.g. HPMC)	12±10	12±7.5	12±5	12±2.5
plasticizer (e.g. PEG)	10±7.5	10±5	10±2.5	10±1.0
antioxidant (e.g. α-tocopherol)	0.2±0.12	0.2±0.1	0.2±0.05	0.2±0.03

wt.-%	X_5	X_6	X_7	X_8
opioid (A) (e.g. oxymorphone HCl)	2.33±1.25	2.33±1.00	2.33±0.75	2.33±0.50
acid (B) (e.g. citric acid)	0.85±0.60	0.85±0.50	0.85±0.25	0.85±0.15
polyalkylene oxide (C)	70±25	70±20	70±15	70±10
cellulose ester or ether (e.g. HPMC)	10±9.5	10±7.5	10±5	10±2.5
plasticizer (e.g. PEG)	16.6±7.5	16.6±5	16.6±2.5	16.6±1.0
antioxidant (e.g. α-tocopherol)	0.2±0.12	0.2±0.1	0.2±0.05	0.2±0.03

wt.-%	X_9	X_{10}	X_{11}	X_{12}
opioid (A) (e.g. oxymorphone HCl)	3.50±1.25	3.50±1.00	3.50±0.75	3.50±0.50
acid (B) (e.g. citric acid)	0.85±0.60	0.85±0.50	0.85±0.25	0.85±0.15
polyalkylene oxide (C)	69±30	69±20	69±15	69±10
cellulose ester or ether (e.g. HPMC)	10±9.5	10±7.5	10±5	10±2.5
plasticizer (e.g. PEG)	16.4±7.5	16.4±5	16.4±2.5	16.4±1.0
antioxidant (e.g. α-tocopherol)	0.2±0.12	0.2±0.1	0.2±0.05	0.2±0.03

wt.-%	X_{13}	X_{14}	X_{15}	X_{16}
opioid (A) (e.g. oxymorphone HCl)	4.65±1.25	4.65±1.00	4.65±0.75	4.65±0.50
acid (B) (e.g. citric acid)	0.85±0.60	0.85±0.50	0.85±0.25	0.85±0.15
polyalkylene oxide (C)	68±30	68±20	68±15	68±10
cellulose ester or ether (e.g. HPMC)	10±9.5	10±7.5	10±5	10±2.5
plasticizer (e.g. PEG)	16.2±7.5	16.2±5	16.2±2.5	16.2±1.0
antioxidant (e.g. α-tocopherol)	0.2±0.12	0.2±0.1	0.2±0.05	0.2±0.03

wt.-%	X_{17}	X_{18}	X_{19}	X_{20}
opioid (A) (e.g. oxymorphone HCl)	6.98±1.25	6.98±1.00	6.98±0.75	6.98±0.50
acid (B) (e.g. citric acid)	0.85±0.60	0.85±0.50	0.85±0.25	0.85±0.15
polyalkylene oxide (C)	66±30	66±20	66±15	66±10
cellulose ester or ether (e.g. HPMC)	10±9.5	10±7.5	10±5	10±2.5
plasticizer (e.g. PEG)	15.8±7.5	15.8±5	15.8±2.5	15.8±1.0
antioxidant (e.g. α-tocopherol)	0.2±0.12	0.2±0.1	0.2±0.05	0.2±0.03

wt.-%	X_{21}	X_{22}	X_{23}	X_{24}
opioid (A) (e.g. oxymorphone HCl)	9.30±1.25	9.30±1.00	9.30±0.75	9.30±0.50
acid (B) (e.g. citric acid)	0.85±0.60	0.85±0.50	0.85±0.25	0.85±0.15
polyalkylene oxide (C)	64±30	64±20	64±15	64±10
cellulose ester or ether (e.g. HPMC)	10±9.5	10±7.5	10±5	10±2.5
plasticizer (e.g. PEG)	15.3±7.5	15.3±5	15.3±2.5	15.3±1.0
antioxidant (e.g. α-tocopherol)	0.2±0.12	0.2±0.1	0.2±0.05	0.2±0.03

wt.-%	X_{25}	X_{26}	X_{27}	X_{28}
opioid (A) (e.g. oxymorphone HCl)	13.95±1.25	13.95±1.00	13.95±0.75	13.95±0.50
acid (B) (e.g. citric acid)	0.85±0.60	0.85±0.50	0.85±0.25	0.85±0.15
polyalkylene oxide (C)	60±30	60±20	60±15	60±10
cellulose ester or ether (e.g. HPMC)	10±9.5	10±7.5	10±5	10±2.5
plasticizer (e.g. PEG)	13.9±7.5	13.9±5	13.9±2.5	13.9±1.0
antioxidant (e.g. α-tocopherol)	0.2±0.12	0.2±0.1	0.2±0.05	0.2±0.03

wt.-%	X_{29}	X_{30}	X_{31}	X_{32}
opioid (A) (e.g. oxymorphone HCl)	18.60±1.25	18.60±1.00	18.60±0.75	18.60±0.50
acid (B) (e.g. citric acid)	0.85±0.60	0.85±0.50	0.85±0.25	0.85±0.15
polyalkylene oxide (C)	57±30	57±20	57±15	57±10
cellulose ester or ether (e.g. HPMC)	10±9.5	10±7.5	10±5	10±2.5
plasticizer (e.g. PEG)	13.6±7.5	13.6±5	13.6±2.5	13.6±1.0
antioxidant (e.g. α-tocopherol)	0.2±0.12	0.2±0.1	0.2±0.05	0.2±0.03

In a preferred embodiment, the pharmaceutical dosage form has a total weight within the range of 100±75 mg, more preferably 100±50 mg, most preferably 100±25 mg. In another preferred embodiment, the pharmaceutical dosage form has a total weight within the range of 200±75 mg, more preferably 200±50 mg, most preferably 200±25 mg. In another preferred embodiment, the pharmaceutical dosage form has a total weight within the range of 250±75 mg, more preferably 250±50 mg, most preferably 250±25 mg. In still another preferred embodiment, the pharmaceutical dosage form has a total weight within the range of 300±75 mg, more preferably 300±50 mg, most preferably 300±25 mg. In yet another preferred embodiment, the pharmaceutical dosage form has a total weight within the range of 400±75 mg, more preferably 400±50 mg, most preferably 400±25 mg.

In a preferred embodiment, the pharmaceutical dosage form has a total weight within the range of 500±250 mg, more preferably 500±200 mg, most preferably 500±150 mg. In another preferred embodiment, the pharmaceutical dosage form has a total weight within the range of 750±250 mg, more preferably 750±200 mg, most preferably 750±150 mg. In another preferred embodiment, the pharmaceutical dosage form has a total weight within the range of 1000±250 mg, more preferably 1000±200 mg, most preferably 1000±150 mg. In still another preferred embodiment, the pharmaceutical dosage form has a total weight within the range of 1250±250 mg, more preferably 1250±200 mg, most preferably 1250±150 mg.

In a preferred embodiment, the pharmaceutical dosage form according to the invention has an overall density within the range of 1.19±0.30 g/cm^3, more preferably 1.19±0.25 g/cm^3, still more preferably 1.19±0.20 g/cm^3, yet more preferably 1.19±0.15 g/cm^3, most preferably 1.19±0.10 g/cm^3, and in particular 1.19±0.05 g/cm^3. Preferably, the overall density of the pharmaceutical dosage form according to the invention is 1.17±0.02 g/cm^3, 1.19±0.02 g/cm^3 or 1.21±0.02 g/cm^3. Methods for measuring the density of a dosage form are known to a person skilled in the art. The overall density of a dosage form can for example be determined by means of the mercury porosimetry method or the helium pycnometer method as described in Ph. Eur.

Preferably, the pharmaceutical dosage form according to the invention is adapted for oral administration. It is also possible, however, to administer the pharmaceutical dosage form via different routes and thus, the pharmaceutical dosage form may alternatively be adapted for buccal, lingual, rectal or vaginal administration. Implants are also possible.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration once daily. In another preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration twice daily. In still another preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration thrice daily.

For the purpose of the specification, "twice daily" means equal or nearly equal time intervals, i.e., about every 12 hours, or different time intervals, e.g., 8 and 16 hours or 10 and 14 hours, between the individual administrations.

For the purpose of the specification, "thrice daily" means equal or nearly equal time intervals, i.e., about every 8 hours, or different time intervals, e.g., 6, 6 and 12 hours; or 7, 7 and 10 hours, between the individual administrations.

Preferably, the pharmaceutical dosage form according to the invention causes an at least partially delayed or prolonged release of opioid (A).

Controlled or prologned release is understood according to the invention preferably to mean a release profile in which the opioid (A) is released over a relatively long period with reduced intake frequency with the purpose of extended therapeutic action. Preferably, the meaning of the term "prolonged release" is in accordance with the European guideline on the nomenclature of the release profile of pharmaceutical dosage forms (CHMP). This is achieved in particular with peroral administration. The expression "at least partially delayed or prolonged release" covers according to the invention any pharmaceutical dosage forms which ensure modified release of the opioids (A) contained therein. The pharmaceutical dosage forms preferably comprise coated or uncoated pharmaceutical dosage forms, which are produced with specific auxiliary substances, by particular processes or by a combination of the two possible options in order purposefully to change the release rate or location of release.

In the case of the pharmaceutical dosage forms according to the invention, the release time profile of a controlled release form may be modified e.g. as follows: extended release, repeat action release, prolonged release and sustained release.

For the purpose of the specification "controlled release" preferably means a product in which the release of active compound over time is controlled by the type and composition of the formulation. For the purpose of the specification "extended release" preferably means a product in which the release of active compound is delayed for a finite lag time, after which release is unhindered. For the purpose of the specification "repeat action release" preferably means a product in which a first portion of active compound is released initially, followed by at least one further portion of active compound being released subsequently. For the purpose of the specification "prolonged release" preferably means a product in which the rate of release of active compound from the formulation after administration has been reduced over time, in order to maintain therapeutic activity, to reduce toxic effects, or for some other therapeutic purpose. For the purpose of the specification "sustained release" preferably means a way of formulating a medicine so that it is released into the body steadily, over a long period of time, thus reducing the dosing frequency. For further details, reference may be made, for example, to K.H. Bauer, Lehrbuch der Pharmazeutischen Technologie, 6th edition, WVG Stuttgart, 1999; and Eur. Ph.

The pharmaceutical dosage form according to the invention may comprise one or more opioids (A) at least in part in a further controlled release form, wherein controlled release may be achieved with the assistance of conventional materials and processes known to the person skilled in the art, for example by embedding the substance in a controlled release matrix or by applying one or more controlled release coatings. Substance release must, however, be controlled such that addition of delayed-release materials does not impair the necessary breaking strength. Controlled release from the pharmaceutical dosage form according to the invention is preferably achieved by embedding the substance in a matrix. Preferably, polyalkylene oxide (C) serves as such a matrix. The auxiliary substances acting as matrix materials control release. Matrix materials may, for example, be hydrophilic, gel-forming materials, from which release proceeds mainly by diffusion, or hydrophobic materials, from which release proceeds mainly by diffusion from the pores in the matrix.

Preferably, the release profile is substantially matrix controlled, preferably by embedding opioid (A) in a matrix comprising polyalkylene oxide (C) and optionally, further matrix materials. Preferably, the release profile is not osmotically driven. Preferably, release kinetics is not zero order.

Preferably, under physiological conditions the pharmaceutical dosage form according to the invention has released after 30 minutes 0.1 to 75%, after 240 minutes 0.5 to 95%, after 480 minutes 1.0 to 100% and after 720 minutes 2.5 to 100% of the opioid (A). Further preferred release profiles R_1 to R_6 are summarized in the table here below [all data in wt.-% of released opioid (A)]:

time	R_1	R_2	R_3	R_4	R_5	R_6
60 min	0-30	0-50	0-50	15-25	20-30	20-50
120 min	0-40	0-75	0-75	25-40	35-50	40-75
240 min	3-55	3-95	10-95	40-70	55-75	60-95
480 min	10-65	10-100	35-100	60-90	80-95	80-100
720 min	20-75	20-100	55-100	70-100	90-100	90-100
960 min	30-88	30-100	70-100	>80	95-100	
1440 min	50-100	50-100	>90			
2160 min	>80	>80				

Further preferred release profiles R_1 to R_6 are summarized in the table here below [all data in wt.-% of released opioid (A)]:

time	R_7	R_8	R_9	R_{10}	R_{11}	R_{12}
30 min	17.5±7.5	17.5±6.5	17.5±5.5	17.5±4.5	17.5±3.5	17.5±2.5
60 min	27.0±8.0	27.0±7.0	27.0±6.0	27.0±5.0	27.0±4.0	27.0±3.0
120 min	41.5±9.5	41.5±8.5	41.5±7.5	41.5±6.5	41.5±5.5	41.5±4.5
240 min	64.5±12.5	64.5±11.5	64.5±10.5	64.5±9.5	64.5±8.5	64.5±7.5
480 min	88.0±12.0	88.0±11.0	88.0±10.0	88.0±9.0	88.0±8.0	88.0±7.0
720 min	96.0±9.0	96.0±8.0	96.0±7.0	96.0±6.0	96.0±5.0	96.0±4.0
840 min	97.5±7.5	97.5±6.5	97.5±5.5	97.5±4.5	97.5±3.5	97.5±2.5

Preferably, the release profile of the pharmaceutical dosage form according to the present invention is stable upon storage, preferably upon storage at elevated temperature, e.g. 37°C, for 3 months in sealed containers. In this regard "stable" means that when comparing the initial release profile with the release profile after storage, at any given time point the release profiles deviate from one another by not more than 20%, more preferably not more than 15%, still more preferably not more than 10%, yet more preferably not more than 7.5%, most preferably not more than 5.0% and in particular not more than 2.5%.

Preferably, under *in vitro* conditions the pharmaceutical dosage form has released after 0.5 h 1.0 to 35 wt.-%, after 1 h 5.0 to 45 wt.-%, after 2 h 10 to 60 wt.-%, after 4 h at least 15 wt.-%, after 6 h at least 20 wt.-%, after 8 h at least 25 wt.-% and after 12 h at least 30 wt.-% of the opioid (A) that was originally contained in the pharmaceutical dosage form.

Suitable in vitro conditions are known to the skilled artisan. In this regard it can be referred to, e.g., the Eur. Ph. Preferably, the release profile is measured under the following conditions: Paddle apparatus equipped with sinker, 50 rpm, 37±5 °C, 900 mL simulated intestinal fluid pH 6.8 (phosphate buffer) or pH 4.5. In a preferred embodiment, to rotational speed of the paddle is increased to 100 rpm.

In a preferred embodiment, after preferably oral administration of the pharmaceutical dosage form according to the invention, *in vivo* the average peak plasma level (C_{max}) is on average reached after t_{max} 4.0±2.5 h, more preferably after t_{max} 4.0±2.0 h, still more preferably after t_{max} 4.0±1.5 h, most preferably after t_{max} 4.0±1.0 h and in particular after t_{max} 4.0±0.5 h. In another preferred embodiment, after preferably oral administration of the pharmaceutical dosage form according to the invention, *in vivo* the average peak plasma level (C_{max}) is on average reached after t_{max} 5.0±2.5 h, more preferably after t_{max} 5.0±2.0 h, still more preferably after t_{max} 5.0±1.5 h, most preferably after t_{max} 5.0±1.0 h and in particular after t_{max} 5.0±0.5 h. In still another preferred embodiment, after preferably oral administration of the pharmaceutical dosage form according to the invention, *in vivo* the average peak plasma level (C_{max}) is on average reached after t_{max} 6.0±2.5 h, more preferably after t_{max} 6.0±2.0 h, still more preferably after t_{max} 6.0±1.5 h, most preferably after t_{max} 6.0±1.0 h and in particular after t_{max} 6.0±0.5 h.

In a preferred embodiment, the average value for $t_{1/2}$ after preferably oral administration of the pharmaceutical dosage form according to the invention *in vivo* is 4.0±2.5 h, more preferably 4.0±2.0 h, still more preferably 4.0±1.5 h, most preferably 4.0±1.0 h, and in particular 4.0±0.5 h. In another preferred embodiment, the average value for $t_{1/2}$ after preferably oral administration of the pharmaceutical dosage form according to the invention *in vivo* is preferably 5.0±2.5 h, more preferably 5.0±2.0 h, still more preferably 5.0±1.5 h, most preferably 5.0±1.0 h, and in particular 5.0±0.5 h. In still another preferred embodiment, the average value for $t_{1/2}$ after preferably oral administration of the pharmaceutical dosage form according to the invention *in vivo* is preferably 6.0±2.5 h, more preferably 6.0±2.0 h, still more preferably 6.0±1.5 h, most preferably 6.0±1.0 h, and in particular 6.0±0.5 h.

Preferably, the pharmaceutical dosage form according to the invention contains a coating, preferably a film-coating. Suitable coating materials are known to the skilled person. Suitable coating materials are commercially available, e.g. under the trademarks Opadry® and Eudragit®.

Examples of suitable materials include cellulose esters and cellulose ethers, such as methylcellulose (MC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), sodium carboxymethylcellulose (Na-CMC), ethylcellulose (EC), cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HPMCP); poly(meth)acrylates, such as aminoalkylmethacrylate copolymers, ethylacrylate methylmethacrylate copolymers, methacrylic acid methylmethacrylate copolymers, methacrylic acid methylmethacrylate copolymers; vinyl polymers, such as polyvinylpyrrolidone, polyvinylacetatephthalate, polyvinyl alcohol, polyvinylacetate; and natural film formers, such as shellack.

In a particularly preferred embodiment, the coating is water-soluble. In a preferred embodiment, the coating is based on polyvinyl alcohol, such as polyvinyl alcohol-part. hydrolyzed, and may additionally contain polyethylene glycol, such as macrogol 3350, and/or pigments. In another preferred embodiment, the coating is based on hydroxypropylmethylcellulose, preferably hypromellose type 2910 having a viscosity of 3 to 15 mPas.

The coating of the pharmaceutical dosage form can increase its storage stability.

The coating can be resistant to gastric juices and dissolve as a function of the pH value of the release environment. By means of this coating, it is possible to ensure that the pharmaceutical dosage form according to the invention passes through the stomach undissolved and the active compound is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5. Corresponding materials and methods for the delayed release of active compounds and for the application of coatings which are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical dosage forms - Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers.

In a preferred embodiment, the pharmaceutical dosage form according to the invention contains no substances which irritate the nasal passages and/or pharynx, i.e. substances which, when administered via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the patient that he/she does not wish to or cannot continue administration, for example burning, or physiologically counteracts taking of the corresponding active compound, for example due to increased nasal secretion or sneezing. Further examples of substances which irritate the nasal passages and/or pharynx are those which cause burning, itching, urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli. Corresponding substances and the quantities thereof which are conventionally to be used are known to the person skilled in the art. Some of the substances which irritate the nasal passages and/or pharynx are accordingly based on one or more constituents or one or more plant parts of a hot substance drug. Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pages 82 et seq.. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

The pharmaceutical dosage form according to the invention furthermore preferably contains no antagonists for the opioid (A), preferably no antagonists against psychotropic substances, in particular no antagonists against opioids (A). Antagonists suitable for a given opioid (A) are known to the person skilled in the art and may be present as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof. The pharmaceutical dosage form according to the invention preferably contains no antagonists selected from among the group comprising naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine or naluphine, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate; and no neuroleptics, for example a compound selected from among the group comprising haloperidol, promethacine, fluphenazine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine, zuclopenthixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol.

The pharmaceutical dosage form according to the invention furthermore preferably contains no emetic. Emetics are known to the person skilled in the art and may be present as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof. The pharmaceutical dosage form according to the invention preferably contains no emetic based on one or more constituents of ipecacuanha (ipecac) root, for example based on the constituent emetine, as are, for example, described in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart, New York, 1982. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure. The pharmaceutical dosage form according to the invention preferably also contains no apomorphine as an emetic.

Finally, the pharmaceutical dosage form according to the invention preferably also contains no bitter substance. Bitter substances and the quantities effective for use may be found in US-2003/0064099 A1, the corresponding disclosure of which should be deemed to be the disclosure of the present application and is hereby introduced as a reference. Examples of bitter substances are aromatic oils, such as peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate.

The pharmaceutical dosage form according to the invention accordingly preferably contains neither substances which irritate the nasal passages and/or pharynx, nor antagonists for the opioid (A), nor emetics, nor bitter substances.

The pharmaceutical dosage form according to the invention is preferably adapted for oral administration.

Typically, the pharmaceutical dosage form according to the invention assumes the form of a tablet. Preferably, the pharmaceutical dosage form is neither in film form, nor multi-particulate.

The pharmaceutical dosage form according to the invention is preferably tamper-resistant. Preferably, tamper-resistance is achieved based on the mechanical properties of the pharmaceutical dosage form so that comminution is avoided or at least substantially impeded. According to the invention, the term comminution means the pulverization of the pharmaceutical dosage form using conventional means usually available to an abuser, for example a pestle and mortar, a hammer, a mallet or other conventional means for pulverizing under the action of force. Thus, tamper-resistance preferably means that pulverization of the pharmaceutical dosage form using conventional means is avoided or at least substantially impeded.

Preferably, the mechanical properties of the pharmaceutical dosage form according to the invention, particularly its breaking strength, substantially rely on the presence and spatial distribution of polyalkylene oxide (C), although its mere presence does typically not suffice in order to achieve said properties. The advantageous mechanical properties of the pharmaceutical dosage form according to the invention may not automatically be achieved by simply processing opioid (A), acid (B), polyalkylene oxide (C), and optionally further excipients by means of conventional methods for the preparation of pharmaceutical dosage forms. In fact, usually suitable apparatuses must be selected for the preparation and critical processing parameters must be adjusted, particularly pressure/force, temperature and time. Thus, even if conventional apparatuses are used, the process protocols usually must be adapted in order to meet the required criteria.

The pharmaceutical dosage form according to the invention has a breaking strength of at least 300 N, preferably at least 400 N, more preferably at least 500 N, still more preferably at least 750 N, yet more preferably at least 1000 N, most preferably at least 1250 N and in particular at least 1500 N.

The "breaking strength" (resistance to crushing) of a pharmaceutical dosage form is known to the skilled person. In this regard it can be referred to, e.g., W.A. Ritschel, Die Tablette, 2. Auflage, Editio Cantor Verlag Aulendorf, 2002; H Liebermann et al., Pharmaceutical dosage forms: Tablets, Vol. 2, Informa Healthcare; 2 edition, 1990; and Encyclopedia of Pharmaceutical Technology, Informa Healthcare; 1 edition.

For the purpose of the specification, the breaking strength is preferably defined as the amount of force that is necessary in order to fracture the pharmaceutical dosage form (= breaking force). Therefore, for the purpose of the specification the pharmaceutical dosage form does preferably not exhibit the desired breaking strength when it breaks, i.e., is fractured into at least two independent parts that are separated from one another. In another preferred embodiment, however, the pharmaceutical dosage form is regarded as being broken if the force decreases by 25% (threshold value) of the highest force measured during the measurement (see below).

The pharmaceutical dosage forms according to the invention are distinguished from conventional pharmaceutical dosage forms in that, due to their breaking strength, they cannot be pulverized by the application of force with conventional means, such as for example a pestle and mortar, a hammer, a mallet or other usual means for pulverization, in particular devices developed for this purpose (tablet crushers). In this regard "pulverization" means crumbling into small particles that would immediately release the pharmacologically active compound (A) in a suitable medium. Avoidance of pulverization virtually rules out oral or parenteral, in particular intravenous or nasal abuse.

Conventional tablets typically have a breaking strength well below 200 N in any direction of extension. The breaking strength of conventional round tablets may be estimated according to the following empirical formula: *Breaking Strength* [in N] = *10 x Diameter Of The Tablet* [in mm]. Thus, according to said empirical formula, a round tablet having a breaking strength of at least 300 N would require a diameter of at least 30 mm). Such a tablet, however, could not be swallowed. The above empirical formula preferably does not apply to the pharmaceutical dosage forms of the invention, which are not conventional but rather special.

Further, the actual mean chewing force is about 220 N (cf., e.g., P.A. Proeschel et al., J Dent Res, 2002, 81(7), 464-468). This means that conventional tablets having a breaking strength well below 200 N may be crushed upon spontaneous chewing, whereas the pharmaceutical dosage forms according to the invention may not.

Still further, when applying a gravitational acceleration of about 9.81 m/s^2, 300 N correspond to a gravitational force of more than 30 kg, i.e. the pharmaceutical dosage forms according to the invention can preferably withstand a weight of more than 30 kg without being pulverised.

Methods for measuring the breaking strength of a pharmaceutical dosage form are known to the skilled artisan. Suitable devices are commercially available.

For example, the breaking strength (resistance to crushing) can be measured in accordance with the Eur. Ph. 5.0, 2.9.8 or 6.0, 2.09.08 "Resistance to Crushing of Tablets". The test is intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing. The apparatus consists of 2 jaws facing each other, one of which moves towards the other. The flat surfaces of the jaws are perpendicular to the direction of movement. The crushing surfaces of the jaws are flat and larger than the zone of contact with the tablet. The apparatus is calibrated using a system with a precision of 1 Newton. The tablet is placed between the jaws, taking into account, where applicable, the shape, the break-mark and the inscription; for each measurement the tablet is oriented in the same way with respect to the direction of application of the force (and the direction of extension in which the breaking strength is to be measured). The measurement is carried out on 10 tablets, taking care that all fragments of tablets have been removed before each determination. The result is expressed as the mean, minimum and maximum values of the forces measured, all expressed in Newton.

A similar description of the breaking strength (breaking force) can be found in the USP. The breaking strength can alternatively be measured in accordance with the method described therein where it is stated that the breaking strength is the force required to cause a tablet to fail (i.e., break) in a specific plane. The tablets are generally placed between two platens, one of which moves to apply sufficient force to the tablet to cause fracture. For conventional, round (circular cross-section) tablets, loading occurs across their diameter (sometimes referred to as diametral loading), and fracture occurs in the plane. The breaking force of tablets is commonly called hardness in the pharmaceutical literature; however, the use of this term is misleading. In material science, the term hardness refers to the resistance of a surface to penetration or indentation by a small probe. The term crushing strength is also frequently used to describe the resistance of tablets to the application of a compressive load. Although this term describes the true nature of the test more accurately than does hardness, it implies that tablets are actually crushed during the test, which is often not the case.

Alternatively, the breaking strength (resistance to crushing) can be measured in accordance with WO 2005/ 016313, WO 2005/016314, and WO 2006/082099, which can be regarded as a modification of the method described in the Eur. Ph. The apparatus used for the measurement is preferably a "Zwick Z 2.5" materials tester, F_{max} = 2.5 kN with a maximum draw of 1150 mm, which should be set up with one column and one spindle, a clearance behind of 100 mm and a test speed adjustable between 0.1 and 800 mm/min together with testControl software. Measurement is performed using a pressure piston with screw-in inserts and a cylinder (diameter 10 mm), a force transducer, F_{max}. 1 kN, diameter = 8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M according to DIN 55350-18 (Zwick gross force F_{max} = 1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany) with Order No BTC-FR 2.5 TH. D09 for the tester, Order No BTC-LC 0050N. P01 for the force transducer, Order No BO 70000 S06 for the centring device.

In a preferred embodiment of the invention, the breaking strength is measured by means of a breaking strength tester e.g. Sotax®, type HT100 or type HT1 (Allschwil, Switzerland). Both, the Sotax® HT100 and the Sotax® HT1can measure the breaking strength according to two different measurement principles: constant speed (where the test jaw is moved at a constant speed adjustable from 5-200 mm/min) or constant force (where the test jaw increases force linearly adjustable from 5-100 N/sec). In principle, both measurement principles are suitable for measuring the breaking strength of the pharmaceutical dosage form according to the invention. Preferably, the breaking strength is measured at constant speed, preferably at a constant speed of 120 mm/min.

In a preferred embodiment, the pharmaceutical dosage form is regarded as being broken if it is fractured into at least two separate pieces.

The pharmaceutical dosage form according to the invention preferably exhibits mechanical strength over a wide temperature range, in addition to the breaking strength (resistance to crushing) optionally also sufficient hardness, impact resistance, impact elasticity, tensile strength and/or modulus of elasticity, optionally also at low temperatures (e.g. below -24 °C, below -40 °C or in liquid nitrogen), for it to be virtually impossible to pulverize by spontaneous chewing, grinding in a mortar, pounding, etc. Thus, preferably, the comparatively high breaking strength of the pharmaceutical dosage form according to the invention is maintained even at low or very low temperatures, e.g., when the pharmaceutical dosage form is initially chilled to increase its brittleness, for example to temperatures below -25°C, below -40 °C or even in liquid nitrogen.

The pharmaceutical dosage form according to the invention is characterized by a certain degree of breaking strength. This does not mean that the pharmaceutical dosage form must also exhibit a certain degree of hardness. Hardness and breaking strength are different physical properties. Therefore, the tamper resistance of the pharmaceutical dosage form does not necessarily depend on the hardness of the pharmaceutical dosage form. For instance, due to its breaking strength, impact strength, elasticity modulus and tensile strength, respectively, the pharmaceutical dosage form can preferably be deformed, e.g. plastically, when exerting an external force, for example using a hammer, but cannot be pulverized, i.e., crumbled into a high number of fragments. In other words, the pharmaceutical dosage form according to the invention is characterized by a certain degree of breaking strength, but not necessarily also by a certain degree of form stability.

Therefore, in the meaning of the specification, a pharmaceutical dosage form that is deformed when being exposed to a force in a particular direction of extension but that does not break (plastic deformation or plastic flow) is preferably to be regarded as having the desired breaking strength in said direction of extension.

A particularly preferred embodiment of the invention relates to a tamper-resistant pharmaceutical dosage form having a breaking strength of at least 300 N and being thermoformed by hot-melt extrusion, said pharmaceutical dosage form comprising

- an opioid (A) selected from the group consisting of oxymorphone, oxycodone, hydromorphone, and the physiologically acceptable salts thereof;

- a free physiologically acceptable multicarboxylic acid (B), preferably citric acid, wherein the content of the acid (B) is within the range of from 0.001 to 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form;
- an antioxidant, wherein the content of the antioxidant, preferably α-tocopherol, is within the range of from 0.001 to 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form; and
- a polyalkylene oxide (C) having a weight average molecular weight M_w of at least 200,000 g/mol;

wherein

- the opioid (A) is embedded in a matrix comprising the polyalkylene oxide (C), said matrix controlling the release of the opioid (A) from the pharmaceutical dosage form; and
- after storage for 4 weeks at 40°C and 75% rel. humidity, the content of opioid (A) amounts to at least 98.0% of its original content before storage.

The pharmaceutical dosage form according to the invention may be produced by different processes, the particularly preferred of which are explained in greater detail below. Several suitable processes have already been described in the prior art. In this regard it can be referred to, e.g., WO 2005/016313, WO 2005/016314, WO 2005/063214, WO 2005/102286, WO 2006/002883, WO 2006/002884, WO 2006/002886, WO 2006/082097, and WO 2006/082099.

The present invention also relates to pharmaceutical dosage forms that are obtainable by any of the processes described here below.

In general, the process for the production of the pharmaceutical dosage form according to the invention preferably comprises the following steps:

(a) mixing all ingredients;

(b) optionally pre-forming the mixture obtained from step (a), preferably by applying heat and/or force to the mixture obtained from step (a), the quantity of heat supplied preferably not being sufficient to heat the polyalkylene oxide (C) up to its softening point;

(c) hardening the mixture by applying heat and force, it being possible to supply the heat during and/or before the application of force and the quantity of heat supplied being sufficient to heat the polyalkylene oxide (C) at least up to its softening point;

(d) optionally singulating the hardened mixture;

(e) optionally shaping the pharmaceutical dosage form; and

(f) optionally providing a film coating.

Heat may be supplied directly, e.g. by contact or by means of hot gas such as hot air, or with the assistance of ultrasound. Force may be applied and/or the pharmaceutical dosage form may be shaped for example by direct tabletting or with the assistance of a suitable extruder, particularly by means of a screw extruder equipped with two screws (twin-screw-extruder) or by means of a planetary gear extruder.

The final shape of the pharmaceutical dosage form may either be provided during the hardening of the mixture by applying heat and force (step (c)) or in a subsequent step (step (e)). In both cases, the mixture of all components is preferably in the plastified state, i.e. preferably, shaping is performed at a temperature at least above the softening point of the polyalkylene oxide (C). However, extrusion at lower temperatures, e.g. ambient temperature, is also possible and may be preferred.

Shaping can be performed, e.g., by means of a tabletting press comprising die and punches of appropriate shape.

A particularly preferred process for the manufacture of the pharmaceutical dosage form of the invention involves hot-melt extrusion. In this process, the pharmaceutical dosage form according to the invention is produced by thermoforming with the assistance of an extruder, preferably without there being any observable consequent discoloration of the extrudate. It has been surprisingly found that acid (B) is capable of suppressing discoloration. In the absence of acid (B), the extrudate tends to develop beige to yellowish coloring whereas in the presence of acid (B) the extrudates are substantially colorless, i.e. white.

This process is characterized in that

a) all components are mixed,

b) the resultant mixture is heated in the extruder at least up to the softening point of the polyalkylene oxide (C) and extruded through the outlet orifice of the extruder by application of force,

c) the still plastic extrudate is singulated and formed into the pharmaceutical dosage form or

d) the cooled and optionally reheated singulated extrudate is formed into the pharmaceutical dosage form.

Mixing of the components according to process step a) may also proceed in the extruder.

The components may also be mixed in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

Before blending with the remaining components, polyalkylene oxide (C) is preferably provided according to the invention with an antioxidant, preferably α-tocopherol. This may proceed by mixing the two components, the polyalkylene oxide (C) and the antioxidant, preferably by dissolving or suspending the antioxidant in a highly volatile solvent and homogeneously mixing this solution or suspension with polyalkylene oxide (C) and removing the solvent by drying, preferably under an inert gas atmosphere.

The, preferably molten, mixture which has been heated in the extruder at least up to the softening point of polyalkylene oxide (C) is extruded from the extruder through a die with at least one bore.

The process according to the invention requires the use of suitable extruders, preferably screw extruders. Screw extruders which are equipped with two screws (twin-screw-extruders) are particularly preferred.

The extrusion is preferably performed so that the expansion of the strand due to extrusion is not more than 30%, i.e. that when using a die with a bore having a diameter of e.g. 6 mm, the extruded strand should have a diameter of not more than 8 mm. More preferably, the expansion of the strand is not more than 25%, still more preferably not more than 20%, most preferably not more than 15% and in particular not more than 10%.

Preferably, extrusion is performed in the absence of water, i.e., no water is added. However, traces of water (e.g., caused by atmospheric humidity) may be present.

The extruder preferably comprises at least two temperature zones, with heating of the mixture at least up to the softening point of the polyalkylene oxide (C) proceeding in the first zone, which is downstream from a feed zone and optionally mixing zone. The throughput of the mixture is preferably from 1.0 kg to 15 kg/hour. In a preferred embodiment, the throughput is from 1 to 3.5 kg/hour. In another preferred embodiment, the throughput is from 4 to 15 kg/hour.

In a preferred embodiment, the die head pressure is within the range of from 25 to 100 bar. The die head pressure can be adjusted inter alia by die geometry, temperature profile and extrusion speed.

The die geometry or the geometry of the bores is freely selectable. The die or the bores may accordingly exhibit a round, oblong or oval cross-section, wherein the round cross-section preferably has a diameter of 0.1 mm to 15 mm and the oblong cross-section preferably has a maximum lengthwise extension of 21 mm and a crosswise extension of 10 mm. Preferably, the die or the bores have a round cross-section. The casing of the extruder used according to the invention may be heated or cooled. The corresponding temperature control, i.e. heating or cooling, is so arranged that the mixture to be extruded exhibits at least an average temperature (product temperature) corresponding to the softening temperature of the polyalkylene oxide (C) and does not rise above a temperature at which the opioid (A) to be processed may be damaged. Preferably, the temperature of the mixture to be extruded is adjusted to below 180 °C, preferably below 150 °C, but at least to the softening temperature of polyalkylene oxide (C). Typical extrusion temperatures are 120 °C and 130 °C.

In a preferred embodiment, the extruder torque is within the range of from 30 to 95%. Extruder torque can be adjusted inter alia by die geometry, temperature profile and extrusion speed.

After extrusion of the molten mixture and optional cooling of the extruded strand or extruded strands, the extrudates are preferably singulated. This singulation may preferably be performed by cutting up the extrudates by means of revolving or rotating knives, water jet cutters, wires, blades or with the assistance of laser cutters.

Preferably, intermediate or final storage of the optionally singulated extrudate or the final shape of the pharmaceutical dosage form according to the invention is performed under oxygen-free atmosphere which may be achieved, e.g., by means of oxygen-scavengers.

The singulated extrudate may be press-formed into tablets in order to impart the final shape to the pharmaceutical dosage form.

The application of force in the extruder onto the at least plasticized mixture is adjusted by controlling the rotational speed of the conveying device in the extruder and the geometry thereof and by dimensioning the outlet orifice in such a manner that the pressure necessary for extruding the plasticized mixture is built up in the extruder, preferably immediately prior to extrusion. The extrusion parameters which, for each particular composition, are necessary to give rise to a pharmaceutical dosage form with desired mechanical properties, may be established by simple preliminary testing.

For example but not limiting, extrusion may be performed by means of a twin-screw-extruder type ZSE 18 or ZSE27 (Leistritz, Nürnberg, Germany), screw diameters of 18 or 27 mm. Screws having eccentric ends may be used. A heatable die with a round bore having a diameter of 7, 8, or 9 mm may be used. The extrusion parameters may be adjusted e.g. to the following values: rotational speed of the screws: 120 Upm; delivery rate2 kg/h for a ZSE 18 or 8 kg/h for a ZSE27; product temperature: in front of die 125 °C and behind die 135 °C; and jacket temperature: 110 °C.

Preferably, extrusion is performed by means of twin-screw-extruders or planetary-gear-extruders, twin-screw extruders (co-rotating or contra-rotating) being particularly preferred.

The pharmaceutical dosage form according to the invention is preferably produced by thermoforming with the assistance of an extruder without any observable consequent discoloration of the extrudates.

The process for the preparation of the pharmaceutical dosage form according to the invention is preferably performed continuously. Preferably, the process involves the extrusion of a homogeneous mixture of all components. It is particularly advantageous if the thus obtained intermediate, e.g. the strand obtained by extrusion, exhibits uniform properties. Particularly desirable are uniform density, uniform distribution of the active compound, uniform mechanical properties, uniform porosity, uniform appearance of the surface, etc. Only under these circumstances the uniformity of the pharmacological properties, such as the stability of the release profile, may be ensured and the amount of rejects can be kept low.

A further aspect of the invention relates to a packaging containing a pharmaceutical dosage form according to the invention and an oxygen scavenger. Suitable packages include blister packages and bottles, such as glass bottles or bottles made from thermoplastic polymers.

Suitable oxygen scavengers are known to the skilled artisan. The oxygen scavenger can be any scavenger known in the art to scavenge oxygen. Both organic and inorganic oxygen scavengers can be used.

In one embodiment, the oxygen scavenger is any metal complex exhibiting oxygen scavenging activity. Examples include complexes containing one or more of aluminum, aluminum ferrosilicon, antimony, beryllium, calcium silicon, cerium, cobalt, gallium, hafnium, iron, magnesium alloy, nickel catalyst, selenium, silicon, silver, strontium, titanium, zinc, and/or zirconium.

In yet another embodiment, one or more elements from Group IA of the periodic table and their alloys and compounds may be used as oxygen scavengers. Examples of Group IA elements include cesium, lithium, potassium, sodium. Further examples of inorganic oxygen scavengers include one or more of sodium azide (NaN_3), sodium sulfite (Na_2SO_3), hydrazine, and hydroxylamine.

In one embodiment, the oxygen scavenger is an organic compound. Examples include one or more of the polyterpenes, ascorbic acid, amino polycarboxylic acid, cyclohexanedione, tetramethyl piperidone, and heterocyclic compounds with N-substituted amino groups.

Oxygen scavengers and the application thereof in pharmaceutical packaging are known to the skilled artisan. In a preferred embodiment, the oxygen scavenger is selected from the group consisting of metal-catalyzed oxidizable organic polymers and anti-oxidants. Particularly preferred are those oxygen scavengers that are able to perform in a dry environment of below 60% relative humidity, preferably below 30% relative humidity and that are combined with a dessicant. Examples of commercially available oxygen scavengers satisfying these requirements include Pharmakeep® KD10 and KD20.

It has been surprisingly found that the storage stability of the pharmaceutical dosage form can be increased when keeping the oxygen content of the atmosphere within the packaging low. Methods for packaging pharmaceutical dosage forms and the application of suitable oxygen scavengers are known to the skilled artisan. In this regard it can be referred to e.g. D.A. Dean, Pharmaceutical Packaging Technology, Taylor & Francis, 1st ed.; F.A. Paine et al., Packaging Pharmaceutical and Healthcare Products, Springer, 1st ed.; and O.G. Piringer et al., Plastic Packaging: Interactions with Food and Pharmaceuticals, Wiley-VCH, 2nd ed.

As far as the packaging is concerned, round bottles made from polyolefins, preferably from HDPE, are preferred. The thickness of the bottle wall is preferably at least 0.25 mm, more preferably at least 0,5 mm, otherwise the bottle may collapse.

As far as the lid of the packaging is concerned, the packaging is preferably induction or heat-sealed with an aluminium foil.

It has been surprisingly found that by selecting an appropriate shape of the packaging and sealing, the vacuum that is produced by the effect of the oxygen scavenger (underpressure of about 20,000 Pa = 2 N/cm^2) can be handled without causing a collapse of the packaging. Induction sealing (e.g. 3 seconds energy) is preferred. When sealing a 75 ml bottle having an opening with a diameter of 1 inch with aluminium foil, an underpressure of 20,000 Pa due to oxygen scavenging results in a force of about 10 N corresponding to the force that is exerted by a weight of 1 kg.

The mechanical stability of the sealing can be tested either by introducing an appropriate amount of oxygen scavenger in the bottle, sealing it and waiting for a sufficient period of time, e.g. 2 days, so that the oxygen is scavenged and an underpressure of about 20,000 Pa has been developed. Alternatively, the bottle may be sealed without any oxygen scavenger in its interior and a weight of 1 kg can be placed on the aluminium foil externally thus, simulating the force.

A further aspect of the invention relates to the use of an opioid (A) for the manufacture of the pharmaceutical dosage form as described above for the treatment of pain.

A further aspect of the invention relates to the use of a pharmaceutical dosage form as described above for avoiding or hindering the abuse of the opioid (A) contained therein.

A further aspect of the invention relates to the use of a pharmaceutical dosage form as described above for avoiding or hindering the unintentional overdose of the opioid (A) contained therein.

In this regard, the invention also relates to the use of a opioid (A) as described above and/or a polyalkylene oxide (C) as described above for the manufacture of the pharmaceutical dosage form according to the invention for the prophylaxis and/or the treatment of a disorder, thereby preventing an overdose of the opioid (A), particularly due to comminution of the pharmaceutical dosage form by mechanical action.

Further, the invention relates to a method for the prophylaxis and/or the treatment of a disorder comprising the administration of the pharmaceutical dosage form according to the invention, thereby preventing an overdose of the opioid (A), particularly due to comminution of the pharmaceutical dosage form by mechanical action. Preferably, the mechanical action is selected from the group consisting of chewing, grinding in a mortar, pounding, and using apparatuses for pulverizing conventional pharmaceutical dosage forms.

The following examples further illustrate the invention but are not to be construed as limiting its scope.

Example 1

Tablets were prepared by hot-melt extrusion of various homogeneous constituent mixtures under the following, identical extrusion conditions:

extruder type: Leistritz Extruder ZSE18PH 40D equipped with high shear screws and a die of 9 mm diameter
throughput: 1.0 kg/h
revolution velocity: 100 rpm
barrel temperature: 100 °C
extrudate temperature: 120 °C

The extrudate was cut into slices of 325 mg containing about 5 mg oxymorphone hydrochloride.

The individual constituents of the extruded mixtures as well as the total amount of decomposition products before and after storage under accelerated storage conditions are summarized in the table here below:

ex.	constituents (wt.-%)					further ingredient (wt.-%)	decomposition products (wt.-%)			
	(A)	PEO	PEG	HPMC	α-toc.		oNo[1]	oNo[2]	Σ[1]	Σ[2]
A_1	1.5	76.9	10.0	10.0	1.5	/	0.06	0.58	0.41	1.93
A_2	1.5	77.5	10.0	10.0	1.0	/	0.09	0.49	0.58	1.81
A_3	1.5	78.0	10.0	10.0	0.5	/	0.08	0.36	0.56	1.64
A_4	1.5	78.3	10.0	10.0	0.2	/	0.08	0.26	0.63	1.51
A_5	1.5	78.5	10.0	10.0	0.0	/	0.07	0.17	0.81	1.69
B_1	1.5	76.9	10.0	10.0	1.5	/	0.06	0.58	0.41	1.93
B_2	1.5	40.0	10.0	46.9	1.5	/	0.09	0.55	0.64	1.76
B_3	1.5	50.0	10.0	36.9	1.5	/	0.00	0.52	0.29	1.64
B_4	1.5	50.0	36.9	10.0	1.5	/	0.11	0.76	0.36	1.74
C_1	1.5	76.9	10.0	10.0	1.5	/	0.06	0.58	0.41	1.93
C_2	1.5	76.9	/	10.0	1.5	10.00 Lutrol® F68	0.05	0.53	0.65	1.83
C_3	1.5	50.0	10.0	10.0	1.5	26.90 mannitol	0.08	0.82	0.39	2.72
C_4	1.5	76.9	/	10.0	1.5	10.00 carnaubawax	0.12	0.53	0.39	1.03
D_1	1.5	76.9	10.0	10.0	1.5	/	0.06	0.58	0.41	1.93

D_2	1.5	76.8	10.0	10.0	1.5	0.10 fumaric acid	0.05	0.48	0.52	1.70
D_3	1.5	76.8	10.0	10.0	1.5	0.10 Na-EDTA	0.07	0.51	0.48	1.77
D_4	1.5	76.8	10.0	10.0	1.5	0.10 citric acid	0.07	0.48	0.37	1.45
E_1	1.5	76.9	10.0	10.0	1.5	/	0.06	0.58	0.41	1.93
E_2	1.5	76.8	10.0	10.0	1.5	0.10 citric acid	0.07	0.48	0.37	1.45
E_3	1.5	76.7	10.0	10.0	1.5	0.20 citric acid	0.00	0.40	0.20	1.13
E_4	1.5	76.4	10.0	10.0	1.5	0.50 citric acid	0.00	0.06	0.12	0.17

(A) : oxymorphone hydrochloride
PEO : polyethylene oxide M_w 7 mio g/mol
PEG : polyethylene glycol 6000
HPMC : hypromellose 100,000 Pa*s
α-toc. : α-tocopherol
oNo : oxymorphone-N-oxide (mixture)
Σ: sum of all impurities
^{1}: after extrusion, before storage
^{2}: after storage, amber glass bottles, plastic cap, 4 weeks, 40 °C, 75% rel. humidity

The decomposition products were analyzed by HPLC-UV. The elution peak for oxymorphone-N-oxide could not be sufficiently base-line separated from a peak of an unknown degradation product (called "UK 0.83"). Thus, both peaks were jointly integrated. It becomes evident from a comparison of examples A_1 to A_5 that the content of oxymorphone-N-oxide before storage (oNo^1) is not substantially changed when the content of antioxidant α-tocopherol is decreased from 1.5 wt.-% to 1.0 wt.-%, 0.5 wt.-%, 0.2 wt.-% and even 0 wt.-%. Upon storage (oNo^2), however, the content of oxymorphone-N-oxide is proportional to the content of α-tocopherol. This is most surprising because oxymorphone-N-oxide is an oxidation product and one would expect that antioxidants usually rather suppress than support the formation of oxidation products.

Nonetheless, the complete omission of antioxidant (α-tocopherol) has disadvantages. It could be shown by viscosity measurements that the high molecular polyethylene oxide is degraded upon extrusion and/or storage in the absence of antioxidant. It has been surprisingly found that about 0.2 wt.-% α-tocopherol suffice in order to stabilize the polyethylene oxide; higher contents of α-tocopherol do not result in higher viscosities of the polyalkylene oxide and, thus, do not prevent PEO more pronounced from degradation. Thus, the content of antioxidant (α-tocopherol) is preferably balanced so that on the one side, the high molecular weight polyethylene oxide is sufficiently stabilized and that on the other side, the undesired formation of oxymorphone-N-oxide is kept low during storage.

Further, it becomes evident from a comparison of examples B_1 to B_4 and examples C_1 to C_4 that the partial replacement of the high molecular weight polyethylene oxide or the total replacement of the polyethylene glycol by an alternative plasticizer does not result in a substantial decrease of the content of undesired oxymorphone-N-oxide. This is surprising because one would expect that polyethylene oxide and polyethylene glycol are potential peroxide carriers and that a reduction thereof would result in a reduction of oxidative processes such as the oxidation of oxymorphone to oxymorphone-N-oxide.

Still further, it becomes evident from a comparison of examples D_1 to D_5 and E_1 to E_4 that the addition of physiologically acceptable acids, particularly citric acid, leads to a reduction of the formation of oxymorphone-N-oxide. This effect is more pronounced when the amount of acid is increased. At a concentration of 0.1 wt.-%, the effect is comparatively weak, but at a concentration of 0.2 wt.-% the effect is stronger and is further enhanced when the concentration of citric acid is increased. Not only the amount of oxymorphone-N-oxide is decreased, but also the total amount of decomposition products, particularly of those having high HPLC retention times.

Example 2

Tablets that had been manufactured in analogy to ex. A_1, B_1, C_1, D_1 and E_1 above were packaged in different packaging materials and stored at 40 °C and 75% rel. humidity. The decomposition products before and after storage under accelerated storage conditions are summarized in the table here below:

	before storage	closed HDPE, sealed with aluminium foil		open amber glass		closed amber glass + oxygen scavenger		closed amber glass + desiccant		closed amber glass + argon	
		4 weeks	8 weeks	4 weeks	8 weeks	4 weeks	8 weeks	4 weeks	8 weeks	4 weeks	8 weeks
	323.64 mg	324.05 mg	325.57 mg	323.56 mg	337.25 mg	325.23 mg	322.65 mg	321.27 mg	322.69 mg	324.62 mg	324.30 mg
content oxymorphone	96.30%	92.90%	89.40%	93.70%	88.50%	96.70%	94.80%	94.60%	92.50%	94.60%	92.50%
purity oxymorphone	99.18%	97.70%	96.70%	98.03%	94.50%	99.10%	98.62%	98.59%	97.98%	98.36%	98.04%
content α-tocopherol	91.69%	91.51%	90.89%	93.51%	79.94%	94.52%	93.62%	90.56%	88.23%	93.51%	92.18%
oxymorphone-N-oxide	0.09%	0.64%	1.16%	0.19%	0.53%	0.03%	0.04%	0.15%	0.24%	0.17%	0.30%
UK 0.83	0.00%	0.00%	0.00%	0.36%	2.15%	0.06%	0.08%	0.32%	0.77%	0.00%	0.00%
Sum of oxymorphone-N-oxide and UK 0.83	0.09%	0.64%	1.16%	0.55%	2.63%	0.09%	0.12%	0.37%	1.01%	0.17%	0.30%
main unknown	0.13%	0.38%	0.43%	0.45%	2.15%	0.16%	0.18%	0.32%	0.77%	0.46%	0.34%
Sum of impurities Σ	0.73%	2.22%	3.21%	1.88%	5.44%	0.82%	0.95%	1.33%	1.94%	1.55%	1.88%

HDPE bottles had a volume of 75 ml. The oxygen scavenger was Pharmakeep® KD20 (Mitsubishi, Japan).

It has been surprisingly found that inclusion of an oxygen scavenger in the packaging results in a further stabilization of the dosage form so that the formation of decomposition products is limited to extremely low values.

Example 3:

Tablets were manufactured as described in example 1, packed into HDPE bottles of 75 ml volume together with an oxygen scavenger combined with a desiccant (Pharmakeep 20 KD), closed with a plastic cap with induction seal.

The individual constituents of the extruded mixtures, the total amount of decomposition products before and after storage under accelerated storage conditions are summarized in the table here below:

ex.	constituents (wt.-%)						decomposition products (wt.-%)					
	(A)	PEO	PEG	HPMC	α–toc.	Citric acid	oNo^1	oNo^2	oNo^3	Σ^1	Σ^2	Σ^3
F_1	1.5	73.8	10.0	14.0	0.2	0.5	nd	nd	nd	nd	nd	0.05
F_2	1.5	77.8	10.0	10.0	0.2	0.5	nd	nd	nd	nd	0.05	0.10

(A) : oxymorphone hydrochloride
PEO : polyethylene oxide M_w 7 mio g/mol
PEG : polyethylene glycol 6000
HPMC : hypromellose 100,000 Pa*s
α-toc. : α-tocopherol
oNo : oxymorphone-N-oxide (mixture)
Σ: sum of all impurities
^{1}: after extrusion, before storage
^{2}: after storage, HDPE bottles, plastic cap with induction seal, oxygen scavenger, 4 weeks, 40 °C, 75% rel. humidity
^{3}: after storage, HDPE bottles, plastic cap with induction seal, oxygen scavenger, 8 weeks, 40 °C, 75% rel. humidity

The results reveal that the purity of the product is very high after manufacturing and that the product exhibit stable during 8 weeks storage under accelerated conditions of 40°C/75% rel. humidity.

Example 4:

Tablets were manufactured as described in example 1 but cut into slices of 215 mg representing 5 mg or 40 mg of oxymorphone HCl, after forming the tablets were coated with about 6.5 mg each of a conventional Opadry II film-coat containing polyvinylalcohol as the film forming excipient, packed into HDPE bottles of 75 ml volume together with an oxygen scavenger combined with a desiccant (Pharmakeep 20 KD), closed with a plastic cap with induction seal.

The individual constituents of the extruded mixtures, the total amount of decomposition products before and after storage under accelerated storage conditions are summarized in the table here below:

ex.	constituents (wt.-%)						decomposition products (wt.-%)			
	(A)	PEO	PEG	HPMC	α-toc.	Citric acid	oNo[1]	oNo[2]	Σ[1]	Σ[2]
G_1	2.33	70.0	16.63	10.0	0.2	0.84	nd	nd	nd	nd
G_2	18.6	56.8	13.56	10.0	0.2	0.84	nd	nd	0.05	0.05

(A) : oxymorphone hydrochloride
PEO : polyethylene oxide M_w 7 mio g/mol
PEG : polyethylene glycol 6000
HPMC : hypromellose 100,000 Pa*s
α-toc. : α-tocopherol
oNo : oxymorphone-N-oxide (mixture)
Σ: sum of all impurities
[1]: after extrusion, before storage
[2]: after storage, HDPE bottles, plastic cap with induction seal, oxygen scavenger, 1 month, 40 °C, 75% rel. humidity

Example 5:

The most preferred dosage form according to example 3 is also suitable for the stabilization of oxycodone. This could be demonstrated for a formulation containing 80 mg of oxycodone HCl manufactured analogue to example 1 but, the extrudate was cut into slices of 400 mg:

ex.	constituents (wt.-%)						decomposition products (wt.-%)			
	(A)	PEO	PEG	HPMC	α-toc.	Citric acid	oNo[1]	oNo[2]	Σ[1]	Σ[2]
H_1	20	54.3	15	10	0.2	0.5	0.06	0.07	0.22	0.13

(A) : oxycodone
PEO : polyethylene oxide M_w 7 mio g/mol
PEG : polyethylene glycol 6000
HPMC : hypromellose 100,000 Pa*s
α-toc. : α-tocopherol
oNo : oxycodone-N-oxide (Impurity D+E)
[1]: after extrusion, before storage
[2]: after storage, amber glass bottles, plastic cap, oxygen scavenger with desiccant (Pharmakeep 20KD) 1 month, 40 °C, 75% rel. humidity

Example 6:

In a single dose (40 mg oxymorphone HCl, tablets of example 4), randomized, three-way crossover study with 1 week between treatments subjects were fasted overnight and meals were served 4 and 10 hours after dosing. No water was given within ± 1 hour of dosing. All tablets were taken with 240 mL of water (example T).

PK samples were taken for oxymorphone and 6-OH-oxymorphone predose and up through 48 hours after dosing.

Bioequivalence was compared to Opana ER® (reference R).

The results are summarized in the tables here below:

	Treatment	Mean	SD	CV
C_{max} [pg/mL]	T	2147	989	46%
	R	2671	1163	44%
AUCT [pg*h/mL]	T	38695	13836	36%
	R	38171	14652	38%
AUC [pg*h/mL]	T	42575	15836	37%
	R	41296	15242	37%

	Point Estimate T/R	Lower Limit 90% CI	Upper Limit 90% CI
C_{max}	79.37	71.69	87.87
AUCT	101.98	95.17	109.29
AUC	102.24	95.48	109.48

CI = confidence interval

It becomes evident that the dosage forms according to the invention having an increased breaking strength are bioequivalent to conventional dosage forms (Opana ER®).

Example 7

Tablets were prepared under identical conditions by hot-melt extrusion of two homogeneous constituent mixtures I_1 and I_2:

	I_1	I_2
Oxymorphone HCl [%]	11.1	11.1
PEO [%]	68.2	63.2
PEG [%]	10.0	15.0
HPMC Shin Etsu [%]	10.0	10.0
α-tocopherol [%]	0.2	0.2
Citric acid, anhydrous [%]	0.5	0.5

Tablet weight [mg]	360	360
PEO:PEG	6.82 : 1	4.21 : 1

under the following, identical extrusion conditions:

extruder type: Leistritz Extruder type Micro 27 GL 40 D equipped with medium shear screws and a die of 8 mm diameter
throughput: 10 kg/h
revolution velocity: 120 rpm
manufacturing time: 30 min
temperature of hottest heating zone: 100°C
die temperature: 130°C.

The extrudate was cut into slices of 360 mg containing about 40 mg oxymorphone hydrochloride.

100 slices were weighed individually and the standard deviation of weight was calculated. Slices of composition I_1 (PEO:PEG = 6.82:1) showed a standard deviation of 2.3 %, whereas slices of composition I_2 (PEO:PEG = 4.21:1) showed a standard deviation of 1.6 % only.

It becomes evident from these comparative tests that surprisingly, the processability of the extruded mass can be improved by adjusting the ratio of PEO to PEG.

Example 8

In order to investigate if also multicarboxylic acids other than citric acid could hamper the formation of oxymorphone-N-oxide, tablets containing maleinic acid or fumaric acid were manufactured as described in example 1. For comparison, also tablets containing the inorganic salt NaH_2PO_4 were manufactured. The samples were stored in open dishes at 40°C and 75% relative humidity for 4 weeks.

The individual constituents of the extruded mixtures as well as the total amount of decomposition products before and after storage under accelerated storage conditions are summarized in the table here below:

ex.	constituents (wt.-%)					further ingredient (wt.-%)	decomposition products (wt.-%)			
	(A)	PEO	PEG	HPMC	α-toc.		oNo[1]	oNo[2]	Σ^1	Σ^2
J_1	1.5	76.0	10.0	10.0	1.5	Maleinic acid 1.0 %	nd	nd	0.20	0.22

J_2	1.5	76.0	10.0	10.0	1.5	Fumaric acid 1.0 %	nd	nd	0.17	0.30
J_3	1.5	76.0	10.0	10.0	1.5	NaH_2PO_4 1.0 %*	nd	0.18	0.06	0.75

(A) : oxymorphone hydrochloride
PEO : polyethylene oxide M_w 7 mio g/mol
PEG : polyethylene glycol 6000
HPMC : hypromellose 100,000 Pa*s
α-toc. : α-tocopherol
*NaH_2PO_4: Used in form of 1.3% of the di-hydrate
oNo : oxymorphone-N-oxide (mixture)
Σ: sum of all impurities; maleinic acid, fumaric acid and related compounds subtracted from sum of impurities
[1]: after extrusion, before storage
[2]: after storage, open dish, 4 weeks, 40 °C, 75% rel. humidity

In case of maleinic and fumaric acid these compounds and for maleinic acid another related compound were detected during the purity tests as impurities (up to about 40%). Their values have been subtracted from the sum of impurities

It becomes evident from a comparison of examples J_1 and J_2 to A_1 and B_1 that the presence of maleinic and fumaric acid protected oxymorphone totally against oxidation to N-oxide and to a large extent against other degradation although the samples were stored in open dishes and not in closed bottles. These results are comparable to those obtained with citric acid (example 1, D_4 and E_2-E_4). Samples containing NaH_2PO_4 (J_3) exhibited protection against N-oxide formation and other degradation when compared to the formulations without any acidic compound (A_1 and B_1) but to a less extent than the multicarboxylic acids like citric, maleinic and fumaric acid.

Example 9

In order to investigate if the presence of citric acid also protects oxidation sensitive opioids other than oxymorphone against N-oxidation, tablets containing oxycodone hydrochloride were manufactured as described in example 1.
For comparison, also tablets containing smaller amounts of α-tocopherol were manufactured. The samples were stored in open dishes at 40°C and 75% relative humidity for 4 weeks.

The individual constituents of the extruded mixtures as well as the total amount of decomposition products before and after storage under accelerated storage conditions are summarized in the table here below:

ex.	constituents (wt.-%)					further ingredient (wt.-%)	decomposition products (wt.-%)			
	(A)	PEO	PEG	HPMC	α-toc.		oNo[1]	oNo[2]	Σ[1]	Σ[2]
K_1	1.5	77.0	10.0	10.0	1.5	/	0.05	0.58	0.31	1.63
K_2	1.5	78.3	10.0	10.0	0.2	/	0.05	0.28	0.58	0.69
K_3	1.5	76.0	10.0	10.0	1.5	Citric acid 1.0	nd	nd	0.19	0.22
K_4	1.5	77.3	10.0	10.0	0.2	Citric acid 1.0	nd	nd	0.18	0.23

(A) : oxycodone hydrochloride
PEO : polyethylene oxide M_w 7 mio g/mol
PEG : polyethylene glycol 6000
HPMC : hypromellose 100,000 Pa*s
α-toc. : α-tocopherol
oNo : oxycodone-N-oxide
Σ: sum of all impurities
[1] : after extrusion, before storage
[2] : after storage, open dish, 4 weeks, 40 °C, 75% rel. humidity

These results show that citric acid protected oxycodone totally against oxidation to the N-oxide and to a large extent against other degradation although the samples were stored in open dishes rather than in closed bottles. Reducing the amount of α-tocopherol resulted in reduced degradation, when formulations were employed not containing citric acid. These results are comparable to those obtained with oxymorphone.

Claims:

1. A thermoformed pharmaceutical dosage form having a breaking strength of at least 300 N and comprising

- an opioid (A),
- a free physiologically acceptable acid (B) in an amount of from 0.3 ± 0.18 wt.-% based on the total weight of the pharmaceutical dosage form, and
- a polyalkylene oxide (C) having a weight average molecular weight M_w of at least 500,000 g/mol,

wherein the acid (B) is a multicarboxylic acid.

2. The pharmaceutical dosage form according to claim 1, wherein the multicarboxylic acid is selected from the group consisting of maleic acid, fumaric acid, glutaric acid, malonic acid and citric acid.

3. The pharmaceutical dosage form according to any of the preceding claims, wherein the content of the acid (B) is within the range of from 0.12 to 0.45 wt.-%, based on the total weight of the pharmaceutical dosage form.

4. The pharmaceutical dosage form according to any of the preceding claims, which comprises a polyalkylene glycol, wherein the relative weight ratio of the polyalkylene oxide to the polyalkylene glycol is within the range of 4.2 ± 2 : 1.

5. The pharmaceutical dosage form according to any of the preceding claims, which comprises an anti-oxidant.

6. The pharmaceutical dosage form according to claim 5, wherein the antioxidant is α-tocopherol.

7. The pharmaceutical dosage form according to claim 5 or 6, wherein the content of the antioxidant is within the range of from 0.001 to 5.0 wt.-%, based on the total weight of the pharmaceutical dosage form.

8. The pharmaceutical dosage form according to any of the preceding claims, wherein after storage for 4 weeks at 40°C and 75% rel. humidity, the content of opioid (A) amounts to at least 98.0% of its original content before storage.

9. The pharmaceutical dosage form according to any of the preceding claims, wherein the opioid (A) is embedded in a matrix comprising the polyalkylene oxide (C), said matrix controlling the release of the opioid from the pharmaceutical dosage form.

10. The pharmaceutical dosage form according to any of the preceding claims, wherein the opioid (A) is selected from the group consisting of oxymorphone, oxycodone, hydromorphone, and the physiologically acceptable salts thereof.

11. The pharmaceutical dosage form according to any of the preceding claims, wherein the relative weight ratio of the polyalkylene oxide (C) and the opioid (A) is at least 1:1.

12. The pharmaceutical dosage form according to any of the preceding claims, which is adapted for administration once daily or twice daily.

13. The pharmaceutical dosage form according to any of the preceding claims, which has a breaking strength of at least 500 N.

14. A packaging containing a pharmaceutical dosage form according to any of claims 1 to 13 and an oxygen scavenger.

Grunenthal GmbH

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON