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(54) Title: TAMPER RESISTANT DOSAGE FORM COMPRISING INORGANIC SALT

(57) Abstract: The invention relates to a pharmaceutical dosage form exhibiting a breaking strength of at least 500 N, said dosage form containing a pharmacologically active ingredient (A); an inorganic salt (B); and a polyalkylene oxide (C) having a weight average molecular weight of at least 200,000 g/mol, wherein the content of the polyalkylene oxide (C) is at least 20 wt.-%, based on the total weight of the dosage form; wherein the pharmacologically active ingredient (A) is present in a controlled-release matrix comprising the inorganic salt (B) and the polyalkylene oxide (C) and wherein, under in vitro conditions, the release profile of the pharmacologically active ingredient (A) from said matrix comprises at least a time interval during which the release follows zero order kinetics.

Tamper Resistant Dosage Form Comprising Inorganic Salt

The invention relates to a pharmaceutical dosage form exhibiting a breaking strength of at least 500 N, said dosage form containing a pharmacologically active ingredient (A); an inorganic salt (B); and a polyalkylene oxide (C) having a weight average molecular weight of at least 200,000 g/mol, wherein the content of the polyalkylene oxide (C) is at least 20 wt.-%, based on the total weight of the dosage form; wherein the pharmacologically active ingredient (A) is present in a controlled-release matrix comprising the inorganic salt (B) and the polyalkylene oxide (C) and wherein, under *in vitro* conditions, the release profile of the pharmacologically active ingredient (A) from said matrix comprises at least a time interval during which the release follows zero order kinetics.

Many pharmacologically active ingredients 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 ingredients 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 pharmacologically active ingredient 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 pharmacologically active ingredient abuse of the pharmacologically active ingredient 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, WO 2008/107149, and WO 2009/092601.

The release kinetics of the pharmacologically active ingredients from such tamper resistant dosage forms is an important factor. It is well known that depending on how a pharmaceutically active ingredient is formulated into a tablet its release pattern can be modified.

On the one hand, formulations providing immediate release upon oral administration have the advantage that they lead to a fast release of the pharmacologically active ingredient in the gastrointestinal tract. As a result, a comparatively high dose of the pharmacologically active ingredient is quickly absorbed leading to high plasma levels within a short period of time and resulting in a rapid onset of medicinal action, i.e. medicinal action begins shortly after administration. At the same time, however, a rapid reduction in the medicinal action is observed, because metabolization and/or excretion of the pharmacologically active ingredient cause a decrease of plasma levels. For that reason, formulations providing immediate release of pharmacologically active ingredients typically need to be administered frequently, e.g. six times per day. This may cause comparatively high peak plasma pharmacologically active ingredient concentrations and high fluctuations between peak and trough plasma pharmacologically active ingredient concentrations which in turn may deteriorate tolerability.

Controlled release (e.g. delayed release, prolonged release, sustained release, and the like) may be based upon various concepts such as coating the pharmaceutical dosage form with a controlled release membrane, embedding the pharmacologically active ingredient in a matrix, binding the pharmacologically active ingredient to an ion-exchange resin, forming a complex of the pharmacologically active ingredient, and the like. In this context it can be referred to, e.g., W.A. Ritschel, Die Tablette, 2. Auflage, Editio Cantor Verlag Aulendorf, 2002.

In comparison to formulations providing immediate release, formulations providing prolonged release upon oral administration have the advantage that they need to be administered less frequently, typically once daily or twice daily. This can reduce peak plasma pharmacologically active ingredient concentrations and fluctuations between peak and trough plasma pharmacologically active ingredient concentrations which in turn may improve tolerability.

The ideal goal in designing a prolonged-release system is to deliver the pharmacologically active ingredient to the desired site at a rate according to the needs of the body. In the absence of feed-back control, one is left with a simple prolonging effect, where the pivotal question is at what rate a pharmacologically active ingredient should be delivered to maintain a constant blood pharmacologically active ingredient level. This constant rate should be the same as that achieved by continuous intravenous infusion where a pharmacologically active ingredient is provided to the patient at a constant rate just equal to its rate of elimination. This implies that the rate of delivery must be independent from the amount of pharmacologically active ingredient remaining in the dosage form and constant over time.

A perfectly invariant pharmacologically active ingredient blood or tissue level versus time profile is the ideal starting goal of a prolonged-release system. The way to achieve this, in the simplest case, is use of a maintenance dose that releases its pharmacologically active ingredient by zero-order kinetics.

US 5,082,668 discloses an osmotically driven dosage form, namely a device comprising a wall that surrounds a compartment. The compartment comprises a beneficial agent composition and a push composition. A passageway in the wall connects the compartment with the exterior of the device for delivering the beneficial agent at a rate governed, in combination, by the wall, the beneficial agent composition and the push composition through the passageway of the device over time.

US 7,300,668 relates to a dosage form comprising: a three-dimensionally printed innermost region comprising a first regional concentration of at least one active pharmaceutical ingredient; and plural three-dimensionally printed non-innermost regions in nested arrangement and comprising: a) one or more nested internal regions, wherein an internal region completely surrounds and is in contact with the innermost regions, and any other internal region present completely surrounds another internal region located to the interior thereof; and b) an outermost region completely surrounding an internal region, wherein the internal and outermost regions are in nested arrangement, wherein the at least one active pharmaceutical ingredient is released in approximately a zero-order release.

WO 2008/086804 discloses abuse resistant polyglycol-based pharmaceutical compositions. The composition contains one or more polyglycols and one or more active substances and it is resistant to crushing, melting and/or extraction. Moreover, such compositions have the same or lower solubility in ethanolic-aqueous medium, i.e. they are not subject to ethanol-induced dose dumping effect.

WO 2008/148798 discloses a layered pharmaceutical composition suitable for oral use in the treatment of diseases where absorption takes place over a large part of the gastrointestinal tract.

WO 03/024426 discloses a controlled release pharmaceutical composition for oral use comprising a solid dispersion of: i) at least one therapeutically, prophylactically and/or diagnostically active substance, which at least partially is in an amorphous form, ii) a pharmaceutically acceptable polymer that has plasticizing properties, and iii) optionally, a stabilizing agent, the at least one active substance having a limited water solubility, and the composition being designed to release the active substance with a substantially zero order release. Zero order release is provided by a coating that remains intact during the release phase and covers the matrix composition in such a manner that only a specific surface area is subject to erosion. Thereby the surface area from which the active substance is released is kept substantially constant during the time period.

WO 2010/057036 discloses a solid composition and methods for making and using the solid composition are provided. The solid composition comprises: (a) at least one active agent with a solubility of less than about 0.3 mg/ml in an aqueous solution with a pH of at most about 6.8 at a temperature of about 37°C; and (b) a hydrophilic polymer matrix composition comprising: i) a hydrophilic polymer selected from the group consisting of METHOCEL®, POLYOX® WSR 1105 and combinations thereof; and optionally ii) a hydrophobic polymer selected from the group consisting of Ethocel 20 premium; and (c) an alkalizer selected from the group consisting of calcium carbonate, magnesium oxide heavy and sodium bicarbonate; wherein the composition provides at least about 70% release of the active between about 7 to about 12 hours following oral administration.

V. Pillay et al., Journal of Controlled Release, 67 (2000) 67-78 discloses an approach for constant rate delivery of highly soluble bioactives from a simple monolithic system prepared by direct compression at ambient conditions.

M.E. McNeill et al., J Biomater Sci Polym 1996, 7(11), 953-63 relates to properties controlling the diffusion and release of water-soluble solutes from poly(ethylene oxide) hydrogels. Part 4 deals with extended constant rate release from partly-coated spheres.

D. Henrist et al. relates to *in vitro* and *in vivo* evaluation of starch-based hot stage extruded double matrix systems. The objective of developing a double matrix system consisting of a

hot stage extruded starch pipe surrounding a hot stage extruded and drug-containing starch core, was to obtain a monolithic matrix system applicable in the domain of sustained drug release. The behaviour of the systems was evaluated through dissolution testing and through a randomised crossover bioavailability study on nine male volunteers. All double matrix systems showed *in vitro* a nearly constant drug release profile after an initial slower release phase of 4 h. This initial slower release phase was avoided by loading the starch pipe with a small amount of drug.

L. Yang et al., J. Pharm. Sciences, 85(2), 1996, 170-173 relates to zero-order release kinetics from a self-correcting floatable asymmetric configuration drug delivery system.

It is an object of the invention to provide pharmaceutical dosage forms having advantages compared to pharmaceutical dosage forms of the prior art.

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

It has been surprisingly found that comparatively low amounts of inorganic salts contained in a polymer matrix provide a further delay of the release of the pharmacologically active ingredients from tamper resistant dosage forms without leading to a substantial increase of the overall weight. Further, it has been surprisingly found that the incorporation of the inorganic salt into the polymer matrix does not substantially alter the mechanical properties of the tamper resistant dosage form which are based upon the polymer matrix, especially the breaking strength. Still further, it has been surprisingly found that the release profile follows zero order kinetics and does not depend upon the pH value of the release medium.

Figure 1 shows the *in vitro* release profile of a pharmaceutical dosage form according to the invention containing 30 wt.-% (Variation E) and 40 wt.-% (Variation F), respectively, of sodium carbonate in comparison to the reference tablets.

Figure 2 shows the *in vitro* release profiles of a pharmaceutical dosage form according to the invention containing 15 wt.-% (Variation F) and 20 wt.-% (Variation G), respectively, each of sodium carbonate and pentasodium triphosphate in comparison to the reference tablets.

Figure 3 shows the *in vitro* release profiles of a pharmaceutical dosage form according to the invention in an acidic medium, containing 30 wt.-% sodium carbonate (Variation E) and 15 wt.-% sodium carbonate with 15 wt.-% pentasodium triphosphate (Variation F) in comparison to the reference tablets.

Figure 4 shows the *in vitro* release profiles of a pharmaceutical dosage form according to the invention in an acidic medium (pH 1.2) and with phosphate buffer (pH 4.5), containing oxymorphone and 30 wt.-% sodium carbonate (Example II) in comparison to reference tablets.

Figure 5 shows the *in vitro* release profiles of a pharmaceutical dosage form according to the invention in an acidic medium (pH 1.2) and with phosphate buffer (pH 4.5), containing oxymorphone and 15 wt.-% each of sodium carbonate and pentasodium triphosphate (Example III) in comparison to reference tablets.

A first aspect of the invention relates to a pharmaceutical dosage form exhibiting a breaking strength of at least 500 N, said dosage form containing

- a pharmacologically active ingredient (A);
- an inorganic salt (B); and
- a polyalkylene oxide (C) having a weight average molecular weight of at least 200,000 g/mol, wherein the content of the polyalkylene oxide (C) is at least 20 wt.-%, based on the total weight of the dosage form;

wherein the pharmacologically active ingredient (A) is present in a controlled-release matrix comprising the inorganic salt (B) and the polyalkylene oxide (C), and wherein, under *in vitro* conditions, the release profile of the pharmacologically active ingredient (A) from said matrix comprises at least a time interval during which the release follows zero order kinetics.

The dosage form according to the invention contains one or more pharmacologically active ingredients (A).

There are generally no limitations as to the pharmacologically active ingredient (A) (pharmacologically active compound) which can be incorporated into the tablet of the invention.

In a preferred embodiment, the pharmaceutical dosage form contains only a single pharmacologically active ingredient (A). In another preferred embodiment, the pharmaceutical dosage form contains a combination of two or more pharmacologically active ingredients (A).

Preferably, pharmacologically active ingredient (A) has potential for being abused. Active ingredients with potential for being abused are known to the person skilled in the art and comprise e.g. tranquillisers, stimulants, barbiturates, narcotics, opioids or opioid derivatives.

Preferably, the pharmacologically active ingredient (A) exhibits psychotropic action.

Preferably, the pharmacologically active ingredient (A) is selected from the group consisting of opiates, opioids, stimulants, tranquilizers, and other narcotics.

Particularly preferably, the pharmacologically active ingredient (A) is an opioid. According to the ATC index, opioids are divided into natural opium alkaloids, phenylpiperidine derivatives, diphenylpropylamine derivatives, benzomorphan derivatives, oripavine derivatives, morphinan derivatives and others.

The following opiates, opioids, tranquillizers or other narcotics are substances with a psychotropic action, i.e. have a potential of abuse, and hence are preferably contained in the pharmaceutical dosage form according to the invention: alfentanil, allobarbital, allylprodine, alphaprodine, alprazolam, amfepramone, amphetamine, amphetaminil, amobarbital, anileridine, apocodeine, axomadol, barbital, bemidone, benzylmorphine, bezitramide, bromazepam, brotizolam, buprenorphine, butobarbital, butorphanol, camazepam, carfentanil, cathine/D-norpseudoephedrine, chlordiazepoxide, clobazam clofedanol, clonazepam, clonitazene, clorazepate, clotiazepam, cloxazolam, cocaine, codeine, cyclobarbital, cyclorphan, cyprenorphine, delorazepam, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, diazepam, dihydrocodeine, dihydromorphine, dihydromorphone, dimenoxadol, dimephetamol, dimethylthiambutene, dioxaphetylbutyrate, dipipanone, dronabinol, eptazocine, estazolam, ethoheptazine, ethylmethylthiambutene, ethyl loflazepate, ethylmorphine, etonitazene, etorphine, faxeladol, fencamfamine, fenethylline, fenpipramide, fenproporex, fentanyl, fludiazepam, flunitrazepam, flurazepam, halazepam, haloxazolam, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, hydroxymethylmorphinan, ketazolam, ketobemidone, levacetylmethadol (LAAM), levomethadone, levorphanol, levophenacylmorphane, levoxemacin, lisdexamfetamine dimesylate, lofentanil, loprazolam, lorazepam, lormetazepam, mazindol, medazepam, mefenorex, meperidine, meprobamate, metapon, meptazinol, metazocine, methylmorphine, metamphetamine, methadone, methaqualone, 3-methylfentanyl, 4-methylfentanyl, methylphenidate, methylphenobarbital, methyprylon, metopon, midazolam, modafinil, morphine, myrophine, nabilone, nalbuphene, nalorphine, narceine, nicomorphine, nimetazepam, nitrazepam, nordazepam, norlevorphanol, normethadone, normorphine,

norpipanone, opium, oxazepam, oxazolam, oxycodone, oxymorphone, Papaver somniferum, papaveretum, pernoline, pentazocine, pentobarbital, pethidine, phenadoxone, phenomorphane, phenazocine, phenoperidine, piminodine, pholcodeine, phenmetrazine, phenobarbital, phentermine, pinazepam, pipradrol, piritramide, prazepam, profadol, proheptazine, promedol, properidine, propoxyphene, remifentanil, secbutabarbital, secobarbital, sufentanil, tapentadol, temazepam, tetrazepam, tilidine (cis and trans), tramadol, triazolam, vinylbital, 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, 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 acid or base addition salts thereof and solvates, e.g. hydrochlorides.

In a preferred embodiment the pharmaceutical dosage form according to the invention contains an opioid selected from the group consisting of DPI-125, M6G (CE-04-410), ADL-5859, CR-665, NRP290 and sebacoyl dinalbuphine ester.

In a preferred embodiment, the pharmaceutical dosage form according to the invention contains one pharmacologically active ingredient (A) or more pharmacologically active

ingredients (A) selected from the group consisting of oxymorphone, hydromorphone, morphine and the physiologically acceptable salts thereof.

In another preferred embodiment, the pharmacologically active ingredient (A) is selected from the group consisting of tapentadol, faxeladol, axomadol and the physiologically acceptable salts thereof.

In still another preferred embodiment, the pharmacologically active ingredient (A) is selected from the group consisting of 1,1-(3-dimethylamino-3-phenylpentamethylene)-6-fluoro-1,3,4,9-tetrahydropyrano[3,4-b]indole, particularly its hemicitrate; 1,1-[3-dimethylamino-3-(2-thienyl)-pentamethylene]-1,3,4,9-tetrahydropyrano[3,4-b]indole, particularly its citrate; and 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydropyrano[3,4-b]-6-fluoroindole, particularly its hemicitrate. These compounds are known from, e.g., WO 2004/043967, WO 2005/066183.

The pharmacologically active ingredient (A) may be present in form of a physiologically acceptable salt, e.g. physiologically acceptable acid addition salt.

Physiologically acceptable acid addition salts comprise the acid addition salt forms which can conveniently be obtained by treating the base form of the active ingredient with appropriate organic and inorganic acids. Active ingredients containing an acidic proton may be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. The term addition salt also comprises the hydrates and solvent addition forms which the active ingredients are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The pharmacologically active ingredient (A) is present in the dosage form in a therapeutically effective amount. The amount that constitutes a therapeutically effective amount varies according to the active ingredients being used, the condition being treated, the severity of said condition, the patient being treated, and whether the dosage form is designed for an immediate or retarded release. The amount of active ingredient(s) used in the present invention preferably ranges from about 0.01 wt.-% to about 95 wt.-%, more preferably from about 0.1 wt.-% to about 80 wt.-%, even more preferably from about 1.0 wt.-% to about 50 wt.-%, yet more preferably from about 1.5 wt.-% to about 30 wt.-%, and most preferably from about 2.0 wt.-% to 20 wt.-%, based on the total weight of the pharmaceutical dosage form.

The content of the pharmacologically active ingredient (A) in the pharmaceutical dosage form is not limited. The dose of the pharmacologically active ingredient (A) which is adapted for administration preferably is in the range of 0.1 mg to 500 mg, more preferably in the range of 1.0 mg to 400 mg, even more preferably in the range of 5.0 mg to 300 mg, and most preferably in the range of 10 mg to 250 mg. In a preferred embodiment, the total amount of the pharmacologically active ingredient (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.

Preferably, the content of the pharmacologically active ingredient (A) 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 pharmacologically active ingredient (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 pharmacologically active ingredient (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 pharmacologically active ingredient (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.

In a preferred embodiment, the pharmacologically active ingredient (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, 160±5 mg, 170±5 mg, 180±5 mg, 190±5 mg, 200±5 mg, 210±5 mg, 220±5 mg, 230±5 mg, 240±5 mg, or 250±5 mg. In another preferred embodiment, the pharmacologically active ingredient (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, 160±2.5 mg, 165±2.5 mg, 170±2.5 mg, 175±2.5 mg,

180±2.5 mg, 185±2.5 mg, 190±2.5 mg, 195±2.5 mg, 200±2.5 mg, 205±2.5 mg, 210±2.5 mg, 215±2.5 mg, 220±2.5 mg, 225±2.5 mg, 230±2.5 mg, 235±2.5 mg, 240±2.5 mg, 245±2.5 mg, or 250±2.5 mg.

Preferably, the pharmaceutically dosage form provides a release of the pharmacologically active ingredient (A) after 1 hour of preferably at most 60 %, more preferably at most 40 %, yet more preferably at most 30 %, still more preferably at most 20 % and most preferably at most 17%; after 2 hours preferably at most 80 %, more preferably at most 60 %, yet more preferably at most 50 %, still more preferably at most 40 % and most preferably at most 32%; after 3 hours preferably at most 85 %, more preferably at most 65 %, yet more preferably at most 55 %, still more preferably at most 48 % and most preferably at most 42%; after 4 hours preferably at most 90 %, more preferably at most 75 %, yet more preferably at most 65 %, still more preferably at most 55 % and most preferably at most 49%; after 7 hours preferably at most 95 %, more preferably at most 85 %, yet more preferably at most 80 %, still more preferably at most 70 % and most preferably at most 68%; after 10 hours preferably at most 99 %, more preferably at most 90 %, yet more preferably at most 88 %, still more preferably at most 83 % and most preferably at most 80%; and after 13 hours preferably at most 99 %, more preferably at most 95 %, yet more preferably at most 93 %, still more preferably at most 91 % and most preferably at most 89%.

In a particularly preferred embodiment, the pharmacologically active ingredient (A) is tapentadol, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily or twice daily. In this embodiment, the pharmacologically active ingredient (A) is preferably contained in the pharmaceutical dosage form in an amount of from 25 to 250 mg.

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

In another particularly preferred embodiment, the pharmacologically active ingredient (A) is oxycodone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for

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

In still another particularly preferred embodiment, the pharmacologically active ingredient (A) is hydromorphone, preferably its HCl, and the pharmaceutical dosage form is adapted for administration twice daily. In this embodiment, the pharmacologically active ingredient (A) is preferably contained in the pharmaceutical dosage form in an amount of from 2 to 52 mg. In another particularly preferred embodiment, the pharmacologically active ingredient (A) is hydromorphone, preferably its HCl, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, the pharmacologically active ingredient (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 durability of the pharmacologically active ingredient (A). Preferably, after storage for 4 weeks at 40°C and 75% rel. humidity, the content of pharmacologically active ingredient (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 pharmacologically active ingredient (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 dosage form according to the invention contains the pharmacologically active ingredient (A) in a controlled-release matrix comprising inorganic salt (B), wherein, under *in vitro* conditions, the release profile of the pharmacologically active ingredient (A) from said matrix comprises at least a time interval during which the release follows a zero order kinetics.

A skilled person knows which requirements need to be satisfied with in order to qualify the *in vitro* release profile of a pharmaceutical dosage form as being of zero order. Pharmacologically active ingredient dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of pharmacologically active ingredient (Q) is a

function of the test time, t or Q = f(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Hixson-Crowell, Weibull, Higuchi, Baker-Lonsdale, Korsmeyer-Peppas and Hopfenberg models. Other release parameters, such as dissolution time (tx%), assay time (tx min), dissolution efficacy (ED), difference factor (f1), similarity factor (f2) and Rescigno index (xi1 and xi2) can be used to characterize pharmacologically active ingredient dissolution/release profiles.

For the purpose of specification the term "zero order kinetics" is preferably defined by the equation $W_0 - W_t = K\,t$, where W_0 is the initial amount of pharmacologically active ingredient (A) in the pharmaceutical dosage form, W_t is the amount of pharmacologically active ingredient (A) in the pharmaceutical dosage form at time t and K is a proportionality constant. Dividing this equation by W_0 and simplifying $f_t = K_0\,t$, where $f_t = 1 - (W_t/W_0)$ and f_t represents the fraction of pharmacologically active ingredient (A) dissolved in time t and K_0 the apparent dissolution rate constant or zero order release constant. In this way, a graphic of the pharmacologically active ingredient-dissolved fraction versus time will be linear. This relation can be used to describe the dissolution of several types of modified release pharmaceutical dosage forms, as in the case of matrix tablets with low soluble pharmacologically active ingredients, coated forms, osmotic systems, etc. The pharmaceutical dosage forms following this profile release the same amount of pharmacologically active ingredient by unit of time and it is the ideal method of pharmacologically active ingredient release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model: $Q_1 = Q_0 + K_0\,t$, where Q_t is the amount of pharmacologically active ingredient dissolved in time t, Q_0 is the initial amount of pharmacologically active ingredient in the solution (most times, Q_0=0) and K_0 is the zero order release constant (cf. e.g., P. Costa et al., Eur J Pharm Sci. 2001, 13(2), 123-33).

It is evident to the skilled artisan that in praxis pharmaceutical dosage forms usually do not provide exact zero order release, particularly not over the full length of the release period, i.e. from the very beginning until the release of 100% of the pharmacologically active ingredient (A) that was originally contained in the pharmaceutical dosage form. Rather, in praxis *in vitro* release profiles can be described with a substantial degree of accuracy by these mathematical models, particularly when not considering the initial phase as well as the end phase of the release.

Preferably, the *in vitro* release profile of the pharmacologically active ingredient (A) from the pharmaceutical dosage form according to the invention comprises a time interval during which the release follows substantially a zero order kinetics, which time interval is preferably

the time needed in order to release 50±5%, more preferably 50±10%, still more preferably 50±15%, yet more preferably 50±20%, even more preferably 50±25%, most preferably 50±30%, and in particular 50±35%, of the pharmacologically active ingredient (A). For example, the time needed in order to release 50±30% of the pharmacologically active ingredient (A) commences with the release of 20% (e.g. after 2.5 hours) and terminates with the release of 80% (e.g. after 10.5 hours) of the pharmacologically active ingredient (A). During such time interval, the *in vitro* release profile of the pharmacologically active ingredient (A) from the pharmaceutical dosage form follows substantially zero order kinetics, i.e. is substantially linear.

In a preferred embodiment, the kinetics for the *in vitro* release of the pharmacologically active ingredient (A) from the pharmaceutical dosage form is approximated by the equation $M_t / M_0 = k\ t^n$ where t is time, M_t is the amount of the pharmacologically active ingredient (A) which has been released at time t, M_0 is the total amount of the pharmacologically active ingredient (A) originally contained in the dosage form, i.e. before exposing the pharmaceutical dosage form to the release medium, k is a constant, and n is the release kinetics exponent. Preferably, the *in vitro* release profile of the pharmaceutical dosage form according to the invention provides a curve which defines the retarded release in percent to the time. For a defined time period, preferably from the beginning or from a point in time after the beginning, e.g. from the time where 20% have been released, to the time where 95% of the pharmacologically active ingredient (A) have been released from the dosage form according to the invention, the release profile is substantially linear.

Preferably, the time interval during which the release follows zero order kinetics, e.g. where the second derivative of the graph is substantially linear, is at least 20%, more preferably at least 30%, still more preferably at least 40%, yet more preferably at least 50%, even more preferably at least 60%, most preferably at least 70% and in particular at least 80% of the total release time needed for a release of 95 wt.-% of the pharmacologically active ingredient (A) that was originally contained in the pharmaceutical dosage form.

Preferably, the margins (limits) of "substantially linear" can be assessed based on the second derivative of the curve fitted to the measuring points. Ideally, said second derivative is zero. Preferably, however, a certain degree of deviation is also within the meaning of "substantially linear" according to the invention. Preferably, said deviations from the ideal linear behavior can be quantified by a Chi-square-test, which is known to a person skilled in the art. Preferably, the value determined according to the Chi-square-test is at most 2.5, more

preferably at most 1.75, still more preferably at most 1.0, yet more preferably at most 0.75, even more preferably at most 0.5, most preferably at most 0.25, and in particular at most 0.1.

Preferably, the zero-order *in vitro* release kinetics can adequately be described by $M_t/M_\infty = k_0 t^n$, where M_t and M_∞ are the amounts of drug released at time t and the overall amount released, respectively, n is a release exponent indicative of profile shape, and k_0 is the zero-order release rate constant.

In a preferred embodiment, when fitting the relevant portion of the overall *in vitro* release profile that shows zero-order release kinetics to the equation $M_t/M_\infty = k_0 t$ (i.e. where n = 1), the correlation coefficient of the fit is preferably at least 0.75, more preferably at least 0.80, still more preferably at least 0.85, yet more preferably at least 0.90, even more preferably at least 0.925, most preferably at least 0.95 and in particular at least 0.975.

In a preferred embodiment, the zero-order release rate constant k_0 is within the range of 0.030±0.028 h^{-1}, more preferably 0.030±0.026 h^{-1}, still more preferably 0.030±0.024 h^{-1}, yet more preferably 0.030±0.020 h^{-1}, even more preferably 0.030±0.015 h^{-1}, most preferably 0.030±0.010 h^{-1}, and in particular 0.030±0.005 h^{-1}. In another preferred embodiment, the zero-order release rate constant k_0 is within the range of 0.040±0.035 h^{-1}, more preferably 0.040±0.030 h^{-1}, still more preferably 0.040±0.025 h^{-1}, yet more preferably 0.040±0.020 h^{-1}, even more preferably 0.040±0.015 h^{-1}, most preferably 0.040±0.010 h^{-1}, and in particular 0.040±0.005 h^{-1}. In still another preferred embodiment, the zero-order release rate constant k_0 is within the range of 0.050±0.035 h^{-1}, more preferably 0.050±0.030 h^{-1}, still more preferably 0.050±0.025 h^{-1}, yet more preferably 0.050±0.020 h^{-1}, even more preferably 0.050±0.015 h^{-1}, most preferably 0.050±0.010 h^{-1}, and in particular 0.050±0.005 h^{-1}. In yet another preferred embodiment, the zero-order release rate constant k_0 is within the range of 0.060±0.035 h^{-1}, more preferably 0.060±0.030 h^{-1}, still more preferably 0.060±0.025 h^{-1}, yet more preferably 0.060±0.020 h^{-1}, even more preferably 0.060±0.015 h^{-1}, most preferably 0.060±0.010 h^{-1}, and in particular 0.060±0.005 h^{-1}. In a further preferred embodiment, the zero-order release rate constant k_0 is within the range of 0.070±0.035 h^{-1}, more preferably 0.070±0.030 h^{-1}, still more preferably 0.070±0.025 h^{-1}, yet more preferably 0.070±0.020 h^{-1}, even more preferably 0.070±0.015 h^{-1}, most preferably 0.070±0.010 h^{-1}, and in particular 0.070±0.005 h^{-1}. In a still further preferred embodiment, the zero-order release rate constant k_0 is within the range of 0.080±0.035 h^{-1}, more preferably 0.080±0.030 h^{-1}, still more preferably 0.080±0.025 h^{-1}, yet more preferably 0.080±0.020 h^{-1}, even more preferably 0.080±0.015 h^{-1}, most preferably 0.080±0.010 h^{-1}, and in particular 0.080±0.005 h^{-1}. In a yet further preferred embodiment, the zero-order release rate constant k_0 is within the range of

0.090±0.035 h^{-1}, more preferably 0.090±0.030 h^{-1}, still more preferably 0.090±0.025 h^{-1}, yet more preferably 0.090±0.020 h^{-1}, even more preferably 0.090±0.015 h^{-1}, most preferably 0.090±0.010 h^{-1}, and in particular 0.090±0.005 h^{-1}. In another preferred embodiment, the zero-order release rate constant k_0 is within the range of 0.100±0.035 h^{-1}, more preferably 0.100±0.030 h^{-1}, still more preferably 0.100±0.025 h^{-1}, yet more preferably 0.100±0.020 h^{-1}, even more preferably 0.100±0.015 h^{-1}, most preferably 0.100±0.010 h^{-1}, and in particular 0.100±0.005 h^{-1}.

In a preferred embodiment, release exponent n is at least 0.65, more preferably at least 0.70, still more preferably at least 0.75, yet more preferably at least 0.80, even more preferably at least 0.85, most preferably at least 0.90 and in particular at least 0.95.

The zero-order release kinetics of the pharmaceutical dosage form according to the invention preferably does not rely on a coating that remains intact during the release phase and covers the matrix composition in such a manner that only a specific surface area is subject to erosion. Thus, the surface area of the pharmaceutical dosage form according to the invention from which the active substance is released is preferably not kept substantially constant by means of such a coating. On the contrary, the zero-order release kinetics of the pharmaceutical dosage form according to the invention is preferably based on the properties of the matrix in which the pharmacologically active ingredient (A) is embedded so that inert coatings can be completely omitted. Thus, while the pharmaceutical dosage form according to the invention may be coated with conventional coating materials such as polyvinyl alcohol, it is preferably not coated with inert coating materials that serve the purpose of permanently covering a substantial portion of the outer surface of the dosage form in order to allow drug release only through a predetermined, uncoated portion. Thus, in a preferred embodiment, the pharmaceutical dosage form according to the invention is uncoated, or it is coated with a coating material that substantially covers the complete outer surface of the dosage form, but does not leave a certain portion uncoated.

The pharmaceutical dosage form according to the invention comprises an inorganic salt (B).

In a preferred embodiment, the pharmaceutical dosage form comprises a single inorganic salt (B).

In another preferred embodiment, the pharmaceutical dosage form comprises a mixture of two or more inorganic salts (B). When the pharmaceutical dosage form according to the invention contains two different inorganic salts (B), e.g. pentasodium triphosphate and

sodium carbonate, the relative weight ratio thereof is preferably within the range of from 8:1 to 1:8, more preferably 7:1 to 1:7, still more preferably 6:1 to 1:6, yet more preferably 5:1 to 1:5, even more preferably 4:1 to 1:4, most preferably 3:1 to 1:3, and in particular 2:1 to 1:2.

In another preferred embodiment, the pharmaceutical dosage form comprises a mixture of two inorganic salts (B). When the pharmaceutical dosage form according to the invention contains two different inorganic salts (B), e.g. pentasodium triphosphate and sodium carbonate, the storage stability at 5°C and 25°C is significantly increased. Concerning this matter the decrease of the content of Vitamin E contained in the pharmaceutical dosage form is more slowly in contrast to the pharmaceutical dosage form containing only one inorganic salt, e.g. sodium carbonate, and the release profile of the pharmacologically active ingredient (A) does not change in comparison to the release profile which is recorded before the storage stability was tested.

Preferably, inorganic salt (B) is salt, preferably an alkali metal or earth alkali metal salt, of a strong inorganic acid having a pK_A value of at most 3, preferably at most 2, more preferably at most 1, still more preferably at most 0 and in particular at most -1. If said inorganic acid is a multi-protonic acid, preferably at least the first proton satisfies the above requirement.

Preferably, the inorganic salt (B) is a salt of carbonic acid (H_2CO_3), phosphoric acid (H_3PO_4), phosphorous acid (H_3PO_3), pyrophosphoric acid ($H_4P_2O_7$), or triphosphoric acid ($H_5P_3O_{10}$), preferably an alkali and/or earth alkali and/or hydrogenate salt thereof.

Preferably, the inorganic salt (B) is selected from the group consisting of alkali carbonates (e.g., Na_2CO_3, K_2CO_3, $NaKCO_3$), earth alkali carbonates (e.g., $MgCO_3$, $CaCO_3$), alkali hydrogen carbonates (e.g., $NaHCO_3$, $KHCO_3$), earth alkali hydrogen carbonates (e.g., $Mg(HCO_3)_2$, $Ca(HCO_3)_2$), alkali phosphates (e.g., Na_3PO_4, Na_2KPO_4, NaK_2PO_4, K_3PO_4), earth alkali phosphates (e.g., $Mg_3(PO_4)_2$, $Ca_3(PO_4)_2$,), alkali pyrophosphates (e.g., $Na_4P_2O_7$, $Na_3KP_2O_7$, $Na_2K_2P_2O_7$, $NaK_3P_2O_7$, $K_4P_2O_7$), earth alkali pyrophosphates (e.g., $Mg_2P_2O_7$, $CaMgP_2O_7$, $Ca_2P_2O_7$), pentaalkali tri(poly)phosphates (alkali triphosphate tribasic) (e.g., $Na_5P_3O_{10}$, $Na_4KP_3O_{10}$, $Na_3K_2P_3O_{10}$, $Na_2K_3P_3O_{10}$, $NaK_4P_3O_{10}$, $K_5P_3O_{10}$, $Na_4KP_3O_{10}$), alkali hydrogen phosphates (e.g., Na_2HPO_4, $NaKHPO_4$, K_2HPO_4), earth alkali hydrogen phosphates (e.g., $MgHPO_4$, $CaHPO_4$), alkali dihydrogen phosphates (e.g., NaH_2PO_4, KH_2PO_4), earth alkali dihydrogen phosphates (e.g., $Mg(H_2PO_4)_2$, $Ca(H_2PO_4)_2$).

Preferably, the inorganic salt (B) is sodium carbonate or pentasodium triphosphate or mixtures thereof.

It has been surprisingly found that the inorganic salt (B) may further extend the release profile of the pharmaceutical dosage form compared to a comparative dosage form not containing inorganic salt (B).

In a preferred embodiment, the content of inorganic salt (B) amounts to 1 to 80 wt.-%, more preferably 5 to 70 wt.-%, still more preferably 12 to 60 wt.-%, yet more preferably 17 to 50 wt.-% and most preferably 25 to 45 wt.-% and in particular 29 to 41 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the content of inorganic salt (B) is within the range of 30±9 wt.-%, more preferably 30±8 wt.-%, still more preferably 30±7 wt.-%, yet more preferably 30±6 wt.-

%, most preferably 30±5 wt.-%, and in particular 30±2.5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In another preferred embodiment, the content of inorganic salt (B) is within the range of 40±9 wt.-%, more preferably 40±8 wt.-%, still more preferably 40±7 wt.-%, yet more preferably 40±6 wt.-%, most preferably 40±5 wt.-%, and in particular 40±2.5 wt.-%, based on the total weight of the pharmaceutical dosage form.

It has been surprisingly found that the mechanical properties of the (tamper-resistant) pharmaceutical dosage form according to the invention, particularly its increased breaking strength are not diminished when adding substantial amounts of inorganic salt (B). This is particularly surprising, as one would expect that a high breaking strength can only be achieved by means of suitable polymers in suitable amounts and processed under appropriate conditions (typically pressure and heat). Inorganic salt (B), however, is no polymer.

Still further, it has been surprisingly found that inorganic salt (B) can influence the release characteristics of a controlled release matrix comprising a polyalkylene oxide (C), although in case of the pharmaceutical dosage forms according to the invention said polyalkylene oxide (C) provides a breaking strength of at least 500 N to the overall pharmaceutical dosage form. There is indication that in conventional hydrophilic monolithic polymeric matrices not exhibiting a breaking strength of at least 500 N, matrix swelling, matrix stiffening, matrix scaffolding via electrolyte interaction and constantly changing peripheral densification play a central role in electrolyte-induced compositional heterogeneity. Surprisingly, such processes also appear to take place in the dosage forms according to the invention, although one would expect a completely different behavior due to the specific mechanical properties.

Furthermore said pharmaceutical dosage form can be produced with a significantly reduced amount of process steps without losing the tamper resistant abilities.

Furthermore, it has been surprisingly found that the *in vitro* release profile of the pharmaceutical dosage form can be substantially independent from the pH value. Preferably, the *in vitro* release profile of the pharmaceutical dosage form follows zero order kinetics within the range of from pH 1 to pH 7.

In a preferred embodiment, inorganic salt (B) is homogeneously distributed in the pharmaceutical dosage form according to the invention. Preferably, the pharmacologically active

ingredient (A) and inorganic salt (B) are intimately homogeneously distributed in the pharmaceutical dosage form so that the pharmaceutical dosage form does not contain any segments where either pharmacologically active ingredient (A) is present in the absence of inorganic salt (B) or where inorganic salt (B) is present in the absence of pharmacologically active ingredient (A).

When the pharmaceutical dosage form is film coated, the inorganic salt (B) is preferably homogeneously distributed in the core of the pharmaceutical dosage form, i.e. the film coating preferably does not contain inorganic salt (B).

The pharmaceutical dosage form according to the invention contains a polyalkylene oxide (C). The active ingredient (A) is present, preferably embedded in a controlled-release matrix comprising said polyalkylene oxide as well as inorganic salt (B).

Preferably, the polyalkylene oxide (C) is selected from polymethylene oxide, polyethylene oxide and polypropylene oxide, or copolymers or mixtures thereof.

The polyalkylene oxide (C) has a weight average molecular weight (M_W), preferably also a viscosity average molecular weight (M_η) of at least 200,000 g/mol or at least 500,000 g/mol, preferably at least 1,000,000 g/mol or at least 2,500,000 g/mol, more preferably in the range of about 1,000,000 g/mol to about 15,000,000 g/mol, and most preferably in the range of about 5,000,000 g/mol to about 10,000,000 g/mol. Suitable methods to determine M_W and M_η are known to a person skilled in the art. M_η is preferably determined by rheological measurements, whereas M_W can be determined by gel permeation chromatography (GPC).

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.-% or 45 to 70 wt.-%, based on the total weight of the pharmaceutical dosage form. The content of the polyalkylene oxide is at least 20 wt.-%, preferably at least 25 wt.-%, more preferably at least 30 wt.-%, still more preferably at least 35 wt.-% and in particular at least 40 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the overall content of polyalkylene oxide (C) is within the range of 25±5 wt.-%. In another preferred embodiment, the overall content of polyalkylene oxide (C) is within the range of 35±15 wt.-%, more 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.-%.

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).

In a preferred embodiment, polyalkylene oxide (C) is homogeneously distributed in the pharmaceutical dosage form according to the invention. Preferably, the pharmacologically active ingredient (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 pharmacologically active ingredient (A) is present in the absence of polyalkylene oxide (C) or where polyalkylene oxide (C) is present in the absence of pharmacologically active ingredient (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, blockcopolymers 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, the relative weight ratio of polyalkylene oxide (C) to inorganic salt (B) is within the range of from 20:1 to 0.1:1, more preferably 15:1 to 0.25:1, still more preferably 10:1 to 0.4:1, yet more preferably 5:1 to 0.5:1, most preferably 3:1 to 0.75:1 and in particular 1.6:1 to 0.85:1. In a preferred embodiment, the content of polyalkylene oxide (C) in the pharmaceutical dosage form exceeds the content of inorganic salt (B). In another preferred embodiment, the content of inorganic salt (B) in the pharmaceutical dosage form exceeds the content of polyalkylene oxide (C).

Preferably, the relative weight ratio of the polyalkylene oxide (C) to the pharmacologically active ingredient (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 (C) to the pharmacologically active ingredient (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.

Besides the pharmacologically active ingredient (A), the inorganic salt (B) and the polyalkylene oxide (C), the pharmaceutical dosage form according to the invention may contain further ingredients, e.g. one or more conventional pharmaceutical excipient(s), e.g. fillers, glidants, binding agents, granulating agents, anti-caking agents, lubricants, flavours, dyes, and/or preservatives.

Preferably, the pharmaceutical dosage form further comprises a plasticizer. The plasticizer improves the processability of the polyalkylene oxide (C) and optionally, also of the inorganic salt (B). 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 (C) 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 (C) 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 been surprisingly found that the surface properties of the extrudate strand can be triggered by the polyalkylene oxide : polyalkylene glycol weight ratio.

Preferably, the pharmaceutical dosage form further comprises an anti-oxidant. Suitable antioxidants include ascorbic acid, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), salts of ascorbic acid, monothioglycerol, phosphorous acid, vitamin C, vitamin E and the derivatives thereof, coniferyl benzoate, nordihydroguajaretic acid, gallus acid esters, sodium bisulfite, particularly preferably butylhydroxytoluene or butylhydroxyanisole and α-tocopherol. The antioxidant is preferably used in quantities of 0.01 to 10 wt.-%, preferably of 0.03 to 5 wt.-%, relative to the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the pharmaceutical dosage form further comprises an acid, preferably citric acid. The amount of acid is preferably in the range of 0.01 to about 20 wt.-%, more preferably in the range of 0.02 to about 10 wt.-%, and most preferably in the range of 0.05 to about 5 wt.-%.

In a preferred embodiment, the pharmaceutical dosage form contains 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.

In a preferred embodiment, the pharmaceutical dosage form further comprises another polymer which is preferably selected from cellulose esters and cellulose ethers, in particular hydroxypropyl methylcellulose (HPMC). The amount of the further polymer, preferably hydroxypropyl methylcellulose, preferably ranges from 0.1 wt.-% to about 30 wt.-%, more

preferably in the range of 1.0 wt.-% to about 20 wt.-%, and most preferably in the range of 2.0 wt.-% to about 15 wt.-%.

In another preferred embodiment, the pharmaceutical dosage form according to the invention does not contain any further polymer besides the polyalkylene oxide (C) and optionally, the polyethylene glycol.

The pharmaceutical dosage form according to the invention is preferably an oral dosage form, particularly a tablet. 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.

Preferably, the pharmaceutical dosage form is monolithic. Preferably, the pharmaceutical dosage form is neither in film form, nor multi-particulate.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is a round tablet. Tablets of this embodiment preferably have a diameter in the range of about 1 mm to about 30 mm, in particular in the range of about 2 mm to about 25 mm, more in particular about 5 mm to about 23 mm, even more in particular about 7 mm to about 13 mm; and a thickness in the range of about 1.0 mm to about 12 mm, in particular in the range of about 2.0 mm to about 10 mm, even more in particular from 3.0 mm to about 9.0 mm, even further in particular from about 4.0 mm to about 8.0 mm.

In another preferred embodiment, the pharmaceutical dosage form according to the invention is an oblong tablet. Tablets of this embodiment preferably have a lengthwise extension (longitudinal extension) of about 1 mm to about 30 mm, in particular in the range of about 2 mm to about 25 mm, more in particular about 5 mm to about 23 mm, even more in particular about 7 mm to about 20 mm; and a thickness in the range of about 1.0 mm to about 12 mm, in particular in the range of about 2.0 mm to about 10 mm, even more in particular from 3.0 mm to about 9.0 mm, even further in particular from about 4.0 mm to about 8.0 mm.

The pharmaceutical dosage form according to the invention has preferably a weight in the range of 0.01 to 1.5 g, more preferably in the range of 0.05 to 1.2 g, still more preferably in the range of 0.1 g to 1.0 g, yet more preferably in the range of 0.2 g to 0.9 g, and most preferably in the range of 0.25 g to 0.8 g.

The pharmaceutical dosage form according to the invention is preferably prepared by thermoforming, preferably by hot-melt 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.

In a preferred embodiment, the pharmaceutical dosage form is prepared by hot melt-extrusion, preferably by means of a twin-screw-extruder. Melt extrusion preferably provides a melt-extruded strand that is preferably cut into monoliths, which are then compressed and 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. Preferably, compression is achieved by means of a die and a punch, preferably from a monolithic mass obtained by melt extrusion. If obtained via melt extrusion, the compressing step is preferably carried out with a monolithic mass exhibiting ambient temperature, that is, a temperature in the range from 20 to 25 °C. The strands obtained by way of extrusion can either be subjected to the compression step as such or can be cut prior to the compression step. This cutting can be performed by usual techniques, for example using rotating knives or compressed air. Alternatively, the shaping can take place as described in EP-A 240 906 by the extrudate being passed between two counter-rotating calender rolls and being shaped directly to tablets. It is of course also possible to subject the extruded strands to the compression step or to the cutting step when still warm, that is more or less immediately after the extrusion step. The extrusion is preferably carried out by means of a twin-screw extruder.

The pharmaceutical dosage form of the invention can optionally be provided, partially or completely, with a conventional coating. The dosage forms of the present invention are preferably film coated with conventional film coating compositions. Particularly preferably, the dosage forms according to the invention are either not coated at all or completely coated, but preferably not partially coated.

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 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 ingredient 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 ingredients 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.

The coating can also be applied e.g. to improve the aesthetic impression and/or the taste of the dosage forms and the ease with which they can be swallowed. Coating the dosage forms of the present invention can also serve other purposes, e.g. improving stability and shelf-life. Suitable coating formulations comprise a film forming polymer such as, for example, polyvinyl alcohol or hydroxypropyl methylcellulose, e.g. hypromellose, a plasticizer such as, for example, a glycol, e.g. propylene glycol or polyethylene glycol, an opacifier, such as, for example, titanium dioxide, and a film smoothener, such as, for example, talc. Suitable coating solvents are water as well as organic solvents. Examples of organic solvents are alcohols, e.g. ethanol or isopropanol, ketones, e.g. acetone, or halogenated hydrocarbons,

e.g. methylene chloride. Optionally, the coating can contain a therapeutically effective amount of one or more active ingredients to provide for an immediate release of said active ingredient (A) and thus for an immediate relief of the symptoms treated by said active ingredient (A). Coated dosage forms of the present invention are preferably prepared by first making the cores and subsequently coating said cores using conventional techniques, such as coating in a coating pan.

According to the invention, the active ingredient (A) is present, preferably embedded in a controlled-release matrix comprising inorganic salt (B) and polyalkylene oxide (C).

Controlled release of an active ingredient from an oral dosage form is known to a person skilled in the art. For the purpose of the specification, controlled release encompasses delayed release, retarded release, sustained release, extended release, prolonged release, and the like.

Controlled or prolonged release is understood according to the invention preferably to mean a release profile in which the pharmacologically active ingredient (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 ingredient 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 ingredient 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 ingredient is released initially, followed by at least one further portion of active ingredient being released subsequently. For the purpose of the specification "prolonged release" preferably means a product in which the rate of release of active ingredient 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.

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 pharmacologically active ingredient (A). Further preferred release profiles R_1 to R_6 are summarized in the table here below [all data in wt.-% of released pharmacologically active ingredient (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 pharmacologically active ingredient (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. 40°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 pharmacologically active ingredient (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, 75 rpm, 37±5 °C, 600 mL simulated intestinal fluid pH 6.8 (phosphate buffer) or pH 4.5. In a preferred embodiment, the rotational speed of the paddle is increased to 100 rpm.

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 releases after 5 h at most 99%, more preferably at most 90%, still more preferably at most 75%, and most preferably at most 60% of the active ingredient (A).

The inorganic salt (B) is preferably hydrophilic, meaning that a matrix comprising inorganic salt (B) and polyalkylene oxide (C) tends to swell upon contact with aqueous fluids following

administration, and preferably results in a viscous, pharmacologically active ingredient release regulating gel layer.

In a preferred embodiment, the matrix comprising the inorganic salt (B) and the polyalkylene oxide (C) contains inorganic salt (B) in such a quantity that under *in vitro* conditions the release of the active ingredient (A) is additionally retarded, and the release profile of the pharmacologically active ingredient (A) from said matrix comprises at least a time interval during which the release follows a zero order kinetics, compared to a thus identical, comparative pharmaceutical dosage form wherein the inorganic salt (B) is substituted with the corresponding amount of hydroxylpropyl methyl cellulose (HPMC) or lactose.

In a particular preferred embodiment,

- the pharmaceutical dosage form is thermoformed, preferably by hot melt-extrusion; and/or
- the pharmaceutical dosage form exhibits a breaking strength of at least 1500 N; and/or
- the pharmaceutical dosage form is adapted for administration once-daily, twice daily or thrice-daily; and/or
- the pharmacologically active ingredients (A) is selected from the group of opioids and opiates; and or
- the content of inorganic salt (B) ranges from 2.0 wt.-% to 50 wt.-%; and/or
- the polyalkylene oxide (C) is selected from polymethylene oxide, polyethylene oxide and polypropylene oxide, or copolymers or mixtures thereof; having a weight average molecular weight (M_W) of at least 500,000 g/mol, more preferably within the range of from 1,000,000 g/mol to 10,000,000 g/mol; and/or
- the content of polyalkylene oxide (C) is at least 30 wt.-%, based on the total weight of the dosage form.

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 ingredient, 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 pharmacologically active ingredient. Corresponding hot substance pharmacologically active ingredients 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 pharmacologically active ingredient (A), preferably no antagonists against psychotropic substances, in particular no antagonists against opioids (A). Antagonists suitable for a given pharmacologically active ingredient (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 pharmacologically active ingredient (A), nor emetics, nor bitter substances.

The pharmaceutical dosage form according to the invention has a breaking strength of at least 500 N.

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 inorganic salt (B) and polyalkylene oxide (C), although their 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 pharmacologically active ingredient (A), inorganic salt (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.

In general, the dosage forms exhibiting the desired properties may be obtained only if, during preparation of the dosage form,

- suitable components
- in suitable amounts

are exposed to

- a sufficient pressure
- at a sufficient temperature
- for a sufficient period of time.

Thus, regardless of the apparatus used, the process protocols must be adapted in order to meet the required criteria. Therefore, the breaking strength is separable from the composition.

The pharmaceutical dosage form according to the invention has a breaking strength of at least 500 N, preferably at least 600 N, more preferably at least 700 N, still more preferably at least 800 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 ingredient (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, 500 N correspond to a gravitational force of more than 50 kg, i.e. the pharmaceutical dosage forms according to the invention can preferably withstand a weight of more than 50 kg without being pulverized.

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 centering 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® HT1 can 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, in direction of extension E_1 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.

In a preferred embodiment the invention relates to a tamper-resistant pharmaceutical dosage form having a retarded release profile, especially a tamper-resistant oral dosage form having a retarded release profile, particularly a tamper-resistant tablet having a retarded release profile comprising at least one pharmaceutically active ingredient (A) (pharmacologically active compound) with potential for abuse.

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.

Preferably, hot-melt extrusion is performed in the absence of additional water.

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.

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.

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 extrusion 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 pharmacologically active ingredient (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 rate 2 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 ingredient, 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 the use of a pharmacologically active ingredient (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 pharmacologically active ingredient (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 pharmacologically active ingredient (A) contained therein.

In this regard, the invention also relates to the use of a pharmacologically active ingredient (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 pharmacologically active ingredient (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 pharmacologically active ingredient (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:

In all examples the dosage forms were tablets assuming a round shape with a diameter of 12 mm.

General procedure

Polyethylene oxide, α-tocopherol, tramadol hydrochloride and all other excipients were weighted and sieved to each other. The powder was mixed and dosed gravimetrically to an extruder. Hot-melt extrusion was performed by means of a twin screw extruder of type Micro 27 GL 40 D (Leistritz, Nürnberg, Germany) that was equipped with a heatable round die having a diameter of 10 mm.

The hot extrudate was cooled on a conveyor belt and the cooled extrusion strand was comminuted to cut pieces. The cut pieces were shaped by means of an excenter press.

The breaking strength of the pharmaceutical dosage forms was measured by means of a Sotax® HT100 at a constant speed of 120 mm/min and/or a Zwick Z 2.5 at a constant speed of 10 mm/min. A tablet was regarded as failing the breaking strength test when during the measurement the force dropped below the threshold value of 25% of the maximum force that was observed during the measurement, regardless of whether the dosage form was fractured into separate pieces or not. All values are given as mean of 3 measurements (Zwick; n = 3) or as a mean of 10 measurements (Sotax, n = 10).

Example I:

Tablets of the following composition containing tramadol were formed:

Excipient	Reference	Variation D	Variation E	Variation F	Variation G
Tramadol-HCl	80.0 mg	80.0 mg	80.0 mg	80.0 mg	80.0 mg
Polyethyleneoxide 7,000,000	365.8 mg	211.0 mg	259.5 mg	259.5 mg	211.0 mg
Polyethylene glycole 6,000	90.0 mg	62.0 mg	76.3 mg	76.3 mg	62.3 mg
Hypromellose 100,000 mPas	60.0 mg	-	-	-	-
α-Tocopherol	1.2 mg	1.2 mg	1.2 mg	1.2 mg	1.2 mg

Citric Acid	3.0 mg	3.0 mg	3.0 mg	3.0 mg	3.0 mg
Sodium carbonate	-	242.8 mg	180.0 mg	90.0 mg	121.4 mg
Pentasodium phosphate	-	-	-	90.0 mg	121.4 mg
Sum	600.0 mg	600.0 mg	600.0 mg	600.0 mg	600.0 mg

For each composition, the *in vitro* release profile of the pharmacologically active ingredient was measured in 600 ml of artificial intestinal juice (pH 6.8, phosphate buffered) at temperature of 37°C with sinker (type 4). The rotation speed of the paddle was adjusted to 75/min. The pharmacologically active ingredient was detected by means of a spectrometric measurement with a wavelength of 271 nm.

According to the preceding table, variation D and E were tested with sodium carbonate. Dissolution curves of the tablets with 30 wt.-% and 40 wt.-% sodium carbonate in comparison to the reference tablets are illustrated in Figure 1. The retardant effect is more pronounced for the formulation with 30 wt.-% sodium carbonate.

Variation F and G were tested with sodium carbonate and pentasodium triphosphate. The dissolution curves of the tablets with 20 wt.-% and 15 wt.-% of each sodium carbonate and pentasodium triphosphate in comparison to the reference are illustrated in Figure 2. Again, the release profile shows a significantly retarded and linear release of the pharmacologically active ingredient. The release profile with the lower content of overall salts shows again the best results.

A comparison of the dissolution in acidic medium with the dissolution curves of the tablets with 30 wt.-% sodium carbonate and 15 wt.-% of each sodium carbonate and pentasodium triphosphate in comparison to the reference tablets in illustrated in Figure 3. The release profile of the 4 curves is comparable and hence does not depend on the pH-value.

Example II:

Tablets of the following composition containing oxymorphone were formed:

Excipient	Per tablet [mg]	[wt.-%]
Oxymorphone HCL anhydrous	80.0	11.1
Polyethylene oxide 7,000,000	337.3	46.9
Sodium Carbonate	216.0	30.0
Macrogol 6000	81.7	11.3
α-Tocopherol	1.4	0.2
Citric Acid anhydrous	3.6	0.5
Sum	720.0	

The *in vitro* release profile of the pharmacologically active ingredient was measured in 900 ml acidic medium (pH 1.2) and in 900 mL acetate buffered medium (pH 4.5), both at temperature of 37°C with sinker (type 4). The rotation speed of the paddle was adjusted to 50/min. The pharmacologically active ingredient was detected by means of a spectrometric measurement with a wavelength of 271 nm.

According to the preceding table, the formulation was made with oxymorphone instead of tramadol. As illustrated in Figure 4 the release profile shows a retarded and linear release of the pharmacologically active ingredient. In the acidic medium the release was accelerated in comparison to the release in the acetate buffered medium (pH 4.5).

Example III:

Tablets of the following composition were formed:

Excipient	Per tablet [mg]	[wt.-%]
Oxymorphone HCL anhydrous	80.0	11.1
Polyethylene oxide 7,000,000	337.3	46.9
Sodium Carbonate	108.0	15.0
Pentasodium phosphate	108.0	15.0
Macrogol 6000	81.7	11.3
α-Tocopherol	1.4	0.2
Citric Acid anhydrous	3.6	0.5
Sum	720.0	

According to Example II, the *in vitro* release profile of the pharmacologically active ingredient was measured in 900 ml acidic medium (pH 1.2) and in 900 mL acetate buffered medium (pH 4.5).

According to the preceding table the formulation was made with oxymorphone instead of tramadol. Moreover the formulation contains sodium carbonate and pentasodium triphosphate each 15 wt.-%. As illustrated in Figure 5, the release profile shows a retarded and linear release of the pharmacologically active ingredient. In the acidic medium the release was accelerated in comparison to the release in the acetate buffered medium (pH 4.5).

Patent claims:

1. A pharmaceutical dosage form exhibiting a breaking strength of at least 500 N and containing

   - a pharmacologically active ingredient (A);
   - an inorganic salt (B), wherein the content of the inorganic salt (B) is from 5 to 70 wt.-%, based on the total weight of the dosage form;
   - a polyalkylene oxide (C) having a weight average molecular weight of at least 200,000 g/mol, wherein the content of the polyalkylene oxide (C) is at least 30 wt.-%, based on the total weight of the dosage form;

   wherein the pharmacologically active ingredient (A) is embedded in a controlled release matrix comprising the inorganic salt (B) and the polyalkylene oxide (C), and

   wherein, under *in vitro* conditions, the release profile of the pharmacologically active ingredient (A) from said matrix comprises at least a time interval during which the release follows a zero order kinetics.

2. The pharmaceutical dosage form according to claim 1, wherein the time interval during which the release follows zero order kinetics is at least 20% of the total release time needed for a release of 95 wt.-% of the pharmacologically active ingredient (A) that was originally contained.

3. The pharmaceutical dosage form according to claim 1 or 2 wherein the release profile follows zero order kinetics within the range of from pH 1 to pH 7

4. The pharmaceutical dosage form according to claim 1 or 2, which is prepared by hot-melt extrusion.

5. The pharmaceutical dosage form according to any of the preceding claims, which is a tablet.

6. The pharmaceutical dosage form according to one of the preceding claims, wherein the pharmacologically active ingredient (A) is an opioid selected from the group consisting of tapentadol, oxymorphone, hydromorphone, oxycodone, morphine and the physiologically acceptable salts thereof.

7. The pharmaceutical dosage form according to claim 6, wherein the inorganic salt (B) contains at least one component selected from the group consisting of alkali carbonates, earth alkali carbonates, alkali hydrogen carbonates, earth alkali hydrogen carbonates, alkali phosphates, earth alkali phosphates, alkali hydrogen phosphates, earth alkali hydrogen phosphates, alkali dihydrogen phosphates, earth alkali dihydrogen phosphates and pentaalkali tri(poly)phosphates.

8. The pharmaceutical dosage form according to claim 7, wherein the inorganic salt (B) is sodium carbonate or pentasodium triphosphate or a mixture thereof.

9. The pharmaceutical dosage form according to claim 8, wherein the amount of the inorganic salt (B) in the pharmaceutical dosage form is within the range of from 25 to 45 wt.-%, based on the total weight of the pharmaceutical dosage form.

10. The pharmaceutical dosage form according to any of the proceeding claims, wherein the polyalkylene oxide (C) has a molecular weight of at least 0.5 million g/mol.

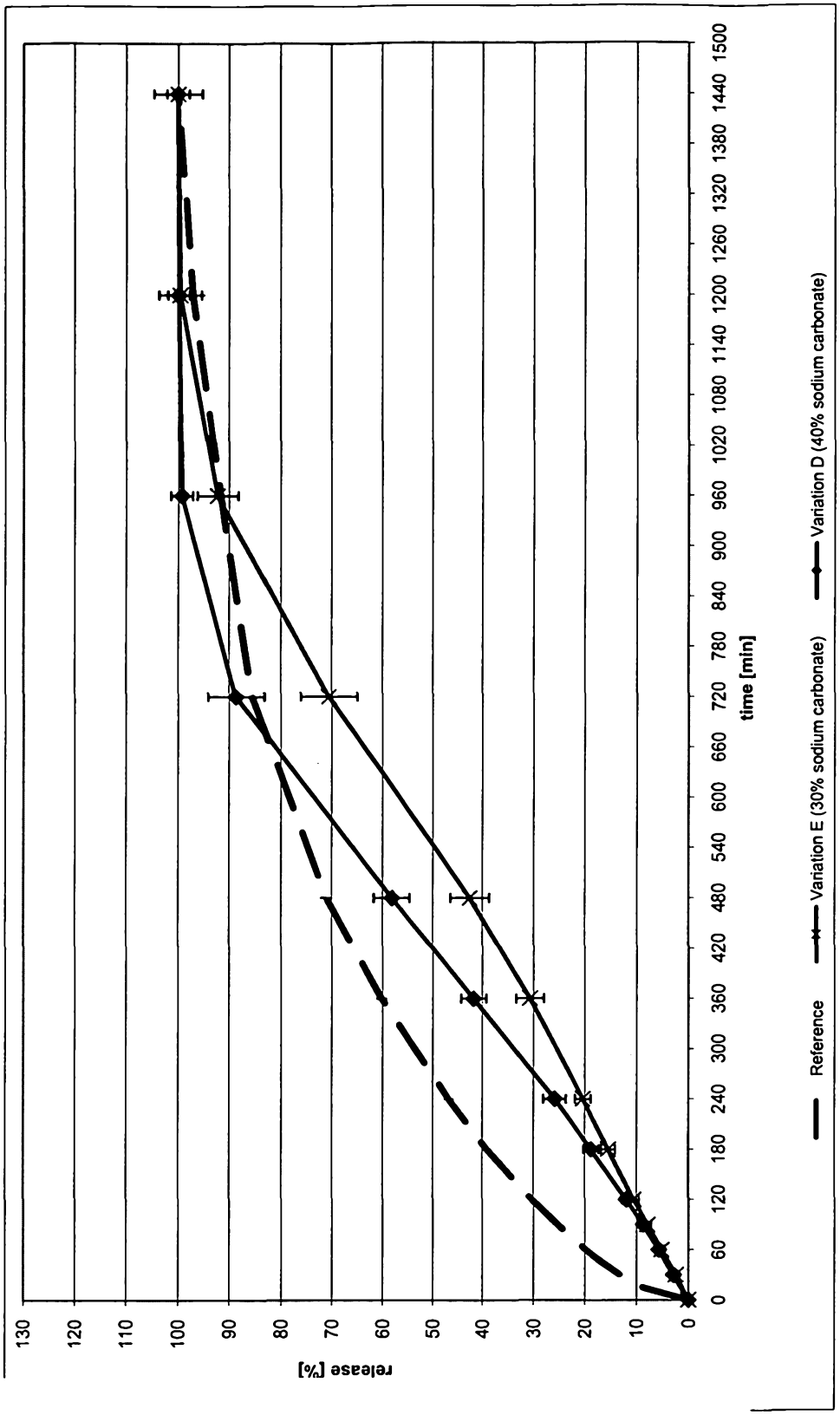
11. The pharmaceutical dosage form according to claim 10, wherein the polyalkylene oxide (C) has a molecular weight of at least 1 million g/mol.

12. The pharmaceutical dosage form according to claim 11, wherein the polyalkylene oxide (C) has a molecular weight within the range of from 1 to 15 million g/mol.

13. The pharmaceutical dosage form according to any of the proceeding claims, which comprises polyalkylenglycole.

14. The pharmaceutical dosage form according to claim 13, wherein the polyalkylenglycole has a molecular weight of at least 1000 g/mol.

Figure 1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480
540
600
660
720
780
840
900
960
1020
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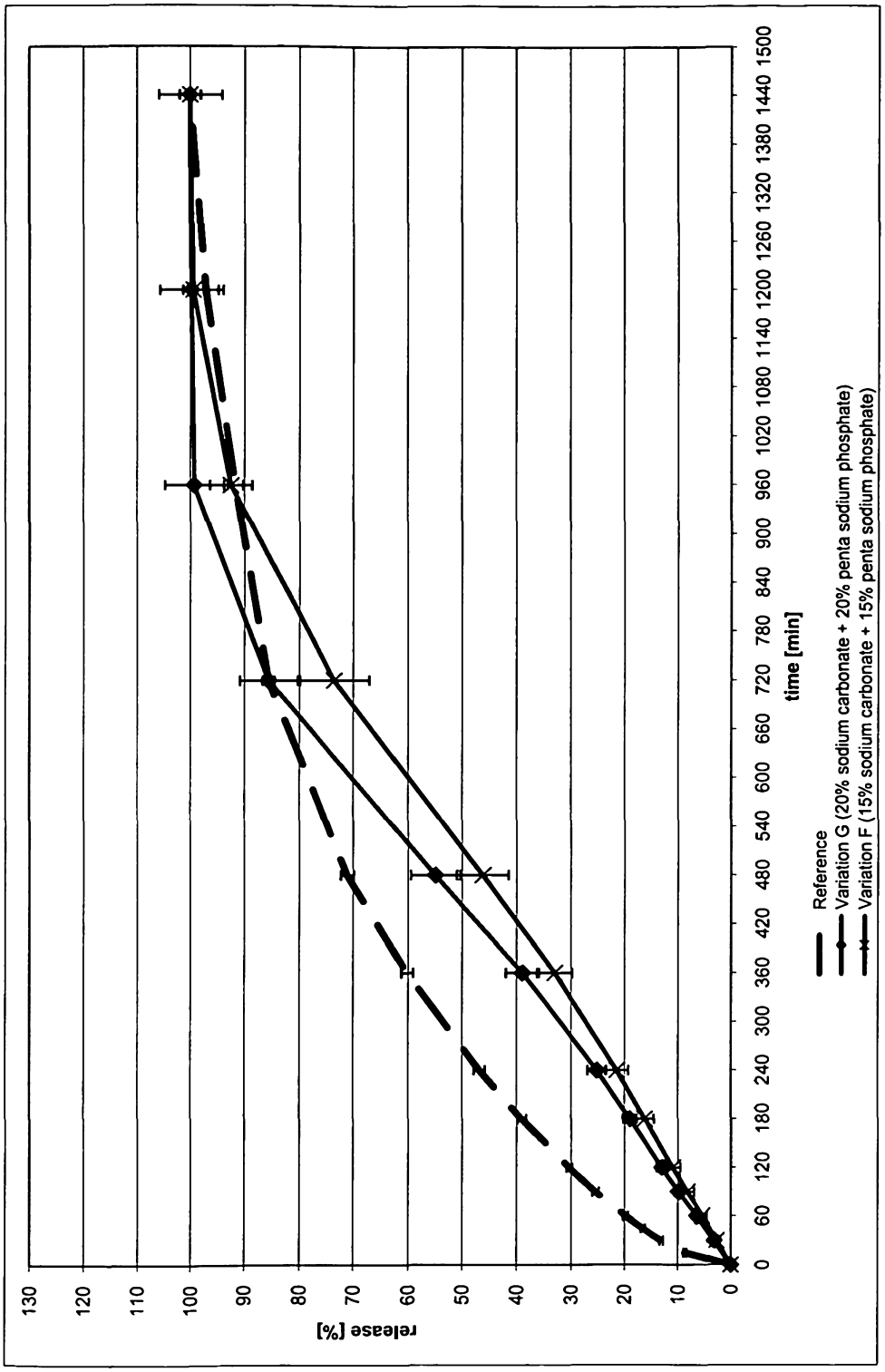
1500
Reference
Variation E (30% sodium carbonate)
Variation D (40% sodium carbonate)

Figure 2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40
30
20
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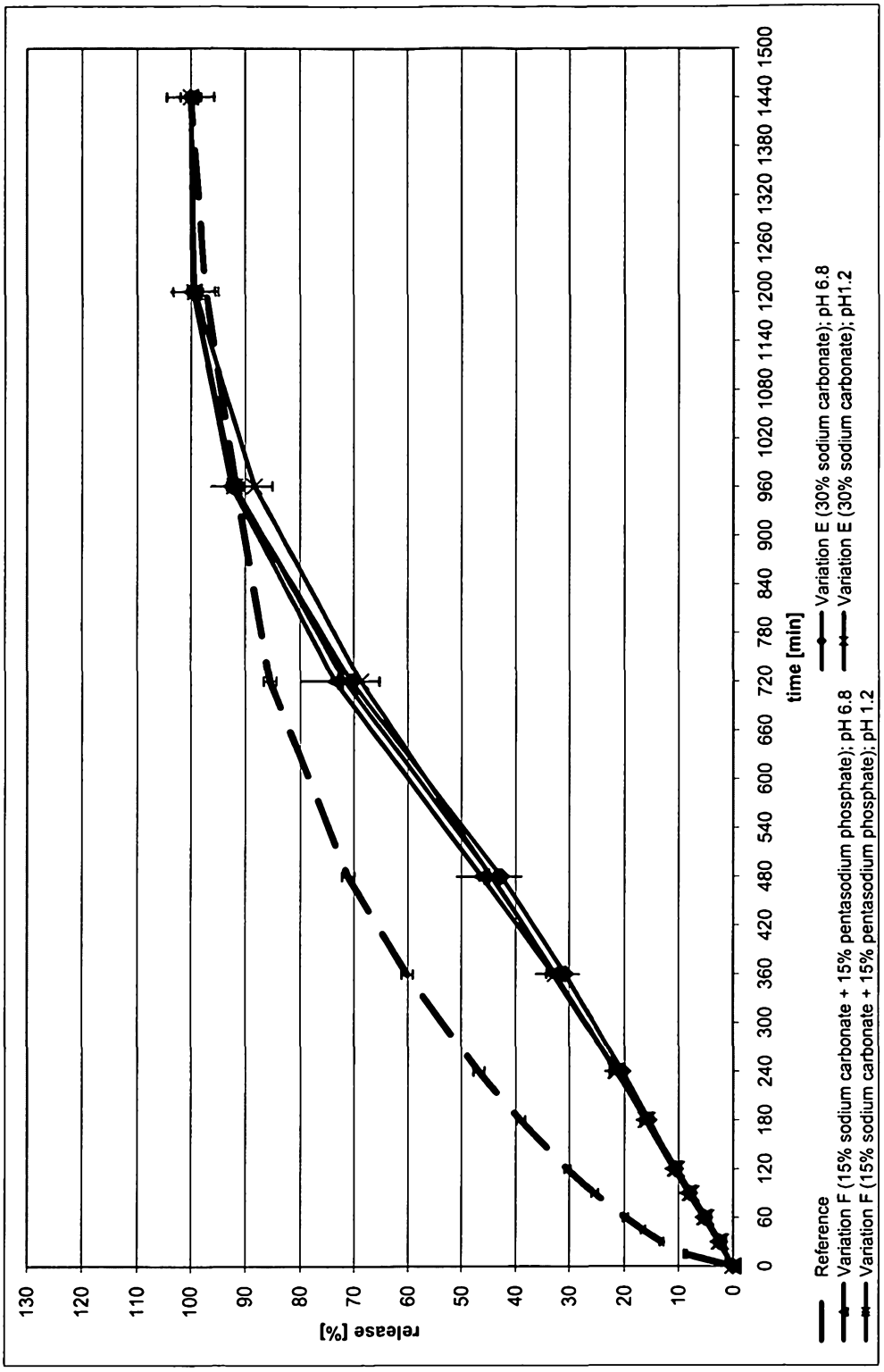
0
0 60 120 180 240 300 360 420 480 540 600 660 720 780 840 900 960 1020 1080 1140 1200 1260 1320 1380 1440 1500
time [min]
Reference
Variation G (20% sodium carbonate + 20% penta sodium phosphate)
Variation F (15% sodium carbonate + 15% penta sodium phosphate)

Figure 3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20
30
40
50
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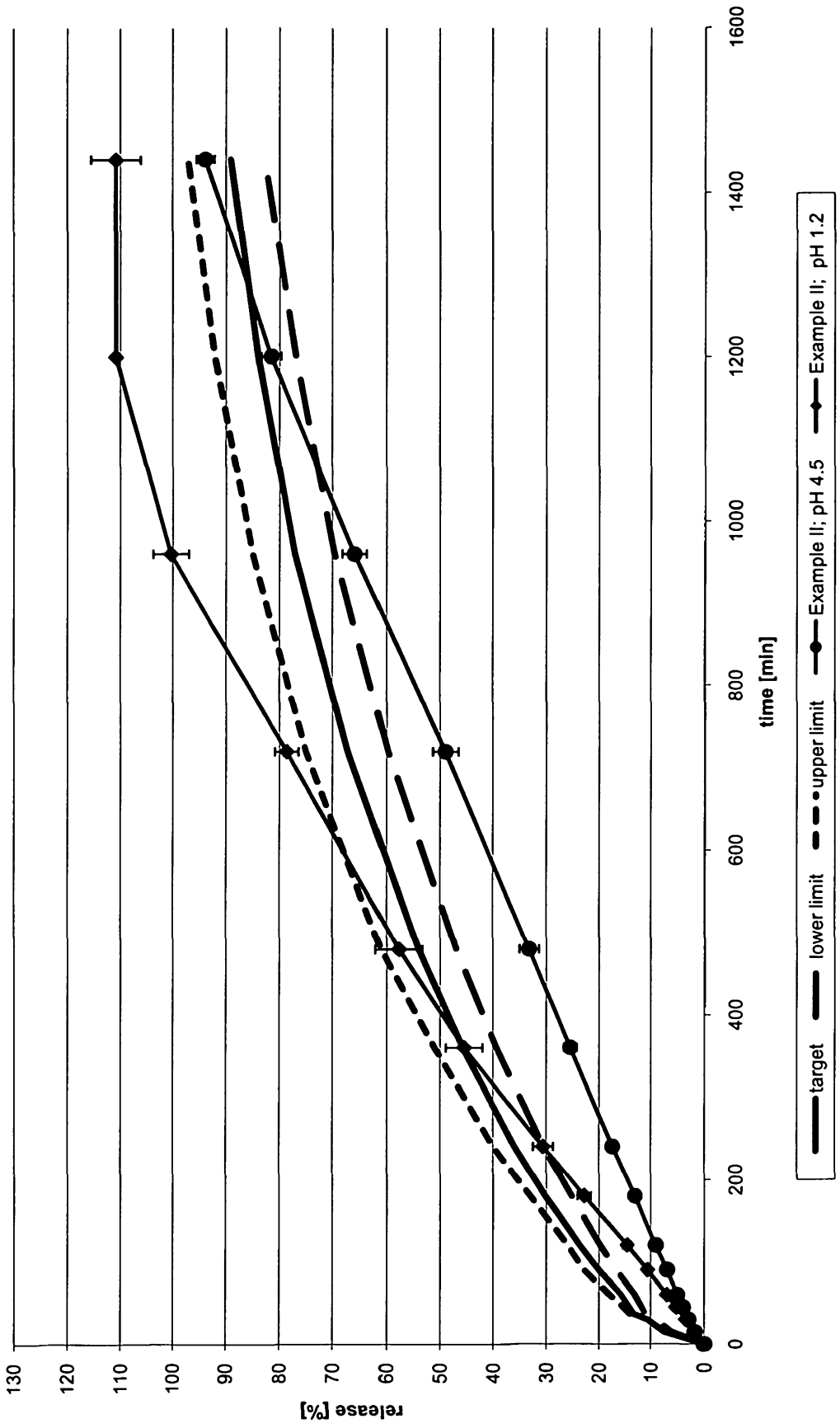
80
90
100
110
120
130
time [min]
0 60 120 180 240 300 360 420 480 540 600 660 720 780 840 900 960 1020 1080 1140 1200 1260 1320 1380 1440 1500
Reference
Variation F (15% sodium carbonate + 15% pentasodium phosphate); pH 6.8
Variation F (15% sodium carbonate + 15% pentasodium phosphate); pH 1.2
Variation E (30% sodium carbonate); pH 6.8
Variation E (30% sodium carbonate); pH1.2

Figure 4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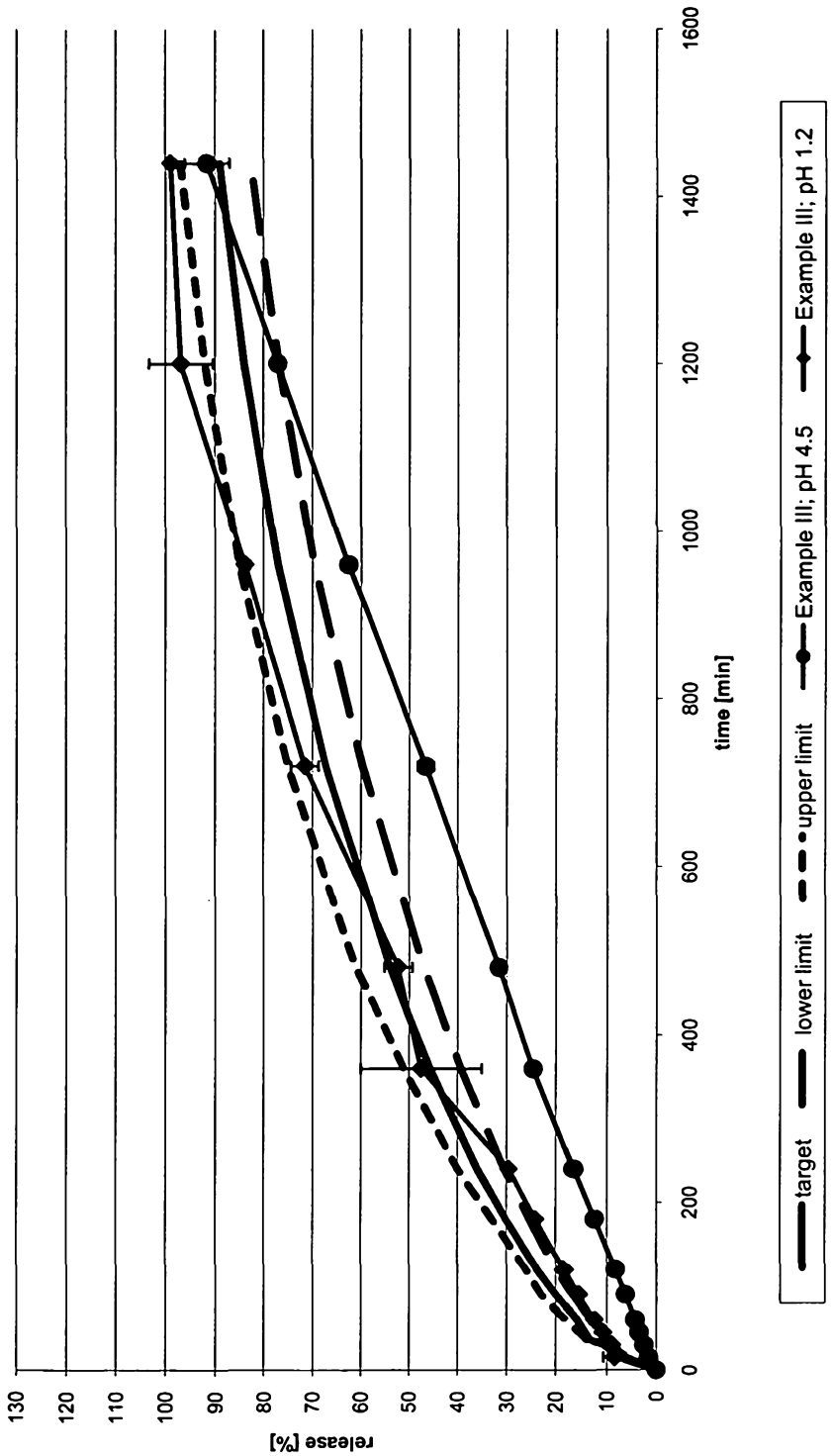
target
lower limit
upper limit
Example II; pH 4.5
Example II; pH 1.2

Figure 5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target
lower limit
upper limit
Example III; pH 4.5
Example III; pH 1.2