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(54) Title: TAMPER-RESISTANT TABLET PROVIDING IMMEDIATE DRUG RELEASE

(57) Abstract: The invention relates to a tamper-resistant tablet comprising a matrix material in an amount of more than one third of the total weight of the tablet; and a plurality of coated particulates in an amount of less than two thirds of the total weight of the tablet; wherein said particulates comprise a pharmacologically active compound and a physiologically acceptable polymer, preferably a polyalkylene oxide; and form a discontinuous phase within the matrix material; which preferably provides under in vitro conditions immediate release of the pharmacologically active compound in accordance with Ph. Eur.

Tamper-resistant tablet providing immediate drug release

FIELD OF THE INVENTION

The invention relates to tamper-resistant tablets comprising a matrix material and a plurality of coated particulates which comprise a pharmacologically active compound and form a discontinuous phase within the matrix material, preferably providing under *in vitro* conditions immediate release of the pharmacologically active compound.

BACKGROUND OF THE INVENTION

A large number of pharmacologically active substances have a potential for being abused or misused, i.e. they can be used to produce effects which are not consistent with their intended use. Thus, e.g. opioids which exhibit an excellent efficacy in controlling severe to extremely severe pain, are frequently abused to induce euphoric states similar to being intoxicated. In particular, active substances which have a psychotropic effect are abused accordingly.

To enable abuse, the corresponding dosage forms, such as tablets or capsules are crushed, for example ground by the abuser, the active substance is extracted from the thus obtained powder using a preferably aqueous liquid and after being optionally filtered through cotton wool or cellulose wadding, the resultant solution is administered parenterally, in particular intravenously. This type of dosage results in an even faster diffusion of the active substance compared to the oral abuse, with the result desired by the abuser, namely the kick. This kick or these intoxication-like, euphoric states are also reached if the powdered dosage form is administered nasally, i.e. is sniffed.

Various concepts for the avoidance of drug abuse have been developed.

It has been proposed to incorporate in dosage forms aversive agents and/or antagonists in a manner so that they only produce their aversive and/or antagonizing effects when the dosage forms are tampered with. However, the presence of such aversive agents is principally not desirable and there is a need to provide sufficient tamper-resistance without relying on aversive agents and/or antagonists.

Another concept to prevent abuse 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. Thus, the pulverization, necessary for abuse, of the dosage forms by the means usually available to a potential abuser is prevented or at least complicated.

Such pharmaceutical dosage forms are useful for avoiding drug abuse of the pharmacologically active compound contained therein, as they may not be powdered by conventional means and thus, cannot be administered in powdered form, e.g. nasally. The mechanical properties, particularly the high breaking strength of these pharmaceutical dosage forms renders them tamper-resistant. In the context of such tamper-resistant pharmaceutical dosage forms it can be referred to, e.g., WO 2005/016313, WO 2005/016314, WO 2005/063214, WO 2005/102286, WO 2006/002883, WO 2006/002884, WO 2006/002886, WO 2006/082097, WO 2006/082099, and WO2009/092601.

These dosage forms secured against abuse are distinguished by a controlled, preferably retarded release of the active substance which has abuse potential. However, a rapid release of the active substance is necessary for numerous therapeutic applications, for example pain relief using active substances with abuse potential.

WO 2010/140007 discloses dosage forms comprising melt-extruded uncoated particulates comprising a drug, wherein said melt-extruded particulates are present as a discontinuous phase in a matrix. The dosage forms provide prolonged release of the drug.

WO 2008/107149 discloses multiparticulate dosage forms with impeded abuse containing, one or more active substances having abuse potential, at least one synthetic or natural polymer, and at least one disintegrant, with the individual particles of the tablet having a breaking strength of at least 500 N and a release of the active substance of at least 75% after 45 minutes. The exemplified capsules provide rapid release of the pharmacologically active compound.

US 2010/0092553 and US 2007/224129 A1 disclose solid multiparticulate oral pharmaceutical forms whose composition and structure make it possible to avoid misuse. The microparticles have an extremely thick coating layer which assures the modified release of the drug and simultaneously imparts crushing resistance to the coated microparticles so as to avoid misuse.

WO 2008/033523 discloses a pharmaceutical composition that may include a granulate which may at least include one active pharmaceutical ingredient susceptible to abuse. The particle contains both an alcohol soluble and alcohol insoluble and at leasts partially water soluble material. Both materials are granulated in the presence of alcohol and water. The granulate may also include a coating on the granulate exhibiting crush resistance. Material deposition on the granule is performed using an alcohol based solvent.

The properties of capsules, however, are not satisfactory in every respect, e.g. with respect to disintegration time, patient compliance (e.g. swallowability) and ease of manufacture. Further, capsules frequently contain gelatine thus causing the risk of bovine spongiform encephalopathy (BSE, or TSE). As far as tamper-resistant dosage forms are concerned, capsules are disadvantageous as they can typically be opened easily thereby releasing the ingredients in powdery or particulate form without requiring any mechanical impact. If components of different type are contained in a capsule, e.g. drug-containing particles besides drug-free particles, a potential abuser might be able to visually distinguish the intact, undisrupted components of different type (e.g. according to their color, size or other macroscopic properties) allowing for manual separation.

The properties of these tamper-resistant dosage forms, however, are not satisfactory in every respect. There is a need for tamper-resistant dosage forms that possess crush resistance and release the pharmacologically active compound as quick as possible (immediate release), i.e. should show a gradual increase reaching 85% to 100% at about 30 to 45 minutes or earlier. The dosage form should advantageously be of a shape, size and weight that can be taken orally with ease. Of course, the dosage form should also be easy to make in a cost effective manner. When trying to tamper the dosage form in order to prepare a formulation suitable for abuse by intravenous administration, the liquid part of the formulation that can be separated from the remainder by means of a syringe should be as less as possible, e.g. should contain not more than 20 wt.-% of the pharmacologically active compound originally contained in the dosage form.

The manufacturing of functionally coated microparticles or granules, however, is not satisfactory with respect to the excessive manufacturing effort by applying the film-coating in an organic spraying procedure, which needs extensive measure to prevent vapor explosions. From an environmental and toxicological perspective the use of organic solvents is further undesirable. Furthermore, applying a functional film coat in general requires high efforts to assure the integrity of the functional barrier and is therefore a production step generating high manufacturing cost.

It is an object according to the invention to provide tamper-resistant pharmaceutical dosage forms that provide rapid release of the pharmacologically active compound and that have advantages compared to the tamper-resistant pharmaceutical dosage forms of the prior art.

This object has been achieved by the patent claims.

SUMMARY OF THE INVENTION

The invention relates to a tamper-resistant tablet, preferably for oral administration, comprising

(i) a matrix material in an amount of more than one third of the total weight of the tablet; and

(ii) a plurality of coated particulates in an amount of less than two thirds of the total weight of the tablet; wherein said particulates comprise a pharmacologically active compound and a physiologically acceptable polymer, preferably a polyalkylene oxide; and form a discontinuous phase within the matrix material;

which preferably provides under *in vitro* conditions immediate release of the pharmacologically active compound in accordance with Ph. Eur.

It has been surprisingly found that the *in vitro* release profile of tamper-resistant dosage forms can be accelerated by embedding particulates containing the pharmacologically active compound in a matrix material and increasing the relative weight ratio of the matrix material to the coated particulates.

Further, it has been surprisingly found that mixtures of matrix material, optionally in pre-compacted or pre-granulated form, can be mixed with the coated particulates and subsequently be compacted to tablets which in turn exhibit excellent, i.e. accelerated disintegration times and *in vitro* release characteristics.

Still further, it has been surprisingly found that oral dosage forms can be designed that provide the best compromise between tamper-resistance, disintegration time and drug release, drug load, processability (especially tablettability) and patient compliance.

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In particular, it has been surprisingly found that disintegration and drug release can be accelerated when providing the particulates with a coating, preferably with a coating material comprising a water-soluble polymer. It has been unexpectedly found that the dissolution of said coating does not additionally impede disintegration and drug release, respectively, but causes a significant acceleration thereof.

In one aspect there is provided a tamper-resistant tablet comprising

(i) a matrix material in an amount of more than one third of the total weight of the tablet; and

(ii) a plurality of coated particulates in an amount of less than two thirds of the total weight of the tablet; wherein said particulates comprise a pharmacologically active compound and a physiologically acceptable polymer; and form a discontinuous phase within the matrix material;

wherein

under physiological conditions the tablet has released after 30 minutes at least 70% of the pharmacologically active compound originally contained in the tablet; and

the particulates are coated with a coating material comprising a water-soluble polymer; and

the pharmacologically active compound is an opioid; and

the content of the polymer is at least 25 wt.-%, based on the total weight of a particulate; and

the water-soluble polymer is selected from the group consisting of cellulose esters, cellulose ethers, poly(meth)acrylates, vinyl polymers, and natural film formers.

DETAILED DESCRIPTION OF THE INVENTION

Figure 1 schematically illustrates a preferred embodiment of the tablets according to the invention.

Figure 2 schematically illustrates another preferred embodiment of the tablets according to the invention.

Figure 3 shows in vitro release profiles of different tablets according to the invention having different compositions and particulate sizes.

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Figure 4 shows in vitro release profiles of different tablets according to the invention having different compositions.

Figure 5 illustrates the behavior of the particulates contained in the tablets according to the invention when being subjected to a breaking strength test, in particular their deformability.

Figure 6 illustrates the behavior of conventional particulates when being subjected to a breaking strength test.

Figure 7 shows the distance-force-diagram obtained by measuring the mechanical properties of conventional particulates.

Figure 8 shows the distance-force-diagram obtained by measuring the mechanical properties of particulates according to the invention.

Figure 9 shows the distance-force-diagram obtained by measuring the mechanical properties of particulates according to the invention.

As used herein, the term "tablet" refers to a pharmaceutical entity that is comprised of a pharmacologically active compound and which is actually administered to, or taken by, a patient. It may be compressed or molded in its manufacture, and it may be of almost any size, shape, weight, and color. Most tablets are intended to be swallowed whole and accordingly, preferred tablets according to the invention are designed for oral administration. However, alternatively tablets may be dissolved in the mouth, chewed, or dissolved in liquid before swallowing, and some may be placed in a body cavity. Thus, the tablet according to the invention may alternatively be adapted for buccal, lingual, rectal or vaginal administration. Implants are also possible.

The tablet according to the invention preferably can be regarded as a MUPS formulation (multiple unit pellet system). In a preferred embodiment, the tablet according to the invention is monolithic. In another preferred embodiment, the tablet according to the invention is not monolithic. In this regard, monolithic preferably means that the tablet is formed or composed of material without joints or seams or consists of or constitutes a single unit.

Preferably, the tablet according to the invention contains all ingredients in a dense compact unit which in comparison to capsules has a comparatively high density.

The tablets according to the invention comprise subunits having different morphology and properties, namely drug-containing particulates and matrix material, wherein the coated particulates form a discontinuous phase within the matrix material. The coated particulates typically have mechanical properties that differ from the mechanical properties of the matrix material. Preferably, the coated particulates have a higher mechanical strength than the matrix material. The coated particulates within the tablets according to the invention can be visualized by conventional means such as solid state nuclear magnetic resonance spectroscopy, raster electron microscopy, terahertz spectroscopy and the like.

An advantage of the tablets according to the invention is that the same particulates may be mixed with matrix material in different amounts to thereby produce tablets of different strengths.

The tablet according to the invention has preferably a total 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 0.3 g to 0.8 g. In a preferred embodiment, the total tablet weight is within the range of

500±450 mg, more preferably 500±300 mg, still more preferably 500±200 mg, yet more preferably 500±150 mg, most preferably 500±100 mg, and in particular 500±50 mg.

It has been surprisingly found that the total tablet weight, which is a function of the total size of the tablet, can be optimized in order to provide the best compromise between tamper-resistance, disintegration time and drug release, drug load, processability (especially tablettability) and patient compliance.

In a preferred embodiment, the tablet 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 tablet 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; a width 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.

The tablets according to the invention can optionally be provided, partially or completely, with a conventional coating. The tablets according to the invention are preferably film coated with conventional film coating compositions. 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 methyl-cellulose (MC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), sodium carboxymethylcellulose (Na-CMC), poly(meth)-acrylates, such as aminoalkylmethacrylate copolymers, methacrylic acid methylmethacrylate copolymers, methacrylic acid methylmethacrylate copolymers; vinyl polymers, such as polyvinylpyrrolidone, polyvinyl alcohol, polyvinylacetate; and natural film formers.

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 tablet according to the invention passes through the stomach undissolved and the active compound is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5.

The coating can also be applied e.g. to improve the aesthetic impression and/or the taste of the tablets and the ease with which they can be swallowed. Coating the tablets according to the 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. Coated tablets according to the invention are preferably prepared by first making the cores and subsequently coating said cores using conventional techniques, such as coating in a coating pan.

As used herein, the term "tamper-resistant" refers to tablets that are resistant to conversion into a form suitable for misuse or abuse, particular for nasal and/or intravenous administration, by conventional means such as grinding in a mortar or crushing by means of a hammer. In this regard, the tablets as such may be crushable by conventional means. However, the coated particulates contained in the tablets according to the invention exhibit mechanical properties such that they cannot be pulverized by conventional means any further. As the coated particulates are of macroscopic size and contain the pharmacologically active compound, they cannot be administered nasally thereby rendering the tablets tamper-resistant. Preferably, when trying to tamper the dosage form in order to prepare a formulation suitable for abuse by intravenous administration, the liquid part of the formulation that can be separated from the remainder by means of a syringe is as less as possible, preferably it contains not more than 20 wt.-%, more preferably not more than 15 wt.-%, still more preferably not more than 10 wt.-%, and most preferably not more than 5 wt.-% of the originally contained pharmacologically active compound. Preferably, this property is tested by (i) dispensing a tablet that is either intact or has been manually comminuted by means of two spoons in 5 ml of purified water, (ii) heating the liquid up to its boiling point, (iii) boiling the liquid in a covered vessel for 5 min without the addition of further purified water, (iv) drawing up the hot liquid into a syringe (needle 21G equipped with a cigarette filter), (v) determining the amount of the pharmacologically active compound contained in the liquid within the syringe.

Further, when trying to disrupt the tablets by means of a hammer or mortar, the coated particulates may also, depending on the circumstances, tend to adhere to one another thereby forming aggregates and agglomerates, respectively, which are larger in size than the untreated coated particulates.

The subjects to which the tablets according to the invention can be administered are not particularly limited. Preferably, the subjects are animals, more preferably human beings.

In the tablets according to the invention, the coated particulates are incorporated into a matrix material. From a macroscopic perspective, the matrix material preferably forms a continuous phase in which the coated particulates are embedded as discontinuous phase.

Preferably, the matrix material is a homogenous coherent mass, preferably a homogeneous mixture of solid constituents, in which the coated particulates are embedded thereby spatially separating the coated particulates from one another. While it is possible that the surfaces of coated particulates are in contact or at least in very close proximity with one another, the plurality of coated particulates preferably cannot be regarded as a single continuous coherent mass within the tablet.

In other words, the tablet according to the invention comprises the coated particulates as volume element(s) of a first type in which the pharmacologically active compound and the physiologically acceptable polymer, preferably the polyalkylene oxide are contained, preferably homogeneously, and the matrix material as volume element of a second type differing from the material that forms the coated particulates, preferably containing neither pharmacologically active compound nor physiologically acceptable polymer, preferably no polyalkylene oxide, but optionally polyethylene glycol which differs from polyethylene oxide in its molecular weight.

A purpose of the matrix material in the tablet according to the invention is to ensure rapid disintegration and subsequent release of the pharmacologically active compound from the disintegrated tablets, i.e. from the coated particulates. Thus, the matrix material preferably does not contain any excipient that might have a retardant effect on disintegration and drug release, respectively. Thus, the matrix material preferably does not contain any polymer that is typically employed as matrix material in prolonged release formulations.

Figure 1 schematically illustrates a preferred embodiment of the tablet according to the invention. Tablet (1) contains a plurality of coated particulates (2) having core (2a) and coating (2b) that form a discontinuous phase within matrix material (3) which in turn forms a continuous phase.

The tamper-resistant tablet according to the invention comprises the matrix material in an amount of more than one third of the total weight of the tablet.

It has been surprisingly found that the content of the matrix material in the tablet can be optimized in order to provide the best compromise between tamper-resistance, disintegration time and drug release, drug load, processability (especially tablettability) and patient compliance.

Preferably, the content of the matrix material is at least 35 wt.-%, at least 37.5 wt.-% or at least 40 wt.-%; more preferably at least 42.5 wt.-%, at least 45 wt.-%, at least 47.5 wt.-% or at least 50 wt.-%; still more preferably at least 52.5 wt.-%, at least 55 wt.-%, at least 57.5 wt.-% or at least 60 wt.-%; yet more preferably at least 62.5 wt.-%, at least 65 wt.-%, at least 67.5 wt.-% or at least 60 wt.-%; most preferably at least 72.5 wt.-%, at least 75 wt.-%, at least 77.5 wt.-% or at least 70 wt.-%; and in particular at least 82.5 wt.-%, at least 85 wt.-%, at least 87.5 wt.-% or at least 90 wt.-%; based on the total weight of the tablet.

Preferably, the content of the matrix material is at most 90 wt.-%, at most 87.5 wt.-%, at most 85 wt.-%, or at most 82.5 wt.-%; more preferably at most 80 wt.-%, at most 77.5 wt.-%, at most 75 wt.-% or at most 72.5 wt.-%; still more preferably at most 70 wt.-%, at most 67.5 wt.-%, at most 65 wt.-% or at most 62.5 wt.-%; yet more preferably at most 60 wt.-%, at most 57.5 wt.-%, at most 55 wt.-% or at most 52.5 wt.-%; most preferably at most 50 wt.-%, at most 47.5 wt.-%, at most 45 wt.-% or at most 42.5 wt.-%; and in particular at most 40 wt.-%, at most 37.5 wt.-%, or at most 35 wt.-%; based on the total weight of the tablet.

In a preferred embodiment, the content of the matrix material is within the range of 40±5 wt.-%, more preferably 40±2.5 wt.-%, based on the total weight of the tablet. In another preferred embodiment, the content of the matrix material is within the range of 45±10 wt.-%, more preferably 45±7.5 wt.-%, still more preferably 45±5 wt.-%, and most preferably 45±2.5 wt.-%, based on the total weight of the tablet. In still another preferred embodiment, the content of the matrix material is within the range of 50±10 wt.-%, more preferably 50±7.5 wt.-%, still more preferably 50±5 wt.-%, and most preferably 50±2.5 wt.-%, based on the total weight of the tablet. In yet another preferred embodiment, the content of the matrix material is within the range of 55±10 wt.-%, more preferably 55±7.5 wt.-%, still more preferably 55±5 wt.-%, and most preferably 55±2.5 wt.-%, based on the total weight of the tablet.

Preferably, the matrix material is a mixture, preferably a homogeneous mixture of at least two different constituents, more preferably of at least three different constituents. In a preferred embodiment, all constituents of the matrix material are homogeneously distributed in the continuous phase that is formed by the matrix material.

In a preferred embodiment, the mixture of all constituents of the matrix material is blended and employed as a powder, i.e. in non-pre-compacted form, subsequently mixed with the particulates that contain the pharmacologically active compound and the polyalkylene oxide, and then compressed into tablets. Tablets having acceptance values between about 5 and 6 according to Ph. Eur. 2.9.40 "Uniformity of Dosage Units" (UDU) can be obtained when properly adjusting the tablet press. Vibrations should be avoided to a maximal extent (e.g. by decoupling of hopper and tablet press) and clearance of equipment parts should be as small as possible. For example, on a rotary tablet press IMA S250 plus with 26 stations, the following parameters are suitable: round punches 10 mm diameter, radius of curvature 8mm without debossing; fill curve 13 mm; tablet weight 500 mg; speed: 13700 - 13800 tablets per hour; pre compression force 4.7 kN; main compression force 6.7 kN and 8.7 kN; fill depth 14.5 mm and 15 mm; height of tablet bar (pre compression): 3.5 mm; height of tablet bar (main compression): 3.3 mm and 3.1 mm; revolution speed of feeder (Filomat): 40 rmp.

In another preferred embodiment, the matrix material is also provided in particulate form, i.e. in the course of the manufacture of the tablets according to the invention, the constituents of the matrix material are preferably processed into particulates, subsequently mixed with the coated particulates that contain the pharmacologically active compound and the physiologically acceptable polymer, preferably the polyalkylene oxide, and then compressed into the tablets.

Preferably, the average size of the particulates of the matrix material is within the range of ±60%, more preferably ±50%, still more preferably ±40%, yet more preferably ±30%, most preferably ±20%, and in particular ±10% of the average size of the coated particulates that contain the pharmacologically active compound and the physiologically acceptable polymer, preferably the polyalkylene oxide.

It has been surprisingly found that when proceeding this way, segregation phenomena upon blending the coated particulates with the matrix material in particulate form can be reduced or even completely suppressed, thereby substantially improving the content uniformity of the tablets according to the invention.

This is particularly surprising, as the larger the particulates are which are to be mixed and compressed to tablets, the more difficult it typically is to satisfy content uniformity requirements. Compared to conventional tablets, the tablets according to the invention are manufactured from comparatively large coated particulates and optionally, also from comparatively large pre-compacted particulates of matrix material. Preferably, the AV (acceptance value) concerning the content uniformity of the tablets according to the invention is at most 15, more preferably at most 14, still more preferably at most 13, yet more preferably at most 12, even more preferably at most 11, most preferably at most 10 and in particular at most 9. Methods to determine the AV are known to the skilled artisan. Preferably, the AV is determined in accordance with Eur. Ph.

This preferred embodiment of the tablets according to the invention is schematically illustrated in Figure 2. Tablet (1) contains a plurality of coated particulates (2) having core (2a) and coating (2b) that form a discontinuous phase within matrix material (3) which in turn forms a continuous phase and is also provided in particulate form, the individual particulates being in intimate contact with one another at boundaries (4). As the particulates of the matrix material typically have a mechanical strength lower than that of the coated particulates (2), the particulates of the matrix material are deformed in the course of the manufacture of the tablets by compression.

The particulates of the matrix material can principally also be coated, optionally with the same coating material of the coated particulates according to the invention or with another coating material. Preferably, however, the particulates of the matrix material are uncoated.

The particulates of the matrix material can be manufactured by conventional methods for the preparation of aggregates and agglomerates from powder mixtures such as granulating and compacting.

In a preferred embodiment, the mixture of all constituents of the matrix material is blended and pre-compacted thereby yielding a pre-compacted matrix material.

Suitable methods for the manufacture of such a pre-compacted matrix material are known to the skilled person. Preferably, pre-compaction proceeds by dry granulation, preferably slugging or roller compaction. When proceeding this way, the process parameters are typically to be adjusted in order to achieve the desired properties (see below). Typical process parameters are compaction force (preferably adjusted within the range of 2 to 12 kN), roller displacement (preferably adjusted within the range of 2 to 5 mm) and granule sieve (preferably adjusted within the range of 1.0 to 2.0 mm). The desired properties of the pre-compacted material include primarily the particle size and the content of fine particles. The density may also play a role. The particle size is preferably within the range for the size of the particulates (preferably at least 60% > 700 µm for particulates having dimensions of 0.8 x 0.8 mm). The content of fine particles (i.e. particles having a size of less than 600 µm) is preferably at most 40%, more preferably at most 30%, most preferably at most 20%. The effect of said process parameters on said desired properties can be easily determined by a skilled person by routine experimentation.

In another preferred embodiment, the mixture of all constituents of the matrix material is dry granulated thereby yielding a granulated matrix material. In still another preferred embodiment, the mixture of all constituents of the matrix material is wet granulated by means of a non-aqueous solvent e.g. ethanol thereby yielding another granulated matrix material. Aqueous granulation, however, is preferably avoided, as this typically has a detrimental influence on disintegration of the tablet. In yet another preferred embodiment, the mixture of all constituents of the matrix material is melt granulated, e.g. by means of an extruder, a heatable high-shear mixer or a granulator.

As already mentioned above, the matrix material in the tablet according to the invention should ensure rapid disintegration and subsequent release of the pharmacologically active compound from the disintegrated tablets, i.e. from the coated particulates. Thus, the matrix material preferably does not contain any excipient that might have a retardant effect on disintegration and drug release, respectively. Further, the matrix material preferably does not contain any pharmacologically active compound.

Preferably, the matrix material comprises a disintegrant. Suitable disintegrants are known to the skilled person and are preferably selected from the group consisting of crosslinked sodium carboxymethylcellulose (Na-CMC) (e.g. Crosscarmellose, Ac-Di-Sol®); crosslinked casein (e.g. Esma-Spreng®); polysaccharide mixtures obtained from soybeans (e.g. Emcosoy®); pretreated maize starch (e.g. Amijel®); sodium alginate; polyvinylpyrrolidone (PVP) (e.g. Kollidone®, Polyplasdone®, Polydone®); crosslinked polyvinylpyrrolidone (PVP Cl) (e.g. Polyplasdone® XL); starch and pretreated starch such as sodium carboxymethyl starch (e.g. Explotab®, Prejel®, Primotab® ET, Starch® 1500, Ulmatryl®). Crosslinked polymers are particularly preferred disintegrants, especially crosslinked sodium carboxymethylcellulose (Na-CMC) or crosslinked polyvinylpyrrolidone (PVP Cl).

Preferably, the disintegrant is contained in the matrix material but not in the coated particulates of the tablet according to the invention.

In a preferred embodiment, the content of the disintegrant in the matrix material is within the range of 5±4 wt.-%, more preferably 5±3 wt.-%, still more preferably 5±2.5 wt.-%, yet more preferably 5±2 wt.-%, most preferably 5±1.5 wt.-%, and in particular 5±1 wt.-%, based on the total weight of matrix material. In another preferred embodiment, the content of the disintegrant in the matrix material is within the range of 7.5±4 wt.-%, more preferably 7.5±3 wt.-%, still more preferably 7.5±2.5 wt.-%, yet more preferably 7.5±2 wt.-%, most preferably 7.5±1.5 wt.-%, and in particular 7.5±1 wt.-%, based on the total weight of matrix material. In still another preferred embodiment, the content of the disintegrant in the matrix material is within the range of 10±4 wt.-%, more preferably 10±3 wt.-%, still more preferably 10±2.5 wt.-%, yet more preferably 10±2 wt.-%, most preferably 10±1.5 wt.-%, and in particular 10±1 wt.-%, based on the total weight of matrix material. In another preferred embodiment, the content of the disintegrant in the matrix material is within the range of 12.5±4 wt.-%, more preferably 12.5±3 wt.-%, still more preferably 12.5±2.5 wt.-%, yet more preferably 12.5±2 wt.-%, most preferably 12.5±1.5 wt.-%, and in particular 12.5±1 wt.-%, based on the total weight of matrix material.

In a preferred embodiment, the content of the disintegrant in the tablet is within the range of 2±1.8 wt.-%, more preferably 2±1.5 wt.-%, still more preferably 2±1.3 wt.-%, yet more preferably 2±1.0 wt.-%, most preferably 2±0.8 wt.-%, and in particular 2±0.5 wt.-%, based on the total weight of tablet. In another preferred embodiment, the content of the disintegrant in the tablet is within the range of 4±1.8 wt.-%, more preferably 4±1.5 wt.-%, still more preferably 4±1.3 wt.-%, yet more preferably 4±1.0 wt.-%, most preferably 4±0.8 wt.-%, and in particular 4±0.5 wt.-%, based on the total weight of tablet. In still another preferred embodiment, the content of the disintegrant in the tablet is within the range of 6±1.8 wt.-%, more preferably 6±1.5 wt.-%, still more preferably 6±1.3 wt.-%, yet more preferably 6±1.0 wt.-%, most preferably 6±0.8 wt.-%, and in particular 6±0.5 wt.-%, based on the total weight of tablet. In another preferred embodiment, the content of the disintegrant in the tablet is within the range of 8±1.8 wt.-%, more preferably 8±1.5 wt.-%, still more preferably 8±1.3 wt.-%, yet more preferably 8±1.0 wt.-%, most preferably 8±0.8 wt.-%, and in particular 8±0.5 wt.-%, based on the total weight of tablet.

Preferably, the matrix material comprises a disintegrant in combination with one or more water insoluble pharmaceutical excipients, preferably fillers/binders and/or lubricants.

Preferably, the matrix material comprises a filler or a binder. As many fillers can be regarded as binders and vice versa, for the purpose of specification "filler/binder" refers to any excipient that is suitable as filler, binder or both. Thus, the matrix material preferably comprises a filler/binder.

Preferred fillers (=filler/binders) are selected from the group consisting of silicium dioxide (e.g. Aerosil®), microcrystalline cellulose (e.g. Avicel®, Elcema®, Emocel®, ExCel®, Vitacell®); cellulose ether (e.g. Natrosol®, Klucel®, Methocel®, Blanose®, Pharmacoat®, Viscontran®); mannitol; dextrines; dextrose; calciumhydrogen phosphate (e.g. Emcompress®); maltodextrine (e.g. Emdex®); lactose (e.g. Fast-Flow Lactose®; Ludipress®, Tablettose®, Zeparox®); polyvinylpyrrolidone (PVP) (e.g. Kollidone®, Polyplasdone®, Polydone®); saccharose (e.g. Nu-Tab®, Sugar Tab®); magnesium salts (e.g. $MgCO_3$, MgO, $MgSiO_3$); starches and pretreated starches (e.g. Prejel®, Primotab® ET, Starch® 1500). Preferred binders are selected from the group consisting of alginates; chitosanes; and any of the fillers mentioned above (= fillers/binders).

Some fillers/binders may also serve other purposes. It is known, for example, that silicium dioxide exhibits excellent function as a glidant. Thus, preferably, the matrix material comprises a glidant such as silicium dioxide.

In a preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the matrix material is within the range of 50±25 wt.-%, more preferably 50±20 wt.-%, still more preferably 50±15 wt.-%, yet more preferably 50±10 wt.-%, most preferably 50±7.5 wt.-%, and in particular 50±5 wt.-%, based on the total weight of matrix material. In another preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the matrix material is within the range of 65±25 wt.-%, more preferably 65±20 wt.-%, still more preferably 65±15 wt.-%, yet more preferably 65±10 wt.-%, most preferably 65±7.5 wt.-%, and in particular 65±5 wt.-%, based on the total weight of matrix material. In still another preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the matrix material is within the range of 80±19 wt.-%, more preferably 80±17.5 wt.-%, still more preferably 80±15 wt.-%, yet more preferably 80±10 wt.-%, most preferably 80±7.5 wt.-%, and in particular 80±5 wt.-%, based on the total weight of matrix material. In another preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the matrix material is within the range of 90±9 wt.-%, more preferably 90±8 wt.-%, still more preferably 90±7 wt.-%, yet more preferably 90±6 wt.-%, most preferably 90±5 wt.-%, and in particular 90±4 wt.-%, based on the total weight of matrix material.

In a preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the tablet is within the range of 25±24 wt.-%, more preferably 25±20 wt.-%, still more preferably 25±16 wt.-%, yet more preferably 25±12 wt.-%, most preferably 25±8 wt.-%, and in particular 25±4 wt.-%, based on the total weight of tablet. In another preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the tablet is within the range of 30±29 wt.-%, more preferably 30±25 wt.-%, still more preferably 30±20 wt.-%, yet more preferably 30±15 wt.-%, most preferably 30±10 wt.-%, and in particular 30±5 wt.-%, based on the total weight of tablet. In still another preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the tablet is within the range of 35±34 wt.-%, more preferably 35±28 wt.-%, still more preferably 35±22 wt.-%, yet more preferably 35±16 wt.-%, most preferably 35±10 wt.-%, and in particular 35±4 wt.-%, based on the total weight of tablet. In another preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the tablet is within the range of 40±39 wt.-%, more preferably 40±32 wt.-%, still more preferably 40±25 wt.-%, yet more preferably 40±18 wt.-%, most preferably 40±11 wt.-%, and in particular 40±4 wt.-%, based on the total weight of tablet.

Preferably, the filler/binder is contained in the matrix material but not in the coated particulates of the tablet according to the invention.

In a preferred embodiment, a portion (e.g. 10% of the total tablet mass) of the matrix is granulated on the coated particulates (preferably by non-aqueous wet granulation, e.g. with isopropylic alcohol) and the remaining matrix material is added to the thus granulated coated particulates and blended prior to compression / processing to tablets. Thus, according to this embodiment, the particulates are coated by a coating that in turn is overcoated a portion of the matrix material, whereas the remainder of the matrix material is preferably employed in non-granulated form.

Preferably, the matrix material comprises a diluent or lubricant, preferably selected from the group consisting of calcium stearate; magnesium stearate; glycerol monobehenate (e.g. Compritol®); Myvatex®; Precirol®; Precirol® Ato5; sodium stearylfumarate (e.g. Pruv®); and talcum. Magnesium stearate is particularly preferred. Preferably, the content of the lubricant in the matrix material is at most 10.0 wt.-%, more preferably at most 7.5 wt.-%, still more preferably at most 5.0 wt.-%, yet more preferably at most 2.0 wt.-%, even more preferably at most 1.0 wt.-%, and most preferably at most 0.5 wt.-%, based on the total weight of the matrix material and based on the total weight of tablet.

In particularly preferred embodiment, the matrix material comprises a combination of disintegrant, filler/binder and lubricant.

Particularly preferred contents of disintegrant, filler/binder and lubricant of the matrix material, relative to the total weight of the matrix material, are summarized as embodiments A^1 to A^6 in the table here below:

wt.-%	A^1	A^2	A^3	A^4	A^5	A^6
disintegrant	11±10	11±7.5	11±5.0	11±3.5	11±2.5	11±1.5
filler/binder	88±12	88±10	88±8	88±6	88±4	88±2.5
lubricant	0.30±0.28	0.30±0.26	0.30±0.24	0.30±0.22	0.30±0.20	0.30±0.15

wherein the disintegrant is preferably crosslinked sodium carboxymethyl cellulose (Na-CMC) or crosslinked polyvinylpyrrolidone (PVP Cl); the filler binder is preferably microcrystalline cellulose or a combination of microcrystalline cellulose with colloidal silicon dioxide; and the lubricant is preferably magnesium stearate.

The matrix material of the tablets according to the invention may additionally contain other excipients that are conventional in the art, e.g. diluents, binders, granulating aids, colourants, flavourants, pore formers, surfactants, glidants, wet-regulating agents and disintegrants. The skilled person will readily be able to determine appropriate quantities of each of these excipients.

Preferred pore formers include, but are not limited to glucose, fructose, mannitol, mannose, galactose, sorbitol, pullulan, dextran, water-soluble hydrophilic polymers, hydroxyalkyl-celluloses, carboxyalkylcelluloses, hydroxypropylmethylcellulose, cellulose ethers, acrylic resins, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, carbowaxes, carbopol, diols, polyols, polyhydric alcohols, polyalkylene glycols, polyethylene glycols, polypropylene glycols or block polymers thereof, polyglycols, poly(α-ω)alkylenediols; inorganic compounds; alkali metal salts; alkaline earth metal salts, or combinations thereof.

Preferred surfactants are nonionic, anionic, cationic or amphoteric surfactants.

In a preferred embodiment, the matrix material contains an ionic surfactant, in particular an anionic surfactant.

Suitable anionic surfactants include but are not limited to sulfuric acid esters such as sodium lauryl sulfate (sodium dodecyl sulfate, e.g. Texapon® K12), sodium cetyl sulfate (e.g. Lanette E®), sodium cetylstearyl sulfate, sodium stearyl sulfate, sodium dioctylsulfosuccinate (docusate sodium); and the corresponding potassium or calcium salts thereof.

Preferably, the anionic surfactant has the general formula (II-a)

$$C_nH_{2n+1}O\text{-}SO_3^- M^+ \text{ (II-a)},$$

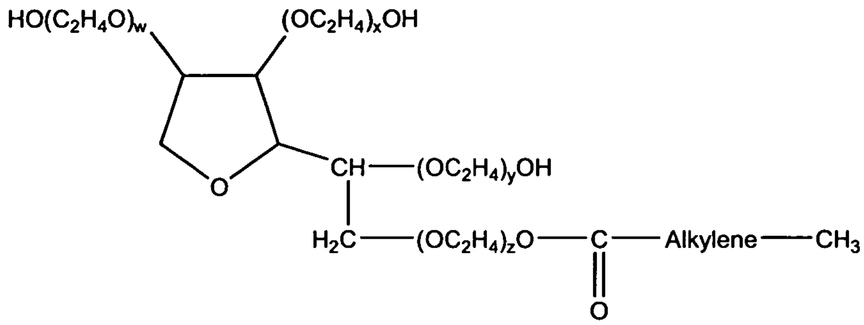
wherein n is an integer of from 8 to 30, preferably 10 to 24, more preferably 12 to 18; and M is selected from Li^+, Na^+, K^+, NH_4^+ 1/2 Mg^{2+} and 1/2 Ca^{2+}.

Further suitable anionic surfactants include salts of cholic acid including sodium glycocholate (e.g. Konakion® MM, Cernevit®), sodium taurocholate and the corresponding potassium or ammonium salts.

In another preferred embodiment, the matrix material contains a non-ionic surfactant. Suitable non-ionic surfactants include but are not limited to

- fatty alcohols that may be linear or branched, such as cetylalcohol, stearylalcohol, cetylstearyl alcohol, 2-octyldodecane-1-ol and 2-hexyldecane-1-ol;
- sterols, such as cholesterole;
- partial fatty acid esters of sorbitan such as sorbitanmonolaurate, sorbitanmonopalmitate, sorbitanmonostearate, sorbitantristearate, sorbitanmonooleate, sorbitansesquioleate and sorbitantrioleate;
- partial fatty acid esters of polyoxyethylene sorbitan (polyoxyethylene-sorbitan-fatty acid esters), preferably a fatty acid monoester of polyoxyethylene sorbitan, a fatty acid diester of polyoxyethylene sorbitan, or a fatty acid triester of polyoxyethylene sorbitan; e.g. mono-

and tri- lauryl, palmityl, stearyl and oleyl esters, such as the type known under the name "polysorbat" and commercially available under the trade name "Tween" including Tween® 20 [polyoxyethylene(20)sorbitan monolaurate], Tween® 21 [polyoxyethylene(4)sorbitan monolaurate], Tween® 40 [polyoxyethylene(20)sorbitan monopalmitate], Tween® 60 [polyoxyethylene(20)sorbitan monostearate], Tween® 65 [polyoxyethylene(20)sorbitan tristearate], Tween® 80 [polyoxyethylene(20)sorbitan monooleate], Tween 81 [polyoxyethylene(5)sorbitan monooleate], and Tween® 85 [polyoxyethylene(20)sorbitan trioleate]; preferably a fatty acid monoester of polyoxyethylenesorbitan according to general formula (II-b)



(II-b)

wherein (w+x+y+z) is within the range of from 15 to 100, preferably 16 to 80, more preferably 17 to 60, still more preferably 18 to 40 and most preferably 19 to 21; and alkylene is an optionally unsaturated alkylene group comprising 6 to 30 carbon atoms, more preferably 8 to 24 carbon atoms and most preferably 10 to 16 carbon atoms;

- polyoxyethyleneglycerole fatty acid esters such as mixtures of mono-, di- and triesters of glycerol and di- and monoesters of macrogols having molecular weights within the range of from 200 to 4000 g/mol, e.g., macrogolglycerolcaprylocaprate, macrogolglycerollaurate, macrogolglycerolococoate, macrogolglycerollinoleate, macrogol-20-glycerolmonostearate, macrogol-6-glycerolcaprylocaprate, macrogolglycerololeate; macrogolglycerolstearate, macrogolglycerolhydroxystearate (e.g. Cremophor® RH 40), and macrogolglycerolrizinoleate (e.g. Cremophor® EL);

- polyoxyethylene fatty acid esters, the fatty acid preferably having from about 8 to about 18 carbon atoms, e.g. macrogololeate, macrogolstearate, macrogol-15-hydroxystearate, polyoxyethylene esters of 12-hydroxystearic acid, such as the type known and commercially available under the trade name "Solutol HS 15"; preferably according to general formula (II-c)

$$CH_3CH_2\text{-}(OCH_2CH_3)_n\text{-}O\text{-}CO\text{-}(CH_2)_mCH_3 \quad \text{(II-c)}$$

wherein n is an integer of from 6 to 500, preferably 7 to 250, more preferably 8 to 100, still more preferably 9 to 75, yet more preferably 10 to 50, even more preferably 11 to 30, most preferably 12 to 25, and in particular 13 to 20; and

wherein m is an integer of from 6 to 28; more preferably 6 to 26, still more preferably 8 to 24, yet more preferably 10 to 22, even more preferably 12 to 20, most preferably 14 to 18 and in particular 16;

- polyoxyethylene fatty alcohol ethers, e.g. macrogolcetylstearylether, macrogollarylether, macrogololeylether, macrogolstearylether;
- polyoxypropylene-polyoxyethylene block copolymers (poloxamers);
- fatty acid esters of saccharose; e.g. saccharose distearate, saccharose dioleate, saccharose dipalmitate, saccharose monostearate, saccharose monooleate, saccharose monopalmitate, saccharose monomyristate and saccharose monolaurate;
- fatty acid esters of polyglycerol, e.g. polyglycerololeate;
- polyoxyethylene esters of alpha-tocopheryl succinate, e.g. D-alpha-tocopheryl-PEG-1000-succinate (TPGS);
- polyglycolyzed glycerides, such as the types known and commercially available under the trade names "Gelucire 44/14", "Gelucire 50/13 and "Labrasol";
- reaction products of a natural or hydrogenated castor oil and ethylene oxide such as the various liquid surfactants known and commercially available under the trade name "Cremophor"; and
- partial fatty acid esters of multifunctional alcohols, such as glycerol fatty acid esters, e.g. mono- and tri-lauryl, palmityl, stearyl and oleyl esters, for example glycerol monostearate, glycerol monooleate, e.g. glyceryl monooleate 40, known and commercially available under the trade name "Peceol"; glycerole dibehenate, glycerole distearate, glycerole monolinoleate; ethyleneglycol monostearate, ethyleneglycol monopalmitostearate, pentaerythritol monostearate.

In a preferred embodiment, the matrix material according to the invention comprises a surfactant or mixture of different surfactants obtainable by

(i) esterifying saturated or unsaturated C_{12}-C_{18}-fatty acids, optionally bearing a hydroxyl group, with a polyethylene glycol and optionally, glycerol; wherein the polyethylene glycol preferably comprises 10 to 40 ethylene oxide units ($-CH_2CH_2O-$); and/or

(ii) etherifying triglycerides of saturated or unsaturated C_{12}-C_{18}-fatty acids bearing a hydroxyl group with ethylene oxide so that a polyethylene glycol moiety is linked to the hydroxyl group of the C_{12}-C_{18}-fatty acids via an ether bond; wherein the polyethylene glycol moiety preferably comprises 30 to 50 ethylene oxide units ($-CH_2CH_2O-$).

In a preferred embodiment, the content of the surfactant is at least 0.001 wt.-% or at least 0.005 wt.-%, more preferably at least 0.01 wt.-% or at least 0.05 wt.-%, still more preferably at least 0.1 wt.-%, at least 0.2 wt.-%, or at least 0.3 wt.-%, yet more preferably at least 0.4 wt.-%, at least 0.5 wt.-%, or at least 0.6 wt.-%, and in particular at least 0.7 wt.-%, at least 0.8 wt.-%, at least 0.9 wt.-%, or at least 1.0 wt.-%, based on the total weight of the tablet.

In a preferred embodiment, however, the matrix material of the tablet according to the invention consists of one or more disintegrants, one or more filler/binder's and one or more lubricants, but does not contain any other constituents.

In a particularly preferred embodiment, the matrix material of the tablet according to the invention does not contain one or more gel-forming agents and/or a silicone.

As used herein the term "gel-forming agent" is used to refer to a compound that, upon contact with a solvent (e.g. water), absorbs the solvent and swells, thereby forming a viscous or semi-viscous substance. Preferred gel-forming agents are not cross-linked. This substance may moderate pharmacologically active compound release from the embedded particulates in both aqueous and aqueous alcoholic media. Upon full hydration, a thick viscous solution or dispersion is typically produced that significantly reduces and/or minimizes the amount of free solvent which can contain an amount of solubilized pharmacologically active compound, and which can be drawn into a syringe. The gel that is formed may also reduce the overall amount of pharmacologically active compound extractable with the solvent by entrapping the pharmacologically active compound within a gel structure. Thus the gel-forming agent may play an important role in conferring tamper-resistance to the tablets according to the invention.

Gel-forming agents that preferably are not contained in the matrix material include pharmaceutically acceptable polymers, typically hydrophilic polymers, such as hydrogels. Representative examples of gel-forming agent include polyethylene oxide, polyvinyl alcohol, hydroxypropylmethyl cellulose, carbomers, poly(uronic) acids and mixtures thereof.

Thus, the physiologically acceptable polymer, preferably the polyalkylene oxide that is contained in the coated particulates of the tablets according to the invention is preferably not also contained in the matrix material.

Preferably, the pharmacologically active compound which is contained in the coated particulates of the tablet according to the invention is preferably not also contained in the matrix material.

Thus, in a preferred embodiment, the total amount of pharmacologically active compound contained in the tablet according to the invention is present in the coated particulates which form a discontinuous phase within the matrix material; and the matrix material forming a continuous phase does not contain any pharmacologically active compound.

The tablet according to the invention contains a plurality of coated particulates. The coated particulates comprise a pharmacologically active compound and a physiologically acceptable polymer, preferably a polyalkylene oxide. Preferably, the pharmacologically active compound is dispersed in the physiologically acceptable polymer, preferably the polyalkylene oxide.

For the purpose of specification, the term "particulate" refers to a discrete mass of material that is solid, e.g. at 20 °C or at room temperature or ambient temperature. Preferably a particulate is solid at 20 °C. Preferably, the coated particulates are monoliths. Preferably, the pharmacologically active compound and the physiologically acceptable polymer, preferably the polyalkylene oxide are intimately homogeneously distributed in the coated particulates so that the coated particulates do not contain any segments where either pharmacologically active compound is present in the absence of physiologically acceptable polymer, preferably polyalkylene oxide or where physiologically acceptable polymer, preferably polyalkylene oxide is present in the absence of pharmacologically active compound.

The particulates are film coated and the physiologically acceptable polymer, preferably the polyalkylene oxide is preferably homogeneously distributed in the core of the pharmaceutical dosage form (tablet), i.e. the film coating preferably does not contain physiologically acceptable polymer, preferably polyalkylene oxide, but optionally polyalkylene glycol that differs from polyalkylene oxide in its lower molecular weight. Nonetheless, the film coating as such may of course contain one or more polymers, which however, preferably differ from the polyalkylene oxide contained in the core.

The coated particulates are of macroscopic size, typically the average diameter is within the range of from 100 µm to 1500 µm, preferably 200 µm to 1500 µm, more preferably 300 µm to 1500 µm, still more preferably 400 µm to 1500 µm, most preferably 500 µm to 1500 µm, and in particular 600 µm to 1500 µm. The tablets according to the invention comprise particulates as a discontinuous phase, i.e. the coated particulates form a discontinuous phase in the matrix material which in turn preferably forms a continuous phase. In this regard, discontinuous means that not each and every particulate is in intimate contact with another particulate but that the coated particulates are at least partially separated from one another by the matrix material in which the coated particulates are embedded. In other words, the coated particulates preferably do not form a single coherent mass within the tablets according to the invention.

The tablet according to the invention comprises particulates in an amount of less than two thirds of the total weight of the tablet.

It has been surprisingly found that the content of particulates in the tablet can be optimized in order to provide the best compromise between tamper-resistance, disintegration time and drug release, drug load, processability (especially tablettability) and patient compliance.

Preferably, the content of the coated particulates in the tablets according to the invention is at most 65 wt.-%, more preferably at most 62.5 wt.-%, still more preferably at most 60 wt.-%, yet more preferably at most 57.5 wt.-%, most preferably at most 55 wt.-% and in particular at most 52.5 wt.-%, based on the total weight of the tablets.

Preferably, the content of the coated particulates in the tablets according to the invention is at least 10 wt.-%, at least 12.5 wt.-%, at least 15 wt.-% or at least 17.5 wt.-%; more preferably at least 20 wt.-%, at least 22.5 wt.-%, at least 25 wt.-% or at least 27.5 wt.-%; most preferably at least 30 wt.-%, at least 32.5 wt.-%, at least 35 wt.-% or at least 37.5 wt.-%; and in particular at least 40 wt.-%, at least 42.5 wt.-%, at least 45 wt.-% or at least 47.5 wt.-%; based on the total weight of the tablet.

In a preferred embodiment, the content of the coated particulates in the tablets according to the invention is within the range of 35±30 wt.-%, more preferably 35±25 wt.-%, still more preferably 35±20 wt.-%, yet more preferably 35±15 wt.-%, most preferably 35±10 wt.-%, and in particular 35±5 wt.-%, based on the total weight of the tablet. In another preferred embodiment, the content of the coated particulates in the tablets according to the invention is within the range of 40±30 wt.-%, more preferably 40±25 wt.-%, still more preferably 40±20 wt.-%, yet more preferably 40±15 wt.-%, most preferably 40±10 wt.-%, and in particular 40±5 wt.-%, based on the total weight of the tablet. In still another preferred embodiment, the content of the coated particulates in the tablets according to the invention is within the range of 45±30 wt.-%, more preferably 45±25 wt.-%, still more preferably 45±20 wt.-%, yet more preferably 45±15 wt.-%, most preferably 45±10 wt.-%, and in particular 45±5 wt.-%, based on the total weight of the tablet. In yet another preferred embodiment, the content of the coated particulates in the tablets according to the invention is within the range of 50±30 wt.-%, more preferably 50±25 wt.-%, still more preferably 50±20 wt.-%, yet more preferably 50±15 wt.-%, most preferably 50±10 wt.-%, and in particular 50±5 wt.-%, based on the total weight of the tablet. In another preferred embodiment, the content of the coated particulates in the tablets according to the invention is within the range of 55±30 wt.-%, more preferably 55±25 wt.-%, still more preferably 55±20 wt.-%, yet more preferably 55±15 wt.-%, most preferably 55±10 wt.-%, and in particular 55±5 wt.-%, based on the total weight of the tablet. In still another preferred embodiment, the content of the coated particulates in the tablets according to the invention is within the range of 60±30 wt.-%, more preferably 60±25 wt.-%, still more preferably 60±20 wt.-%, yet more preferably 60±15 wt.-%, most preferably 60±10 wt.-%, and in particular 60±5 wt.-%, based on the total weight of the tablet.

The shape of the coated particulates is not particularly limited. As the coated particulates are preferably manufactured by hot-melt extrusion, preferred coated particulates present in the tablets according to the invention are generally cylindrical in shape. The diameter of such coated particulates is therefore the diameter of their circular cross section. The cylindrical shape is caused by the extrusion process according to which the diameter of the circular cross section is a function of the extrusion die and the length of the cylinders is a function of the cutting length according to which the extruded strand of material is cut into pieces of preferably more or less predetermined length.

The suitability of cylindrical, i.e. a spherical particulates for the manufacture of the tablets according to the invention is unexpected. Typically, the aspect ratio is regarded as an important measure of the spherical shape. The aspect ratio is defined as the ratio of the maximal diameter (d_{max}) and its orthogonal Feret-diameter. For aspherical particulates, the aspect ratio has values above 1. The smaller the value the more spherical is the particulate. Aspect ratios below 1.1 are typically considered satisfactory, aspect ratios above 1.2, however, are typically considered not suitable for the manufacture of conventional tablets. The inventors have surprisingly found that when manufacturing the tablets according to the invention, even particulates having aspect ratios above 1.2 can be processed without difficulties and that it is not necessary to provide spherical particulates. In a preferred embodiment, the aspect ratio of the coated particulates is at most 1.40, more preferably at most 1.35, still more preferably at most 1.30, yet more preferably at most 1.25, even more preferably at most 1.20, most preferably at most 1.15 and in particular at most 1.10. In another preferred embodiment, the aspect ratio of the coated particulates is at least 1.10, more preferably at least 1.15, still more preferably at least 1.20, yet more preferably at least 1.25, even more preferably at least 1.30, most preferably at least 1.35 and in particular at least 1.40.

The coated particulates in the tablets according to the invention are of macroscopic size, i.e. typically have an average particle size of at least 50 µm, more preferably at least 100 µm, still more preferably at least 150 µm or at least 200 µm, yet more preferably at least 250 µm or at least 300 µm, most preferably at least 400 µm or at least 500 µm, and in particular at least 550 µm or at least 600 µm.

Preferred coated particulates have an average length and average diameter of about 1000 µm or less. When the coated particulates are manufactured by extrusion technology, the "length" of coated particulates is the dimension of the coated particulates that is parallel to the direction of extrusion. The "diameter" of coated particulates is the largest dimension that is perpendicular to the direction of extrusion.

Particularly preferred coated particulates have an average diameter of less than about 1000 µm, more preferably less than about 800 µm, still more preferably of less than about 650 µm. Especially preferred coated particulates have an average diameter of less than 700 µm, particularly less than 600 µm, still more particularly less than 500 µm, e.g. less than 400 µm. Particularly preferred particulates have an average diameter in the range 200-1000 µm, more preferably 400-800 µm, still more preferably 450-700 µm, yet more preferably 500-650 µm, e.g. about 500-600 µm. Further preferred particulates have an average diameter of between about 300 µm and about 400 µm, of between about 400 µm and 500 µm, or of between about 500 µm and 600 µm, or of between 600 µm and 700 µm or of between 700 µm and 800 µm.

Preferred particulates that are present in the tablets according to the invention have an average length of less than about 1000 µm, preferably an average length of less than about 800 µm, still more preferably an average length of less than about 650 µm, e.g. a length of about 800 µm, about 700 µm about 600 µm, about 500 µm, about 400 µm or about 300 µm. Especially preferred particulates have an average length of less than 700 µm, particularly less than 650 µm, still more particularly less than 550 µm, e.g. less than 450 µm. Particularly preferred particulates therefore have an average length in the range 200-1000 μm, more preferably 400-800 μm, still more preferably 450-700 μm, yet more preferably 500-650 μm, e.g. about 500-600 μm. The minimum average length of the microparticulates is determined by the cutting step and may be, e.g. 500 μm, 400 μm, 300 μm or 200 μm.

In a preferred embodiment, the coated particulates have (i) an average diameter of about 1000±300 μm, more preferably 1000±250 μm, still more preferably 1000±200 μm, yet more preferably 100±150 μm, most preferably 1000±100 μm, and in particular 1000±50 μm; and/or (ii) an average length of about 750±300 μm, more preferably 750±250 μm, still more preferably 750±200 μm, yet more preferably 750±150 μm, most preferably 750±100 μm, and in particular 750±50 μm.

In another preferred embodiment, the coated particulates have (i) an average diameter of about 750±300 μm, more preferably 750±250 μm, still more preferably 750±200 μm, yet more preferably 750±150 μm, most preferably 750±100 μm, and in particular 750±50 μm; and/or (ii) an average length of about 750±300 μm, more preferably 750±250 μm, still more preferably 750±200 μm, yet more preferably 750±150 μm, most preferably 750±100 μm, and in particular 750±50 μm.

It has been surprisingly found that the size of the coated particulates in the tablet can be optimized in order to provide the best compromise between tamper-resistance, disintegration time and drug release, drug load, processability (especially tablettability) and patient compliance.

The size of particulates may be determined by any conventional procedure known in the art, e.g. laser light scattering, sieve analysis, light microscopy or image analysis.

Preferably, the plurality of coated particulates that is contained in the tablet according to the invention has an arithmetic average weight, in the following referred to as "aaw", wherein at least 70%, more preferably at least 75%, still more preferably at least 80%, yet more preferably at least 85%, most preferably at least 90% and in particular at least 95% of the individual particles contained in said plurality of coated particulates has an individual weight within the range of aaw±30%, more preferably aaw±25%, still more preferably aaw±20%, yet more preferably aaw±15%, most preferably aaw±10%, and in particular aaw±5%. For example, if the tablet according to the invention contains a plurality of 100 particulates and aaw of said plurality of coated particulates is 1.00 mg, at least 75 individual particles (i.e. 75%) have an individual weight within the range of from 0.70 to 1.30 mg (1.00 mg ±30%).

The particulates are coated, preferably film coated. It has been surprisingly found that when the particulates are film coated, the disintegration time and/or the drug release from the tablets can be further accelerated, which is particularly significant for tablets with immediate drug release.

Preferably, the plurality of coated particulates contained in the dosage form according to the invention encompasses the total quantity of particulates which contain the pharmacologically active compound, i.e. preferably all active compound containing particulates are coated.

Preferably, the coating material does not contain a disintegrant.

The particulates according to the invention are provided, partially or preferably completely, with a coating. The particulates according to the invention are preferably film coated with film coating compositions. Suitable coating materials are commercially available, e.g. under the trademarks Opadry® and Eudragit®.

Preferably, the coating material comprises a water-soluble polymer. For the purpose of specification, a water-soluble polymer is preferably a non-enteric polymer that rapidly dissolves when being exposed to an acidic medium such as gastric juice. Preferably, the water-solubility of the polymer in 100 g artificial gastric juice (HCl aq.) at pH 1.2 and 21 °C is at least 1.0 g, more preferably at least 2.0 g, still more preferably at least 3.0 g, yet more preferably at least 4.0 g, most preferably at least 5.0 g, and in particular at least 6.0 g.

Examples of suitable coating 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, polyvinyl alcohol-polyethylene glycol graft copolymers, polyvinylacetate; and natural film formers.

The coating material may contain excipients such as stabilizers (e.g. surfactants such as macrogol cetostearylether, sodium dodecylsulfate, and the like). Suitable excipients of film coating materials are known to the skilled person.

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 hydroxypropylmethyl-cellulose, preferably hypromellose type 2910 having a viscosity of 3 to 15 mPas.

A particularly preferred coating contains polyvinyl alcohol and optionally, further excipients such as xanthan gum and/or talcum.

The particulates are film coated and the content of the dried film coating is preferably at most 5 wt.-%, more preferably at most 4 wt.-%, still more preferably at most 3.5 wt.-%, yet more preferably at most 3 wt.-%, most preferably at most 2.5 wt.-%, and in particular at most 2 wt.-%, based on the total weight of the coated particulates. In a particularly preferred embodiment, the weight increase relative to the total weight of the particulates (uncoated starting material) is within the range of from 3.0 to 4.7 wt.-%, more preferably 3.1 to 4.6 wt.-%, still more preferably 3.2 to 4.5 wt.-%, yet more preferably 3.3 to 4.4 wt.-%, most preferably 3.4 to 4.3 wt.-%, and in particular 3.5 to 4.2 wt.-%.

It has been surprisingly found that the relative weight ratio of matrix material : particulates in the tablet can be optimized in order to provide the best compromise between tamper-resistance, disintegration time and drug release, drug load, processability (especially tablettability) and patient compliance.

Preferably, said relative weight ratio is within the range of 1 : 1.00±0.75, more preferably 1 : 1.00±0.50, still more preferably 1 : 1.00±0.40, yet more preferably 1 : 1.00±0.30, most preferably 1 : 1.00±0.20, and in particular 1 : 1.00±0.10.

The coated particulates contain at least a pharmacologically active compound and a physiologically acceptable polymer, preferably a polyalkylene oxide. Preferably, however, the coated particulates contain additional pharmaceutical excipients such as antioxidants and plasticizers.

The pharmacologically active compound is not particularly limited. Preferably, the pharmacologically active compound is an opioid.

In a preferred embodiment, the coated particulates and the tablet, respectively, contain only a single pharmacologically active compound. In another preferred embodiment, the coated particulates and the tablet, respectively, contain a combination of two or more pharmacologically active compounds.

Preferably, pharmacologically active compound is an active ingredient with potential for being abused. Active ingredients with potential for being abused are known to the person skilled in the art and comprise e.g. tranquillizers, stimulants, barbiturates, narcotics, opioids or opioid derivatives.

Preferably, the pharmacologically active compound exhibits psychotropic action.

Preferably, the pharmacologically active compound is selected from the group consisting of opiates, opioids, stimulants, tranquilizers, and other narcotics.

Particularly preferably, the pharmacologically active compound 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 tablet and the coated particulates, respectively: 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-dimethyl-aminomethyl-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-di-methylaminomethyl-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 pharmacologically active compound is 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 pharmacologically active compound is selected from the group consisting of oxymorphone, hydromorphone and morphine.

In another preferred embodiment, the pharmacologically active compound is selected from the group consisting of tapentadol, faxeladol and axomadol.

In still another preferred embodiment, the pharmacologically active compound 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 compound 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.

It has been surprisingly found that the content of the pharmacologically active compound in the tablet and in the coated particulates, respectively, can be optimized in order to provide the best compromise between tamper-resistance, disintegration time and drug release, drug load, processability (especially tablettability) and patient compliance.

The pharmacologically active compound is present in the tablet 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 the frequency of administration.

The content of the pharmacologically active compound in the tablet is not limited. The dose of the pharmacologically active compound 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 compound that is contained in the tablet 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 compound 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 tablet.

In a preferred embodiment, the content of pharmacologically active compound is within the range of from 5.0±4.5 wt.-%, or 7.5±7.0 wt.-%, or 10±9.0 wt.-%, or 12.5±12.0 wt.-%, or 15±14 wt.-%, or 17.5±17.0 wt.-%, or 20±19 wt.-%, or 22.5±22.0 wt.-%, or 25±24 wt.-%; more preferably 5.0±4.0 wt.-%, or 7.5±6.0 wt.-%, or 10±8.0 wt.-%, or 12.5±12.0 wt.-%, or 15±12 wt.-%, or 17.5±15.0 wt.-%, or 20±19 wt.-%, or 22.5±22.0 wt.-%, or 25±24 wt.-%; still more preferably 5.0±3.5 wt.-%, or 7.5±5.0 wt.-%, or 10±7.0 wt.-%, or 12.5±10.0 wt.-%, or 15±10 wt.-%, or 17.5±13.0 wt.-%, or 20±17 wt.-%, or 22.5±19.0 wt.-%, or 25±21 wt.-%; yet more preferably 5.0±3.0 wt.-%, or 7.5±4.0 wt.-%, or 10±6.0 wt.-%, or 12.5±8.0 wt.-%, or 15±8.0 wt.-%, or 17.5±11.0 wt.-%, or 20±15 wt.-%, or 22.5±16.0 wt.-%, or 25±18 wt.-%; even more preferably 5.0±2.5 wt.-%, or 7.5±3.0 wt.-%, or 10±5.0 wt.-%, or 12.5±6.0 wt.-%, or 15±6.0 wt.-%, or 17.5±9.0 wt.-%, or 20±13 wt.-%, or 22.5±13.0 wt.-%, or 25±15 wt.-%; most preferably 5.0±2.0 wt.-%, or 7.5±2.0 wt.-%, or 10±4.0 wt.-%, or 12.5±4.0 wt.-%, or 15±4.0 wt.-%, or 17.5±7.0 wt.-%, or 20±11 wt.-%, or 22.5±10.0 wt.-%, or 25±12 wt.-%; and in particular 5.0±1.5 wt.-%, or 7.5±1.0 wt.-%, or 10±3.0 wt.-%, or 12.5±2.0 wt.-%, or 15±2.0 wt.-%, or 17.5±5.0 wt.-%, or 20±9 wt.-%, or 22.5±7.0 wt.-%, or 25±9 wt.-%; in each case based on the total weight of the tablet.

In a further preferred embodiment, the content of pharmacologically active compound 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 tablet. In another preferred embodiment, the content of pharmacologically active compound is within the range of from 25±6 wt.-%, more preferably 25±5 wt.-%, still more preferably 25±4 wt.-%, most preferably 25±3 wt.-%, and in particular 25±2 wt.-%, based on the total weight of the tablet.

The skilled person may readily determine an appropriate amount of pharmacologically active compound to include in a tablet. For instance, in the case of analgesics, the total amount of pharmacologically active compound present in the tablet is that sufficient to provide analgesia. The total amount of pharmacologically active compound administered to a patient in a dose will vary depending on numerous factors including the nature of the pharmacologically active compound, the weight of the patient, the severity of the pain, the nature of other therapeutic agents being administered etc.

In a preferred embodiment, the pharmacologically active compound is contained in the tablet 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, 250±5 mg, 260±5 mg, 270±5 mg, 280±5 mg, 290±5 mg, or 300±5 mg. In another preferred embodiment, the pharmacologically active compound is contained in the tablet 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, 250±2.5 mg, 255±2.5 mg, 260±2.5 mg, or 265±2.5 mg.

In a particularly preferred embodiment, the pharmacologically active compound is tapentadol, preferably its HCl salt, and the tablet is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, pharmacologically active compound is preferably contained in the tablet in an amount of from 25 to 100 mg.

In a particularly preferred embodiment, the pharmacologically active compound is oxymorphone, preferably its HCl salt, and the tablet is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, the pharmacologically active compound is preferably contained in the tablet in an amount of from 5 to 40 mg. In another particularly preferred embodiment, the pharmacologically active compound is oxymorphone, preferably its HCl salt, and the tablet is adapted for administration once daily. In this embodiment, the pharmacologically active compound is preferably contained in the tablet in an amount of from 10 to 80 mg.

In another particularly preferred embodiment, the pharmacologically active compound is oxycodone, preferably its HCl salt, and the tablet is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, the pharmacologically active compound is preferably contained in the tablet in an amount of from 5 to 80 mg.

In still another particularly preferred embodiment, the pharmacologically active compound is hydromorphone, preferably its HCl, and the tablet is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, the pharmacologically active compound is preferably contained in the tablet in an amount of from 2 to 52 mg. In another particularly preferred embodiment, the pharmacologically active compound is hydromorphone, preferably its HCl, and the tablet is adapted for administration once daily, twice daily, thrice daily or more frequently. In this embodiment, the pharmacologically active compound is preferably contained in the tablet in an amount of from 4 to 104 mg.

The coated particulates present in the tablets according to the invention preferably comprise 3 to 75 wt.-% of pharmacologically active compound, more preferably 5 to 70 wt.-% of pharmacologically active compound, still more preferably 7.5 to 65 wt.-% of pharmacologically active compound, based on the total weight of a particulate.

Preferably, the content of the pharmacologically active compound is at least 25 wt.-%, more preferably at least 30 wt.-%, still more preferably at least 35 wt.-%, yet more preferably at least 40 wt.-%, most preferably at least 45 wt.-%, based on the total weight of a particulate.

Preferably, the content of the pharmacologically active compound is at most 70 wt.-%, more preferably at most 65 wt.-%, still more preferably at most 60 wt.-%, yet more preferably at most 55 wt.-%, most preferably at most 50 wt.-%, based on the total weight of a particulate.

In a preferred embodiment, the content of the pharmacologically active compound is within the range of 35±30 wt.-%, more preferably 35±25 wt.-%, still more preferably 35±20 wt.-%, yet more preferably 35±15 wt.-%, most preferably 35±10 wt.-%, and in particular 35±5 wt.-%, based on the total weight of a particulate. In another preferred embodiment, the content of the pharmacologically active compound is within the range of 45±30 wt.-%, more preferably 45±25 wt.-%, still more preferably 45±20 wt.-%, yet more preferably 45±15 wt.-%, most preferably 45±10 wt.-%, and in particular 45±5 wt.-%, based on the total weight of a particulate. In still another preferred embodiment, the content of the pharmacologically active compound is within the range of 55±30 wt.-%, more preferably 55±25 wt.-%, still more preferably 55±20 wt.-%, yet more preferably 55±15 wt.-%, most preferably 55±10 wt.-%, and in particular 55±5 wt.-%, based on the total weight of a particulate.

The pharmacologically active compound that is included in the preparation of the tablets according to the invention preferably has an average particle size of less than 500 microns, still more preferably less than 300 microns, yet more preferably less than 200 or 100 microns. There is no lower limit on the average particle size and it may be, for example, 50 microns. The particle size of pharmacologically active compounds may be determined by any technique conventional in the art, e.g. laser light scattering, sieve analysis, light microscopy or image analysis. Generally speaking it is preferable that the largest dimension of the pharmacologically active compound particle be less than the size of the coated particulates (e.g. less than the smallest dimension of the coated particulates).

A skilled person knows how to determine pharmacokinetic parameters such as $t_{1/2}$, T_{max}, C_{max}, AUC and bioavailability. For the purposes of the description, the pharmacokinetic parameters, which may be determined from the blood plasma concentrations of 3-(2-dimethylaminomethylcyclohexyl)phenol, are defined as follows:

C_{max}	maximum measured plasma concentration of the active ingredient after single administration (≡ average *peak plasma level*)
t_{max}	interval of time from administration of the active ingredient until C_{max} is reached
AUC	total area of the plasma concentration/time curve including the subarea from the final measured value extrapolated to infinity
$t_{1/2}$	half-life

The above parameters are in each case stated as mean values of the individual values for all investigated patients/test subjects.

A person skilled in the art knows how the pharmacokinetic parameters of the active ingredient may be calculated from the measured concentrations of the active ingredient in the blood plasma. In this connection, reference may be made, for example, to Willi Cawello (ed.) *Parameters for Compartment-free Pharmacokinetics*, Shaker Verlag Aachen (1999).

In a preferred embodiment, the pharmacologically active compound is tapentadol or a physiologically acceptable salt thereof, e.g. the hydrochloride. Preferably, the tablet according to the invention provides a mean absolute bioavailability of of tapentadol at least 22%, more preferably at least 24%, still more preferably at least 26%, yet more preferably at least 28%, most preferably at least 30%, and in particular at least 32%. T_{max} of tapentadol is preferably within the range of 1.25±1.20 h, more preferably 1.25±1.00 h, still more preferably 1.25±0.80 h, yet more preferably 1.25±0.60 h, most preferably 1.25±0.40 h, and in particular 1.25±0.20 h. $t_{1/2}$ of tapentadol is preferably within the range of 4.0±2.8 h, more preferably 4.0±2.4 h, still more preferably 4.0±2.0 h, yet more preferably 4.0±1.6 h, most preferably 4.0±1.2 h, and in particular 4.0±0.8 h. Preferably, when normalized to a dose of 100 mg tapentadol, C_{max} of tapentadol is preferably within the range of 90±85 ng/mL, more preferably 90±75 ng/mL, still more preferably 90±65 ng/mL, yet more preferably 90±55 ng/mL, most preferably 90±45 ng/mL, and in particular 90±35 ng/mL; and/or AUC of tapentadol is preferably within the range of 420±400 ng/mL·h, more preferably 420±350 ng/mL·h, still more preferably 420±300 ng/mL·h, yet more preferably 420±250 ng/mL·h, most preferably 420±200 ng/mL·h, and in particular 420±150 ng/mL·h.

In another preferred embodiment, the pharmacologically active compound is oxymorphone or a physiologically acceptable salt thereof, e.g. the hydrochloride. Preferably, the tablet according to the invention provides a mean absolute bioavailability of oxymorphone of at least 1%, more preferably at least 2%, still more preferably at least 4%, yet more preferably at least 6%, most preferably at least 8%, and in particular at least 10%. T_{max} of oxymorphone is preferably within the range of 0.5±0.45 h, more preferably 0.5±0.40 h, still more preferably 0.5±0.35 h, yet more preferably 0.5±0.30 h, most preferably 0.5±0.25 h, and in particular 0.5±0.20 h. $t_{1/2}$ of oxymorphone is preferably within the range of 9.5±8.0 h, more preferably 9.5±7.0 h, still more preferably 9.5±6.0 h, yet more preferably 9.5±5.0 h, most preferably 9.5±4.0 h, and in particular 9.5±3.0 h. Preferably, when normalized to a dose of 20 mg oxymorphone, C_{max} of oxymorphone is preferably within the range of 4.4±3.5 ng/mL, more preferably 4.4±3.0 ng/mL, still more preferably 4.4±2.5 ng/mL, yet more preferably 4.4±2.0 ng/mL, most preferably 4.4±1.5 ng/mL, and in particular 4.4±1.0 ng/mL; and/or AUC of oxymorphone is preferably within the range of 20.0±15.0 ng/mL·h, more preferably 20.0±12.5 ng/mL·h, still more preferably 20.0±10.0 ng/mL·h, yet more preferably 20.0±7.5 ng/mL·h, most preferably 20.0±6.0 ng/mL·h, and in particular 20.0±5.0 ng/mL·h.

In another preferred embodiment, the pharmacologically active compound is oxycodone or a physiologically acceptable salt thereof, e.g. the hydrochloride. Preferably, the tablet according to the invention provides a mean absolute bioavailability of oxycodone of at least 40%, more preferably at least 45%, still more preferably at least 50%, yet more preferably at least 55%, most preferably at least 60%, and in particular at least 70%. T_{max} of oxycodone is preferably within the range of 2.6±2.5 h, more preferably 2.6±2.0 h, still more preferably 2.6±1.8 h, yet more preferably 2.6±0.1.6 h, most preferably 2.6±1.4 h, and in particular 2.6±1.20 h. $t_{1/2}$ of oxycodone is preferably within the range of 3.8±3.5 h, more preferably 3.8±3.0 h, still more preferably 3.8±2.5 h, yet more preferably 3.8±2.0 h, most preferably 3.8±1.5 h, and in particular 3.8±1.0 h. Preferably, when normalized to a dose of 30 mg oxycodone, C_{max} of oxycodone is preferably within the range of 40±35 ng/mL, more preferably 40±30 ng/mL, still more preferably 40±25 ng/mL, yet more preferably 40±20 ng/mL, most preferably 40±15 ng/mL, and in particular 40±10 ng/mL; and/or AUC of oxycodone is preferably within the range of 270±250 ng/mL·h, more preferably 270±200 ng/mL·h, still more preferably 270±150 ng/mL·h, yet more preferably 270±100 ng/mL·h, most preferably 270±75 ng/mL·h, and in particular 270±50 ng/mL·h.

In still another preferred embodiment, the pharmacologically active compound is morphine or a physiologically acceptable salt thereof, e.g. the sulfate. Preferably, the tablet according to the invention provides a mean absolute bioavailability of morphine of at least 15%, more preferably at least 20%, still more preferably at least 25%, yet more preferably at least 30%, most preferably at least 35%, and in particular at least 40%. T_{max} of morphine is preferably within the range of 0.625±0.60 h, more preferably 0.625±0.50 h, still more preferably 0.625±0.40 h, yet more preferably 0.625±0.30 h, most preferably 0.625±0.20 h, and in particular 0.625±0.15 h. Preferably, when normalized to a dose of 30 mg morphine sulfate, C_{max} of morphine is preferably within the range of 25±20 ng/mL, more preferably 25±15 ng/mL, still more preferably 25±10 ng/mL, yet more preferably 25±5 ng/mL; and/or AUC of morphine is preferably within the range of 50±45 ng/mL·h, more preferably 50±40 ng/mL·h, still more preferably 50±35 ng/mL·h, yet more preferably 50±30 ng/mL·h, most preferably 50±25 ng/mL·h, and in particular 50±20 ng/mL·h.

The tablets according to the invention may also comprise one or more additional pharmacologically active compounds. The additional pharmacologically active compound may be susceptible to abuse or another pharmaceutical. Additional pharmacologically active compounds may be present within the coated particulates ("intragranular") or within the matrix (e.g. "extragranular", or when the matrix material is also provided in form of particulates, also "intragranular"). Where an additional pharmacologically active compound is present intragranularly, it may be present either in combination with one or more pharmacologically active compounds within the same particulates or in a discrete population of particulates alone and separate from any other pharmacologically active compounds present in the tablet.

In a preferred embodiment, the tablet according to the invention, preferably the coated particulates comprise an opioid (agonist) as well as an opioid antagonist.

Any conventional opioid antagonist may be present, e.g. naltrexone or naloxone or their pharmaceutically acceptable salts. Naloxone, including its salts, is particularly preferred. The opioid antagonist may be present within the coated particulates or within the matrix. Alternatively, opioid antagonist may be provided in separate particulates to the pharmacologically active compounds. The preferred composition of such particulates is the same as that described for pharmacologically active compound-containing particulates.

The ratio of opioid agonist to opioid antagonist in the tablets according to the invention is preferably 1 :1 to 3:1 by weight, for example, about 2:1 by weight.

In another preferred embodiment, neither the coated particulates nor the tablet comprise any opioid antagonist.

The coated particulates according to the invention contain a physiologically acceptable polymer, preferably a polyalkylene oxide.

Preferably, the physiologically acceptable polymer is selected from the group consisting of polyalkylene oxide, preferably polymethylene oxide, polyethylene oxide, polypropylene oxide; polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyvinyl-pyrrolidone, poly(alk)acrylate, poly(hydroxy fatty acids), such as for example poly(3-hydroxy-butyrate-co-3-hydroxyvalerate) (Biopol®), poly(hydroxyvaleric acid); polycaprolactone, polyvinyl alcohol, polyesteramide, polyethylene succinate, polylactone, polyglycolide, polyurethane, polyamide, polylactide, polyacetal (for example polysaccharides optionally with modified side chains), polylactide/glycolide, polylactone, polyglycolide, polyorthoester, polyanhydride, block polymers of polyethylene glycol and polybutylene terephthalate (Polyactive®), polyanhydride (Polifeprosan), copolymers thereof, block-copolymers thereof (e.g., Poloxamer®), and mixtures of at least two of the stated polymers, or other polymers with the above characteristics. Polyalkylene oxide is particularly preferred.

Preferably, the physiologically acceptable polymer is a polyalkylene oxide, more preferably selected from polymethylene oxide, polyethylene oxide and polypropylene oxide, or copolymers thereof. Polyethylene oxide is preferred.

In a preferred embodiment, the physiologically acceptable polymer, preferably the polyalkylene oxide has a weight average molecular weight (M_W) or viscosity average molecular weight (M_η) of at least 200,000 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).

The physiologically acceptable polymer, preferably the polyalkylene oxide may comprise a single polymer 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 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 tablet 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.

In a preferred embodiment, the physiologically acceptable polymer, preferably the polyalkylene oxide is homogeneously distributed in the coated particulates according to the invention. Preferably, the pharmacologically active compound and the physiologically acceptable polymer, preferably the polyalkylene oxide are intimately homogeneously distributed in the coated particulates so that the coated particulates do not contain any segments where either pharmacologically active compound is present in the absence of physiologically acceptable polymer, preferably polyalkylene oxide or where physiologically acceptable polymer, preferably polyalkylene oxide is present in the absence of pharmacologically active compound.

The particulates are film coated and the physiologically acceptable polymer, preferably the polyalkylene oxide is preferably homogeneously distributed in the core of the coated particulates, i.e. the film coating preferably does not contain physiologically acceptable polymer, preferably polyalkylene oxide. Nonetheless, the film coating as such may of course contain one or more polymers, which however, preferably differ from the physiologically acceptable polymer, preferably the polyalkylene oxide contained in the core.

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

Polyethylene oxide that is suitable for use in the tablets according to the invention is commercially available from Dow. For example, Polyox WSR N-12K, Polyox N-60K, Polyox WSR 301 NF or Polyox WSR 303NF may be used in the tablets according to the invention. For details concerning the properties of these products, it can be referred to e.g. the product specification.

Preferably, the content of the physiologically acceptable polymer, preferably the polyalkylene oxide is within the range of from 1 to 60 wt.-%, more preferably 3 to 55 wt.-%, still more preferably 5 to 50 wt.-%, yet more preferably 7 to 45 wt.-%, most preferably 10 to 40 wt.-% and in particular 15 to 35 wt.-%, based on the total weight of the tablet. In a preferred embodiment, the content of the physiologically acceptable polymer, preferably the polyalkylene oxide is at least 2 wt.-%, more preferably at least 5 wt.-%, still more preferably at least 10 wt.-%, yet more preferably at least 15 wt.-% and in particular at least 20 wt.-%, based on the total weight of the tablet.

In a preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 10±8 wt.-%, more preferably 10±6 wt.-%, most preferably 10±4 wt.-%, and in particular 10±2 wt.-%, based on the total weight of the tablet. In another preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 15±12 wt.-%, more preferably 15±10 wt.-%, most preferably 15±7 wt.-%, and in particular 15±3 wt.-%, based on the total weight of the tablet. In still another preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 20±16 wt.-%, more preferably 20±12 wt.-%, most preferably 20±8 wt.-%, and in particular 20±4 wt.-%, based on the total weight of the tablet. In yet another preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 25±20 wt.-%, more preferably 25±15 wt.-%, most preferably 25±10 wt.-%, and in particular 25±5 wt.-%, based on the total weight of the tablet. In a further preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 30±20 wt.-%, more preferably 30±15 wt.-%, most preferably 30±10 wt.-%, and in particular 30±5 wt.-%, based on the total weight of the tablet. In still a further a preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 35±20 wt.-%, more preferably 35±15 wt.-%, most preferably 35±10 wt.-%, and in particular 35±5 wt.-%. In a still further a preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 40±20 wt.-%, more preferably 40±15 wt.-%, and most preferably 40±10 wt.-%, and in particular 40±5 wt.-%, based on the total weight of the tablet.

Preferably, the content of the physiologically acceptable polymer, preferably the polyalkylene oxide is within the range of from 1 to 99 wt.-%, more preferably 5 to 95 wt.-%, still more preferably 10 to 90 wt.-%, yet more preferably 15 to 85 wt.-%, most preferably 20 to 80 wt.-%

and in particular 25 to 75 wt.-%, based on the total weight of the coated particulates. In a preferred embodiment, the content of the physiologically acceptable polymer, preferably the polyalkylene oxide is at least 10 wt.-%, more preferably at least 15 wt.-%, still more preferably at least 20 wt.-%, yet more preferably at least 25 wt.-% and in particular at least 30 wt.-%, based on the total weight of the coated particulates.

In a preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 30±20 wt.-%, more preferably 30±15 wt.-%, most preferably 30±10 wt.-%, and in particular 30±5 wt.-%, based on the total weight of the coated particulates. In another preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 35±20 wt.-%, more preferably 35±15 wt.-%, most preferably 35±10 wt.-%, and in particular 35±5 wt.-%, based on the total weight of the coated particulates. In still another preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 40±20 wt.-%, more preferably 40±15 wt.-%, most preferably 40±10 wt.-%, and in particular 40±5 wt.-%, based on the total weight of the coated particulates. In yet another preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 45±20 wt.-%, more preferably 45±15 wt.-%, most preferably 45±10 wt.-%, and in particular 45±5 wt.-%, based on the total weight of the coated particulates. In a further preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 50±20 wt.-%, more preferably 50±15 wt.-%, most preferably 50±10 wt.-%, and in particular 50±5 wt.-%, based on the total weight of the coated particulates. In still a further a preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide 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 still further a preferred embodiment, the overall content of physiologically acceptable polymer, preferably polyalkylene oxide is within the range of 60±15 wt.-%, more preferably 60±10 wt.-%, most preferably 60±5 wt.-%, and in particular 60±5 wt.-%, based on the total weight of the coated particulates.

Preferably, the relative weight ratio of the physiologically acceptable polymer, preferably the polyalkylene oxide to the pharmacologically active compound is within the range of 1 : 1.00±0.75, more preferably 1 : 1.00±0.50, still more preferably 1 : 1.00±0.40, yet more preferably 1 : 1.00±0.30, most preferably 1 : 1.00±0.20, and in particular 1 : 1.00±0.10.

The coated particulates according to the invention may contain additional pharmaceutical excipients conventionally contained in tablets in conventional amounts, such as antioxidants, preservatives, lubricants, plasticizer, fillers, binders, and the like.

The skilled person will readily be able to determine appropriate further excipients as well as the quantities of each of these excipients. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate the tablets according to the invention are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

In a preferred embodiment, the coated particulates do not contain a disintegrant.

Preferably, the coated particulates further comprise an antioxidant. 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 present in quantities of 0.01 wt.-% to 10 wt.-%, more preferably of 0.03 wt.-% to 5 wt.-%, most preferably of 0.05 wt.-% to 2.5 wt.-%, based on the total weight of the coated particulates.

In a preferred embodiment, the coated particulates further comprise an acid, preferably citric acid. The amount of acid is preferably in the range of 0.01 wt.-% to about 20 wt.-%, more preferably in the range of 0.02 wt.-% to about 10 wt.-%, and still more preferably in the range of 0.05 wt.-% to about 5 wt.-%, and most preferably in the range of 0.1 wt.-% to about 1.0 wt.-%, based on the total weight of the coated particulates.

In a preferred embodiment, the coated particulates further comprise another polymer which is preferably selected from cellulose esters and cellulose ethers, in particular hydroxypropyl methylcellulose (HPMC).

Other preferred polymers are polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymers, such as the one commercially available under the trade name Soluplus®.

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.-%, most preferably in the range of 2.0 wt.-% to about 15 wt.-%, and in particular in the range of 3.5 wt.-% to about 10.5 wt.-%, based on the total weight of the coated particulates.

In a preferred embodiment, the relative weight ratio of the physiologically acceptable polymer, preferably the polyalkylene oxide to the further polymer is within the range of 4.5±2 : 1, more preferably 4.5±1.5 : 1, still more preferably 4.5±1 : 1, yet more preferably 4.5±0.5 : 1, most preferably 4.5±0.2 : 1, and in particular 4.5±0.1 : 1. In another preferred embodiment, the relative weight ratio of the physiologically acceptable polymer, preferably the polyalkylene oxide to the further polymer is within the range of 8±7 : 1, more preferably 8±6 : 1, still more preferably 8±5 : 1, yet more preferably 8±4 : 1, most preferably 8±3 : 1, and in particular 8±2 : 1. In still another preferred embodiment, the relative weight ratio of the physiologically acceptable polymer, preferably the polyalkylene oxide to the further polymer is within the range of 11±8 : 1, more preferably 11±7 : 1, still more preferably 11±6 : 1, yet more preferably 11±5 : 1, most preferably 11±4 : 1, and in particular 11±3 : 1.

In another preferred embodiment, the coated particulates according to the invention do not contain any further polymer besides the physiologically acceptable polymer, preferably the polyalkylene oxide and optionally, polyethylene glycol.

In a preferred embodiment, the coated particulates contain at least one lubricant. In another preferred embodiment, the coated particulates contain no lubricant. Especially preferred lubricants are selected from

- magnesium stearate and stearic acid;
- glycerides of fatty acids, including monoglycerides, diglycerides, triglycerides, and mixtures thereof; preferably of C_6 to C_{22} fatty acids; especially preferred are partial glycerides of the C_{16} to C_{22} fatty acids such as glycerol behenat, glycerol palmitostearate and glycerol monostearate;
- polyoxyethylene glycerol fatty acid esters, such as mixtures of mono-, di- and triesters of glycerol and di- and monoesters of macrogols having molecular weights within the range of from 200 to 4000 g/mol, e.g., macrogolglycerolcaprylocaprate, macrogolglycerollaurate, macrogolglycerolococoate, macrogolglycerollinoleate, macrogol-20-glycerolmonostearate, macrogol-6-glycerolcaprylocaprate, macrogolglycerololeate; macrogolglycerolstearate, macrogolglycerolhydroxystearate, and macrogolglycerolrizinoleate;
- polyglycolyzed glycerides, such as the one known and commercially available under the trade name "Labrasol";

- fatty alcohols that may be linear or branched, such as cetylalcohol, stearylalcohol, cetylstearyl alcohol, 2-octyldodecane-1-ol and 2-hexyldecane-1-ol;
- polyethylene glycols having a molecular weight between 10.000 and 60.000 g/mol; and
- natural semi-synthetic or synthetic waxes, preferably waxes with a softening point of at least 50 °C, more preferably 60 °C, and in particular carnauba wax and bees wax.

Preferably, the amount of the lubricant ranges from 0.01 wt.-% to about 10 wt.-%, more preferably in the range of 0.05 wt.-% to about 7.5 wt.-%, most preferably in the range of 0.1 wt.-% to about 5 wt.-%, and in particular in the range of 0.1 wt.-% to about 1 wt.-%, based on the total weight of the coated particulates.

Preferably, the coated particulates further comprise a plasticizer. The plasticizer improves the processability of the physiologically acceptable polymer, preferably the polyalkylene oxide. A preferred plasticizer is polyalkylene glycol, like polyethylene glycol, triacetin, fatty acids, fatty acid esters, waxes and/or microcrystalline waxes. Particularly preferred plasticizers are polyethylene glycols, such as PEG 6000.

Preferably, the content of the plasticizer is within the range of from 0.5 to 30 wt.-%, more preferably 1.0 to 25 wt.-%, still more preferably 2.5 wt.-% to 22.5 wt.-%, yet more preferably 5.0 wt.-% to 20 wt.-%, most preferably 6 to 20 wt.-% and in particular 7 wt.-% to 17.5 wt.-%, based on the total weight of the coated particulates.

In a preferred embodiment, the plasticizer is a polyalkylene glycol having a content within the range of 7±6 wt.-%, more preferably 7±5 wt.-%, still more preferably 7±4 wt.-%, yet more preferably 7±3 wt.-%, most preferably 7±2 wt.-%, and in particular 7±1 wt.-%, based on the total weight of the coated particulates.

In another 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 coated particulates.

In a preferred embodiment, the relative weight ratio of the physiologically acceptable polymer, preferably the polyalkylene oxide to the polyalkylene glycol is within the range of 5.4±2 : 1, more preferably 5.4±1.5 : 1, still more preferably 5.4±1 : 1, yet more preferably 5.4±0.5 : 1, most preferably 5.4±0.2 : 1, and in particular 5.4±0.1 : 1. This ratio satisfies the requirements of relative high polymer content and good extrudability.

Plasticizers can sometimes act as a lubricant, and lubricants can sometimes act as a plasticizer.

The coated particulates and the matrix material of the tablets according to the invention preferably do not contain any polymers selected from the group consisting of

- acrylates (such as acrylic and methacrylic polymers including acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers; e.g., Eudragit® NE, NM, RS or RL).
- alkylcelluloses and hydroxy alkyl celluloses (such as methylcellulose, ethylcellulose, hydroxy propyl cellulose and hydroxylpropyl methylcellulose); and
- gelling agents which hydrate to form gels to control the movement of water, such as high molecular weight grade (high viscosity) hydroxypropylmethyl cellulose (HPMC), pectin, locust bean gum and xanthan gum.

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

The tablet according to the invention furthermore preferably contains no antagonists for the pharmacologically active compound, preferably no antagonists against psychotropic substances, in particular no antagonists against opioids. Antagonists suitable for a given pharmacologically active compound 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 tablet 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 tablet 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 tablet 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 tablet according to the invention preferably also contains no apomorphine as an emetic.

Finally, the tablet 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 tablet according to the invention accordingly preferably contains neither substances which irritate the nasal passages and/or pharynx, nor antagonists for the pharmacologically active compound, nor emetics, nor bitter substances.

Particularly preferred contents of pharmacologically active compound, physiologically acceptable polymer, preferably polyalkylene oxide, plasticizer and antioxidant of the coated particulates, relative to the total weight of the coated particulates, are summarized as embodiments B^1 to B^6 in the table here below:

wt.-%	B^1	B^2	B^3	B^4	B^5	B^6
active compound	45±30	45±25	45±20	45±15	45±10	45±5
polymer	45±30	45±25	45±20	45±15	45±10	45±5
plasticizer	8±6	8±5	8±4	8±3	8±2	8±1
antioxidant	0.10±0.08	0.10±0.06	0.10±0.04	0.10±0.03	0.10±0.02	0.10±0.01
coating	4.5±3.7	4.5±3.5	4.5±3.0	4.5±2.5	4.5±2.0	4.5±1.5

wherein the pharmacologically active compound is preferably an opioid, particularly preferably tapentadol or a physiologically acceptable salt thereof; the polymer is preferably a polyalkylene oxide, more preferably a polyethylene oxide having a weight average molecular weight of at least 500,000 g/mol; the plasticizer preferably is a poylethylene glycol; and the antioxidant preferably is α-tocopherol.

Besides the coated particulates and the preferably pre-compacted or granulated matrix material, the tablet according to the invention may comprise one or more pharmaceutical excipients such as binders, fillers, lubricants and the like.

In a preferred embodiment, the table additionally comprises a lubricant. Magnesium stearate is preferred. Further preferred lubricants are described above and therefore are not repeated hereinafter.

If the tablet contains an additional lubricant outside the preferably pre-compacted or pre-granulated matrix material, its content is preferably not more than 1 wt.-%, more preferably not more than 0.5 wt.-%, based on the total weight of the tablet.

While the coated particulates that are contained in the tablet according to the invention preferably exhibit increased mechanical strength, the tablet as such preferably has conventional mechanical properties. Typically, the tablet according to the invention can be crushed e.g. by means of a hammer thereby yielding a fractured composition containing the matrix material, the coated particulates and any other ingredients contained in the tablet.

However, the coated particulates thereby obtained in more or less isolated form preferably cannot be further crushed and fractured by means of a hammer.

Preferably, the coated particulates are hot melt-extruded and/or have a breaking strength of at least 300 N.

The tablet according to the invention is tamper-resistant. Preferably, tamper-resistance is achieved based on the mechanical properties of the coated particulates so that comminution is avoided or at least substantially impeded. According to the invention, the term comminution means the pulverization of the coated particulates 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 coated particulates using conventional means is avoided or at least substantially impeded.

Preferably, the mechanical properties of the coated particulates according to the invention, particularly their breaking strength and deformability, substantially rely on the presence and spatial distribution of physiologically acceptable polymer, preferably polyalkylene oxide, although their mere presence does typically not suffice in order to achieve said properties. The advantageous mechanical properties of the coated particulates according to the invention may not automatically be achieved by simply processing pharmacologically active compound, physiologically acceptable polymer, preferably polyalkylene oxide, and optionally further excipients by means of conventional methods for the preparation of tablets. 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 coated particulates exhibiting the desired properties may be obtained only if, during preparation of the particulates,

- suitable components
- in suitable amounts

are exposed to

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

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

The coated particulates contained in the tablet according to the invention preferably have a breaking strength of at least 300 N, at least 400 N, or 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.

In order to verify whether a particulate exhibits a particular breaking strength of e.g. 300 N or 500 N it is typically not necessary to subject said particulate to forces much higher than 300 N and 500 N, respectively. Thus, the breaking strength test can usually be terminated once the force corresponding to the desired breaking strength has been slightly exceeded, e.g. at forces of e.g. 330 N and 550 N, respectively.

The "breaking strength" (resistance to crushing) of a tablet and of a particulate 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., Tablets: Tablets, Vol. 2, Informa Healthcare; 2 edition, 1990; and Encyclopedia of Pharmaceutical Technology, Informa Healthcare; 1 edition.

For the purpose of specification, the breaking strength is preferably defined as the amount of force that is necessary in order to fracture the particulate (= breaking force). Therefore, for the purpose of specification a particulate 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 particulate is regarded as being broken if the force decreases by 50% (threshold value) of the highest force measured during the measurement (see below).

For the purpose of specification, the mechanical properties of the coated particulates according to the invention essentially refer to the mechanical properties of the core of said coated particulates, but not to its coating. Thus, if the coated particulates according to the invention are exerted to an external force causing the coating material to separate partially of fully from the core, which in turn, however, is not disrupted, the coated particulates still exhibit the desired properties.

The coated particulates according to the invention are distinguished from conventional particulates that can be contained in tablets 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. Avoidance of pulverization virtually rules out oral or parenteral, in particular intravenous or nasal abuse.

Conventional particulates typically have a breaking strength well below 200 N.

The breaking strength of conventional round tablets/particulates may be estimated according to the following empirical formula: Breaking Strength [in N] = 10 x Diameter Of The Tablet/Particulate [in mm]. Thus, according to said empirical formula, a round tablet/particulate having a breaking strength of at least 300 N would require a diameter of at least 30 mm). Such a particulate, however, could not be swallowed, let alone a tablet containing a plurality of such particulates. The above empirical formula preferably does not apply to the coated particulates according to 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 particulates having a breaking strength well below 200 N may be crushed upon spontaneous chewing, whereas the coated particulates according to the invention may preferably not.

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

Methods for measuring the breaking strength of a tablet 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 and particulates, respectively, 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 and particulate, respectively. The apparatus is calibrated using a system with a precision of 1 Newton. The tablet and particulate, respectively, is placed between the jaws, taking into account, where applicable, the shape, the break-mark and the inscription; for each measurement the tablet and particulate, respectively, 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 and particulates, respectively, taking care that all fragments 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 and particulate, respectively, to fail (i.e., break) in a specific plane. The tablets and particulates, respectively, are generally placed between two platens, one of which moves to apply sufficient force to the tablet and particulate, respectively, to cause fracture. For conventional, round (circular cross-section) tablets and particulates, respectively, loading occurs across their diameter (sometimes referred to as diametral loading), and fracture occurs in the plane. The breaking force of tablets and particulates, respectively, 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 and particulate, respectively, 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 and particulate, respectively, 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 2008/107149, 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. A skilled person knows how to properly adjust the test speed, e.g. to 10 mm/min, 20 mm/min, or 40 mm/min, for example. Measurement is performed using a pressure piston with screw-in inserts and a cylinder (diameter 10 mm), a force transducer, F_{max}. 1 kN, diameter = 8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M according to DIN 55350-18 (Zwick gross force F_{max} = 1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany) with Order No BTC-FR 2.5 TH. D09 for the tester, Order No BTC-LC 0050N. P01 for the force transducer, Order No BO 70000 S06 for the centring device.

When using the testControl software (testXpert V10.11), the following exemplified settings and parameters have revealed to be useful: LE-position: clamping length 150 mm. LE-speed: 500 mm/min, clamping length after pre-travel: 195 mm, pre-travel speed: 500 mm/min, no pre-force control – pre-force: pre-force 1N, pre-force speed 10 mm/min – sample data: no sample form, measuring length traverse distance 10 mm, no input required prior to testing – testing / end of test; test speed: position-controlled 10 mm/min, delay speed shift: 1, force shut down threshold 50% F_{max}, no force threshold for break-tests, no max length variation, upper force limit: 600N – expansion compensation: no correction of measuring length – actions after testing: LE to be set after test, no unload of sample – TRS: data memory: TRS distance interval until break 1 µm, TRS time interval 0.1s, TRS force interval 1N – machine; traverse distance controller: upper soft end 358 mm, lower soft end 192 mm – lower test space. Parallel arrangement of the upper plate and the ambos should be ensured - these parts must not touch during or after testing. After testing, a small gap (e.g. 0.1 or 0.2 mm) should still be present between the two brackets in intimated contact with the tested particulate, representing the remaining thickness of the deformed particulate.

In a preferred embodiment, the particulate is regarded as being broken if it is fractured into at least two separate pieces of comparable morphology. Separated matter having a morphology different from that of the deformed particulate, e.g. dust, is not considered as pieces qualifying for the definition of breaking.

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

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The particulate according to the invention is characterized by a certain degree of breaking strength. This does not mean that the particulate must also exhibit a certain degree of hardness. Hardness and breaking strength are different physical properties. Therefore, the tamper-resistance of the tablet does not necessarily depend on the hardness of the coated particulates. For instance, due to its breaking strength, impact strength, elasticity modulus and tensile strength, respectively, the coated particulates 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 coated particulates according to the invention are 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 particulate 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.

Preferred particulates present in the tablets according to the invention are those having a suitable tensile strength as determined by a test method currently accepted in the art. Further preferred particulates are those having a Youngs Modulus as determined by a test method of the art. Still further preferred particulates are those having an acceptable elongation at break.

Irrespective of whether the particulates according to the invention have an increased breaking strength or nor, the particulates according to the invention preferably exhibit a certain degree of deformability. The particulates contained in the tablet according to the invention preferably have a deformability such that they show an increase, preferably a steady increase of the force at a corresponding decrease of the displacement in the force-displacement-diagram when being subjected to a breaking strength test as described above.

This mechanical property, i.e. the deformability of the individual particulates, is illustrated in Figures 5 and 6.

Figure 5 schematically illustrates the measurement and the corresponding force- displacement-diagram. In particular, Figure 5A shows the initial situation at the beginning of the measurement. The sample particulate (9) is placed between upper jaw (8a) and lower jaw (8b) which each are in intimate contact with the surface of the particulate (9). The initial displacement d_0 between upper jaw (8a) and lower jaw (8b) corresponds to the extension of the particulate orthogonal to the surfaces of upper jaw (8a) and lower jaw (8b). At this time, no force is exerted at all and thus, no graph is displayed in the force- displacement-diagram below. When the measurement is commenced, the upper jaw is moved in direction of lower jaw (8b), preferably at a constant speed. Figure 5B shows a situation where due to the movement of upper jaw (8a) towards lower jaw (8b) a force is exerted on particulate (9). Because of its deformability, the particulate (9) is flattened without being fractured. The force-displacement-diagram indicates that after a reduction of the displacement d_0 of upper jaw (8a) and lower jaw (8b) by distance x_1, i.e. at a displacement of $d_1 = d_0 - x_1$, a force F_1 is measured. Figure 5C shows a situation where due to the continuous movement of upper jaw (8a) towards lower jaw (8b), the force that is exerted on particulate (9) causes further deformation, although the particulate (9) does not fracture. The force- displacement-diagram indicates that after a reduction of the displacement d_0 of upper jaw (8a) and lower jaw (8b) by distance x_2, i.e. at a displacement of $d_2 = d_0 - x_2$, a force F_2 is measured. Under these circumstances, the particulate (9) has not been broken (fractured) and a substantially steady increase of the force in the force-displacement-diagram is measured.

In contrast, Figure 6 schematically illustrates the measurement and the corresponding force-displacement-diagram of a conventional comparative particulate not having the degree of deformability as the particulates according to the invention. Figure 6A shows the initial situation at the beginning of the measurement. The comparative sample particulate (9) is placed between upper jaw (8a) and lower jaw (8b) which each are in intimate contact with the surface of the comparative particulate (9). The initial displacement d_0 between upper jaw (8a) and lower jaw (8b) corresponds to the extension of the comparative particulate orthogonal to the surfaces of upper jaw (8a) and lower jaw (8b). At this time, no force is exerted at all and thus, no graph is displayed in the force- displacement-diagram below. When the measurement is commenced, the upper jaw is moved in direction of lower jaw (8b), preferably at a constant speed. Figure 6B shows a situation where due to the movement of upper jaw (8a) towards lower jaw (8b) a force is exerted on comparative particulate (9). Because of some deformability, the comparative particulate (9) is slightly flattened without being fractured. The force-displacement-diagram indicates that after a reduction of the displacement d_0 of upper jaw (8a) and lower jaw (8b) by distance x_1, i.e. at a displacement of $d_1 = d_0 - x_1$, a force F_1 is measured. Figure 6C shows a situation where due to the continuous movement of upper jaw (8a) towards lower jaw (8b), the force that is exerted on particulate (9) causes sudden fracture of the comparative particulate (9). The force- displacement-diagram indicates that after a reduction of the displacement d_0 of upper jaw (8a) and lower jaw (8b) by distance x_2, i.e. at a displacement of $d_2 = d_0 - x_2$, a force F_2 is measured that suddenly drops when the particulate fractures. Under these circumstances, the particulate (9) has been broken (fractured) and no steady increase of the force in the force- displacement-diagram is measured. The sudden drop (decrease) of the force can easily be recognized and does not need to be quantified for the measurement. The steady increase in the force- displacement-diagram ends at displacement $d_2 = d_0 - x_2$ when the particulate breaks.

In a preferred embodiment, the particulates contained in the tablet according to the invention have a deformability such that they show an increase, preferably a substantially steady increase of the force at a corresponding decrease of the displacement in the force- displacement-diagram when being subjected to a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant speed), preferably at least until the displacement d of upper jaw (8a) and lower jaw (8b) has been reduced to a value of 90% of the original displacement d_0 (i.e. $d = 0.9 \cdot d_0$), preferably to a displacement d of 80% of the original displacement d_0, more preferably to a displacement d of 70% of the original displacement d_0, still more preferably to a displacement d of 60% of the original displacement d_0, yet more preferably to a displacement d of 50% of the original displacement d_0, even more preferably to a displacement d of 40% of the original displacement d_0, most preferably to a displacement d of 30% of the original displacement d_0, and in particular to a displacement d of 20% of the original displacement d_0, or to a displacement d of 15% of the original displacement d_0, to a displacement d of 10% of the original displacement d_0, or to a displacement d of 5% of the original displacement d_0.

In another preferred embodiment, the particulates contained in the tablet according to the invention have a deformability such that they show an increase, preferably a substantially steady increase of the force at a corresponding decrease of the displacement in the force-displacement-diagram when being subjected to a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant speed), preferably at least until the displacement d of upper jaw (8a) and lower jaw (8b) has been reduced to 0.80 mm or 0.75 mm, preferably 0.70 mm or 0.65 mm, more preferably 0.60 mm or 0.55 mm, still more preferably 0.50 mm or 0.45 mm, yet more preferably 0.40 mm or 0.35 mm, even more preferably 0.30 mm or 0.25 mm, most preferably 0.20 mm or 0.15 mm and in particular 0.10 or 0.05 mm.

In still another preferred embodiment, the particulates contained in the tablet according to the invention have a deformability such that they show an increase, preferably a substantially steady increase of the force at a corresponding decrease of the displacement in the force-displacement-diagram when being subjected to a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant speed), at least until the displacement d of upper jaw (8a) and lower jaw (8b) has been reduced to 50% of the original displacement d_0 (i.e. $d = d_0/2$), whereas the force measured at said displacement ($d = d_0/2$) is at least 25 N or at least 50 N, preferably at least 75 N or at least 100 N, still more preferably at least 150 N or at least 200 N, yet more preferably at least 250 N or at least 300 N, even more preferably at least 350 N or at least 400 N, most preferably at least 450 N or at least 500 N, and in particular at least 625 N, or at least 750 N, or at least 875 N, or at least 1000 N, or at least 1250 N, or at least 1500 N.

In another preferred embodiment, the particulates contained in the tablet according to the invention have a deformability such that they show an increase, preferably a substantially steady increase of the force at a corresponding decrease of the displacement in the force-displacement-diagram when being subjected to a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant speed), at least until the displacement d of upper jaw (8a) and lower jaw (8b) has been reduced by at least 0.1 mm, more preferably at least 0.2 mm, still more preferably at least 0.3 mm, yet more preferably at least 0.4 mm, even more preferably at least 0.5 mm, most preferably at least 0.6 mm, and in particular at least 0.7 mm, whereas the force measured at said displacement is within the range of from 5.0 N to 250 N, more preferably from 7.5 N to 225 N, still more preferably from 10 N to 200 N, yet more preferably from 15 N to 175 N, even more preferably from 20 N to 150 N, most preferably from 25 N to 125 N, and in particular from 30 N to 100 N.

In yet another embodiment, the particulates contained in the tablet according to the invention have a deformability such that they are deformed without being fractured when subjected to a constant force of e.g. 50 N, 100 N, 200 N, 300 N, 400 N, 500 N or 600 N in a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant force), until the displacement d of upper jaw (8a) and lower jaw (8b) is reduced so that no further deformation takes place at said constant force, whereas at this equilibrated state the displacement d of upper jaw (8a) and lower jaw (8b) is at most 90% of the original displacement d_0 (i.e. $d \leq 0.9 \cdot d_0$), preferably at most 80% of the original displacement d_0 (i.e. $d \leq 0.8 \cdot d_0$), more preferably at most 70% of the original displacement d_0 (i.e. $d \leq 0.7 \cdot d_0$), still more preferably at most 60% of the original displacement d_0 (i.e. $d \leq 0.6 \cdot d_0$), yet more preferably at most 50% of the original displacement d_0 (i.e. $d \leq 0.5 \cdot d_0$), even more preferably at most 40% of the original displacement d_0 (i.e. $d \leq 0.4 \cdot d_0$), most preferably at most 30% of the original displacement d_0 (i.e. $d \leq 0.3 \cdot d_0$), and in particular at most 20% of the original displacement d_0 (i.e. $d \leq 0.2 \cdot d_0$), or at most 15% of the original displacement d_0

(i.e. $d \leq 0.15 \cdot d_0$), at most 10% of the original displacement d_0 (i.e. $d \leq 0.1 \cdot d_0$), or at most 5% of the original displacement d_0 (i.e. $d \leq 0.05 \cdot d_0$).

Preferably, the particulates contained in the tablet according to the invention have a deformability such that they are deformed without being fractured when subjected to a constant force of e.g. 50 N, 100 N, 200 N, 300 N, 400 N, 500 N or 600 N in a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant force), until the displacement d of upper jaw (8a) and lower jaw (8b) is reduced so that no further deformation takes place at said constant force, whereas at this equilibrated state the displacement d of upper jaw (8a) and lower jaw (8b) is at most 0.80 mm or at most 0.75 mm, preferably at most 0.70 mm or at most 0.65 mm, more preferably at most 0.60 mm or at most 0.55 mm, still more preferably at most 0.50 mm or at most 0.45 mm, yet more preferably at most 0.40 mm or at most 0.35 mm, even more preferably at most 0.30 mm or at most 0.25 mm, most preferably at most 0.20 mm or at most 0.15 mm and in particular at most 0.10 or at most 0.05 mm.

In another embodiment, the particulates contained in the tablet according to the invention have a deformability such that they are deformed without being fractured when subjected to a constant force of e.g. 50 N, 100 N, 200 N, 300 N, 400 N, 500 N or 600 N in a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant force), until the displacement d of upper jaw (8a) and lower jaw (8b) is reduced so that no further deformation takes place at said constant force, whereas at this equilibrated state the displacement d of upper jaw (8a) and lower jaw (8b) is at least 5% of the original displacement d_0 (i.e. $d \geq 0.05 \cdot d_0$), preferably at least 10% of the original displacement d_0 (i.e. $d \geq 0.1 \cdot d_0$), more preferably at least 15% of the original displacement d_0 (i.e. $d \geq 0.15 \cdot d_0$), still more preferably at least 20% of the original displacement d_0 (i.e. $d \geq 0.2 \cdot d_0$), yet more preferably at least 30% of the original displacement d_0 (i.e. $d \geq 0.3 \cdot d_0$), even more preferably at least 40% of the original displacement d_0 (i.e. $d \geq 0.4 \cdot d_0$), most preferably at least 50% of the original displacement d_0 (i.e. $d \geq 0.5 \cdot d_0$), and in particular at least 60% of the original displacement d_0 (i.e. $d \geq 0.6 \cdot d_0$), or at least 70% of the original displacement d_0 (i.e. $d \geq 0.7 \cdot d_0$), at least 80% of the original displacement d_0 (i.e. $d \geq 0.8 \cdot d_0$), or at least 90% of the original displacement d_0 (i.e. $d \geq 0.9 \cdot d_0$).

Preferably, the particulates contained in the tablet according to the invention have a deformability such that they are deformed without being fractured when subjected to a constant force of e.g. 50 N, 100 N, 200 N, 300 N, 400 N, 500 N or 600 N in a breaking strength test as described above ("Zwick Z 2.5" materials tester, constant force), until the displacement d of upper jaw (8a) and lower jaw (8b) is reduced so that no further deformation takes place at said constant force, whereas at this equilibrated state the displacement d of upper jaw (8a) and lower jaw (8b) is at least 0.05 mm or at least 0.10 mm, preferably at least 0.15 mm or at least 0.20 mm, more preferably at least 0.25 mm or at least 0.30 mm, still more preferably at least 0.35 mm or at least 0.40 mm, yet more preferably at least 0.45 mm or at least 0.50 mm, even more preferably at least 0.55 mm or at least 0.60 mm, most preferably at least 0.65 mm or at least 0.70 mm and in particular at least 0.75 or at least 0.80 mm.

Preferably, the tablet according to the invention provides under *in vitro* conditions immediate release of the pharmacologically active compound in accordance with Ph. Eur.

The term "immediate release" as applied to tablets is understood by persons skilled in the art which has structural implications for the respective tablets. The term is defined, for example, in the current issue of the US Pharmacopoeia (USP), General Chapter 1092, "THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION", heading "STUDY DESIGN", "Time Points". For immediate-release dosage forms, the duration of the procedure is typically 30 to 60 minutes; in most cases, a single time point specification is adequate for Pharmacopeia purposes. Industrial and regulatory concepts of product comparability and performance may require additional time points, which may also be required for product registration or approval. A sufficient number of time points should be selected to adequately characterize the ascending and plateau phases of the dissolution curve. According to the Biopharmaceutics Classification System referred to in several FDA Guidances, highly soluble, highly permeable drugs formulated with rapidly dissolving products need not be subjected to a profile comparison if they can be shown to release 85% or more of the active drug substance within 15 minutes. For these types of products a one-point test will suffice. However, most products do not fall into this category. Dissolution profiles of immediate-release products typically show a gradual increase reaching 85% to 100% at about 30 to 45 minutes. Thus, dissolution time points in the range of 15, 20, 30, 45, and 60 minutes are usual for most immediate-release products.

Preferably, under physiological conditions the tablet according to the invention has released after 30 minutes at least 70%, more preferably at least 75%, still more preferably at least 80%, yet more preferably at least 82%, most preferably at least 84% and in particular at east 86% of the pharmacologically active compound originally contained in the tablet.

Preferably, under physiological conditions the tablet according to the invention has released after 10 minutes at least 70%, more preferably at least 73%, still more preferably at least 76%, yet more preferably at least 78%, most preferably at least 80% and in particular at east 82% of the pharmacologically active compound originally contained in the tablet.

Further preferred release profiles C^1 to C^{10} are summarized in the table here below [all data in wt.-% of released pharmacologically active compound]:

time	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}
10 min	≥ 30	≥ 35	≥ 40	≥ 45	≥ 50	≥ 60	≥ 70	≥ 80	≥ 80	≥ 80
20 min	≥ 50	≥ 55	≥ 60	≥ 65	≥ 70	≥ 75	≥ 80	≥ 85	≥ 90	≥ 95
30 min	≥ 55	≥ 60	≥ 65	≥ 70	≥ 75	≥ 85	≥ 90	≥ 95	≥ 95	≥ 95
40 min	≥ 60	≥ 65	≥ 70	≥ 80	≥ 85	≥ 90	≥ 95	≥ 95	≥ 95	≥ 95
50 min	≥ 65	≥ 70	≥ 80	≥ 85	≥ 88	≥ 92	≥ 95	≥ 95	≥ 95	≥ 95
60 min	≥ 75	≥ 80	≥ 85	≥ 90	≥ 92	≥ 94	≥ 95	≥ 95	≥ 95	≥ 95

Preferably, the release profile, the drug and the pharmaceutical excipients of the tablet according to the invention are stable upon storage, preferably upon storage at elevated temperature, e.g. 40°C, for 3 months in sealed containers.

In connection with the release profile "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%.

In connection with the drug and the pharmaceutical excipients "stable" means that the tablets satisfy the requirements of EMEA concerning shelf-life of pharmaceutical products.

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 without sinker, 50 rpm, 37±5 °C, 900 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 75 rpm.

In a preferred embodiment, the tablet according to the invention is adapted for administration once daily. In another preferred embodiment, the tablet according to the invention is adapted for administration twice daily. In still another preferred embodiment, the tablet according to the invention is adapted for administration thrice daily. In yet another preferred embodiment, the tablet according to the invention is adapted for administration more frequently than thrice daily, for example 4 times daily, 5 times daily, 6 times daily, 7 times daily or 8 times daily.

For the purpose of 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 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 tablet according to the invention has under *in vitro* conditions a disintegration time measured in accordance with Ph. Eur. of at most 5 minutes, more preferably at most 4 minutes, still more preferably at most 3 minutes, yet more preferably at most 2.5 minutes, most preferably at most 2 minutes and in particular at most 1.5 minutes.

It has been surprisingly found that oral dosage forms can be designed that provide the best compromise between tamper-resistance, disintegration time and drug release, drug load, processability (especially tablettability) and patient compliance.

It has been found that the disintegration time of the tablets according to the invention can be influenced by the relative weight ratio of matrix material: particulates. In general, it was observed that the higher this ratio the faster disintegration. However, this ratio cannot be increased ad ultimo, as further tablet properties need to be taken into account, particularly drug load and total tablet size and weight. As a certain dosage of pharmacologically active compound needs to be administered, the content of particulates should still be sufficiently high and the total tablet weight should not exceed a certain limit, as this would deteriorate patient compliance, e.g. swallowability.

The situation is more complicated by trends in opposite direction. In particular, it has been found that the tablettability of the tablets according to the invention can also be influenced by the relative weight ratio of matrix material : particulates. In general, it was observed that the lower this ratio the better the tablettability. This trend parallels the trend of the drug load.

Thus, disintegration time on the one hand and tablettability/drug load on the other hand can be optimized by finding the best compromise.

Similarly, tamper-resistance and drug release also antagonize each other. While smaller particulates should typically show a faster release of the pharmacologically active compound, tamper-resistance requires some minimal size of the coated particulates in order to effectively prevent abuse, e.g. i.v. administration. The larger the coated particulates are the less they are suitable for being abused nasally. The smaller the coated particulates are the faster gel formation occurs.

Thus, drug release on the one hand and tamper-resistance on the other hand can be optimized by finding the best compromise.

Preferred embodiments D^1 to D^4 of the tablets according to the invention are summarized in the table here below:

[wt.-%, relative to weight of tablet]	D^1	D^2	D^3	D^4
tablet				
- total weight [mg]	500±300	500±250	500±200	500±150
coated particulates				
- total content [wt.-%]	50±15	50±12.5	50±10	50±7.5
- average particle size [µm]	800±400	800±300	800±200	800±100
- content of ph. active compound	23±20	23±15	23±10	23±5
- content of polymer [wt.-%]	22±12	22±10	22±8	22±6
- content of plasticizer [wt.-%]	4±3.5	4±3	4±2.5	4±2
- content of further excipients [wt.-%]	0.05±0.05	0.05±0.04	0.05±0.03	0.05±0.02
- content of coating material [wt.-%]	2.0±1.8	2.0±1.6	2.0±1.4	2.0±1.2
matrix material				
- total content [wt.-%]	49±15	49±12	49±9	49±6
- content of filler(s)/binder(s) [wt.-%]	43±10	43±8	43±6	43±4
- content of disintegrant [wt.-%]	5±4	5±3.5	5±3	5±2.5
- content of lubricant [wt.-%]	0.15±0.15	0.15±0.14	0.15±0.13	0.15±0.12

The coated particulates according to the invention are preferably prepared by melt-extrusion, although also other methods of thermoforming may be used in order to manufacture the coated particulates according to the invention such as press-molding at elevated temperature or heating of particulates that were manufactured by conventional compression in a first step and then heated above the softening temperature of the physiologically acceptable polymer, preferably the polyalkylene oxide in the coated particulates 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 coated particulates are thermoformed by hot-melt extrusion.

In a preferred embodiment, the coated particulates are 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 optionally compressed and formed into particulates. 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, at elevated temperature, e.g. when the extruded stand is still warm due to hot-melt extrusion, or at ambient temperature, i.e. after the extruded strand has been allowed to cool down. When the extruded strand is still warm, singulation of the extruded strand into extruded particulates is preferably performed by cutting the extruded strand immediately after it has exited the extrusion die. However, when the extruded strand is cut in the cooled state, subsequent singulation of the extruded strand into extruded particulates is preferably performed by optionally transporting the still hot extruded strand by means of conveyor belts, allowing it to cool down and to congeal, and subsequently cutting it into extruded particulates. 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 particulates. 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 coated particulates 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.

In general, the process for the production of the coated particulates 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 physiologically acceptable polymer, preferably the polyalkylene oxide 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 physiologically acceptable polymer, preferably the polyalkylene oxide at least up to its softening point; and thereafter allowing the material to cool and removing the force

(d) optionally singulating the hardened mixture;

(e) optionally shaping the particulates; and

(f) providing a coating, preferably 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; or is indirectly supplied by friction and/or shear. Force may be applied and/or the particulates 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 one or two screws (single-screw-extruder and twin-screw-extruder, respectively) or by means of a planetary gear extruder.

The final shape of the particulates 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 physiologically acceptable polymer, preferably the polyalkylene oxide. 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.

Suitable methods for providing particulates with a coating, preferably with a film coating, are known to the skilled person such as fluidized bed coating, pan-coating, coazervation, , dry powder coating, extrusion coating, and phoqus technology (copy-coating). Preferably, the particulates are coated by spraying (top-spray or bottom-spray) e.g. in a fluidized bed spray dry granulator.

A particularly preferred process for the manufacture of the coated particulates according to the invention involves hot-melt extrusion. In this process, the coated particulates according to the invention are 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 physiologically acceptable polymer, preferably the polyalkylene oxide and extruded through the outlet orifice of the extruder by application of force,

c) the still plastic extrudate is singulated and formed into the particulates or

d) the cooled and optionally reheated singulated extrudate is formed into the particulates.

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 physiologically acceptable polymer, preferably polyalkylene oxide is extruded from the extruder through a die with at least one bore.

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

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 physiologically acceptable polymer, preferably the polyalkylene oxide 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 0.5 kg/hour 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 200 bar. The die head pressure can be adjusted inter alia by die geometry, temperature profile, extrusion speed, number of bores in the dies, screw configuration, first feeding steps in the extruder, and the like.

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 2 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 physiologically acceptable polymer, preferably the polyalkylene oxide and does not rise above a temperature at which the pharmacologically active compound 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 the physiologically acceptable polymer, preferably the polyalkylene oxide. Typical extrusion temperatures are 120 °C and 150 °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, extrusion speed, number of bores in the dies, screw configuration, first feeding steps in the extruder, and the like.

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, 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 particulates 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 particulates in order to impart the final shape to the particulates.

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 tablet 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 or blunt ends may be used. A heatable die with a round bore or with a multitude of bores each having a diameter of 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 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 3 kg/h, 8 kg/h, or even 10 kg/h and more for a ZSE27; product temperature: in front of die 125 °C and behind die 135 °C; and jacket temperature: 110 °C. The throughput can generally be increased by increasing the number of dies at the extruder outlet.

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

Preferably, the coated particulates according to the invention can be regarded as "extruded pellets". The term "extruded pellets" has structural implications which are understood by persons skilled in the art. A person skilled in the art knows that pelletized dosage forms can be prepared by a number of techniques, including:

- drug layering on nonpareil sugar or microcrystalline cellulose beads,
- spray drying,
- spray congealing,
- rotogranulation,

- hot-melt extrusion,
- spheronization of low melting materials, or
- extrusion-spheronization of a wet mass.

Accordingly, "extruded pellets" can be obtained either by hot-melt extrusion or by extrusion-spheronization.

"Extruded pellets" can be distinguished from other types of pellets, as extruded pellets typically have a different shape. The shape of the extruded pellets is typically more cut-rod-like than perfectly globated round.

"Extruded pellets" can be distinguished from other types of pellets because they are structurally different. For example, drug layering on nonpareils yields multilayered pellets having a core, whereas extrusion typically yields a monolithic mass comprising a homogeneous mixture of all ingredients. Similarly, spray drying and spray congealing typically yield spheres, whereas extrusion typically yields cylindrical extrudates which can be subsequently spheronized.

The structural differences between “extruded pellets” and “agglomerated pellets” are significant because they may affect the release of active substances from the pellets and consequently result in different pharmacological profiles. Therefore, a person skilled in the pharmaceutical formulation art would not consider “extruded pellets” to be equivalent to “agglomerated pellets”.

The tablets according to the invention may be prepared by any conventional method. Preferably, however, the tablets are prepared by compression. Thus, coated particulates as hereinbefore defined are preferably mixed, e.g. blended and/or granulated (e.g. wet granulated), with matrix material and the resulting mix (e.g. blend or granulate) is then compressed, preferably in moulds, to form tablets. It is also envisaged that the coated particulates herein described may be incorporated into a matrix using other processes, such as by melt granulation (e.g. using fatty alcohols and/or water-soluble waxes and/or water-insoluble waxes) or high shear granulation, followed by compression.

When the tablets according to the invention are manufactured by means of an eccentric press, the compression force is preferably within the range of from 5 to 15 kN. When the tablets according to the invention are manufactured by means of a rotating press, the compression force is preferably within the range of from 5 to 40 kN, in certain embodiments >25 kN, in other embodiments about 13 kN.

The tablets according to the invention may optionally comprise a coating, e.g. a cosmetic coating. The coating is preferably applied after formation of the tablet. The coating may be applied prior to or after the curing process. Preferred coatings are Opadry® coatings available from Colorcon. Other preferred coating are Opaglos® coatings, also commercially available from Colorcon.

The tablet according to the invention is characterized by excellent storage stability. Preferably, after storage for 4 weeks at 40°C and 75% rel. humidity, the content of pharmacologically active compound 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 compound in the tablet 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 tablet is stored in closed, preferably sealed containers.

Further aspects according to the invention - basis for additional claim categories

The coated particulates and tablets according to the invention may be used in medicine, e.g. as an analgesic. The coated particulates and tablets are therefore particularly suitable for the treatment or management of pain. In such tablets, the pharmacologically active compound is preferably an analgesic.

A further aspect according to the invention relates to the tablet as described above for use in the treatment of pain.

A further aspect according to the invention relates to the use of a tablet as described above for avoiding or hindering the abuse of the pharmacologically active compound contained therein.

A further aspect according to the invention relates to the use of a tablet as described above for avoiding or hindering the unintentional overdose of the pharmacologically active compound contained therein.

In this regard, the invention also relates to the use of a pharmacologically active compound as described above and/or a physiologically acceptable polymer, preferably a polyalkylene oxide as described above for the manufacture of the tablet according to the invention for the prophylaxis and/or the treatment of a disorder, thereby preventing an overdose of the pharmacologically active compound, particularly due to comminution of the tablet by mechanical action.

EXAMPLES

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

Example 1:

The relevance of the particulate size on tamper resistance was investigated.

It was found that comparatively small particulates, e.g. particulates having a diameter and length of 0.5 mm x 0.5 mm already provide a certain degree of tamper resistance: when administered nasally they cause an unpleasant feeling and furthermore, due to the lack of water on the mucous membrane, do not release the pharmacologically active compound as quick as when being administered orally. Therefore, a kick or rush can unlikely be achieved by nasal administration of such particulates. Thus, even when being administered nasally, such comparatively small particulates already provide tamper resistance, i.e. avoid drug abuse or at least make drug abuse substantially more difficult. Furthermore, such comparatively small particulates have excellent swelling properties thereby effectively preventing conversion into a liquid formulation for intravenous administration.

It was found that tamper-resistance can even further be improved by increasing the particulate size, e.g. to a diameter and length of 1.0 mm x 1.0 mm. Such particulates even provide a more unpleasant feeling when being administered nasally and in the absence of sufficient water, rather slowly release the pharmacologically active compound. Further, they cannot be easily converted into a liquid formulation for intravenous administration either.

As such a more pronounced retardant effect, however, is detrimental for the desired immediate release upon prescribed oral administration of the tablets, a compromise must be found between tamper resistance on the one hand and immediate drug release upon prescribed oral administration on the other hand, particularly with respect to disintegration time and drug release kinetics. Furthermore, drug load, processability (especially tablettability) and patient compliance are also important requirements to be satisfied with.

A predetermined particulate size of 800 µm x 800 µm was considered most appropriate, i.e. it was considered most appropriate to adjust the diameter of the extrusion die as well as cutting length of the extruded stand to 800 µm taking into consideration that die swelling may occur during the extrusion process, particularly when the strand exits the die, so that the diameter of the extruded strand in fact is expanded, depending upon the composition and the extrusion parameters to a diameter of about 1000 µm. Thus, when proceedings this way, it was considered most appropriate to manufacture extruded particulates having a diameter of about 1000 µm (after die swelling, diameter of extrusion die 800 µm) and a length of about 800 µm.

Example 2:

Different particulate compositions were investigated and particulates of different sizes were manufactured thereform.

The particulate compositions are summarized in the table here below:

[wt.-%]	1	2	3	4	5	6	7	8	9
Tramadol HCl	46.59	46.59	46.59	38.83	-	-	-	-	45.59
Tapentadol HCl	-	-	-	-	46.59	46.59	46.59	33.28	-
PEG 6000	5.31	6.32	4.31	8.33	8.31	8.31	8.32	10.00	8.40
HPMC 100 000	5.00	6.00	4.00	9.33	-	-	8.00	12.57	8.00
PEO 7 Mio	33.00	35.99	45.00	43.49	45.00	45.00	36.99	44.14	36.99
α-tocopherol	0.10	0.10	0.10	0.01	0.10	0.10	0.1	0.01	0.01
Lutrol 127	10.00	-	-	-	-	-	-	-	-
PVP CL	-	5.00	-	-	-	-	-	-	-
total weight [mg]	250 mg	250 mg	250 mg	300 mg	250 mg	250 mg	250 mg	350 mg	250 mg
film coating AMB varnish	-	-	-	-	-	3.88	-	-	-

All materials were weighed, sieved (manual sieve, 1 mm), blended (Bohle LM40 with MC5 or MC10, depending on size of bath) for 15 minutes at 14 rpm, and hot-melt extruded (Leistritz extruder Type ZSE18 with different configuration of screws).

The compositions 1 to 9 were extruded under the following extrusion conditions:

	1, 4, 7, 9	2	3	5 and 6	8
Heating zone 1	20°C	20°C	20°C	20	25
Heating zone 2	100°C	100°C	100°C	100	100
Heating zone 3	100°C	100°C	100°C	100	100
Heating zone 4	120°C	140°C	120°C	120	100
Heating zone 5	120°C	120°C	120°C	120	100
Heating zone 6	120°C	120°C	120°C	120	100
Heating zone 7	120°C	140°C	120°C	120	100
Heating zone 8	120°C	140°C	120°C	120	100
Heating zone 10	120°C	140°C	120°C	120	120
Heating zone 11	130°C	150°C	130°C	130	120
Screw speed [rpm]	100	100	100	100	100
Throughput [g/min]	10.00-16.66	16.66-28.04	16.66	16.66	16.66
Screw configuration	low shear	low shear	low shear	extreme shear	low shear

For larger scales, screw configuration can be adopted and temperatures can be raised (e.g., HZ8 and 10: 130°C, HZ11: 145°C; or HZ11: 150°C and extreme shear configuration, throughput 25 g/min).

The in vitro release characteristics were monitored in 900mL 0.1N HCl at 37°C, using a paddle apparatus 50 rpm. The results are depicted in Figure 3.

Example 3:

The influence of the content of particulates in the tablet was investigated.

The following compositions were tested:
300 mg particulates in tablets having a total weight of 600 mg
250 mg particulates in tablets having a total weight of 600 mg
200 mg particulates in tablets having a total weight of 600 mg

The most promising compromise between tablettability and size revealed to be 250 mg particulates in tablets having a total weight of 500 mg. Tablets having a total weight of 600 mg were considered too large with respect to patient compliance, although the relative weight ratio of particulates to matrix material of about 1:1 appeared advantageous with respect to disintegration time and dissolution time.

Example 4-1:

The influence of the matrix material was investigated - wet granulation.

Granules having the following composition were prepared for manufacturing of pellet-tablets. Granules for outer the phase, i.e. the matrix material, were manufactured by wet granulation. Granules and pellets were blended. Segregation (optically) and disintegration of tablets after compression were evaluated. Tablets were manufactured "manually" (components were separately weighed for each tablet and mixed directly prior to tabletting) using a single station press (Korsch EK0):

a	Galen IQ, Na carboxymethylstarch (5%) aqueous granulation in Diosna	no segregation in mixture detectable,	disintegration test: no detectable disintegration after 3 min.
b	Galen IQ, Kollidon CL (5%) aqueous granulation in Diosna	no segregation in mixture detectable mixture showed substantial punch deposit upon compression of 3 tablets already	disintegration test: slightly dissolved surface after 3 min.
c	Avicel with PVP-solution granulated	significant segregation in mixture detectable	disintegration test: partial disintegration after 3 min.
d	MCC+lactose(20:80) with PVP-solution granulated	no segregation in mixture detectable	disintegration test: no detectable disintegration after 3 min.
d	MCC+lactose (50:50) with PVP-solution granulated	slight segregation in mixture detectable	disintegration test: partial disintegration after 3 min.
e	Gelcarin + lactose (20%+80%) + water (57% + 43%)	no segregation in mixture detectable	disintegration test: no detectable disintegration after 3 min.
f	sugar ester S-1570 + tricalcium-phosphate + Acivel + Gelcarin	significant segregation in mixture detectable	disintegration test: no detectable disintegration after 3 min.
g	incrustation granulate from saccharose	the granulate could not be processed or only with difficulties blending with particulates is not possible -> thus, no tablets were manufactured	no tablets manufactured

It was not possible to manufacture rapidly disintegrating tablets from the above compositions, probably because the disintegrants lose the disintegrating capacity in the course of the wet granulation process.

Example 4-2:

The influence of the matrix material was investigated - dry granulation - roller compaction.

The following compositions were processed by slugging involving the steps of:

- weighing / dispensing of components
- sieving / blending
- manufacture of bi-planar tablets of 20 mm diameter using a single station press (Korsch EK0), 25 kN compression force
- breaking the tablets into parts (manually) and sieving using a Frewitt Sieving machine (1.5 mm mesh size)
- employing granules as outer phase / matrix material for pellet-tablets

The experimental results are summarized in the following table:

	released after 30 min	excipient	Tramadol Pellets	Avicel 101	Lactose	Mg-stearate	PVP CL	Esma-spreng	Primojel	NaCMC	compacted material (compression force 20-25kN)	tablet surface (compression force 7.5 kN)	disinte-gration	film coated	form
a	87,4 (5 kN)		50.00%	22.25%	22.25%	0.50%	5.00%				OK	-	+	no	Round 12 mm biplan (5 kN and 10 kN), oblong 7x17 mm (7.5 kN)
b	64.1		50.00%	45.00%			5.00%				OK	0	+	no	Round 12 mm biplan
c	n.d.	15% PEG6000	50.00%	29.5%		0.50%	5.00%				OK	-	--	no	Round 12 mm biplan
d	87.7		50.00%	45.00%				5.00%			slightly unstable	++	++	no	Round 12 mm biplan
e	72.2		50.00%	45.00%						5.00%	OK	0	+	no	Round 12 mm biplan
f	n.d.		50.00%	45.00%					5.00%		OK	0	-	no	Round 12 mm biplan
g	n.d.	15% $NaHCO_3$ 10% citric acid	50.00%	25.00%							adheres punch to matrix	-	--	no	Round 12 mm biplan
i	71.1	1% xanthan	50.00%	44.00%			5.00%				can only be compacted with difficulties	-	0	no	Round 12 mm biplan
j-1	77.4	45% Prosolv SMCCHD90	50.00%				5.00%				OK	+	++	no	Round 12 mm

															biplan
j-2	81.2	50% Prosolv SMCCHD90	50.00%								OK	0	++	no	Round 12 mm biplan
k	28.4	45% Parteck	50.00%				5.00%				OK	0	+	no	
l	n.d.	50% Zaldiar effervescent tablet	50.00%								adheres punch to matrix	-	--	no	Round 12 mm biplan
m	77.6		50.00%	22.25%	22.25%	0.50%				5.00%	OK	+		no	Round 12 mm biplan
m'	89.9		50.98%	21.81%	21.81%	0.49%				4.90%	OK	+		yes	Round 12 mm biplan
n	78.2		50.00%	22.25%	22.25%	0.50%		5.00%			OK	0		no	Round 12 mm biplan
n'	92.9		50.98%	21.81%	21.81%	0.49%		4.90%			OK	0		yes	Round 12 mm biplan
n"	86.3		50.98%	21.81%	21.81%	0.49%		4.90%			OK	0		yes	penta-gonal
o	60.0	45% Prosolv SMCCHD90	50.00%							5.00%	OK	0		no	Round 12 mm biplan
o'	90.5	44.12% Prosolv SMCCHD90	50.98%							4.90%	OK	0		yes	Round 12 mm biplan
o"	75.4	44.12% Prosolv SMCCHD90	50.98%							4.90%	OK	0		yes	penta-gonal
p	74.3	45% Prosolv SMCCHD90	50.00%					5.00%			OK	0		no	Round 12 mm biplan
p'	93.5	44.12% Prosolv SMCCHD90	50.98%					4.90%			OK	0		yes	Round 12 mm biplan
q	54.3		50.00%	42.50%						7.50%	OK	0		no	Round 12

															mm biplane
q'	60.2		50.98%	41.67%						7.35%	OK	0		yes	Round 12 mm biplane
r	69.3		50.00%	42.50%					7.50%		OK	0		no	Round 12 mm biplane
r'	84.8		50.98%	41.67%					7.35%		OK	0		yes	Round 12 mm biplane
u	39.9	50% MicroceLac	50.00%											no	Round 12 mm biplane
u'	70.3	50% MicroceLac	50.00%											yes	Round 12 mm biplane
v	78.6	50% EASYtab SP	50.00%											no	Round 12 mm biplane
v'	93.5	50% EASYtab SP	50.00%									+	+	yes	Round 12 mm biplane
w	n.d.	50% EASYtab SP	50.00%									+	++	no	Round 12 mm biplane
w'	n.d.	50% EASYtab SP	50.00%											yes	Round 12 mm biplan

++ good, + satisfactory, 0 acceptable, - deficient, -- inacceptable

It is clear from the experimental data provided in the above table (column 3, "released after 30 min") that the coating of the particulates causes a substantial acceleration of drug release (m vs. m'; n vs. n' and n''; o vs. o' and o''; p vs. p'; q vs. q'; r vs. r'; u vs. u'; v vs. v'; w vs. w').

The release characteristics of tablets containing the thus compacted matrix material were investigated. The results are depicted in Figure 4 (900 mL HCl, 50 rpm, paddle apparatus without sinker).

Example 4-3:

Since the slugging method is not state of the art for dry granulation, corresponding tests concerning dry granulation were conducted by means of a roller compactor. This has the advantage that all relevant parameters (roller displacement, compression force, granulator size) can be adjusted such that a granulate having the desired properties is obtained (particle size, hardness, compressibility, density).

Parameters (Gerteis MiniPactor):
roller displacement: 2 to 3 mm
revolution velocity: 2 to 5 rpm
compaction force: 3 to 15 kN/cm
screen size: 1.0 to 1.25 to 1.5 to 2.0 mm

The thus prepared compacts (dry granulates) were blended with particulates and compressed to tablets. Upon blending, lubricant (magnesium stearate and sodium stearylfumarate, respectively) was added as an external excipient neither contained in the compacts nor in the particulates.

Batch	#1	#2	#3	#4	#5
Avicel PH 101	95.00%		50.00%		
Esma Spreng	5.00%				
Prosolv SMCC HD 90		95.00%		100.00%	
Na-CMC		5.00%			
Lactose Monohydrate 230			50.00%		
Prosolv Easytab					100.00%

The experiments revealed that tablets made from compacts and made from slugging-granulates show a similarly fast release.

Confirming experiments:

Batch	#6	#7	#8	#9	#10	#11	#12

Avicel PH 101	89.5%	94.5		89%	89.50%		89.70%
Avicel DG						89.5%	
Esma Spreng	10.00%	5%					
Prosolv SMCC HD 90			87.5%				
Na-CMC			12%				
PVP CL				10%	10%	10%	10%
Na-stearylfumarate				1%			
Mg stearate	0.5	0.5	0.5%		0.5	0.5%	0.3%

Example 4-4:

Tablets (500 mg) were prepared from the particulates according to Example 2-5 (250 mg) and the matrix material according to Example 4-3 #12 (250 mg).

The in vitro release was determined according to Ph. Eur.:

time	% released (n=6)
0	0.0
5	56.8
10	83.4
15	93.3
20	98.1
25	99.9
30	101.1
35	101.4
40	101.7
45	101.9
50	102.0
55	102.0
60	102.0

The in vitro release of the tablets was compared to a non-tamper resistant commercial product containing Tapentadol HCl (film coated tablets). After 30 minutes (according to Ph. Eur. 2.9.3), both formulations released the entire amount of the pharmacologically active ingredient (100%).

Example 5:

The mechanical properties of conventional, commercial neutral pellets were investigated under the following conditions:

	5-1 (comparative)	5-2	5-3
product	pellets neutral (Hans G. Werner GmbH & Co.)	tramadol TRF IR pellets	tramadol TRF IR pellets
Tramadol HCl		46.59 wt.-%	4.17 wt.-%
PEG 6000		8.31 wt.-%	8.33 wt.-%
vitamin E		0.10 wt.-%	0.20 wt.-%
PEO		45.00 wt.-%	87.30 wt.-%
diameter pellets	0.85 mm - 1.00 mm		
test equipment	Zwick / Roell		
type	BTC-FR2.5TH.D09		
force sensor	KAF-TC / 2.5 kN		
software applications	testXpert V10.11		
measuring equipment	plate 2.5 cm x 9.0 cm + ambos 2.0 cm x 4.0 cm		
speed	10 mm/min		
softend	192 mm	192 mm	192 mm

The reduction of the displacement between plate and ambos x in mm (= "compression [c]") and the corresponding force f in N were measured. The maximum force f_{max} measured during the measurement and the corresponding reduction of displacement x_{max} are summarized in the table here below:

	5-1 (Figure 7)		5-2 (Figure 8)		5-3 (Figure 9)	
	f_{max} [N]	x_{max} [mm]	f_{max} [N]	x_{max} [mm]	f_{max} [N]	x_{max} [mm]
mean	5.272	0.01	587.285	0.87	588.255	0.89
s	2.129	0.03	2.320	0.06	2.897	0.05
v	40.37	198.70	0.40	6.73	0.49	5.13
min	2.260	0.00	585.226	0.82	583.385	0.82
max	8.432	0.08	592.581	1.00	592.413	0.96

It becomes clear from the above data that the comparative particulates of example 5-1 break at very low forces of only about 5 N and can be deformed by less than 0.1 mm. In contrast, the inventive particulates of examples 5-2 and 5-3 do not break at all, and can be deformed (flattened) by more than 0.8 mm.

The corresponding force-displacement-diagrams are shown in Figures 7, 8 and 9, respectively.

2012289764 16 Jan 2017

CLAIMS

1. A tamper-resistant tablet comprising
   (i) a matrix material in an amount of more than one third of the total weight of the tablet; and
   (ii) a plurality of coated particulates in an amount of less than two thirds of the total weight of the tablet; wherein said particulates comprise a pharmacologically active compound and a physiologically acceptable polymer; and form a discontinuous phase within the matrix material;

   wherein

   under physiological conditions the tablet has released after 30 minutes at least 70% of the pharmacologically active compound originally contained in the tablet; and

   the particulates are coated with a coating material comprising a water-soluble polymer; and

   the pharmacologically active compound is an opioid; and

   the content of the polymer is at least 25 wt.-%, based on the total weight of a particulate; and

   the water-soluble polymer is selected from the group consisting of cellulose esters, cellulose ethers, poly(meth)acrylates, vinyl polymers, and natural film formers.

2. The tablet according to claim 1, which has under in vitro conditions a disintegration time measured in accordance with Ph. Eur. of at most 3 minutes.

3. The tablet according to any of the preceding claims, wherein the content of the matrix material is at least 40 wt.-%, based on the total weight of the tablet.

4. The tablet according to any of the preceding claims, wherein the particulates have an average diameter of about 1000±250 μm and/or an average length of about 750±250 μm.

5. The tablet according to any of the preceding claims, wherein the content of the pharmacologically active compound is at least 25 wt.-%, based on the total weight of a particulate.

6. The tablet according to any of the preceding claims, which has a total weight of 500±300 mg and contains

(i) 50±15 wt.-% coated particulates having an average particle size of 800±400 µm, wherein the coated particulates comprise

- 23±20 wt.-% pharmacologically active compound,
- 22±12 wt.-% physiologically acceptable polymer,
- optionally, 4.0±3.5 wt.-% plasticizer, and
- optionally, 0.05±0.05 wt.-% further excipients; and

(ii) 49±15 wt.-% matrix material, wherein the matrix material comprises

- 43±10 wt.-% filler and/or binder,
- optionally, 5±4 wt.-% disintegrant and
- optionally, 0.15±0.15 wt.-% lubricant;

all wt.-% being expressed relative to the total weight of the tablet.

7. The tablet according to any of the preceding claims, wherein the particulates are hot melt-extruded.

8. The tablet according to any of the preceding claims, wherein the polymer is a polyalkylene oxide having molecular weight of more than 20,000 g/mol.

9. The tablet according to any of the preceding claims, wherein the matrix material is also present in particulate form.

10. The tablet according to any of the preceding claims, wherein the matrix material comprises binder, filler, disintegrant and/or lubricant.

Grunenthal GmbH

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON

Figure 1

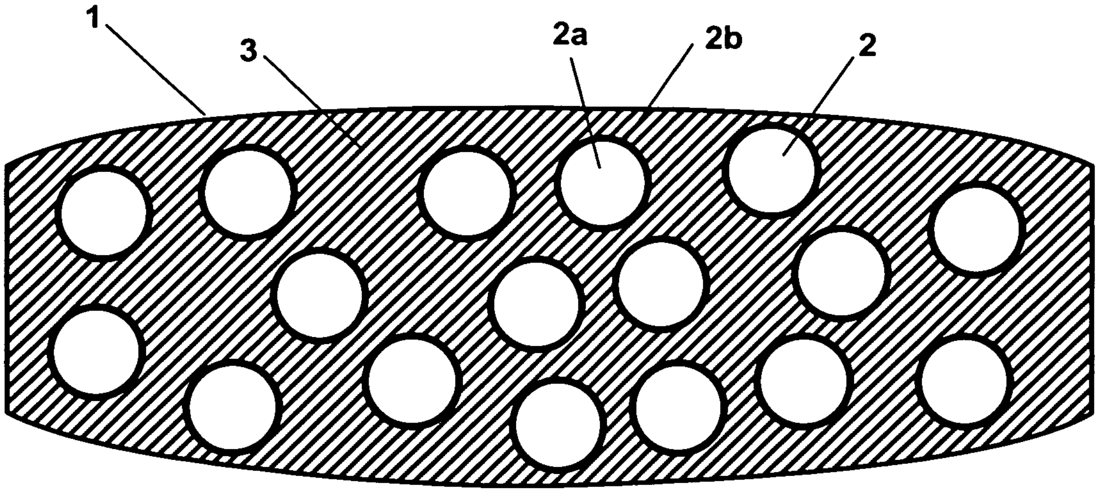


Figure 2

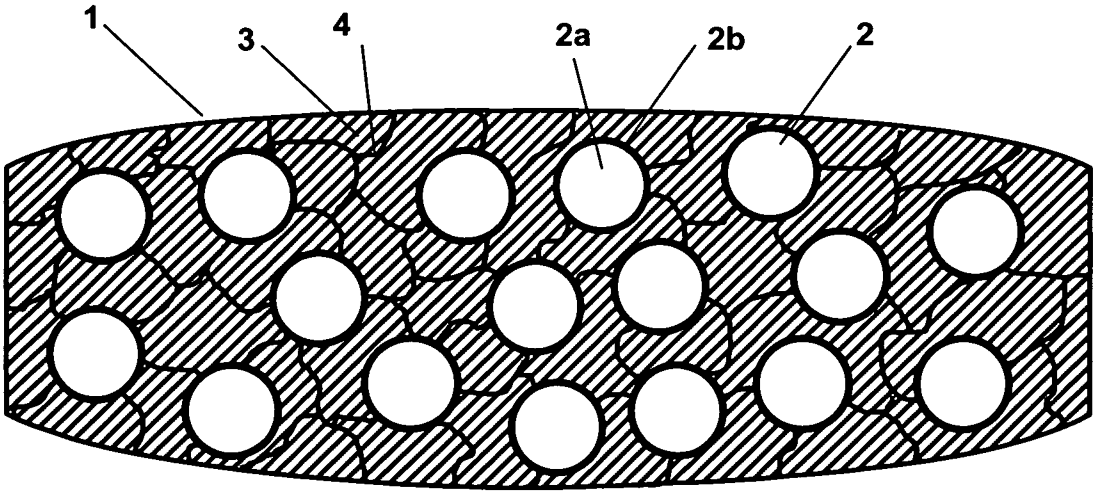


Figure 3

Optimization of pellets

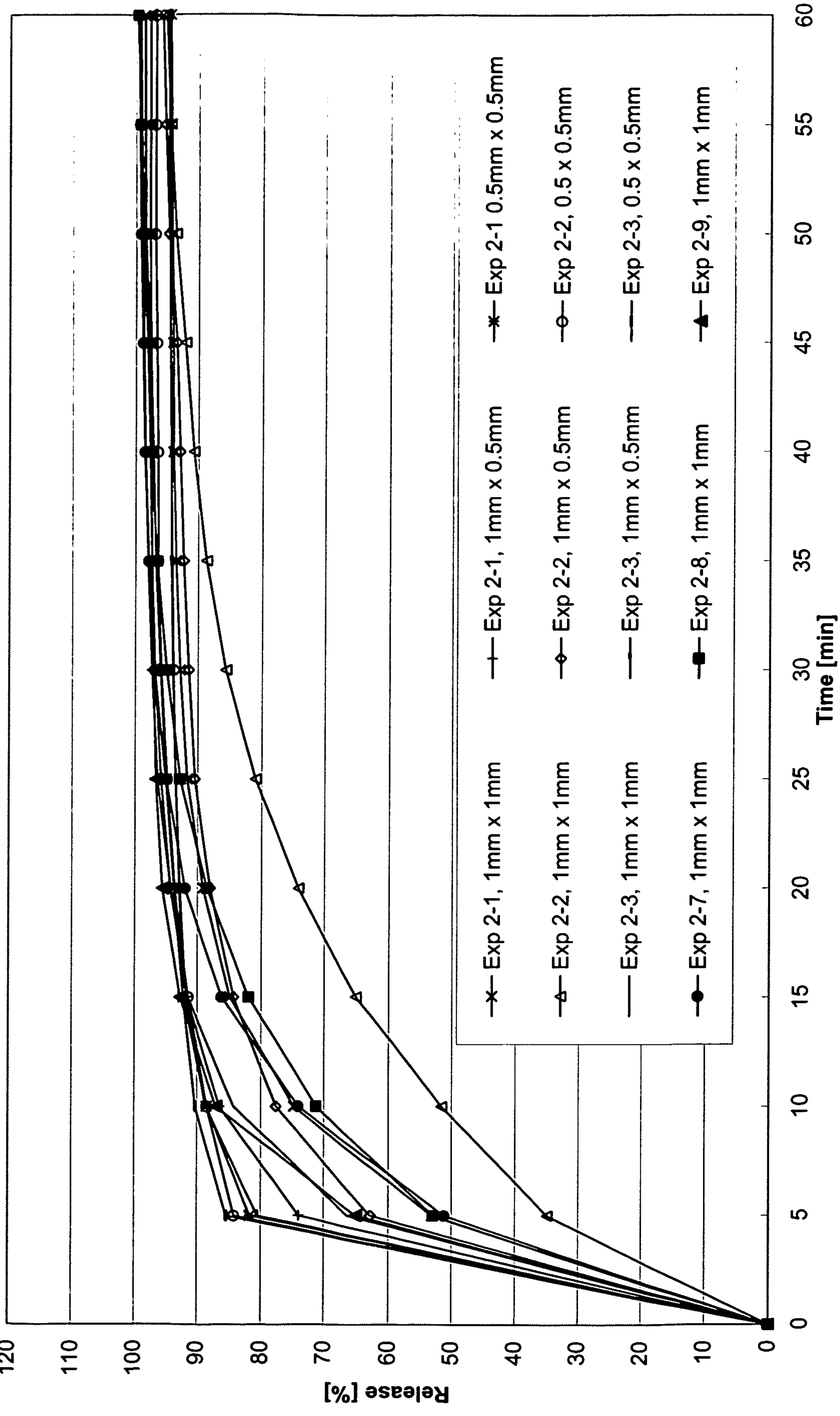


Figure 4

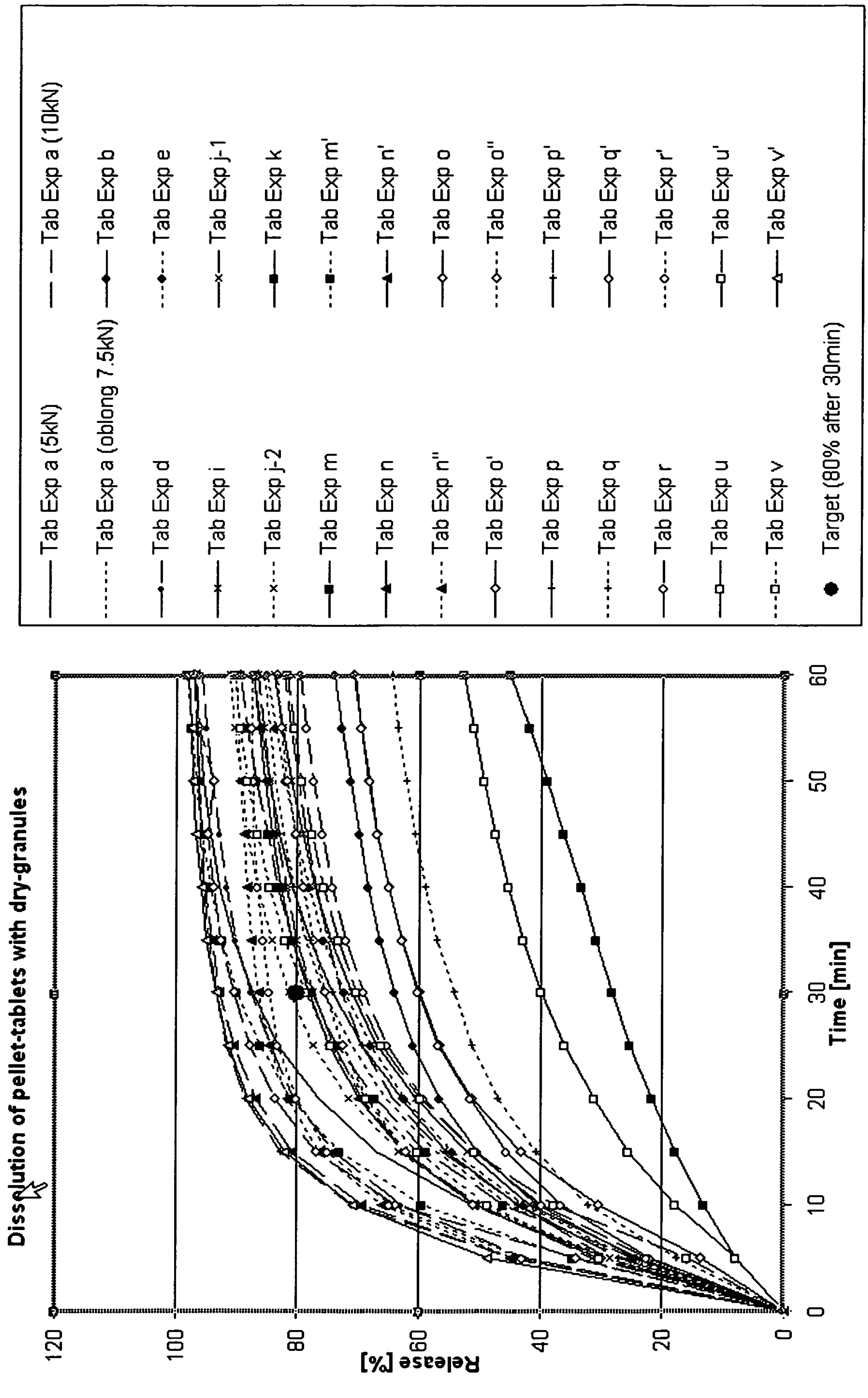
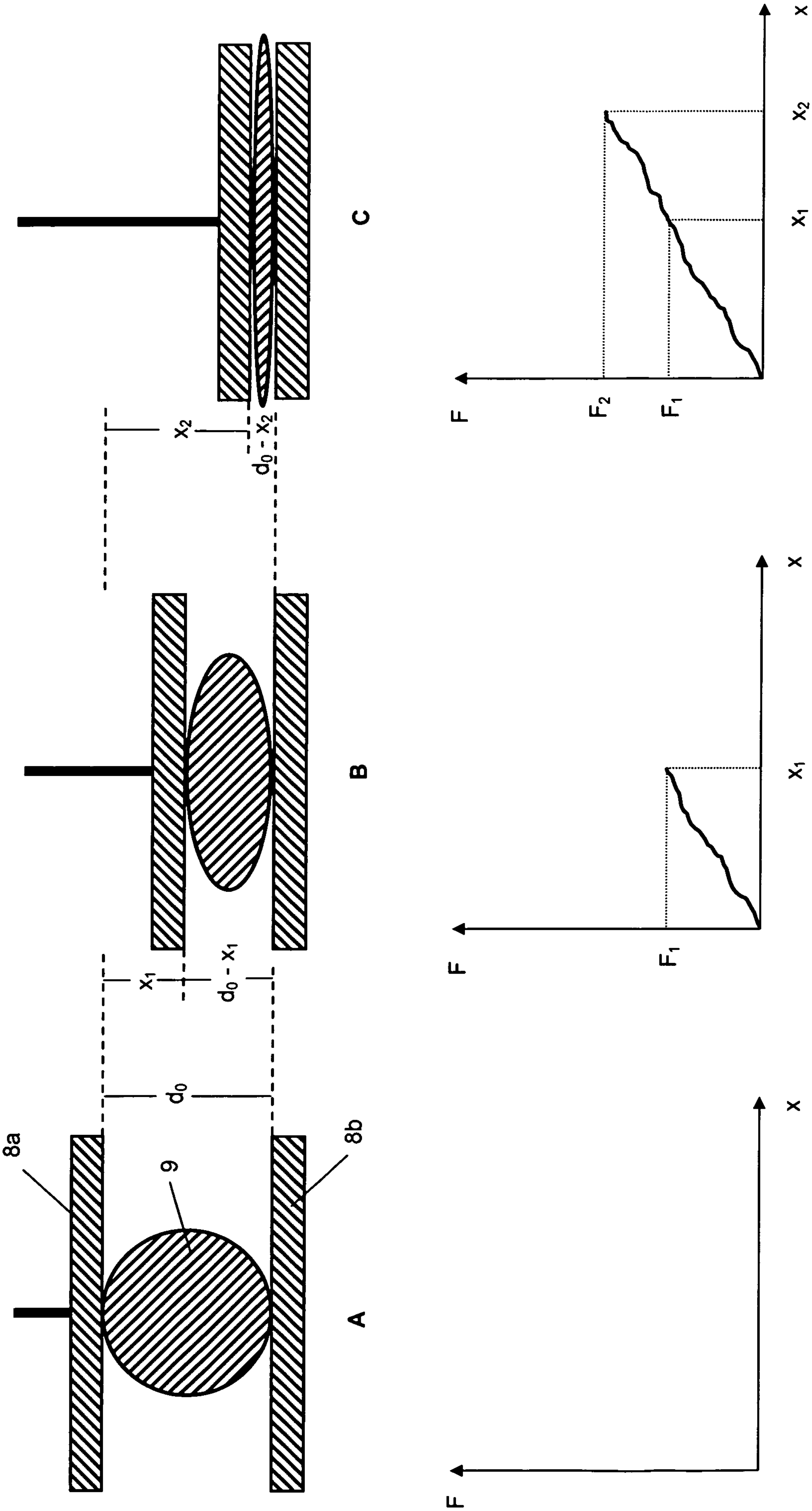

Dissolution of pellet-tablets with dry-granules
Release [%]
Time [min]
0
20
40
60
80
100
120
0
10
20
30
40
50
60
Tab Exp a (5kN)
Tab Exp a (10kN)
Tab Exp a (oblong 7.5kN)
Tab Exp b
Tab Exp d
Tab Exp e
Tab Exp i
Tab Exp j-1
Tab Exp j-2
Tab Exp k
Tab Exp m
Tab Exp m'
Tab Exp n
Tab Exp n'
Tab Exp n''
Tab Exp o
Tab Exp o'
Tab Exp o''
Tab Exp p
Tab Exp p'
Tab Exp q
Tab Exp q'
Tab Exp r
Tab Exp r'
Tab Exp u
Tab Exp u'
Tab Exp v
Tab Exp v'
Target (80% after 30min)

Figure 5



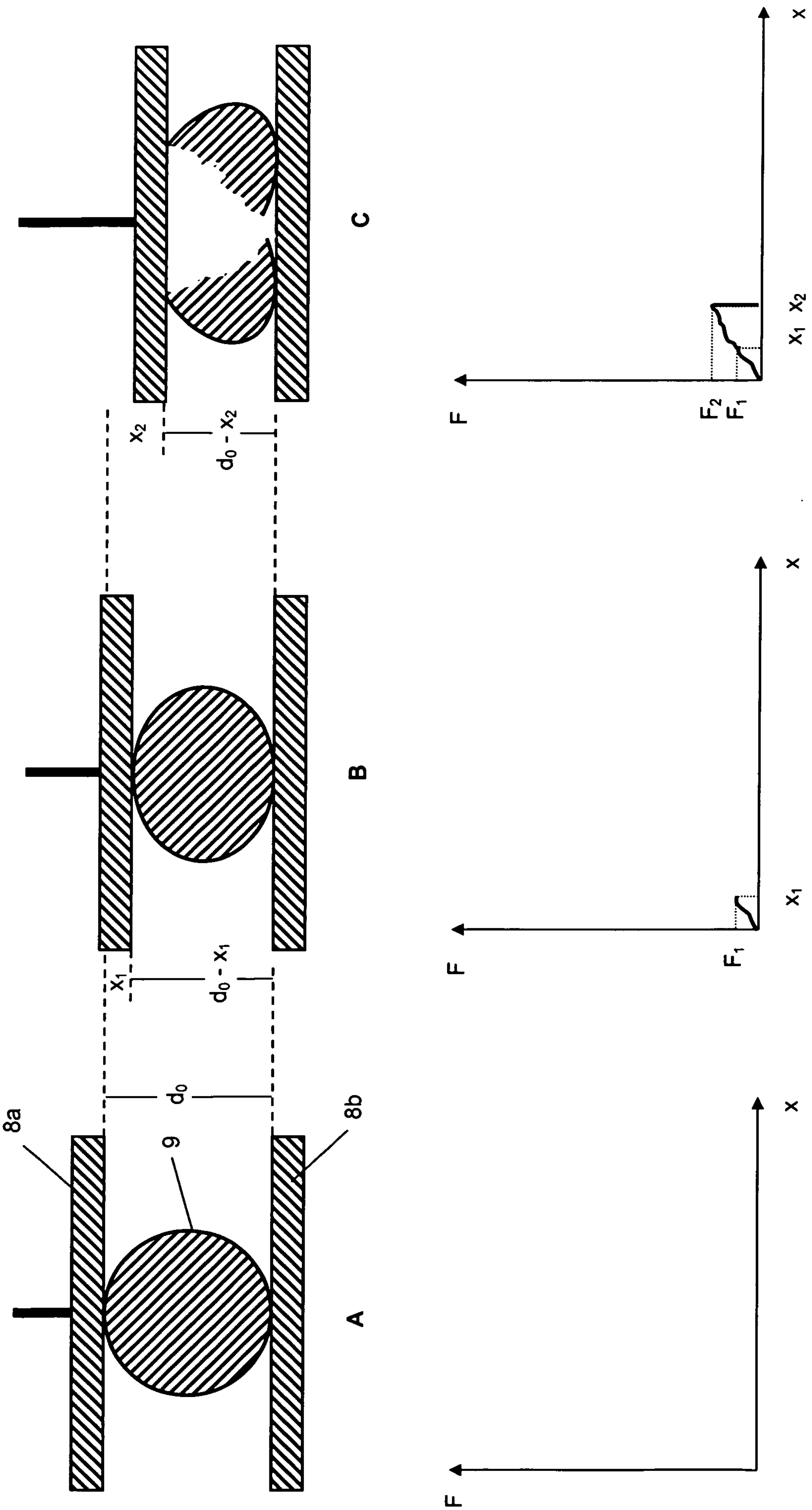


Figure 6

Figure 7

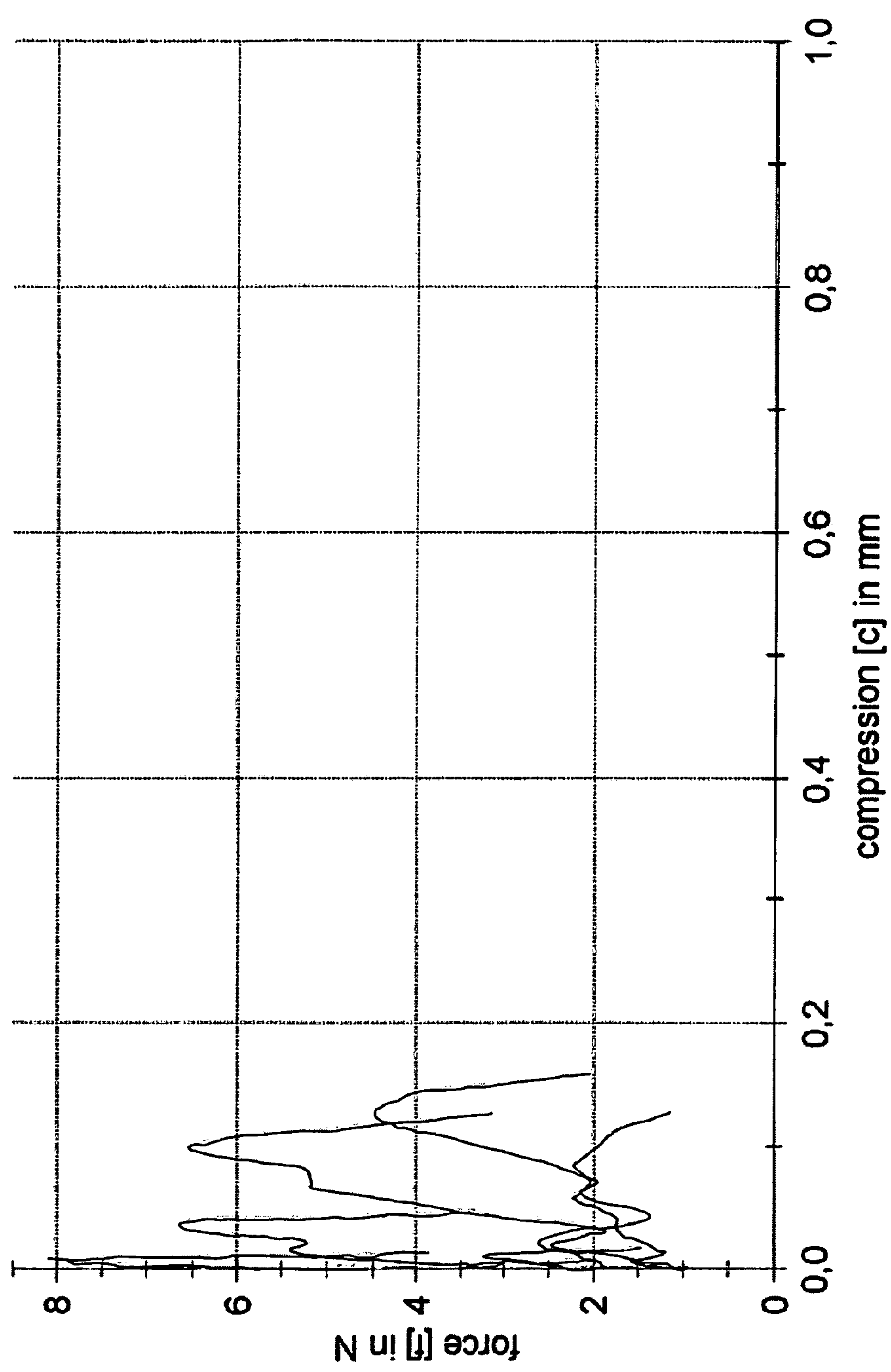


Figure 8

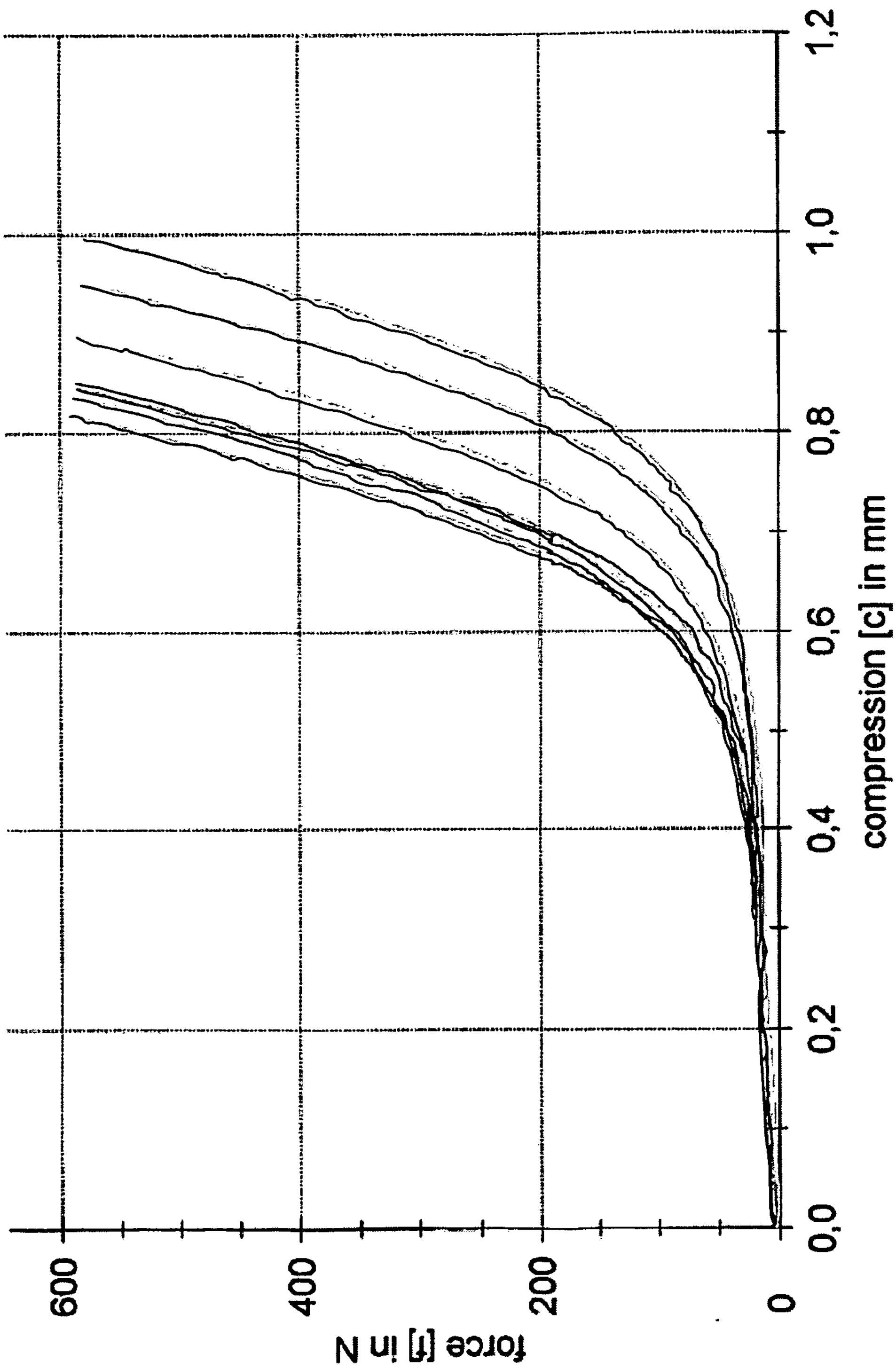


Figure 9