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(54) **Titre : FORME DOSIFIEE INVIOLABLE A PROFIL DE LIBERATION BIMODALE**
(54) **Title: TAMPER RESISTANT DOSAGE FORM WITH BIMODAL RELEASE PROFILE**

(57) **Abrégé/Abstract:**
The invention relates to a pharmaceutical dosage form comprising: (i) at least one formed segment (S_1), which contains a first pharmacologically active ingredient (A_1) and provides prolonged release thereof, and (ii) at least one further segment (S_2), which contains a second pharmacologically active ingredient (A_2) and provides immediate release thereof, wherein the at least one formed segment (S_1) exhibits a higher breaking strength than the at least one further segment (S_2) and the at least one formed segment (S_1) exhibits a breaking strength of more than 500 N.

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(54) **Title**: TAMPER RESISTANT DOSAGE FORM WITH BIMODAL RELEASE PROFILE

(57) **Abstract**: The invention relates to a pharmaceutical dosage form comprising: (i) at least one formed segment (S_1), which contains a first pharmacologically active ingredient (A_1) and provides prolonged release thereof, and (ii) at least one further segment (S_2), which contains a second pharmacologically active ingredient (A_2) and provides immediate release thereof, wherein the at least one formed segment (S_1) exhibits a higher breaking strength than the at least one further segment (S_2) and the at least one formed segment (S_1) exhibits a breaking strength of more than 500 N.

Tamper resistant dosage form with bimodal release profile

FIELD OF THE INVENTION

The invention relates to a pharmaceutical dosage form comprising

(i) at least one formed segment (S_1), which contains a first pharmacologically active ingredient (A_1) and provides prolonged release thereof, and

(ii) at least one further segment (S_2), which contains a second pharmacologically active ingredient (A_2) and provides immediate release thereof,

wherein the at least one formed segment (S_1) exhibits a higher breaking strength than the at least one further segment (S_2) and the at least one formed segment (S_1) exhibits a breaking strength of more than 500 N.

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 pharmaceutical dosage forms, such as pharmaceutical dosage forms 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 pharmaceutical 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 pharmaceutical dosage forms aversive agents and/or antagonists in a manner so that they only produce their aversive and/or antagonizing effects when the pharmaceutical 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 pharmaceutical 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 ingredient 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.

Besides tampering of pharmaceutical dosage forms in order to abuse the drugs contained therein, the potential impact of concomitant intake of ethanol on the in vivo release of drugs from modified release oral formulations (dose-dumping) has recently become an increasing concern. Controlled or modified release formulations typically contain a higher amount of the pharmacologically active ingredient relative to its immediate release counterpart. If the controlled release portion of the formulation is easily defeated, the end result is a potential increase in exposure to the active drug and possible safety concerns. In order to improve safety and circumvent intentional tampering (e.g. dissolving a controlled release pharmaceutical dosage form in ethanol to extract the drug), a reduction in the dissolution of the modified release fractions of such formulations, in ethanol, may be of benefit. Accordingly, the need exists to develop new formulations having reduced potential for dose dumping in alcohol.

Furthermore, the release kinetics of the pharmacologically active ingredients is an important factor. It is well known that depending on how a pharmaceutically pharmacologically active ingredient is formulated into a tablet its release pattern can be modified.

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

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

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

However, especially patients starting their treatment with controlled release formulations often desire a rapid onset of medicinal action. Therefore, a need exists to develop tamper resistant formulations which provide a quick medicinal action while at the same time having the benefits of controlled or modified release formulations.

US 2009/0005408 relates to a process for the production of solid pharmaceutical dosage forms with at least reduced potential for abuse, by a) shaping a formulation mixture containing at least one active ingredient with potential for abuse and at least one synthetic or natural polymer (C), which exhibits a breaking strength of at least 500 N, into formed articles by application of force, b) optionally singulating the formed articles and optionally in each case grading them by size and, c) after or during heating at least to the softening point of the polymer (C), exposing the formed articles to force until they have a breaking hardness of at least 500 N, optionally providing them with a cover and optionally mixing all the formed articles back together again.

US 2009/0022798 and WO 2009/014534, respectively, discloses formulations and methods for the delivery of drugs, particularly drugs of abuse, having an abuse-relevant drug substantially confined in the core and a non-abuse relevant drug in a non-core region. These formulations have reduced potential for abuse. In the formulation, preferably the abuse relevant drug is an opioid and the non-abuse relevant drug is acetaminophen or ibuprofen. More preferably, the opioid is hydrocodone, and the non-abuse relevant analgesic is acetaminophen. In certain preferred embodiments, the dosage forms are characterized by resistance to solvent extraction; tampering, crushing or grinding. In a preferred embodiment, the dosage forms have a breaking strength of at least 500 N. Certain embodiments relate to dosage forms providing an initial burst of release of drug followed by a prolonged period of controllable drug release. When providing these dosage forms with tamper resistant properties, however, the initial burst of release of drug is difficult to achieve, as tamper-resistance and in particular the breaking strength typically relies on the presence of polymers that act as release matrix material slowing down the release of the drug from the dosage form. Therefore, it is only meaningful to provide a combination of tamper resistance, in particular a high breaking strength, and an initial burst of release of the drug when this drug has a potential for being abused. Further, the non-core layer of the drug product is explicitly applied using a film-coating process. A film-coating process is disadvantageous due to the high cost it produces during manufacturing. The film-forming layer material is first dissolved, then sprayed on the core and finally the solvent is removed, all leading to long process times with high energy consumption. Due to the high amount of active that needs to be present in the film-layer, this is a significant disadvantage for a cost-competitive manufacturing of the drug product.

EP 1 980 245 A1 relates to a bilayer dosage form comprising: (i) an upper layer (a) comprising a lyophilized dosage form of active pharmaceutical ingredient(s) (API(s)); and (ii) a base line layer (b) formulated to adhere to the oral mucosa and intended for delayed, sustained or extended release of API(s) and/or excipient(s).

WO 2009/005803 A1 relates to a pharmaceutical composition in the form of a combination tablet. The tablet has a rapidly absorbed component that enters the circulation by traversing the buccal mucosa, and a more slowly absorbed component that is swallowed. The therapeutic agent in the swallowed portion is absorbed across the gastric mucosa. The rapid and slow components may have identical or different therapeutic agents depending on the application to a specific medical condition One embodiment of the combination tablet includes a prostaglandin inhibitor in the rapidly absorbed component in order to mitigate the side effects of immediate release niacin that is in the slow absorbing component.

The properties of the pharmaceutical dosage forms of the prior art are not satisfactory in every respect.

It is an object of the invention to provide pharmaceutical dosage forms which have advantages over the pharmaceutical dosage forms of the prior art. The pharmaceutical dosage forms should provide prolonged release of a first pharmacologically active ingredient and immediate release of a second pharmacologically active ingredient, wherein particularly the first pharmacologically active ingredient is safeguarded from abuse.

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

A first aspect of the invention relates to a pharmaceutical dosage form comprising

(i) at least one formed segment (S_1), which contains a first pharmacologically active ingredient (A_1) and provides prolonged release thereof, and

(ii) at least one further segment (S_2), which contains a second pharmacologically active ingredient (A_2) and provides immediate release thereof,

wherein the at least one formed segment (S_1) exhibits a higher breaking strength than the at least one further segment (S_2) and the at least one formed segment (S_1) exhibits a breaking strength of more than 500 N.

Another aspect of the invention relates to a process for the production of said pharmaceutical dosage form comprising the steps of

(i) thermoforming at least one formed segment (S_1) comprising a first pharmacologically active ingredient (A_1) and a natural or synthetic polymer (C), preferably such that said formed segment (S_1) provides prolonged release of said first pharmacologically active ingredient (A_1);

(ii) providing at least one further segment (S_2) comprising a second pharmacologically active ingredient (A_2) and preferably providing immediate release thereof; and

(iii) combining the at least one formed segment (S_1), the at least one further segment (S_2) and optionally further excipients.

A further aspect of the invention relates to said pharmaceutical dosage form for use in the treatment of pain, wherein the dosage form is swallowed as a whole.

It has been surprisingly found that tamper-resistant pharmaceutical dosage forms can be provided that contain a first pharmacologically active ingredient in a prolonged release form and a second pharmacologically active ingredient in an immediate release form. Patient compliance can be improved by providing a rapid but also prolonged medicinal effect.

Unless expressly stated otherwise, all percentages are by weight (wt.-%).

For the purpose of specification, the term "pharmaceutical dosage form" refers to a pharmaceutical entity which contains the first pharmacologically active ingredient (A_1) and the second pharmacologically active ingredient (A_2) and which is to be administered to a patient (dose unit). It may be compressed or molded during manufacture, and it may be of almost any size, shape, weight, and color. The pharmaceutical dosage form is preferably solid or semisolid.

The pharmaceutical dosage form is preferably intended for oral administration. It is preferably provided in form of a single body that can be easily swallowed by a patient. Typical examples of pharmaceutical dosage forms according to the invention include, but are not limited to tablets (e.g. coated tablets, multilayer tablets, and the like) and capsules.

For the purpose of specification, the term “segment” as used herein refers to any physically distinct entity of the pharmaceutical dosage form that contains the first pharmacologically active ingredient (A_1) or the second pharmacologically active ingredient (A_2) and that can be distinguished from another physically distinct entity of the pharmaceutical dosage form. Preferably, every segment is solid or semisolid.

The formed segment (S_1) and the further segment (S_2) of the pharmaceutical dosage form preferably do not consist of the first pharmacologically active ingredient (A_1) and the second pharmacologically active ingredient (A_2), respectively, but contain further ingredients such as pharmaceutical excipients. Thus, the formed segment (S_1) and the further segment (S_2) can be regarded as greater units of compacted, granulated, congealed or otherwise agglomerated material, comprising *inter alia* but preferably not consisting of the first pharmacologically active ingredient (A_1) and the second pharmacologically active ingredient (A_2), respectively.

In a preferred embodiment, besides the first pharmacologically active ingredient (A_1) the formed segment(s) (S_1) comprise(s) at least a portion of the total amount of the second pharmacologically active ingredient (A_2) that is contained in the pharmaceutical dosage form.

In another preferred embodiment, besides the first pharmacologically active ingredient (A_2) the further segment(s) (S_2) comprise(s) at least a portion of the total amount of the first pharmacologically active ingredient (A_1) that is contained in the pharmaceutical dosage form.

Besides the content of the first pharmacologically active ingredient (A_1) and the second pharmacologically active ingredient (A_2), the formed segment (S_1) and the further segment (S_2) of the pharmaceutical dosage form preferably differ in at least one of the following properties and can be distinguished by said property: composition of ingredients (e.g. nature and/or amount), total weight, density, hardness, breaking strength, size, shape, color, morphology, coherence (e.g. monolithic mass vs. multitude of particulates) and/or porosity.

Typically, any segment of the pharmaceutical dosage form covers at least 1 vol.-%, or at least 2 vol.-%, or at least 5 vol.-%, more preferably at least 10 vol.-% or at least 15 vol.-%, still more preferably at least 17.5 vol.-% or at least 20 vol.-%, yet more preferably at least 22.5 vol.-% or at least 25 vol.-%, even more preferably at least 30 vol.-% or at least 35 vol.-%, most preferably at least 40 vol.-%, and in particular at least 45 vol.-%, of the total volume of the pharmaceutical dosage form. Thus, physically distinct entities that are so small that they do not cover such portion of the total volume of the pharmaceutical dosage form are typically not to be regarded as "segment" in the meaning of the invention.

The formed segment (S_1) and the further segment (S_2) of the pharmaceutical dosage form are separate of one another, i.e. are at different locations of the pharmaceutical dosage form. However, it is possible that one segment partially or completely surrounds the other segment. Nevertheless, it is not possible that a given location of the pharmaceutical dosage form contains both, matter of the formed segment (S_1) and simultaneously matter of the further segment (S_2).

For example, a segment may be a powdery material, a coherent matrix material in which e.g. another segment may be embedded, or a spatially confined area within the pharmaceutical dosage form such as a layer of the pharmaceutical dosage form or a coating of the pharmaceutical dosage form.

In particular, when the pharmaceutical dosage form is provided in form of a multilayered tablet, every layer of the multilayered tablet constitutes a segment of the dosage form. When the pharmaceutical dosage form is provided in form of a coated tablet, the tablet core constitutes one segment whereas the coating constitutes another segment of the dosage form.

When the pharmaceutical dosage form is particulate, e.g. provided in form of a capsule filled with a multitude of pellets and a powder, respectively, the situation can be different. Under these circumstances, every pellet that contains the first pharmacologically active ingredient (A_1) or the second pharmacologically active ingredient (A_2) can be regarded as an individual formed segment (S_1) within a plurality of formed segments (S_1) and as an individual further segment (S_2) within a plurality of further segments (S_2), respectively.

When the first pharmacologically active ingredient (A_1) or the second pharmacologically active ingredient (A_2) is contained as a constituent of a powdery material, however, the mesoscopic or microscopic particles of the first pharmacologically active ingredient (A_1) or the second pharmacologically active ingredient (A_2) are typically not to be regarded as formed segment (S_1) and further segment (S_2), respectively; under these circumstances, the entire powdery material is to be regarded as formed segment (S_1) and further segment (S_2), respectively. Accordingly, when the pharmaceutical dosage form is a capsule filled with a multitude of pellets containing the

first pharmacologically active ingredient (A_1) and with a powdery material containing the second pharmacologically active ingredient (A_2) in powderous form, said multitude of pellets constitutes a multitude of formed segments (S_1), whereas said powdery material constitutes a (single) further segment (S_2), although the pellets and the powdery material may be homogeneously admixed with one another.

The formed segment (S_1) and the further segment (S_2) of the pharmaceutical dosage form can be distinguished from one another.

The pharmaceutical dosage form according to the invention comprises at least one formed segment (S_1) (monolith) but may also contain a plurality of formed segments (S_1) (e.g. multitude of particles). When the pharmaceutical dosage form according to the invention comprises a plurality of formed segments (S_1), the individual formed segments (S_1) are preferably of essentially the same type and nature, e.g. composition, total weight, density, hardness, breaking strength, size, shape, color, morphology, coherence and/or porosity. Preferably, the pharmaceutical dosage form contains not more than 10 formed segments (S_1), more preferably not more than 9, still more preferably not more than 8, yet more preferably not more than 7, even more preferably not more than 6, most preferably not more than 5, and in particular not more than 4 formed segments (S_1). Preferably, the pharmaceutical dosage form contains 1, 2 or 3 formed segments (S_1).

The pharmaceutical dosage form according to the invention comprises at least one further segment (S_2) (monolith) but may also contain a plurality of further segments (S_2) (multitude of particles). When the pharmaceutical dosage form according to the invention comprises a plurality of further segments (S_2), the individual further segments (S_2) are preferably of essentially the same type and nature, e.g. composition, total weight, density, hardness, breaking strength, size, shape, color, morphology, coherence and/or porosity. Preferably, the pharmaceutical dosage form contains not more than 10 further segments (S_2), more preferably not more than 9, still more preferably not more than 8, yet more preferably not more than 7, even more preferably not more than 6, most preferably not more than 5, and in particular not more than 4 further segments (S_2). Preferably, the pharmaceutical dosage form contains 1, 2 or 3 further segments (S_2). When the pharmaceutical dosage form contains 1 further segment (S_2), said further segment (S_2) can preferably be a coherent mass or in form of a powdery material.

When the pharmaceutical dosage form contains more than one formed segment (S_1) and/or more than one further segment (S_2), the pharmaceutical dosage form is particulate.

In a preferred embodiment, the pharmaceutical dosage form contains additional segments (S_3), e.g. segments which contain pharmacologically active ingredient but are essentially not of the same type and nature as formed segments (S_1) and further segments (S_2), respectively. For example, the additional segments (S_3) may contain the first pharmacologically active ingredient (A_1) and/or the second pharmacologically active ingredient (A_2) and/or a third pharmacologically active ingredient (A_3) and provide e.g. prolonged release thereof. Prolonged release may be achieved e.g. by embedding the pharmacologically active ingredient in a polymer matrix differing from the polymer matrix that is preferably contained in formed segment(s) (S_1). Thus, under these circumstances, the

polymer matrices of formed segment(s) (S_1) and additional segments (S_3) differ from one another and accordingly, the *in vitro* release profile may differ as well.

While the pharmaceutical dosage form may contain additional segments (S_3), e.g. segments which contain pharmacologically active ingredient but are essentially not of the same type and nature as formed segments (S_1) and further segments (S_2), respectively, the pharmaceutical dosage form preferably consists of the at least one formed segment (S_1) and the at least one further segment (S_2), but does not contain additional segments (S_3). In a preferred embodiment, the at least one formed segment (S_1) and the at least one further segment (S_2) are present in a container, e.g. a hard gelatine capsule.

Preferably, when the pharmaceutical dosage form is particulate,

(i) the formed segments (S_1) as well as the further segments (S_2), or

(ii) the formed segments (S_1) but not the further segment (S_2), or

(iii) the further segments (S_2) but not the formed segment (S_1)

are particulate.

When (i) the formed segment (S_1) as well as the further segment (S_2) are each particulate (but not powdery), the formed segments (S_1) can be admixed with the further segments (S_2). Nevertheless, even under these specific circumstances, the formed segments (S_1) each constitute a physically distinct entity of the pharmaceutical dosage form that can be distinguished from the further segments (S_2) each constituting another physically distinct entity of the pharmaceutical dosage form.

In a preferred embodiment, the formed segment(s) (S_1) and the further segment(s) (S_2) each constitute a spatially confined area within the pharmaceutical dosage form. According to this embodiment, the formed segment (S_1) and/or further segment (S_2) preferably forms a layer, a coating, a core or a mantle of the pharmaceutical dosage form which is preferably in the form of a tablet.

Preferred embodiments of tablets comprising the formed segment (S_1) and the further segment (S_2) are illustrated in Figure 1.

Figure 1A schematically illustrates a two-layer tablet comprising a formed segment (S_1) as first layer (1) and a further segment (S_2) as second layer (2).

Figure 1B schematically illustrates a mantle tablet comprising a formed segment (S_1) as a core (3) and a further segment (S_2) (4) surrounding said core (3).

Figure 1C schematically illustrates a three-layer tablet comprising a formed segment (S_1) as first layer (5) and two further segments (S_2) as layer (6) and layer (7).

Figure 1D schematically illustrates a multicomponent tablet comprising two formed segments (S_1) (8) and (9) that are embedded and form a discontinuous phase in a further segment (S_2) forming a matrix (10).

In another preferred embodiment, the formed segment(s) (S_1) and the further segment(s) (S_2) are both contained in a container, e.g. a hard gelatine capsule.

Preferred embodiments of capsules comprising formed segment(s) (S_1) and further segment(s) (S_2) are illustrated in Figure 2.

Figure 2A schematically illustrates a capsule formed of capsule body (11) and capsule lid (12). The capsule contains a formed segment (S_1) (13) as well as a further segment (S_2) (14).

Figure 2B schematically illustrates a capsule containing a formed segment (S_1) (15) as well as a plurality of further segments (S_2) (16).

Figure 2C schematically illustrates a capsule containing a plurality of formed segments (S_1) (17) as well as a plurality of further segments (S_2) (18).

Figure 2D schematically illustrates a capsule containing a plurality of formed segments (S_1) (19) as well as a plurality of particles (20) that are smaller than further segments (S_2) (18) of Figure 2C. Nevertheless, every particle (20) contains the second pharmacologically active ingredient (A_2) and thus, every particle (20) constitutes an individual further segment (S_2) so that this capsule also contains a plurality of further segments (S_2) (20).

Figure 2E schematically illustrates a capsule containing a plurality of formed segments (S_1) (21), a plurality of particles (22), and a plurality of particles (23). Particles (22) contain the second pharmacologically active ingredient (A_2), whereas particles (23) contain neither the first pharmacologically active ingredient (A_1) nor the second pharmacologically active ingredient (A_2). Every particle (22) constitutes an individual further segment (S_2) so that this capsule also contains a plurality of further segments (S_2) (20). However, particles (23) do not constitute a segment within the meaning of the invention.

Figure 2F schematically illustrates a capsule containing a plurality of formed segments (S_1) (24) as well as a powdery material (25). The powdery material (25) contains the second pharmacologically active ingredient (A_2), but not as a constituent of a greater physical entity, but if appropriate, simply in admixture with other excipients that are contained in the powdery material. Under these circumstances, the entirety of the powdery material (25) constitutes one further segment (S_2).

Figure 3 shows the force distance diagram of cut rods having a breaking strength of more than 500 N.

Figure 4 shows the release profiles of one cut rod determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Figure 5 shows the release profiles of two cut rods determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. (one sinker per cut rod) at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Figure 6 shows the release profiles of one cut rod in a capsule determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Figure 7 shows the release profiles of two cut rods and a lactose tablet in a capsule determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Figure 8 shows the release profiles of a mantle tablet determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Figure 9 shows the release profiles of a mantle tablet determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Figures 10 to 14 show combinations of the release profiles obtained in Reference Examples 2 to 7 (Figures 4 to 9).

Preferably, the total content of the formed segment(s) (S_1) in the pharmaceutical dosage form according to the invention is at most 95 wt.-%, more preferably at most 85 wt.-%, still more preferably at most 75 wt.-%, yet more preferably at most 65 wt.-%, most preferably at most 55 wt.-% and in particular at most 50 wt.-%, based on the total weight of the pharmaceutical dosage form.

Preferably, the total content of the formed segment(s) (S_1) in the pharmaceutical dosage form according to the invention is at least 5 wt.-% or at least 10 wt.-%, more preferably at least 15 wt.-% or at least 20 wt.-%, still more preferably at least 25 wt.-% or at least 30 wt.-%, even more preferably at least 35 wt.-% or at least 40 wt.-%, yet more preferably at least 45 wt.-% or at least 50 wt.-%, most preferably at least 55 wt.-% or at least 60 wt.-%, and in particular at least 65 wt.-% or at least 70 wt.-%; based on the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the formed segment (S_1) and/or the further segment (S_2) is monolithic, i.e. the dosage form contains a single formed segment (S_1) and/or a single further segment (S_2), respectively.

In this regard, monolithic preferably refers to a single coherent entity (monolith) preferably having a weight of 100 mg or more. According to this embodiment, the monolith preferably has a weight of at least 120 mg, more preferably at least 140 mg, still more preferably at least 160 mg, most preferably at least 180 mg and in particular at least 200 mg. Preferably, the monolith has a weight of from 100 to 1000 mg, more preferably 120 to 900 mg, still more preferably 140 to 800 mg, yet more preferably 150 to 700 mg, even more preferably 160 to 600 mg, most preferably 170 to 500 mg and in particular 200 to 400 mg. For the purpose of definition, a monolithic segment that is film-coated is also to be regarded as a monolithic segment according to the invention.

In another preferred embodiment, the formed segments (S_1) and/or the further segments (S_2) are particulate, preferably oligoparticulate or multiparticulate, i.e. the dosage form contains a multitude of formed segments (S_1) and/or a multitude of further segment (S_2), respectively. For the purpose of the specification, the term "particulate", "oligoparticulate" or "multiparticulate" refers to a discrete mass of material, i.e. multitude of particles, which are solid, e.g. at 20 °C or at room temperature or ambient temperature. Preferably a particle is solid at 20 °C.

In a preferred embodiment, the formed segments (S_1) and/or the further segments (S_2) are oligoparticulate. In this regard, oligoparticulate preferably means that all individual oligoparticles, i.e. formed segments (S_1) and/or further segments (S_2), each have a weight of 20 mg or more. According to this embodiment, all individual oligoparticles, i.e. formed segments (S_1) and/or further segments (S_2), each preferably have a weight of at least 30 mg, more preferably at least 40 mg, still more preferably at least 50 mg, most preferably at least 60 mg and in particular at least 100 mg. Preferably, all individual oligoparticles, i.e. formed segments (S_1) and/or further segments (S_2), each have a weight of from 20 to 1000 mg, more preferably 30 to 800 mg, still more preferably 40 to 600 mg, yet more preferably 50 to 400 mg, even more preferably 60 to 200 mg, most preferably 70 to 150 mg and in particular 80 to 120 mg.

Further, according to this embodiment, the pharmaceutical dosage form preferably comprises at most 10, more preferably at most 9, still more preferably at most 8, yet more preferably at most 7, even more preferably at most 6, most preferably at most 5, and in particular at most 4 or 3 or 2 formed segments (S_1) and/or further segments (S_2). When the formed segments (S_1) and/or the further segments (S_2) are oligoparticulate, the pharmaceutical dosage form may further comprise drug-free particles, which may each have an individual weight of less than 20 mg.

In another preferred embodiment, the formed segments (S_1) and/or the further segments (S_2) are multiparticulate. In this regard, multiparticulate preferably means that all individual multiparticles, i.e. formed segments (S_1) and/or further segments (S_2), each have a weight of less than 20 mg. According to this embodiment, all multiparticles, i.e. formed segments (S_1) and/or further segments (S_2), each preferably have a weight of less than 18 mg, more preferably less than 16 mg, still more preferably less than 14 mg, yet more preferably less than 12 mg, even more preferably less than 10 mg, most preferably less than 8 mg, and in particular less than 6 or 4 mg. Further, according to this embodiment, the pharmaceutical dosage form preferably comprises at least 2, more preferably at least 4, still more preferably at least 6, yet more preferably at least 8, even more preferably at least

10, most preferably at least 15 and in particular at least 20 or at least 100 or at least 1000 particles, i.e. formed segments (S_1) and/or further segments (S_2).

However, multiparticulate segments are less preferred than monolithic segments and oligoparticulate segments.

In a preferred embodiment, the pharmaceutical dosage form contains a single, monolithic formed segment (S_1), or a multitude of particulate formed segments (S_1).

In a particularly preferred embodiment, monolithic or particulate formed segment(s) (S_1) and/or further segment(s) (S_2) of the pharmaceutical dosage form each has/have an extension in any given direction of at least 2.0 mm, more preferably at least 2.2 mm, still more preferably at least 2.5 mm, yet more preferably at least 2.8 mm, even more preferably at least 3.0 mm, most preferably at least 3.2 mm, and in particular at least 3.5 mm or 4.0 mm. According to this embodiment, the monolithic or particulate formed segment(s) (S_1) and/or further segment(s) (S_2) particularly preferably each have an extension in any given direction of at least 2.0 mm or 3.0 mm and have a weight of at least 20 mg.

Particularly preferably, the pharmaceutical dosage form contains a single, monolithic formed segment (S_1) having an extension in any direction of at least 2.0 mm; or a multitude of particulate formed segments (S_1) each having an extension in any direction of at least 2.0 mm.

For the purpose of specification, “in any direction” preferably means in every direction in the three-dimensional space.

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

The shape of the particles and/or monoliths, i.e. the shape of the formed segment(s) (S_1) and/or the further segment(s) (S_2), is not particularly limited. Preferably, the particles and/or the monolith are essentially cylindrical in shape, e.g. cut extruded rods. The diameter of such particles and/or monolith is therefore the diameter of their circular cross section. The cylindrical shape can be caused by hot-melt extrusion 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 segment (S_1) is "formed". In this regard, the term "formed" refers to any measure providing the material of segment (S_1) with a predetermined or arbitrary outer shape. Forming may but does not need to be achieved by means of a die. Preferably, formed segment (S_1) is thermoformed. For example, extruding a heated material, e.g. by means of hot-melt extrusion, and subsequently cutting the extruded strand into segments of predetermined length provides formed segments (S_1) according to the invention.

In a preferred embodiment, the formed segment(s) (S_1) and/or the further segment(s) (S_2) is/are not film coated.

In another preferred embodiment, the formed segment(s) (S_1) and/or the further segment(s) (S_2) is/are film coated. The formed segment(s) (S_1) and/or the further segment(s) (S_2) according to the invention can optionally be provided, partially or completely, with a conventional coating. The formed segment(s) (S_1) and/or the further segment(s) (S_2) 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 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, polyvinyl-acetatephthalate, 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.

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

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

For the purpose of specification, the term “pharmacologically active ingredient” as used herein may refer to either one or more pharmacologically active ingredients, i.e. the terms “first pharmacologically ingredient (A_1)” and “second pharmacologically ingredient (A_2)” may each refer to a single pharmacologically active ingredient or a combination of one or more pharmacologically active ingredients.

There are generally no limitations as to the pharmacologically active ingredient (pharmacologically active compound) which can be incorporated in the segments of the pharmaceutical dosage form according to the invention. Furthermore, the term "pharmacologically active ingredient" preferably includes any physiologically acceptable salt, e.g. physiologically acceptable acid addition salt, of the base form of the pharmacologically active ingredient. Physiologically acceptable acid addition salts comprise any acid addition salts which can conveniently be obtained by treating the base form of a pharmacologically active ingredient with appropriate organic and inorganic acids. Pharmacologically 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 a pharmacologically active ingredient is able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

Unless explicitly stated otherwise, all amounts of the first pharmacologically active ingredient (A_1) and the second pharmacologically active ingredient (A_2) specified in the following are given according to the corresponding amount of the free compound.

Preferably, the first pharmacologically active ingredient (A_1) is an opioid and the second pharmacologically active ingredient (A_2) is another analgesic, but preferably no opioid, e.g. paracetamol (acetaminophen), an NSAID or COX-2-inhibitor.

In a particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol.

In a preferred embodiment, the first pharmacologically active ingredient (A_1) and the second pharmacologically active ingredient (A_2) are spatially separated from one another. According to this embodiment, the formed segment (S_1) preferably contains less than 0.1 ppm, more preferably less than 0.01 ppm, most preferably less than 0.001 ppm and in particular less than 0.0001 ppm of the second pharmacologically active ingredient (A_2). Further, according to this embodiment, the further segment (S_2) preferably contains less than 0.1 ppm, more preferably less than 0.01 ppm, most preferably less than 0.001 ppm and in particular less than 0.0001 ppm of the first pharmacologically active ingredient (A_1). In a particularly preferred embodiment, the formed segment (S_1) contains no second pharmacologically active ingredient (A_2) and the further segment (S_2) contains no first pharmacologically active ingredient (A_1).

Preferably, at least 99 wt.-%, more preferably at least 99.9 wt.-%, most preferably at least 99.99 wt.-% and in particular at least 99.999 wt.-% of the total amount of the first pharmacologically active ingredient (A_1) contained in the pharmaceutical dosage form are contained in the formed segment (S_1).

Preferably, at least 99 wt.-%, more preferably at least 99.9 wt.-%, most preferably at least 99.99 wt.-% and in particular at least 99.999 wt.-% of the total amount of the second pharmacologically active ingredient (A_2) contained in the pharmaceutical dosage form are contained in the further segment (S_2).

The term "prolonged release" is known to the skilled artisan. For the purpose of specification, the term "prolonged release" preferably refers to a release rate of the pharmacologically active ingredient from the formulation that has been reduced over time in order to maintain therapeutic activity, to reduce toxic effects, or for some other therapeutic purpose such as reducing the dosing frequency.

The term "immediate release" is known to the skilled artisan. For the purpose of specification, the term "immediate release" preferably refers to a release rate of the pharmacologically active ingredient from the formulation that is comparatively fast and not retarded.

Preferably, when the formed segment(s) (S_1) and/or the further segment(s) (S_2) are particulate, the pharmaceutical dosage form according to the invention comprises the particles as a discontinuous phase, i.e. the particles form a discontinuous phase in an outer matrix material which in turn preferably forms a continuous phase (cf. Figure 1D). In this regard, discontinuous means that not each and every particle is in intimate contact with another particle but that the particles are at least partially separated from one another by the outer matrix material in which the particles are embedded. In other words, the particles preferably do not form a single coherent mass within the pharmaceutical dosage forms according to the invention (multicomponent tablet).

In a preferred embodiment, the further segment(s) (S_2) form(s) an outer matrix material in which the formed segment(s) (S_1) is/are embedded. According to this embodiment, the pharmaceutical dosage form according to the invention can preferably be a MUPS formulation (multiple unit pellet system) or a capsule.

Preferably, the formed segment(s) (S_1) and the further segment(s) (S_2) have different morphology and properties, more preferably the formed segment (S_1) is monolithic or particulate and the further segment (S_2) forms the outer matrix material. When the formed segments (S_1) are particulate, the particles preferably form a discontinuous phase within the outer matrix material formed by the further segment (S_2) (cf. Figure 1D) (multicomponent tablet). When the formed segment (S_1) contains a prolonged release matrix material, the outer matrix material is to be distinguished from said prolonged release matrix material, since the outer matrix material preferably does not provide for a prolonged release.

When the formed segment (S_1) is monolithic or particulate and the further segment (S_2) forms the outer matrix material, the pharmaceutical dosage form according to the invention preferably is in form of a capsule, i.e. a soft capsule or a hard capsule.

The formed segment(s) (S_1) typically has/have mechanical properties that differ from the mechanical properties of the outer matrix material. Preferably, the formed segment(s) (S_1) has/have a higher mechanical strength than the outer matrix material. The formed segment(s) (S_1) can preferably be visualized by conventional means such as solid state nuclear magnetic resonance spectroscopy, scanning electron microscopy, terahertz spectroscopy and the like.

In a further preferred embodiment, the formed segment (S_1) and/or the further segment (S_2) constitute a spatially confined area within the pharmaceutical dosage form. According to this embodiment, the formed segment (S_1)

and/or further segment (S_2) preferably form a layer, a coating, a core or a mantle of the pharmaceutical dosage form.

When the formed segment (S_1) and/or further segment (S_2) forms a layer, the pharmaceutical dosage form preferably is in form of a layered tablet (cf. Figure 1A and Figure 1C).

The formed segment (S_1) or the further segment (S_2) may also form the coating of the pharmaceutical dosage form. Preferably, the formed segment (S_1) forms the core of the pharmaceutical dosage form that is coated by the further segment (S_2). Preferably, however, neither the formed segment (S_1) nor the further segment (S_2) forms a coating of the pharmaceutical dosage form, particularly no spray coating. Rather, the first segment (S_1) and the further segment (S_2) are preferably both coated by another material such as a sugar coating.

In a preferred embodiment, the pharmaceutical dosage form is in form of a mantle tablet (cf. Figure 1B). According to this embodiment, the formed segment (S_1) preferably forms the core and the further segment (S_2) preferably forms the mantle.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is a tablet, which comprises

(i) a single formed segment (S_1) and a single further segment (S_2) that are arranged to form a bilayer tablet (cf. Figure 1A);

(ii) a single formed segment (S_1) forming a core that is surrounded by a single further segment (S_2) such that formed segment (S_1) and further segment (S_2) are arranged to form a mantle tablet (cf. Figure 1B);

(iii) a single formed segment (S_1) and two further segments (S_2) that are arranged to form a trilayer tablet, wherein formed segment (S_1) forms the middle layer and the two further segments (S_2) form the outer layers (cf. Figure 1C);

(iv) a plurality of formed segments (S_1) and a plurality of further segments (S_2) that are arranged to form a multilayer tablet, wherein preferably each of the formed segments (S_1) is arranged in between two adjacent further segments (S_2);

(v) a plurality of formed segments (S_1) which form a discontinuous phase embedded in further segment (S_2) which forms a matrix (cf. Figure 1D) (multicomponent tablet); or

(vi) a single formed segment (S_1) and one or more further segments (S_2) that are together coated by a sugar coating thus forming a sugar-coated tablet (dragée)

(vii) .

In another preferred embodiment, the pharmaceutical dosage form according to the invention is a capsule, which is filled with

(i) a single formed segment (S_1) and a single further segment (S_2), which can optionally be present in form of a monolith or in form of a powdery material (cf. Figure 2A);

(ii) a single formed segment (S_1) and a plurality of further segments (S_2) (cf. Figure 2B);

(iii) a plurality of formed segments (S_1) and a single further segment (S_2), which can optionally be present in form of a monolith or in form of a powdery material (cf. Figure 2F); or

(iv) a plurality of formed segments (S_1) and a plurality of further segment (S_2) (cf. Figures 2C, D and E).

The pharmaceutical dosage form comprises a formed segment (S_1), which contains a first pharmacologically active ingredient (A_1) and provides prolonged release thereof.

In a preferred embodiment, the first pharmacologically active ingredient (A_1) is only a single pharmacologically active ingredient. In another preferred embodiment, the first pharmacologically active ingredient (A_1) is a combination of two or more pharmacologically active ingredients.

Preferably, the first pharmacologically active ingredient (A_1) has potential for being abused. Pharmacologically 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 first pharmacologically active ingredient (A_1) has a psychotropic effect, i.e. crosses the blood-brain barrier and acts primarily upon the central nervous system where it affects brain function, resulting in alterations in perception, mood, consciousness, cognition, and behavior.

Preferably, the first pharmacologically active ingredient (A_1) is selected from the group consisting of opioids, stimulants, tranquilizers, and other narcotics.

Particularly preferably, the first pharmacologically active ingredient (A_1) is an opioid or a physiologically acceptable salt thereof. According to the Anatomical Therapeutic Chemical (ATC) classification system by WHO (ATC index), opioids are divided into natural opium alkaloids, phenylpiperidine derivatives, diphenyl-propylamine derivatives, benzomorphan derivatives, oripavine derivatives, morphinan derivatives and others. Preferably, the second pharmacologically active ingredient (A_2) is selected from ATC classes [M01A], [M01C], [N02B] and [N02C] according to the WHO.

The following 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 formed segment (S_1) of the pharmaceutical dosage form according to the invention: alfentanil, allobarbital, allylprodine, alphaprodine, alprazolam, amfepramone, amphetamine, amphetaminil, amobarbital, anileridine, apocodeine, axomadol, barbital, bemidone, benzylmorphine, bezitramide, bromazepam, brotizolam, buprenorphine, butobarbital, butorphanol, camazepam, carfentanil, cathine/D-norpseudoephedrine, chlordiazepoxide, clobazam clofedanol, clonazepam, clonitazene, clorazepate, clotiazepam, cloxazolam, cocaine, codeine, cyclobarbital, cyclorphan, cyprenorphine, delorazepam, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, diazepam, dihydrocodeine, dihydromorphine, dihydromorphone, dimenoxadol, dimephetamol, dimethylthiambutene, dioxaphetylbutyrate, dipipanone, dronabinol, eptazocine, estazolam, ethoheptazine, ethylmethylthiambutene, ethyl loflazepate, ethylmorphine, etonitazene, etorphine, faxeladol, fencamfamine, fenethylline, fenpipramide,

fenproporex, fentanyl, fludiazepam, flunitrazepam, flurazepam, halazepam, haloxazolam, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, hydroxymethylmorphinan, ketazolam, ketobemidone, levacetylmethadol (LAAM), levomethadone, levorphanol, levophenacylmorphane, levoxemacin, lisdexamfetamine dimesylate, lofentanil, loprazolam, lorazepam, lormetazepam, mazindol, medazepam, mefenorex, meperidine, meprobamate, metapon, meptazinol, metazocine, methylmorphine, metamphetamine, methadone, methaqualone, 3-methylfentanyl, 4-methylfentanyl, methylphenidate, methylphenobarbital, methyprylon, metopon, midazolam, modafinil, morphine, myrophine, nabilone, nalbuphene, nalorphine, narceine, nicomorphine, nimetazepam, nitrazepam, nordazepam, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxazepam, oxazolam, oxycodone, oxymorphone, Papaver somniferum, papaveretum, pernoline, pentazocine, pentobarbital, pethidine, phenadoxone, phenomorphane, phenazocine, phenoperidine, piminodine, pholcodeine, phenmetrazine, phenobarbital, phentermine, pinazepam, pipradrol, piritramide, prazepam, profadol, proheptazine, promedol, properidine, propoxyphene, remifentanil, secbutabarbital, secobarbital, sufentanil, tapentadol, temazepam, tetrazepam, tilidine (cis and trans), tramadol, triazolam, vinylbital, N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluorobenzyloxy)-1-(m-methoxyphenyl)-cyclohexanol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, (1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, preferably as racemate, 3-(2-dimethylamino-methyl-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-dimethylamino-methyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-4-chloro-2-hydroxy-benzoic acid 3-(2-dimethylamino-methyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methyl-benzoic acid 3-(2-dimethylamino-methyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethylamino-methyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-5-nitro-benzoic acid 3-(2-dimethyl-aminomethyl-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 formed segment (S_1) contains an opioid selected from the group consisting of DPI-125, M6G (CE-04-410), ADL-5859, CR-665, NRP290 and sebacoyl dinalbuphine ester.

In a preferred embodiment, the formed segment (S_1) contains the first pharmacologically active ingredient (A_1) which is one pharmacologically active ingredient or more pharmacologically active ingredients selected from the group consisting of oxycodone, oxymorphone, hydromorphone, hydrocodone, morphine, tapentadol, tramadol, buprenorphine, and the physiologically acceptable salts thereof.

In another preferred embodiment, the first pharmacologically active ingredient (A_1) is selected from the group consisting of tapentadol, faxeladol, axomadol and the physiologically acceptable salts thereof.

In still another preferred embodiment, the first pharmacologically active ingredient (A_1) is selected from the group consisting of 1,1-(3-dimethylamino-3-phenylpentamethylene)-6-fluoro-1,3,4,9-tetrahydropyrano[3,4-b]indole (cebranopadol), 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 first pharmacologically active ingredient (A_1) is present in the pharmaceutical dosage form in a therapeutically effective amount. In general, the amount that constitutes a therapeutically effective amount varies according to the pharmacologically active ingredients being used, the condition being treated, the severity of said condition, the patient being treated, and whether the pharmaceutical dosage form or the segment in which the pharmacologically active ingredient is contained is designed for an immediate or retarded release.

The content of the first pharmacologically active ingredient (A_1) preferably ranges from about 0.01 wt.-% to about 95 wt.-%, more preferably from about 0.1 wt.-% to about 80 wt.-%, even more preferably from about 1.0 wt.-% to about 50 wt.-%, yet more preferably from about 1.5 wt.-% to about 30 wt.-%, and most preferably from about 2.0 wt.-% to 20 wt.-%, based on the total weight of the formed segment(s) (S_1) or based on the total weight of the pharmaceutical dosage form.

Preferably, the content of the first pharmacologically active ingredient (A_1) is within the range of from 0.01 to 80 wt.-%, more preferably 0.1 to 50 wt.-%, still more preferably 1 to 25 wt.-%, based on the total weight of the pharmaceutical dosage form. In a preferred embodiment, the content of the first pharmacologically active ingredient (A_1) is within the range of from 7±6 wt.-%, more preferably 7±5 wt.-%, still more preferably 5±4 wt.-%, 7±4 wt.-% or 9±4 wt.-%, most preferably 5±3 wt.-%, 7±3 wt.-% or 9±3 wt.-%, and in particular 5±2 wt.-%, 7±2 wt.-% or 9±2 wt.-%, based on the total weight of the pharmaceutical dosage form. In another preferred embodiment, the content of the first pharmacologically active ingredient (A_1) is within the range of from 11±10 wt.-%, more preferably 11±9 wt.-%, still more preferably 9±6 wt.-%, 11±6 wt.-%, 13±6 wt.-% or 15±6 wt.-%, most preferably 11±4 wt.-%, 13±4 wt.-% or 15±4 wt.-%, and in particular 11±2 wt.-%, 13±2 wt.-% or 15±2 wt.-%, based on the total weight of the pharmaceutical dosage form. In a further preferred embodiment, the content of the first pharmacologically active ingredient (A_1) is within the range of from 20±6 wt.-%, more preferably 20±5 wt.-%, still more preferably 20±4 wt.-%, most preferably 20±3 wt.-%, and in particular 20±2 wt.-%, based on the total weight of the pharmaceutical dosage form.

Preferably, the content of the first pharmacologically active ingredient (A_1) is within the range of from 0.01 to 80 wt.-%, more preferably 0.1 to 60 wt.-%, still more preferably 5 to 50 wt.-%, based on the total weight of the formed segment(s) (S_1). In a preferred embodiment, the content of the first pharmacologically active ingredient (A_1) is within the range of from 7±6 wt.-%, more preferably 7±5 wt.-%, still more preferably 5±4 wt.-%, 7±4

wt.-% or 9±4 wt.-%, most preferably 5±3 wt.-%, 7±3 wt.-% or 9±3 wt.-%, and in particular 5±2 wt.-%, 7±2 wt.-% or 9±2 wt.-%, based on the total weight of the formed segment(s) (S_1). In another preferred embodiment, the content of the first pharmacologically active ingredient (A_1) is within the range of from 11±10 wt.-%, more preferably 11±9 wt.-%, still more preferably 9±6 wt.-%, 11±6 wt.-%, 13±6 wt.-% or 15±6 wt.-%, most preferably 11±4 wt.-%, 13±4 wt.-% or 15±4 wt.-%, and in particular 11±2 wt.-%, 13±2 wt.-% or 15±2 wt.-%, based on the total weight of the formed segment(s) (S_1). In a further preferred embodiment, the content of the first pharmacologically active ingredient (A_1) is within the range of from 20±6 wt.-%, 25±6 wt.-% or 30±6 wt.-%, more preferably 20±5 wt.-%, 25±5 wt.-% or 30±5 wt.-%, still more preferably 20±4 wt.-%, 25±4 wt.-% or 30±4 wt.-%, most preferably 20±3 wt.-%, 25±3 wt.-% or 30±3 wt.-% and in particular 20±2 wt.-%, 25±2 wt.-% or 30±2 wt.-%, based on the total weight of the formed segment(s) (S_1).

The total dose of the first pharmacologically active ingredient (A_1) in the formed segment (S_1) and the pharmaceutical dosage form, respectively, is not limited. The dose of the first pharmacologically active ingredient (A_1) which is adapted for administration preferably is in the range of 0.01 mg to 2,000 mg or 0.01 mg to 1,000 mg or 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 1.0 mg to 10.0 mg or 5.0 mg to 300 mg, and most preferably in the range of 1.5 mg to 8 mg or 10 mg to 250 mg. In a preferred embodiment, the total amount of the first pharmacologically active ingredient (A_1) which is contained in the formed segment (S_1) and the pharmaceutical dosage form, respectively, is within the range of from 0.01 to 200 mg, more preferably 0.1 to 190 mg, still more preferably 1.0 to 180 mg, yet more preferably 1.5 to 160 mg, most preferably 2.0 to 100 mg and in particular 2.5 to 80 mg. In another preferred embodiment, the total amount of the first pharmacologically active ingredient (A_1) which is contained in the formed segment (S_1) and the pharmaceutical dosage form, respectively, is within the range of from 10 to 500 mg, more preferably 12 to 450 mg, still more preferably 14 to 400 mg, yet more preferably 16 to 350 mg, most preferably 18 to 325 mg and in particular 20 to 300 mg.

In a preferred embodiment, the first pharmacologically active ingredient (A_1) is contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of 10±5 µg, 20±5 µg, 30±5 µg, 40±5 µg, 50±5 µg, 60±5 µg, 70±5 µg, 80±5 µg, 90±5 µg, 100±5 µg, 125±25 µg, 150±25 µg, 175±25 µg, 200±25 µg, 250±50 µg, 300±50 µg, 350±50 µg, 400±50 µg, 450±50 µg, 500±50 µg, 550±50 µg, 600±50 µg, 650±50 µg, 700±50 µg, 750±50 µg, 800±50 µg, 850±50 µg, 900±50 µg, 950±50 µg, or 1000±50 µg. In another preferred embodiment, the first pharmacologically active ingredient (A_1) is contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of 7.5±5 mg, 10±5 mg, 20±5 mg, 30±5 mg, 40±5 mg, 50±5 mg, 60±5 mg, 70±5 mg, 80±5 mg, 90±5 mg, 100±5 mg, 110±5 mg, 120±5 mg, 130±5, 140±5 mg, 150±5 mg, 160±5 mg, 170±5 mg, 180±5 mg, 190±5 mg, 200±5 mg, 210±5 mg, 220±5 mg, 230±5 mg, 240±5 mg, or 250±5 mg. In another preferred embodiment, the first pharmacologically active ingredient (A_1) is contained in the formed segment (S_1) and the pharmaceutical dosage form, respectively, in a total amount of 5±2.5 mg, 7.5±2.5 mg, 10±2.5 mg, 15±2.5 mg, 20±2.5 mg, 25±2.5 mg, 30±2.5 mg, 35±2.5 mg, 40±2.5 mg, 45±2.5 mg, 50±2.5 mg, 55±2.5 mg, 60±2.5 mg, 65±2.5 mg, 70±2.5 mg, 75±2.5 mg, 80±2.5 mg, 85±2.5 mg, 90±2.5 mg, 95±2.5 mg, 100±2.5 mg, 105±2.5 mg, 110±2.5 mg, 115±2.5 mg, 120±2.5 mg, 125±2.5 mg, 130±2.5 mg, 135±2.5 mg, 140±2.5 mg, 145±2.5 mg, 150±2.5 mg, 155±2.5 mg, 160±2.5 mg, 165±2.5 mg, 170±2.5 mg, 175±2.5 mg, 180±2.5 mg, 185±2.5 mg, 190±2.5 mg, 195±2.5 mg, 200±2.5 mg, 205±2.5 mg, 210±2.5 mg,

215±2.5 mg, 220±2.5 mg, 225±2.5 mg, 230±2.5 mg, 235±2.5 mg, 240±2.5 mg, 245±2.5 mg, or 250±2.5 mg. In still another preferred embodiment, the first pharmacologically active ingredient (A_1) is contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of 250±10 mg, 275±10 mg, 300±10 mg, 325±10 mg, 350±10 mg, 375±10 mg, 400±10 mg, 425±10 mg, 450±10 mg, 475±10 mg, 500±10 mg, 525±10 mg, 550±10 mg, 575±10 mg or 600±10 mg.

In a particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is oxycodone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration twice daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 1 to 80 mg. In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is oxycodone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 2 to 320 mg.

In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is oxymorphone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration twice daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 5 to 40 mg. In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is oxymorphone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 10 to 80 mg.

In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is tapentadol, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily or twice daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 25 to 250 mg.

In still another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is hydromorphone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration twice daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 2 to 52 mg. In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is hydromorphone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 4 to 104 mg.

In yet another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is tramadol, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration twice daily. In this

embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 5 to 300 mg. In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is tramadol, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 10 to 500 mg.

In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is hydrocodone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration twice daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 5 to 250 mg. In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is hydrocodone, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 5 to 250 mg.

In still another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is morphine, preferably its HCl or H_2SO_4 salt, and the pharmaceutical dosage form is adapted for administration twice daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 5 to 250 mg. In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is morphine, preferably its HCl or H_2SO_4 salt, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 5 to 250 mg.

In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is buprenorphine, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration twice daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 1 to 12 mg. In another particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is buprenorphine, preferably its HCl salt, and the pharmaceutical dosage form is adapted for administration once daily. In this embodiment, the first pharmacologically active ingredient (A_1) is preferably contained in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, in a total amount of from 2 to 12 mg.

The first pharmacologically active ingredient (A_1) that is employed in the preparation of the formed segment(s) (S_1) 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 ingredients may be determined by any technique conventional in the art, e.g. laser light scattering, sieve analysis, light microscopy or image analysis.

The formed segment(s) (S_1) provide prolonged release of the first pharmacologically active ingredient (A_1). While such prolonged release may principally be achieved by providing the formed segment(s) (S_1) with a prolonged release coating containing pore formers, prolonged release is preferably achieved by a prolonged release matrix.

Thus, the formed segment(s) (S_1) preferably comprise(s) a prolonged release matrix. The prolonged release matrix in turn preferably comprises a prolonged release matrix material that serves the function of providing prolonged release of the first pharmacologically active ingredient (A_1), optionally further pharmaceutical excipients that do not substantially influence the release profile, and the first pharmacologically active ingredient (A_1).

The first pharmacologically active ingredient (A_1) is preferably embedded, particularly preferably dispersed in the prolonged release matrix material.

The total content of the prolonged release matrix (first pharmacologically active ingredient (A_1) + prolonged release matrix material + optionally present excipients that do not substantially influence the release profile) that is contained in the formed segment(s) (S_1) is preferably at least 30 wt.-%, more preferably at least 40 wt.-%, still more preferably at least 50 wt.-%, yet more preferably at least 60 wt.-%, even more preferably at least 70 wt.-%, most preferably at least 80 wt.-%, and in particular at least 90 wt.-%, relative to the total weight of the formed segment(s) (S_1).

The total content of the prolonged release matrix (first pharmacologically active ingredient (A_1) + prolonged release matrix material + optionally present excipients that do not substantially influence the release profile) that is contained in the formed segment(s) (S_1) is preferably within the range of from 5 to 95 wt.-%, more preferably 7 to 90 wt.-%, still more preferably 9 to 80 wt.-%, yet more preferably 11 to 70 wt.-%, even more preferably 13 to 60 wt.-%, most preferably 14 to 50 wt.-%, and in particular 15 to 40 wt.-%, relative to the total weight of the pharmaceutical dosage form.

Preferably, the first pharmacologically active ingredient (A_1) and the prolonged release matrix material are intimately homogeneously distributed within the formed segment(s) (S_1) so that the formed segment(s) (S_1) do(es) not contain any portions where either the first pharmacologically active ingredient (A_1) is present in the absence of prolonged release matrix material or where prolonged release matrix material is present in the absence of the first pharmacologically active ingredient (A_1).

When the formed segment (S_1) is film coated, the prolonged release matrix material is preferably homogeneously distributed in the body of the formed segment (S_1), i.e. the film coating preferably does not contain prolonged release matrix material.

Apart from the prolonged release matrix material, the formed segment(s) (S_1) preferably contain(s) conventional pharmaceutical excipients that do not substantially influence the release profile.

Preferably, the total content of the prolonged release matrix material, i.e. material that serves the function of providing prolonged release of the first pharmacologically active ingredient (A_1), is within the range of from 20 to 99 wt.-%, relative to the total weight of the formed segment(s) (S_1). When the formed segments (S_1) are particulate, these percent values preferably are related to the total weight of all particles of the formed segment(s) (S_1).

In a preferred embodiment, the content of the prolonged release matrix material is at least 5 wt.-%, or at least 10 wt.-%, or at least 15 wt.-%, more preferably at least 20 wt.-%, or at least 25 wt.-%, or at least 30 wt.-%, still more preferably at least 35 wt.-%, or at least 40 wt.-%, or at least 45 wt.-%, yet more preferably at least 50 wt.-%, or at least 55 wt.-%, or at least 60 wt.-%, most preferably at least 65 wt.-%, or at least 70 wt.-%, or at least 75 wt.-%, and in particular at least 80 wt.-%, or at least 85 wt.-%, or at least 90 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a preferred embodiment, the total content of prolonged release matrix material 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 formed segment(s) (S_1).

In another preferred embodiment, the total content of prolonged release matrix material 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 formed segment(s) (S_1).

In still another preferred embodiment, the total content of prolonged release matrix material 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 formed segment(s) (S_1).

In a yet another preferred embodiment, the total content of prolonged release matrix material 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 formed segment(s) (S_1).

In a further preferred embodiment, the total content of prolonged release matrix material is within the range of 45±20 wt.-%, more preferably 45±15 wt.-%, and most preferably 45±10 wt.-%, and in particular 45±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In still a further preferred embodiment, the total content of prolonged release matrix material is within the range of 50±20 wt.-%, more preferably 50±15 wt.-%, and most preferably 50±10 wt.-%, and in particular 50±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In yet a further preferred embodiment, the total content of prolonged release matrix material is within the range of 55±20 wt.-%, more preferably 55±15 wt.-%, and most preferably 55±10 wt.-%, and in particular 55±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In another preferred embodiment, the total content of prolonged release matrix material is within the range of 60±20 wt.-%, more preferably 60±15 wt.-%, and most preferably 60±10 wt.-%, and in particular 60±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In still another preferred embodiment, the total content of prolonged release matrix is within the range of 65±20 wt.-%, more preferably 65±15 wt.-%, and most preferably 65±10 wt.-%, and in particular 65±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In yet another preferred embodiment, the total content of prolonged release matrix material is within the range of 70±20 wt.-%, more preferably 70±15 wt.-%, and most preferably 70±10 wt.-%, and in particular 70±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a further preferred embodiment, the total content of prolonged release matrix material is within the range of 75±20 wt.-%, more preferably 75±15 wt.-%, and most preferably 75±10 wt.-%, and in particular 75±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In still a further preferred embodiment, the total content of prolonged release matrix material is within the range of 80±15 wt.-%, more preferably 80±12 wt.-%, and most preferably 80±10 wt.-%, and in particular 80±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In yet a further preferred embodiment, the total content of prolonged release matrix material is within the range of 85±10 wt.-%, more preferably 85±8 wt.-%, and most preferably 85±6 wt.-%, and in particular 85±4 wt.-%, based on the total weight of the formed segment(s) (S_1).

In another preferred embodiment, the total content of prolonged release matrix material is within the range of 90±8 wt.-%, more preferably 90±7 wt.-%, and most preferably 90±6 wt.-%, and in particular 90±4 wt.-%, based on the total weight of the formed segment(s) (S_1).

In still another preferred embodiment, the total content of prolonged release matrix material is within the range of 95±3 wt.-%, more preferably 95±2 wt.-%, and most preferably 95±1 wt.-%, and in particular 95±0.5 wt.-%, based on the total weight of the formed segment(s) (S_1).

Preferably, the total content of the prolonged release matrix material, i.e. material that serves the function of providing prolonged release of the first pharmacologically active ingredient (A_1), contained in the formed segment(s) (S_1) is within the range of from 5 to 95 wt.-%, more preferably 15 to 80 wt.-% or 20 to 80 wt.-% relative to the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the content of the prolonged release matrix material is at least 5 wt.-% or 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.-%, or at least 35 wt.-%, or at least 40 wt.-%, or at least 45 wt.-%, or at

least 50 wt.-%, or at least 55 wt.-%, or at least 60 wt.-%, based on the total weight of the pharmaceutical dosage form.

In still another preferred embodiment, the total content of prolonged release matrix material 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 pharmaceutical dosage form.

In yet another preferred embodiment, the total content of prolonged release matrix material 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 pharmaceutical dosage form.

In a further preferred embodiment, the total content of prolonged release matrix material 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 pharmaceutical dosage form.

In still a further preferred embodiment, the total content of prolonged release matrix material 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 pharmaceutical dosage form.

In a still further preferred embodiment, the total content of prolonged release matrix material 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 pharmaceutical dosage form.

In a yet further preferred embodiment, the total content of prolonged release matrix material is within the range of 45±20 wt.-%, more preferably 45±15 wt.-%, and most preferably 45±10 wt.-%, and in particular 45±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In another preferred embodiment, the total content of prolonged release matrix material is within the range of 50±20 wt.-%, more preferably 50±15 wt.-%, and most preferably 50±10 wt.-%, and in particular 50±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a yet further preferred embodiment, the total content of prolonged release matrix material is within the range of 55±20 wt.-%, more preferably 55±15 wt.-%, and most preferably 55±10 wt.-%, and in particular 55±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In another preferred embodiment, the total content of prolonged release matrix material is within the range of 60±20 wt.-%, more preferably 60±15 wt.-%, and most preferably 60±10 wt.-%, and in particular 60±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In still another preferred embodiment, the total content of prolonged release matrix material is within the range of 65±20 wt.-%, more preferably 65±15 wt.-%, and most preferably 65±10 wt.-%, and in particular 65±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

Preferably, the relative weight ratio of the prolonged release matrix material, i.e. material that serves the function of providing prolonged release of the first pharmacologically active ingredient (A_1), to the first pharmacologically active ingredient (A_1) is within the range of from 40:1 to 1: 40 or 35:1 to 1: 35 or 30:1 to 1:30 or 20:1 to 1:20, more preferably 15:1 to 1:15, still more preferably 10:1 to 1:10, yet more preferably 7:1 to 1:7, most preferably 5:1 to 1:5, and in particular 2:1 to 1:2.

The prolonged release matrix material, i.e. material that serves the function of providing prolonged release of the first pharmacologically active ingredient (A_1), preferably comprises at least one synthetic or natural polymer (C) and/or optionally a waxy material. Preferably, the prolonged release matrix material comprises only one synthetic or natural polymer (C). In a preferred embodiment, the prolonged release matrix material consists of synthetic or natural polymer (C).

In a preferred embodiment, the first pharmacologically active ingredient (A_1) is embedded in a prolonged release matrix comprising a synthetic or natural polymer (C).

The total content of the synthetic or natural polymer (C) is preferably at least 65 wt.-%, more preferably at least 70 wt.-%, still more preferably at least 75 wt.-%, yet more preferably at least 80 wt.-%, even more preferably at least 85 wt.-%, most preferably at least 90 wt.-%, and in particular at least 95 wt.-%, relative to the total weight of the prolonged release matrix material, i.e. material that serves the function of providing prolonged release of the first pharmacologically active ingredient (A_1).

The total content of the synthetic or natural polymer (C) is preferably at least 20 wt.-%, more preferably at least 30 wt.-%, still more preferably at least 40 wt.-%, yet more preferably at least 50 wt.-%, even more preferably at least 60 wt.-%, most preferably at least 70 wt.-%, and in particular at least 80 wt.-%, relative to the total weight of the prolonged release matrix (first pharmacologically active ingredient (A_1) + prolonged release matrix material + optionally present excipients that do not substantially influence the release profile).

Preferably, the total content of the synthetic or natural polymer (C) is at least 20 wt.-%, more preferably at least 30 wt.-%, still more preferably at least 40 wt.-%, yet more preferably at least 50 wt.-%, even more preferably at least 60 wt.-%, most preferably at least 70 wt.-%, and in particular at least 80 wt.-%, relative to the total weight of the formed segment(s) (S_1).

In a preferred embodiment, the total content of the synthetic or natural polymer (C) is at least 5 wt.-%, more preferably at least 10 wt.-%, still more preferably at least 15 wt.-%, yet more preferably at least 20 wt.-% and in particular at least 25 wt.-%, relative to the total weight of the formed segment(s) (S_1). In a particularly preferred embodiment, the content of the synthetic or natural polymer (C) is at least 30 wt.-% relative to the total weight of the formed segment(s) (S_1).

In a preferred embodiment, the total content of the synthetic or natural polymer (C) 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 formed segment(s) (S_1).

In another preferred embodiment, the total content of the synthetic or natural polymer (C) 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 formed segment(s) (S_1).

In still another preferred embodiment, the total content of the synthetic or natural polymer (C) 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 formed segment(s) (S_1).

In yet another preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 25±20 wt.-%, more preferably 25±15 wt.-%, most preferably 25±10 wt.-%, and in particular 25±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a further preferred embodiment, the total content of the synthetic or natural polymer (C) 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 formed segment(s) (S_1).

In still a further preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 35±20 wt.-%, more preferably 35±15 wt.-%, most preferably 35±10 wt.-%, and in particular 35±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a still further preferred embodiment, the total content of the synthetic or natural polymer (C) 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 formed segment(s) (S_1).

In a yet further preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 45±20 wt.-%, more preferably 45±15 wt.-%, and most preferably 45±10 wt.-%, and in particular 45±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In another preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 50±20 wt.-%, more preferably 50±15 wt.-%, and most preferably 50±10 wt.-%, and in particular 50±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a yet further preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 55±20 wt.-%, more preferably 55±15 wt.-%, and most preferably 55±10 wt.-%, and in particular 55±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In another preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 60±20 wt.-%, more preferably 60±15 wt.-%, and most preferably 60±10 wt.-%, and in particular 60±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a yet further preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 65±20 wt.-%, more preferably 65±15 wt.-%, and most preferably 65±10 wt.-%, and in particular 65±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In another preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 70±20 wt.-%, more preferably 70±15 wt.-%, and most preferably 70±10 wt.-%, and in particular 70±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a yet further preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 75±20 wt.-%, more preferably 75±15 wt.-%, and most preferably 75±10 wt.-%, and in particular 75±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In another preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 80±20 wt.-%, more preferably 80±15 wt.-%, and most preferably 80±10 wt.-%, and in particular 80±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

Preferably, the total content of the polymer (C) is within the range of from 1 to 99 wt.-%, more preferably 3 to 90 wt.-%, still more preferably 5 to 75 wt.-%, yet more preferably 7 to 70 wt.-%, most preferably 10 to 65 wt.-% and in particular 10 to 60 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the total content of the polymer (C) 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 pharmaceutical dosage form.

In a preferred embodiment, the total content of the synthetic or natural polymer (C) 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 pharmaceutical dosage form.

In another preferred embodiment, the total content of the synthetic or natural polymer (C) 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 pharmaceutical dosage form.

In still another preferred embodiment, the total content of the synthetic or natural polymer (C) 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 pharmaceutical dosage form.

In yet another preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 25±20 wt.-%, more preferably 25±15 wt.-%, most preferably 25±10 wt.-%, and in particular 25±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a further preferred embodiment, the total content of the synthetic or natural polymer (C) 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 pharmaceutical dosage form.

In still a further preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 35±20 wt.-%, more preferably 35±15 wt.-%, most preferably 35±10 wt.-%, and in particular 35±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In a still further preferred embodiment, the total content of the synthetic or natural polymer (C) 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 pharmaceutical dosage form.

In a yet further preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 45±20 wt.-%, more preferably 45±15 wt.-%, and most preferably 45±10 wt.-%, and in particular 45±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In another preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 50±20 wt.-%, more preferably 50±15 wt.-%, and most preferably 50±10 wt.-%, and in particular 50±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In still another preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 60±20 wt.-%, more preferably 60±15 wt.-%, and most preferably 60±10 wt.-%, and in particular 60±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

In yet another preferred embodiment, the total content of the synthetic or natural polymer (C) is within the range of 70±20 wt.-%, more preferably 70±15 wt.-%, and most preferably 70±10 wt.-%, and in particular 70±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

Preferably, the relative weight ratio of the polymer (C) to the first pharmacologically active ingredient (A_1) is within the range of 40:1 to 1: 40 or 35:1 to 1: 35 or 30:1 to 1:30 or 20:1 to 1:20, more preferably 15:1 to 1:15, still more preferably 10:1 to 1:10, yet more preferably 7:1 to 1:7, most preferably 5:1 to 1:5, and in particular 2:1 to 1:2.

The synthetic or natural polymer (C) is preferably selected from the group consisting of polyalkylene oxides (preferably polymethylene oxide, polyethylene oxide, polypropylene oxide), polyethylenes, polypropylenes, polyvinyl chlorides, polycarbonates, polystyrenes, polyacrylates, poly(hydroxy fatty acids), poly(hydroxyvaleric acids); polycaprolactones, polyvinyl alcohols, polyesteramides, polyethylene succinates, polylactones,

polyglycolides, cellulose ethers (preferably methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose), polyurethanes, polyvinylpyrrolidones, polyamides, polylactides, polyacetals, polylactide/glycolides, polylactones, polyglycolides, polyorthoesters, polyanhydrides, copolymers thereof, block-copolymers thereof, and mixtures of at least two of the stated polymers.

In a preferred embodiment, polymer (C) is non-ionic. In another preferred embodiment, polymer (C) is anionic. In still another preferred embodiment, polymer (C) is cationic.

Preferably, the synthetic or natural polymer (C) is selected from acrylic polymers or polyalkylene oxides.

In a particularly preferred embodiment,

(i) the content of the synthetic or natural polymer (C) is at least 30 wt.-% relative to the total weight of the formed segment(s) (S_1); and/or

(ii) polymer (C) is selected from acrylic polymers or polyalkylene oxides.

In a preferred embodiment, polymer (C) is an acrylic polymer which is preferably derived from a monomer mixture comprising a first C_{1-4}-alkyl (meth)acrylate and a second C_{1-4}-alkyl (meth)acrylate differing from said first C_{1-4}-alkyl (meth)acrylate.

When the prolonged release matrix material of the prolonged release matrix comprises an acrylic polymer, it preferably does not additionally comprise an polyalkylene oxide or a waxy material, and vice versa. However, it is principally possible that the prolonged release matrix material of the prolonged release matrix comprises a combination of an acrylic polymer, a polyalkylene oxide and/or a waxy material.

Preferred C_{1-4}-alkyl (meth)acrylates include methyl methacrylate, methyl acrylate, ethyl methacrylate, ethyl acrylate, propyl methacrylate, propyl acrylate, butyl methacrylate, and butyl acrylate.

For the purpose of the specification, "(meth)acryl" refers to acryl as well as methacryl.

Preferably, the acrylic polymer has a weight average molecular weight within the range of from 100,000 g/mol to 2,000,000 g/mol. In a preferred embodiment, the acrylic polymer has a weight average molecular weight (M_W) or viscosity average molecular weight (M_η) of at least 150,000 or at least 200,000 g/mol, preferably at least 250,000 g/mol or at least 300,000 g/mol, more preferably in the range of about 300,000 g/mol to about 2,000,000 g/mol, and most preferably in the range of about 300,000 g/mol to about 1,000,000 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 acrylic polymer can be a nonionic acrylic polymer or an ionic acrylic polymer. For the purpose of specification, "nonionic polymer" refers to a polymer not containing more than 1 mole.-% ionic, i.e. anionic or cationic, monomer units, preferably containing no ionic monomer units at all.

In a preferred embodiment, the synthetic or natural polymer (C) is a nonionic acrylic polymer which is preferably derived from a monomer mixture comprising a first C_{1-4}-alkyl (meth)acrylate and a second C_{1-4}-alkyl (meth)acrylate differing from said first C_{1-4}-alkyl (meth)acrylate.

Preferably, the first C_{1-4}-alkyl (meth)acrylate is ethyl acrylate and the second C_{1-4}-alkyl (meth)acrylate is methyl methacrylate.

Preferably, the relative molar content of the ethyl acrylate within the nonionic acrylic polymer is greater than the relative molar content of the methyl methacrylate within the nonionic acrylic polymer.

Preferably, the molar ratio of the first C_{1-4}-alkyl (meth)acrylate, which is preferably ethyl acrylate, to the second C_{1-4}-alkyl (meth)acrylate, which is preferably methyl methacrylate, is within the range of from 5:1 to 1:3, more preferably from 4.5:1 to 1:2.5, still more preferably from 4:1 to 1:2, yet more preferably from 3.5:1 to 1:1.5, even more preferably from 3:1 to 1:1, most preferably from 2.5:1 to 1.5:1, and in particular about 2:1.

Preferably, the nonionic acrylic polymer has a weight average molecular weight within the range of from 100,000 g/mol to 2,000,000 g/mol. In a preferred embodiment, the nonionic acrylic polymer has a weight average molecular weight (M_W) or viscosity average molecular weight (M_η) of at least 150,000 or at least 200,000 g/mol, preferably at least 250,000 g/mol or at least 300,000 g/mol, more preferably in the range of about 300,000 g/mol to about 2,000,000 g/mol, and most preferably in the range of about 300,000 g/mol to about 1,000,000 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).

In a preferred embodiment, the weight average molecular weight of the nonionic acrylic polymer is within the range of 675,000±500,000 g/mol, more preferably 675,000±450,000 g/mol, still more preferably 675,000±400,000 g/mol, yet more preferably 675,000±350,000 g/mol, even more preferably 675,000±300,000 g/mol, most preferably 675,000±250,000 g/mol, and in particular 675,000±200,000 g/mol.

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

In a preferred embodiment, the nonionic acrylic polymer is homogeneously distributed in the formed segment(s) (S_1). According to this embodiment, the first pharmacologically active ingredient (A_1) and the nonionic acrylic polymer are intimately homogeneously distributed in the formed segment(s) (S_1), so that the formed segment(s) (S_1) do(es) not contain any portions where either the first pharmacologically active ingredient (A_1) is present in

the absence of nonionic acrylic polymer or where nonionic acrylic polymer is present in the absence of the first pharmacologically active ingredient (A_1).

When the formed segment(s) (S_1) is/are film coated, the nonionic acrylic polymer is preferably homogeneously distributed in the body of the formed segment(s) (S_1), i.e. the film coating preferably does not contain nonionic acrylic polymer. Nonetheless, the film coating as such may of course contain one or more polymers, which however, preferably differ from the nonionic acrylic polymer contained in the body.

The nonionic acrylic polymer preferably has a glass transition temperature (T_g) within the range of 1±15 °C, more preferably 1±11 °C.

The nonionic acrylic polymer preferably has a minimum film forming temperature (MFT) within the range of 5±5 °C, more preferably 5±2 °C.

Nonionic acrylic polymers that are suitable for use in the formed segment (S_1) according to the invention are commercially available, e.g. from Evonik. For example, Eudragit® NE30D, Eudragit® NE40D and Eudragit® NM30D, which are provided as aqueous dispersions of poly(ethyl acrylate-co-methyl methacrylate) 2:1, may be used in the formed segment (S_1) according to the invention. For details concerning the properties of these products, it can be referred to e.g. the product specification.

In a preferred embodiment, the synthetic or natural polymer (C) is an ionic acrylic polymer.

In a preferred embodiment, the ionic acrylic polymer is homogeneously distributed in the formed segment(s) (S_1). According to this embodiment, the first pharmacologically active ingredient (A_1) and the ionic acrylic polymer are intimately homogeneously distributed in the formed segment(s) (S_1), so that the formed segment(s) (S_1) do(es) not contain any portions where either the first pharmacologically active ingredient (A_1) is present in the absence of ionic acrylic polymer or where ionic acrylic polymer is present in the absence of the first pharmacologically active ingredient (A_1).

When the formed segment(s) (S_1) is/are film coated, the ionic acrylic polymer is preferably homogeneously distributed in the body of the formed segment(s) (S_1), i.e. the film coating preferably does not contain ionic acrylic polymer. Nonetheless, the film coating as such may of course contain one or more polymers, which however, preferably differ from the ionic acrylic polymer contained in the body.

Preferred ionic acrylic polymers are anionic acrylic polymers. Preferred anionic acrylic polymers include but are not limited to copolymers of one or two different C_{1-4}-alkyl (meth)acrylate monomers and copolymerizable anionic monomers such as acrylic acid. Preferred representatives are ternary copolymers of methyl acrylate, methyl methacrylate and methacrylic acid, wherein the relative molar content of the monomers is preferably methyl acrylate > methyl methacrylate > methacrylic acid. Preferably, the anionic acrylic polymer has a weight average molecular weight within the range of 280,000±250,000 g/mol, more preferably 280,000±200,000 g/mol, still more preferably 280,000±180,000 g/mol, yet more preferably 280,000±160,000 g/mol, even more

preferably 280,000±140,000 g/mol, most preferably 280,000±120,000 g/mol, and in particular 280,000±100,000 g/mol. Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 having an average molecular weight of about 280,000 g/mol is commercially available as Eudragit® FS.

Other preferred ionic acrylic polymers are cationic acrylic polymers. Preferred cationic acrylic polymers include but are not limited to copolymers of one or two different C_{1-4}-alkyl (meth)acrylate monomers and copolymerizable cationic monomers such as trimethylammonioethyl methacrylate chloride. Preferred representatives are ternary copolymers of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups, preferably trimethylammonioethyl methacrylate chloride, wherein the relative molar content of the monomers is preferably methyl methacrylate > ethyl acrylate > copolymerizable cationic monomers. Preferably, the cationic acrylic polymer has a weight average molecular weight within the range of 32,000±30,000 g/mol, more preferably 32,000±27,000 g/mol, still more preferably 32,000±23,000 g/mol, yet more preferably 32,000±20,000 g/mol, even more preferably 32,000±17,000 g/mol, most preferably 32,000±13,000 g/mol, and in particular 32,000±10,000 g/mol. Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1 and 1:2:0.2, respectively, having an average molecular weight of about 32,000 g/mol is commercially available as Eudragit® RS-PO and Eudragit® RL-PO, respectively. Because of its lower content of trimethylammonioethyl methacrylate chloride, Eudragit® RS-PO is particularly preferred. Another preferred cationic acrylic polymer is Eudragit® RL 100 which is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups.

In a preferred embodiment, the synthetic or natural polymer (C) is a polyalkylene oxide, preferably a polyethylene oxide, particularly preferably having an weight average molecular weight of at least 500,000 g/mol.

When the prolonged release matrix material of the prolonged release matrix comprises a polyalkylene oxide, it preferably does not additionally comprise an acrylic polymer or a waxy material, and vice versa.

In a preferred embodiment, the polyalkylene oxide is homogeneously distributed in the formed segment(s) (S_1). According to this embodiment, the first pharmacologically active ingredient (A_1) and the polyalkylene oxide are intimately homogeneously distributed in the formed segment(s) (S_1), so that the formed segment(s) (S_1) do(es) not contain any portions where either the first pharmacologically active ingredient (A_1) is present in the absence of polyalkylene oxide or where polyalkylene oxide is present in the absence of the first pharmacologically active ingredient (A_1).

When the formed segment(s) (S_1) is/are film coated, the polyalkylene oxide is preferably homogeneously distributed in the body of the formed segment(s) (S_1), i.e. the film coating preferably does not contain polyalkylene oxide. 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 body.

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

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

Preferably, the molecular weight dispersity M_w/M_n of 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 polyalkylene oxide preferably has a viscosity at 25°C of 30 to 17,600 mPa·s, more preferably 55 to 17,600 mPa·s, still more preferably 600 to 17,600 mPa·s, yet more preferably 4,500 to 17,600 mPa·s, even more preferably 4,500 to 12,000 mPa·s, most preferably 5,000 to 10,500 mPa·s and in particular 5,500 to 7,500 mPa·s or 7,500 to 10,000 mPa·s, measured in a 1 wt.-% aqueous solution.

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

For the purpose of 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. The weight average over all molecular weights of all polyalkylene oxides that are contained in the pharmaceutical dosage form is more than 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 particularly preferred embodiment, the synthetic or natural polymer (C) is a polyalkylene oxide the content of which is at least 30 wt.-% relative to the total weight of the formed segment(s) (S_1).

Preferably, the polyalkylene oxide is combined with another polymer, preferably a cellulose ether, particularly preferably a cellulose ether selected from the group consisting of methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose. Hydroxypropylmethylcellulose is particularly preferred.

Preferably, the relative weight ratio of the polyalkylene oxide and the cellulose ether is within the range of from 14:1 to 1:2, more preferably 13:1 to 1:1, still more preferably 12:1 to 2:1, yet more preferably 11:1 to 3:1, even more preferably 10:1 to 4:1, most preferably 9:1 to 5:1, and in particular 8:1 to 6:1.

In another preferred embodiment, the prolonged release matrix material comprises a waxy material, preferably selected from the group consisting of

- glycerides, especially monoglycerides, diglycerides, triglycerides,
- esters of fatty acids with fatty alcohols, and
- paraffins.

When the prolonged release matrix material of the prolonged release matrix comprises a waxy material, it preferably does not additionally comprise an acrylic polymer or a polyalkylene oxide, and vice versa.

As used herein a "waxy material" refers to a material which melts into liquid form having low viscosity upon heating and sets again to a solid state upon cooling. Preferably, the waxy material has a melting point of at least 30 °C, more preferably at least 35 °C, still more preferably at least 40 °C, yet more preferably at least 45 °C, even more preferably at least 50 °C, most preferably at least 55 °C, and in particular at least 60 °C.

When the waxy material is or comprises a monoglyceride, diglyceride, triglyceride or a mixture thereof, it is preferably a mono-, di- or triester of glycerol and carboxylic acids, whereas the carboxylic acid is preferably selected from the group consisting of fatty acids, hydroxy fatty acids and aromatic acids.

In another preferred embodiment, the glyceride is a fatty acid macrogolglyceride, e.g. lauroyl macrogolglyceride, such as Gelucire 44/14 that can be regarded as a non-ionic water dispersible surfactant composed of well-characterized PEG-esters, a small glyceride fraction and free PEG.

Preferred glycerides of fatty acids include 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 monostearate, glycerol palmitostearate and glyceryl distearate as well as triglycerides of the C_{16} to C_{22} fatty acids such as glycerol tristearate.

The term "fatty acid" is well acknowledged in the art and includes for example unsaturated representatives such as myristoleic acid, palmitoleic acid, sapienic acid, oleic acid, elaidic acid, vaccenic acid, linoleic acid, linoelaidic acid, α-linolenic acid, arachidonic acid, eicosapentaenoic acid, erucic acid, and docosahexaenoic acid; as well as saturated representatives such as caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, and cerotic acid.

The term "hydroxy fatty acid" is also well acknowledged in the art and includes for example 2-hydroxyhexanoic acid, 2-hydroxyoctanoic acid, 2-hydroxydecanoic acid, 2-hydroxydodecanoic acid, β-hydroxylauric acid, 2-hydroxytetradecanoic acid, β-hydroxymyristic acid, 15-hydroxypentadecanoic acid, 16-hydroxyhexadecanoic acid, β-hydroxypalmitic acid, 12-hydroxyoctadecanoic acid, α-hydroxystearic acid, and α-hydroxyarachidic acid.

The fatty acids and the hydroxy fatty acids are preferably saturated.

When the waxy material is or comprises a diglyceride or a triglyceride, the fatty acids, hydroxy fatty acids and aromatic acids, respectively, may be identical or different.

According to this embodiment of the invention, the waxy material is preferably a hard fat (adeps solidus) in accordance with Ph. Eur.

Preferably, the waxy material is a monoglyceride, diglyceride, triglyceride or a mixture thereof, selected from the group consisting of hydrogenated soybean oil, hydrogenated palm oil, hydrogenated castor oil, hydrogenated cottonseed oil, and mixtures thereof.

When the waxy material is or comprises an ester of a fatty acid with a fatty alcohol, the fatty acid is preferably a saturated fatty acid. Preferred examples of fatty acids are already mentioned above in connection with the glycerides. The fatty alcohol is preferably derived from a fatty acid and preferably also saturated.

Preferred representatives of esters of fatty acids with fatty alcohols include but are not limited to natural waxes such as beeswax, carnaubawax, candelilla wax, ouricury wax, sugarcane wax, cetyl palmitate, oleyl oleate, cetaceum and retamo wax.

When the waxy material is or comprises paraffin, the paraffin is preferably a hard paraffin (paraffinum solidum, ceresin, zeresin) in accordance with Ph. Eur.

The waxy material may comprise a single waxy material, or a mixture (blend) of different waxy materials, such as two, three, four or five waxy materials, each of which preferably being selected from the group consisting of glycerides, especially monoglycerides, diglycerides, triglycerides; esters of fatty acids with fatty alcohols; and paraffins.

In a preferred embodiment, the waxy material is homogeneously distributed in the formed segment(s) (S_1). According to this embodiment, the first pharmacologically active ingredient (A_1) and the waxy material are intimately homogeneously distributed in the formed segment(s) (S_1), so that the formed segment(s) (S_1) do(es) not contain any portions where either the first pharmacologically active ingredient (A_1) is present in the absence of waxy material or where waxy material is present in the absence of the first pharmacologically active ingredient (A_1).

When the formed segment(s) (S_1) is/are film coated, the waxy material is preferably homogeneously distributed in the formed segment(s) (S_1), i.e. the film coating preferably does not contain waxy material. Nonetheless, the film coating as such may of course contain one or more waxy materials, which however, preferably differ from the waxy materials contained in the body.

Waxy materials that are suitable for use in the pharmaceutical dosage forms according to the invention are commercially available, e.g. Cera alba, Cera flava, Kolliwax™ HCO, Dynasan® 118, Compritol® 888 ATO,

Precirol® ATO 5, Gelucire® 44/14, and the like. For details concerning the properties of these products, it can be referred to e.g. the product specification.

The total content of the waxy material is preferably within the range of from 5.0 to 95 wt.-%, more preferably 10 to 90 wt.-%, still more preferably 15 to 85 wt.-%, yet more preferably 20 to 80 wt.-%, even more preferably 25 to 75 wt.-%, most preferably 30 to 70 wt.-%, and in particular 35 to 75 wt.-%, relative to the total weight of the prolonged release matrix.

Preferably, the total content of the waxy material is within the range of from 1 to 90 wt.-%, more preferably 3 to 85 wt.-%, still more preferably 5 to 80 wt.-%, yet more preferably 7 to 75 wt.-%, most preferably 10 to 70 wt.-% and in particular 15 to 65 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a preferred embodiment, the total content of the waxy material 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 formed segment(s) (S_1).

In a preferred embodiment, the total content of waxy material 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 formed segment(s) (S_1).

In another preferred embodiment, the total content of waxy material 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 formed segment(s) (S_1).

In still another preferred embodiment, the total content of waxy material 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 formed segment(s) (S_1).

In yet another preferred embodiment, the total content of waxy material 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 formed segment(s) (S_1).

In a further preferred embodiment, the total content of waxy material 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 formed segment(s) (S_1).

In still a further preferred embodiment, the total content of waxy material 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 formed segment(s) (S_1).

In a still further preferred embodiment, the total content of waxy material 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 formed segment(s) (S_1).

In a yet further preferred embodiment, the total content of waxy material is within the range of 45±20 wt.-%, more preferably 45±15 wt.-%, and most preferably 45±10 wt.-%, and in particular 45±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In another preferred embodiment, the total content of waxy material is within the range of 50±20 wt.-%, more preferably 50±15 wt.-%, and most preferably 50±10 wt.-%, and in particular 50±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a yet further preferred embodiment, the total content of waxy material is within the range of 55±20 wt.-%, more preferably 55±15 wt.-%, and most preferably 55±10 wt.-%, and in particular 55±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In another preferred embodiment, the total content of waxy material is within the range of 60±20 wt.-%, more preferably 60±15 wt.-%, and most preferably 60±10 wt.-%, and in particular 60±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a yet further preferred embodiment, the total content of waxy material is within the range of 65±20 wt.-%, more preferably 65±15 wt.-%, and most preferably 65±10 wt.-%, and in particular 65±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In another preferred embodiment, the total content of waxy material is within the range of 70±20 wt.-%, more preferably 70±15 wt.-%, and most preferably 70±10 wt.-%, and in particular 70±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In a yet further preferred embodiment, the total content of waxy material is within the range of 75±20 wt.-%, more preferably 75±15 wt.-%, and most preferably 75±10 wt.-%, and in particular 75±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

In another preferred embodiment, the total content of waxy material is within the range of 80±20 wt.-%, more preferably 80±15 wt.-%, and most preferably 80±10 wt.-%, and in particular 80±5 wt.-%, based on the total weight of the formed segment(s) (S_1).

Preferably, the relative weight ratio of the waxy material to the first pharmacologically active ingredient (A_1) is within the range of 20:1 to 1:20, more preferably 15:1 to 1:15, still more preferably 10:1 to 1:10, yet more preferably 7:1 to 1:7, most preferably 5:1 to 1:5, and in particular 2:1 to 1:2.

Besides the first pharmacologically active ingredient (A_1) and the optionally present prolonged release matrix material the formed segment(s) (S_1) may optionally further comprise additional pharmaceutical excipients conventionally contained in pharmaceutical dosage forms 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 are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

In a preferred embodiment, the formed segment (S_1) does not contain a disintegrant.

Preferably, the formed segment(s) (S_1) further comprise(s) 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 formed segment(s) (S_1).

In a preferred embodiment, the formed segment(s) (S_1) further comprise(s) an acid, preferably a carboxylic acid, more preferably a multicarboxylic acid, particularly citric acid. The content 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 formed segment(s) (S_1).

In a preferred embodiment, the formed segment(s) (S_1) contain(s) at least one lubricant. In another preferred embodiment, the formed segment(s) (S_1) contain(s) no lubricant.

Especially preferred lubricants are selected from

- magnesium stearate, calcium stearate and stearic acid;

- 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; and

- polyethylene glycols having a molecular weight between 10.000 and 60.000 g/mol.

Particularly preferred lubricants comprise stearic acid, calcium stearate and stearyl alcohol or a mixture thereof.

Preferably, the content of the lubricant ranges from 0.01 wt.-% to about 10 or 15 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.-% or 1.5 wt.-% to about 4 wt, and in particular in the range of 0.1 wt.-% to about 1 wt.-% or 3.5 to about 5.5 wt.-%, based on the total weight of the formed segment(s) (S_1).

When the formed segment(s) (S_1) contain(s) more than one lubricant, preferably, the overall content of the lubricant ranges from 3 wt.-% to about 20 wt.-%, more preferably in the range of 5 wt.-% to about 15 wt.-%, most preferably in the range of 7 wt.-% to about 12 wt.-%, and in particular in the range of 8 wt.-% to about 10 wt.-%, based on the total weight of the formed segment(s) (S_1).

Preferably, the formed segment(s) (S_1) further comprise(s) a plasticizer. The plasticizer improves the processability of the prolonged release matrix material. A preferred plasticizer is polyalkylene glycol, like polyethylene glycol, triethyl citrate (TEC), triacetin, fatty acids, fatty acid esters, waxes and/or microcrystalline waxes. Particularly preferred plasticizers are polyethylene glycols, such as PEG 6000. Further particularly preferred plasticizers comprise triethyl citrate (TEC), stearic acid, calcium stearate and stearyl alcohol or a mixture thereof.

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 formed segment(s) (S_1).

When the formed segment (S_1) contains more than one plasticizer, preferably, the overall amount of the plasticizer ranges from 3 wt.-% to about 20 wt.-%, more preferably in the range of 5 wt.-% to about 20 wt.-% or to about 15 wt.-%, most preferably in the range of 7 wt.-% to about 20 wt.-% or to about 12 wt.-%, and in particular in the range of 8 wt.-% to about 20 wt.-% or to about 10 wt.-%, based on the total weight of the formed segment(s) (S_1).

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

Preferably, the formed segment(s) (S_1) further comprise(s) a filler/binder. A preferred filler/binder is selected from celluloses, cellulose derivatives such as cellulose ethers and cellulose esters, and tricalcium phosphate. A particularly preferred filler/binder is selected from cellulose esters and cellulose ethers, in particular hydroxypropyl methylcellulose (HPMC).

The content of the filler/binder, preferably HPMC, preferably ranges from 0.1 wt.-% to about 30 wt.-%, more preferably in the range of 1.0 wt.-% to about 20 wt.-%, and most preferably in the range of 2.0 wt.-% to about 15 wt.-% relative to the total weight of the formed segment(s) (S_1).

In a preferred embodiment, besides the first pharmacologically active ingredient (A_1) that may have any solubility in aqueous ethanol, relative to the total weight of the formed segment(s) (S_1), the formed segment(s) (S_1) according to the invention preferably contain(s) at most 25 wt.-%, more preferably at most 20 wt.-%, still more preferably at most 15 wt.-%, yet more preferably at most 10 wt.-%, even more preferably at most 5.0 wt.-%, most preferably at most 2.5 wt.-%, and in particular at most 1.0 wt.-% of ingredients (prolonged release matrix material, excipients, and the like) having at room temperature in aqueous ethanol (40 vol.-%) a solubility of at least 100 mg/ml, more preferably a solubility of at least 75 mg/ml, still more preferably a solubility of at least 50 mg/ml, yet more preferably a solubility of at least 25 mg/ml, even more preferably a solubility of at least 10 mg/ml, most preferably a solubility of at least 5.0 mg/ml, and in particular a solubility of at least 1.0 mg/ml.

Preferred contents of the first pharmacologically active ingredient (A_1), prolonged release matrix material, and excipients, relative to the total weight of the formed segment(s) (S_1), are summarized as embodiments B^1 to B^{28} in the tables here below:

wt.-%	B^1	B^2	B^3	B^4
first pharmacologically active ingredient (A_1)	40±30	40±20	40±10	40±5
synthetic or natural polymer (C)	50±30	50±20	50±10	50±5
pharmaceutical excipients	20±20	20±20	20±20	20±20

wt.-%	B^5	B^6	B^7	B^8
first pharmacologically active ingredient (A_1)	30±25	30±20	30±10	30±5
synthetic or natural polymer (C)	50±30	50±20	50±10	50±5
pharmaceutical excipients	20±20	20±20	20±20	20±20

wt.-%	B^9	B^{10}	B^{11}	B^{12}
first pharmacologically active ingredient (A_1)	20±15	20±12.5	20±10	20±5
synthetic or natural polymer (C)	50±30	50±20	50±10	50±5
pharmaceutical excipients	20±20	20±20	20±20	20±20

wt.-%	B^{13}	B^{14}	B^{15}	B^{16}
first pharmacologically active ingredient (A_1)	10±7.5	10±7.5	10±5	10±5
synthetic or natural polymer (C)	50±30	50±20	50±10	50±10
pharmaceutical excipients	20±20	20±20	20±20	20±20

wt.-%	B^{17}	B^{18}	B^{19}	B^{20}
first pharmacologically active ingredient (A_1)	20±15	20±12.5	20±10	20±5
synthetic or natural polymer (C)	40±30	40±20	40±10	40±5
pharmaceutical excipients	20±20	20±20	20±20	20±20

wt.-%	B^{21}	B^{22}	B^{23}	B^{24}
first pharmacologically active ingredient (A_1)	20±15	20±12.5	20±10	20±5
synthetic or natural polymer (C)	60±40	60±30	60±20	60±10
pharmaceutical excipients	20±20	20±20	20±20	20±20

wt.-%	B^{25}	B^{26}	B^{27}	B^{28}
first pharmacologically active ingredient (A_1)	10±9	10±7	10±5	10±3
synthetic or natural polymer (C)	70±40	60±30	60±20	60±10
pharmaceutical excipients	20±20	20±20	20±20	20±20

The formed segment(s) (S_1) provide(s) prolonged release of the first pharmacologically active ingredient (A_1). Preferably, the prolonged release matrix provides for a prolonged release of the first pharmacologically active ingredient (A_1) from the formed segment (S_1).

Preferably, under in vitro conditions the pharmaceutical dosage form has released after 30 minutes 0.1 to 75%, after 240 minutes 0.5 to 95%, after 480 minutes 1.0 to 100% and after 720 minutes 2.5 to 100% of the first pharmacologically active ingredient (A_1).

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, 600 mL simulated intestinal fluid pH 6.8 (phosphate buffer) or pH 4.5. In a preferred embodiment, the rotational speed of the paddle is increased to 75 rpm. In another preferred embodiment, the release profile is determined under the following conditions: basket method, 75 rpm, 37±5 °C, 600 mL 0.1 N HCl or 600 mL of SIF sp (pH 6.8) or 600 mL of 0.1 N HCl+40% ethanol.

Preferred release profiles R^1 to R^6 are summarized in the table here below [all data in wt.-% of released first pharmacologically active ingredient (A_1)]:

time	R^1	R^2	R^3	R^4	R^5	R^6
60 min	0-30	0-50	0-50	15-25	20-30	20-50
120 min	0-40	0-75	0-75	25-40	35-50	40-75
240 min	3-55	3-95	10-95	40-70	55-75	60-95
480 min	10-65	10-100	35-100	60-90	80-95	80-100
720 min	20-75	20-100	55-100	70-100	90-100	90-100
960 min	30-88	30-100	70-100	>80	95-100	
1440 min	50-100	50-100	>90			
2160 min	>80	>80				

Further preferred release profiles R^7 to R^{13} are summarized in the table here below [all data in wt.-% of released first pharmacologically active ingredient (A_1)]:

time	R^7	R^8	R^9	R^{10}	R^{11}	R^{12}	R^{13}
30 min	17.5±7.5	17.5±6.5	17.5±5.5	17.5±4.5	17.5±3.5	17.5±2.5	15±6.5
60 min	27.0±8.0	27.0±7.0	27.0±6.0	27.0±5.0	27.0±4.0	27.0±3.0	20±7.0
120 min	41.5±9.5	41.5±8.5	41.5±7.5	41.5±6.5	41.5±5.5	41.5±4.5	25±8.5
240 min	64.5±12.5	64.5±11.5	64.5±10.5	64.5±9.5	64.5±8.5	64.5±7.5	37±11.5
480 min	88.0±12.0	88.0±11.0	88.0±10.0	88.0±9.0	88.0±8.0	88.0±7.0	50±11.0
720 min	96.0±9.0	96.0±8.0	96.0±7.0	96.0±6.0	96.0±5.0	96.0±4.0	58±8.0
840 min	97.5±7.5	97.5±6.5	97.5±5.5	97.5±4.5	97.5±3.5	97.5±2.5	67±15

In a particularly preferred embodiment; under in vitro conditions in 600 mL 0.1 N HCl, using the basket method according to Ph. Eur. at 75 rpm, after 1 h under physiological conditions, the pharmaceutical dosage form has

released at most 50%, more preferably at most 45%, still more preferably at most 40%, yet more preferably at most 30%, even more preferably at most 28%, most preferably at most 25% and in particular at most 23% of the first pharmacologically active ingredient (A_1) relative to the total amount of the first pharmacologically active ingredient (A_1) originally contained in the pharmaceutical dosage form.

Preferably, the release profile, the first pharmacologically active ingredient (A_1) and optionally present pharmaceutical excipients of the formed segment (S_1) 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" preferably 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 a pharmacologically active ingredient and pharmaceutical excipients "stable" preferably means that the segments and the pharmaceutical dosage form satisfy the requirements of EMA concerning shelf-life of pharmaceutical products.

Preferably, after storage for 4 weeks, more preferably 6 months, at 40°C and 75% rel. humidity, the content of the first pharmacologically active ingredient (A_1) in the formed segment(s) (S_1) and the pharmaceutical dosage form, respectively, 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.

The formed segment(s) (S_1) exhibit(s) a higher breaking strength than the further segment (S_2). Further, the formed segment(s) (S_1) exhibit(s) a breaking strength of more than 500 N.
When the formed segments (S_1) are particulate, preferably at least a fraction of the individual particles, i.e. at least one formed segment (S_1) has a breaking strength of more than 500 N.

Preferably, the mechanical properties, particularly the breaking strength, substantially relies on the presence and spatial distribution of the prolonged release matrix material, although its mere presence does typically not suffice in order to achieve said properties. The advantageous mechanical properties may not automatically be achieved by simply processing first pharmacologically active ingredient (A_1), prolonged release matrix material, and optionally further excipients by means of conventional methods for the preparation of pharmaceutical dosage forms. In fact, usually suitable apparatuses must be selected for the preparation and critical processing parameters must be adjusted, particularly pressure/force, temperature and time. Thus, even if conventional apparatuses are used, the process protocols usually must be adapted in order to meet the required criteria.

In general, the desired properties may be obtained only if, during preparation of the formed segment(s) (S_1),

- suitable components
- in suitable amounts

are exposed to

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

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

The formed segment(s) (S_1) has/have a breaking strength of more than 500 N. Preferably, the formed segment(s) (S_1) has/have a breaking strength of at least 600 N, more preferably at least 700 N, still more preferably at least 800 N, yet more preferably at least 1000 N, most preferably at least 1250 N and in particular at least 1500 N.

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

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

When the pharmaceutical dosage form is a capsule, e.g. a hard gelatine capsule, the true quantitative breaking strength of the capsule is difficult to measure; it may occur that the capsule does not fracture in the course of the measurement because of its flexibility. As conventional capsules apparently to not exhibit any increased breaking strength, for the purpose of specification the quantitative breaking strength of a capsule can preferably be regarded as being 0 N.

The formed segment (S_1) according to the invention is distinguished from conventional pharmaceutical dosage forms and particulate or monolithic segments, respectively, in that due to its breaking strength, it 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 (pharmaceutical dosage form 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.

Preferably, the formed segment (S_1) is tamper resistant and provides resistance against grinding.

Conventional pharmaceutical dosage forms and particulate or monolithic segments, respectively, typically have a breaking strength well below 200 N.

The breaking strength of conventional round pharmaceutical dosage forms/particulate or monolithic segments may be estimated according to the following empirical formula:

Breaking Strength [in N] = 10 x Diameter of pharmaceutical dosage form/particulate [in mm].

Thus, according to said empirical formula, a round pharmaceutical dosage form/ particulate or monolithic segment having a breaking strength of at least 300 N would require a diameter of at least 30 mm. Such a particle however, could not be swallowed, let alone a pharmaceutical dosage form containing a plurality of such particles. The above empirical formula preferably does not apply to the formed segment (S_1) according to the invention, which is 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 pharmaceutical dosage forms and particles, respectively, having a breaking strength well below 200 N may be crushed upon spontaneous chewing, whereas the formed segment (S_1) 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 formed segment (S_1) according to the invention can preferably withstand a weight of more than 30 kg without being pulverized.

Methods for measuring the breaking strength 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 Pharmaceutical dosage forms". The segments may be subjected to the same or similar breaking strength test as the pharmaceutical dosage form. The test is intended to determine, under defined conditions, the resistance to crushing of pharmaceutical dosage forms, segments and individual particles, 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 pharmaceutical dosage form, segments and individual particle, respectively. The apparatus is calibrated using a system with a precision of 1 Newton. The pharmaceutical dosage form, segment and particle, respectively, is placed between the jaws, taking into account, where applicable, the shape, the break-mark and the inscription; for each measurement the pharmaceutical dosage form, segment and particle, 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 pharmaceutical dosage forms, segments and particles, 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 pharmaceutical dosage form, segments and individual particles, respectively, to fail (i.e., break) in a specific plane. The pharmaceutical dosage form, segment and individual particle, respectively, is generally placed between two platens, one of which moves to apply sufficient force to the pharmaceutical dosage form, segment and individual particle, respectively, to cause fracture. For conventional, round (circular cross-section) pharmaceutical dosage form, segments and individual particles, respectively, loading occurs across their diameter (sometimes referred to as diametral loading), and fracture occurs in the plane. The breaking force of pharmaceutical dosage form, segment and individual particle, 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 pharmaceutical dosage form, segments and individual particles, 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 pharmaceutical dosage form, segments and individual particles, 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. Measurement is performed using a pressure piston with screw-in inserts and a cylinder (diameter 10 mm), a force transducer, F_{max}. 1 kN, diameter = 8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M according to DIN 55350-18 (Zwick gross force F_{max} = 1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany) with Order No BTC-FR 2.5 TH. D09 for the tester, Order No BTC-LC 0050N. P01 for the force transducer, Order No BO 70000 S06 for the centring device.

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

The formed segment(s) (S_1) according to the invention preferably exhibit(s) mechanical strength over a wide temperature range, in addition to the breaking strength (resistance to crushing) optionally also sufficient hardness, impact resistance, impact elasticity, tensile strength and/or modulus of elasticity, optionally also at low temperatures (e.g. below -24 °C, below -40 °C or 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 formed segment(s) (S_1) according to the invention is maintained

even at low or very low temperatures, e.g., when the pharmaceutical dosage form is initially chilled to increase its brittleness, for example to temperatures below -25°C, below -40 °C or even in liquid nitrogen.

The formed segment(s) (S_1) according to the invention is/are characterized by a certain degree of breaking strength. This does not mean that it must also exhibit a certain degree of hardness. Hardness and breaking strength are different physical properties. Therefore, the preferred tamper-resistance of the formed segment(s) (S_1) does not necessarily depend on the hardness of the formed segment(s) (S_1). For instance, due to its breaking strength, impact strength, elasticity modulus and tensile strength, respectively, the formed segment(s) (S_1) 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 formed segment(s) (S_1) according to the invention is/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 pharmaceutical dosage form, segment and individual particle, respectively, 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 pharmaceutical dosage forms, segments and individual particles, respectively, are those having a suitable tensile strength as determined by a test method currently accepted in the art. Further pharmaceutical dosage form, segments and individual particles, respectively, are those having a Youngs Modulus as determined by a test method of the art. Still further pharmaceutical dosage form, segments and individual particles, respectively, are those having an acceptable elongation at break.

In a preferred embodiment, the formed segment(s) (S_1) is/are tamper resistant and provide(s) resistance against grinding and/or resistance against solvent extraction and/or resistance against dose-dumping in aqueous ethanol.

Tamper-resistant preferably means that the formed segment(s) (S_1)

(i) preferably provide(s) resistance against solvent extraction, and/or

(ii) preferably provide(s) resistance against grinding, and/or

(iii) preferably provide(s) resistance against dose-dumping in aqueous ethanol.

Thus, the formed segment(s) (S_1) according to the invention do(es) not necessarily need to exhibit any of resistances (i) to (iii); but may preferably exhibit any of resistances (i) to (iii) as well as any combination thereof; namely only (i); only (ii); only (iii); a combination of only (i) and (ii); a combination of only (i) and (iii); a combination of only (ii) and (iii); or a combination of (i) and (ii) and (iii).

Preferably, prolonged release of the first pharmacologically active ingredient (A_1) is achieved by a prolonged release matrix contained in the formed segment(s) (S_1) which prolonged release matrix additionally provides

tamper resistance in terms of resistance against solvent extraction, resistance against grinding, and resistance against dose-dumping in aqueous ethanol.

As used herein, the term "tamper-resistant" refers to pharmaceutical dosage forms or segments that are resistant to conversion into a form suitable for misuse or abuse, particular for nasal and/or intravenous administration, by conventional means.

In this regard, the pharmaceutical dosage form as such it may be crushable by conventional means such as grinding in a mortar or crushing by means of a hammer. However, the formed segment(s) (S_1) contained in the pharmaceutical dosage form preferably exhibit(s) mechanical properties such that they cannot be pulverized by conventional means any further. As the formed segment(s) (S_1) is/are of macroscopic size and contain(s) the pharmacologically active ingredient, it/they cannot be administered nasally thereby rendering the pharmaceutical dosage form tamper-resistant.

Further, when trying to disrupt the pharmaceutical dosage forms by means of a hammer or mortar, the formed segments (S_1) tend to adhere to one another thereby forming aggregates and agglomerates, respectively, which are larger in size than the untreated particles.

Preferably, the prolonged release matrix of the formed segment(s) (S_1) provides resistance against solvent extraction.

Preferably, when trying to tamper the pharmaceutical 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 at room temperature is as less as possible, preferably it contains not more than 45 or 40 wt.-%, more preferably not more than 35 wt.-%, still more preferably not more than 30 wt.-%, yet more preferably not more than 25 wt.-%, even more preferably not more than 20 wt.-%, most preferably not more than 15 wt.-% and in particular not more than 10 wt.-% of the originally contained first pharmacologically active ingredient (A_1).

Preferably, this property is tested by (i) dispensing a pharmaceutical dosage form that is either intact or has been manually comminuted by means of two spoons in 5 ml of solvent, either purified water or aqueous ethanol (40 vol.%), (ii) allowing the dispersion to stand for 10 min at room temperature, (iii) drawing up the hot liquid into a syringe (needle 21G equipped with a cigarette filter), and (iv) determining the amount of the pharmacologically active ingredient contained in the liquid within the syringe.

Preferably, the prolonged release matrix of the formed segment(s) (S_1) contained in the pharmaceutical dosage form according to the invention provides resistance against grinding.

Preferably, when the formed segment(s) (S_1) is/are treated with a commercial coffee mill, preferably type Bosch MKM6000, 180W, Typ KM13 for 2 minutes, 42±17.5 wt.-%, more preferably 42±15 wt.-%, still more preferably 42±12.5 wt.-%, yet more preferably 42±10 wt.-%, even more preferably 42±7.5 wt.-%, most

preferably 42±5 wt.-%, and in particular 42±2.5 wt.-%, of the total weight of the thus obtained material does not pass a sieve having a mesh size of 1.000 mm.

Preferably, when the formed segment(s) (S_1) is/are treated with a commercial coffee mill, preferably type Bosch MKM6000, 180W, Typ KM13, for 2 minutes, 57±17.5 wt.-%, more preferably 57±15 wt.-%, still more preferably 57±12.5 wt.-%, yet more preferably 57±10 wt.-%, even more preferably 57±7.5 wt.-%, most preferably 57±5 wt.-%, and in particular 57±2.5 wt.-%, of the total weight of the thus obtained material does not pass a sieve having a mesh size of 1.000 mm.

Preferably, when the formed segment(s) (S_1) is/are treated with a commercial coffee mill, preferably type Bosch MKM6000, 180W, Typ KM13, for 2 minutes, at least 50 wt.-%, more preferably at least 55 wt.-%, still more preferably at least 60 wt.-%, yet more preferably at least 65 wt.-%, even more preferably at least 70 wt.-%, most preferably at least 75 wt.-%, and in particular at least 80 wt.-%, of the total weight of the thus obtained material does not pass a sieve having a mesh size of 1.000 mm.

Preferably, when the pharmaceutical dosage form treated with a commercial coffee mill, preferably type Bosch MKM6000, 180W, Typ KM13 for 2 minutes, 42±17.5 wt.-%, more preferably 42±15 wt.-%, still more preferably 42±12.5 wt.-%, yet more preferably 42±10 wt.-%, even more preferably 42±7.5 wt.-%, most preferably 42±5 wt.-%, and in particular 42±2.5 wt.-%, of the total weight of the thus obtained material does not pass a sieve having a mesh size of 1.000 mm.

Preferably, when the pharmaceutical dosage form is/are treated with a commercial coffee mill, preferably type Bosch MKM6000, 180W, Typ KM13, for 2 minutes, 57±17.5 wt.-%, more preferably 57±15 wt.-%, still more preferably 57±12.5 wt.-%, yet more preferably 57±10 wt.-%, even more preferably 57±7.5 wt.-%, most preferably 57±5 wt.-%, and in particular 57±2.5 wt.-%, of the total weight of the thus obtained material does not pass a sieve having a mesh size of 1.000 mm.

Preferably, when the pharmaceutical dosage form is treated with a commercial coffee mill, preferably type Bosch MKM6000, 180W, Typ KM13, for 2 minutes, at least 50 wt.-%, more preferably at least 55 wt.-%, still more preferably at least 60 wt.-%, yet more preferably at least 65 wt.-%, even more preferably at least 70 wt.-%, most preferably at least 75 wt.-%, and in particular at least 80 wt.-%, of the total weight of the thus obtained material does not pass a sieve having a mesh size of 1.000 mm.

Particle size distributions of the ground pharmaceutical dosage form are preferably determined by sieve analysis.

In a preferred embodiment, after treatment with a commercial coffee mill as described above, more than 55%, more preferably more than 60%, still more preferably more than 65%, yet more preferably more than 70%, most preferably 75% and in particular more than 80% of the particles of the ground formed segment (S_1) and pharmaceutical dosage form, respectively, have a size in the range of from 0.2 to 3.3 nm, more preferably of from 0.4 to 3.1 nm, most preferably of from 0.6 to 2.9 and in particular of from 0.7 to 2.8 nm.

Preferred particle size distributions P^1 to P^6 are summarized in the table underneath:

particle size [nm]	amount [wt.-%]					
	P^1	P^2	P^3	P^4	P^5	P^6
< 0.045	0.5±0.4	0.1±0.09	0.3±0.29	0.3±0.29	0.3±0.29	0.3±0.29
0.045-0.063	0.5±0.4	0.3±0.29	0.3±0.29	0.3±0.29	0.3±0.29	0.3±0.29
0.063-0.090	0.5±0.4	0.3±0.29	0.3±0.29	1.0±0.9	0.3±0.29	0.3±0.29
0.090-0.125	0.5±0.4	0.3±0.29	0.3±0.29	1.0±0.9	0.3±0.29	1.0±0.9
0.125-0.180	0.5±0.4	3.0±2.9	2.0±1.5	2.0±1.5	1.0±0.9	1.0±0.9
0.180-0.250	1.5±1.4	1.0±0.8	2.0±1.5	1.0±0.9	2.0±1.5	1.0±0.9
0.250-0.355	4.0±3.5	5.0±4.0	4.0±3.5	3.5±2.5	5.0±4.0	3.0±2.9
0.355-0.500	7.0±6.0	5.0±4.0	6.0±4.5	7.0±6.0	7.0±6.0	7.0±6.0
0.500-0.710	11.0±8.0	9.0±7.0	11.0±8.0	10.0±7.0	13.0±10.0	9.0±7.0
0.710-1.000	15.0±12.0	10.0±7.0	17.0±14.0	18.0±15.0	18.0±15.0	13.0±10.0
1.000-1.400	20.0±17.0	18.0±15.0	23.0±20.0	28.0±25.0	25.0±22.0	20.0±17.0
1.400-2.000	23.0±20.0	19.0±16.0	12.0±9.0	18.0±15.0	10.0±7.0	22.0±19.0
2.000-2.800	13.0±10.0	16.0±13.0	13.0±10.0	11.0±8.0	14.0±11.0	12.0±9.0
2.800-4.000	1.0±0.8	14.0±11.0	12.0±9.0	0.3±0.29	4.0±3.5	9.0±7.0
>4.00	0.5±0.45	0.3±0.29	0.3±0.29	0.5±0.45	0.3±0.29	0.5±0.45

Preferably, the prolonged release matrix of the formed segment(s) (S_1) contained in the pharmaceutical dosage form according to the invention provides resistance against dose-dumping in aqueous ethanol.

The pharmaceutical dosage form can be tested *in vitro* using ethanol / simulated gastric fluid of 0%, 20% and 40% to evaluate alcohol extractability. Testing is preferably performed using standard procedures, e.g. USP Apparatus 1 (basket) or USP Apparatus 2 (paddle) at e.g. 50 rpm in e.g. 500 ml of media at 37°C, using a Perkin Elmer UV/VIS Spectrometer Lambda 20, UV at an appropriate wavelength for detection of the first pharmacologically active ingredient (A_1) present therein. Sample time points preferably include 0.5 and 1 hour.

Preferably, when comparing the *in vitro* release profile at 37°C in simulated gastric fluid with the *in vitro* release profile in ethanol / simulated gastric fluid (40 vol.-%) at 37°C, the *in vitro* release in ethanol / simulated gastric fluid (40 vol.-%) is preferably not substantially accelerated compared to the *in vitro* release in simulated gastric fluid. Preferably, in this regard "substantially" means that at any given time point the *in vitro* release in ethanol / simulated gastric fluid (40 vol.-%) relatively deviates from the *in vitro* release in simulated gastric fluid by not more than +25%, more preferably not more than +20%, still more preferably not more than +15%, yet more preferably not more than +10%, even more preferably not more than +7.5%, most preferably not more than +5.0% and in particular not more than +2.5%.

A substantial relative acceleration of the *in vitro* release in ethanol / simulated gastric fluid (40 vol.-%) compared to the *in vitro* release in simulated gastric fluid is to be prevented according to the invention. However, a substantial relative deceleration of the *in vitro* release in ethanol / simulated gastric fluid (40 vol.-%) compared to the *in vitro* release in simulated gastric fluid, e.g., a relative deviation by -25% or more, may be possible and can even be desirable.

The further segment(s) (S_2) comprise(s) the second pharmacologically active ingredient (A_2) and provide immediate release thereof.

Preferably, the second pharmacologically active ingredient (A_2) is different from the first pharmacologically active ingredient (A_1).

In a preferred embodiment, the second pharmacologically active ingredient (A_2) exhibits no psychotropic action.

In another preferred embodiment, the second pharmacologically active ingredient (A_2) is selected from ATC classes [M01A], [M01C], [N02B] and [N02C] according to the WHO.

In a particularly preferred embodiment,

(i) the first pharmacologically active ingredient (A_1) has a psychotropic effect; and/or

(ii) the second pharmacologically active ingredient (A_2) is selected from ATC classes [M01A], [M01C], [N02B] and [N02C] according to the WHO.

Preferably, the second pharmacologically active ingredient (A_2) is selected from the group consisting of acetylsalicylic acid, aloxiprin, choline salicylate, sodium salicylate, salicylamide, salsalate, ethenzamide, morpholine salicylate, dipyrocetyl, benorilate, diflunisal, potassium salicylate, guacetisal, carbasalate calcium, imidazole salicylate, phenazone, metamizole sodium, aminophenazone, propyphenazone, nifenazone, paracetamol, phenacetin, bucetin, propacetamol, rimazolium, glafenine, floctafenine, viminol, nefopam, flupirtine, ziconotide, methoxyflurane, nabiximols, dihydroergotamine, ergotamine, methysergide, lisuride, flumedroxone, sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan, frovatriptan, pizotifen, clonidine, iprazochrome, dimetotiazine, oxetorone, phenylbutazone, mofebutazone, oxyphenbutazone, clofezone, kebuzone, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, alclofenac, bumadizone, etodolac, lonazolac, fentiazac, acemetacin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, piroxicam, tenoxicam, droxicam, lornoxicam, meloxicam, ibuprofen, naproxen, ketoprofen, fenoprofen, fenbufen, benoxaprofen, suprofen, pirprofen, flurbiprofen, indoprofen, tiaprofenic acid, oxaprozin, ibuproxam, dexibuprofen, flunoxaprofen, alminoprofen, dexketoprofen, naproxcinod, mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, nabumetone, niflumic acid, azapropazone, glucosamine, benzydamine, glucosaminoglycan polysulfate, proquazone, orgotein, nimesulide, feprazone, diacerein, morniflumate, tenidap, oxaceprol, chondroitin sulfate, oxycinchophen, sodium aurothiomalate, sodium aurotiosulfate, auranofin, aurothioglucose, aurotioprol, penicillamine, bucillamine, their physiologically acceptable salts, as well as mixtures thereof.

In a preferred embodiment, the second pharmacologically active ingredient (A_2) is paracetamol (acetaminophen) or ibuprofen, more preferably paracetamol.

In a particularly preferred embodiment, the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol.

Preferred combinations C^1 to C^{32} of the first pharmacologically active ingredient (A_1) and the second pharmacologically active ingredient (A_2) are summarized in the table here below, wherein the first

pharmacologically active ingredient (A_1) as well as the second pharmacologically active ingredient (A_2) each also refer to the physiologically acceptable salts thereof, particularly to the hydrochlorides:

	A_1	A_2		A_1	A_2
C^1	oxycodone	ibuprofen	C^9	oxycodone	paracetamol
C^2	oxymorphone	ibuprofen	C^{10}	oxymorphone	paracetamol
C^3	hydrocodone	ibuprofen	C^{11}	hydrocodone	paracetamol
C^4	hydromorphone	ibuprofen	C^{12}	hydromorphone	paracetamol
C^5	morphine	ibuprofen	C^{13}	morphine	paracetamol
C^6	tapentadol	ibuprofen	C^{14}	tapentadol	paracetamol
C^7	tramadol	ibuprofen	C^{15}	tramadol	paracetamol
C^8	buprenorphine	ibuprofen	C^{16}	buprenorphine	paracetamol
C^{17}	oxycodone	diclofenac	C^{25}	oxycodone	acetylsalicylic acid
C^{18}	oxymorphone	diclofenac	C^{26}	oxymorphone	acetylsalicylic acid
C^{19}	hydrocodone	diclofenac	C^{27}	hydrocodone	acetylsalicylic acid
C^{20}	hydromorphone	diclofenac	C^{28}	hydromorphone	acetylsalicylic acid
C^{21}	morphine	diclofenac	C^{29}	morphine	acetylsalicylic acid
C^{22}	tapentadol	diclofenac	C^{30}	tapentadol	acetylsalicylic acid
C^{23}	tramadol	diclofenac	C^{31}	tramadol	acetylsalicylic acid
C^{24}	buprenorphine	diclofenac	C^{32}	buprenorphine	acetylsalicylic acid

The second pharmacologically active ingredient (A_2) is present in the pharmaceutical dosage form in a therapeutically effective amount. In general, the amount that constitutes a therapeutically effective amount varies according to the pharmacologically active ingredients being used, the condition being treated, the severity of said condition, the patient being treated, and whether the pharmaceutical dosage form or the segment in which the pharmacologically active ingredient is contained is designed for an immediate or retarded release.

The total content of the second pharmacologically active ingredient (A_2) preferably ranges from about 0.01 wt.-% to about 95 wt.-%, more preferably from about 0.1 wt.-% to about 80 wt.-%, even more preferably from about 1.0 wt.-% to about 50 wt.-%, yet more preferably from about 1.5 wt.-% to about 30 wt.-%, and most preferably from about 2.0 wt.-% to 20 wt.-%, based on the total weight of the further segment(s) (S_2) or based on the total weight of the pharmaceutical dosage form.

Preferably, the total content of the second pharmacologically active ingredient (A_2) is within the range of from 0.01 to 80 wt.-%, more preferably 0.1 to 50 wt.-%, still more preferably 1 to 25 wt.-%, based on the total weight of the pharmaceutical dosage form. In a preferred embodiment, the total content of the second pharmacologically active ingredient (A_2) is within the range of from 20±15 wt.-%, more preferably 20±12 wt.-%, still more preferably 20±10 wt.-%, most preferably 20±7 wt.-%, and in particular 20±5 wt.-%, based on the total weight of the pharmaceutical dosage form. In a preferred embodiment, the total content of the second pharmacologically active ingredient (A_2) is within the range of from 30±15 wt.-%, more preferably 30±12 wt.-%, still more preferably 30±10 wt.-%, most preferably 30±7 wt.-%, and in particular 30±5 wt.-%, based on the total weight of the pharmaceutical dosage form. In a preferred embodiment, the total content of the second pharmacologically active ingredient (A_2) is within the range of from 40±15 wt.-%, more preferably 40±12 wt.-%, still more preferably 40±10 wt.-%, most preferably 40±7 wt.-%, and in particular 40±5 wt.-%, based on the total weight of the pharmaceutical dosage form. In a preferred embodiment, the total content of the second pharmacologically active ingredient (A_2) is within the range of from 50±15 wt.-%, more preferably 50±12 wt.-%, still more

preferably 50±10 wt.-%, most preferably 50±7 wt.-%, and in particular 50±5 wt.-%, based on the total weight of the pharmaceutical dosage form. In a preferred embodiment, the total content of the second pharmacologically active ingredient (A_2) is within the range of from 60±15 wt.-%, more preferably 60±12 wt.-%, still more preferably 60±10 wt.-%, most preferably 60±7 wt.-%, and in particular 60±5 wt.-%, based on the total weight of the pharmaceutical dosage form.

Preferably, the total content of the second pharmacologically active ingredient (A_2) is within the range of from 0.01 to more than 99.99 wt.-%, more preferably 0.1 to 99.9 wt.-%, still more preferably 5 to 95 wt.-%, based on the total weight of the further segment(s) (S_2). In a preferred embodiment, the total content of the second pharmacologically active ingredient (A_2) is within the range of from 20±6 wt.-%, 30±6 wt.-% or 40±6 wt.-%, more preferably 20±5 wt.-%, 30±5 wt.-% or 40±5 wt.-%, still more preferably 20±4 wt.-%, 30±4 wt.-% or 40±4 wt.-%, most preferably 20±3 wt.-%, 30±3 wt.-% or 40±3 wt.-% and in particular 20±2 wt.-%, 30±2 wt.-% or 40±2 wt.-%, based on the total weight of the further segment(s) (S_2). In another preferred embodiment, the total content of the second pharmacologically active ingredient (A_2) is within the range of from 50±20 wt.-%, 60±20 wt.-%, 70±20 wt.-% or 80±20 wt.-%, more preferably 50±15 wt.-%, 60±15 wt.-%, 70±15 wt.-% or 80±15 wt.-%, still more preferably 50±12 wt.-%, 60±12 wt.-%, 70±12 wt.-% or 80±12 wt.-%, most preferably 50±10 wt.-%, 60±10 wt.-%, 70±10 wt.-% or 80±10 wt.-%, and in particular 50±5 wt.-%, 60±5 wt.-%, 70±5 wt.-% or 80±5 wt.-%,based on the total weight of the further segment(s) (S_2). In still another preferred embodiment, the total content of the second pharmacologically active ingredient (A_2) is within the range of from 90±10 wt.-%, more preferably 90±8 wt.-%, still more preferably 90±6 wt.-%, most preferably 90±4 wt.-% and in particular 90±2 wt.-%, based on the total weight of the further segment(s) (S_2).

The total amount of the second pharmacologically active ingredient (A_2) in the further segment (S_2) and the pharmaceutical dosage form, respectively, is not limited. The total amount of the second pharmacologically active ingredient (A_2) which is adapted for administration preferably is in the range of 0.1 mg to 2,000 mg or 0.1 mg to 1,000 mg or 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 second pharmacologically active ingredient (A_2) which is contained in the further segment (S_2) and the pharmaceutical dosage form, respectively, is within the range of from 10 to 1,000 mg, more preferably 50 to 900 mg, still more preferably 100 to 800 mg, yet more preferably 200 to 600 mg, most preferably 250 to 500 mg and in particular 300 to 400 mg. In another preferred embodiment, the total amount of the second pharmacologically active ingredient (A_2) which is contained in the further segment (S_2) and the pharmaceutical dosage form, respectively, is within the range of from 10 to 500 mg, more preferably 12 to 450 mg, still more preferably 14 to 400 mg, yet more preferably 16 to 350 mg, most preferably 18 to 325 mg and in particular 20 to 300 mg.

In a preferred embodiment, the second pharmacologically active ingredient (A_2) is contained in the further segment(s) (S_2) and the pharmaceutical dosage form, respectively, in an amount of 7.5±5 mg, 10±5 mg, 20±5 mg, 30±5 mg, 40±5 mg, 50±5 mg, 60±5 mg, 70±5 mg, 80±5 mg, 90±5 mg, 100±5 mg, 110±5 mg, 120±5 mg, 130±5, 140±5 mg, 150±5 mg, 160±5 mg, 170±5 mg, 180±5 mg, 190±5 mg, 200±5 mg, 210±5 mg, 220±5 mg, 230±5 mg, 240±5 mg, or 250±5 mg. In another preferred embodiment, the second pharmacologically active

ingredient (A_2) is contained in the further segment(s) (S_2) and the pharmaceutical dosage form, respectively, in an amount of 5±2.5 mg, 7.5±2.5 mg, 10±2.5 mg, 15±2.5 mg, 20±2.5 mg, 25±2.5 mg, 30±2.5 mg, 35±2.5 mg, 40±2.5 mg, 45±2.5 mg, 50±2.5 mg, 55±2.5 mg, 60±2.5 mg, 65±2.5 mg, 70±2.5 mg, 75±2.5 mg, 80±2.5 mg, 85±2.5 mg, 90±2.5 mg, 95±2.5 mg, 100±2.5 mg, 105±2.5 mg, 110±2.5 mg, 115±2.5 mg, 120±2.5 mg, 125±2.5 mg, 130±2.5 mg, 135±2.5 mg, 140±2.5 mg, 145±2.5 mg, 150±2.5 mg, 155±2.5 mg, 160±2.5 mg, 165±2.5 mg, 170±2.5 mg, 175±2.5 mg, 180±2.5 mg, 185±2.5 mg, 190±2.5 mg, 195±2.5 mg, 200±2.5 mg, 205±2.5 mg, 210±2.5 mg, 215±2.5 mg, 220±2.5 mg, 225±2.5 mg, 230±2.5 mg, 235±2.5 mg, 240±2.5 mg, 245±2.5 mg, or 250±2.5 mg. In still another preferred embodiment, the second pharmacologically active ingredient (A_2) is contained in the further segment(s) (S_2) and the pharmaceutical dosage form, respectively, in an amount of 250±10 mg, 275±10 mg, 300±10 mg, 325±10 mg, 350±10 mg, 375±10 mg, 400±10 mg, 425±10 mg, 450±10 mg, 475±10 mg, 500±10 mg, 525±10 mg, 550±10 mg, 575±10 mg or 600±10 mg.

In a particularly preferred embodiment, the second pharmacologically active ingredient (A_2) is paracetamol (acetaminophen). In this embodiment, the paracetamol is preferably contained in the further segment(s) (S_2) or the pharmaceutical dosage form in an amount of from 100 to 600 mg, more preferably 150 to 550 mg, still more preferably 200 to 500 mg, most preferably 250 to 450 mg and in particular 275 to 400 mg.

In another particularly preferred embodiment, the second pharmacologically active ingredient (A_2) is ibuprofen. In this embodiment, the ibuprofen is preferably contained in the further segment(s) (S_2) or the pharmaceutical dosage form in an amount of from 100 to 600 mg, more preferably 150 to 550 mg, still more preferably 200 to 500 mg, most preferably 250 to 450 mg and in particular 275 to 400 mg.

In a preferred embodiment, the relative weight ratio of the total content of the first pharmacologically active ingredient (A_1) to the total content of the second pharmacologically active ingredient (A_2) [A_1:A_2] is within the range of (8±1):1, more preferably (7±1):1, still more preferably (6±1):1, yet more preferably (5±1):1, even more preferably (4±1):1, most preferably (3±1):1 and in particular (2±1):1.

In still another preferred embodiment, the relative weight ratio of the total content of the second pharmacologically active ingredient (A_2) to the total content of the first pharmacologically active ingredient (A_1) [A_2:A_1] is within the range of (8±1):1, more preferably (7±1):1, still more preferably (6±1):1, yet more preferably (5±1):1, even more preferably (4±1):1, most preferably (3±1):1 and in particular (2±1):1.

The further segment(s) (S_2) provide(s) immediate release of the second pharmacologically active ingredient (A_2). Preferably, under physiological conditions the pharmaceutical dosage form has released after 5 minutes at least 10%, after 10 minutes at least 20%, after 15 minutes at least 30%, after 20 minutes at least 40%, after 30 minutes at least 60%, after 40 minutes at least 70%, after 50 minutes at least 80%, after 60 minutes at least 90% or 99% of the second pharmacologically active ingredient (A_2).

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, 600 mL simulated intestinal fluid pH 6.8 (phosphate buffer) or pH 4.5. In a preferred embodiment, the rotational speed of the paddle is increased to 75 rpm. In another preferred embodiment, the release profile is determined under the following conditions: basket method, 75 rpm, 37±5 °C, 600 mL 0.1 N HCl or 600 mL of SIF sp (pH 6.8) or 600 mL of 0.1 N HCl+40% ethanol.

In a particularly preferred embodiment; under in vitro conditions in 600 mL 0.1 N HCl, using the basket method according to Ph. Eur. at 75 rpm, after 1 h under physiological conditions the pharmaceutical dosage form has released at least 60% more preferably at least 65%, still more preferably at least 70%, yet more preferably at least 75%, even more preferably at least 80%, most preferably at least 85% and in particular at least 90% or at least 95% or at least 99% of the second pharmacologically active ingredient (A_2) relative to the total amount of A_2 originally contained in the pharmaceutical dosage form.

Preferably, the content of the further segment(s) (S_2) is at least 2.5 wt.-%, at least 5 wt.-%, at least 7.5 wt.-% or at least 10 wt.-%; at least 12.5 wt.-%, at least 15 wt.-%, at least 17.5 wt.-% or at least 20 wt.-%; at least 22.5 wt.-%, at least 25 wt.-%, at least 27.5 wt.-% or at least 30 wt.-%; at least 32.5 wt.-%, 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 pharmaceutical dosage form.

Preferably, the content of the further segment(s) (S_2) 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 pharmaceutical dosage form.

Preferably, the relative weight ratio of the formed segment(s) (S_1) to the further segment(s) (S_2) in the pharmaceutical dosage form is from 1:10 to 10:1, more preferably 1:8 to 8:1, still more preferably 1:7 to 6:1, even more preferably 1:6 to 5:1, yet more preferably 1:5 to 4:1, most preferably 1:4 to 3:1 and in particular 1:3 to 2:1 or 1:2 to 1:1, based on the total weight of the formed segment(s) (S_1) and on the total weight of the further segments (S_2).

The further segment(s) (S_2) may optionally comprise conventional pharmaceutical excipients.

Preferably, the further segment(s) (S_2) comprise(s) one or more fillers or binders. As many fillers can be regarded as binders and vice versa, for the purpose of the specification "filler/binder" refers to any excipient that is suitable as filler, binder or both. Thus, the further segment(s) (S_2) preferably comprise(s) 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®); tricalcium phosphate, maltodextrine (e.g. Emdex®); lactose (e.g. Fast-Flow Lactose®; Ludipress®, Pharmaceutical dosage formtose®, 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. Preferably, the further segment(s) (S_2) comprise(s) a glidant such as silicium dioxide.

In a preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the further segment(s) (S_2) 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 further segment(s) (S_2). In another preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the further segment(s) (S_2) 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 further segment(s) (S_2). In still another preferred embodiment, the content of the filler/binder or mixture of fillers/binders in further segment(s) (S_2) 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 further segment(s) (S_2). In another preferred embodiment, the content of the filler/binder or mixture of fillers/binders in the further segment(s) (S_2) 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 further segment(s) (S_2).

In a preferred embodiment, the total content of the filler/binder or mixture of fillers/binders in the pharmaceutical dosage form 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 pharmaceutical dosage form. In another preferred embodiment, the total content of the filler/binder or mixture of fillers/binders in the pharmaceutical dosage form 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 pharmaceutical dosage form. In still another preferred embodiment, the total content of the filler/binder or mixture of fillers/binders in the pharmaceutical dosage form 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 pharmaceutical dosage form. In another preferred embodiment, the total content of the filler/binder or mixture of fillers/binders in the pharmaceutical dosage form

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 pharmaceutical dosage form.

Preferably, the filler/binder is contained in the further segment(s) (S_2) but not in the formed segment(s) (S_1) of the pharmaceutical dosage form according to the invention.

Preferably, the further segment(s) (S_2) comprise(s) one or more diluents or lubricants, 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 further segment(s) (S_2) 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 further segment(s) (S_2) or based on the total weight of pharmaceutical dosage form.

Preferably, the further segment(s) (S_2) comprise(s) one or more disintegrants, preferably selected from the group consisting of carmellose and salts thereof, croscarmellose sodium, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, partly pregelatinized starch and low-substituted hydroxypropyl cellulose. Crosscarmellose is particularly preferred. Preferably, the content of the disintegrant in the further segment(s) (S_2) is at most 20.0 wt.-%, more preferably at most 15 wt.-%, still more preferably at most 12.5 wt.-%, yet more preferably at most 10 wt.-%, even more preferably at most 8.0 wt.-%, and most preferably within the range of from 6.0 wt.-% to 8.0 wt.-%, based on the total weight of the further segment(s) (S_2) or based on the total weight of pharmaceutical dosage form.

Preferably, the further segment(s) (S_2) comprise(s) one or more dispersing agents or a wetting agents, preferably selected from the group consisting of poloxamers such as Lutrol F68. Preferably, the content of the dispersing agent or a wetting agent in the further segment(s) (S_2) is at most 50 wt.-%, more preferably at most 45 wt.-%, still more preferably at most 40 wt.-%, yet more preferably at most 35 wt.-%, even more preferably at most 30 wt.-%, and most preferably within at most 30 wt.-%, based on the total weight of the further segment(s) (S_2) or based on the total weight of pharmaceutical dosage form.

In particularly preferred embodiment, the further segment(s) (S_2) comprise(s) a combination of filler/binder and lubricant and optionally disintegrant and optionally dispersing agent/wetting agent.

The further segment(s) (S_2) of the pharmaceutical dosage form according to the invention may additionally contain other excipients that are conventional in the art, e.g. diluents, binders, granulating aids, colorants, flavourants, glidants, wet-regulating agents and disintegrants. The skilled person will readily be able to determine appropriate quantities of each of these excipients.

In a preferred embodiment, however, besides the second pharmacologically active ingredient (A_2), the further segment(s) (S_2) of the pharmaceutical dosage form 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 further segment(s) (S_2) of the pharmaceutical dosage form according to the invention do(es) not contain one or more gel-forming agents and/or a silicone.

In a preferred embodiment, the further segment(s) (S_2) of the pharmaceutical dosage form according to the invention do(es) not contain polyalkylene oxides, acrylic polymers or waxy materials. If the further segment(s) (S_2) contain(s) polyalkylene oxides, acrylic polymers and/or waxy materials, the total content of polyalkylene oxides, acrylic polymers and waxy materials preferably is not more than 30 wt.-%, more preferably not more than 25 wt.-%, still more preferably not more than 20 wt.-%, yet more preferably not more than 15 wt.-%, even more preferably not more than 10 wt.-%, most preferably not more than 5.0 wt.-%, and in particular not more than 1.0 wt.-%, relative to the total weight of the further segment(s) (S_2).

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 ingredient 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 ingredient, and which can be drawn into a syringe. The gel that is formed may also reduce the overall amount of pharmacologically active ingredient extractable with the solvent by entrapping the pharmacologically active ingredient within a gel structure. Thus the gel-forming agent may play an important role in conferring tamper-resistance to the pharmaceutical dosage forms according to the invention.

Gel-forming agents that preferably are not contained in the further segment(s) (S_2) include pharmaceutically acceptable polymers, typically hydrophilic polymers, such as hydrogels. Representative examples of gel-forming agent include polyalkylene oxide such as polyethylene oxide, polyvinyl alcohol, hydroxypropylmethyl cellulose, carbomers, poly(uronic) acids and mixtures thereof.

The optional excipients preferably do not impart to the further segment(s) (S_2) any significant resistance against dose-dumping in aqueous ethanol. According to this embodiment, the further segment(s) (S_2) preferably do(es) not contain any compound which would impart to the further segment(s) (S_2) any substantial resistance against dose-dumping in aqueous ethanol such as polyalkylene oxides, nonionic acrylic polymers or waxy materials.

The formed segment(s) (S_1) may be incorporated in an outer matrix material formed by the further segment(s) (S_2). From a macroscopic perspective, the outer matrix material formed by the further segment(s) (S_2) preferably forms a continuous phase in which the formed segment(s) (S_1) is/are embedded. When the formed segments (S_1) are particulate, the particles preferably form a discontinuous phase within an outer matrix material that is formed by further segment (S_2).

For the purpose of definition, the "outer matrix material" is preferably the further segment (S_2) and thus, preferably comprises the second pharmacologically active ingredient (A_2) and optionally conventional pharmaceutical excipients which have already been described above.

In a preferred embodiment, the further segment(s) (S_2) essentially consist(s) of the second pharmacologically active ingredient (A_2), i.e. the further segment(s) (S_2) do(es) not comprise any pharmaceutical excipient. According to this embodiment, the pharmaceutical dosage form is preferably a capsule that is filled with the formed segment(s) (S_1) and the second pharmacologically active ingredient (A_2), which may be powdery or agglomerated, e.g. granulated, and which preferably forms a further segment (S_2) as an outer matrix material.

Preferably, the outer matrix material is a homogenous powdery or coherent mass, preferably a homogeneous mixture of solid constituents, in which the monolithic or particulate formed segment(s) (S_1) is/are embedded. According to this embodiment, when the formed segment (S_1) is particulate, the particulate formed segments (S_1) are preferably spatially separated from one another. While it is possible that the surfaces of particulate formed segments (S_1) are in contact or at least in very close proximity with one another, the plurality of particulate formed segments (S_1) preferably cannot be regarded as a single continuous coherent mass within the pharmaceutical dosage form.

In other words, when the formed segments (S_1) are particulate and the particles are contained in an outer matrix material formed by the further segments (S_2), the pharmaceutical dosage form according to the invention preferably comprises the particles of the formed segment (S_1) as volume elements of a first type and the outer matrix material formed by the further segment (S_2) as volume element of a second type differing from the material that forms the particles of the formed segment (S_1), and preferably containing no prolonged release matrix.

When the formed segment(s) (S_1) is/are contained in an outer matrix material formed by the further segment (S_2), the relative weight ratio of the monolith or the particles of the formed segment(s) (S_1) to the outer matrix material is not particularly limited. Preferably, said relative weight ratio is within the range of 1 : 2.00±1.75, more preferably 1 : 2.00±1.50, still more preferably 1 : 1.00±1.00, most preferably 1 : 1.00±0.75, and in particular 1 : 1.00±0.50.

The further segment (S_2) in turn may also be in particulate form. When the further segment (S_2) is particulate form, however, the particles are preferably not thermoformed and preferably do not contain synthetic or natural polymer (C). When the further segment (S_2) is in particulate form, the particles are preferably obtained by conventional methods for the preparation of aggregates and agglomerates from powder mixtures such as granulating and compacting.

The further segment(s) (S_2) exhibit(s) a breaking strength that is lower than that of formed segment(s) (S_1). Typically, the breaking strength of further segment(s) is not increased compared to the breaking strength of conventional dosage forms, i.e. well below 200 N. When the further segment(s) (S_2) are powdery, the "breaking

strength" of the powder is so low that it cannot be measured by conventional means. Thus, for the purpose of specification, the breaking strength of the powder should be regarded as "0 Newton". When quantifying the breaking strength of the further segment(s) (S_2) by "0 Newton", the further segment(s) is/are typically present in form of a (free-flowing) powder, and when quantifying the breaking strength of the further segment(s) (S_2) by values above "0 Newton", this implies that according to these embodiments the further segment(s) (S_2) is/are at least to some minimal degree present in form of granulated, compacted, congealed or otherwise agglomerated matter, but not as a (free-flowing) powder.

In a preferred embodiment, the further segment(s) (S_2) exhibit(s) a breaking strength within the range of from 0 N to at most 500 N. Preferably, the further segment(s) (S_2) exhibit(s) a breaking strength within the range of from 0 N to 450 N, more preferably 0 N to 400 N, still more preferably 0 N to 350 N, yet more preferably 0 N to 300 N, most preferably 0 N to 250 N and in particular 0 N to 200 N.

The at least one formed segment (S_1) of the pharmaceutical dosage form exhibits a higher breaking strength than the at least one further segment (S_2) of the pharmaceutical dosage form.

Preferably, the breaking strength of the formed segment(s) (S_1) is relatively at least 50 N higher, more preferably at least 100 N higher, still more preferably at least 150 N higher, yet more preferably at least 200 N higher, even more preferably at least 250 N higher, most preferably at least 300 N higher, and in particular at least 350 N higher than the breaking strength of the further segment(s) (S_2).

In a preferred embodiment, the further segment (S_2) exhibits a breaking strength of at most 500 N, more preferably at most 300 N, still more preferably at most 250 N, yet more preferably at most 200 N, even more preferably at most 150 N, most preferably at most 100 N, and in particular at most 50 N.

According to this embodiment, the second pharmacologically active ingredient (A_2) preferably does not have potential for being abused; more preferably, the second pharmacologically active ingredient (A_2) is selected from ATC classes [M01A], [M01C], [N02B] and [N02C] according to the WHO; and most preferably, the second pharmacologically active ingredient (A_2) is selected from paracetamol and ibuprofen.

In general, it is very difficult to provide any segment exhibiting a high breaking strength, preferably such a high breaking strength that crushing of the segment is impeded, while at the same time providing immediate release of a pharmacologically active ingredient contained in said segment. This is because the breaking strength typically relies on the presence of polymers that act as release matrix material slowing down the release of the pharmacologically active ingredient. Therefore, it is only meaningful to provide a segment exhibiting a combination of a high breaking strength and immediate release of the pharmacologically active ingredient contained therein when said pharmacologically active ingredient has a potential for being abused.

In a preferred embodiment,

(i) the formed segment (S_1) exhibits a breaking strength of preferably at least 750 N, more preferably at least 1000 N, most preferably at least 1250 N, and in particular at least 1500 N; and/or

(ii) the further segment (S_2) exhibits a breaking strength of at most 500 N, more preferably at most 300 N, still more preferably at most 250 N, yet more preferably at most 200 N, even more preferably at most 150 N, most preferably at most 100 N, and in particular at most 50 N.

Because of the different breaking strength of the formed segment(s) (S_1) and the further segment(s) (S_2), when measuring the breaking strength of the pharmaceutical dosage form according to the invention, a distance-to-force diagram can be obtained that contains at least two steps; the first platform in the distance-to-force diagram is reached once the further segment(s) (S_2) fracture and the second platform in the distance-to-force diagram is reached once the formed segment(s) (S_1) fracture. When the further segment (S_2) is present in powdery form, however, the "first platform" corresponds to the baseline, i.e. is not visible. Furthermore, depending upon the upper measuring limit of the breaking strength tester, the formed segment(s) (S_1) might not have fractured once said upper limit is reached.

In a preferred embodiment, the at least one formed segment (S_1) of the pharmaceutical dosage form exhibits a higher breaking strength than the overall pharmaceutical dosage form comprising the formed segment(s) (S_1) and the further segment(s) (S_2). According to this embodiment, the breaking strength of the pharmaceutical dosage form is preferably defined as the amount of force that is necessary in order to fracture a pharmaceutical dosage form into two or more fragments, wherein said fragments preferably contain the still intact formed segment(s) (S_1).

Preferably, the breaking strength of the formed segment(s) (S_1) is relatively at least 50 N higher, more preferably at least 100 N higher, still more preferably at least 150 N higher, yet more preferably at least 200 N higher, even more preferably at least 250 N higher, most preferably at least 300 N higher, and in particular at least 350 N higher than the breaking strength of the pharmaceutical dosage form comprising the formed segment(s) (S_1) and the further segment(s) (S_2).

Another aspect of the invention relates to a process for the production of a pharmaceutical dosage form comprising the steps of

(i) thermoforming at least one formed segment (S_1) comprising a first pharmacologically active ingredient (A_1) and a natural or synthetic polymer (C);

(ii) providing at least one further segment (S_2) comprising a second pharmacologically active ingredient (A_2); and

(iii) combining the at least one formed segment (S_1), the at least one further segment (S_2) and optionally further excipients.

In a preferred embodiment, the formed segment(s) (S_1) is/are thermoformed. According to this embodiment, the formed segment(s) (S_1) is/are preferably melt-extruded. Further according to this embodiment, the formed segment(s) (S_1) is/are preferably monolithic or particulate.

Thermoforming preferably means that in the course of the manufacture of the formed segment(s) (S_1) the mass is heated to a temperature above ambient temperature, preferably to at least 30 °C, at least 40 °C, at least 50 °C, at least 60 °C, at least 70 °C, or at least 80 °C, and compressed, preferably at pressures that are sufficient to yield a coherent, not dripping form, preferably at pressures of at least 10 bar or at least 30 bar. The compression force may be exerted prior to, during or subsequent to application of heat.

The formed segment(s) (S_1) is/are preferably thermoformed, preferably by melt-extrusion, although also other methods of thermoforming may be useful, such as press-molding at elevated temperature or heating of compacts that were manufactured by conventional compression in a first step and then heated above the softening temperature of the prolonged release matrix material in a second step to form break resistant, hardened compacts, i.e. monolithic formed segment(s) (S_1). In this regard, thermoforming preferably means the forming, or molding of a mass after, before or during the application of heat. In a preferred embodiment, thermoforming is performed by hot-melt extrusion.

In a preferred embodiment, hot melt-extrusion is performed 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. 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 monoliths and particles, respectively, 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 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. 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 the formed segment (S_1). 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 preferably monolithic or particulate formed segment (S_1) 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 preferably monolithic or particulate formed segment (S_1), 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 prolonged release matrix material, preferably the natural or synthetic polymer (C), up to its softening point;

(c) hardening the mixture by applying heat and force, it being possible to supply the heat during and/or before and/or after the application of force and the quantity of heat supplied being sufficient to heat the prolonged release matrix material, preferably the natural or synthetic polymer (C), 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 monoliths or particles; and

(f) optionally providing a film coating.

Heat may be supplied directly, e.g. by contact or by means of hot gas such as hot air, or with the assistance of ultrasound; or is indirectly supplied by friction and/or shear. Force may be applied and/or the monoliths or particles may be shaped for example by direct formed segment (S_1) forming 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 monoliths and particles, respectively, 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 prolonged release matrix material. 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 forming press comprising die and punches of appropriate shape.

A particularly preferred process for the manufacture of the formed segment(s) (S_1) according to the invention involves hot-melt extrusion. In this process, the formed segment(s) (S_1) is/are produced by thermoforming with the assistance of an extruder, preferably without there being any observable consequent discoloration of the extrudate.

This process is preferably 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 prolonged release matrix material and extruded through the outlet orifice of the extruder by application of force,

c) the still plastic extrudate is singulated and formed into the monoliths or particles of the formed segment (S_1), or

d) the cooled and optionally reheated singulated extrudate is formed into the monoliths or particles of the formed segment (S_1), respectively.

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 prolonged release matrix material is extruded from the extruder through a die with at least one bore.

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

In a preferred embodiment, 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.

In another preferred embodiment, particularly when the prolonged release matrix material is employed in the form of an aqueous dispersion, extrusion is performed in the presence of water and the water is evaporated from the extruded material in the course of the extrusion process, i.e. preferably before the extruded material exits the outlet orifice of the extruder. Therefore a vacuum pump mechanism is used to extract the (evaporated) water from the extruded material. Thus, the extruded strand is preferably water-free, which preferably means that the water content of the extruded strand is preferably at most 10 wt.-%, or at most 7.5 wt.-%, or at most 5.0 wt.-%, or at most 4.0 wt.-%, or at most 3.0 wt.-%, or at most 2.0 wt.-%, more preferably at most 1.7 wt.-%, still more preferably at most 1.5 wt.-%, yet more preferably at most 1.3 wt.-%, even more preferably at most 1.0 wt.-%, most preferably at most 0.7 wt.-%, and in particular at most 0.5 wt.-%. For that purpose, extrusion is preferably performed at a temperature above the boiling point of water under the given conditions; when extrusion is performed under vacuum, the boiling point of water may be substantially below 100 °C. However, even if extrusion is performed under vacuum the preferred extrusion temperature is above 100 °C.

The extruder preferably comprises at least two temperature zones, with heating of the mixture at least up to the softening point of the prolonged release matrix material 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 0.2 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 0.5 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.

In a preferred embodiment, the die head pressure is within the range of from 20±19 bar, more preferably 20±15 bar, and in particular 20±10 bar; or the die head pressure is within the range of from 30±20 bar, more preferably 30±15 bar, and in particular 30±10 bar; or the die head pressure is within the range of from 40±20 bar, more preferably 40±15 bar, and in particular 40±10 bar; or the die head pressure is within the range of from 50±20 bar, more preferably 50±15 bar, and in particular 50±10 bar; or the die head pressure is within the range of from 60±20 bar, more preferably 60±15 bar, and in particular 60±10 bar; or the die head pressure is within the range of from 70±20 bar, more preferably 70±15 bar, and in particular 70±10 bar; or the die head pressure is within the range of from 80±20 bar, more preferably 80±15 bar, and in particular 80±10 bar; or the die head pressure is within the range of from 90±20 bar, more preferably 90±15 bar, and in particular 90±10 bar; or the die head pressure is within the range of from 100±20 bar, more preferably 100±15 bar, and in particular 100±10 bar.

The die geometry or the geometry of the bores is freely selectable. The die or the bores may accordingly exhibit a flat (film), round, oblong or oval cross-section, wherein the round cross-section preferably has a diameter of 0.1 mm to 2 mm for extruded particles and a larger diameter for extruded monolithic pharmaceutical dosage forms. 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 prolonged release matrix material and does not rise above a temperature at which the pharmacologically active ingredient 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 prolonged release matrix material. 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 monoliths or particles of the formed segment (S_1) is performed under oxygen-free atmosphere which may be achieved, e.g., by means of oxygen-scavengers.

The singulated extrudate may be press-formed in order to impart the final shape to the monolithic or particulate formed segment(s) (S_1).

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

For example but not limiting, extrusion may be performed by means of a twin-screw-extruder type ZSE 18 or ZSE27 (Leistritz, Nürnberg, Germany), screw diameters of 18 or 27 mm. Screws having eccentric 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, 1.0, 2.0, 3.0, 4.0, 5.0 or 0.6 mm may be used. The extrusion parameters may be adjusted e.g. to the following values: rotational speed of the screws: 120 Upm; delivery rate 2 kg/h for a ZSE 18 or 8 kg/h for a ZSE27; product temperature: in front of die 125 °C and behind die 135 °C; and jacket temperature: 110 °C. Another suitable extruder that is equipped with a vacuum pump is a Thermo Scientific* Pharma 16 HME hot melt twin-screw extruder.

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 preferably monolithic or particulate formed segment(s) (S_1) according to the invention is preferably produced by thermoforming with the assistance of an extruder without any observable consequent discoloration of the extrudates.

The process for the preparation of the preferably monolithic or particulate formed segment (S_1) 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 formed segment(s) (S_1) is/are monolithic or particulate, preferably oligoparticular or multiparticulate, and the monolith or particles according to the invention can be regarded as "extruded pellet(s)".

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 segments or pharmaceutical 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 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 pharmaceutical dosage forms according to the invention may be prepared from the formed segment(s) (S_1) and the further segment(s) (S_2) by any conventional method.

When the pharmaceutical dosage forms are prepared by compression, the particles or monoliths of the formed segment(s) (S_1), are preferably mixed, e.g. blended and/or granulated (e.g. wet granulated), with the material of the further segment(s) (S_2) as outer matrix material and the resulting mix (e.g. blend or granulate) is then either filled in capsules or compressed, preferably in molds, to form pharmaceutical dosage forms. It is also envisaged that the monoliths or particles 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 pharmaceutical dosage forms 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 pharmaceutical dosage forms 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.

Another aspect of the invention relates to a pharmaceutical dosage for that is obtainable by any of the methods described above.

Examples of pharmaceutical dosage forms according to the invention include, but are not limited to, capsules, tablets, pills, granules, pellets, films, sachets and effervescent, powders, and the like.

In a preferred embodiment, the pharmaceutical dosage form is selected from the group consisting of capsules, sugar-coated tablets, dry-coated tablets, mantle tablets, and layered tablets.

In a particularly preferred embodiment of the invention, the composition is formulated in a capsule. In accordance with this embodiment, the pharmaceutical dosage form comprises a hard or soft gelatin capsule.

Most pharmaceutical dosage forms are intended to be swallowed whole and accordingly, preferred pharmaceutical dosage forms according to the invention are designed for oral administration.

In a preferred embodiment, the pharmaceutical dosage form is to be administered orally.

Particularly preferably, the pharmaceutical dosage form is to be administered as a whole. This preferably means that the dosage form is neither intended to be chewed on nor to be sucked on prior to being swallowed. Further, the dosage forms are preferably not intended to adhere to the oral mucosa. It is preferably not possible to completely crush or comminute the dosage form by chewing because of the high breaking strength of the segment(s) (S_1). Thus, preferably the dosage form according to the invention is swallowed as a whole, i.e. in one piece.

However, alternatively pharmaceutical dosage forms may be dissolved in the mouth, chewed, and some may be placed in a body cavity. Thus, the pharmaceutical dosage form according to the invention may alternatively be adapted for buccal, lingual, rectal or vaginal administration. Implants are also possible.

The pharmaceutical dosage form 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 weight of the pharmaceutical dosage form is within the range of 600±450 mg, more preferably 600±300 mg, still more preferably 600±200 mg, yet more preferably 600±150 mg, most preferably 600±100 mg, and in particular 600±50 mg.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is a capsule, more preferably a hard capsule and most preferably a hard gelatin capsule. Pharmaceutical dosage forms 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.

In another preferred embodiment, the pharmaceutical dosage form according to the invention is a round pharmaceutical dosage form. Pharmaceutical dosage forms 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 still another preferred embodiment, the pharmaceutical dosage form according to the invention is an oblong pharmaceutical dosage form. Pharmaceutical dosage forms 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.

Preferably, the pharmaceutical dosage form according to the invention is not in form of a film.

The pharmaceutical dosage form according to the invention may optionally comprise a coating, e.g. a cosmetic coating. In a preferred embodiment, the coated pharmaceutical dosage form according to the invention is monolithic. The coating is preferably applied after formation of the pharmaceutical dosage form. The coating may be applied prior to or after the curing process. The pharmaceutical dosage forms 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 methylcellulose (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.

The coating can be resistant to gastric juices and dissolve as a function of the pH value of the release environment. By means of this coating, it is possible to ensure that the pharmaceutical dosage form according to the invention passes through the stomach undissolved and the active compound is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5.

The coating can also be applied e.g. to improve the aesthetic impression and/or the taste of the pharmaceutical dosage forms and the ease with which they can be swallowed. Coating the pharmaceutical dosage forms 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 pharmaceutical dosage forms 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.

Preferably, the coating does not contain the second pharmacologically active ingredient (A_2), more preferably the coating does not contain any pharmacologically active ingredient.

Apart from the formed segment(s) (S_1) and the further segment(s) (S_2), the pharmaceutical dosage form may optionally further comprise conventional pharmaceutical excipients.

Preferred pharmaceutical excipients are those which may also be contained in the further segment (S_2) and have already been disclosed above, in particular fillers/binders, lubricants, diluents, granulating aids, colorants, flavourants, glidants, wet-regulating agents and disintegrants.

The skilled person will readily be able to determine appropriate quantities of each of these excipients.

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

The pharmaceutical dosage form according to the invention furthermore preferably contains no antagonists for the pharmacologically active ingredients, preferably no antagonists against psychotropic substances, in particular no antagonists against opioids. Antagonists suitable for a given pharmacologically active ingredient are known to

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

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

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

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

Preferably, the formed segment(s) (S_1), more preferably the entire pharmaceutical dosage form according to the invention contains more than 20 wt.-%, more preferably more than 30 wt.-%, still more preferably more than 40 wt.-%, yet more preferably more than 50 wt.-%, most preferably more than 60 wt.-%, and in particular more than 70 wt.-% of compounds which are not or hardly soluble in ethanol with respect to the total weight of the pharmaceutical dosage form.

For the purpose of specification, compounds which are not or hardly soluble in ethanol have a maximum solubility in aqueous ethanol (96 %) at room temperature of preferably less than 1000 mg/L, more preferably

less than 800 mg/L, even more preferably less than 500 mg/L, most preferably less than 100 mg/L and in particular less than 10 mg/L or less than 1 mg/L.

Preferably, the formed segment (S_1), more preferably the entire pharmaceutical dosage form according to the invention contains more than 50 wt.-%, more preferably more than 60 wt.-%, still more preferably more than 70 wt.-%, yet more preferably more than 80 wt.-%, most preferably more than 90 wt.-%, and in particular more than 95 wt.-% of polymers which are not or hardly soluble in ethanol with respect to the overall amount of polymers contained in the pharmaceutical dosage form.

Preferred polymers which are not or hardly soluble in ethanol according to the invention are xanthan, guar gum and some types of HPMC. The skilled person knows what types of HPMC are not or hardly soluble in ethanol within the sense of the invention.

In a particularly preferred embodiment, formed segment (S_1), more preferably the entire pharmaceutical dosage form according to the invention contains polymers which are not or hardly soluble in ethanol and polymers which are soluble in ethanol, wherein the amount of polymers which are not or hardly soluble in ethanol relative to the total amount of polymers contained in the dosage form is 30 to 100 wt.-%, more preferably 50 to 100 wt.-%, still more preferably 60 to 95 wt.-% or 100 wt.-%, yet more preferably 70 to 90 wt.-% or 100 wt.-%, most preferably 80 to 90 wt.-% or 90 to 100 wt.-%, and in particular more than 95 wt.-% or more than 99 wt.-%.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration once daily, preferably orally. In another preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration twice daily, preferably orally. In still another preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration thrice daily, preferably orally. In yet another preferred embodiment, the pharmaceutical dosage form 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, in each case preferably orally.

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

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

In preferred embodiments, the pharmaceutical dosage form according to the invention is a tablet, preferably selected from the group consisting of bilayer tablets, mantle tablets, trilayer tablets, multilayer tablets (preferably having more than three layers), multicomponent tablets, and sugar coated tablets (dragées). As all these embodiments relate to tablets, the formed segment(s) (S_1) and further segment(s) (S_2) form a coherent compacted mass so that the overall tablet constitutes a single unit of matter that can be administered to a patient. In particular, the further segment(s) (S_2) contained in the tablets is/are not present in form of a powdery material. The total weight of the tablets is not particularly limited. Typically, it is within the range of from 50 mg to 1250

mg. The number of formed segment(s) (S_1) and further segment(s) (S_2) that are contained in the tablets according to the invention is not particularly limited. Typically, the tablets according to the invention contain 1, 2, or 3, but not more formed segments (S_1), as well as 1, 2, or 3, but not more further segments (S_2). All preferred embodiments that have been generally defined above fully apply to the preferred tablets according to the invention and are therefore not reiterated. Nevertheless, particularly preferred embodiments of tablets according to the invention will be described in further detail hereinafter.

Preferably,

(a) the tablet is configured for oral administration once daily, twice daily or thrice daily; and/or

(b) the formed segment(s) (S_1) contain(s) as first pharmacologically active ingredient (A_1) an opioid, preferably selected from the group consisting of oxycodone, oxymorphone, hydromorphone, hydrocodone, morphine, tapentadol, tramadol, buprenorphine, and the physiologically acceptable salts thereof; and/or

(c) the formed segment(s) (S_1) contain(s) a release matrix material in which the first pharmacologically active ingredient (A_1) is embedded such that prolonged release thereof is achieved; and/or

(d) the formed segment(s) (S_1) contain(s) a release matrix material comprising a polymer (C) that is preferably selected from the group consisting of polyalkylene oxides, nonionic acrylates, anionic acrylates or cationic acrylates; more preferably a polyethylene oxide having a weight average molecular weight of at least 500,000 g/mol;

(e) the formed segment(s) (S_1) contain(s) a release matrix material comprising a polymer (C), wherein the content of said polymer (C) is preferably at least 20 wt.-%, at least 25 wt.-% or at least 30 wt.-%, still more preferably at least 35 wt.-%, yet more preferably at least 40 wt.-%, even more preferably at least 45 wt.-%, most preferably at least 50 wt.-%, and in particular at least 55 wt.-%, relative to the total weight of the single formed segment (S_1); and/or

(f) the further segment(s) (S_2) contain(s) as second pharmacologically active ingredient (A_2) an analgesic, preferably selected from the group consisting of ibuprofen, diclofenac, paracetamol, acetylsalicylic acid and the physiologically acceptable salts thereof; and/or

(g) the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol; and/or

(h) the tablet is to be administered as a whole.

In the above definition, the features (a), (b), (c) ... (h) are linked with "and/or". For the purpose of specification, this means that the tablet according to the invention preferably realizes all of said features (a), (b), (c) ... (h) or merely a subgroup of said features (a), (b), (c) ... (h). Preferred tablets according to the invention realize at least feature (a); or at least features (a) and (b); or at least features (a), (b) and (c); or at least features (a), (b), (c) and (d); or at least features (a), (b), (c), (d), and (e); or at least features (a), (b), (c), (d), (e) and (f); or at least features (a), (b), (c), (d), (e), (f) and (g).

Preferably, the pharmaceutical dosage form according to the invention is a bilayer tablet. In the bilayer tablet according to the invention, a single formed segment (S_1) and a single further segment (S_2) are arranged to form a bilayer tablet (cf. Figure 1A). Optionally, the bilayer tablet can be sugar coated (dragée).

Preferably,

(a) the bilayer tablet is configured for oral administration once daily, twice daily or thrice daily; and/or

(b) the total weight of the single formed segment (S_1) that forms one layer of the bilayer tablet is within the range of 210±200 mg (i.e. 10 mg to 410 mg), more preferably 210±180 mg, still more preferably 210±160 mg, yet more preferably 210±140 mg, even more preferably 210±120 mg, most preferably 210±100 mg, and in particular 210±80 mg; and/or

(c) the single formed segment (S_1) contains as first pharmacologically active ingredient (A_1) an opioid, preferably selected from the group consisting of oxycodone, oxymorphone, hydromorphone, hydrocodone, morphine, tapentadol, tramadol, buprenorphine, and the physiologically acceptable salts thereof; and/or

(d) the single formed segment (S_1) contains a release matrix material in which the first pharmacologically active ingredient (A_1) is embedded such that prolonged release thereof is achieved; and/or

(e) the single formed segment (S_1) contains a release matrix material comprising a polymer (C) that is preferably selected from the group consisting of polyalkylene oxides, nonionic acrylates, anionic acrylates or cationic acrylates; more preferably a polyethylene oxide having a weight average molecular weight of at least 500,000 g/mol;

(f) the single formed segment (S_1) contains a release matrix material comprising a polymer (C), wherein the content of said polymer (C) is preferably at least 30 wt.-%, still more preferably at least 35 wt.-%, yet more preferably at least 40 wt.-%, even more preferably at least 45 wt.-%, most preferably at least 50 wt.-%, and in particular at least 55 wt.-%, relative to the total weight of the single formed segment (S_1); and/or

(g) the total weight of the single further segment (S_2) that forms another layer of the bilayer tablet is within the range of 485±450 mg (i.e. 35 mg to 935 mg), more preferably 485±300 mg, still more preferably 485±250 mg, yet more preferably 485±200 mg, even more preferably 485±150 mg, most preferably 485±75 mg, and in particular 485±35 mg; and/or

(h) the single further segment (S_2) contains as second pharmacologically active ingredient (A_2) an analgesic, preferably selected from the group consisting of ibuprofen, diclofenac, paracetamol, acetylsalicylic acid and the physiologically acceptable salts thereof; and/or

(i) the single further segment (S_2) contains a filler, preferably microcrystalline cellulose; wherein the content of said filler is preferably 30±25 wt.-%, more preferably 30±20 wt.-%, still more preferably 30±15 wt.-%, yet more preferably 30±13 wt.-%, even more preferably 30±10 wt.-%, most preferably 30±7 wt.-%, and in particular 30±5 wt.-%, relative to the total weight of the single further segment (S_2); and/or

(j) the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol; and/or

(k) the bilayer tablet is to be administered as a whole.

In the above definition, the features (a), (b), (c) ... (k) are linked with "and/or". For the purpose of specification, this means that the bilayer tablet according to the invention preferably realizes all of said features (a), (b), (c) ... (k) or merely a subgroup of said features (a), (b), (c) ... (k). Preferred bilayer tablets according to the invention realize at least feature (a); or at least features (a) and (b); or at least features (a), (b) and (c); or at least features (a), (b), (c) and (d); or at least features (a), (b), (c), (d), and (e); or at least features (a), (b), (c), (d), (e), and (f); or

at least features (a), (b), (c), (d), (e), (f), and (g); or at least features (a), (b), (c), (d), (e), (f), (g) and (h); or at least features (a), (b), (c), (d), (e), (f), (g), (h) and (i); or at least features (a), (b), (c), (d), (e), (f), (g), (h), (i) and (j).

Preferably, the pharmaceutical dosage form according to the invention is a mantle tablet. In the mantle tablet according to the invention, a single formed segment (S_1) forming a core is surrounded by a single further segment (S_2) forming a shell such that formed segment (S_1) and further segment (S_2) are arranged to form a mantle tablet (cf. Figure 1B). Optionally, the mantle tablet can be sugar coated (dragée).

Preferably,

(a) the mantle tablet is configured for oral administration once daily, twice daily or thrice daily; and/or

(b) the total weight of the single formed segment (S_1) that forms the core of the mantle tablet is within the range of 210±200 mg (i.e. 10 mg to 410 mg), more preferably 210±180 mg, still more preferably 210±160 mg, yet more preferably 210±140 mg, even more preferably 210±120 mg, most preferably 210±100 mg, and in particular 210±80 mg; and/or

(c) the single formed segment (S_1) contains as first pharmacologically active ingredient (A_1) an opioid, preferably selected from the group consisting of oxycodone, oxymorphone, hydromorphone, hydrocodone, morphine, tapentadol, tramadol, burprenorphine, and the physiologically acceptable salts thereof; and/or

(d) the single formed segment (S_1) contains a release matrix material in which the first pharmacologically active ingredient (A_1) is embedded such that prolonged release thereof is achieved; and/or

(e) the single formed segment (S_1) contains a release matrix material comprising a polymer (C) that is preferably selected from the group consisting of polyalkylene oxides, nonionic acrylates, anionic acrylates or cationic acrylates; more preferably a polyethylene oxide having a weight average molecular weight of at least 500,000 g/mol;

(f) the single formed segment (S_1) contains a release matrix material comprising a polymer (C), wherein the content of said polymer (C) is preferably at least 30 wt.-%, still more preferably at least 35 wt.-%, yet more preferably at least 40 wt.-%, even more preferably at least 45 wt.-%, most preferably at least 50 wt.-%, and in particular at least 55 wt.-%, relative to the total weight of the single formed segment (S_1); and/or

(g) the total weight of the single further segment (S_2) that forms the shell of the mantle tablet is within the range of 485±450 mg (i.e. 35 mg to 935 mg), more preferably 485±300 mg, still more preferably 485±250 mg, yet more preferably 485±200 mg, even more preferably 485±150 mg, most preferably 485±75 mg, and in particular 485±35 mg; and/or

(h) the single further segment (S_2) contains as second pharmacologically active ingredient (A_2) an analgesic, preferably selected from the group consisting of ibuprofen, diclofenac, paracetamol, acetylsalicylic acid and the physiologically acceptable salts thereof; and/or

(i) the single further segment (S_2) contains a filler, preferably microcrystalline cellulose; wherein the content of said filler is preferably 30±25 wt.-%, more preferably 30±20 wt.-%, still more preferably 30±15 wt.-%, yet more preferably 30±13 wt.-%, even more preferably 30±10 wt.-%, most preferably 30±7 wt.-%, and in particular 30±5 wt.-%, relative to the total weight of the single further segment (S_2); and/or

(j) the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol; and/or

(k) the mantle tablet is to be administered as a whole.

In the above definition, the features (a), (b), (c) ... (k) are linked with "and/or". For the purpose of specification, this means that the mantle tablet according to the invention preferably realizes all of said features (a), (b), (c) ... (k) or merely a subgroup of said features (a), (b), (c) ... (k). Preferred mantle tablets according to the invention realize at least feature (a); or at least features (a) and (b); or at least features (a), (b) and (c); or at least features (a), (b), (c) and (d); or at least features (a), (b), (c), (d), and (e); or at least features (a), (b), (c), (d), (e), and (f); or at least features (a), (b), (c), (d), (e), (f), and (g); ; or at least features (a), (b), (c), (d), (e), (f), (g) and (h); or at least features (a), (b), (c), (d), (e), (f), (g), (h) and (i); or at least features (a), (b), (c), (d), (e), (f), (g), (h), (i) and (j).

Preferably, the pharmaceutical dosage form according to the invention is a trilayer tablet. In the trilayer tablet according to the invention, a single formed segment (S_1) and two further segments (S_2) are arranged to form a trilayer tablet, wherein formed segment (S_1) forms the middle layer and the two further segments (S_2) form the outer layers (cf. Figure 1C). Preferably, the outer layers of the trilayer tablet formed by said two further segments (S_2) have essentially the same compoistion and total weight. Optionally, the trilayer tablet can be sugar coated (dragée).

Preferably,

(a) the trilayer tablet is configured for oral administration once daily, twice daily or thrice daily; and/or

(b) the total weight of the single formed segment (S_1) that forms the middle layer of the trilayer tablet is within the range of 210±200 mg (i.e. 10 mg to 410 mg), more preferably 210±180 mg, still more preferably 210±160 mg, yet more preferably 210±140 mg, even more preferably 210±120 mg, most preferably 210±100 mg, and in particular 210±80 mg; and/or

(c) the single formed segment (S_1) contains as first pharmacologically active ingredient (A_1) an opioid, preferably selected from the group consisting of oxycodone, oxymorphone, hydromorphone, hydrocodone, morphine, tapentadol, tramadol, buprenorphine, and the physiologically acceptable salts thereof; and/or

(d) the single formed segment (S_1) contains a release matrix material in which the first pharmacologically active ingredient (A_1) is embedded such that prolonged release thereof is achieved; and/or

(e) the single formed segment (S_1) contains a release matrix material comprising a polymer (C) that is preferably selected from the group consisting of polyalkylene oxides, nonionic acrylates, anionic acrylates or cationic acrylates; more preferably a polyethylene oxide having a weight average molecular weight of at least 500,000 g/mol;

(f) the single formed segment (S_1) contains a release matrix material comprising a polymer (C), wherein the content of said polymer (C) is preferably at least 30 wt.-%, still more preferably at least 35 wt.-%, yet more preferably at least 40 wt.-%, even more preferably at least 45 wt.-%, most preferably at least 50 wt.-%, and in particular at least 55 wt.-%, relative to the total weight of the single formed segment (S_1); and/or

(g) the total weight of each of the two further segment (S_2) that form the outer layers of the trilayer tablet is within the range of 250±220 mg (i.e. 30 mg to 470 mg), more preferably 250±200 mg, still more preferably 250±175 mg, yet more preferably 250±150 mg, even more preferably 250±100 mg, most preferably 250±75 mg, and in particular 250±35 mg; and/or

(h) each of the two further segments (S_2) contains as second pharmacologically active ingredient (A_2) an analgesic, preferably selected from the group consisting of ibuprofen, diclofenac, paracetamol, acetylsalicylic acid and the physiologically acceptable salts thereof; and/or

(i) each of the two further segments (S_2) contains a filler, preferably microcrystalline cellulose; wherein the content of said filler is preferably 30±25 wt.-%, more preferably 30±20 wt.-%, still more preferably 30±15 wt.-%, yet more preferably 30±13 wt.-%, even more preferably 30±10 wt.-%, most preferably 30±7 wt.-%, and in particular 30±5 wt.-%, relative to the total weight of one of the two further segments (S_2); and/or

(j) the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol; and/or

(k) the trilayer tablet is to be administered as a whole.

In the above definition, the features (a), (b), (c) ... (k) are linked with "and/or". For the purpose of specification, this means that the trilayer tablet according to the invention preferably realizes all of said features (a), (b), (c) ... (k) or merely a subgroup of said features (a), (b), (c) ... (k). Preferred trilayer tablets according to the invention realize at least feature (a); or at least features (a) and (b); or at least features (a), (b) and (c); or at least features (a), (b), (c) and (d); or at least features (a), (b), (c), (d), and (e); or at least features (a), (b), (c), (d), (e), and (f); or at least features (a), (b), (c), (d), (e), (f), and (g); or at least features (a), (b), (c), (d), (e), (f), (g) and (h); or at least features (a), (b), (c), (d), (e), (f), (g), (h) and (i); or at least features (a), (b), (c), (d), (e), (f), (g), (h), (i) and (j).

Preferably, the pharmaceutical dosage form according to the invention is a multilayer tablet. In the multilayer tablet according to the invention, a plurality of formed segments (S_1) and a plurality of further segments (S_2) are arranged to form a multilayer tablet, wherein preferably each of the formed segments (S_1) is arranged in between two adjacent further segments (S_2). Preferably, the multilayer tablet comprises 4, 5, or 6 layers, but not more. Preferably, the multilayer tablet comprises m layers that are each formed by a formed segment (S_1), i.e. m formed segments (S_1), and n layers that are each formed by a further segment (S_2), i.e. m further segment (S_2), wherein m and n are independently integers of 1, 2, 3 or 4, preferably with the proviso that $m+n \leq 6$. Optionally, the multilayer tablet can be sugar coated (dragée).

Preferably,

(a) the multilayer tablet is configured for oral administration once daily, twice daily or thrice daily; and/or

(b) the total weight of each of the m formed segments (S_1) that form layers of the multilayer tablet is within the range of 120±90 mg (i.e. 30 mg to 210 mg), more preferably 120±80 mg, still more preferably 120±70 mg, yet more preferably 120±60 mg, even more preferably 120±50 mg, most preferably 120±40 mg, and in particular 120±30 mg; and/or

(c) each of the m formed segments (S_1) contains as first pharmacologically active ingredient (A_1) an opioid, preferably selected from the group consisting of oxycodone, oxymorphone, hydromorphone, hydrocodone, morphine, tapentadol, tramadol, buprenorphine, and the physiologically acceptable salts thereof; and/or

(d) each of the m formed segments (S_1) contains a release matrix material in which the first pharmacologically active ingredient (A_1) is embedded such that prolonged release thereof is achieved; and/or

(e) each of the m formed segments (S_1) contains a release matrix material comprising a polymer (C) that is preferably selected from the group consisting of polyalkylene oxides, nonionic acrylates, anionic acrylates

or cationic acrylates; more preferably a polyethylene oxide having a weight average molecular weight of at least 500,000 g/mol;

(f) each of the m formed segments (S_1) contains a release matrix material comprising a polymer (C), wherein the content of said polymer (C) is preferably at least 30 wt.-%, still more preferably at least 35 wt.-%, yet more preferably at least 40 wt.-%, even more preferably at least 45 wt.-%, most preferably at least 50 wt.-%, and in particular at least 55 wt.-%, relative to the total weight of one of the m formed segments (S_1); and/or

(g) the total weight of each of the n further segments (S_2) that form layers of the multilayer tablet is within the range of 160±120 mg (i.e. 40 mg to 280 mg), more preferably 160±105 mg, still more preferably 160±80 mg, yet more preferably 160±65 mg, even more preferably 160±50 mg, most preferably 160±35 mg, and in particular 160±20 mg; and/or

(h) each of the n further segments (S_2) contains as second pharmacologically active ingredient (A_2) an analgesic, preferably selected from the group consisting of ibuprofen, diclofenac, paracetamol, acetylsalicylic acid and the physiologically acceptable salts thereof; and/or

(i) each of the n further segments (S_2) contains a filler, preferably microcrystalline cellulose; wherein the content of said filler is preferably 30±25 wt.-%, more preferably 30±20 wt.-%, still more preferably 30±15 wt.-%, yet more preferably 30±13 wt.-%, even more preferably 30±10 wt.-%, most preferably 30±7 wt.-%, and in particular 30±5 wt.-%, relative to the total weight of one of the n further segments (S_2); and/or

(j) the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol; and/or

(k) the multilayer tablet is to be administered as a whole.

In the above definition, the features (a), (b), (c) ... (k) are linked with "and/or". For the purpose of specification, this means that the multilayer tablet according to the invention preferably realizes all of said features (a), (b), (c) ... (k) or merely a subgroup of said features (a), (b), (c) ... (k). Preferred multilayer tablets according to the invention realize at least feature (a); or at least features (a) and (b); or at least features (a), (b) and (c); or at least features (a), (b), (c) and (d); or at least features (a), (b), (c), (d), and (e); or at least features (a), (b), (c), (d), (e), and (f); or at least features (a), (b), (c), (d), (e), (f), and (g); or at least features (a), (b), (c), (d), (e), (f), (g) and (h); or at least features (a), (b), (c), (d), (e), (f), (g), (h) and (i); or at least features (a), (b), (c), (d), (e), (f), (g), (h), (i) and (j).

Preferably, the pharmaceutical dosage form according to the invention is a multicomponent tablet. In the multicomponent tablet according to the invention, a plurality of formed segments (S_1) form a discontinuous phase embedded in a single further segment (S_2) which forms a matrix (cf. Figure 1D). Preferably, the multicomponent tablet comprises m formed segments (S_1) and a single further segment (S_2) forming a matrix in which the m formed segments (S_1) are embedded, wherein m is an integer of 2, 3, 4, 5 or 6; preferably 2 or 3. Optionally, the multicomponent tablet can be sugar coated (dragée).

Preferably,

(a) the multicomponent tablet is configured for oral administration once daily, twice daily or thrice daily; and/or

(b) the total weight of each of the m formed segments (S_1) that form layers of the multilayer tablet is within the range of 120±90 mg (i.e. 30 mg to 210 mg), more preferably 120±80 mg, still more preferably 120±70 mg, yet more preferably 120±60 mg, even more preferably 120±50 mg, most preferably 120±40 mg, and in particular 120±30 mg; and/or

(c) each of the m formed segments (S_1) contains as first pharmacologically active ingredient (A_1) an opioid, preferably selected from the group consisting of oxycodone, oxymorphone, hydromorphone, hydrocodone, morphine, tapentadol, tramadol, buprenorphine, and the physiologically acceptable salts thereof; and/or

(d) each of the m formed segments (S_1) contains a release matrix material in which the first pharmacologically active ingredient (A_1) is embedded such that prolonged release thereof is achieved; and/or

(e) each of the m formed segments (S_1) contains a release matrix material comprising a polymer (C) that is preferably selected from the group consisting of polyalkylene oxides, nonionic acrylates, anionic acrylates or cationic acrylates; more preferably a polyethylene oxide having a weight average molecular weight of at least 500,000 g/mol;

(f) each of the m formed segments (S_1) contains a release matrix material comprising a polymer (C), wherein the content of said polymer (C) is preferably at least 30 wt.-%, still more preferably at least 35 wt.-%, yet more preferably at least 40 wt.-%, even more preferably at least 45 wt.-%, most preferably at least 50 wt.-%, and in particular at least 55 wt.-%, relative to the total weight of one of the m formed segments (S_1); and/or

(g) the total weight of the single further segment (S_2) that forms a matrix of the multicomponent tablet in which the m formed segments (S_1) are embedded is within the range of 485±450 mg (i.e. 35 mg to 935 mg), more preferably 485±300 mg, still more preferably 485±250 mg, yet more preferably 485±200 mg, even more preferably 485±150 mg, most preferably 485±75 mg, and in particular 485±35 mg; and/or

(h) the single further segment (S_2) contains as second pharmacologically active ingredient (A_2) an analgesic, preferably selected from the group consisting of ibuprofen, diclofenac, paracetamol, acetylsalicylic acid and the physiologically acceptable salts thereof; and/or

(i) the single further segment (S_2) contains a filler, preferably microcrystalline cellulose; wherein the content of said filler is preferably 30±25 wt.-%, more preferably 30±20 wt.-%, still more preferably 30±15 wt.-%, yet more preferably 30±13 wt.-%, even more preferably 30±10 wt.-%, most preferably 30±7 wt.-%, and in particular 30±5 wt.-%, relative to the total weight of one of the two further segments (S_2); and/or

(j) the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol; and/or

(k) the multicomponent tablet is to be administered as a whole.

In the above definition, the features (a), (b), (c) ... (k) are linked with "and/or". For the purpose of specification, this means that the multicomponent tablet according to the invention preferably realizes all of said features (a), (b), (c) ... (k) or merely a subgroup of said features (a), (b), (c) ... (k). Preferred multicomponent tablets according to the invention realize at least feature (a); or at least features (a) and (b); or at least features (a), (b) and (c); or at least features (a), (b), (c) and (d); or at least features (a), (b), (c), (d), and (e); or at least features (a), (b), (c), (d), (e), and (f); or at least features (a), (b), (c), (d), (e), (f), and (g); or at least features (a), (b), (c), (d), (e), (f), (g) and (h); or at least features (a), (b), (c), (d), (e), (f), (g), (h) and (i); or at least features (a), (b), (c), (d), (e), (f), (g), (h), (i) and (j).

In other preferred embodiments, the pharmaceutical dosage form according to the invention is a capsule, preferably selected from the group consisting of capsules filled with a single formed segment (S_1) and a single further segment (S_2), capsules filled with a single formed segment (S_1) and a plurality of further segments (S_2), capsules filled with a plurality of formed segments (S_1) and a single further segment (S_2), and capsules filled with a plurality of formed segments (S_1) and a plurality of further segment (S_2). As all these embodiments relate to capsules that are filled with the formed segment(s) (S_1) and further segment(s) (S_2). While formed segment(s) (S_1) typically form(s) a coherent compacted mass, the further segment(s) may either form a coherent compacted mass or may be present in form of a powdery material. The overall capsule constitutes a single unit of matter that can be administered to a patient. The total weight of the capsules is not particularly limited. Typically, it is within the range of from 50 mg to 1250 mg. The number of formed segment(s) (S_1) and further segment(s) (S_2) that are contained in the capsules according to the invention is not particularly limited. Typically, the capsules according to the invention contain 1, 2, or 3, but not more formed segments (S_1), as well as 1, 2, or 3, but not more further segments (S_2). All preferred embodiments that have been generally defined above fully apply to the preferred capsules according to the invention and are therefore not reiterated. Nevertheless, particularly preferred embodiments of capsules according to the invention will be described in further detail hereinafter.

Preferably, the pharmaceutical dosage form according to the invention is a capsule filled with formed segment(s) (S_1) and further segment(s) (S_2). In these capsules according to the invention, the formed segment(s) (S_1) is/are preferably present as cut rods and the further segment(s) (S_2) is/are preferably present as tablets of such a size that they fit into the interior of the capsule.

Preferably,

(a) the capsule is configured for oral administration once daily, twice daily or thrice daily; and/or

(b) the total weight of each of the formed segment(s) (S_1) is within the range of 270±210 mg (i.e. 60 mg to 480 mg), more preferably 270±180 mg, still more preferably 270±150 mg, yet more preferably 270±120 mg, even more preferably 270±90 mg, most preferably 270±60 mg, and in particular 270±30 mg; and/or

(c) each of the formed segment(s) (S_1) contain(s) as first pharmacologically active ingredient (A_1) an opioid, preferably selected from the group consisting of oxycodone, oxymorphone, hydromorphone, hydrocodone, morphine, tapentadol, tramadol, buprenorphine, and the physiologically acceptable salts thereof; and/or

(d) each of the formed segment(s) (S_1) contain(s) a release matrix material in which the first pharmacologically active ingredient (A_1) is embedded such that prolonged release thereof is achieved; and/or

(e) each of the formed segment(s) (S_1) contain(s) a release matrix material comprising a polymer (C) that is preferably selected from the group consisting of polyalkylene oxides, nonionic acrylates, anionic acrylates or cationic acrylates; more preferably a polyethylene oxide having a weight average molecular weight of at least 500,000 g/mol;

(f) each of the formed segment(s) (S_1) contain(s) a release matrix material comprising a polymer (C), wherein the content of said polymer (C) is preferably at least 30 wt.-%, still more preferably at least 35 wt.-%, yet more preferably at least 40 wt.-%, even more preferably at least 45 wt.-%, most preferably at least 50 wt.-%, and in particular at least 55 wt.-%, relative to the total weight of one formed segment (S_1); and/or

(g) the total weight of each of the further segment(s) (S_2) is within the range of 360±350 mg (i.e. 10 mg to 710 mg), more preferably 360±300 mg, still more preferably 360±250 mg, yet more preferably 360±200 mg, even more preferably 360±150 mg, most preferably 360±100 mg, and in particular 360±50 mg; and/or

(h) each of the further segment(s) (S_2) contain(s) as second pharmacologically active ingredient (A_2) an analgesic, preferably selected from the group consisting of ibuprofen, diclofenac, paracetamol, acetylsalicylic acid and the physiologically acceptable salts thereof; and/or

(i) each of the further segment(s) (S_2) contain(s) a filler, preferably pregelled maize starch; wherein the content of said filler is preferably 10±9 wt.-%, more preferably 10±8 wt.-%, still more preferably 10±7 wt.-%, yet more preferably 10±6 wt.-%, even more preferably 10±5 wt.-%, most preferably 10±4 wt.-%, and in particular 10±3 wt.-%, relative to the total weight of one further segment (S_2); and/or

(j) the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol; and/or

(k) the capsule is to be administered as a whole.

In the above definition, the features (a), (b), (c) ... (k) are linked with "and/or". For the purpose of specification, this means that the capsule according to the invention preferably realizes all of said features (a), (b), (c) ... (k) or merely a subgroup of said features (a), (b), (c) ... (k). Preferred capsules according to the invention realize at least feature (a); or at least features (a) and (b); or at least features (a), (b) and (c); or at least features (a), (b), (c) and (d); or at least features (a), (b), (c), (d), and (e); or at least features (a), (b), (c), (d), (e), and (f); or at least features (a), (b), (c), (d), (e), (f), and (g); or at least features (a), (b), (c), (d), (e), (f), (g) and (h); or at least features (a), (b), (c), (d), (e), (f), (g), (h) and (i); or at least features (a), (b), (c), (d), (e), (f), (g), (h), (i) and (j).

The pharmaceutical dosage forms according to the invention may be used in medicine, e.g. as an analgesic. The pharmaceutical dosage forms are therefore particularly suitable for the treatment or management of pain. In such pharmaceutical dosage forms, the pharmacologically active ingredients (A_1) and (A_2) preferably are analgesically effective. Preferably, the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol.

A further aspect of the invention relates to the pharmaceutical dosage form as described above for use in the treatment of pain.

A further aspect of the invention relates to the use of the first pharmacologically active ingredient (A_1) and of the second pharmacologically active ingredient (A_2) for the manufacture of a pharmaceutical dosage form as described above for treating pain.

A further aspect of the invention relates to the pharmaceutical dosage form as described above for use in the treatment of pain, wherein the dosage form is swallowed as a whole.

A further aspect of the invention relates to a method of treating pain comprising the administration of the pharmaceutical dosage form as described above to a subject in need thereof.

A further aspect according to the invention relates to the use of a pharmaceutical dosage form as described above for avoiding or hindering the abuse of the first pharmacologically active ingredient (A_1) contained therein.

A further aspect according to the invention relates to the use of a pharmaceutical dosage form as described above for avoiding or hindering the unintentional overdose of the first pharmacologically active ingredient (A_1) contained therein.

In this regard, the invention also relates to the use of a pharmaceutical dosage form as described above for the prophylaxis and/or the treatment of a disorder, thereby preventing an overdose of the first pharmacologically active ingredient (A_1), particularly due to comminution of the pharmaceutical dosage form by mechanical action.

EXAMPLES

The following prophetic and non-prophetic examples further illustrate the invention but are not to be construed as limiting its scope:

Prophetic examples A1 to A6 - tablets

Example A1:

A single formed segment (S_1) and a single further segment (S_2) that are arranged to form a bilayer tablet (cf. Figure 1A). Bilayer tablets of the following composition can be prepared:

Formed segment (S_1):

	A1-S_1-1		A1-S_1-2		A1-S_1-3		A1-S_1-4	
Excipient	mg	wt.-%	mg	wt.-%	mg	wt.-%	mg	wt.-%
Oxycodone HCl	5.00	2.33	5.00	3.33	50.00	18.60	50.00	20.00
Polyethylene Oxide 7,000,000	150.51	70.00	143.50	95.67	152.65	56.80	197.50	79.00
Hypromellose	21.50	10.00	-		26.88	10.00	-	
Polyethylene Glycol	35.75	16.63	-		36.44	13.56	-	
Alpha – Tocopherole	0.43	0.20	-		0.54	0.20	-	
Citric acid, anhydrous	1.81	0.84	-		2.26	0.84	-	
Magnesium stearate	-		1.50	1.00	-		2.50	1.00
Total	*215.00*	*100.00*	*150.00*	*100.00*	*268.77*	*100.00*	*250.00*	*100.00*

Further segment (S_2):

	A1-S_2-1		A1-S_2-2	
Excipient	mg	wt.-%	mg	wt.-%
Paracetamol	325.00	64.94	325.00	69.04
Microcrystalline cellulose	174.96	34.96	115.24	24.48
Crosscarmellose	-		30.03	6.38
Magnesium stearate	0.50	0.10	0.47	0.10
Total	*500.46*	*100.00*	*470.74*	*100.00*

Example A2:

A single formed segment (S_1) forming a core that is surrounded by a single further segment (S_2) forming a shell such that formed segment (S_1) and further segment (S_2) are arranged to form a mantle tablet (cf. Figure 1B). Mantle tablets of the following composition can be prepared:

Formed segment (S_1) - core:

	A2-S_1-1		A2-S_1-2		A2-S_1-3		A2-S_1-4	
Excipient	mg	wt.-%	mg	wt.-%	mg	wt.-%	mg	wt.-%
Oxycodone HCl	5.00	2.33	5.00	3.33	50.00	18.60	50.00	20.00
Polyethylene Oxide 7.000.000	150.51	70.00	143.50	95.67	152.65	56.80	197.50	79.00
Hypromellose	21.50	10.00	-		26.88	10.00	-	
Polyethylene Glycol	35.75	16.63	-		36.44	13.56	-	
Alpha – Tocopherole	0.43	0.20	-		0.54	0.20	-	
Citric acid, anhydrous	1.81	0.84	-		2.26	0.84	-	
Magnesium stearate	-		1.50	1.00	-		2.50	1.00
Total	*215.00*	*100.00*	*150.00*	*100.00*	*268.77*	*100.00*	*250.00*	*100.00*

Further segment (S_2) - shell:

	A2-S_2-1		A2-S_2-2	
Excipient	mg	wt.-%	mg	wt.-%
Paracetamol	325.00	64.94	325.00	69.04
Microcrystalline cellulose	174.96	34.96	115.24	24.48
Crosscarmellose	-		30.03	6.38
Magnesium stearate	0.50	0.10	0.47	0.10
Total	*500.46*	100.00	*470.74*	100.00

Example A3:

A single formed segment (S_1) and two further segments (S_2) that are arranged to form a trilayer tablet, wherein formed segment (S_1) forms the middle layer and the two further segments (S_2) form the outer layers (cf. Figure 1C). Trilayer tablets of the following composition can be prepared:

Formed segment (S_1):

	A3-S_1-1		A3-S_1-2		A3-S_1-3		A3-S_1-4	
Excipient	mg	wt.-%	mg	wt.-%	mg	wt.-%	mg	wt.-%
Oxycodone HCl	5.00	2.33	5.00	3.33	50.00	18.60	50.00	20.00
Polyethylene Oxide 7.000.000	150.51	70.00	143.50	95.67	152.65	56.80	197.50	79.00
Hypromellose	21.50	10.00	-		26.88	10.00	-	
Polyethylene Glycol	35.75	16.63	-		36.44	13.56	-	
Alpha – Tocopherole	0.43	0.20	-		0.54	0.20	-	
Citric acid, anhydrous	1.81	0.84	-		2.26	0.84	-	
Magnesium stearate	-		1.50	1.00	-		2.50	1.00
Total	*215.00*	*100.00*	*150.00*	*100.00*	*268.77*	*100.00*	*250.00*	*100.00*

Further segments (S_2):

	A3-S_2-1		A3-S_2-2	
Excipient	mg	wt.-%	mg	wt.-%
Paracetamol	162.50	64.94	162.50	69.04
Microcrystalline cellulose	87.48	34.96	57.62	24.48
Crosscarmellose	-		15.02	6.38
Magnesium stearate	0.25	0.10	0.24	0.10
Total	*250.23*	*100.00*	*235.38*	*100.00*

Example A4:

A plurality of formed segments (S_1) and a plurality of further segments (S_2) that are arranged to form a multilayer tablet, wherein preferably each of the formed segments (S_1) is arranged in between two adjacent further segments (S_2). Multilayer tablets of the following composition can be prepared:

Formed segments (S_1):

	A4-S_1-1		A4-S_1-2		A4-S_1-3	
Excipient	mg	wt.-%	mg	wt.-%	mg	wt.-%
Oxycodone HCl	2.50	2.33	25.00	18.60	25.00	18.60
Polyethylene Oxide 7.000.000	75.25	70.00	76.33	56.80	72.30	53.80
Hypromellose	10.75	10.00	13.44	10.00	13.44	10.00
Xanthan-Gum	-	-	-	-	4.03	3.00
Polyethylene Glycol	17.87	16.62	18.22	13.56	18.22	13.56
Alpha – Tocopherole	0.22	0.20	0.27	0.20	0.27	0.20
Citric acid, anhydrous	0.91	0.85	1.13	0.84	1.13	0.84
Total	*107.50*	*100.00*	*134.39*	*100.00*	*134.39*	*100.00*

Further segments (S_2):

	A4-S_2-1		A4-S_2-2	
Excipient	mg	wt.-%	mg	wt.-%
Paracetamol	108.33	64.94	108.33	69.04
Microcrystalline cellulose	58.32	34.96	38.41	24.48
Crosscarmellose	-		10.01	6.38
Magnesium stearate	0.16	0.10	0.16	0.10
Total	*166.81*	*100.00*	*156.91*	*100.00*

Example A5:

A plurality of formed segments (S_1) which form a discontinuous phase embedded in further segment (S_2) which forms a matrix (cf. Figure 1D). Multicomponent tablets of the following composition can be prepared:

Formed segments (S_1):

	A5-S_1-1		A5-S_1-2	
Excipient	mg	wt.-%	mg	wt.-%
Oxycodone HCl	2.50	2.33	25.00	18.60
Polyethylene Oxide 7.000.000	75.25	70.00	76.33	56.80
Hypromellose	10.75	10.00	13.44	10.00
Polyethylene Glycol	17.87	16.62	18.22	13.56
Alpha – Tocopherole	0.22	0.20	0.27	0.20
Citric acid, anhydrous	0.91	0.85	1.13	0.84
Total	*107.50*	*100.00*	*134.39*	*100.00*

Further segment (S_2):

	A5-S_2-1		A5-S_2-2	
Excipient	mg	wt.-%	mg	wt.-%
Paracetamol	325.00	64.94	325.00	69.04
Microcrystalline cellulose	174.96	34.96	115.24	24.48
Crosscarmellose	-		30.03	6.38

Magnesium stearate	0.50	0.10	0.47	0.10
Total	*500.46*	*100.00*	*470.74*	*100.00*

Example A6:

A single formed segment (S_1) and one or more further segments (S_2) that are together coated by a sugar coating thus forming a sugar-coated tablet (dragée). Sugar coated tablets of the compositions according to any of above Examples A1 to A3 can be prepared.

Prophetic examples B1 to B4 - filled capsules

Example B1:

A single formed segment (S_1) and a single further segment (S_2) (cf. Figure 2A). Capsules of the following composition can be prepared:

Excipient	mg	wt.-%	Segment
Oxycodone HCl	50.00	6.31	S_1
Polyethylene oxide 7.000.000	152.65	19.28	
Hypromellose 100000 mPa*s Ph.Eur	26.88	3.65	
Macrogol 6000 Ph.Eur.	36.44	4.60	
α-Tocopherol Ph.Eur.	0.54	0.06	
Critic acid anhydrous Ph.Eur.	2.26	0.28	
Paracetamol	325.00	41.05	S_2
Pregelled maize starch	36.00	4.55	
Hard gelatin capsule size 000	162.00	20.46	Capsule
Total	*791.77*	*100.00*	

Capsule containing paracetamol and a cut rod comprising oxycodone HCl

Cut rods of 268.77 mg can be produced by weighing the ingredients (S_1), sieving (Mesh size 1.0 mm), blending in a Bohle LM 40 MC 20, followed by extrusion using a ZSE 27 Micro PH 40 D (melt temperature 124°C, screw rotation speed 100 rpm, die diameter 5.0 mm, melt pressure ca. 80 bar) equipped with 6 cooling injectors. The extruded strands can be cut with a Combi Cutting unit CC 250.

Tablets of 361.00 mg can be prepared by directly compressing a granulate of the ingredients (S_2) by direct compression. The granulate is commercially available as “Paracetamol DC APC 230 F/MS” from manufacturer Atabay/Turkey.

One cut rod and one tablet can be filled in a hard gelatin capsule.

Example B2:

A single formed segment (S_1) and a plurality of further segments (S_2) (cf. Figure 2B). Capsules of the following composition can be prepared:

Excipient	mg	wt.-%	Segment
Oxycodone HCl	50.00	6.31	S_1
Polyethylene oxide 7.000.000	152.65	19.28	
Hypromellose 100000 mPa*s Ph.Eur	26.88	3.65	
Macrogol 6000 Ph.Eur.	36.44	4.60	
α-Tocopherol Ph.Eur.	0.54	0.06	
Critic acid anhydrous Ph.Eur.	2.26	0.28	
Paracetamol	325.00	41.05	S_2
Pregelled maize starch	36.00	4.55	
Hard gelatin capsule size 000	162.00	20.46	Capsule
Total	*791.77*	*100.00*	

Capsule containing paracetamol and a cut rod comprising oxycodone HCl

Cut rods of 268.77 mg can be produced by weighing the ingredients (S_1), sieving (Mesh size 1.0 mm), blending in a Bohle LM 40 MC 20, followed by extrusion using a ZSE 27 Micro PH 40 D (melt temperature 124°C, screw rotation speed 100 rpm, die diameter 5.0 mm, melt pressure ca. 80 bar) equipped with 6 cooling injectors. The extruded strands can be cut with a Combi Cutting unit CC 250.

Tablets of 180.50 mg can be prepared by directly compressing a granulate of the ingredients (S_2) by direct compression. The granulate is commercially available as “Paracetamol DC APC 230 F/MS” from manufacturer Atabay/Turkey.

One cut rod and two tablets can be filled in a hard gelatin capsule.

Example B3:

A plurality of formed segments (S_1) and a single further segment (S_2), which can optionally be present in form of a monolith or in form of a powdery material (cf. Figure 2F). Capsules of the following composition can be prepared:

Excipient	mg	wt.-%	Segment
Oxycodone HCl	50.00	6.31	S_1
Polyethylene oxide 7.000.000	152.65	19.28	
Hypromellose 100000 mPa*s Ph.Eur	26.88	3.65	
Macrogol 6000 Ph.Eur.	36.44	4.60	
α-Tocopherol Ph.Eur.	0.54	0.06	
Critic acid anhydrous Ph.Eur.	2.26	0.28	
Paracetamol	325.00	41.05	S_2
Pregelled maize starch	36.00	4.55	
Hard gelatin capsule size 000	162.00	20.46	Capsule
Total	*791.77*	*100.00*	

Capsule containing paracetamol and a cut rod comprising oxycodone HCl

Cut rods of 134.385 mg can be produced by weighing the ingredients (S_1), sieving (Mesh size 1.0 mm), blending in a Bohle LM 40 MC 20, followed by extrusion using a ZSE 27 Micro PH 40 D (melt temperature 124°C, screw

rotation speed 100 rpm, die diameter 5.0 mm, melt pressure ca. 80 bar) equipped with 6 cooling injectors. The extruded strands can be cut with a Combi Cutting unit CC 250.

Tablets of 361.00 mg can be prepared by directly compressing a granulate of the ingredients (S_2) by direct compression. The granulate is commercially available as "Paracetamol DC APC 230 F/MS" from manufacturer Atabay/Turkey.

Two cut rods and one tablet can be filled in a hard gelatin capsule.

Example B4:

A plurality of formed segments (S_1) and a plurality of further segment (S_2) (cf. Figures 2C, D and E). Capsules of the following composition can be prepared:

Excipient	mg	wt.-%	Segment
Oxycodone HCl	50.00	6.31	S_1
Polyethylene oxide 7.000.000	152.65	19.28	
Hypromellose 100000 mPa*s Ph.Eur	26.88	3.65	
Macrogol 6000 Ph.Eur.	36.44	4.60	
α-Tocopherol Ph.Eur.	0.54	0.06	
Critic acid anhydrous Ph.Eur.	2.26	0.28	
Paracetamol	325.00	41.05	S_2
Pregelled maize starch	36.00	4.55	
Hard gelatin capsule size 000	162.00	20.46	Capsule
Total	*791.77*	*100.00*	

Capsule containing paracetamol and a cut rod comprising oxycodone HCl

Cut rods of 134.385 mg can be produced by weighing the ingredients (S_1), sieving (Mesh size 1.0 mm), blending in a Bohle LM 40 MC 20, followed by extrusion using a ZSE 27 Micro PH 40 D (melt temperature 124°C, screw rotation speed 100 rpm, die diameter 5.0 mm, melt pressure ca. 80 bar) equipped with 6 cooling injectors. The extruded strands can be cut with a Combi Cutting unit CC 250.

Tablets of 180.50 mg can be prepared by directly compressing a granulate of the ingredients (S_2) by direct compression. The granulate is commercially available as "Paracetamol DC APC 230 F/MS" from manufacturer Atabay/Turkey.

Two cut rods and two tablets can be filled in a hard gelatin capsule.

Non-prophetic examples

Example 1:

Capsule containing paracetamol and a cut rod comprising oxycodone HCl

Cut rods were produced by weighing the ingredients, sieving (Mesh size 1.0 mm), blending in a Bohle LM 40 MC 20, followed by extrusion using a ZSE 27 Micro PH 40 D (melt temperature 124°C, screw rotation speed 100 rpm, die diameter 5.0 mm, melt pressure ca. 80 bar) equipped with 6 cooling injectors. The extruded strands were cut with a Combi Cutting unit CC 250. One cut rod and paracetamol in powder form were filled in a hard gelatin capsule. Composition of capsule containing paracetamol and a cut rod comprising oxycodone HCl:

Excipient	mg	wt.-%
Oxycodone HCl	50.00	7.26
Polyethylene oxide 7.000.000	152.65	22.16
Hypromellose 100000 mPa*s Ph.Eur	26.88	3.90
Macrogol 6000 Ph.Eur.	36.44	5.29
α-Tocopherol Ph.Eur.	0.54	0.08
Critic acid anhydrous Ph.Eur.	2.26	0.33
Paracetamol Ph.Eur.	325.00	47.19
Hard gelatin capsule size 0	95.00	13.79
Total	*688.77*	*100*

The capsules were subjected to different tests in order to assess the tamper-resistance with respect to the oxycodone HCl contained in the cut rods.

The hammer test was performed with a weight of 500 g falling from a height of 1000 mm. After the test, the cut rods were still intact.

The breaking strength (resistance to crushing) was measured using a Zwick Z 2.5 materials tester, F_{max} = 2.5 kN with a maximum draw of 1150 mm. The cut rods displayed a breaking strength of > 500 N. Figure 3 shows the corresponding force distance diagram.

The release profiles of oxycodone HCl from the capsules were determined under in vitro conditions using the basket method according to Ph. Eur. at 75 rpm in 600 mL of 0.1 N HCl, SIF sp (pH 6.8) and 0.1 N HCl +40% ethanol, respectively. The results are summarized in the table here below.

Results of the dissolution tests:

dissolution [%]			
t [min]	in 0.1 N HCl	in SIFsp pH 6.8	in 0.1 N HCl + 40% ethanol
60	23	25	16
120	36	39	26
480	82	84	65
600	88	90	73
720	93	93	78

Extraction of oxycodone HCl from the capsule was tested (30 mL, 30 min) in 40% ethanol, water at room temperature and boiling water, respectively. The results are summarized in the below table.

To simulate an addict's attempt at preparing an i.v. injection, a capsule was ground with a commercial coffee mill, type Bosch MKM6000, 180W, Typ KM13 for 2 min followed by extraction in boiled water for 5 min. The results are summarized in the below table.

Results of the extraction test and the i.v. injection preparation:

	amount of oxycodone HCl [%]
intact dosage form	96.5
extraction in water at room temperature	0.6
extraction in boiled water	25.7
extraction in 40% ethanol	0.9
i.v. injection preparation	21.9 (n=2)

Reference Examples

The following Examples 2-7 are Reference Examples which relate to segments comprising a pharmacologically active ingredient and having a breaking strength of more than 500 N.

Reference Examples 2 to 4 and 6 relate to only one segment and a dosage form comprising said one segment, respectively. Reference Example 5 relates to a dosage form comprising two identical segments having the same breaking strength.

The skilled person is able to combine any of these segments exemplified in the Reference Examples with another segment comprising a pharmacologically active ingredient and having e.g. a lower breaking strength than the segments of the Reference Examples.

Reference Example 2:

Cut rods were produced according to the procedure disclosed in Example 1 and having the composition as disclosed in A1-S_1-1 with a total weight of each cut rod of 215 mg. The composition is summarized in the table below:

	m per capsule [mg]	wt.-%
Oxycodone HCl	5.00	2.33
Polyethylene oxide 7.000.000	150.51	70.00
Hypromellose 100000 mPa*s Ph.Eur	21.50	10.00
Macrogol 6000 Ph.Eur.	35.75	16.63
α-Tocopherol Ph.Eur.	0.43	0.20
Critic acid anhydrous Ph.Eur.	1.81	0.84
Total	*215.00*	*100.00*

The breaking strength (resistance to crushing) was measured using a Sotax HT 100 (DEAC-IN-00705). The cut rods displayed a breaking strength of 1000 N (mean value; n = 3, with measured values $b_1 = b_2 = b_3 = 1000N$).

Figure 4 shows the release profiles of one cut rod determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Reference Example 3:

Cut rods were produced according to the procedure disclosed in Example 1 and having the composition as disclosed in A1-S_1-1 with the only exception that the total weight of each cut rod was adjusted to 107.5 mg. The composition is summarized in the table below:

	m per capsule [mg]	wt.-%
Oxycodone HCl	2.50	2.33
Polyethylene oxide 7.000.000	75.255	70.00
Hypromellose 100000 mPa*s Ph.Eur	10.75	10.00
Macrogol 6000 Ph.Eur.	17.875	16.63
α-Tocopherol Ph.Eur.	0.215	0.20
Critic acid anhydrous Ph.Eur.	0.905	0.84
Total	*107.50*	*100.00*

Figure 5 shows the release profiles of two cut rods determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. (one sinker per cut rod) at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Reference Example 4:

Capsules comprising one cut rod were produced according to the procedure disclosed in Example 1. One cut rod (215 mg) was filled in a capsule (size 1). The composition of the capsule is summarized in the table below:

	m per capsule [mg]	wt.-%
Oxycodone HCl	5.00	1.72
Polyethylene oxide 7.000.000	150.51	51.90
Hypromellose 100000 mPa*s Ph.Eur	21.50	7.41
Macrogol 6000 Ph.Eur.	35.75	12.33
α-Tocopherol Ph.Eur.	0.43	0.15
Critic acid anhydrous Ph.Eur.	1.81	0.62
empy capsule size 1	75.00	25.86
Total	*290.00*	*100.00*

The breaking strength (resistance to crushing) was measured using a Sotax HT 100 (DEAC-IN-00705). The capsules displayed a breaking strength of 63 N (mean value; n = 3*; with measured values b_1 = 50 N; b_2 = 76 N; b_3 = 1000 N*).

*The measured value b_3 was not included in the mean value of the breaking strength because it was obtained from an incorrect measurement (the capsule was crushed and the breaking strength of the cut rod was measured instead).

Figure 6 shows the release profiles of one cut rod in a capsule determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Reference Example 5:

Capsules comprising two cut rods and a lactose tablet were produced according to the procedure disclosed in Example 1. Two cut rods (107.5 mg each) and a lactose tablet (72 mg) as spacer were filled in a capsule (size 1). The composition of the capsule is summarized in the table below:

	m per capsule [mg]	wt.-%
Oxycodone HCl	5.00	1.38
Polyethylene oxide 7.000.000	150.51	41.58
Hypromellose 100000 mPa*s Ph.Eur	21.50	5.94
Macrogol 6000 Ph.Eur.	35.75	9.88
α-Tocopherol Ph.Eur.	0.43	0.12
Critic acid anhydrous Ph.Eur.	1.81	0.50
empy capsule size 1	75.00	20.72
Lactose tablet	72.00	19.89
Total	*362.00*	*100.00*

The breaking strength (resistance to crushing) was measured using a Sotax HT 100 (DEAC-IN-00705). The capsules displayed a breaking strength of 38 N (mean value; n = 3*; with measured values b_1 = 1000 N*; b_2 = 31 N; b_3 = 45 N).

*The measured value b_1 was not included in the mean value of the breaking strength because it was obtained from an incorrect measurement (the capsule was crushed and the breaking strength of the cut rod was measured instead).

Figure 7 shows the release profiles of two cut rods and a lactose tablet in a capsule determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Reference Example 6:

Layer-core-tablets (mantle-core-tablets) (9 x 21 mm, oblong) were produced using one cut rod (215 mg) as the core and an MCC-based mixture as the mantle. The MCC-based mixture was a mixture of microcrystalline cellulose (MCC) with 2 wt.-% maize starch as disintegrant and 1 wt.-% magnesium stearate. The composition of the mantle-core-tablets is summarized in the table below:

	m per capsule [mg]	wt.-%
Oxycodone HCl	5.00	0.61
Polyethylene oxide 7.000.000	150.51	18.47
Hypromellose 100000 mPa*s Ph.Eur	21.50	2.64
Macrogol 6000 Ph.Eur.	35.75	4.39
α-Tocopherol Ph.Eur.	0.43	0.05
Critic acid anhydrous Ph.Eur.	1.81	0.22
MCC	582.00	71.41
Maize starch	12.00	1.47
Magnesium stearate	6.00	0.74
Total	*815.00*	*100.00*

The breaking strength (resistance to crushing) was measured using a Sotax HT 100 (DEAC-IN-00705). The mantle tablets displayed a breaking strength of 65 N (mean value; n = 3; with measured values b_1 = 63 N; b_2 = 58 N; b_3 = 73 N).

Figure 8 shows the release profiles of a mantle tablet determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Reference Example 7:

Layer-core-tablets (mantle-core-tablets) (9 x 21 mm, oblong) were produced using two cut rods and a lactose tablet (72 mg) as cores and an MCC-based mixture as the mantle. The MCC-based mixture was a mixture of microcrystalline cellulose (MCC) with 2 wt.-% maize starch as disintegrant and 1 wt.-% magnesium stearate. The composition of the mantle-core-tablets is summarized in the table below:

	m per capsule [mg]	wt.-%
Oxycodone HCl	5.00	0.64
Polyethylene oxide 7.000.000	150.51	19.12
Hypromellose 100000 mPa*s Ph.Eur	21.50	2.73
Macrogol 6000 Ph.Eur.	35.75	4.54
α-Tocopherol Ph.Eur.	0.43	0.05
Critic acid anhydrous Ph.Eur.	1.81	0.23
Lactose tablet	72.00	9.15
MCC	485.00	61.63
Maize starch	10.00	1.27
Magnesium stearate	5.00	0.64
Total	*787.00*	*100.00*

The breaking strength (resistance to crushing) was measured using a Sotax HT 100 (DEAC-IN-00705). The mantle tablets displayed a breaking strength of 19 N (mean value; n = 3; with measured values b_1 = 18 N; b_2 = 21 N; b_3 = 17 N).

Figure 9 shows the release profiles of a mantle tablet determined under in vitro conditions (n=3) using the basket method with sinker according to Ph. Eur. at 75 rpm in 600 mL of SGF (pH 1.2) and SGF (pH 1.2) + 40% ethanol, respectively.

Figures 10 to 14

Figures 10 to 14 show combinations of the release profiles obtained in Reference Examples 2 to 7.

Figure 10 shows the release profiles of the cut rod (m = 215 mg) as such (Reference Example 2, Figure 4), in a capsule (Reference Example 4, Figure 6), and in form of a mantle tablet (Reference Example 6, Figure 8).

Figure 11 shows the release profiles of one cut rod (m = 215 mg) (Reference Example 2, Figure 4) and two cut rods (m = 107.5 mg) (Reference Example 3, Figure 5).

Figure 12 shows the release profile of a capsule containing one cut rod (Reference Example 4, Figure 6) and a capsule containing two cut rods (Reference Example 5, Figure 7).

Figure 13 shows the release profiles of a mantle tablet containing one cut rod (Reference Example 6, Figure 8) and a mantle tablet containing two cut rods (Reference Example 7, Figure 9).

Figure 14 shows the release profiles of two cut rods (m = 107.5 mg) as such (Reference Example 3, Figure 5), in a capsule (Reference Example 5, Figure 7), and in form of a mantle tablet (Reference Example 7, Figure 9).

Patent claims:

1. A pharmaceutical dosage form comprising

(i) at least one formed segment (S_1), which contains a first pharmacologically active ingredient (A_1) and provides prolonged release thereof, and

(ii) at least one further segment (S_2), which contains a second pharmacologically active ingredient (A_2) and provides immediate release thereof,

wherein the at least one formed segment (S_1) exhibits a higher breaking strength than the at least one further segment (S_2) and the at least one formed segment (S_1) exhibits a breaking strength of more than 500 N.

2. The pharmaceutical dosage form according to claim 1, wherein the at least one further segment (S_2) exhibits a breaking strength of at most 500 N.

3. The pharmaceutical dosage form according to claim 1 or 2, wherein the second pharmacologically active ingredient (A_2) is different from the first pharmacologically active ingredient (A_1).

4. The pharmaceutical dosage form according to any of the preceding claims, wherein

(i) the first pharmacologically active ingredient (A_1) has a psychotropic effect; and/or

(ii) the second pharmacologically active ingredient (A_2) is selected from ATC classes [M01A], [M01C], [N02B] and [N02C] according to the WHO.

5. The pharmaceutical dosage form according to any of the preceding claims, wherein the first pharmacologically active ingredient (A_1) is an opioid or a physiologically acceptable salt thereof.

6. The pharmaceutical dosage form according to any of the preceding claims, wherein the second pharmacologically active ingredient (A_2) is selected from the group consisting of acetylsalicylic acid, aloxiprin, choline salicylate, sodium salicylate, salicylamide, salsalate, ethenzamide, morpholine salicylate, dipyrocetyl, benorilate, diflunisal, potassium salicylate, guacetisal, carbasalate calcium, imidazole salicylate, phenazone, metamizole sodium, aminophenazone, propyphenazone, nifenazone, paracetamol, phenacetin, bucetin, propacetamol, rimazolium, glafenine, floctafenine, viminol, nefopam, flupirtine, ziconotide, methoxyflurane, nabiximols, dihydroergotamine, ergotamine, methysergide, lisuride, flumedroxone, sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan, frovatriptan, pizotifen, clonidine, iprazochrome, dimetotiazine, oxetorone, phenylbutazone, mofebutazone, oxyphenbutazone, clofezone, kebuzone, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, alclofenac, bumadizone, etodolac, lonazolac, fentiazac, acemetacin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, piroxicam, tenoxicam, droxicam, lornoxicam, meloxicam, ibuprofen, naproxen, ketoprofen, fenoprofen, fenbufen, benoxaprofen, suprofen,

pirprofen, flurbiprofen, indoprofen, tiaprofenic acid, oxaprozin, ibuproxam, dexibuprofen, flunoxaprofen, alminoprofen, dexketoprofen, naproxcinod, mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, nabumetone, niflumic acid, azapropazone, glucosamine, benzydamine, glucosaminoglycan polysulfate, proquazone, orgotein, nimesulide, feprazone, diacerein, morniflumate, tenidap, oxaceprol, chondroitin sulfate, oxycinchophen, sodium aurothiomalate, sodium aurotiosulfate, auranofin, aurothioglucose, aurotioprol, penicillamine and bucillamine.

7. The pharmaceutical dosage form according to any of the preceding claims, wherein the first pharmacologically active ingredient (A_1) is hydrocodone or a physiologically acceptable salt thereof and the second pharmacologically active ingredient (A_2) is paracetamol.

8. The pharmaceutical dosage form according to any of the preceding claims, wherein the first pharmacologically active ingredient (A_1) is embedded in a prolonged release matrix comprising a synthetic or natural polymer (C).

9. The pharmaceutical dosage form according to claim 8, wherein

(i) the content of the synthetic or natural polymer (C) is at least 30 wt.-% relative to the total weight of the formed segment(s) (S_1); and/or

(ii) the synthetic or natural polymer (C) is selected from acrylic polymers or polyalkylene oxides.

10. The pharmaceutical dosage form according to any of the preceding claims, which under in vitro conditions in 600 mL 0.1 N HCl, using the basket method according to Ph. Eur. at 75 rpm, after 1 h under physiological conditions has released at most 50% of the first pharmacologically active ingredient (A_1) relative to the total amount of A_1 originally contained in the pharmaceutical dosage form.

11. The pharmaceutical dosage form according to any of the preceding claims, which under in vitro conditions in 600 mL 0.1 N HCl, using the basket method according to Ph. Eur. at 75 rpm, after 1 h under physiological conditions has released at least 60% of the second pharmacologically active ingredient (A_2) relative to the total amount of the second pharmacologically active ingredient (A_2) originally contained in the pharmaceutical dosage form.

12. The pharmaceutical dosage form according to any of the preceding claims, wherein the at least one formed segment (S_1) is tamper resistant and provides resistance against grinding and/or resistance against solvent extraction and/or resistance against dose-dumping in aqueous ethanol.

13. The pharmaceutical dosage form according to any of the preceding claims which is selected from the group consisting of capsules, sugar-coated tablets, dry-coated tablets, mantle tablets, and layered tablets.

14. The pharmaceutical dosage form according to any of the preceding claims, wherein the at least one formed segment (S_1) is thermoformed.

15. The pharmaceutical dosage form according to any of the preceding claims, which contains a single, monolithic formed segment (S_1), or a multitude of particulate formed segments (S_1).

16. The pharmaceutical dosage form according to claim 15, wherein the formed segment/s (S_1) has/have an extension in any direction of at least 2.0 mm.

17. The pharmaceutical dosage form according to any of the preceding claims, which is to be administered orally.

18. The pharmaceutical dosage form according to any of the preceding claims, which is to be administered as a whole.

19. A process for the production of a pharmaceutical dosage form according to any of the preceding claims comprising the steps of

(i) thermoforming at least one formed segment (S_1) comprising a first pharmacologically active ingredient (A_1) and a natural or synthetic polymer (C);

(ii) providing at least one further segment (S_2) comprising a second pharmacologically active ingredient (A_2); and

(iii) combining the at least one formed segment (S_1), the at least one further segment (S_2) and optionally further excipients.

20. The pharmaceutical dosage form according to any of claims 1 to 16 for use in the treatment of pain, wherein the dosage form is swallowed as a whole.

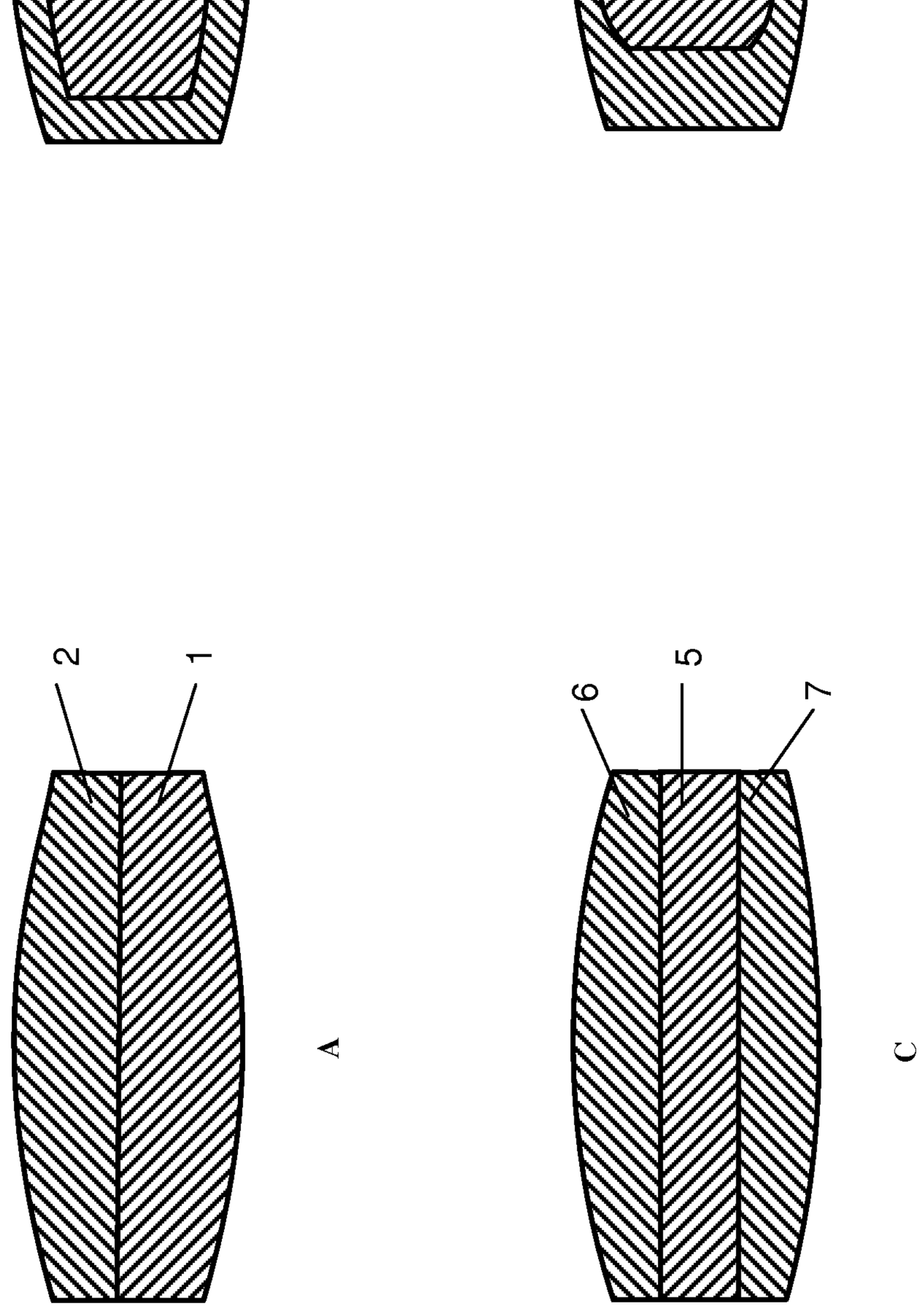


Figure 1

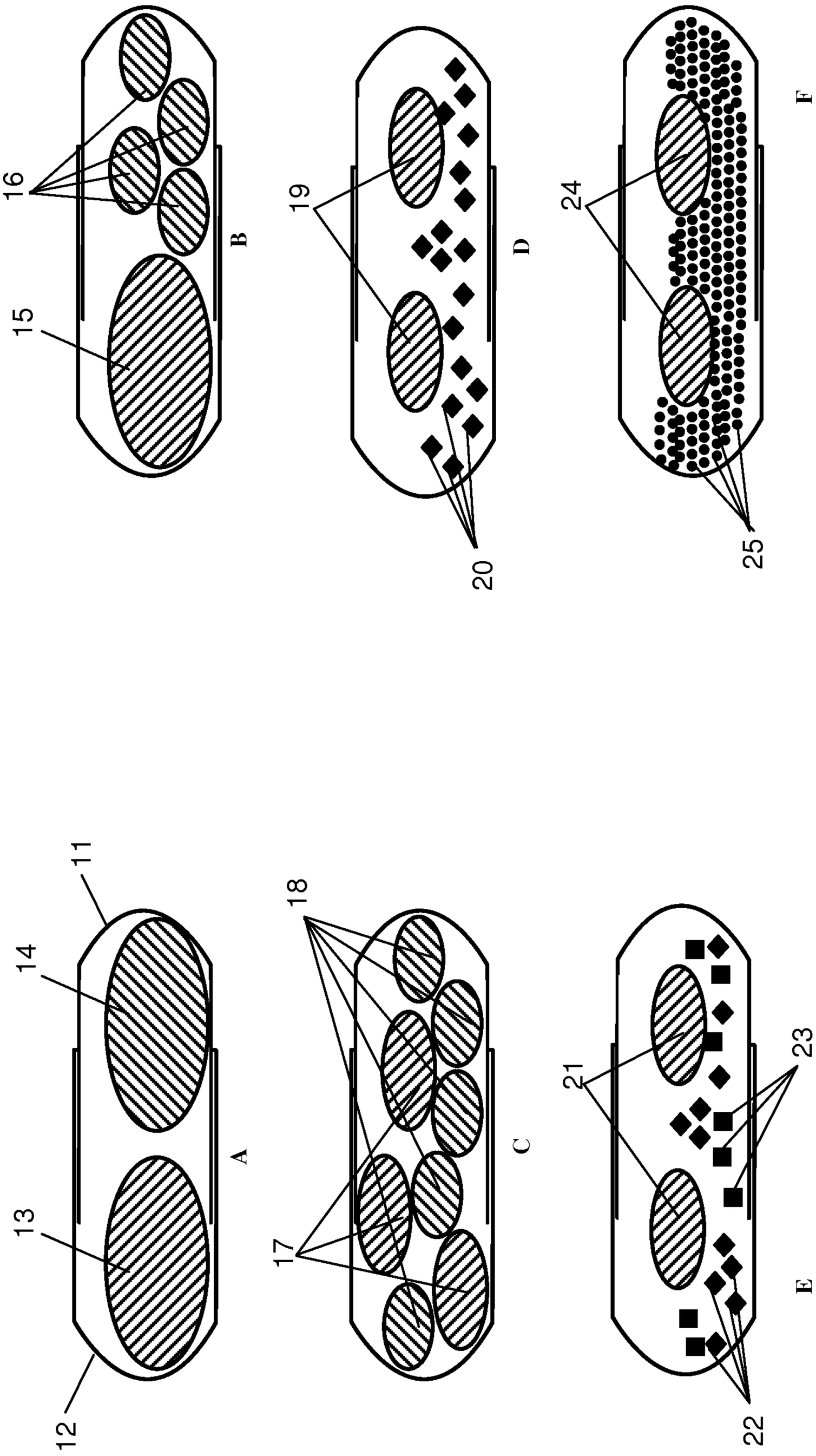


Figure 2

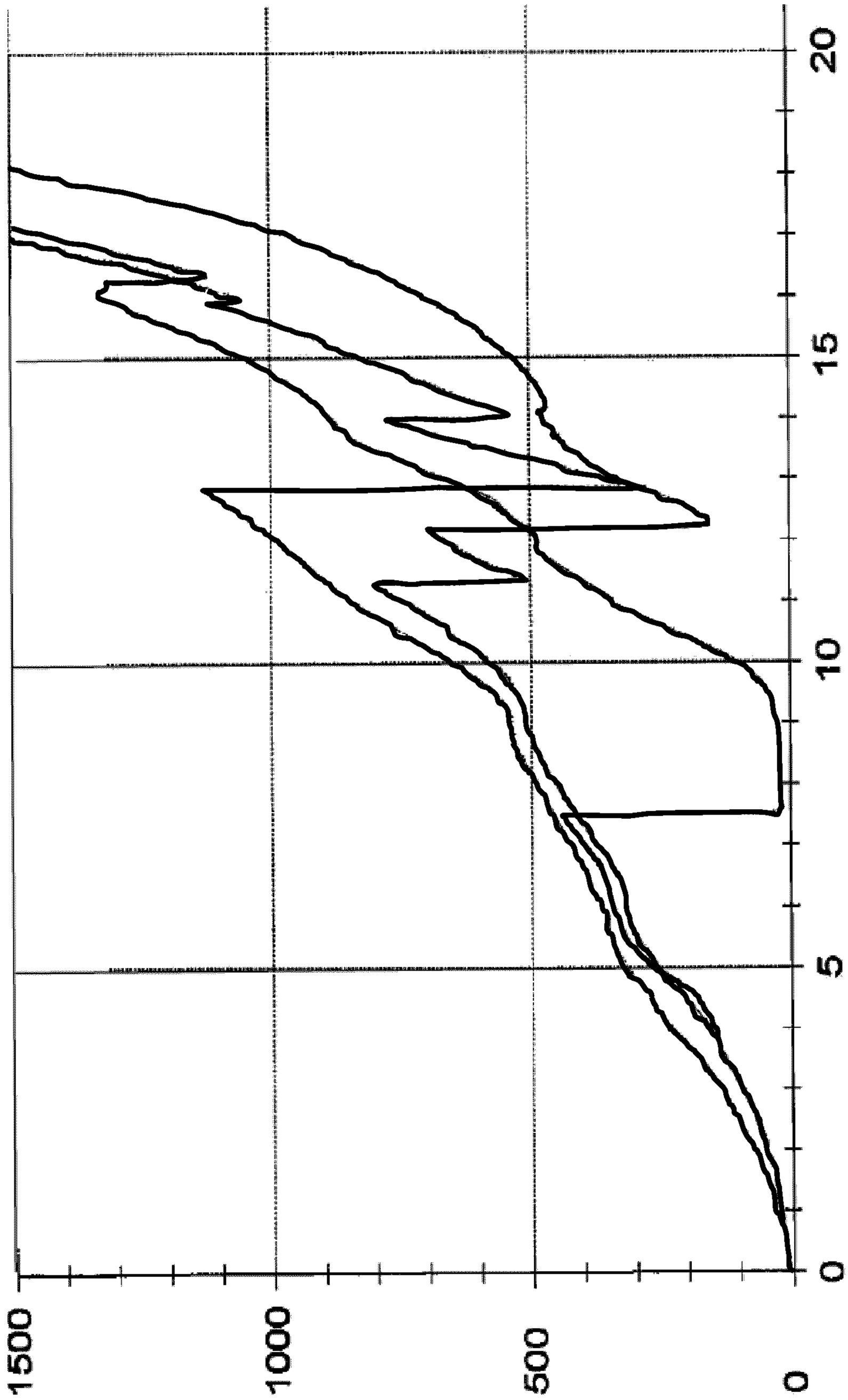


Figure 3

Figure 4

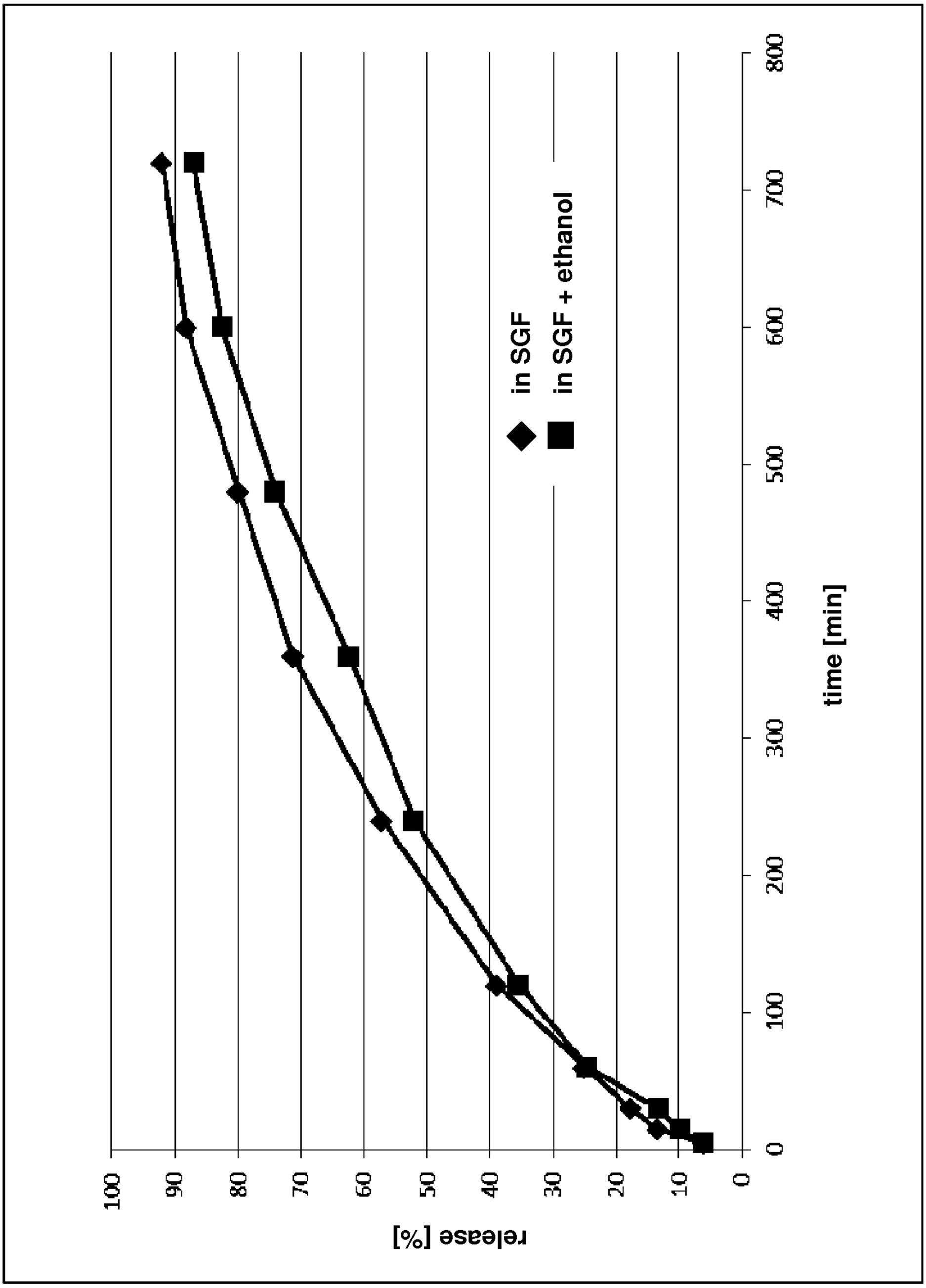
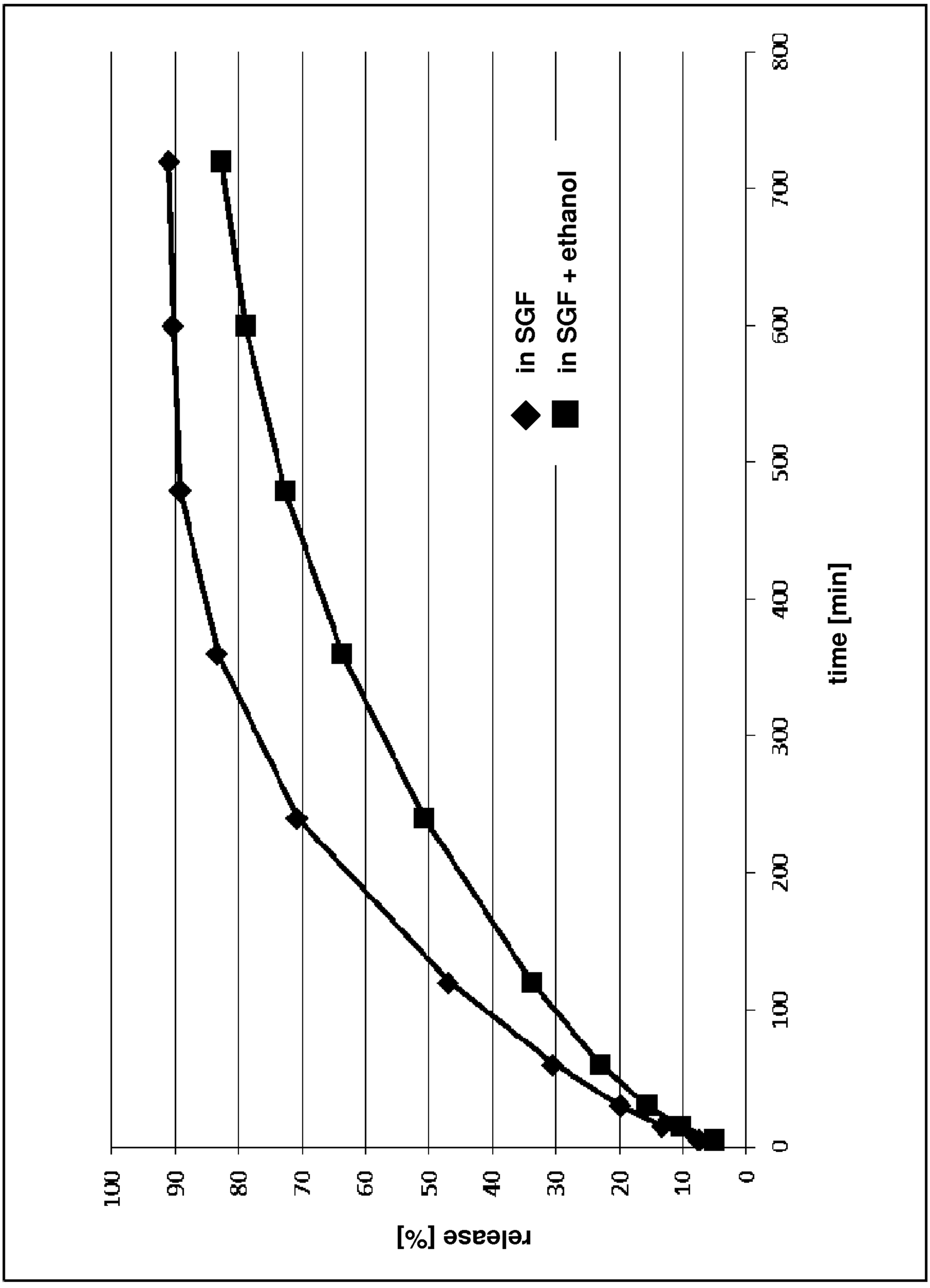

in SGF
in SGF + ethanol
release [%]
time [min]
0
10
20
30
40
50
60
70
80
90
100
0
100
200
300
400
500
600
700
800

Figure 5


in SGF
in SGF + ethanol
time [min]
release [%]
0
100
200
300
400
500
600
700
800
0
10
20
30
40
50
60
70
80
90
100

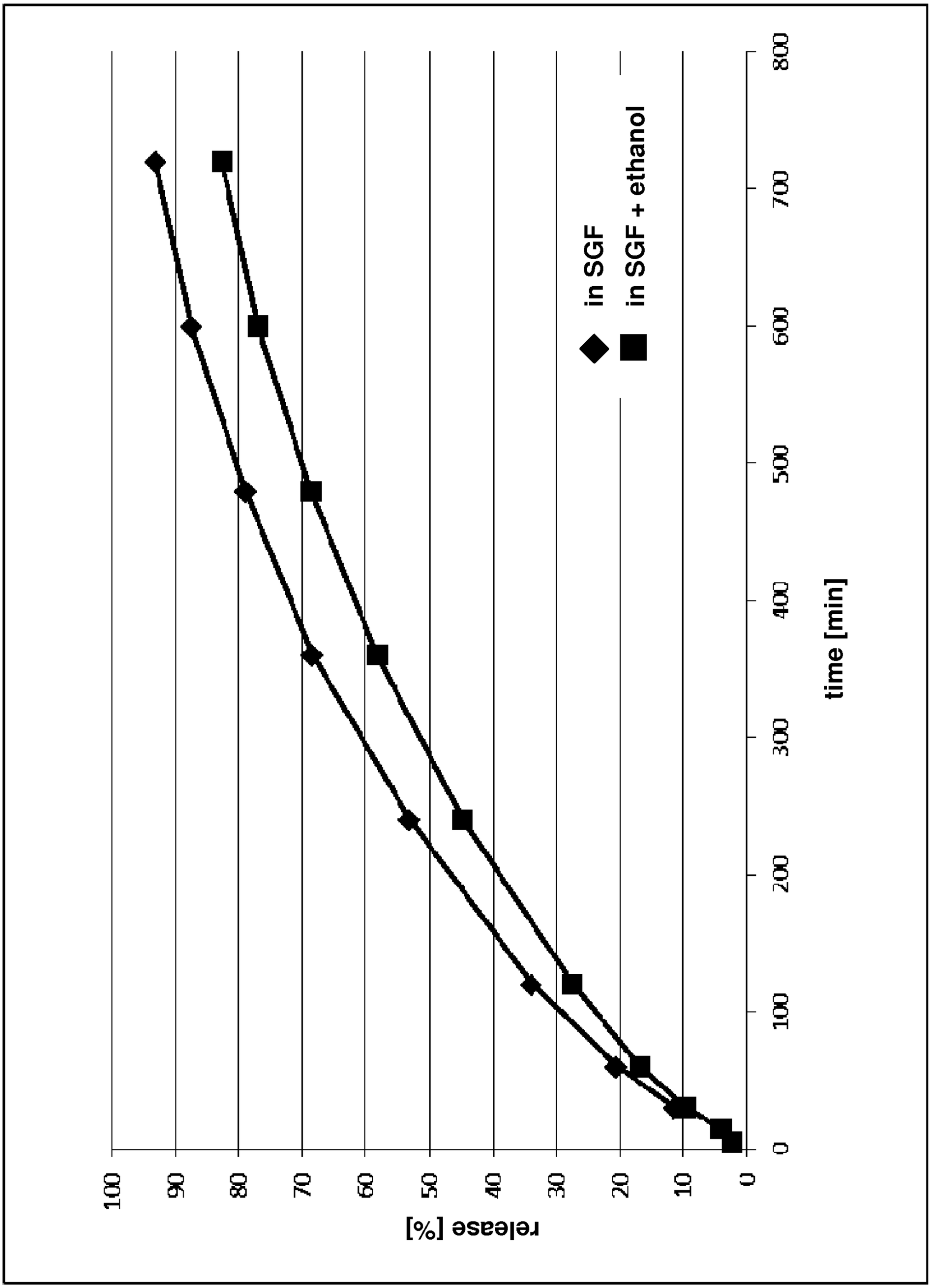

release [%]
100
90
80
70
60
50
40
30
20
10
0
time [min]
100
200
300
400
500
600
700
800
in SGF
in SGF + ethanol
0

Figure 6

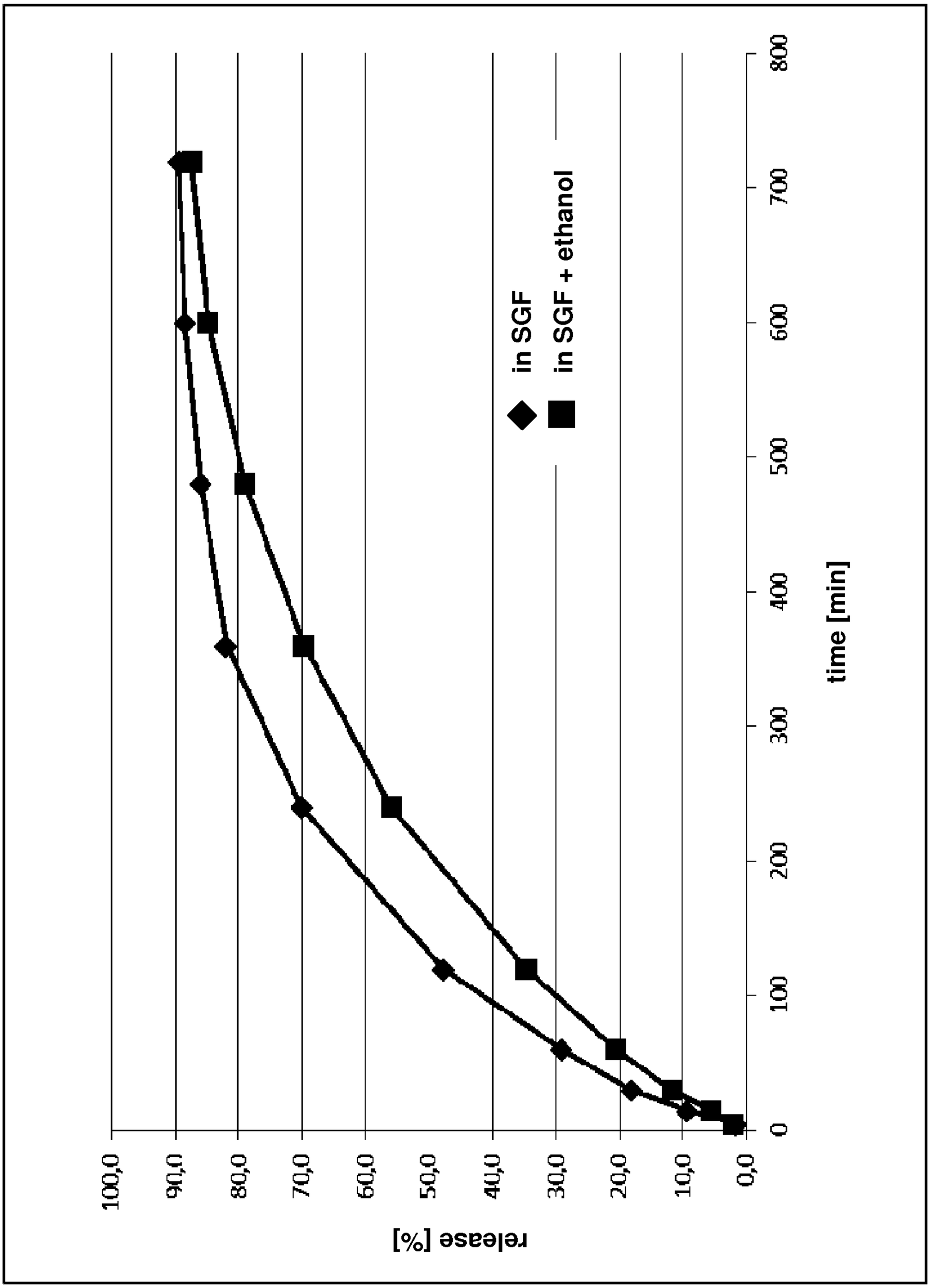

release [%]
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
time [min]
0
100
200
300
400
500
600
700
800
in SGF
in SGF + ethanol

Figure 7

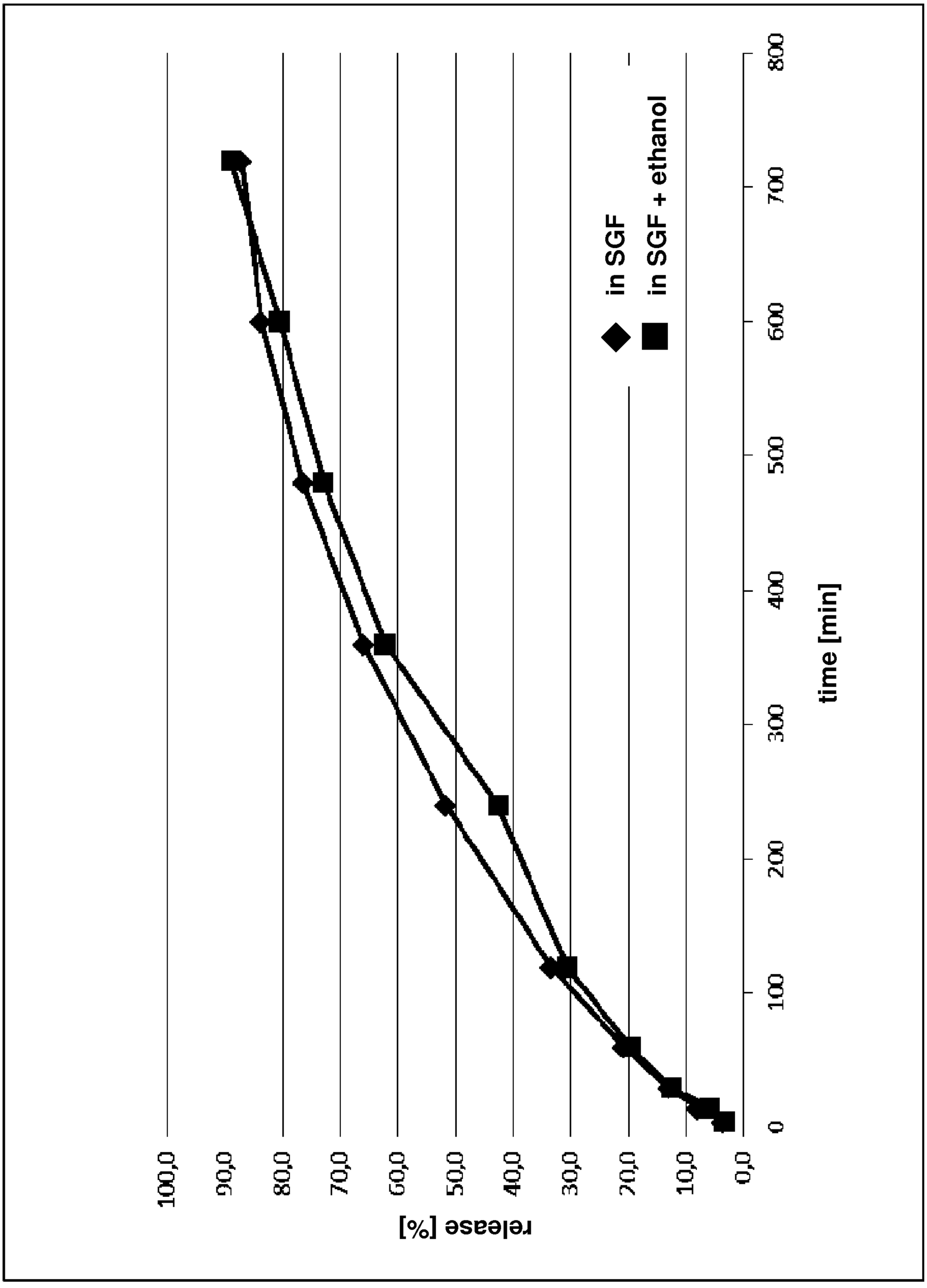

in SGF
in SGF + ethanol
time [min]
release [%]
0
100
200
300
400
500
600
700
800
0,0
10,0
20,0
30,0
40,0
50,0
60,0
70,0
80,0
90,0
100,0

Figure 8

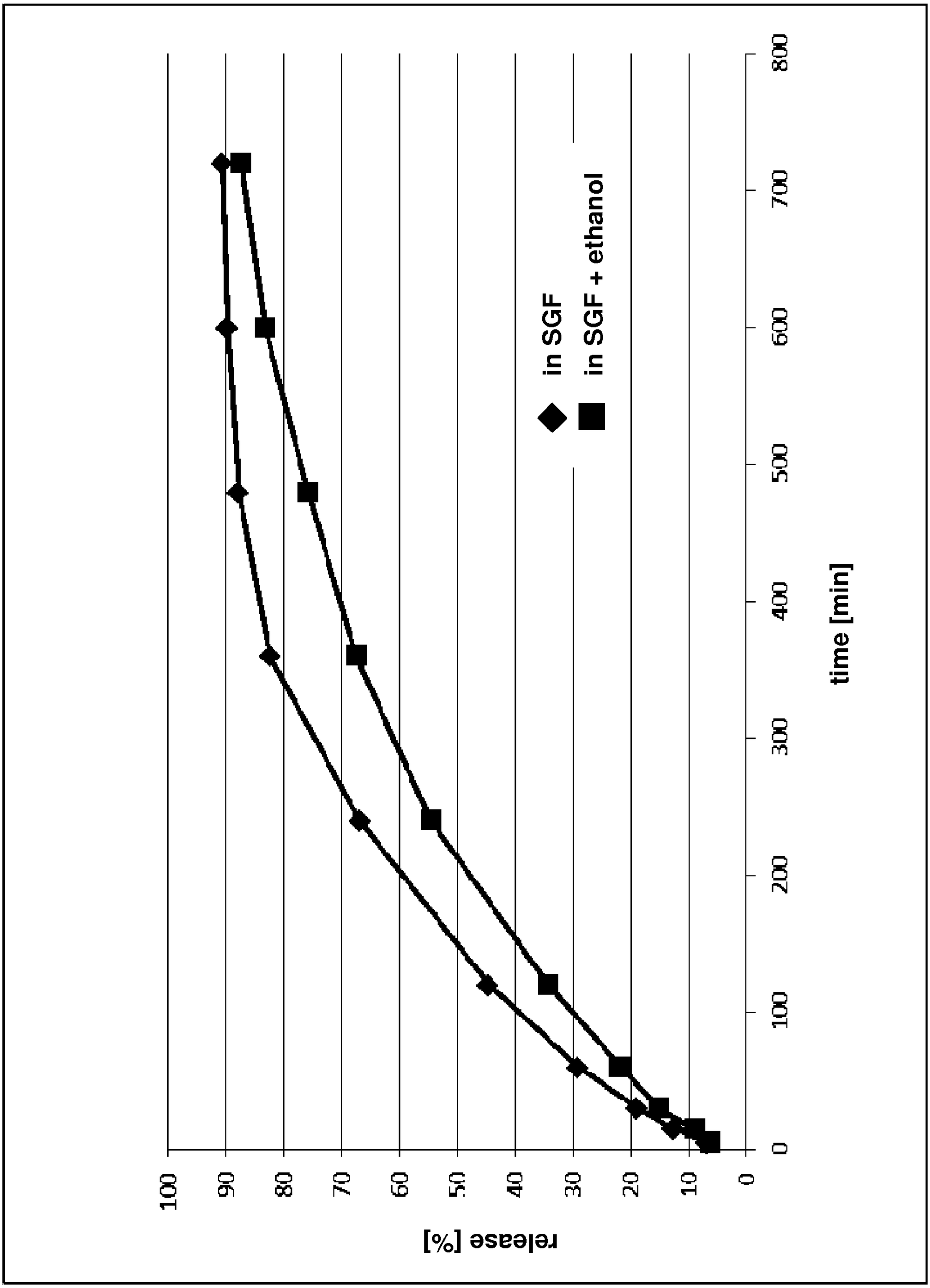

release [%]
time [min]
in SGF
in SGF + ethanol
0
10
20
30
40
50
60
70
80
90
100
100
200
300
400
500
600
700
800

Figure 9

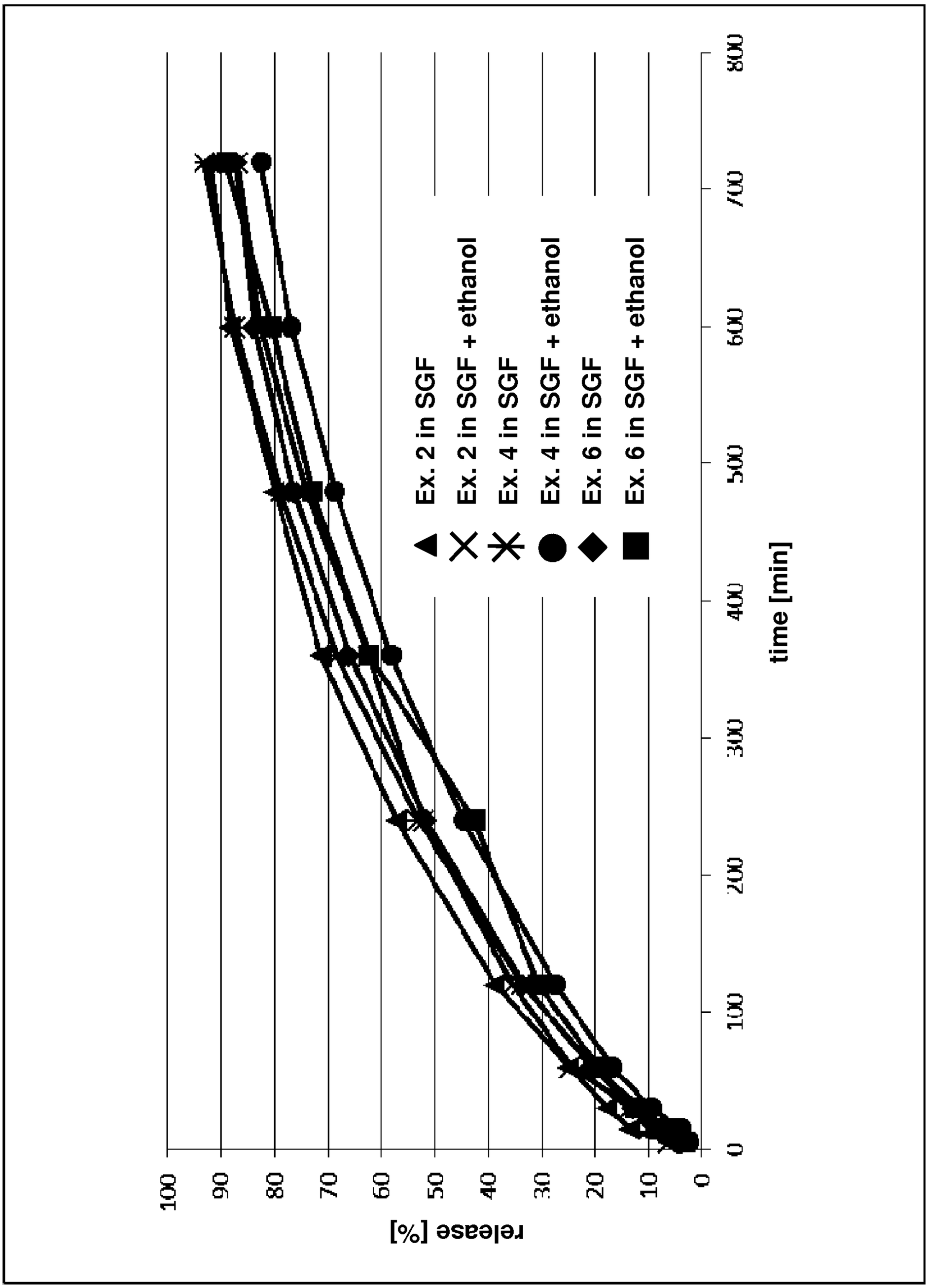

release [%]
time [min]
Ex. 2 in SGF
Ex. 2 in SGF + ethanol
Ex. 4 in SGF
Ex. 4 in SGF + ethanol
Ex. 6 in SGF
Ex. 6 in SGF + ethanol

Figure 10

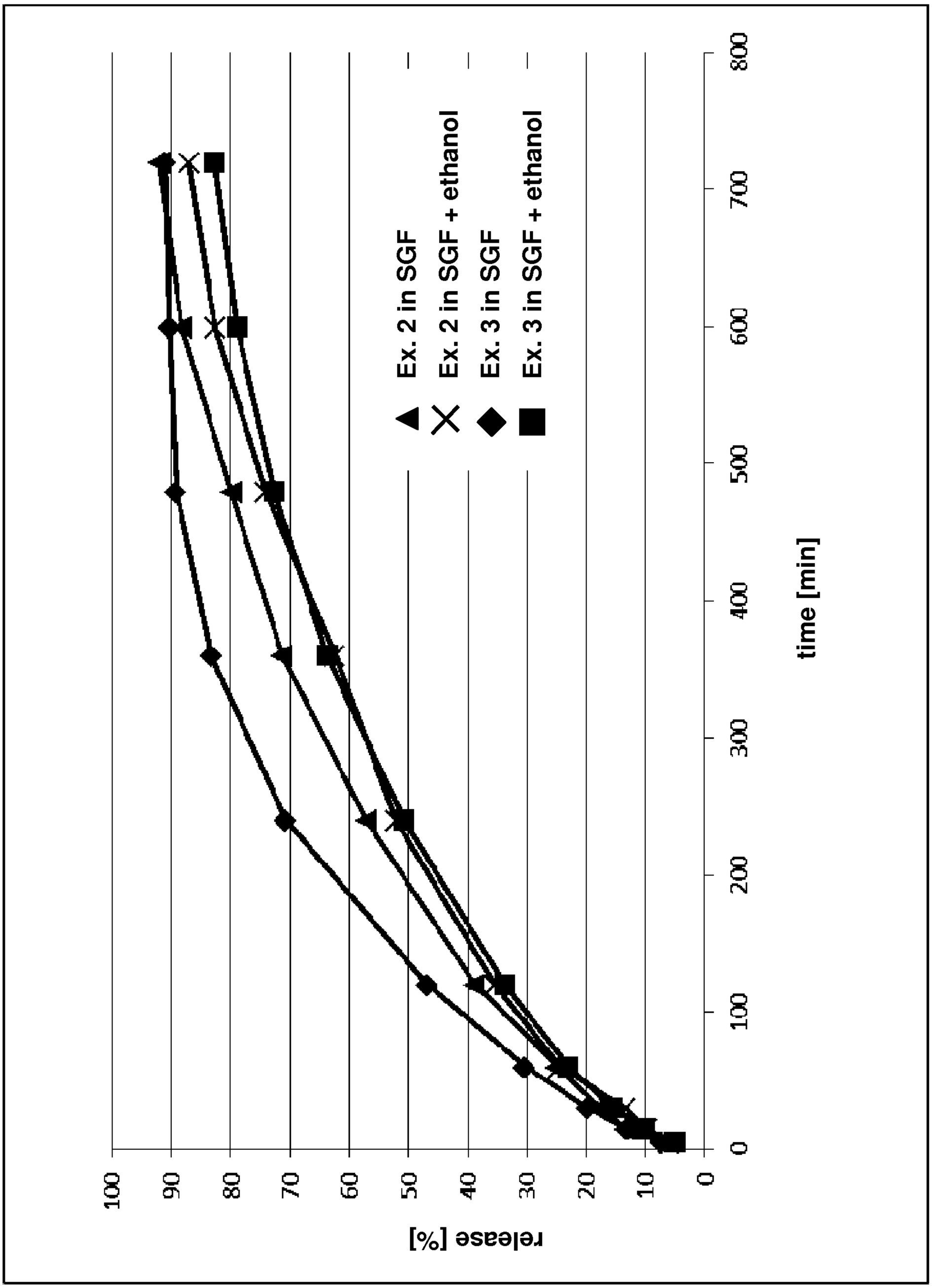

release [%]
100
90
80
70
60
50
40
30
20
10
0
time [min]
0
100
200
300
400
500
600
700
800
Ex. 2 in SGF
Ex. 2 in SGF + ethanol
Ex. 3 in SGF
Ex. 3 in SGF + ethanol

Figure 11

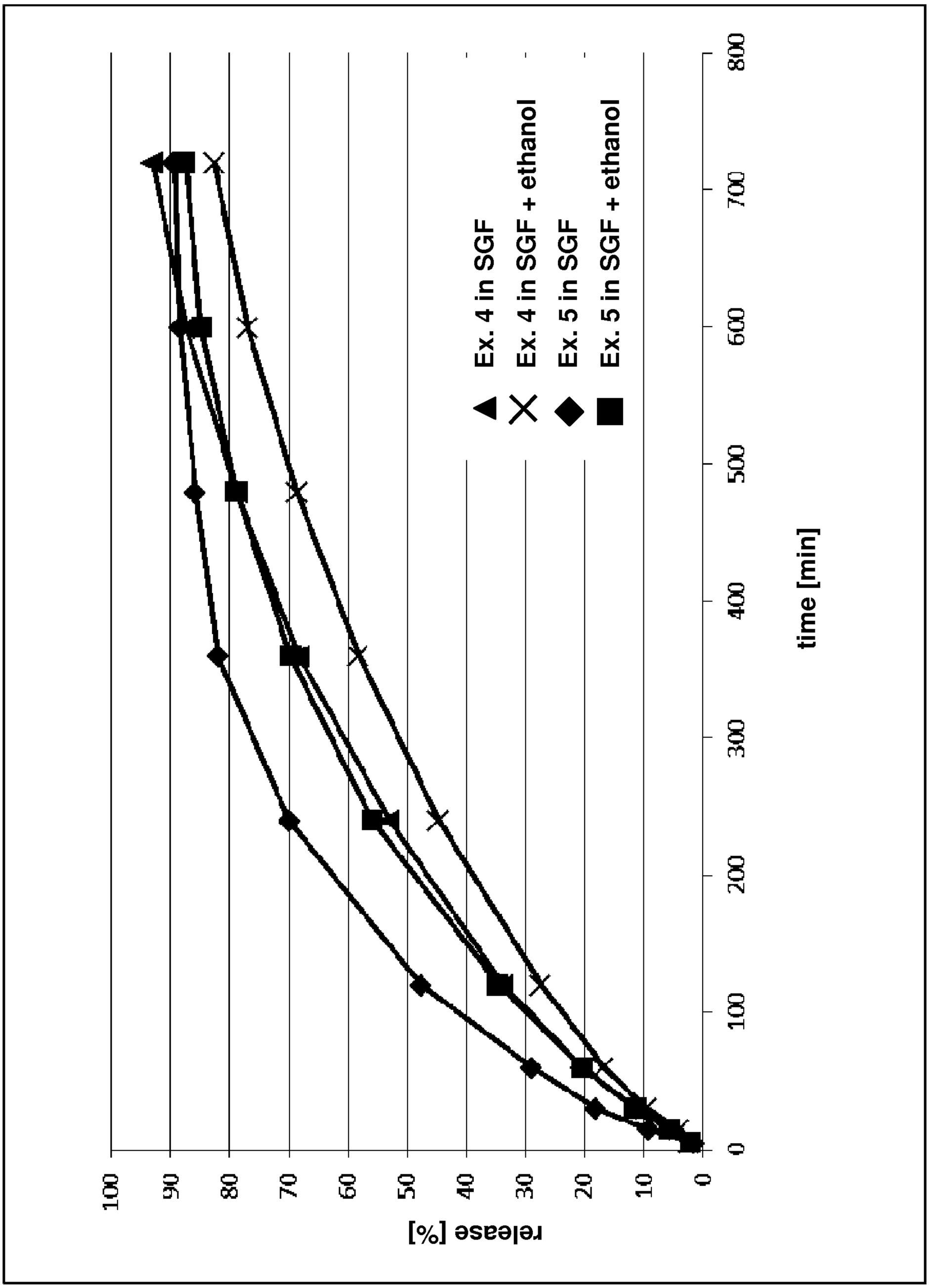

release [%]
time [min]
Ex. 4 in SGF
Ex. 4 in SGF + ethanol
Ex. 5 in SGF
Ex. 5 in SGF + ethanol

Figure 12

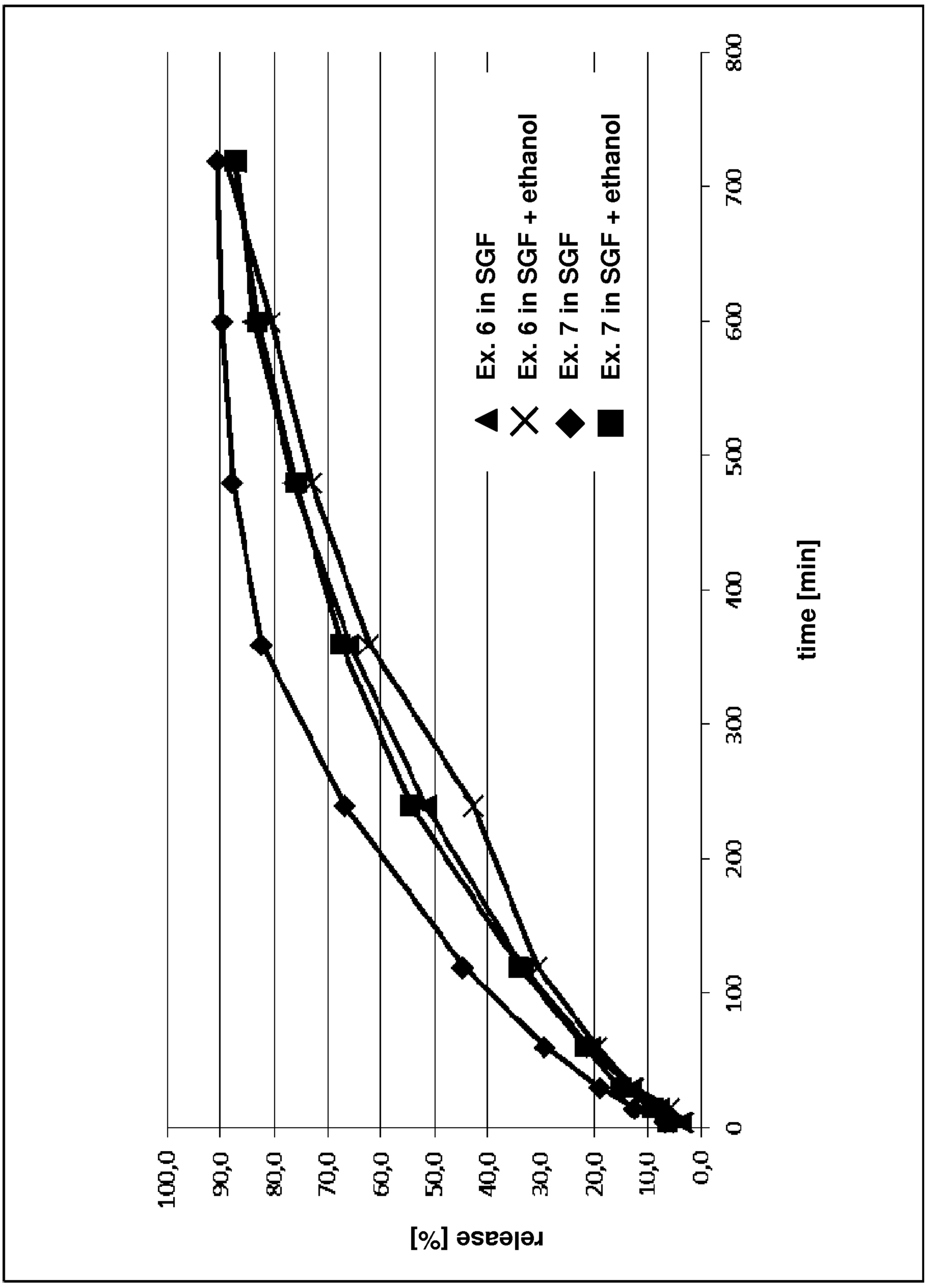
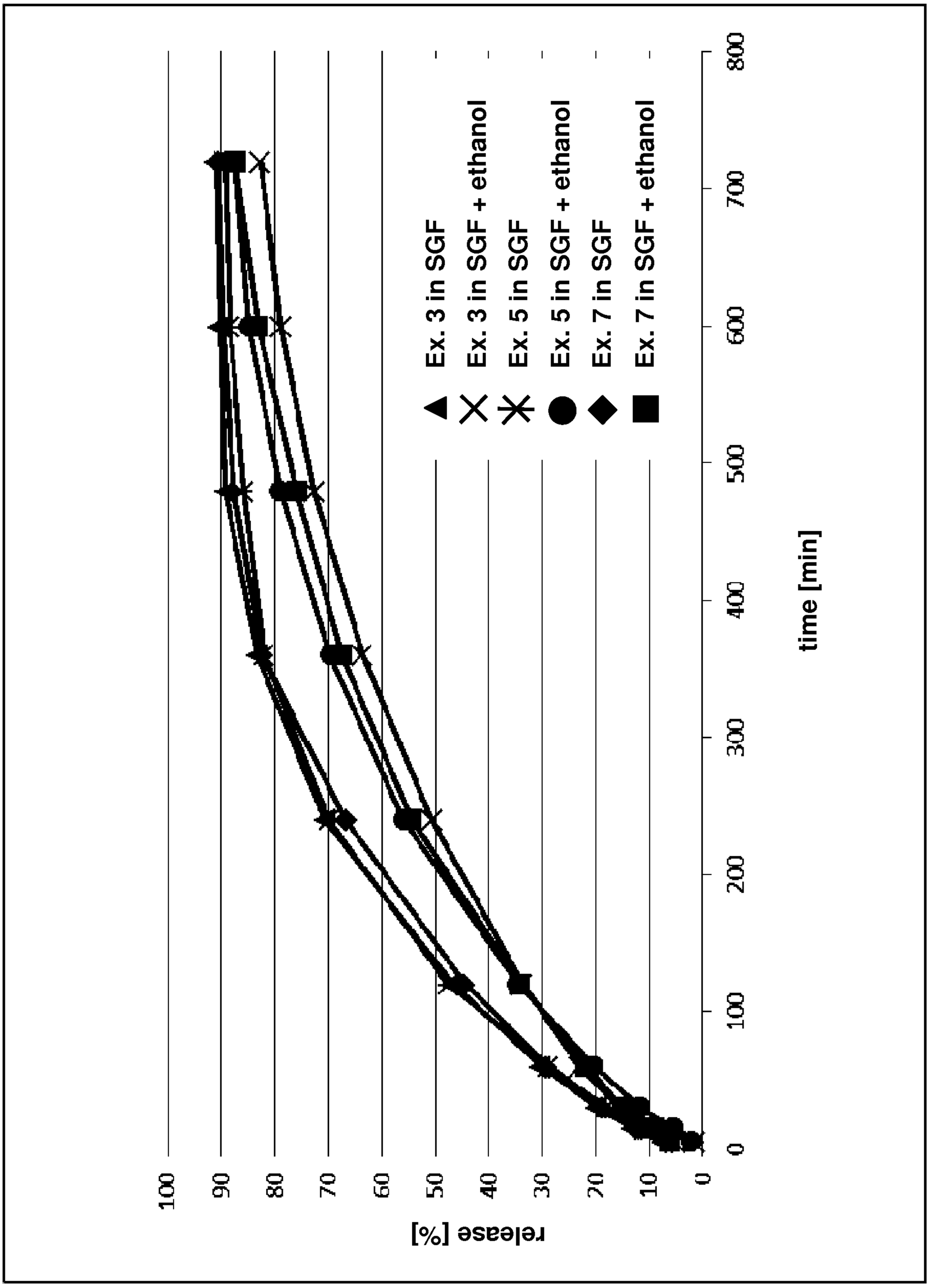

release [%]
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
time [min]
0
100
200
300
400
500
600
700
800
Ex. 6 in SGF
Ex. 6 in SGF + ethanol
Ex. 7 in SGF
Ex. 7 in SGF + ethanol

Figure 13

Figure 14


release [%]
time [min]
Ex. 3 in SGF
Ex. 3 in SGF + ethanol
Ex. 5 in SGF
Ex. 5 in SGF + ethanol
Ex. 7 in SGF
Ex. 7 in SGF + ethanol