Solid pharmaceutical dosage forms which can be administered orally and have rapid release of active ingredient

The present invention relates to solid pharmaceutical dosage forms which can be administered orally and comprise 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide in amorphous form and/or thermodynamically metastable crystal modification and have rapid release of active ingredient, and to process for the production thereof, the use thereof as medicament, the use thereof for the prophylaxis, secondary prophylaxis and/or treatment of disorders, and to the use thereof for producing a medicament for the prophylaxis, secondary prophylaxis and/or treatment of disorders.

5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (I) is a low molecular weight inhibitor of coagulation factor Xa which can be administered orally and can be employed for the prophylaxis, secondary prophylaxis and/or treatment of various thromboembolic disorders (concerning this, see WO- 01/47919, the disclosure of which is hereby incorporated by reference). When active ingredient (I) is mentioned hereinafter, this encompasses all crystal modifications and the amorphous form of 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (I) and the respective hydrates, solvates and cocrystals.

It is necessary in the development of formulations to take account of the physicochemical and biological properties of the active ingredient (I), for example the relatively low solubility in water (about 7 mg/l; 25°C) and the relatively high melting point of about 230°C of the active ingredient (I) in the crystal modification in which the active ingredient (I) is obtained when prepared by the route described in Example 44 of WO 01/47919 (*Chem. Abstr.* **2001**, *135*, 92625) and which is referred to hereinafter as crystal modification I.

WO 2005/060940 describes pharmaceutical dosage forms which comprise the active ingredient (I) in hydrophilized form. Preference is given in this connection to rapid-release tablets which have a Q value (30 minutes) of 75% in the USP (United States Pharmacopeia) release method with apparatus 2 (paddle).

It has surprisingly now been found that dosage forms which comprise active ingredient (I) in amorphous form and/or in the form of thermodynamically metastable crystal modifications display improved bioavailability.

The present invention relates to solid dosage forms which can be administered orally and have rapid release of active ingredient and comprise 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-

morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (I), characterized in that they comprise active ingredient (I) in amorphous form and/or thermodynamically metastable crystal modification, and that 80% of the active ingredient (I) are released over a period not exceeding 2 hours in the USP release method with apparatus 2 (paddle; 75 rpm). The further conditions of these in vitro release investigations according to USP release method are described in the experimental section (sink conditions). The amount of 80% of active ingredient (I) released is based on the total amount of active ingredient (I) present in the dosage form.

Preference is given to solid pharmaceutical dosage forms which can be administered orally and have rapid release of active ingredient and comprise 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (I), characterized in that they comprise active ingredient (I) in amorphous form and that 80% of active ingredient (I) are released over a period not exceeding 2 hours in USP release method with apparatus 2 (paddle; 75 rpm).

In a preferred embodiment of the present invention, 80% of active ingredient (I) are released in a period not exceeding 1 hour in USP release method with apparatus 2 (paddle; 75 rpm).

The active ingredient (I) may be present in the dosage forms according to the invention partly or completely in amorphous form and/or thermodynamically metastable crystal modification. The dosage forms according to the invention preferably comprise active ingredient (I) in amorphous form and/or in the form of metastable crystal modifications in an amount of at least 50%, particularly preferably more than 50%, in particular at least 90%, based on the total amount of active ingredient (I) present.

The active ingredient (I) can preferably be present in the dosage forms according to the invention partly or completely in amorphous form. The dosage forms according to the invention preferably comprise active ingredient (I) in amorphous form in an amount of at least 50%, particularly preferably more than 50%, in particular at least 90%, based on the total amount of active ingredient (I) present.

In a preferred embodiment of the present invention, the partial or complete presence of the active ingredient (I) in amorphous form and/or in the form of one or more thermodynamically metastable crystal modifications also increases the active ingredient solubility, besides a rapid release rate. In this embodiment too, the dosage forms according to the invention comprise active ingredient (I) in amorphous form and/or in the form of metastable crystal modifications preferably in an amount of at least 50%, particularly preferably more than 50%, in particular at least 90%, based on the total amount of active ingredient (I) present. The increase in the active ingredient solubility or

"supersaturation" is demonstrated in vitro release tests: The term "supersaturation" means in this connection that the formulations according to the invention display a release of active ingredient which is a factor of at least 1.5 times higher under the in vitro release conditions defined in the experimental section under non-sink conditions with a dose of 20 mg active ingredient (I) after one hour compared with crystalline micronized active ingredient (I) in crystal modification I. In this embodiment, the dosage forms according to the invention comprise active ingredient (I) in a total amount of 20 mg and release an amount of active ingredient (I) in a period of one hour in USP release method with apparatus 2 (paddle) which is a factor of at least 1.5 times higher compared with 20 mg of micronized crystalline active ingredient (I) in crystal modification I. If, for example, the micronized active ingredient (I) exhibits a release of 40% (8 mg) after one hour under these conditions, the formulations according to the invention show release levels of at least 60% (12 mg). The micronized active ingredient (I) in this case has an average particle size X_{50} value (50% proportion) of from 1 to 8 μm and an X_{90} value (90% proportion) of less than 20 μm.

In a preferred embodiment of the present invention, the partial or complete presence of the active ingredient (I) in amorphous form also increases the active ingredient solubility, besides a rapid release rate. In this embodiment too, the dosage forms according to the invention comprise active ingredient (I) in amorphous form preferably in an amount of at least 50%, particularly preferably more than 50%, in particular at least 90%, based on the total amount of active ingredient (I) present. The increase in the active ingredient solubility or "supersaturation" is demonstrated in vitro release tests: The term "supersaturation" means in this connection that the formulations according to the invention display a release of active ingredient which is a factor of at least 1.5 times higher under the in vitro release conditions defined in the experimental section under non-sink conditions with a dose of 20 mg active ingredient (I) after one hour compared with crystalline micronized active ingredient (I) in crystal modification I. In this embodiment, the dosage forms according to the invention comprise active ingredient (I) in a total amount of 20 mg and release an amount of active ingredient (I) in a period of one hour in USP release method with apparatus 2 (paddle) which is a factor of at least 1.5 times higher compared with 20 mg of micronized crystalline active ingredient (I) in crystal modification I. If, for example, the micronized active ingredient (I) exhibits a release of 40% (8 mg) after one hour under these conditions, the formulations according to the invention show release levels of at least 60% (12 mg). The micronized active ingredient (I) in this case has an average particle size X_{50} value (50% proportion) of from 1 to 8 μm and an X_{90} value (90% proportion) of less than 20 μm.

It is possible to employ for producing the pharmaceutical dosage forms according to the invention all crystal modifications and the amorphous form of 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (I) and the respective

hydrates, solvates and cocrystals.

Various pharmaceutically suitable production methods are possible for amorphization of active ingredients and for generating thermodynamically metastable crystal modifications, and for stabilizing these active ingredient forms in formulations. The dissolving method, the melting method or a combination of these two methods are frequently employed [Chiou, W.L.; Riegelman, S., "Pharmaceutical Applications of Solid Dispersion Systems", Journal of Pharmaceutical Sciences 60 (1971), 1281-1302; Ford, J. L., "The Current Status of Solid Dispersions", Pharm. Acta Helv. 61 (1986), 69-88; Rasenack, N., "Poorly Water-soluble Drugs for Oral Delivery – A Challenge for Pharmaceutical Development, Part III: Drug delivery systems containing the drug molecularly dispersed/Aspects on in vitro and in vivo characterization", Pharmazeutische Industrie 67, No. 5 (2005), 583-591].

The dissolving method, in which an active ingredient and excipient(s) employed where appropriate, such as, for example, polyvinylpyrrolidone, are dissolved and then further processed is less suitable for the crystalline active ingredient (I) in the thermodynamically stable crystal modification I, because it has only a limited solubility in pharmaceutically suitable organic solvents such as, for example, acetone or ethanol, and therefore disproportionately large amounts of solvent must be used. Pure acetic acid forms an exception, being a suitable solvent for the crystalline active ingredient (I) – a suitable production method is described in the experimental section.

The active ingredient (I) is present in the mixture present after the dissolving method according to the invention preferably in a concentration of from 0.1 to 30%, particularly preferably from 0.1 to 20%, in particular from 5 to 15%, based on the total mass of the dissolved components.

The method preferred according to the invention for amorphizing active ingredient (I) and for generating thermodynamically metastable crystal modifications, and for stabilizing the amorphous state of active ingredient (I) in the pharmaceutical preparations is the melting method, in which an active ingredient is melted together with or in one or more suitable excipients.

Examples of excipients suitable for the melting method are urea, citric acid, stearic acid, sugars, sugar alcohols such as, for example, mannitol or xylitol and hydrophilic polymers such as, for example, polyethylene glycols (PEG), polyethylene oxides, polyoxyethylene-polyoxypropylene block copolymers and vinylpyrrolidone-vinyl acetate copolymers, hydroxypropylcellulose (HPC), saturated polyglycolized glycerides (Gelucire, Gattefosse) or mixtures of these excipients. Preferred excipients are polyethylene glycols, mixtures of polyethylene glycols and mixtures of one or more polyethylene glycols with one or more other suitable excipients, particular preferably

polyethylene glycols and mixtures of polyethylene glycols, in particular polyethylene glycols. The active ingredient (I) is added to the molten excipient or excipient mixture, and the temperature is raised until a clear melt is present, or the active ingredient (I) and the excipient(s) are initially mixed and then melted. The melting is followed by cooling and subsequent comminution to result in a powder or granules, which can also be referred to as "solid solution". Alternatively, the melt can after comminution for example be packed into capsules or as sachet, where appropriate after admixture of suitable pharmaceutical excipients. It must be ensured, by choice of a suitable formulation and suitable production parameters, in this melting method that the degradation of active ingredient does not exceed pharmaceutically acceptable limits during the melting process. This is a difficult task with a melting point of about 230°C for the active ingredient (I) in crystal modification I, because significant rates of decomposition of the active ingredient and/or the excipients are usually to be expected in this high temperature range.

The active ingredient (I) is present in the mixture present after the melting process according to the invention preferably in a concentration of from 0.1 to 30%, particularly preferably from 0.1 to 20%, especially from 5 to 15%, based on the total mass of the melt.

The melt extrusion method is particularly preferred for producing pharmaceutical dosage forms comprising active ingredient (I) in amorphous form or metastable crystal modifications [Breitenbach, J., "Melt extrusion: From process to drug delivery technology", European Journal of Pharmaceutics and Biopharmaceutics 54 (2002), 107-117; Breitenbach, J., "Feste Lösungen durch Schmelzextrusion – ein integriertes Herstellkonzept", Pharmazie in unserer Zeit 29 (2000), 46-49].

It must also be ensured in this production method, through choice of a suitable formulation and suitable production parameters, that the degradation of active ingredient does not exceed pharmaceutically acceptable limits.

The melt extrusion method for preparing the active ingredient (I) in amorphous form or in the form of metastable crystal modifications is preferably carried out in the presence of a polymer such as, for example, polyvinylpyrrolidone (PVP), polyethylene glycol, polymethacrylate, polymethylmethacrylate, polyethylene oxide, polyoxyethylene-polyoxypropylene block copolymers, vinylpyrrolidone-vinyl acetate copolymers or a cellulose ether such as, for example, hydroxypropylcellulose (HPC) or of mixtures of various polymers. The preferred polymer in this connection is hydroxypropylcellulose (HPC), polyvinylpyrrolidone (PVP) or a mixture of HPC and PVP. Hydroxypropylcellulose (HPC) or polyvinylpyrrolidone (PVP) is particularly preferred.

The proportion of polymer in the melt extrudate is preferably according to the invention at least 40% of the total mass of the melt extrudate.

The active ingredient (I) is preferably present according to the invention in the melt extrudate in a concentration of from 0.1 to 20%, in particular from 5 to 15%, based on the total mass of the melt extrudate.

It has proved advantageous in the melt extrusion method for preparing or stabilizing the active ingredient (I) in amorphous form to add one or more pharmaceutically suitable substances to depress the melting point of the active ingredient or as plasticizer of the polymer, in order to facilitate processing and reduce the degradation of active ingredient taking place during the extrusion process.

These pharmaceutically suitable substances are preferably added according to the invention in a concentration of from 0.2 to 40%, based on the total mass of the melt extrudate.

Examples suitable for this purpose are urea, polymers such as polyethylene glycol, polymethacrylates, polymethylmethacrylates, polyethylene oxide, polyoxyethylene-polyoxypropylene block copolymers, vinylpyrrolidone-vinyl acetate copolymers, saturated polyglycolized glycerides (Gelucire, Gattefosse) or sugar alcohols such as, for example, erythritol, maltitol, mannitol, sorbitol and xylitol. Sugar alcohols are preferably employed. It must be ensured in this connection, by choice of suitable preparation parameters, that the active ingredient (I) is converted as completely as possible into the amorphous or thermodynamically metastable state in order to increase the active ingredient solubility.

The product which has been obtained for example by the dissolving method, the melting or the melt extrusion method and which comprises active ingredient (I) in amorphous form or metastable crystal modification(s) can be further processed in various ways: it can for example be comminuted and administered as powder or granules, where appropriate after packing as sachet or in capsules. It is moreover possible to add conventional pharmaceutical excipients such as, for example, fillers, flow regulators, adsorbents, wetting agents, flavours and colours.

The product comprising the active ingredient (I) in amorphous form or metastable crystal modifications may additionally be further processed to tablet formulations. It can for this purpose be cut, ground and mixed with conventional tabletting excipients such as fillers and dry binders (for example cellulose powder, microcrystalline cellulose, silicified microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, magnesium trisilicate, mannitol, maltitol, sorbitol, xylitol, lactose, dextrose, maltose, sucrose, glucose, fructose or maltodextrins), disintegration promoters/disintegrants (for example carboxymethylcellulose, croscarmellose (crosslinked carboxymethylcellulose), crospovidone (crosslinked polyvinylpyrrolidone), L-HPC (low-substituted hydroxypropylcellulose), sodium carboxymethylstarch, sodium glycolate of potato

starch, partially hydrolysed starch, wheat starch, maize starch, rice starch or potato starch), lubricants, glidants and flow regulators such as fumaric acid, stearic acid, magnesium stearate, calcium stearate, sodium stearyl fumarate, high molecular weight fatty alcohols, polyethylene glycols, starch (wheat, rice, maize or potato starch), talc, colloidal silicon dioxide, magnesium oxide, magnesium carbonate or calcium silicate, adsorbents, flavours and colours, and compressed to tablets, and the latter can then where appropriate also be coated. Suitable materials for a photoprotective and/or colouring coating are for example polymers such as polyvinyl alcohol, hydroxypropylcellulose and/or hydroxypropylmethylcellulose, where appropriate combined with suitable plasticizers such as, for example, polyethylene glycol or polypropylene glycol and pigments such as, for example, titanium dioxide or iron oxides. The tablets are preferably tablets which disintegrate rapidly and have a disintegration time not exceeding 30 minutes.

The present invention further relates to a process for producing the tablet formulation according to the invention, where a solid solution or extrudate comprising an active ingredient (I) in amorphous form or metastable crystal modification is produced with the aid of the dissolving method, preferably with the aid of the melting method, very particularly preferably with the aid of melt extrusion, and is then ground, mixed with further pharmaceutical excipients known to the skilled person and packed into capsules or as sachet, or mixed with further tabletting aids (see above) known to the skilled person and then compressed preferably by direct tabletting to tablets which can finally be covered with a coating. Active ingredient (I) is particularly preferably present in amorphous form.

A product which has been obtained by the melting process and comprises active ingredient (I) in amorphous form and/or metastable crystal modification can furthermore be produced in the form of multiparticulate dosage forms. The term "multiparticulate dosage forms" means according to the invention those formulations which consist of a plurality of small particles such as, for example, spherical granules (pellets) or minitablets. The diameter of these particles is ordinarily from 0.5 to 3.0 mm. The cut and rounded extrudates or small-format tablets (minitablets with diameter not exceeding 3 mm) can be coated where appropriate and packed in capsules or prepared as sachet. A further possibility consists of further processing to larger tablets which, after contact with water/gastric juice, release the primary granules/pellets by rapid disintegration. Active ingredient (I) is particularly preferably present in amorphous form.

The present invention further relates to pharmaceutical dosage forms, preferably capsules, sachets or tablets, comprising the multiparticulate dosage forms described above.

The present invention further relates to a process for producing the multiparticulate pharmaceutical

dosage forms according to the invention, where an extrudate comprising active ingredient (I) in amorphous form and/or thermodynamically metastable crystal modification is preferably obtained by melt extrusion. In a preferred embodiment of the present invention, a multiparticulate dosage form in pellet form is produced directly by cutting this extrudate strand and, where appropriate, subsequent rounding. The pellets obtained in this way can then be covered with a coating and packed in capsules or as sachet. Active ingredient (I) is particularly preferably present in amorphous form.

The present invention further relates to medicaments comprising a solid pharmaceutical dosage form according to the invention which can be administered orally, comprises active ingredient (I) in amorphous form and/or thermodynamically metastable crystal modification(s) and has rapid release of active ingredient. Active ingredient (I) is particularly preferably present in amorphous form.

The present invention further relates to the use of the solid pharmaceutical dosage form according to the invention which can be administered orally and has rapid release of active ingredient, and which comprises amorphous and/or thermodynamically metastable active ingredient (I) for the prophylaxis, secondary prophylaxis and/or treatment of disorders, in particular of arterial and/or venous thromboembolic disorders such as myocardial infarction, angina pectoris (including unstable angina), reocclusions and restenoses following angioplasty or aortocoronary bypass, stroke, transient ischaemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep vein thromboses. Active ingredient (I) is particularly preferably present in amorphous form.

The present invention further relates to the use of the solid pharmaceutical dosage form according to the invention which can be administered orally, comprises the amorphous and/or thermodynamically metastable active ingredient (I) and has rapid release of active ingredient for producing a medicament for the prophylaxis, secondary prophylaxis and/or treatment of disorders, in particular of arterial and/or venous thromboembolic disorders such as myocardial infarction, angina pectoris (including unstable angina), reocclusions and restenoses following angioplasty or aortocoronary bypass, stroke, transient ischaemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep vein thromboses. Active ingredient (I) is particularly preferably present in amorphous form.

The present invention further relates to the use of 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (I) for producing a solid pharmaceutical dosage form according to the invention which can be administered orally and has rapid release of active ingredient.

The present invention further relates to a method for the prophylaxis, secondary prophylaxis and/or treatment of arterial and/or venous thromboembolic disorders by administering a solid pharmaceutical dosage form according to the invention which can be administered orally, comprises active ingredient (I) in amorphous form and/or thermodynamically metastable crystal modification and has rapid release of active ingredient. Active ingredient (I) is particularly preferably present in amorphous form.

The invention is explained in more detail below by preferred exemplary embodiments, to which it is not restricted, however. Unless indicated otherwise, all statements of amounts below refer to percentages by weight.

Experimental section

The in vitro release investigations are carried out by USP release method with apparatus 2 (paddle) at a temperature of 37°C. The speed of rotation of the stirrer is 75 rpm (revolutions per minute) in 900 ml of an acetate buffer solution of pH 4.5, which is prepared from 29.9 g of sodium acetate trihydrate and 16.6 ml of glacial acetic acid in 10 l of water.

The investigations in this connection take place under sink or non-sink conditions.

Sink conditions: The active ingredient release rate is determined under sink conditions. Depending on the active ingredient dose to be tested it is possible to employ a surfactant, preferably sodium lauryl sulphate, for setting up the sink conditions. The solubility of the medium for the active ingredient (I) is adjusted where appropriate by adding surfactant, preferably sodium lauryl sulphate, so that it is a factor of 3 to 10 higher than the saturation solubility of the active ingredient dose to be tested.

Non-sink conditions: The investigations for examining the supersaturation (increase in solubility) take place without addition of a surfactant and with a dose of 20 mg of active ingredient (I) to be released.

The in vitro release investigations described below were carried out under non-sink conditions in order to demonstrate the supersaturation behaviour of the exemplary formulations.

Comparative formulations:

To illustrate the supersaturation behaviour of exemplary formulations 1 to 6 (see below), as comparison the in vitro release (non-sink conditions) of the micronized crystalline active ingredient (I) in the thermodynamically stable crystal modification I and of a rapid-release tablet formulation produced by fluidized bed granulation and comprising micronized crystalline active ingredient (I) in crystal modification I were determined.

Comparative formulation 1.1

In vitro release (non-sink conditions) of the micronized (X_{50} = 4 µm; X_{90} = 10 µm) crystalline active ingredient (I) in crystal modification I; active ingredient dose 20 mg:

Time [min]	15	30	60	90
Release [%]	23	34	41	44

(USP paddle, 75 rpm, 900 ml of acetate buffer of pH 4.5)

Comparative formulation 1.2

In vitro release (non-sink conditions) of a tablet formulation comprising 10 mg of micronized crystalline active ingredient (I) in crystal modification I; active ingredient dose 20 mg by application of 2 tablets per vessel:

Time [min]	15	30	60	90
Release [%]	46	50	52	52

(USP paddle, 75 rpm, 900 ml of acetate buffer of pH 4.5)

The tablet formulation took the form of tablet B described in terms of composition and production in section 5.1 in the experimental section in WO 2005/060940 and which had then been coated, with the following composition of the coating (in mg/tablet):

Hydroxypropylmethylcellulose 15 cp	1.5 mg
Polyethylene glycol 3350	0.5 mg
Titanium dioxide	0.485 mg
Iron oxide red	0.015 mg

Exemplary formulation 1:

Active ingredient melt in PEG 6000 comprising active ingredient (I) in thermodynamically metastable crystal modification:

Active ingredient (I), micronized (MOD 1)	200 g
Polyethylene glycol 6000	1.800 g
	2.000 g

Production:

Polyethylene glycol is melted in a heatable reaction vessel (with stirrer and temperature sensor). After a temperature of about 210°C is reached, the micronized active ingredient (I) is added and heating is continued. After a temperature of 220-230°C is reached, the clear melt is discharged into foils and these are cooled with the aid of dry ice. Grating is followed by comminution in an impact mill to result in a product in powder form.

In vitro release (non-sink conditions) of exemplary formulation 1 (active ingredient dose 20 mg):

Time [min]	15	30	60	90
Release [%]	48	71	82	87

(USP paddle, 75 rpm, 900 ml of acetate buffer of pH 4.5)

It is clear that exemplary formulation 1 displays a distinctly increased solubility (supersaturation) compared with micronized active ingredient (I) (comparison 1.1). A solubility higher by a factor of 2 is detectable after 1 hour.

Exemplary formulation 2:

Melt extrudate with hydroxypropylcellulose comprising amorphous active ingredient (I):

Active ingredient (I), micronized (MOD 1)	450 g
Hydroxypropylcellulose (type HPC-M, Nisso)	3900 g
Xylitol	900 g
	5250 g

Production:

Micronized active ingredient (I), hydroxypropylcellulose and xylitol are mixed and processed in a twin screw extruder (Leistritz Micro 18 PH) with a die diameter of 2 mm. The mixture is extruded with a throughput of about 1 kg/h and the following temperatures of the heating zones: 20°C (zone 1), 100°C (zone 2), 174°C (zone 3) and 194°C (zones 4-8 and die outlet). The resulting extrudate strand is cut into pieces about 1 mm in size and then ground in an impact mill.

In vitro release (non-sink conditions) of exemplary formulation 2 (active ingredient dose 20 mg; sieve fraction < 315 µm):

Time [min]	15	30	60	90
Release [%]	36	66	85	90

(USP paddle, 75 rpm, 900 ml of acetate buffer of pH 4.5)

It is clear that exemplary formulation 2 displays a distinctly increased solubility (supersaturation) compared with micronized active ingredient (I) (comparison 1.1). A solubility higher by a factor of 2.1 is detectable after 1 hour.

Exemplary formulation 3:

Melt extrudate with polyvinylpyrrolidone comprising amorphous active ingredient (I):

Active ingredient (I), micronized (MOD 1)	220 g
Polyvinylpyrrolidone (Kollidon 25, BASF)	1985 g
Xylitol	245 g
	2450 g

Production:

Micronized active ingredient (I), polyvinylpyrrolidone and xylitol are mixed and processed in a twin screw extruder (Leistritz Micro 18 PH) with a die diameter of 2 mm. The mixture is extruded with a throughput of about 1 kg/h and the following temperatures of the heating zones: 20°C (zone 1), 100°C (zone 2), 180°C (zone 3) and 200°C (zones 4-8 and die outlet). The resulting extrudate strand is cut into pieces about 1 mm in size and then ground in an impact mill.

In vitro release of exemplary formulation 3 (active ingredient dose 20 mg; sieve fraction < 315 µm):

Time [min]	15	30	60	90
Release [%]	66	93	97	97

(USP paddle, 75 rpm, 900 ml of acetate buffer of pH 4.5)

It is clear that exemplary formulation 3 displays a distinctly increased solubility (supersaturation) compared with micronized active ingredient (I) (comparison 1.1). A solubility higher by a factor of 2.4 is detectable after 1 hour.

Exemplary formulation 4:

Tablets comprising active ingredient (I) in metastable crystal modification in the form of a PEG melt

Composition for 10 mg active ingredient (I) containing tablets (mg/tablet):

Active ingredient (I)-PEG 6000 melt (see Example 1)	100 mg *
Microcrystalline cellulose	270 mg
Mannitol (Pearlitol SD 200, Roquette)	200 mg
Croscarmellose (Ac-Di-Sol, FMC)	20 mg
Colloidal silicon dioxide (Aerosil 200, Degussa)	4 mg
Magnesium stearate	6 mg
	600 mg

(* Amount is adapted according to the current active ingredient content; compensating substance is microcrystalline cellulose)

Production:

An active ingredient (I)-PEG melt is produced as described in Example 1. After sieving (0.63 mm), the further excipients (see above table) are admixed, and this mixture is compressed in a tablet press to tablets in oblong format 17 × 7 mm with a flexural strength of about 40 N.

In vitro release (non-sink conditions) of exemplary formulation 4 (active ingredient dose 20 mg; 2 tablets/vessel):

Time [min]	15	30	60	90
Release [%]	65	78	88	93

(USP paddle, 75 rpm, 900 ml of acetate buffer of pH 4.5)

It is clear that exemplary formulation 4 displays a distinctly increased solubility (supersaturation) compared with micronized active ingredient (I) (comparison 1.1). A solubility higher by a factor of 2.1 is detectable after 1 hour.

Exemplary formulation 5:

Tablets comprising amorphous active ingredient (I) in the form of an HPC melt extrudate

Composition for 10 mg active ingredient (I) containing tablets (mg/tablet):

Active ingredient (I)-HPC extrudate (see Example 2)	117 mg *
Microcrystalline cellulose	253 mg
Lactose (Tablettose, Meggle)	200 mg
Croscarmellose (Ac-Di-Sol, FMC)	20 mg
Colloidal silicon dioxide (Aerosil 200, Degussa)	4 mg
Magnesium stearate	6 mg
	600 mg

(* Amount is adapted according to the current active ingredient content; compensating substance is microcrystalline cellulose)

Production:

An active ingredient (I)-HPC melt is produced as described in Example 2. After sieving (0.4 mm), the further excipients (see above table) are admixed, and this mixture is compressed in a tablet press to tablets in oblong format 17 × 7 mm with a flexural strength of about 40 N.

In vitro release (non-sink conditions) of exemplary formulation 5 (active ingredient dose 20 mg; 2 tablets/vessel):

Time [min]	15	30	60	90
Release [%]	100	101	101	101

(USP paddle, 75 rpm, 900 ml of acetate buffer of pH 4.5)

It is clear that exemplary formulation 5 displays a distinctly increased solubility (supersaturation) compared with micronized active ingredient (I) (comparison 1.1). A solubility which is higher by a factor of 2.5 is detectable after 1 hour.

Exemplary formulation 6:

Granules produced by the dissolving method with polyvinylpyrrolidone containing active ingredient (I) in amorphous form:

Active ingredient (I), micronized (MOD 1)	4.0 g
Polyvinylpyrrolidone 25	28.0 g
Glacial acetic acid (acetic acid pure)	140.0 g
	172.0 g

Production:

Active ingredient (I) is dissolved in glacial acetic acid at a temperature of about 90 – 100°C in a rotary evaporator, and the solvent is then distilled out in vacuo. The remaining mass is coarsely comminuted and transferred into a vacuum drying oven. Drying takes place in vacuo at a temperature of 100 – 120°C for about 48 hours. The granules are ground in a mortar and sieved (< 1 mm).

In vitro release (non-sink conditions) of exemplary formulation 6 (active ingredient dose 20 mg):

Time [min]	15	30	60	90
Release [%]	79	82	83	83

(USP paddle, 75 rpm, 900 ml of acetate buffer of pH 4.5)

It is clear that exemplary formulation 6 displays a distinctly increased solubility (supersaturation) compared with micronized active ingredient (I) (comparison 1.1). A solubility which is higher by a factor of 2 is detectable after 1 hour.

Bioavailability

1) Comparative study in rats (3 mg/kg)

The bioavailability was investigated by administering 3 mg/kg active ingredient (I) in each case to male Wistar rats:

a) in the form of exemplary formulation 1 (suspended in water)

b) in the form of exemplary formulation 2 (suspended in water)

c) in the form of exemplary formulation 3 (suspended in water)

d) in the form of the micronized crystalline active ingredient in thermodynamically stable crystal modification I (suspended in 0.5% strength aqueous methylhydroxyethylcellulose (proprietary name: Tylose MH 300))

The corresponding pharmacokinetic parameters are listed in the table below (geometric means):

	AUC (0-24) [mg·h/l]	AUC $(0\text{-}24)_{norm}$ [kg·h/l]	C_{max} [mg/l]	$C_{max,\ norm}$ [kg/l]
Exemplary formulation 1	2.45	0.818	0.721	0.240
Exemplary formulation 2	2.70	0.900	0.996	0.332
Exemplary formulation 3	2.79	0.931	0.961	0.320
Crystalline, micronized active ingredient	0.762	0.254	0.222	0.074

Result:

Exemplary formulation 1 comprising active ingredient (I) in thermodynamically metastable crystal modification and exemplary formulations 2 and 3 comprising active ingredient (I) in amorphous form display a distinctly improved bioavailability compared with administration of the crystalline micronized active ingredient in the thermodynamically stable crystal modification I (factor of 3.2 for exemplary formulation 1; factor 3.5 for exemplary formulation 2 and factor of 3.7 for exemplary formulation 3).

2) Comparative study in dogs (150 mg/kg)

The bioavailability was investigated by crossover administration of 150 mg/kg active ingredient (I) in each case to 4 Beagle dogs:

e) in the form of exemplary formulation 1 (suspended in water)

f) in the form of the micronized crystalline active ingredient in crystal modification I (suspended in aqueous methylhydroxyethylcellulose (0.5%) (proprietary name: Tylose MH 300) with addition of 2% Solutol HS 15)

The corresponding pharmacokinetic parameters are listed in the table below (geometric means):

	AUC (0-24) [mg·h/l]	AUC $(0\text{-}24)_{norm}$ [kg·h/l]	C_{max} [mg/l]	$C_{max,\ norm}$ [kg/l]
Exemplary formulation 1	44.5	0.297	7.54	0.050
Crystalline, micronized active ingredient	12.2	0.081	2.22	0.015

Result:

Exemplary formulation 1 comprising active ingredient (I) in thermodynamically metastable crystal modification displays a distinctly improved bioavailability compared with administration of the crystalline micronized active ingredient in the thermodynamically stable crystal modification I (factor of 3.6).

3) Comparative study in dogs (20 mg per dog equivalent to about 2 mg/kg)

The bioavailability was investigated by crossover administration of 20 mg (that is about 2 mg/kg) active ingredient (I) in the form of the following tablet formulations in each case to 4 female Beagle dogs:

a) in the form of comparative formulation 1.2 (administration of in each case 2 tablets/dog)

b) in the form of exemplary formulation 4 (administration of in each case 2 tablets/dog)

The corresponding pharmacokinetic parameters are listed in the table below (geometric means):

	AUC (0-24) [mg·h/l]	AUC $(0\text{-}24)_{norm}$ [kg·h/l]	C_{max} [mg/l]	$C_{max,\ norm}$ [kg/l]
Comparative formulation 1.2	1.84	0.938	0.447	0.228
Exemplary formulation 4	2.71	1.39	0.665	0.341

Result:

Exemplary formulation 4 comprising active ingredient (I) in thermodynamically metastable crystal modification displays an improved bioavailability compared with comparative formulation 1.2 (tablet comprising crystalline micronized active ingredient (I) in the thermodynamically stable crystal modification I) (factor of about 1.5).

Claims

1. Solid pharmaceutical dosage form which can be administered orally, comprises 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (I) and has rapid release, characterized in that

   (a) it comprises active ingredient (I) in amorphous form or thermodynamically metastable crystal modification, and

   (b) 80% of active ingredient (I) are released in a period of less than 2 hours in USP release method with apparatus 2 (paddle).

2. Pharmaceutical dosage form according to Claim 1, characterized in that 80% of active ingredient (I) are released in a period not exceeding 1 hour in USP release method with apparatus 2 (paddle).

3. Pharmaceutical dosage form according to Claim 1 or 2, characterized in that this dosage form shows supersaturation behaviour in in vitro release tests under non-sink conditions compared with micronized active ingredient (I) in the thermodynamically stable crystal modification I.

4. Pharmaceutical dosage form according to Claim 3, characterized in that this dosage form releases, in in vitro release tests in USP release method with apparatus 2 (paddle) under non-sink conditions in 900 ml of acetate buffer at pH 4.5 without surfactant addition with a speed of rotation of the stirrer of 75 rpm in a period of one hour with a total amount of active ingredient to be tested of 20 mg of active ingredient (I), at least an amount of active ingredient (I) which is higher by a factor of 1.5 than 20 mg of micronized active ingredient (I) in the thermodynamically stable crystal modification I.

5. Pharmaceutical dosage form according to Claim 1 to 4, characterized in that the active ingredient (I) is amorphized or converted into a thermodynamically metastable crystal modification by a dissolving method.

6. Pharmaceutical dosage form according to Claim 5, characterized in that acetic acid is employed as solvent, and one or more suitable excipients, preferably polyvinylpyrrolidone, are added, and the active ingredient (I) is present in a concentration of from 0.1 to 30% in the mixture resulting from the dissolving method.

7. Pharmaceutical dosage form comprising granules comprising the active ingredient (I)

according to Claim 5.

8. Pharmaceutical dosage form according to Claim 7 in the form of a capsule, of a sachet or of a tablet.

9. Process for producing a pharmaceutical dosage form according to Claim 5 to 8, characterized in that a mixture comprising the active ingredient (I) is prepared with the aid of the dissolving method and is ground, mixed with further pharmaceutically suitable excipients and then packed as sachet or capsule or, after mixing with tabletting excipients, compressed preferably by direct tabletting to tablets, which can finally be coated.

10. Pharmaceutical dosage form according to Claim 1 to 4, characterized in that the active ingredient (I) is amorphized or converted into a thermodynamically metastable crystal modification by a melting method.

11. Pharmaceutical dosage form according to Claim 10, characterized in that one or more suitable excipients, preferably a polyethylene glycol, are employed in the melting method, and the active ingredient (I) is present in a concentration of from 0.1 to 30% in the mixture resulting after the melting process.

12. Pharmaceutical dosage form comprising an active ingredient melt according to Claim 10 comprising the active ingredient (I).

13. Pharmaceutical dosage form according to Claim 12 in the form of a capsule, of a sachet or of a tablet.

14. Process for producing a pharmaceutical dosage form according to Claim 10 to 13, characterized in that a mixture comprising the active ingredient (I) is prepared with the aid of the melting method and is ground, mixed with further pharmaceutically suitable excipients and then packed as sachet or capsule or, after mixing with tabletting excipients, compressed preferably by direct tabletting to tablets, which can finally be coated.

15. Pharmaceutical dosage form according to Claim 1 to 4, characterized in that the active ingredient (I) is amorphized or converted into a thermodynamically metastable crystal modification by melt extrusion.

16. Pharmaceutical dosage form according to Claim 15, characterized in that hydroxypropylcellulose (HPC) or polyvinylpyrrolidone (PVP) is employed as polymer in the melt extrusion, the proportion of polymer in the melt extrudate is at least 40%, and the

active ingredient (I) is present in the melt extrudate in a concentration of from 0.1 to 20%.

17. Pharmaceutical dosage form according to either of Claims 15 or 16, characterized in that at least one pharmaceutically suitable substance is added in a concentration of from 0.2 to 40% as plasticizer for the polymer and/or for depressing the melting point of the active ingredient (I).

18. Pharmaceutical dosage form according to Claim 17, characterized in that the pharmaceutically suitable additive is a sugar alcohol.

19. Pharmaceutical dosage form comprising a melt extrudate according to Claim 15 comprising the active ingredient (I).

20. Pharmaceutical dosage form according to Claim 19 in the form of a capsule, of a sachet or of a tablet.

21. Process for producing a pharmaceutical dosage form according to Claim 15 to 20, characterized in that an extrudate comprising the active ingredient (I) is produced by melt extrusion and is ground, mixed with further pharmaceutically suitable excipients and then packed as sachet or capsule or, after mixing with tabletting excipients, compressed preferably by direct tabletting to tablets, which can finally be coated.

22. Multiparticulate pharmaceutical dosage form according to any of Claims 1 to 6, 10 to 12 and 15 to 19.

23. Multiparticulate pharmaceutical dosage form according to Claim 22, characterized in that the diameter of the particles is from 0.5 to 3.0 mm.

24. Pharmaceutical dosage form comprising multiparticulate pharmaceutical dosage forms according to either of Claims 22 or 23.

25. Pharmaceutical dosage form according to Claim 24 in the form of a capsule, of a sachet or of a tablet.

26. Process for producing a multiparticulate pharmaceutical dosage form as defined in any of Claims 22 to 25, characterized in that an extrudate strand comprising the active ingredient (I) is produced by melt extrusion and is cut.

27. Process according to Claim 26, characterized in that the shaped articles obtained after cutting the extrudate strand are rounded.

28. Process according to either of Claims 26 or 27, characterized in that the resulting shaped articles are coated.

29. Medicament comprising a solid pharmaceutical dosage form which can be administered orally and has a rapid release, as defined in Claim 1, of the active ingredient (I).

30. Use of a solid pharmaceutical dosage form which comprises the active ingredient (I) and has rapid release of active ingredient, as defined in Claim 1, for the prophylaxis, secondary prophylaxis and/or treatment of disorders.

31. Use of a solid pharmaceutical dosage form which comprises the active ingredient (I) and has rapid release, as defined in Claim 1, for producing a medicament for the prophylaxis, secondary prophylaxis and/or treatment of disorders.

32. Use according to Claim 30 or 31 for producing a medicament for the prophylaxis, secondary prophylaxis and/or treatment of thromboembolic disorders.

33. Use according to Claims 32 for the prophylaxis, secondary prophylaxis and/or treatment of myocardial infarction, angina pectoris, reocclusions and restenoses following angioplasty or aortocoronary bypass, stroke, transient ischaemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep vein thromboses.

34. Use of 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (I) for producing a pharmaceutical dosage form as defined in Claim 1.

35. Method for the prophylaxis, secondary prophylaxis and/or treatment of thromboembolic disorders by administering a solid pharmaceutical dosage form which can be administered orally, comprises the active ingredient (I) and has rapid release of active ingredient, as defined in Claim 1.