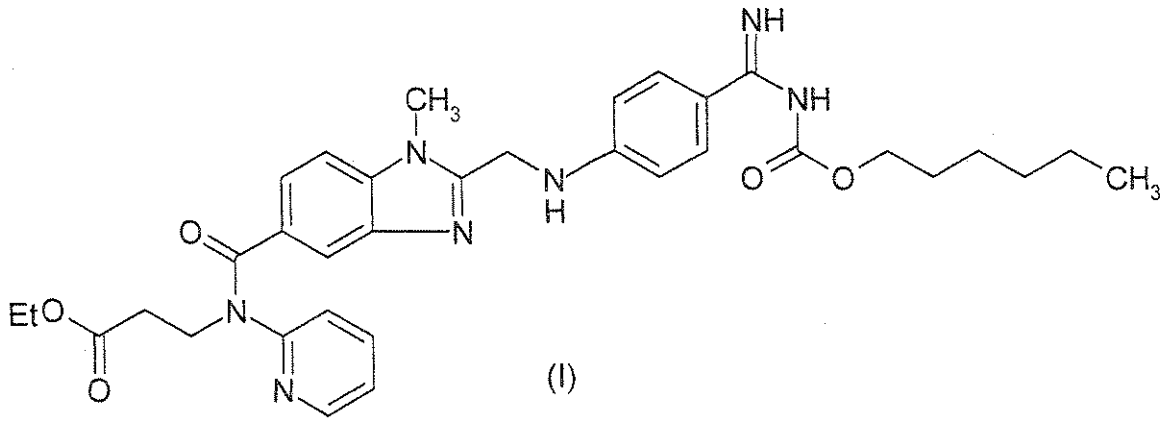
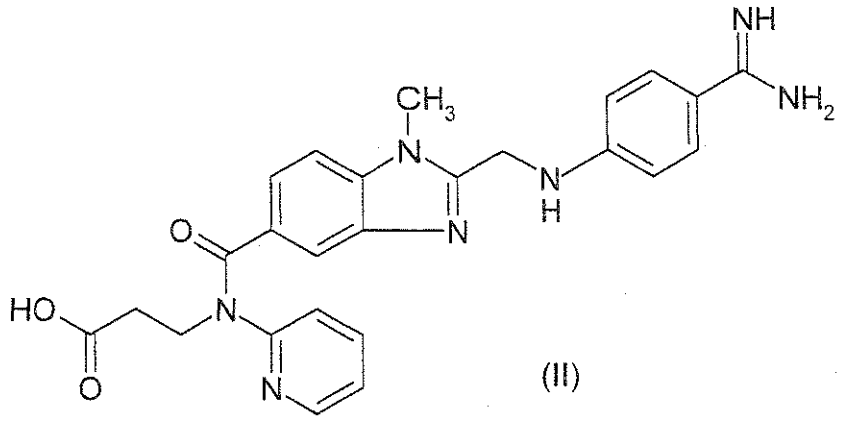
Polymorphs of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate

The invention relates to new polymorphs of the active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, processes for the preparation thereof and the use thereof as pharmaceutical compositions. This active substance with the chemical formula



(I)

is already known from WO 98/37075, wherein compounds with a thrombin-inhibiting and thrombin time-prolonging activity are disclosed, under the name 1-methyl-2-[*N*-[4-(*N*-n-hexyloxycarbonylamidino)phenyl]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-*N*-(2-pyridyl)-*N*-(2-ethoxycarbonylethyl)-amide. The compound of formula I is a double prodrug of the compound



(II)

i.e. the compound of formula I is only converted into the actual effective compound, namely the compound of formula II, in the body. The main fields of application of the compound of

chemical formula I are the post-operative prophylaxis of deep vein thrombosis and the prevention of stroke.

The aim of the invention is to provide new polymorphs of the compound of formula I having advantageous properties for pharmaceutical use.

The above-mentioned pharmacologically beneficial properties of the disubstituted bicyclic heterocycles disclosed in the prior art are the main prerequisite for effective use of the compounds as pharmaceutical compositions. An active substance must, however, also meet other requirements in order to be capable of being used as a pharmaceutical composition. These parameters are to a large extent connected with the physicochemical nature of the active substance.

Without being restricted thereto, examples of these parameters are the stability of effect of the starting substance under different ambient conditions, stability in the course of the preparation of the pharmaceutical formulation and stability in the final compositions of the pharmaceutical preparation. The pharmaceutical active substance used to prepare the pharmaceutical compositions should therefore have high stability, which should also be guaranteed even under different environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the active substance itself, breakdown products thereof, for example. In such cases the content of active substance found in the pharmaceutical formulations might be less than specified.

The absorption of moisture reduces the content of pharmaceutically active substance as a result of the increased weight caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from moisture during storage, e.g. by the addition of suitable drying agents or by storing the drug in an environment where it is protected from moisture. In addition, the uptake of moisture may reduce the content of pharmaceutically active substance during manufacture if the pharmaceutical substance is exposed to the environment without being protected from moisture in any way. Preferably, therefore, a pharmaceutically active substance should be only slightly hygroscopic.

As the crystal modification of an active substance is important to the reproducible active substance content of a preparation, there is a need to clarify as far as possible any existing

polymorphism of an active substance present in crystalline form. If there are different polymorphic modifications of an active substance, care must be taken to ensure that the crystalline modification of the substance does not change in the pharmaceutical preparation later produced from it. Otherwise, this could have a harmful effect on the reproducible potency of the drug.

Another criterion which may be of exceptional importance under certain circumstances depending on the choice of formulation or the choice of manufacturing process is the solubility of the active substance. If for example pharmaceutical solutions are prepared (e.g. for infusions), it is essential that the active substance should be sufficiently soluble in physiologically acceptable solvents. It is also very important for drugs which are to be taken orally that the active substance should be sufficiently soluble.

The problem of the present invention is to provide a pharmaceutically active substance which not only is characterised by high pharmacological potency but also satisfies the above-mentioned physicochemical requirements as far as possible.

Surprisingly it has now been found that the novel polymorphs of the compound of formula I (dabigatran etexilate) meet these requirements and have advantageous properties.

The invention therefore relates to the polymorphs of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate referred to as anhydrous form I, anhydrous form II and tetrahydrate. The invention also relates to pharmaceutical compositions containing at least one of the above-mentioned polymorphs as well as processes for preparing pharmaceutical compositions which are suitable for the prevention of venous thrombosis and stroke and which contain the polymorphs according to the invention.

In a first to third aspects, there are provided the three above-mentioned polymorphic forms of the active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, preferably in crystalline form, characterised by melting points of $T_{mp.}$ = 135 ± 3°C (anhydrous form I), $T_{mp.}$ = 150 ± 3°C (anhydrous form II) or $T_{mp.}$ = 90 ± 5°C (tetrahydrate) (determined by DSC; evaluation by peak maximum; heating rate: 10°C/min).

The DSC diagram of the anhydrous form I is characterised in that four other weakly endothermic signals can be observed at about 53, 75, 98 and 118°C. These signals can be attributed to fully reversible solid-to-solid phase transitions, i.e. in the temperature range between 53 – 75, 75 – 98, 98 – 118 and 118 – 135°C there are four other high temperature phases of the anhydrous form I.

In a fourth aspect, there is provided use of a compound as defined above for preparing a pharmaceutical composition with a thrombin time prolonging effect.

In a fifth aspect, there is provided use of a compound as defined above for preparing a pharmaceutical composition for the prevention of venous thromboses and stroke.

In a sixth aspect, there is provided a pharmaceutical composition containing a compound as defined above, optionally together with one or more inert carriers and/or diluents.

In a seventh aspect, there is provided a process for preparing a pharmaceutical composition as defined above, characterised in that by a non-chemical method a compound as defined above is incorporated in one or more inert carriers and/or diluents.

The disclosure also relates to the methods of selectively producing the three polymorphic forms as well as the modifications which may be obtained by these methods.

According to an eighth aspect, the anhydrous form I of ethyl 3-[2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate is obtained by

a) dissolving 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester base in ethyl acetate at reflux temperature,
b) cooling the solution to a temperature of about 30°C to 35°C and stirring for a further 60 minutes at this temperature,
c) cooling to about 15°C to 20°C and stirring for about another 60 minutes at this temperature,
d) suction filtering the precipitated crystals, washing them with ethyl acetate and
e) drying the product thus obtained at 40 to 50°C in a circulating air dryer.

According to a ninth aspect, the anhydrous form II of ethyl 3-[2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate is obtained by

a) combining 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester base with a little ethyl acetate,
b) heating the resulting suspension to a temperature of about 80°C, to obtain a clear solution,
c) refluxing the solution for about one hour,
d) filtering off the precipitated crystals and

e) drying the product thus obtained in the air.

According to a tenth aspect, the tetrahydrate of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate is obtained by

a) dissolving ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base in acetone/water (80 : 20) with shaking, at a temperature of about 60°C,
b) cooling the solution to a temperature of about 30°C and filtering it into a sealable vessel,
c) cooling the sealed vessel containing the solution to a temperature of about -9°C and leaving it for about 30 minutes at this temperature,
d) adding a mixture of acetone and water (80 : 20) which has been pre-cooled to -9°C and shaking the mixture,
e) suction filtering the precipitated crystals and washing them with a mixture of acetone and water (80 : 20) which has been cooled to -9°C, and
f) drying the product thus obtained in the air at ambient temperature.

According to an eleventh aspect, there is provided ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, anhydrous form I, obtainable by the process as defined above.

According to a twelfth aspect, there is provided ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, anhydrous form II, obtainable by the process as defined above.

According to a thirteenth aspect, there is provided ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate tetrahydrate, obtainable by the process as defined above.

The crystalline forms of 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester according to the invention were investigated in more detail by x-ray powder diffraction. The diagrams obtained are shown in Figures 1 to 3.

Tables 1 to 3 that follow list the data obtained in this analysis:

Table 1: X-ray powder reflections (up to 30 ° 2 Θ) and intensities (standardised) of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate (anhydrous form I)

2 Θ [°]	d [Å]	I/I_0 [%]
3.39	26.07	1
4.31	20.51	1
4.87	18.12	10
5.62	15.70	1
7.28	12.14	1
7.43	11.88	1
8.82	10.02	69
10.46	8.45	100
11.56	7.65	25
12.92	6.84	11
13.25	6.67	32
13.78	6.42	50
14.12	6.27	12
14.36	6.16	9
14.67	6.03	5
15.49	5.72	63
16.61	5.33	28
17.76	4.99	4
18.03	4.92	12
18.93	4.69	4
20.12	4.41	65
20.79	4.27	6
21.54	4.12	46
22.15	4.01	15
22.72	3.91	6
23.28	3.82	11
23.51	3.78	11
23.92	3.72	18
24.18	3.68	8
24.58	3.62	10
25.18	3.53	8
25.70	3.46	69

26.75	3.33	10
27.69	3.22	21
28.27	3.15	14
28.80	3.10	9
29.41	3.03	2
30.16	2.96	2

Table 2: X-ray powder reflections (up to 30 ° 2 Θ) and intensities (standardised) of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate (anhydrous form II)

2 Θ [°]	**d [Å]**	**I/I_0 [%]**
7.55	11.70	6
8.25	10.71	24
8.50	10.40	18
9.06	9.75	44
10.04	8.80	86
11.08	7.98	5
11.99	7.37	33
12.17	7.27	51
13.11	6.75	4
13.77	6.42	19
14.04	6.30	5
14.67	6.04	3
14.98	5.91	13
15.10	5.86	11
15.93	5.56	3
16.34	5.42	20
16.52	5.36	55
17.03	5.20	68
17.63	5.03	47
17.99	4.93	7
18.17	4.88	5
18.74	4.73	6
19.00	4.67	19
19.23	4.61	6
19.69	4.51	17
20.02	4.43	53

20.43	4.34	11
20.63	4.30	48
20.92	4.24	3
21.24	4.18	7
21.39	4.15	10
21.75	4.08	4
22.15	4.01	9
22.41	3.96	6
22.77	3.90	17
23.02	3.86	6
23.17	3.84	10
23.70	3.75	10
23.92	3.72	19
24.49	3.63	13
24.69	3.60	15
24.89	3.57	12
25.17	3.53	26
25.66	3.47	6
25.88	3.44	10
26.36	3.38	100
26.67	3.34	21
26.85	3.32	15
27.96	3.19	7
28.24	3.16	7
28.52	3.13	5
28.79	3.10	9
29.81	2.99	5
30.11	2.97	9

Table 3: X-ray powder reflections (up to 30 ° 2 Θ) and intensities (standardised) of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate (tetrahydrate)

2 Θ [°]	d [Å]	I/I_0 [%]
4.67	18.91	100
6.63	13.32	2
8.10	10.90	45
9.36	9.44	20
9.82	9.00	52
10.55	8.38	2
11.18	7.91	32
11.91	7.42	2
12.57	7.04	10
13.01	6.80	9
13.52	6.54	5
14.05	6.30	23
14.59	6.06	18
15.52	5.70	8
15.99	5.54	10
16.31	5.43	8
16.56	5.35	14
16.94	5.23	21
17.76	4.99	16
18.62	4.76	33
18.93	4.68	26
19.69	4.51	10
20.10	4.42	15
20.56	4.32	52
20.86	4.26	7
21.38	4.15	19
21.83	4.07	24
22.51	3.95	22
23.10	3.85	34
24.04	3.70	33
24.74	3.60	83
25.23	3.53	8
25.58	3.48	12
26.35	3.38	9
26.96	3.30	21

28.31	3.15	9
28.87	3.09	2
29.32	3.04	5
23.92	3.72	19
24.49	3.63	13
24.69	3.60	15
24.89	3.57	12
25.17	3.53	26
25.66	3.47	6
25.88	3.44	10
26.36	3.38	100
26.67	3.34	21
26.85	3.32	15
27.96	3.19	7
28.24	3.16	7
28.52	3.13	5
28.79	3.10	9
29.81	2.99	5
30.11	2.97	9

In the preceding Tables 1 to 3 the value "2 Θ [°]" denotes the angle of diffraction in degrees and the value "d [Å]" denotes the distances in Å determined between the lattice planes.

The x-ray powder diagrams were recorded, within the scope of the present invention, using a STOE STADI P diffractometer fitted with a location-sensitive detector (OED) and a Cu anode as the x-ray source and a primary monochromator ($CuK_{\alpha 1}$ radiation, λ = 1.54056 Å, 40 kV, 40 mA).

Brief description of the Figures

Figures 1 to 3 show the X-ray powder diffractograms of the three crystalline forms of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate.

Figures 4 to 6 show the thermoanalysis (DSC/TG) for the three crystalline forms of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate.

Examples

The melting points were determined by DSC, using an apparatus obtained from Mettler-Toledo (type: DSC 821). The melting temperature used was the peak temperature of the corresponding melting peak in the DSC diagram. The accuracy of the melting points specified is about ± 3°C, or ± 5°C in the case of the tetrahydrate, as the tetrahydrate, as it melts, releases the crystal water locked in the crystal lattice and produces a greatly propagated endothermic signal.

The starting compound 3-[(2-{[4-(amino-hexyloxycarbonylimino-methyl)-phenylamino]-methyl}-1-methyl-*1H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester may for example be prepared as described in International Application WO 98/37075, Example 113.

Example 1

3-[(2-{[4-(amino-hexyloxycarbonylimino-methyl)-phenylamino]-methyl}-1-methyl-*1H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester (anhydrous form I)

1500 g (2.389 mol) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base (prepared as described in WO 98/37075) are dissolved in 12 litres of ethyl acetate at reflux temperature. The solution is cooled to 30-35°C. After a few minutes the product began to crystallise out. It was stirred for another 60 minutes at 30-35°C and for another 60 minutes at 15-20°C, then the precipitate was suction filtered, washed with 3 litres of ethyl acetate and dried at 40-50°C in the circulating air dryer.

Yield: 88.5 % of theory

Example 2

3-[(2-{[4-(amino-hexyloxycarbonylimino-methyl)-phenylamino]-methyl}-1-methyl-*1H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester (anhydrous form II)

2.0 g of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base (prepared as described in WO 98/37075) were combined with 10 ml of ethyl acetate. The resulting suspension was heated to 80°C (substance goes into solution) and refluxed for 1 hour. After

about 30 minutes at reflux temperature form II begins to crystallise. Then the precipitated substance was filtered off and dried in the air.

Yield: 85 % of theory

Example 3

3-[(2-{[4-(amino-hexyloxycarbonylimino-methyl)-phenylamino]-methyl}-1-methyl-*1H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester tetrahydrate

0.5 g of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base (prepared as described in WO 98/37075) are dissolved in 5 ml of a mixture of acetone/water = 80 : 20 at 60°C with agitation. The solution was cooled to about 30°C and filtered through a filter, for example through a Sartorius Minisart Filter SRP 15 into a 10 ml glass vial, and the flask was sealed. The solution was then cooled in an ice/ethanol mixture to about -9°C. The substance began to crystallise out by itself. After about 30 minutes in the ice bath, about 3 ml of a mixture of acetone and water (80 : 20) cooled to -9°C were added, the mixture was agitated and then suction filtered through a filter, for example a Schleicher & Schüll round filter no. 595.

It was rinsed with approximately another 5 ml of a mixture of acetone and water (80 : 20) cooled to -9°C. The substance filtered off was scraped off the round filter into a crystallising dish and dried in the air at ambient temperature.

Yield: 97 % of theory

Example 4

Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

Active substance	75.0 mg
Mannitol	50.0 mg
water for injections	ad 10.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

Example 5

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
water for injections	ad 2.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

To produce the solution ready for use, the product is dissolved in water for injections.

Example 6

Tablet containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 9 mm.

Example 7

Tablet containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 12 mm.

Example 8

Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Dried maize starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

Example 9

Capsules containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Dried maize starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 0 hard gelatine capsules in a capsule filling machine.

Example 10

Suppositories containing 100 mg of active substance

1 suppository contains:

Active substance	100.0 mg
Polyethyleneglycol (M.W. 1500)	600.0 mg
Polyethyleneglycol (M.W. 6000)	460.0 mg
Polyethylenesorbitan monostearate	840.0 mg
	2,000.0 mg

Example 11

	percentage composition				per capsule [mg]	per capsule [mg]
	core material	insulating layer	active substance layer	total		
tartaric acid	61.3	-	-	61.3	176.7	353.4
gum arabic	3.1	2.8		5.9	17.0	34.0
talc	-	5.6	3.2	8.8	25.4	50.7
hydroxypropylcellulose	-	-	4.0	4.0	11.5	23.1
active substance (in relation to the base)	-	-	20.0	20.0	50.0	100.0
total				100.0	288.3	576.5

Example 12

	percentage composition				per capsule [mg]	per capsule [mg]
	core material	insulating layer	active substance layer	total		
tartaric acid	38.5	-	-	38.5	55.5	166.5
gum arabic	1.9	1.7		3.6	5.2	15.6
talc	-	3.5	6.4	9.9	14.3	42.8
hydroxypropylcellulose	-	-	8.0	8.0	11.5	34.6
active substance (in relation to the base)	-	-	40.0	40.0	50.0	150.0
total				100.0	144.2	432.5

The preparation and structure of the pellets according to Example 11 and 12 are described in detail in WO 03/074056.

Patent Claims

1. ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate in crystalline form, characterised by a melting point of $T_{mp.}$ = 135 ± 3°C (anhydrous form I) (determined by DSC; evaluated by peak maximum; heating rate: 10°C/min).

2. ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate in crystalline form, characterised by a melting point of $T_{mp.}$ = 150 ± 3°C (anhydrous form II) (determined by DSC; evaluated by peak maximum; heating rate: 10°C/min).

3. ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate tetrahydrate in crystalline form, characterised by a melting point of $T_{mp.}$ = 90 ± 5°C with simultaneous release of the crystal water locked into the crystal lattice (tetrahydrate) (determined by DSC; evaluated by peak maximum; heating rate: 10°C/min).

4. Use of a compound according to one of claims 1 to 3 for preparing a pharmaceutical composition with a thrombin time prolonging effect.

5. Use of a compound according to one of claims 1 to 3 for preparing a pharmaceutical composition for the prevention of venous thromboses and stroke.

6. Pharmaceutical composition containing a compound according to one of claims 1 to 3, optionally together with one or more inert carriers and/or diluents.

7. Process for preparing a pharmaceutical composition according to claim 6, characterised in that by a non-chemical method a compound according to one of claims 1 to 3 is incorporated in one or more inert carriers and/or diluents.

8. Process for preparing the anhydrous form I of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, characterised in that

a) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base is dissolved in ethyl acetate at reflux temperature,
b) the solution is cooled to a temperature of about 30°C to 35°C and stirred for another 60 minutes at this temperature,
c) cooled to about 15°C to 20°C and stirred for roughly another 60 minutes at this temperature,
d) the precipitated crystals are suction filtered, washed with ethyl acetate and
e) the product thus obtained is dried at 40 to 50°C in the circulating air dryer.

9. Process for preparing the anhydrous form II of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, characterised in that

a) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base is combined with a little ethyl acetate,
b) the suspension thus obtained is heated to a temperature of about 80°C, whereupon a clear solution is formed,
c) the solution is refluxed for about one hour,
d) the crystals precipitated are filtered off and
e) the product thus obtained is dried in the air.

10. Process for preparing the tetrahydrate of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, characterised in that

a) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base is dissolved in acetone/water (80 : 20) with agitation at a temperature of about 60°C,

b) the solution is cooled to a temperature of about 30°C and filtered into a sealable vessel,

c) the sealed vessel containing the solution is cooled to a temperature of about -9°C and left for about 30 minutes at this temperature,

d) a mixture of acetone and water (80 : 20) pre-cooled to -9°C is added and the mixture is shaken,

e) the crystals precipitated are suction filtered and washed with a mixture of acetone and water (80 : 20) cooled to -9°C and

f) the product thus obtained is dried in the air at ambient temperature.

11. ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, anhydrous form I, obtainable by the process according to claim 8.

12. ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, anhydrous form II, obtainable by the process according to claim 9.

13. ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate tetrahydrate, obtainable by the process according to claim 10.

Abstract

The invention relates to new polymorphs of the active substance 3-[(2-{[4-(hexyloxy-carbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester, the preparation thereof and the use thereof as pharmaceutical compositions.