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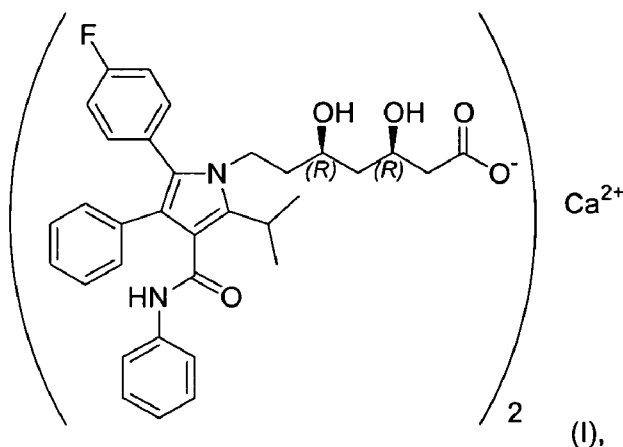
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[Continued on next page]

(54) Title: A METHOD OF INDUSTRIAL PRODUCTION OF AN AMORPHOUS FORM OF ATORVASTATIN WITH A HIGH SPECIFIC SURFACE AREA AND ITS USE IN A DOSAGE FORM



(57) Abstract: The invention deals with an amorphous form of the hemicalcium salt of (3R,5R) 7-[3-phenyl-4-phenylcarbamoyl-2-(4-fluorophenyl)-5-isopropylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid (atorvastatin of formula I) with a high specific surface area, based on controlled precipitation, and its use in a medical dosage form. (I)



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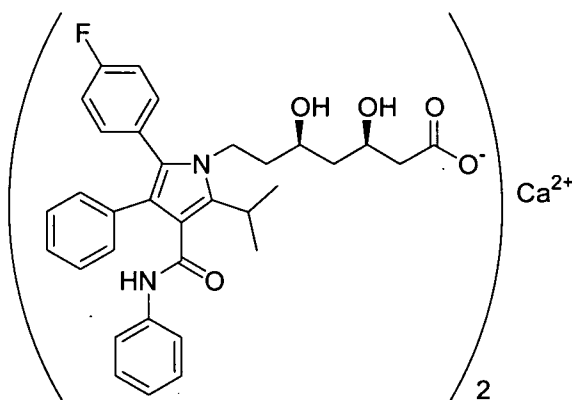
A method of industrial production of an amorphous form of atorvastatin with a high specific surface area and its use in a dosage form

5 Technical Field

The present invention deals with an amorphous form of the hemicalcium salt of (3*R*,5*R*) 7-[3-phenyl-4-phenylcarbamoyl-2-(4-fluorophenyl)-5-isopropylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid (atorvastatin of formula I) with a high specific surface area, based on
10 controlled precipitation, and its use in a medicament dosage form.

Background Art

Atorvastatin of formula I is an important representative of hypolipidemic and hypocholesteric
15 drugs and is the object of a number of patents.



(I)

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Depending on the mode of carrying out atorvastatin is obtained in one of the crystalline forms, or as amorphous atorvastatin. The original patents US 4 681 893 and US 5 273 995 are silent about the form of the substance obtained in accordance with these patents. Later patents US 5 969 156 and US 6 121 461, describing crystalline forms of atorvastatin, declare that the
25 substance obtained in accordance with the original patents was amorphous. The EP 839,132

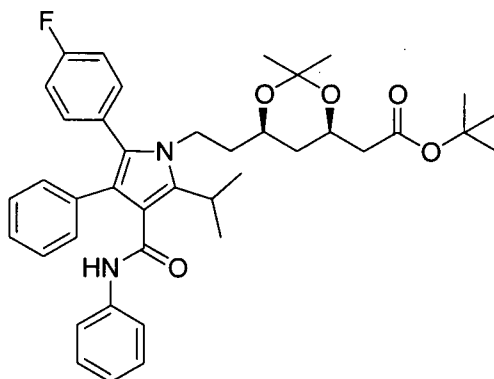
patent, describing a new method of obtaining the amorphous form of atorvastatin by dissolution of crystalline atorvastatin and its drying repeats again that the original patents provide amorphous atorvastatin; however, their procedure is difficult to reproduce. The possibility of obtaining amorphous atorvastatin by dissolving crystalline atorvastatin in a suitable solvent, evaporating and grinding, described in EP 0 839 132, has the drawback of a considerable heat stress of the substance leading to the formation of various decomposition products, which results in unacceptable purity of amorphous atorvastatin obtained this way.

Egis' application (WO 01/28999 A1) describes preparation of amorphous atorvastatin by crystallization from lower alcohols; however, when repeating the procedure, we obtained partially crystalline samples.

Another attractive possibility of obtaining amorphous atorvastatin is spray drying of a solution of atorvastatin in a suitable solvent using an inert carrier gas, e.g. nitrogen, described in CZ patent application No. 2005-94. A disadvantage of this method is the need to purchase high-cost spray-drying equipment and considerable consumption of the inert gas.

Recently, a great number of various crystalline modifications have been protected by patents (e.g. US 5 969 156; US 6 121 461; WO 01/36384 A1; WO 03/004470); in spite of this, for some applications (EP 0 839 132) the use of the amorphous form of atorvastatin is suitable. The original patent, US 4 681 893, already mentioned the possibility of purification of an unsuitable substance by dissolution in ethyl acetate and precipitation with hexane. In substantially the same way, using various solvents for dissolution of atorvastatin and anti-solvents for precipitation, amorphous atorvastatin is also obtained in accordance with applications of Lek (WO 01/42209 A1), Ranbaxy (WO 00/71116 A1), Biocon (WO 02/057228 A1), Cadila (WO 02/08367 A1; WO 02/08368 A1) and Morepen (WO 03/018547 A2). In some cases the opposite possibility is also mentioned when into a solvent in which atorvastatin does not dissolve at all or in a limited way only (anti-solvent) a solution of atorvastatin in a suitable solvent is added dropwise (WO 02/057228 A1, CZ 2002-413). In some cases a concentrated solution of atorvastatin in a suitable solvent is not obtained by dissolution of crystalline or semi-crystalline atorvastatin, but is obtained directly in the last reaction stage of atorvastatin production (CZ 2002-413, WO 03/018547 A2). In our patent (CZ 296967; WO 2003/068739; EP 1 470 106; US 7 208 608; AU 2003/213986; UA 76826) we

started, in the production of a solution of atorvastatin in a suitable solvent, from (3*R*,5*R*) tert-butyl (6-{2-[3-phenyl-4-phenylcarbamoyl-2-(4-fluorophenyl)-5-isopropylpyrrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetate (II).



(II)

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Accordingly, the precipitation method discussed above appears to be the most convenient industrially feasible method. However, a considerable disadvantage of the above mentioned procedures of obtaining amorphous atorvastatin resides in the fact that in the production of larger amounts (in the order of kilograms) homogeneity of the obtained amorphous atorvastatin is difficult to achieve. Moreover, in some cases a poorly filterable product is obtained or residual solvents are hard to remove from the final product. Most of these disadvantages have been solved by Czech patent application CZ 2003-987 (or in Czech utility model No. CZ 13296 U), protecting a method based on precipitation of amorphous atorvastatin by forcing a solution of atorvastatin in a suitable solvent into a suitable anti-solvent under pressure of a suitable gas with the use of a special device, the principle of which was also part of the above mentioned patent application. Although atorvastatin produced this way is suitable for currently produced medicament dosage forms, it has turned out not to provide a sufficient release rate of the active substance for other types of dosage forms, which may result in a slower onset of the effect or lower bioavailability of the drug containing atorvastatin.

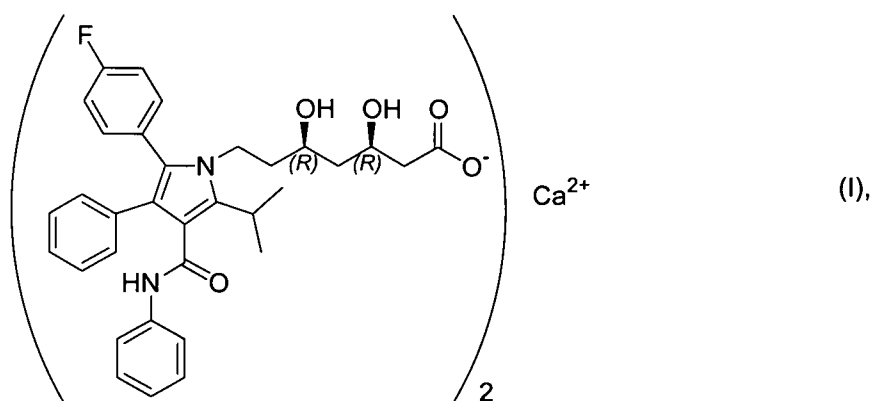
This invention describes a new, improved method of production of an amorphous form of the hemicalcium salt of (3*R*,5*R*) 7-[3-phenyl-4-phenylcarbamoyl-2-(4-fluorophenyl)-5-isopropylpyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (atorvastatin I) with a high specific

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surface area suitable for industrial use, which would not exhibit the above mentioned disadvantages, and its use in a dosage form.

Disclosure of Invention

The invention consists in an amorphous calcium salt of (3R,5R) 7-[3-phenyl-4-phenylcarbamoyl-2-(4-fluorophenyl)-5-isopropylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid, known under the non-proprietary name atorvastatin, of formula I with a high specific surface area.



It is an amorphous substance with a specific surface area, as measured by the standard BET method, of from 40 to 70 m²/g, preferably from 50 to 70 m²/g, most preferably from 60 to 70 m²/g.

Another aspect of the invention provides a pharmaceutical composition containing amorphous atorvastatin of formula I with a high specific surface area as characterized above. The composition with thus defined active substance allows a release rate of atorvastatin of formula I higher than 75% by weight in 15 minutes. In a preferable formulation more than 85% by weight in 15 minutes can be achieved.

An important aspect of the invention also provides a new production method of this amorphous form of the hemicalcium salt of (3R,5R)7-[3-phenyl-4-phenylcarbamoyl-2-(4-fluorophenyl)-5-isopropylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid with a high specific surface area, suitable for industrial use, based on precipitation and optimized isolation.

This entire procedure consists in:

- a) obtaining a solution of atorvastatin in a suitable solvent or mixture of solvents, either by dissolution of crystalline or amorphous atorvastatin, or this solution is obtained directly in the last reaction stage of atorvastatin production;
- 5 b) precipitation of amorphous atorvastatin by forcing this solution of atorvastatin in a suitable solvent into a suitable anti-solvent under pressure of a suitable gas by means of a device as described in CZ 2003-987 (CZ 13296 U) under precisely defined conditions;
- c) washing the obtained product to keep the content of residual solvents in the filter cake
10 in the defined range;
- d) drying of the product in a standard manner.

Suitable solvents are those where the solubility of the atorvastatin calcium salt is equal to or higher than 5 g in 1 l.

- 15 Examples of suitable solvents for obtaining an atorvastatin solution include especially esters of carboxylic acids, ethers, including cyclic ethers, alcohols, nitriles, chlorinated solvents, ketones.

Especially suitable solvents include esters of the RCOOR^1 type wherein R is an alkyl, e.g. methyl or ethyl, or hydrogen and R^1 is an alkyl, e.g. methyl, ethyl or isopropyl. As regards
20 ethers, tetrahydrofuran, *tert*-butyl methyl ether or dioxane are the most suitable ones. The most suitable alcohols are methanol, ethanol, isopropyl alcohol, n-butanol. Out of nitriles acetonitrile is the most suitable one. The most convenient ketones are acetone, ethyl methyl ketone, methyl isobutyl ketone.

- 25 Suitable anti-solvents include those where the solubility of atorvastatin is lower than 1 g per litre. Alkanes, especially pentane, hexane and its isomers, or heptane are especially suitable ones. Suitable ethers include diethyl ether, diisopropyl ether or their mixtures.

It has been surprisingly found out that if optimum conditions of isolation of the amorphous
30 product are met, the overall specific surface area S_g of the product is in the range of 40 to 67 m^2/g and its dissolution characteristics are much more favourable than those of the amorphous product isolated under the previously described conditions. Measurement of the specific surface area of the amorphous product depending on the drying of residual solvents and on the

composition of the solution used for precipitation has revealed surprising correlation with the content of residual solvents in the filter cake before drying of the final product. At the same time it has turned out that a higher specific surface area facilitates the drying since the proportion of glass particles that close solvents in their structure decreases.

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It is preferred that the solvent/anti-solvent ratio in the filter cake is reduced below 5% by washing with the anti-solvent.

Detailed Description of the Invention

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It has been shown in production of atorvastatin in accordance with CZ 2003-987 that amorphous atorvastatin usually exhibited a specific surface area that considerably fluctuated from one lot to another, amounting to from 15 to 39 m²/g (Table 1). Experimental measurements of the specific surface area of the substance have surprisingly showed a relation to the content of residual solvents in the filter cake before drying of the final product. On the other hand, no influence of stirring or the size of the nozzle on the specific surface of the product has been proved. It has turned out that the differences in the specific surface area of the amorphous product in the existing production of atorvastatin are caused by the content of residual solvents before isolation of the product, in the present case by the proportion of ethyl acetate and pentane. In case where the isolated product contained a larger amount of ethyl acetate, pentane was selectively dried off during the drying and the specific surface area of amorphous atorvastatin was reduced. Another surprising finding was that the particle size was not related to the specific surface area and thus amorphous forms with variable dissolution rates can be obtained with virtually the same particle size (Table 2).

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Table 1:

Lot	Sg m ² /g
1 130606	28.8
1 140606	38.8
1 150606	34.2
1 160606	29.4
1 170706	33.4
1 180706	28.0
1 010907	32.8
1 010508	16.6
1 020508	15.6
1 030608	15.3

S_g.....total specific surface area

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Table 2:

Experiment	Surface area m ² /g	Particle size		
		d(0.1) μm	d(0.5) μm	d(0.9) μm
31	6.5	2.634	12.255	36.512
32	19.2	3.224	18.988	42.995
33	67.1	3.376	10.082	21.986
34	22.5	3.352	17.255	39.576
35	22.0	3.057	12.663	29.888
36	25.6	3.485	16.433	38.745
37	27.9	3.821	19.084	53.643
38	22.6	3.196	13.088	31.935
39	33.5	3.719	16.471	38.694
40	18.8	3.776	19.777	45.947

d (p) ... wherein p is 0.1; 0.5 or 0.9 refers to sizes which are larger than 100p% of all measured particles.

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It has been shown in thorough monitoring of the ethyl acetate/pentane proportion that in standard washing the weight ratio is usually between 6 and 9%; nevertheless such ratio is sufficient for standard drying of residual solvents. Better washing of the product with pentane causes a surprising increase of the specific surface area up to the values of 67 m²/g. It can be said that thorough washing of the filter cake stabilizes the specific surface area of the amorphous product at the values approximating the condition immediately after the precipitation, which, however, cannot be measured. Accordingly, it is possible to obtain, by this method, an amorphous form of atorvastatin with a significantly higher dissolution rate, which is directly proportional to the specific surface area of the product (Table 3).

Table 3:

Experiment	Specific surface area m ² /g	Weight ratio of EtAc/pentane (%)
61	15.5	7.8
62	28.4	6.8
63	19.3	8.0
64	58.4	4.0
65	67.5	3.4
66	54.9	4.4
67	46.4	4.5
68	42.7	4.9
69	65.0	2.4
70	67.0	2.7

Description of experiments 61 – 68: Atorvastatin (0.3 kg) dissolved in ethyl acetate (1 l) was precipitated into pentane (7 l) with a nozzle under pressure of nitrogen; the product was isolated on a nutsch filter and washed with pentane, the pentane/ethyl acetate ratio being measured before drying in the filter cake. The product was dried in vacuo and its specific surface area was measured.

The total specific surface area S_g was measured after processing of the sample at the volume flow of helium of 1.5 l/h. The measurement of the total specific surface area was performed in the commercial Pulse Chemisorb 2700 device of Micromeritics, which works on the principle of a dynamic, chromatographic method. The total specific surface area was determined from the measured data of nitrogen physisorption at three different partial pressures in the area of validity of the BET equation and at the temperature of 77 K. For mathematical processing of the measured data and for determination of the total specific surface area the linearized form of the BET equation was used.

A pharmaceutical composition containing atorvastatin of formula I with a high specific surface area as described above significantly differs in its characteristics from known pharmaceutical compositions with amorphous atorvastatin. This difference is demonstrated in example 5. Compositions A1 and A2 characterize extreme values of the specific surface area of atorvastatin prepared according to the prior art, in particular CZ 2003-987. It turns out that the release rate significantly differs from one lot to another, which may even render this particular composition unusable. Using the active substance in accordance with the invention (composition A3) reproducible high values of release rate of the active substance are achieved.

It is desirable for a tablet containing the calcium salt of atorvastatin of formula I to quickly disintegrate and release the active substance in a fast manner. Fillers from the group of substances such as pre-gelatinized starch, microcrystalline cellulose, cellulose, mannitol, sorbitol, xylitol, anhydrous lactose, lactose monohydrate, calcium phosphate, hydrogen or dihydrogen calcium phosphate and the like can be used. Out of this group a mixture of lactose monohydrate and microcrystalline cellulose is preferred.

Out of other excipients, the basic constituent can include an organic or inorganic base, such as sodium or potassium hydroxide, meglumine, arginine, calcium, magnesium, sodium or potassium hydroxide, oxide, carbonate or hydrogen carbonate, and the like. Meglumine or magnesium oxide can conveniently be used.

Substances from the group of polyvinylpyrrolidones can be used as binders, for example various types of povidones, povidone 25, povidone 30, or povidone 90; copolymers of vinylpyrrolidones with other vinyl derivatives, such as povidone VA 64; microcrystalline

cellulose, hydroxypropyl methyl cellulose, hydroxyl propyl cellulose, methyl cellulose or pre-gelatinized starch. Out of this group of substances the use of hydroxypropyl cellulose is preferred.

- 5 For quick disintegration, disintegrants from the group of substances such as maize starch, pre-gelatinized starch, low substituted hydroxypropyl methyl cellulose, microcrystalline cellulose, are used, as well as substances from the group of super disintegrants such as the sodium salt of crosscarmellose, sodium salt of carboxymethyl starch of type A, B or C, or crosspovidone. For this layer a mixture of low substituted hydroxypropyl cellulose and sodium salt of
10 crosscarmellose is preferred.

For improvement of flow characteristics substances from the group of substances such as colloidal silicon oxide, talc, and the like are used. Colloidal silicon oxide is conveniently used.

- 15 A substance such as sodium stearyl fumarate, stearic acid, calcium stearate, magnesium stearate, talc, Cutina, and the like can be used as the lubricant. Out of this group of substances magnesium stearate is mainly preferred.

Description of preparation of the tablet substance of atorvastatin of formula I:

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Several various methods of preparation of the tablet substance of atorvastatin of formula I can be used. Atorvastatin calcium salt of formula I is in the amorphous form in the tablets.

- a/ Granulation by kneading with dissolution of atorvastatin in ethanol* - Atorvastatin in the
25 form of the calcium salt of formula I is dissolved in anhydrous ethanol and, in a granulation vessel, mixed with the other ingredients such as microcrystalline cellulose, lactose, hydroxypropyl cellulose, and optionally with a portion of crosscarmellose, or with magnesium oxide or calcium carbonate. This mixture is granulated with an aqueous or aqueous-alcoholic solution of meglumine, or only with water or a water/ethanol mixture. The resulting granulate
30 is dried by fluidization or on metal sheets. The dried granulate is sieved to a suitable size of granules, which are subsequently additionally mixed with extragranular excipients such as magnesium stearate and colloidal silicon oxide, or a portion of crosscarmellose.

b/ Granulation by kneading - Atorvastatin in the form of the calcium salt of formula I is mixed with the other ingredients such as microcrystalline cellulose, lactose, hydroxypropyl cellulose, and optionally with a portion of crosscarmellose, or with magnesium oxide or calcium carbonate. This mixture is granulated with an aqueous or aqueous-alcoholic solution of meglumine, or only with water or a water/ethanol mixture. The resulting granulate is dried by fluidization or on metal sheets. The dried granulate is sieved to a suitable size of granules, which are subsequently additionally mixed with extragranular excipients such as magnesium stearate and colloidal silicon oxide, or a portion of crosscarmellose.

c/ Dry granulation - Atorvastatin in the form of the calcium salt of formula I is mixed with the other ingredients such as microcrystalline cellulose, lactose, hydroxypropyl cellulose, and optionally with a portion of crosscarmellose, or with magnesium oxide, or meglumine. The resulting mixture is compacted in a suitable compactor or compressed in a tableting press with the use of large dies. The resulting compactates are sieved to a suitable size of granules, which are subsequently additionally mixed with extragranular excipients such as magnesium stearate and colloidal silicon oxide, or a portion of crosscarmellose.

d/ Direct blending - Atorvastatin in the form of the calcium salt of formula I is mixed with the other ingredients such as microcrystalline cellulose, lactose, hydroxypropyl cellulose, and optionally with a portion of crosscarmellose, or with magnesium oxide, or meglumine. The resulting mixture is additionally mixed with extragranular excipients such as magnesium stearate and colloidal silicon oxide, or a portion of crosscarmellose.

Compression, coating and packing of tablets

The tablet substance prepared in one of the above mentioned manners is compressed to form tablets, which are coated with a layer of a film-forming substance containing plasticizers, pigments and other fillers.

The coated tablets are preferably adjusted in Al/Al blister packs, optionally under inert atmosphere.

For the preparation of the tablet substance according to the procedure described sub *a/ Granulation by kneading with dissolution of atorvastatin in ethanol*, the ease of formation of solution of the active substance in anhydrous ethanol and stability of this solution in dependence on the specific surface area was verified.

- 5 The active pharmaceutical ingredient (API) with the specific surface area of 15 m²/g (lot no.: 103 06 08) did not form a clear solution in anhydrous ethanol at the concentrations of API : EtOH = 1 : 6.3 (wt./wt.) even at a higher temperature (50 °C). Moreover, during dissolution under these conditions a nebular precipitate appeared after 20 to 60 minutes, which was identified as a crystallization nucleus.
- 10 Active pharmaceutical ingredients with the specific surface areas of 32 m²/g and 58 m²/g (lot no.: 101 09 07, and 101 04 09, respectively) already formed clear solutions in anhydrous ethanol at the concentrations of API : EtOH = 1 : 4.5 (wt./wt.) at a common laboratory temperature (20 to 25 °C). The solutions were monitored in terms of stability for 90 to 120 min. No changes of the amorphous state of the API were registered.
- 15 The results indicate that it is possible to ensure the required amorphous purity in the course of production of a dosage form by using the API with a suitable specific surface area.

The invention is described in a more detail in the working examples below. These examples, which illustrate preferred alternatives of production of atorvastatin of formula I in accordance with the invention, have an exclusively illustrative character and do not limit the scope of the invention in any respect.

Working Examples

25 Example 1

Atorvastatin (0.3 kg) dissolved in ethyl acetate (1 l) was precipitated into pentane (7 l) with a nozzle under pressure of nitrogen, the product was isolated on a nutsch filter and washed with pentane (4 x 2.5 l). The weight ratio of ethyl acetate/pentane was 4.4%. After drying at 60 °C

30 in vacuo 276 g of the product with the specific surface area of 54,9 m²/g was obtained.

Example 2

Atorvastatin (1000 g) in crystalline modification I was dissolved in tetrahydrofuran (2.5 l). After dissolution the solution was filtered and concentrated to the volume of 1.5 l and ethyl acetate (2 l) was added. After concentration and addition of ethyl acetate in such a way to make the content of tetrahydrofuran 3% wt. the solution was injected under the surface of the stirred anti-solvent - pentane (30 l) with a nozzle under slight overpressure. The separated product was aspirated, washed with pentane (5 x 5 l; weight ratio of ethyl acetate/pentane 3.5%) and dried in vacuo at the temperature of 25 °C for 7 days. 965 g of amorphous atorvastatin of formula I with the specific surface area of 59.6 m²/g was obtained.

Example 3

To the weighed ester II (500 g) was added THF (7.5 l) and after dissolution of all the substance 10% HCl (1620 ml) was added under stirring during 5 minutes. The mixture was stirred at 23 °C - 25 °C for 6 h 15 min and a 40% solution of NaOH (1 l) was added under moderate cooling during 10 minutes in order not to allow the temperature exceed 31 °C and the mixture was stirred under spontaneous cooling for 14 hours. After this time period demineralised water (15 l) and heptane (5 l) were added. After shaking the mixture was left to stand, the organic layer was removed and the aqueous phase was extracted again with a mixture of heptane (4 l) and THF (1 l). The aqueous phase containing the sodium salt of atorvastatin was extracted with ethyl acetate (4 l and 4 x 2 l). The ethyl acetate extract was shaken with a solution of calcium acetate in demineralised water (100 g of acetate in 500 ml of water) 3 times. It was washed with demineralised water (2 x 500 ml) and dried with CaSO₄ (1 kg) after thorough separation of water. After 1 h of drying it was filtered, the desiccant was washed with 1 l of ethyl acetate and the extract was concentrated to the volume of ca. 1600 ml. The resulting solution of atorvastatin was injected into stirred pentane (16 l) under pressure of nitrogen by means of a nozzle. After aspiration and washing with pentane (5 x 6 l; ethyl acetate/pentane ratio 4.0%) and drying 398.9 g of amorphous atorvastatin (90%) with the surface area of 47 m²/g was obtained.

Example 4

To the weighed ester II (8 kg) was added THF (120 l) and after dissolution of all the substance 10% HCl (27 l) was added under stirring during 15 minutes. The mixture was stirred at 25 °C for 6 h and a 40% solution of NaOH (16 l) was added under moderate cooling during 30 minutes in order not to allow the temperature exceed 31 °C. Then, the mixture was stirred under spontaneous cooling for 14 hours. After this time period demineralised water (140 l) and heptane (80 l) were poured in. After separation the aqueous phase containing the sodium salt of atorvastatin was extracted with ethyl acetate (60 l and 2 x 30 l). The ethyl acetate extract was shaken with a solution of calcium acetate in demineralised water (1.6 kg of acetate in 6.5 l of water) 3 times. It was washed with demineralised water (3 x 5 l). After filtration the solution was concentrated to the final volume of 26 l (water content 0.2% wt., tetrahydrofuran content 2.7% wt.) and then injected into stirred pentane (170 l) under pressure of nitrogen by means of a nozzle. After aspiration and washing with pentane (5 x 30 l; weight ratio of ethyl acetate/pentane 3.3%) and drying 6.4 kg of amorphous atorvastatin (90%) with the specific surface area of 64 m²/g was obtained.

Example 5

In order to monitor the influence of the specific surface area of the active substance used in the formulation on the rate of dissolution from the dosage form and on the dissolution kinetics itself the method of preparing the tablet substance by direct blending has been selected. The compositions of various formulations are summarized in the table below. All the percentages mentioned below are weight percentages.

Formulation	A1	A2	A3
Specific surface area of the API (m ² /g)	4	32	58
Composition	%/tbl.	%/tbl.	%/tbl.
Atorvastatin Ca	7.31	7.31	7.31
Meglumine	2.97	2.97	2.97
Microcrystalline cellulose	49.49	49.49	49.49
Lactose	25.28	25.28	25.28
Crosscarmellose Na	0.99	0.99	0.99
Hydroxypropyl cellulose	9.90	9.90	9.90
Colloidal silicon dioxide	0.35	0.35	0.35
Magnesium stearate	0.49	0.49	0.49
Coating layer	3.22	3.22	3.22

The release rate of the active substance was monitored in a dissolution device by the paddle method in the dissolution media of a 0.01 M HCl solution at pH 2.0.

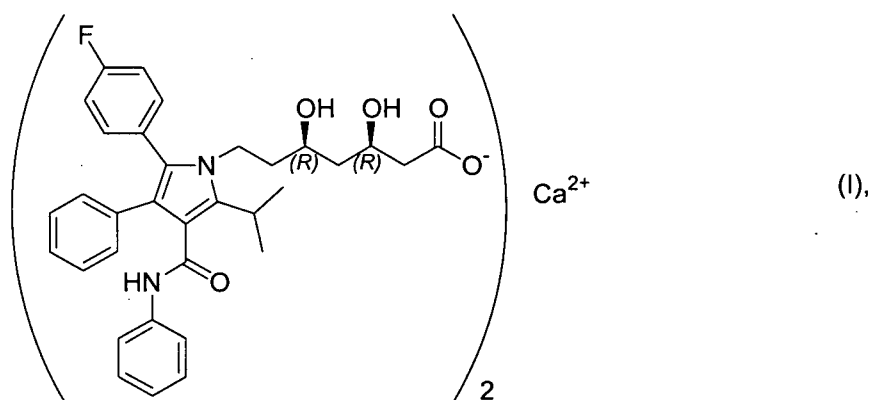
- 5 Under these conditions the following amounts of the active ingredient in % wt. were released from various formulations:

	[% of dissolved API]							
	0 min	5 min	10 min	15 min	20 min	25 min	30 min	45 min
Formulation A1	0	25	35	41	46	50	53	60
Formulation A2	0	43	57	63	67	69	71	75
Formulation A3	0	77	86	91	93	94	94	95

- 10 The results show that the kinetics of releasing of the active substance from the formulation is governed by the specific surface area, i.e. the higher the specific area is, the faster is the dissolution. As Atorvastatin Ca as the active substance is classified to BCS group II, it can be assumed that the required *in vivo* bioavailability can be achieved by using the active substance with a suitable surface area.

CLAIMS

1. Amorphous hemicalcium salt of (3R,5R) 7-[3-phenyl-4-phenylcarbamoyl-2-(4-fluorophenyl)-5-isopropylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid, i.e, atorvastatin, of formula I



- with a high specific surface in the range of 40 to 70 m²/g, as measured by the BET method.
2. The amorphous form according to claim 1, wherein the specific surface area values are 50 to 70 m²/g.
 3. The amorphous form according to claims 1 and 2, wherein the specific surface area values are 60 to 70 m²/g.
 4. A pharmaceutical composition, characterized in that the content of the active substance is 1 to 80% wt. of amorphous atorvastatin with a high specific surface area according to any one of claims 1 to 3.
 5. The pharmaceutical composition according to claim 4, characterized in that the release rate of the active substance is at least 75% wt. in 15 min., measured by the test of Pharm. Eur. carried out by the paddle method in the dissolution media of a 0.01 M HCl solution at pH 2,0.

6. The pharmaceutical composition according to claim 5, characterized in that the release rate is at least 85% wt. in 15 min.
7. The pharmaceutical composition according to any one of claims 4 to 6, characterized in that it further contains at least one excipient selected from the group consisting of fillers, disintegrants, organic and inorganic bases and their mixtures, sliding agents and lubricants.
8. The pharmaceutical composition according to any one of claims 4 to 6, characterized in that it further contains at least one of microcrystalline cellulose; lactose; hydroxypropyl methyl cellulose; a base selected from calcium carbonate, magnesium oxide, meglumine and sodium hydroxide and their mixtures; crosscarmellose; colloidal silicon oxide and magnesium stearate.
9. A method for the production of the amorphous form of atorvastatin of formula I with a high specific surface area as defined in claims 1 to 3, characterized in that a solution of atorvastatin in a solvent is forced into an anti-solvent under pressure of a gas, preferably nitrogen, by means of a device, and precipitated amorphous atorvastatin is then filtered off, washed with the anti-solvent and dried.
10. The method according to claim 9, characterized in that said solvent is any solvent or mixture of solvents wherein the solubility of atorvastatin is higher than 5 g per 1 l.
11. The method according to claim 9, characterized in that said anti-solvent is a solvent or mixture of solvents in which less than 1 g of atorvastatin per 1 l dissolves.
12. The method according to claim 10, characterized in that said solvent is a carboxylic acid ester of formula RCOOR^1 , an ether except diethyl ether and diisopropyl alcohol, an alcohol of formula ROH , acetonitrile, or a ketone of formula RCOR^1 , wherein R and R^1 in the formulae are alkyl residues, said alkyl residues being linear or arbitrarily branched.

13. The method according to claim 11, characterized in that said anti-solvent is selected from the group consisting of pentane, hexane and its isomers, heptane, diethyl ether or diisopropyl ether and mixtures of these solvents.
14. The method according to claim 12, characterized in that said solvent is ethyl acetate or its mixture with tetrahydrofuran.
15. The method according to claim 13, characterized in that said anti-solvent is pentane.
16. The method according to claims 9 to 15, characterized in that the precipitated amorphous atorvastatin is washed with the anti-solvent resulting in reduction of the solvent/anti-solvent ratio in the filter cake below 5%.
17. The method for the production of the pharmaceutical composition according to claims 4 to 8, characterized in that it comprises granulation by kneading with dissolution of atorvastatin in ethanol or its mixture with water.
18. The method according to claim 17, characterized in that dissolved atorvastatin is mixed with microcrystalline cellulose, lactose, hydroxypropyl methyl cellulose and a portion of crosscarmellose, followed by granulation with an aqueous, aqueous-alcoholic or alcoholic solution of meglumine.
19. The method according to claim 17, characterized in that dissolved atorvastatin is mixed with microcrystalline cellulose, lactose, hydroxypropyl methyl cellulose, and optionally a portion of crosscarmellose, wherein the mixture of excipients has been moistened either with an aqueous or aqueous-alcoholic or alcoholic solution of meglumine or only with water before the addition of the solution of atorvastatin, followed by granulation of the obtained mixture.