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Kerc

(54) **STABLE PHARMACEUTICAL FORMULATION COMPRISING A HMG-COA REDUCTASE INHIBITOR**

(75) Inventor: **Janez Kerc**, Ljubljana (SI)

Correspondence Address:
DARBY & DARBY P.C.
P.O. BOX 770, Church Street Station
New York, NY 10008-0770 (US)

(73) Assignee: **Lek Pharmaceuticals d.d.**, Ljubljana (SI)

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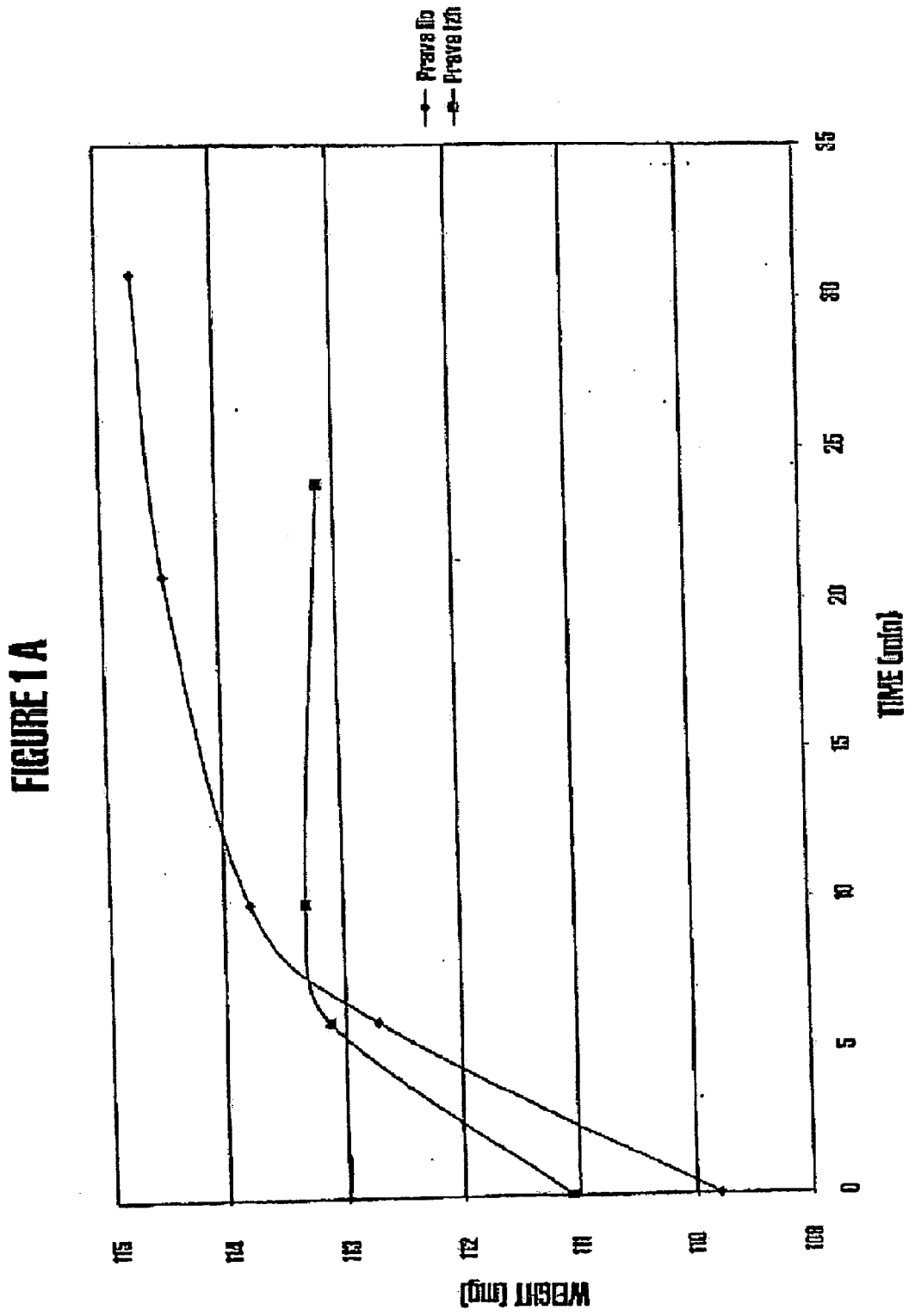
(57) **ABSTRACT**

Lovastatin, pravastatin, simvastatin, mevastatin, atorvastatin, and derivatives and analogs thereof are known as HMG-CoA reductase inhibitors and are used as antihypercholesterolemic agents. The majority of them are produced by fermentation using microorganisms of different species identified as species belonging to *Aspergillus, Monascus, Nocardia, Amycolatopsis, Mucor* or *Penicillium* genus, and some are obtained by treating the fermentation products using the methods of chemical synthesis or they are the products of total chemical synthesis.

The aforementioned active substances may be destabilized by the environmental factors, their degradation may also be accelerated by interactions with other pharmaceutical ingredients, such as fillers, binders, lubricants, glidants and disintegrating agents, therefore the pharmaceutical ingredients and the process for preparation of the pharmaceutical formulation should be meticulously chosen to avoid the aforementioned undesired interactions and reactions.

The present invention relates to a stable solid pharmaceutical formulation for the treatment of hypercholesterolemia and hyperlipidemia. More precisely, the present invention relates to the new stable solid pharmaceutical formulation containing as an active ingredient a HMG-CoA reductase inhibitor, such as atorvastatin, pravastatin, fluvastatin and cerivastatin or pharmaceutically acceptable salts thereof.


Prava lib
Prava lzh
WEIGHT (mg)
TIME (min)
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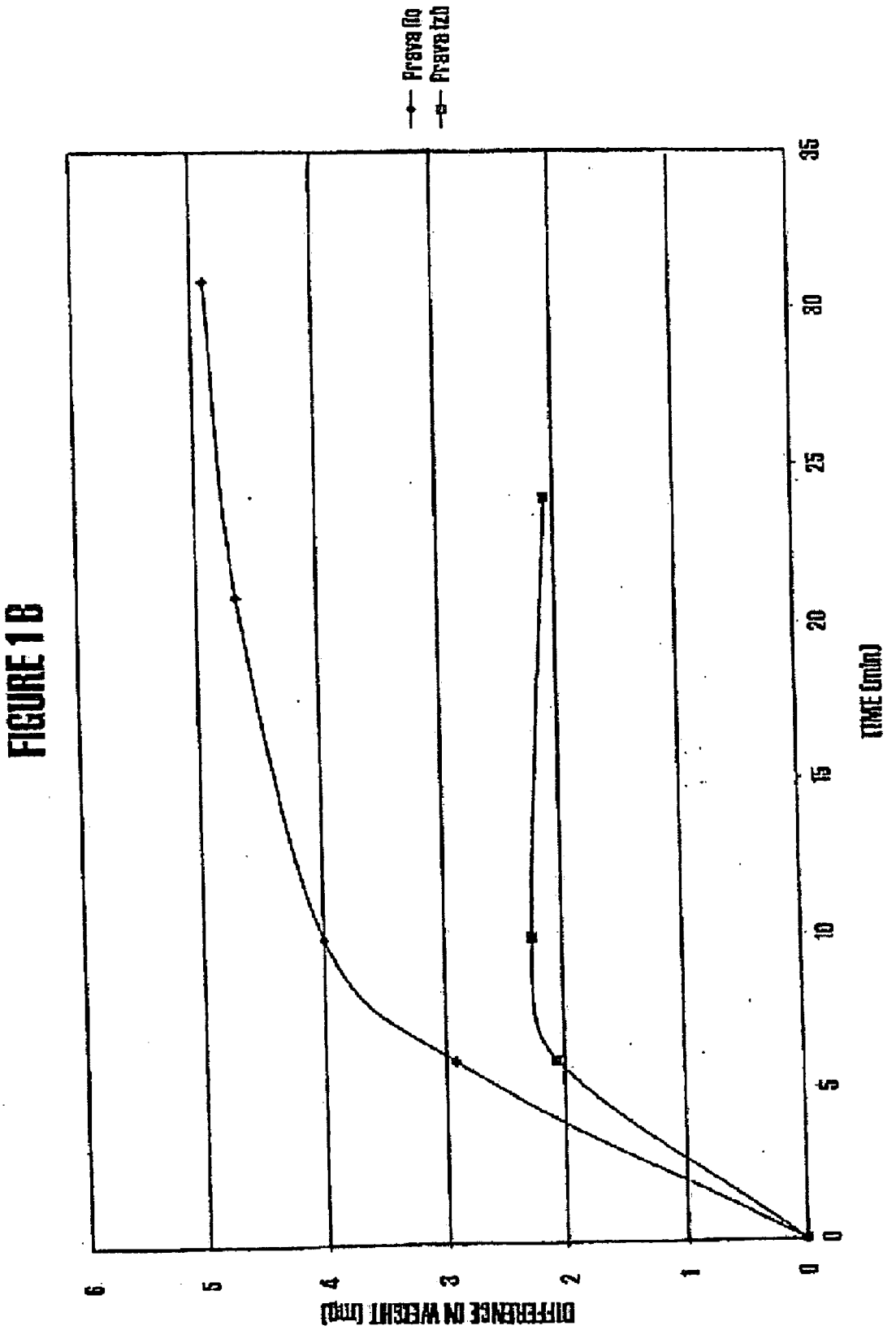
114
113
112
111
110
109
0
5
10
15
20
25
30
35

FIGURE 1 A


Prava flo
Pravastin
DIFFERENCE IN WEIGHT (mg)
TIME (min)
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1
2
3
4
5
6
0
5
10
15
20
25
30
35

FIGURE 1B

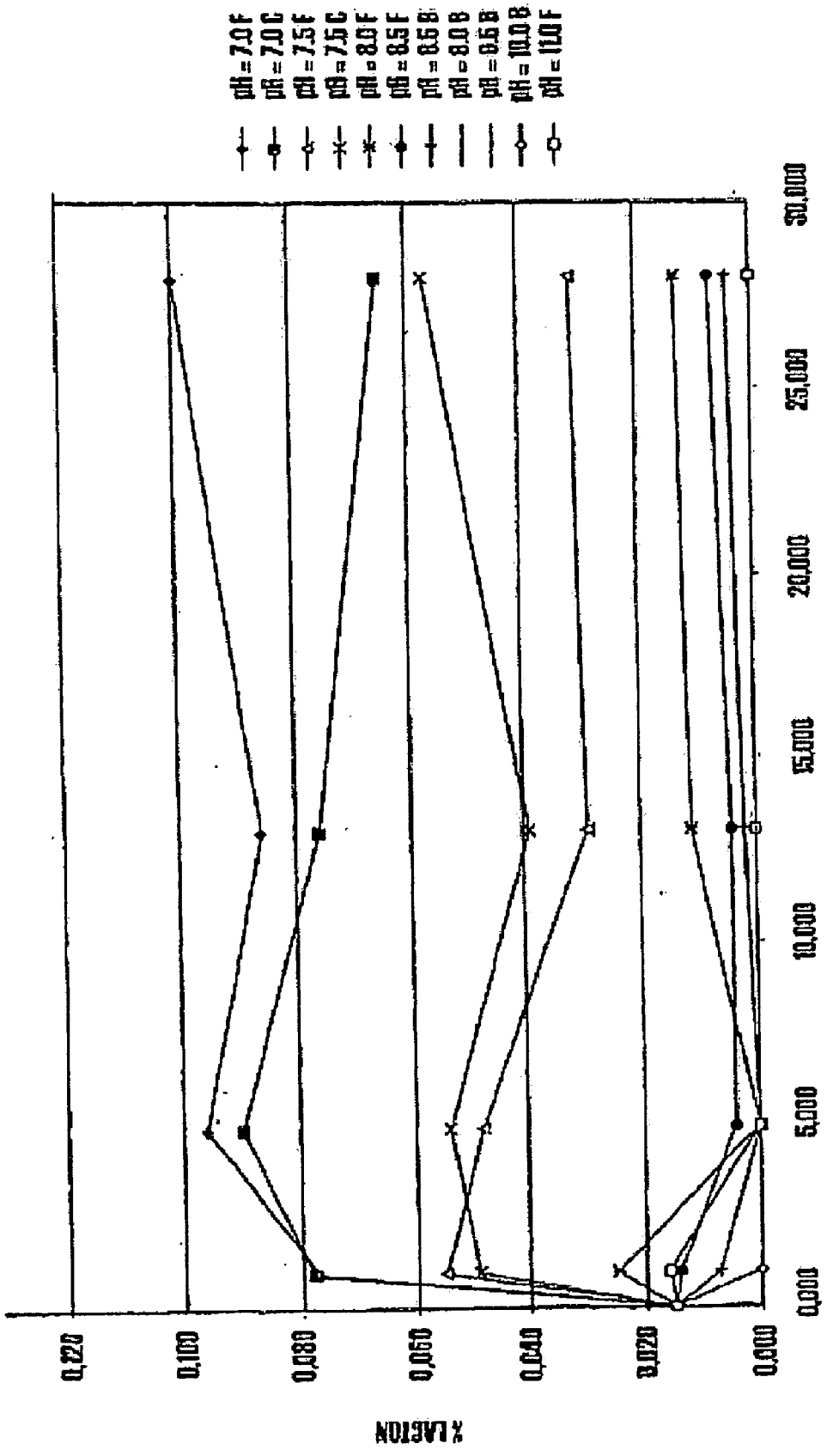

Figure 2 PRAVASTATIN, AT DIFFERENT pH, LACTON

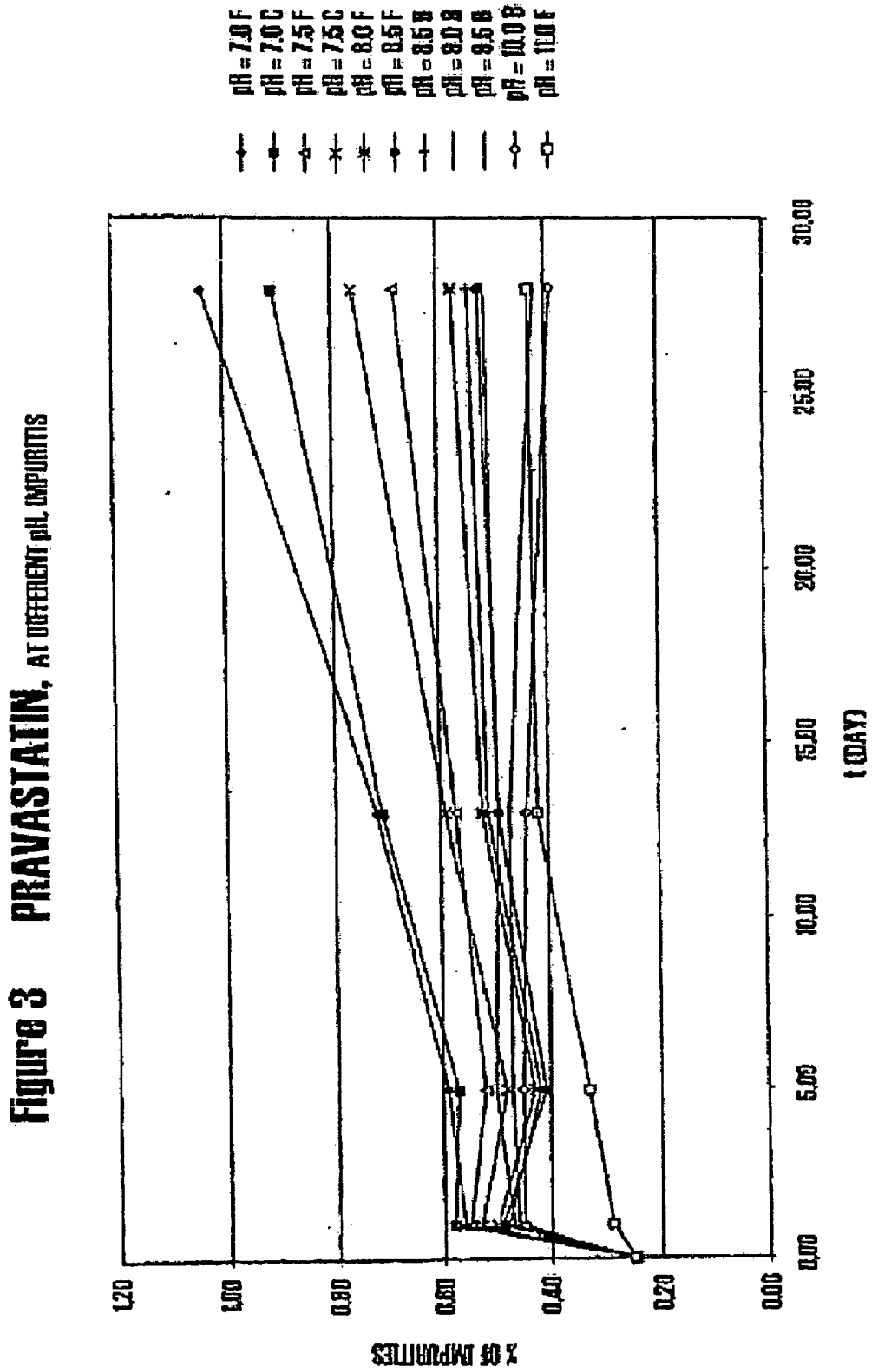

Figure 3 PRAVASTATIN, AT DIFFERENT pH, IMPURITIS

STABLE PHARMACEUTICAL FORMULATION COMPRISING A HMG-COA REDUCTASE INHIBITOR

FIELD OF THE INVENTION

[0001] The present invention relates to a new stable solid pharmaceutical formulation which is particularly suitable for the treatment of hypercholesterolemia and hyperlipidemia. More precisely, the present invention relates to the new stable solid pharmaceutical formulation containing as an active substance a HMG-CoA reductase inhibitor, such as atorvastatin, pravastatin, fluvastatin and cerivastatin, or pharmaceutically active salts thereof.

BACKGROUND OF THE INVENTION

[0002] Lovastatin, pravastatin, simvastatin, mevastatin, atorvastatin, fluvastatin and cerivastatin, derivatives and analogs thereof are known as HMG-CoA reductase inhibitors and are used as antihypercholesterolemic agents. The majority of them are produced by fermentation using microorganisms of different species identified as species belonging to *Aspergillus, Monascus, Nocardia, Amycolatopsis, Mucor* or *Penicillium* genus. Some are obtained by treating the fermentation products using the methods of chemical synthesis like simvastatin or they are the products of total chemical synthesis like fluvastatin, atorvastatin and cerivastatin.

[0003] The purity of the active substance is an important factor for manufacturing a safe and effective pharmaceutical formulation. Maximum possible purity of the product is of particular importance if the pharmaceutical product must be taken on a longer term basis in the treatment or prevention of high cholesterol levels in blood. Accumulation of impurities from drugs of a lower level of purity may cause a variety of side effects during treatment. Besides impurities, that cannot be completely eliminated in the process of preparation of the active substance, degradation products occurring by subjecting the final pharmaceutical formulation to various environmental factors such as temperature, moisture, low pH and light, may also impose a problem. HMG-CoA reductase inhibitors occurring in the form of salts in the final pharmaceutical formulation, such as atorvastatin, pravastatin, fluvastatin and cerivastatin, are particularly sensitive to an acidic environment in which hydroxy acids are degraded into a lactone.

[0004] Apart from the fact that the aforementioned active substance may be destabilized by the environmental factors, their degradation may also be accelerated by interactions with other pharmaceutical ingredients, such as fillers, binders, lubricants, glidants and disintegrating agents. Therefore, the pharmaceutical ingredients and the process for preparation of the pharmaceutical formulation should be meticulously chosen to avoid the aforementioned undesired interactions and reactions.

[0005] The stability of the active substance in an acidic environment is one of the major problems in the case of statins in the form of salts. One of possible solutions of the aforementioned problem is described in EP 0 336 298, disclosing a stable pharmaceutical formulation for pravastatin. The essence of the formulation is to maintain an alkaline environment so that the aqueous dispersion of the pharmaceutical formulation reaches a pH above 9, preferably about 10. In addition to the active substance pravastatin, the composition of the invention includes a basifying agent, such as magnesium oxide which imparts a pH to an aqueous dispersion of the aforementioned formulation above 9. In view of the stability of the active substance such a formulation is effective. However, the local alkaline environment occurring at the site of dissolution of the pharmaceutical formulation may have a negative impact on the gastric mucosa with its normally acidic environment. This negative impact may be particularly evident for patients with a damaged gastric mucous membrane where the mucosa per se is not able to create a sufficient acidic environment inside the stomach for normal digestive functioning. It is particularly important in chronic therapies as in the case of prophylaxis or treatment with HMG-CoA reductase inhibitors.

SUMMARY OF THE INVENTION

[0006] It is an object of the present invention to provide a pharmaceutical formulation containing as an active substance a HMG-CoA reductase inhibitor which exerts an excellent stability while avoiding the afore mentioned disadvantages. It is a particular object to provide a stabilized active substance as such where the HMG-CoA reductase inhibitor is precautionary protected from being degraded.

[0007] It is a further object to provide a process for the preparation of a stable pharmaceutical formulation which exerts an excellent stability while avoiding the afore mentioned disadvantages.

[0008] These and further objects are accomplished by the present invention.

[0009] According to the present invention, there is provided a stable solid pharmaceutical formulation containing as an active substance a HMG-CoA reductase inhibitor, wherein an active substance is contained which is capable of providing a pH in the range from 7 to 11. Within the meaning of the present invention, the term "active substance" denotes a HMG-CoA reductase inhibitor alone or a mixture thereof with a small amount of a buffering agent. Therefore, the present invention also makes available a stabilized pharmaceutically active substance as such, which active substance consists of a HMG-CoA reductase inhibitor and a low amount of a buffering agent.

[0010] According to the present invention, there is further provided a stable solid pharmaceutical formulation containing as an active substance a HMG-CoA reductase inhibitor, wherein the pharmaceutical formulation is capable of providing a pH below 9.

[0011] In addition, according to the present invention, there is provided suitable processes for the preparation of the above specified stable solid pharmaceutical formulation.

[0012] According to the present invention, there is further provided a method for the stabilization of a HMG-CoA reductase inhibitor as an active substance in a solid pharmaceutical formulation, wherein an HMG-CoA reductase inhibitor being capable of providing a pH in the range from 7 to 11 is incorporated into a pharmaceutical formulation which is capable of providing a pH below 9.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. **1***a* is a diagram which shows the growth of weight of a sample of pravastatin in crystal form and a sample of lyophilised pravastatin when exposed to air moisture. FIG. **1***b* shows the corresponding difference in the starting weight and the weight in time.

[0014] FIG. **2** is a diagram which shows the occurrence of pravastatin in lactone form when pravastatin was dissolved in different buffers with the pH in a range between 7 and 11 (F=phosphate, C=citrate, B=borate).

[0015] FIG. **3** is a diagram which shows the formation of different degradation products (impurities) when pravastatin was dissolved in different buffers with the pH in a range between 7 and 11 (F=phosphate, C=citrate, B=borate).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0016] In the inventor's investigations, it was found that there are three major reasons for instability problems in case of a pharmaceutical formulation containing an active substance and in case of a bulk active substance.

[0017] First, the active substance as such is very hygroscopic and it is impossible to remove all water from it. This is illustrated by the following experiment: 111.07 mg of pravastatin in crystal form (prava izh) and 109.8 mg of lyophilized pravastatin (prava lio) were exposed to air moisture. Their weights were measured in different time intervals. The growth of weight of both samples and the difference in the starting weight and the weight in time are illustrated in FIGS. **1***a* and **1***b*.

[0018] Another observation was that carbon dioxide from the air can irreversibly bind to the active substance and can cause a drop of pH. This is illustrated by the following experiment: 5 g of pravastatin sodium were dissolved in 30 ml of methanol, the pH was adjusted to 10 with 3% aqueous solution of NaOH. 400 ml of ethylacetate were added and the crystals of pravastatin sodium were formed. Crystals were filtered and dried and then put into three different atmospheres: normal air, nitrogen atmosphere and carbon dioxide atmosphere. In normal air and in the nitrogen atmosphere the pH remained the same during a period of 24 hours (normal air: 9.2, nitrogen: 9.5), but in the carbon dioxide atmosphere the pH dropped in the first two minutes from 9.2 to 6.9. After 12 minutes the pH was 6.6 and after 1 hour the pH was 6.5. After that, the pH remained constant. The third observation is that a sufficient stabilization of the active substance is already obtained at a pH of at least 7.0, but a beneficially high stability is effected at a pH of at least 8.0. We have noticed that at a pH below 8 the formation of lactone has occurred and also the amount of other impurities has increased. The presence of humidity in the air and a carbon dioxide-rich atmosphere makes the negative effect of a low pH even stronger. This is illustrated by the following experiment: Pravastatin was dissolved in different buffers with the pH in a range between 7 and 11 (F=phosphate, C citrate, B borate). The occurrence of pravastatin in lactone form and the formation of different degradation products (impurities) was measured after 1, 5, 13 and 28 days. The results are shown in FIGS. **2** and **3**.

[0019] In the present invention, we have surprisingly found that a sufficient stability of the active substance, which is a HMG-CoA reductase inhibitor preferably in the form of salt, can be also obtained by using a pharmaceutical formulation which does not create a marked alkaline environment in an aqueous dispersion.

[0020] Further, we have found that for the stability and digestibility of a pharmaceutical formulation both the pH generated by the formulation in an aqueous medium (usually being a dispersion) and the pH of the active substance (HMG-CoA reductase inhibitor) are of great importance.

[0021] Another surprising finding was that a sufficient stability of a HMG-CoA reductase inhibitor in the form of a salt in bulk can be obtained by the addition of small amounts of a buffering agent to the pure HMG-CoA reductase inhibitor in the form of salt. Such an addition of small amounts of buffering agents avoids the negative effect of water already present in the bulk substance and of moisture from the air, to avoid the negative effect of low pH caused by other ingredients which will be co-admixed to the pharmaceutical formulation, and to avoid the possible lowering of the pH caused by carbon dioxide.

[0022] The active substance and the pharmaceutical formulation according to the present invention were designed to avoid the negative effect of the water present in the bulk substance and in the pharmaceutical formulation, to avoid the negative effect of low pH which can be caused by other ingredients of the pharmaceutical formulation and to avoid possible lowering of the pH caused by carbon dioxide.

[0023] The most acceptable stability of the active substance in the formulations is obtained with an active substance which is capable of providing a pH in the range from 7 to 11. The pH value is the one which is obtained when the pH of an aqueous medium containing said active substance would be measured. In the stable pharmaceutical formulation according to the present invention, the basic pH of the active substance has a minimal influence on the pH of the formulation which is lower than 9. By creating locally an environment around the active substance which affords the best stability for the active substance, the potential of negative impact of other ingredients of the composition of the pharmaceutical formulation is reduced, and possible reactions among the active substance and the rest of the ingredients of the composition of the pharmaceutical formulation are also less favoured. Accordingly, the active substance is maintained in a stable form when an active substance which is capable of providing a pH in an aqueous medium in the range from 7 to 11 is added to the pharmaceutical formulation.

[0024] The active substance being added to the formulation of the present invention generally is a HMG-CoA reductase inhibitor in the form of a salt. The pH of the active substance may be adjusted within the above specified range in the course of preparing the salt of the HMG-CoA reductase inhibitor from the acid form and an alkaline substance. As an example, the preparation of pravastatin sodium from pravastatin acid and sodium hydroxide may be mentioned. For a preferred adjustment of the pH of the active substance to be incorporated into the formulation within the above specified range of 7 to 11, the active substance is further mixed with an appropriate buffering agent. Accordingly, the active substance may contain small amounts of a buffering agent, preferably less than 1%, more preferably 0.1 to 0.5%, most preferably approximately 0.3%, based on the weight of the active substance added to the formulation. A suitable buffering agent for this purpose is carbonate buffer or phosphate buffer, such as sodium carbonate of sodium phosphate. For example, an amount 0.3% of sodium carbonate in pravastatin results in a pH of pravastatin between 9 and 10. Thus, it is possible to mix pravastatin with other ingredients of the pharmaceutical formulation without fear that a degradation can be caused by the contact of pravastatin with acidic ingredients as a microenvironment of pravastatin is still basic due to the addition of small amounts of a buffering agent. This addition of small amounts of a buffering agent is also important for an easier handling of the pravastatin bulk without special

requirements for a carbon dioxide free atmosphere. Preferably, the acidifying effect of carbon dioxide on the final formulation is neutralised by further addition of an appropriate buffering agent to adjust the pH of the formulation in the above specified range, preferably by addition of 20%, more preferably of 10% per weight based on the total weight of the tablet Any buffering agent capable of adjusting the pH of the total formulation in the desired range is suitable, including sodium or potassium citrate, sodium phosphate, dibasic sodium phosphate, calcium carbonate, hydrogen phosphate, phosphate, sulphate, sodium or magnesium carbonate, sodium ascorbinate, benzoate, sodium or potassium hydrogen carbonate, lauryl sulphate, or mixtures of such buffering agents. Citrate buffer, carbonate buffer and phosphate or hydrogen phosphate buffer may be mentioned as specific examples.

[0025] Preferably, an active substance contained in the pharmaceutical formulation according to the present invention is capable of providing a pH in the range from 8 to 10.

[0026] Furthermore, the active substance may be selected from the group consisting of pravastatin, atorvastatin, fluvastatin, cerivastatin and a pharmaceutically acceptable salt thereof. Preferably, the active substance is a sodium salt of pravastatin (pravastatin Na) or a calcium salt of atorvastatin (atorvastatin Ca).

[0027] As mentioned above, it is a further significant aspect of the present invention that the pharmaceutical formulation is capable of providing a pH below 9, preferably below 8.5. The lower limit of the pH generated by the pharmaceutical formulation suitably is 6, preferably 7.

[0028] By following the concepts of the present invention, the solid pharmaceutical formulation is stable such that the HMG-CoA reductase inhibitor as the active substance does not tend to be decomposed and essentially retains its activity. Thereby, it is ensured that the active substance in the pharmaceutical formulation according to the present invention shows a sufficient stability while, at the same time, avoiding the negative impact of a high local alkaline environment at the site of dissolution of the pharmaceutical formulation on the gastric mucosa which would occur if the pH of an aqueous dispersion of the pharmaceutical formulation is 9 or more and which results in anormal digestive functioning.

[0029] The pharmaceutical formulation of this invention may include, in addition to the HMG-CoA reductase inhibitor which is sensitive to a low pH environment, one or more fillers, such as microcrystalline cellulose, lactose, sugars, starches, modified starch, mannitol, sorbitol and other polyols, dextrin, dextran and maltodextrin, calcium carbonate, calcium phosphate and/or hydrogen phosphate, sulphate, one or more binders, such as lactose, starches, modified starch, dextrin, dextran and maltodextrin, microcrystalline cellulose, sugars, polyethylene glycols, hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethyl cellulose, methylcellulose, carboxymethyl cellulose, gelatin, acacia gum, tragacanth, polyvinylpyrrolidone, magnesium aluminium silicate, one or more disintegrating agents such as croscarmellose sodium, cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl starch, starches and microcrystalline cellulose, magnesium aluminium silicate, polyacrylin potassium, one or more different glidants such as magnesium stearate, calcium stearate, zinc stearate, calcium behenate, sodium stearyl fumarate, talc, magnesium trisilicate, stearic acid, palmitic acid, carnauba wax, silicon dioxide, one or more buffering agents such as sodium or potassium citrate, sodium phosphate, dibasic sodium phosphate, calcium carbonate, hydrogen phosphate, phosphate, sulphate, sodium or magnesium carbonate, sodium ascorbinate, benzoate, sodium or potassium hydrogen carbonate, lauryl sulphate, or mixtures of such buffering agents.

[0030] If required any, the formulation may also include surfactants and other conventional components for solid, pharmaceutical formulations such as colouring agents, lakes, aromas and adsorbents. As surfactants the following may be used: ionic surfactants, such as sodium lauryl sulphate or non-ionic surfactants such as different poloxamers (polyoxyethylene and polyoxypropylene copolymers), natural or synthesized lecithins, esters of sorbitan and fatty acids (such as Span®, manufactured by Atlas Chemie), esters of polyoxyethylenesorbitan and fatty acids (such as Tween®, manufactured by Atlas Chemie), polyoxyethylated hydrogenated castor oil (such as Cremophor®, manufactured by BASF), polyoxyethylene stearates (such as Brij®, manufactured by Atlas Chemie), dimethylpolysiloxane or any combination of the above mentioned surfactants.

[0031] If the solid pharmaceutical formulation is in the form of coated tablets, the coating may be prepared from at least one film-former such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, at least from one plasticizer such as polyethylene glycols, dibutyl sebacate, triethyl citrate, and other pharmaceutical auxiliary substances conventional for film coatings, such as pigments, fillers and others.

[0032] The solid pharmaceutical formulations according to the present invention may be prepared as described below:

[0033] The mixture of the active substance, filler, binder, buffering agent, disintegrating agent and if required a surfactant and other conventional ingredients for solid pharmaceutical formulations is homogenised employing suitable mixers. Glidants and/or lubricants are added and the mixture is re-homogenised. The resulting mixture is compressed into tablets or filled into capsules. If needed, tablets can be film-coated.

[0034] The mixture of the active substance, filler, binder, buffering agent, disintegrating agent and if required a surfactant and other conventional ingredients for solid pharmaceutical formulations is homogenised employing suitable mixers, granulated with a suitable solvent such as water, ethanol, methanol, isopropyl alcohol, n-butyl alcohol, acetone, diethyl ether, ethyl acetate, isopropyl acetate, methyl acetate, dichloromethane and methanol, and mixtures of these solvents such as ethanol and acetone, methanol and acetone, dichloromethane and methanol, and the mixtures thereof. The resulting granulation is dried in suitable dryers such as standard plate dryers, fluid bed dryers, vacuum and microwave dryers. To the dried granulation, glidants and/or lubricants and if required other conventional ingredients for solid pharmaceutical formulations are added. The resulting mixture is rehomogenized and compressed into tablets or filled into capsules. Optionally, tablets are film-coated.

[0035] Moreover, according to the present invention the HMG-CoA reductase inhibitor as an active substance in a solid pharmaceutical formulation can be effectively stabilized by incorporating a HMG-CoA reductase inhibitor, which is capable of providing a pH in the range from 7 to 11, into a pharmaceutical formulation which is capable of providing a pH below 9. The pH generated by the pharmaceutical formulation may be adjusted by the incorporation of appropriate agents such as buffering agents and the like.

[0036] The present invention is illustrated but by no means limited by the following examples.

EXAMPLES

Example 1

[0037] The pharmaceutical formulation with the active ingredient pravastatin sodium in the form of tablets was prepared as follows: the hereinunder listed ingredients were homogenised and the resulting mixture was then compressed into tablets each containing 5, 10, 20 or 40 mg of pravastatin sodium.

[0038] The pH of the aqueous dispersion of this formulation is 8.3.

Ingredients	% by weight
Pravastatin sodium (pH 8.2)	5%
Lactose	37.5%
Microcrystalline cellulose	38%
Sodium citrate	10%
Magnesium aluminium silicate	2%
Polyacrylin potassium	3%
Talc	3%
Silicon dioxide	0.5%
Magnesium stearate	1%

Example 2

[0039] The pharmaceutical formulation with the active ingredient pravastatin sodium in the form of tablets was prepared as follows: the hereinunder listed ingredients were homogenised and the resulting mixture was then compressed into tablets each containing 5, 10, 20, 40 or 80 mg of pravastatin sodium.

[0040] The pH of the aqueous dispersion of this formulation is 8.0.

Ingredients	% by weight
Pravastatin sodium (pH 8.5)	10%
Lactose	32%
Microcrystalline cellulose	37%
Sodium citrate	10%
Croscarmellose sodium	2%
Sodium lauryl sulphate	0.5%
Polyacrylin potassium	3%
Talc	3%
Silicon dioxide	0.5%
Calcium stearate	2%

Example 3

[0041] The pharmaceutical formulation with the active ingredient pravastatin sodium in the form of tablets was prepared as follows: the first six hereinunder listed ingredients were homogenised, granulated with water, dried, the remainder of the below listed ingredients were added and homogenised and the resulting mixture was then compressed into tablets each containing 5, 10, 20 or 40 mg of pravastatin sodium.

[0042] The pH of the aqueous dispersion of this formulation is 8.2.

Ingredients	% by weight
Pravastatin sodium (pH 9)	5%
Lactose	20%
Microcrystalline cellulose	20%
Hydroxypropyl cellulose	1.5%
Sodium citrate	10%
Magnesium aluminium silicate	2%
Polyacrylin potassium	3%
Microcrystalline cellulose	35%
Talc	3%
Magnesium stearate	0.5%

Example 4

[0043] The pharmaceutical formulation with the active ingredient pravastatin sodium in the form of tablets was prepared as follows (ingredients are listed in the following table): the mixture of the active substance, filler, buffering agent, disintegrant and surfactant is homogenised employing suitable mixers. Glidants and lubricants are added and the mixture is re-homogenised. The resulting mixture is compressed into tablets. The pH of the aqueous dispersion of this formulation is 8.5.

Ingredient	% by weight	function
pravastatin sodium*	8.3	active substance
lactose	58.3	filler
microcrystalline cellulose	14.4	filler
Na_2HPO_4	10	buffering agent
Na lauryl sulphate	0.4	absorption accelerator, surfactant
cross-linked carboxymethylcellulose	4	disintegrant
colloidal silicon dioxide	0.5	glidant
talc	3	glidant, lubricant
magnesium stearate	1	lubricant

*pravastatin contains 0.3% of Na_2CO_3, so that the pH of the active substance is between 9 and 10. The percentage in the above mentioned formulation is calculated for the tablets containing 40 mg of pravastatin. The amount of pravastatin can be 80, 40, 20, 10 or 5 mg.

Example 5

[0044] The pharmaceutical formulation with the active ingredient pravastatin sodium in the form of tablets was prepared as in Example 4. The resulting mixture is compressed into tablets. The pH of the aqueous dispersion of this formulation is 8.3.

Ingredient	% by weight	function
pravastatin sodium*	8.3	active substance
lactose	58.3	filler
microcrystalline cellulose	16.5	filler
Na_2HPO_4 (dried)	7.9	buffering agent
sodium lauryl sulphate	0.4	absorption accelerator, surfactant
cross-linked carboxymethylcellulose	4	disintegrant

-continued

Ingredient	% by weight	function
colloidal silicon dioxide	0.5	glidant
talc	3	glidant, lubricant
magnesium stearate	1	lubricant

*pravastatin contains 0.3% of Na_2CO_3, so that the pH of the active substance is between 9 and 10. The amount of pravastatin can be 80, 40, 20, 10 or 5 mg.

Example 6

[0045] The pharmaceutical formulation with the active ingredient atorvastatin calcium in the form of tablets was prepared as in Example 4. The resulting mixture is compressed into tablets.

Ingredient	weight (mg)	function
Atorvastatin calcium	20.0	active substance
lactose	140.0	filler
macrocrystalline cellulose	34.8	filler
Na_2HPO_4 (dried)	24.0	buffering agent
Na lauryl sulphate	2.0	absorption accelerator, surfactant
cross-linked carboxymethylcellulose	9.6	disintegrant
colloidal silicon dioxide	1.2	glidant
talc	7.2	glidant, lubricant
magnesium stearate	1.2	lubricant

In case of higher or lower dosages of atorvastatin calcium (80, 40, 10 or 5 mg), proportional higher or smaller amounts of other ingredients are used, or proportional bigger or smaller tablets are prepared.

[0046] Tablets containing pravastatin or atorvastatin which were formed according to Examples 1 to 6 were subjected to stability studies and it was found that the tablets provide an excellent stability; essentially no degradation products of pravastatin or atorvastatin were observed.

1-38. (canceled)

39. A process for the preparation of a stable solid pharmaceutical formulation containing as an active ingredient a HMG-CoA reductase inhibitor, the process comprising the steps of:

a) homogenizing a mixture of an active composition consisting of said active ingredient and a buffering agent, wherein the active composition has a pH in the range from 7 to 11, with at least one constituent selected from the group consisting of a filler binder, buffering agent, disintegrating agent and optionally surfactant and other commonly used ingredients for solid pharmaceutical formulations in suitable mixers,

b) adding glidants and/or lubricants,

c) re-homogenizing the mixture and

d) compressing the resulting mixture into tablets, or filling the resulting mixture into capsules;

e) optionally film-coating the tablets,

wherein said HMG-CoA reductase inhibitor is selected from the group consisting of pravastatin and atorvastatin and a pharmaceutically acceptable salt thereof, and wherein the pharmaceutical formulation has a pH in the range from 6 to 9.

40. The process according to claim **39** wherein a second buffering agent is mixed in the homogenizing step.

41. A process for the preparation of a stable solid pharmaceutical formulation the process comprising the steps of:

a) homogenizing a mixture of an active composition consisting of an active ingredient and a buffering agent, wherein said active ingredient is a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin and atorvastatin and a pharmaceutically acceptable salt thereof, and wherein the active composition has a pH in the range from 7 to 11 with at least one constituent selected from the group consisting of a filler, binder, buffering agent, disintegrating agent and optionally surfactant and other commonly used ingredients for solid pharmaceutical formulations in suitable mixes,

b) granulating the mixture with a suitable solvent,

c) drying the resulting granulation in suitable dryers,

d) adding the dried granulations glidants and/or lubricants and optionally other ingredients for solid pharmaceutical formulations,

e) re-homogenizing the mixture, and

f) compressing the resulting mixture into tablets, or filling the resulting mixture into capsules;

g) optionally film-coating the tablets,

wherein the pharmaceutical formulation has a pH in the range from 6 to 9.

42. The process according to claim **41**, wherein a second buffering agent is mixed in the homogenizing step.

43. A method for stabilizing an active substance in a solid pharmaceutical formulation, the method comprising;

preparing a mixture of said active substance and a buffering agent imparting a pH in the local environment around the active substance in the range from 7 to 11 wherein said active substance is a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin and atorvastatin and a pharmaceutically acceptable salt there and said buffering agent is present in an amount less than 1% based on the total weight of the pharmaceutically active substance, an

incorporating said mixture as an active substance into a pharmaceutical formulation, thus having a pH in the range from 6 to 9.

44. The method according to claim **43**, wherein the pharmaceutical formulation has a pH in the range from 7 to 8.5.

45. The method according to claim **43**, wherein the active substance is a HMG-CoA reductase inhibitor in the form of a salt.

46. The method according to claim **43**, wherein the active substance contains a buffering agent in order to provide a pH for said active substance in the range from 7 to 11 and additional amounts of a buffering agent are incorporated into the pharmaceutical formulation in order to provide a pH for said pharmaceutical formulation below 9 and a lower pH limit of 6.

47. The method according to claim **43**, wherein the active substance is a sodium salt of pravastatin or a calcium salt of atorvastatin.

48. The method according to claim **43**, wherein said stable solid pharmaceutical formulation further comprises at least on constituent selected from the group consisting of a filler, a binder, a disintegrated agent, a glidant; optionally further comprising at least one constituent selected among coloring agents, lakes, aromas, adsorbents, film formers and plasticizers.

49. A process for the preparation of a stable solid pharmaceutical formulation the process comprising the steps of:

a) homogenizing a mixture of an active composition consisting of an active ingredient and a buffering agent, wherein said active ingredient is a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin and atorvastatin and a pharmaceutically acceptable salt thereof, and

wherein the active composition has a pH in the range from 7 to 11, and said buffering agent is present in an amount less than 1% based on the total weight of the pharmaceutically active substance, with at least on constituent selected from the group consisting of a filler, binder, buffering agent, disintegrating agent and optionally surfactant and other commonly used ingredients for solid pharmaceutical formulations in suitable mixers,

b) adding glidants and/or lubricants,

c) re-homogenizing the mixture and

d) compressing the resulting mixture into tablets or filling the resulting mixture into capsules;

e) optionally film-coating the tablets,

wherein the pharmaceutical formulation has a pH below 9 and a lower pH limit of 6.

50. A process for the preparation of a stable solid pharmaceutical formulation containing as an active ingredient a HMG-CoA reductase inhibitor, the process comprising the steps of:

a) mixing a combination of said active ingredient and a buffering agent, wherein the active composition has a pH in the range from 7 to 11, with at least one constituent selected from the group consisting of a filler binder, buffering agent, disintegrating agent and optionally surfactant and other commonly used ingredients for solid pharmaceutical formulations in suitable mixers to form a mixture;

b) adding glidants and/or lubricants,

c) combining said mixture from (a) and said ingredients added in (b), and

d) compressing the resulting mixture into tablets, or filling the resulting mixture into capsules;

e) optionally film-coating the tablets,

wherein said HMG-CoA reductase inhibitor is selected from the group consisting of pravastatin and atorvastatin and a pharmaceutically acceptable salt thereof, and wherein the pharmaceutical formulation has a pH in the range from 6 to 9.

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