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(54) Title: STABLE PHARMACEUTICAL DOSAGE FORM COMPRISING HMG-CoA REDUCTASE INHIBITOR

(57) Abstract: The present invention relates to stable pharmaceutical dosage forms comprising the active substances sensitive to environmental influences and pharmaceutical excipients which provide stability of one or more active substance to pH of the environment and do not contain alkalizing or buffering substances or combinations thereof. Said invention also discloses the stable pharmaceutical dosage forms comprising the active substances sensitive to pH of the environment, oxidation and/or environmental humidity, pharmaceutical excipients which provide stability of the active substance to pH of the environment and the coating which provides protection of the active substance from environment influences, in particular from oxidation and/or environmental humidity. Further the invention discloses the procedures for the preparation of the stable pharmaceutical dosage form and use of such active substances for the preparation of the pharmaceutical dosage forms for the treatment of dyslipidemias, cardiovascular disease and other diseases.

WO 2004/071402 A2

Stable pharmaceutical dosage form comprising HMG-CoA reductase inhibitor

Field of the invention

The present invention relates to the field of pharmaceutical industry, in particular to stable pharmaceutical dosage forms comprising the active substances which are sensitive to environmental influences. Preferably the active substance is sensitive to the pH of the environment, oxidation and/or environmental humidity and is selected from the group of HMG-CoA reductase inhibitors. Most preferably the active substance is atorvastatin.

The stable pharmaceutical dosage form of the present invention comprises one or more active substances, sensitive to pH of the environment, and one or more pharmaceutical excipients which provide stability of one or more active substances to pH of the environment wherein said pharmaceutical dosage form has the water content below 3.5%, preferably below 3% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof. Said pharmaceutical dosage form comprises one or more excipients selected from the group consisting of various types of microcrystalline cellulose and modified forms of microcrystalline cellulose.

Further, the stable pharmaceutical dosage form contain uncoated or coated particles comprising the active substance sensitive to environmental influences and is particularly sensitive to pH of the environment, oxidation and/or environmental humidity and is selected from the group of HMG-CoA reductase inhibitors.

The coated particles of the present invention are the particles of the active substance which are protected from environmental influences and in particular from oxidation and/or

environmental humidity by coating. Such coated particles are either in an uncoated pharmaceutical dosage form or in a coated pharmaceutical dosage form wherein the coating of such dosage form affords protection of the active substance and pharmaceutical excipients from environmental influences and in particular from oxidation and/or environmental humidity.

Other pharmaceutical dosage forms of said invention comprise uncoated particles of the active substance, one or more pharmaceutical excipients which afford stability of the active substance at the pH of the environment where said pharmaceutical dosage form has the water content below 3.5%, preferably below 3% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof, and the coating which affords protection of the active substance and pharmaceutical excipients from environmental influences, in particular from oxidation and/or environmental humidity.

The coated pharmaceutical dosage forms of the invention are stable to environmental influences, that is, afford stability of the active substance and pharmaceutical excipients to environmental influences and thus protect the active substance and pharmaceutical excipients from the environmental influences.

The present invention also relates to the methods and the processes for the preparation of stable pharmaceutical dosage forms according to this invention. The present invention further relates to use of the active substance for the preparation of stable pharmaceutical dosage forms according to said invention for the treatment and to the methods of treatment for a variety of diseases by administering the coated particles and/or pharmaceutical dosage forms of the present invention wherein the diseases are selected from the group including dyslipidemia, hyperlipidemia, hypercholesterolemia, atherosclerosis, arteriosclerosis, cardiovascular disease, coronary arterial disease, coronary heart disease, vascular disorders, inflammatory disease, allergic disease, neurodegenerative disease, malignant disease, viral disease (WO 0158443), abnormal bone states, (WO 0137876), amyloid-β precursor protein processing disorders such as Alzheimer's disease or Down's Syndrome (WO 0132161).

Background of the invention

Many therapeutic substances are sensitive to influences of the environment and due to these impacts their active forms are transformed to degradation products which are often less effective than the active forms. Apart from lower efficacy, degradation products may also cause undesirable effects thus affecting safe use of a medicament. Already a very low percent of impurities or degradation products of the active substance may significantly impair a drug safety. Therefore, it is important that the therapeutic substance is as pure as possible when administered, that is, the percent of degradation products and impurities should be minimal. Procedures for the preparation of an active substance *per se* (e.g., processes of isolation and purification), and interim phases of storage of the active substance and/or its intermediates during the production and the phases of storage of the active substance up to the procedure of pharmaceutical dosage form production and during the course of its production have an influence on the percent of impurities and degradation products of the active substance. At the same, excipients comprised in the pharmaceutical dosage form have an influence on the percent of degradation products and impurities in the active substance. . Said pharmaceutical excipients are selected from the group consisting of fillers or diluents, binders, lubricants, glidants, disintegrants, colorants, flavors, adsorbents, plasticizers and the like.

Not only an active substance undergoes degradation by environmental influences but also excipients in a pharmaceutical dosage form may be degraded. Degradation products of the latter act as the reactive sites which trigger degradation reactions of the active substance in a pharmaceutical dosage form.

Among the environmental factors which have an impact on an active substance are, for example, temperature, humidity, light, (e.g. UV light) and gases, present in the environment such as, e.g., oxygen or carbon dioxide. An important factor is also the pH of the environment, that is, presence of substances which have influence on acidity or alkalinity of the environment (e.g., acids, alkalis, salts, metal oxides) and the reactivity of the ambient medium or active substance (free radicals, heavy metals), etc.

The majority of therapeutic active substances are sensitive to temperature, in particular high temperature. Temperature increase accelerates chemical reactions and thus more degradation products are formed in a shorter period of time. In certain cases at elevated

temperature the reactions take place which would not at normal temperature. Thus, the temperature has an impact on the kinetic and thermodynamic parameters of the chemical reactions leading to occurrence of degradation products.

Many active substances are sensitive to humidity. At increased humidity water is bound to the active substance itself and/or pharmaceutical excipients surrounding the active substance which associated with one or more other environmental influences may thustrigger degradation reactions of the active substance. It is known from the prior art that HGM-CoA reductase inhibitors, e.g. pravastatin and atorvastatin, are also sensitive to humidity.

Compounds containing structural elements which at low pH are converted to a lactone form are generally sensitive to an acidic environment. Among them the best known are HGM-CoA reductase inhibitors (statins) and related compounds which comprise 7-substituted-3,5-dihydroxyheptanoic and/or 7-substituted-3,5-dihydroxyheptanoic acid groups. Apart from conversion to a lactone form, other mechanisms of degradation of said active substances may take place in an acidic environment, for example, isomerization in case of pravastatin. (Serrajuddin, A. T. M. et al, Biopharm. Sci. 80, 830-834, 1991; Kearney, A. S. et al, Pharm. Res. 10, 1993, 1461-1465).

Statins and related compounds are in the form of a cyclic ester – lactone, therefore, among others they are also sensitive to an alkaline medium, where they are transformed to an acid form.

Compounds in the environment which increase acidity or alkalinity of the environment trigger degradation reactions of an active substance sensitive to acidic or alkaline environment. Carbon dioxide in the presence of humidity or water, in which it is freely soluble, forms carbonic acid which increases the acidity of the environment.

Light and in particular UV light induce degradation reactions of active substances, especially organic ones. It is known that among others levofloxacin (Sato, Y.Y.E. and Moroi, R., Arzneim, Forsch. / Drug Res. 43, 1993, 601 – 606) and atorvastatin are also sensitive to light (Hurley, T. R. et al, Tetrahedron 49, 1993, 1979-1984).

Oxygen induces oxidation, that is, oxidative degradation reactions of an active substance and/or pharmaceutical excipients resulting in formation of the reactive sites and/or degradation products which lead to further oxidation or further oxidative degradation reactions of the active substance and/or pharmaceutical excipients. It is known in the prior art that HMG-CoA reductase inhibitors, for example, pravastatin, atorvastatin, simvastatin and lovastatin, are also sensitive to oxidation (Javernik, S., et al, Pharmazie 56, 2001, 738–740; Smith, G. B., et al, Tetrahedron 49, 1993, 4447-4462; patent application P-200200244).

HMG-CoA reductase inhibitors (statins) are also among the active substances sensitive to pH of the environment, humidity, light, temperature, carbon dioxide and oxygen. They are known as the most effective therapeutically active substances for the treatment of dyslipidemias and cardiovascular disease, selected from the group consisting of dyslipidemia, hyperlipidemia, hypercholesterolemia, atherosclerosis, arteriosclerosis, coronary artery diseases, coronary heart disease and the like, associated with the metabolism of lipids and cholesterol. The mechanism of action of statins is the inhibition of the biosynthesis of cholesterol and other sterols in the liver of humans or animals. They are competitive inhibitors of HMG-CoA reductase or 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, an enzyme which catalyses the conversion of HMG-CoA to mevalonate in the liver of humans or animals, which is an important step in the biosynthesis of cholesterol in the liver. Recent studies indicate that, in addition to the said therapeutic effects, statins also have other therapeutic effects and thus they are useful for the treatment of diseases, abnormal conditions and disorders which are selected from the group consisting of vascular disorders, inflammatory disease, allergic disease, neurodegenerative disease, malignant disease, viral disease (WO 0158443), abnormal bone states, (WO 0137876), amyloid-β precursor protein processing disorders such as Alzheimer's disease or Down's Syndrome (WO 0132161).

Among the statins, for example, the following are known: pravastatin, atorvastatin, simvastatin, lovastatin, mevastatin or compactin, fluvastatin or fluindostatin, cer(i)vastatin or rivastatin, rosuvastatin or visastatin, and itavastatin or pitavastatin, or nisvastatin.

Pravastatin is chemically (betaR*, deltaR,1S,2S,6S,8S,8aR)-1,2,6,8,8a-hexahydro-beta, delta, 6-trihydroxy-2-methyl-8-((2S)-2-methyl-1-oxobutoxy)-1-naphthalene heptanoic acid.

A sodium salt of said acid is sodium pravastatin. It was described first time in US Pat. No. 4346227.

Atorvastatin is chemically a (R-(R*,R*))-2-(4-fluorophenyl-beta, delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-((phenylamino)carbonyl)-1H-pyrrole-1-heptanoic acid hemicalcium salt. It was described first time in US Pat. No. 5273995.

Rosuvastatin is chemically (2:1) (3R,5S,6E)-7-(4-(4-fluorophenyl)-6-(1- methylethyl)-2-(methyl(metylsulfonyl)amino)-5-pyrimidinyl)-3,5-dihydroxy-6- heptenoic acid calcium salt. It was described first time in US Pat. No. 5260440.

Fluvastatin is chemically R*,S*-(E)-(+-)-7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid. Fluvastatin sodium is a sodium salt of said acid. It was described first time in European patent 114027.

Simvastatin is chemically (1S-(1alpha, 3alpha, 7beta, 8beta (2S*, 4S*) 8a beta))-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-(2-(tetrahydro-4-hydroxy-6-oxo-2H-pyrran-2-il)ethyl)-1-naphthalenyl-2,2-dimetylbutanoate. It was described first time in US Pat. No. 4444784.

Lovastatin is chemically (1S-(1alpha, 3alpha, 7beta, 8beta (2S*, 4S*) 8a beta))-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-(2-(tetrahydro-4-hydroxy-6-oxo-2H-pyrran-2-yl)ethyl)-1-naphthalenyl-2-methylbutanoate. It was described first time in US Pat. No. 4231938 and JP 8425599.

Itavastatin is chemically (S-(R*,S*-(E)))-7-(2-cyclopropyl-4-(4-fluorophenyl)-3-quinolynyl)-3,5-dihydroxy-6-heptenoic acid. Pitavastatin is a lactone form of itavastatin. They were described first time in European patent no. 304063 and US Pat. No. 5011930, respectively.

Mevastatin is chemically (3R, 5R)-3,5-dihydroxy-7-((1S, 2S, 6S, 8S, 8aR)-2-methyl-8-((2S)-2-methylbutanoyl)oxy)-1,2,6,7,8,8a-hexahydronaphthalen-1-yl)heptanoic acid. It was described first time US Pat. No. 3983140.

Cerivastatin is chemically (S-(R*,S*-(E)))-7-(4-(4-fluorophenyl)-5-(methoxymethyl)-2,6-bis (1-methylethyl)-3-pyridinyl)-3,5-dihydroxy-6-heptanoic acid. It was described first time in European patent no. 491226.

Many of the above statins are sensitive in particular to environmental influences, for example, atmospheric influences and pH of the environment. In the prior art it is known that certain statins are sensitive, to acidic environment (low pH values) wherein they are degraded to their lactone forms and different isomers. For example, pravastatin, atorvastatin, itavastatin, and fluvastatin are converted to their lactone forms in an acidic environment.

Kearney, A.S., et al, in The Interconversion Kinetics, Equilibrium, and Solubilities of the Lactone and Hydroxyacid Forms of the HMG-CoA Reductase Inhibitor, CI-981, Pharmaceutical Research Vol. 10, No. 10, 1993, 1461-1465, describe conversion of atorvastatin in the form of hydroxy acid to the lactone form at low pH which starts at the pH of the environment of about 4, moreover by increasing acidity of the medium the equilibrium reaction of conversion shifts towards formation of the lactone.

An impact of humidity and a diluent lactose on formation of atorvastatin lactone was investigated in amorphous and four polymorphic forms of atorvastatin. The samples of amorphous and polymorphic forms I to IV of atorvastatin and binary mixtures with lactose in the ratio 1 : 2 were exposed at 80°C in normal atmosphere (air) with relative humidity 5% and 100% for 3 days. The assay of atorvastatin was determined by liquid chromatography. All of the selected forms of atorvastatin, stored at 4°C were analyzed as reference samples.

Table 1. Increase in the assay of atorvastatin lactone in an amorphous form and different crystalline forms of atorvastatin in binary mixtures with lactose, stored at 80°C in normal atmosphere (air) with relative humidity 5% and 100% for 3 days in respect to reference samples.

Increase of atorvastatin lactone %	Amorphous atorvastatin	Crystalline form I	Crystalline form II	Crystalline form III	Crystalline form IV
Relative humidity 5%	0.21	0.43	0.40	0.32	0.15
Relative humidity 100 %	0.62	0.49	1.15	1.00	0.88
Relative humidity 5% Mixture with lactose 1:2	0.37	0.58	0.70	0.48	0.27
Relative humidity 100 % Mixture with lactose 1:2	8.60	1.43	3.29	5.43	9.27

The study shows that different forms of atorvastatin are proportionately similar sensitive to humidity impact in respect of the formation of atorvastatin lactone. At higher relative humidity an increase of lactone is significantly higher in all forms except for crystalline form I.

At low relative humidity lactose has no significant effect on formation of atorvastatin lactone, while said effect is very strong at high relative humidity. The above phenomenon may be explained as follows: lactose in the presence of water has an acidic action influencing formation of atorvastatin lactone.

In the prior art it is also known that statins which are in the lactone form, e.g. lovastatin and simvastatin, are sensitive to alkaline environment wherein they are converted to the acid form.

The sensitivity of different pharmaceutical active substances to oxidative degradation is described by Waterman, K.C., et al, in "Stabilization of Pharmaceuticals to Oxidative Degradation", Pharmaceutical Development and Technology, 7(1), 2002, 1-32, and possible approaches to stabilize pharmaceutical active substances against oxidative

degradation are also presented. The above mentioned article suggests that study of oxidative mechanism in solid pharmaceutical dosage forms is difficult and demanding as indicated by few reports in said area. An active substance per *se* and more frequently an active substance in a pharmaceutical dosage form may oxidize. During the processing of drug to form a solid dosage form, it is possible to mechanically generate amorphous drug. The percent of formed amorphous form is usually small and below 1%. Amorphous drug regions have greater mobility and lack crystal-lattice stabilization energy, and a result oxygen permeability and solubility will be higher. Greater mobility and higher oxygen concentration present in amorphous active substance also facilitate electron transfer to oxygen. (Waterman, K.C., et al, Stabilization of Pharmaceuticals to Oxidative Degradation, Pharmaceutical Development and Technology, 7(1), 2002, 1-32).

Byrn, S.R., et al. (Solid-State Chemistry of Drugs, 2nd Ed., SSCI, West Lafayette, 1999) disclose that molecular oxygen from atmosphere reacts with organic crystals and said reactivity depends on a crystal form and morphology, respectively, which determines permeability to oxygen and its solubility in the crystal lattice. In some examples the reactivity decreases with increased melting point indicating that higher crystalline lattice energy inhibits diffusion of oxygen.

It is in general more difficult to remove an electron from a drug when it is more positively charged. Therefore drug stability against oxidation is often greater under lower pH conditions. The sensitivity of an active substance to oxidationalso depends on a pharmaceutical dosage form *per se* and pharmaceutical excipients in it. Pharmaceutical excipients also influence oxidation of the active substance in a pharmaceutical dosage form. They can potentially solvate some of the active substance either directly or by bringing in low levels of moisture. In a solid solution form, the active substance will be amorphous with all the corresponding reactivity discussed above. Excipients themselves can be a source of oxidants or metals (e.g. present impurities) and may be involved in occurrence of mobile oxidative species, such as peroxyl radicals, superoxide and hydroxyl radicals. This willdepend on the hydrogen bond strength of the excipient and whether there are good electron donor sites (e.g. amines) Peroxide impurities are often present in polymeric excipients and these is a major source of oxidation in pharmaceutical formulations. (Waterman, K.C., et al, Stabilization of Pharmaceuticals to Oxidative Degradation, Pharmaceutical Development and Technology, 7(1), 2002, 1-32).

In the studies we have found that some of the above statins are particularly sensitive to oxidation. Among them particularly sensitive are certain polymorphic or amorphous forms of atorvastatin, pravastatin, lovastatin, simvastatin and rosuvastatin.

The influence of oxygen on occurrence of degradation products of amorphous and four polymorphic forms of atorvastatin was investigated. The samples of atorvastatin amorphous and polymorphic forms I to IV were exposed at 80°C in normal (air) and oxygen atmosphere for 3 days. The assay of oxidation products was determined by liquid chromatography. All of the chosen forms of atorvastatin stored at 4°C were analyzed as the reference samples.

Table 2. Increase of the degradation products of amorphous and different crystalline forms of atorvastatin stored at 80°C in normal (air) and oxygen atmosphere for 3 days in respect to reference samples

Increase of degradation products %	Amorphous ATV	Crystalline form I	Crystalline form II	Crystalline form III	Crystalline form IV
AIR	1.04	0.04	0.25	0.11	1.14
OXYGEN	3.4	0.07	0.71	0.47	3.67

The above study showed that different forms of atorvastatin are variably sensitive to the impact of oxygen regarding the formation of degradation products. In case of amorphous atorvastatin and crystalline form IV the percent of oxidation degradation products essentially increased in oxygen atmosphere and normal atmosphere (air). In case of crystalline forms I, II and III the percent of said degradation products was low in air atmosphere, while in oxygen atmosphere the percent of oxidation degradation products increased in crystalline forms II and III.

We can conclude that crystalline form I is stable to oxygen and oxidation, moreover crystalline forms II and III are slightly sensitive to oxidation and crystalline form IV and amorphous atorvastatin are highly sensitive to oxidation.

Prior art

The patent documents which solve the problem of maintaining the stability of some of the listed statins at low pH of the environment are:

- for atorvastatin with alkaline compounds US Pat. No. 5686104, US Pat. No. 6126971, WO 9416693 and European patent no. 680320, and with alkaline and/or buffering compounds WO 02072073;
- for pravastatin with alkaline compounds European patent no. 336298, US Pat. No. 5030447 and US Pat. No. 5180589, with alkaline and/or buffering compounds and other pharmaceutical excipients WO 02076376, with buffering compounds WO 03000239 and WO 03000177;
- for fluvastatin with alkaline medium European patent no. 547000 and US Pat. No. 5356896;
- for itavastatin with alkaline compound WO 9723200 European patent no. 814782;
- for atorvastatin, pravastatin and other statins with polymers which contain amino groups or amido groups, WO 0176566 and US Pat. No. 20020035142;
- for atorvastatin, pravastatin, fluvastatin, cerivastatin, mevastatin, pitavastatin, rosuvastatin, lovastatin and simvastatin with amino sugars WO 02089788;
- for atorvastatin, pravastatin, fluvastatin and cerivastatin with buffering compounds WO 0035425;
- for atorvastatin, pravastatin, fluvastatin and cerivastatin with alkaline and/or buffering compound WO 0193860.

WO 02/076376 discloses stabilization of pravastatin with carriers which comprise at least one diluent and at least one lubricant wherein a diluent is further specified as water-soluble and is selected from the group consisting for example of calcium carbonate, calcium phosphate, calcium hydrogen phosphate, calcium phosphate tribasic, calcium sulfate, sugar compressible, lactose, saccharose, sorbitol, mannitol, dextrates, dextrins, dextrose, maltodextrin and mixtures thereof, or as water-dispersible and is selected from the group consisting of e.g. cellulose and its derivatives, starch and its derivatives, kaolin and kaolin minerals and mixtures thereof, and a lubricant is selected from the group consisting of sodium stearyl fumarate, palmitic acid, calcium stearate, magnesium stearate, zinc stearate, talc, carnauba wax, silicon dioxide, hydrogenated vegetable oil and mixtures thereof.

WO 0176566 and US Pat. No. 20020035142, respectively, disclose stable pharmaceutical dosage forms for the treatment of dyslipidemias comprising as the active substance at least one open-chained 7-substituted-3,5-dihydroxyheptanoic acid or open-chained 7-substituted-3,5-dihydroxyheptenoic acid and a polymer compound comprising at least one amido group (e.g., PVP, crosslinked PVP, copolymers of vinylpyrrolidone and vinylacetate, polynoxylin), or a polymer group comprising at least one amino group (a polymer with a quaternary ammonium group such as, e.g., cholestyramine), or a combination of both wherein other stabilizing agents such as buffers and bases are excluded. Said polymers are present in the amount which provides effective stabilization.

WO 02089788 discloses stabilization of the statins, including pravastatin, atorvastatin, fluvastatin, mevastatin, rivastatin, pitavastatin, rosuvastatin, lovastatin and simvastatin with amino sugars such as, e.g., meglumine or N-methyl-glucamine.

European patent no. 336298 and US Pat. No. 5030447 and US Pat. No. 5180589, respectively, disclose stabilization of pravastatin with basifying substances, among, which, before all, strong bases such as hydroxides of alkali metals and alkaline earth metals, and ammonium hydroxide, preferably specifying the substances such as magnesium oxide, magnesium hydroxide, calcium hydroxide sodium hydroxide, potassium hydroxide and lithium hydroxide, and ammonium hydroxide and magaldrate.

WO 9416693, US Pat. No. 5686104 and European patent no. 0680320, respectively, disclose stabilization of atorvastatin with a metallic salt as an additive which is an alkaline earth metal salt, for example calcium or magnesium carbonate, calcium or magnesium hydroxide, magnesium silicate, magnesium aluminate and aluminium magnesium hydroxide.

WO 0035425 discloses stabilization of the statins with buffers, among which are listed, for example sodium and potassium citrate, sodium phosphate, disodium phosphate, calcium carbonate, calcium hydrogen phosphate, calcium phosphate, calcium sulfate, sodium or magnesium carbonate, sodium ascorbinate, benzoate, sodium or potassium hydrogen carbonate, sodium or potassium lauryl sulfate and mixtures thereof.

WO 0193860 discloses stabilization of statins with co-crystallization and/or co-

precipitation of a statin and a buffering or basifying substance in a homogeneous mixture of statins and said buffering or basifying substance. The following buffering substances are described, for example sodium and potassium citrate, sodium and potassium phosphate or hydrogen phosphate, dibasic sodium phosphate, sodium, potassium, magnesium or calcium carbonate or hydrogen carbonate, sulfates, aminoguanidine carbonate or hydrogen carbonate, guanidine carbonate or hydrogen carbonate, succinimide carbonate or hydrogen carbonate, 1-adamantil amine carbonate or hydrogen carbonate etc. The following basifying substances are described, for example metallic oxides such as magnesium oxide, aluminium oxide, hydroxides of alkaline and alkaline earth metals and organic bases such as succinimide, 1-adamantil amine, N,N'-bis (2-hydroxyethyl) ethylenediamine, tris(hydroxymethyl)aminomethane, D(-)-N-methylglucamine and organic acids with alkaline character such as 3-(N-morpholino) propanesulfonic acid, 4-(cyclohexyl amino)-1-butanesulfonic acid, 4-(cyclohexyl amino)-1-ethansulfonic acid and salts of alkali and alkaline earth metals with said acids or with arginine, ornithine, lysine, etc.

WO 9723200 and European patent no. 0814782, respectively, disclose stabilization of NK-104 or itavastatin (pitavastatin) with a basifying compound such as, e.g. antacids from the group consisting of magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium aluminate, aluminium hydroxide, synthetic hydrotalcite, synthetic aluminium silicate, magnesium carbonate, calcium carbonate, magnesium oxide, aluminium hydroxide, sodium hydrogen carbonate, and such as, e.g., pH regulators from the group consisting of L-arginine, sodium phosphate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium phosphate, dipotassium hydrogen phosphate, potassium dihydrogen phosphate, disodium citrate, sodium succinate, ammonium chloride and sodium benzoate.

European patent no. 547000 and US Pat. No. 5356896, respectively, disclose stabilization of fluvastatin with an alkaline medium which is either an alkali or a buffer and specifies water-soluble alkaline substances from the group consisting of inorganic carbonate salts such as sodium or potassium carbonate, sodium bicarbonate, potassium hydrogen carbonate, phosphate salts such as anhydrous sodium, potassium or calcium dibasic phosphate, trisodium phosphate and hydroxides of alkaline metals such as sodium, potassium or lithium hydroxide and mixtures thereof. Further it also specifies water-insoluble or low soluble alkaline substances such as magnesium oxide, hydroxide or

carbonate, magnesium hydrogen carbonate, aluminium or calcium hydroxide and carbonate, combined compounds of aluminum and magnesium such as magnesium aluminium hydroxide, and the phosphoric acid salts such as tribasic calcium phosphate and mixtures thereof.

WO 03000239 describes stabilization of pravastatin with buffers such as, e.g. TRIS – trometamine and disodium hydrogen phosphate.

Among the patent documents which solve the problem of maintaining the stability of some of the listed statins at high humidity and temperature is WO 9949896 which discloses stabilization of pravastatin with beta-cyclodextrin.

A review of the known methods (antioxidants, packaging) for stabilization of the active substances from oxidation is presented , e.g., in Waterman, K. C., et al, Pharm. Dev. and Technol. 7, 2002, 1-32.

For the prevention or reduction of active substances oxidation in a pharmaceutical dosage form, different approaches are used, for example:

- increase of the concentration of the active substance in a pharmaceutical dosage form when oxidation is caused by peroxide and metallic impurities in pharmaceutical excipients;
- addition of chelating agents (such as, e.g. citric acid, EDTA, fumaric and malic acid) to the formulation for mitigation of metallic impurities;
- use of high-purity pharmaceutical excipients;
- use of alternative excipients or decrease their amount in the pharmaceutical dosage form, especially when peroxide impurities are the cause of oxidation ;
- use of antioxidants which can reduce formation of peroxides , but maybe less effective at eliminating peroxides already present in a dosage form.

For individual active substances there is no general way to predict optimal solution for oxidation prvention and the publications available are scarce (Waterman, K.C., et al, Stabilization of Pharmaceuticals to Oxidative Degradation, Pharmaceutical Development and Technology, 7(1), 2002, 1-32).

Among suitable antioxidants there are described:

- chain terminators (e.g. thiols and phenols);
- sacrificial reductants which are oxidized more readily than the active substance and thus remove present oxygen (e.g. sulfites and ascorbic acid) wherein their combination may act synergistically (e.g. a combination of ascorbic palmitate and tocopherol);
- peroxide quenchers(e.g. Fe^{2+}) which degrade peroxides by Fentonprocess. Their use is limited because in this process a free hydroxyl radical is formed.
- cyclodextrins which cover the site of an active substance, subjected to oxidation (Waterman, K.C., et al, Stabilization of Pharmaceuticals to Oxidative Degradation, Pharmaceutical Development and Technology, 7(1), 2002, 1-32).
-

In addition to above-mentioned solutions, prevention from oxidation can be achievedby packaging where the oxygen content in a space surrounding an active substance and permeability of oxygen through the package walls and cap are regulated. Packaging in nitrogen is possible to reduce the oxygen content contained in the package. When drugs are concerned, a blister is the most suitable. Blisters which are less permeable or impermeable to oxygen (e.g. foil-foil) are usually more expensive. Despite the described methods of stabilization in different ways, for example, with the addition of antioxidants to a pharmaceutical dosage form by packaging a pharmaceutical dosage form into a suitable package, these solutions have not shown to be convenient for all active substances and all markets, respectively (Waterman, K.C., et al, Stabilization of Pharmaceuticals to Oxidative Degradation, Pharmaceutical Development and Technology, 7(1), 2002, 1-32).

Different types of packaging materials for the protection of pharmaceutical active substances and pharmaceutical dosage form from oxidation are disclosed in numerous patents.

WO 0076879 discloses the barrier pack comprising a cover portion bonded to a base portion to form a sealed unit package wherein the cover portion comprises at least one cavity containing a product, and the cover portion and/or base portion has an absorbing agent material (desiccant).

European patent no. 370755 discloses a packaging material for drugs which is specially designed with the foil comprising an inner polypropylene film, an intermediate olefin film

and an outer polypropylene film. Further, said package may also comprise aluminium foil.

European patent no. 595800 discloses a packaging material comprising a layer which removes oxygen from a package by means of an enzyme reaction; the package has an outer film which is impermeable to gas and water vapours (e.g. a laminate such as polyamide and polyethylene), an inner film which is permeable to gas and impermeable to liquid (e.g. polyethylene and copolymers thereof), and intermediate film which removes oxygen and comprises a liquid phase with an enzyme for oxygen removal (oxidase such as glucose oxidase) wherein an insoluble filler is suspended in a liquid phase.

The methods of coating the substances or products sensitive to oxidation with coatings which protect said substances or products from oxidation are known in the prior art in the food industry. The coatings from milk proteins are described which also comprise carboxymethylcellulose to prevent oxidative browning of apples and potatoes (Le Tien, C., et al, Protein Coatings Prevent Oxidative Browning of Apples and Potatoes, Journal of Food Science Vol. 66, No. 4, 2001, 512-516).

In the field of pharmacy the use of ethylcellulose for coating of ascorbic acid granules for protection against oxidation is known (Wade, A., et al, Handbook of Pharmaceutical Excipients, 2nd Ed, American Pharmaceutical Association, Washington, and The Pharmaceutical Press, London, 1994, 186-190).

Sensitivity of lovastatin to oxidation and its stabilisation and protection from oxidation with natural antioxidants are described by Javernik, S., et al, in Pharmazie 56(9), September 2001, 738-740.

Sensitivities of lovastatin and simvastatin and other substances (e.g. alkaline substances with pKa from 1 to 10 and from 5 to 9, respectively, which further have redox potential of about 1300 mV and about 1000 mV, respectively) to oxidation are disclosed in US Pat. No. 20020132359 and European patent no. 1241110 which solve the problem of oxidation by a special package form of where each unit dose comprising oxygen-sensitive drug, is individually encapsulated in the pharmaceutical packaging construction such that when one unit dose is dispensed the other unit doses remained encapsulated. An oxygen-absorber is also incorporated into the construction. Oxygen absorber is selected from the

group consisting of absorbents which are activated themselves or by moisture (e.g. Copper powder, zinc powder), UV rays, electron ray, irradiation, microwaves or a combination thereof.

Prevention of oxidation of atorvastatin by means of suitable packaging (in the nitrogen atmosphere) is also disclosed in the patent application P-200200244.

In the patent documents and other prior art documents, no documents have been found relating to different modes of solving the problem of protection of pharmaceutical active substances from pH of the environment, oxidation and/or ambient humidity, and pharmaceutical dosage forms from oxidation and/or ambient humidity. Insofar, the problem of conversion of HMG-CoA reductase inhibitors in the form of hydroxyl acids such as, e.g. atorvastatin, pravastatin, mevastatin, cerivastatin, rosuvastatin, fluvastatin and itavastatin, to the lactone form and different isomers at low pH, has been solved by the addition of alkaline or basifying or alkalizing substances and/or buffering substances to the pharmaceutical dosage form.

Therefore, the object of the present invention is to stabilize the active substance, sensitive to environmental influences, and to stabilize the pharmaceutical dosage form comprising such active substance and pharmaceutical excipients. Further, the object of the present invention is to stabilize the active substance which is sensitive to pH of the environment, oxidation and/or environmental humidity, and to stabilize the pharmaceutical dosage form comprising said active substance and pharmaceutical excipients. Preferably, the object of the present invention is to stabilize the active substance which is statin, and the most preferably atorvastatin, to environmental influences and preferably to the pH of the environment, oxidation and/or environmental humidity.

Description of the invention

The object of the invention is a stable pharmaceutical dosage form which comprises the active substance HMG-CoA reductase inhibitor and provides protection of the active substance from the environmental influences and preferably from the pH of the environment, oxidation and/or environmental humidity. Preferably, the active substance is atorvastatin.

The object of the invention is further the pharmaceutical dosage form which surprisingly prevents conversion of the active substance HMG-CoA reductase inhibitor from a hydroxyl acid form to a lactone form under the conditions of low water content, that is, at 3.5% loss on drying (LOD below 3.5%) and preferably LOD below 3%, without adding alkalizing substances or alkalizing substances or buffers to the pharmaceutical dosage form. The stable pharmaceutical dosage form of the present invention comprises one or more active substances, sensitive to pH of the environment, and one or more pharmaceutical excipients which afford stability of one or more active substances to pH of the environment, wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and preferably below 3% and does not comprise alkalizing or buffering substances or combinations thereof.

The pharmaceutical excipient of the stable pharmaceutical dosage forms of the present invention is selected from the group consisting of different types of microcrystalline cellulose and modified forms of microcrystalline cellulose. Preferably, it is selected from the group of physical mixtures of microcrystalline cellulose and colloidal SiO_2 and the most preferably it is selected from different types of microcrystalline cellulose such as, for example ProSolv™ SMCC® 90, ProSolv™ HD 90 and Avicel® PH 200.

The object of the present invention is also a stable pharmaceutical dosage form which comprises:

a) one or more uncoated particles of one or more active substances which are sensitive to pH of the environment, environmental humidity and/or oxidation;
b) one or more pharmaceutical excipients which afford stability of the active substance to pH of the environment where said pharmaceutical dosage form has the water content below pH 3.5% by weight and preferably below 3% by weight to weight of the entire pharmaceutical dosage form and does not comprise alkalizing or buffering substances or combinations thereof; and
c) the coating s which affords protection of one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity and where the coating

comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

In said dosage form the active substance is preferably HMG-CoA reductase inhibitor.

Further the object of the present invention is also the stable pharmaceutical dosage form which comprises:

a) one or more coated particles of one or more active substances which are sensitive to pH of the environment, oxidation and/or environmental humidity wherein a particle of the active substance is coated with the coat which affords the stability of the active substance to oxidation and/or moisture and which comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol; and

b) one or more pharmaceutical excipients which afford stability of the active substance in the pH of the environment wherein said pharmaceutical dosage form has the water content below 3.5% by weight and preferably below 3% by weight to weight of the entire pharmaceutical dosage form and does not comprise alkalizing or buffering substances and combinations thereof.

Such pharmaceutical dosage form may be also coated with the coat which protects one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity wherein the coat of the coated particle and the pharmaceutical dosage form comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

Buffering components excluded from the stable pharmaceutical dosage form of the present invention are salts of weak acids and strong bases or salts of strong acids and weak bases or other similar substances which maintain the pH within the determined range. Preferably they are buffering components selected from the group consisting of:

a) alkaline metal salts, alkaline earth metal salts and ammonium salts of citric acid, ascorbic acid, maleic acid, sorbic acid, succinic acid, benzoic acid, phosphoric acid, carbonic acid, sulfuric acid, nitric acid, boric acid and silicic acid;

b) amines in combination with a strong or weak acid (e.g., trometamine, EDTA);

c) ion exchangers; and
d) combinations thereof.

Alkalizing agents or alkaline components, respectively, excluded from the stable pharmaceutical dosage form of the present invention are organic or inorganic compounds which contain the groups having alkaline action, and are selected from the group consisting of:

a) oxides and hydroxides of alkaline and/or alkaline earth metals, oxides of the 4, 5 and/or 6 group of the periodic system such as, e.g. MgO, MgOH, NaOH, $Ca(OH)_2$;
b) amines such as, e.g. TRIS (trometamine), etanolamine, diethanolamine, triethanolamine, N-methyl-glucamine, glucosamine, ethylenediamine, diethylamine, triethylamine, isopropylamine, diisopropylamine;
c) alkali amino acids such as, e.g. arginine, histidine and lysine.

The active substance itself or the active substance with one or more pharmaceutical excipients may be in the form of particles which are regular or irregular in shape. The formed particles may be, for example, microcapsules, microspheres, granules, pellets. Said particles may be uncoated or coated. More said particles which may be uncoated or coated, may constitute larger formed or unformed units (pharmaceutical dosage forms) which may be coated with a coating.

The pharmaceutical dosage form of the invention is preferably the solid pharmaceutical dosage form and may in the form of particles, regular or irregular in shape, and is selected from the group of pharmaceutical dosage forms that are, for example, powders, powders for suspensions, granules, tablets and capsules.

The pharmaceutical dosage form of the present invention comprises in addition to one or more coated active substances and/or one or more uncoated active substances and the selected filler, further one or more pharmaceutical excipients which are selected from the group consisting of:

a) one or more binders;
b) one or more disintegrants;
c) one or more glidants;
d) one or more surfactants;

e) and other components for solid pharmaceutical dosage forms which are known in the prior art and are selected from the group consisting of colorants, flavors and adsorbing materials.

The binder of the pharmaceutical dosage form of the present invention is selected from the group consisting of different types of starch, modified forms of starch, microcrystalline cellulose (MCC), hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethyl cellulose, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and combinations thereof.

The disintegrant of the pharmaceutical dosage form of the present invention is selected from the group consisting of crosslinked sodium carboxymethylcellulose, crosslinked carboxymethyl starch, different types of starch and microcrystalline cellulose and combinations thereof.

The glidant of the pharmaceutical dosage form of the present invention is selected from the group consisting of magnesium, calcium and zinc stearate, calcium behenate, talc, carnauba wax, silicon dioxide and combinations thereof.

The surfactant of the pharmaceutical dosage form of the present invention is selected from the group consisting of ionic surfactants such as sodium lauryl sulfate, nonionic surfactants such as different types of poloxamers (copolymers of polyoxyethylene and polyoxypropylene), natural or synthesized lecithins and esters of sorbitan and fatty acids (such as Span® (Atlas Chemie)), esters of polyoxyethylenesorbitan and fatty acids (e.g. polyoxyethelene (20) sorbitan monooleate such as Polysorbate 80 and Tween® (Atlas Chemie), respectively), polyoxyethylated hydrogenated castor oil (such as Cremophor® (BASF)), polyoxyethelene stearates (such as Myrj® (Atlas Chemie)) or cationic surfactants such as cetylpyridine chloride or any combination of said surfactants.

Other components for solid pharmaceutical dosage forms are the components which are known and are conventional in the prior art and are used for solid pharmaceutical dosage forms in the said art. They are selected from the group consisting of colorants, flavoring agents and adsorbing materials.

The pharmaceutical dosage forms of the present invention can be prepared in the following ways:

a) a mixture of one or more coated and/or one or more uncoated therapeutic active substances, a filler, a binder, a disintegrant and if required a surfactant and other conventional ingredients for a solid pharmaceutical dosage form is homogenized in suitable mixers, the mixture is compacted in suitable compressing machines or slugged in slugging machines or conventional compressing machines, the compacts and or sluggs are milled and/or sieved, fillers, disintegrants, glidants, lubricants and other conventional pharmaceutical excipients for tablets or capsules are added, and the mixture is homogenized. The resulting mixture is compressed into tablets or filled into capsules;

b) A mixture of one or more coated and/or one or more uncoated therapeutic active substances, a filler, a binder, a disintegrant and if required surfactant and other conventional ingredients for a solid pharmaceutical dosage forms is homogenized in a suitable mixers, glidants and lubricants are added and the mixture is homogenized. The resulting mixture is compressed into tablets or filled into capsules;

c) a mixture of one or more coated and/or one or more uncoated therapeutic active substance, a filler, a binder, a disintegrant and if required a surfactant and other conventional ingredients for a solid pharmaceutical dosage form is homogenized in suitable mixers, granulated with a suitable solvent such as water, ethanol, methanol, isopropyl alcohol, n-butyl alcohol, acetone, diethylether, ethylacetate, isopropylacetate, methylacetate, dichloromethane, chloroform, mixtures of said solvents such as ethanol and acetone, methanol and acetone, dichloromethane and methanol, and mixtures thereof. The resulting granulate is dried in suitable dryers such as standard plate dryers, fluidized bed dryers, vacuum and microwave dryers, at a temperature not exceeding 60°C. To the dried granulate are added fillers, disintegrants, glidants and lubricators and if required other conventional ingredients for solid pharmaceutical dosage

forms. The resulting mixture is homogenized and compressed into tablets or filled into capsules.

The particles of regular or irregular shapes (microcapsules, microspheres, granules, pellets) can be prepared according to one of known technological procedures.

The active substance, particles of regular or irregular shapes such as, e.g. microcapsules, microspheres, granules, pellets and the like, and larger formed or unformed units such as, e.g. tablets, capsules and the like, when required can be coated with the film coating which of said invention and provides protection of the active substance from the environmental factors, or coated with any other in the prior art known film coating.

In the context of the said invention the term coating is a layer of material applied directly onto the core which is either an active substance itself or an active substance with one or more pharmaceutical excipients in the form of the particles of regular or irregular shapes which are selected from the group consisting of microcapsules, microspheres, granules, pellets and the like or a pharmaceutical dosage forms selected from the group consisting of tablets, capsules or similar pharmaceutical dosage forms known in the prior art. Such coating may be a coating which affords protection of the active substance and pharmaceutical excipients and pharmaceutical dosage forms, respectively, from oxidation and/or environmental humidity. In the context of said invention coating means also any other known film coating which is applied directly onto the tablet, capsule or the similar pharmaceutical dosage forms comprising the coated active substance within the context of said invention.

In the context of the present invention the coating is a a layer of material applied on the active substance or onthe core of the pharmaceutical dosage form comprising one or more film-formers. A suitable film-former is any film-former which applied in the form of a coating onto the particle of the active substance or the core of the pharmaceutical dosage form comprising the active substance (sensitive to said environment influences) affords protection of the active substance from said environment influences and preferably against oxidation and/or environmental humidity. Most preferably such film former is any film-former which affords protection of the active substance from oxidation. Said film-former is selected from the group consisting of polyvinyl alcohol (PVA) and derivatives of cellulose. Among the derivatives of cellulose a film-former is preferably sodium

carboxymethylcellulose (Na CMC) or hydroxyethyl cellulose (HEC) and most preferably sodium carboxymethylcellulose (Na CMC). A film-former may be also a combination of one or more said film-formers in all possible ratios.

In the context of said invention the coating may further comprise one or more pharmaceutically acceptable excipients which are selected from the group consisting of:

d) one or more plasticizers;
e) one or more viscosity-increasing agents for coating dispersion;
f) one o more glidants;
g) one or more colorants;
h) one or more surfactants; and
i) and other pharmaceutical substances used in the prior art for film coatings.

The plasticizer of the coating may be selected from the group consisting of glycerol, diglycerol, ethanolamines, ethylene glycol, polyethylene glycol, glycerol α-monomethyl ether, glycerol monochloridine, 2,3-butylene glycol, 1,2,6-hexanetriol, 2-nitro-2-methyl-1,3-propandiol, propylene glycol, glyceryl triacetate, polyoxyethylene/polyoxypropylene copolymers, triethyl citrate, oleic acid, fractionated coconut oil and combinations thereof. The plasticizer is added in concentrations 1–50%, preferably in concentrations 5–40% to the amount of the film-former in the coating, more preferably in concentrations 10–30%.

The viscosity-increasing agent of the coating dispersion may be selected from the group consisting of carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, xanthan, alginates, chitosan and combination thereof. Viscosity-increasing agents are added in concentrations 0–50%, preferably in concentrations 0–20%.

The glidant of the coating may be selected from the group consisting of talc, magnesium stearate, calcium stearate and combinations thereof.

The colorant of the coating may be selected from the group consisting of aluminium lakes, insoluble pigments, water-soluble dyes, titanium dioxide, talc, and combinations thereof.

The surfactant of the coating may be selected from the group consisting of ionic surfactants such as sodium lauryl sulfate, nonionic surfactants such as different types of

poloxamers (polyoxyethylene and polyoxypropylene copolymers), natural and synthetic lecithins and esters of sorbitan fatty acids (such as Span® (Atlas Chemie)), polyoxyethylenesorbitan and fatty acid esters (e.g., polyoxyethylene (20) sorbitan monooleate such as Polysorbate 80 or Tween® (Atlas Chemie)), polyoxyethylated hydrogenated castor oil (such as Cremophor® (BASF)), polyoxyethelene stearates (such as Myrj® (Atlas Chemie)) or cationic surfactants such as cetylpyridine chloride or any of combinations of said surfactants.

Other pharmaceutical excipients of the coating are the substances used in the art for film coating and are known in the prior art.

The solvent used for the coating dispersion may be water, different combinations of organic solvents or combinations of organic solvents and water.

The amount of the film coating applied onto the active substance, particles of regular or irregular shapes (microcapsules, microspheres, granules, pellets) and larger formed or unformed units (tablets, capsules) is within the range 2–30% by weight to core weight, preferably 4–20%.

The object of the present invention is further use of the active substance in the context of said invention for the preparation of the coated particles and/or pharmaceutical dosage forms of said invention for the treatment and the method of treatment of different diseases by administering the coated particles and/or pharmaceutical dosage forms of said invention wherein the diseases are selected from the group consisting of dyslipidemia, hyperlipidemia, hypercholesterolemia, atherosclerosis, arteriosclerosis, cardiovascular disease, coronary artery disease, coronary heart disease, vascular disorder, inflammatory disease, allergic disease, neurodegenerative disease, malignant disease, viral disease (WO 0158443), abnormal bone states (WO 0137876), amyloid-β precursor protein processing disorders such as Alzheimer's disease of Down's Syndrome (WO0132161).

Examples

Example 1

Composition of one film-coated tablet

1.1. Tablet core

Table 3. Composition of the core

Ingredient	Weight (mg)
Atorvastatin (in the form of atorvastatin Ca)	40.00
Sodium lauryl sulfate	5.00
ProSolv SMCC 90	139.00
Pregelatinized corn starch	3.00
Cross-linked carboxymethylcellulose	10.00
Magnesium stearate	1.00
Talc	2.00

Preparation of tablet core

A solution of sodium lauryl sulfate was sprayed in the stream of warm air onto atorvastatin Ca. The resulting granulate was dried and sieved. ProSolv SMCC 90, pregelatinized corn strach and crosslinked carboxymethylcellulose were added and homogeneously mixed. Magnesium stearate and talc were added, homogeneously mixed and compressed into tablets, weight 200 mg.

1.2. Tablet coating

Table 4. Composition of a coating

Coating ingredients	Weight of coating to weight of a core (%) and weight of ingredients in the coating (mg)
	8 %
Sodium carboxymethylcellulose	14.90 mg
Glycerol	1.50 mg

Preparation of a coating dispersion and coating of tablet core

Sodium carboxymethylcellulose (Blanose CMC 7LF PH, Aqualon), (109.00 g) with viscosity 25 to 50 mPas and glycerol (11.00 g) while mixing were dissolved in water (2513.60 g). The resulting dispersion was sprayed onto the cores to an 8% coating by

weight to core weight. During the coating process the tablet weight was controlled and the coating film estimated.

1.3. Determination the tablet pH value

The pH value of the tablet of Example 1, determined potentiometrically, was 6.7. By the same procedure, the pH value of the mixture atorvastatin Ca and ProSolv SMCC 90 (mixture in a ratio equivalent to their ratio by weight in a tablet) was determined, and it was 7.93.

The pH values of the tablet and the mixture of the active substance and the filler ProSolvSMCC 90 were determined in 20 ml aqueous dispersion of 1 tablet with the assay of 40 mg atorvastain Caand in the dispersion of the mixture of the active substance and the filler ProSolv SMCC 90 in the amount present in said tablet. The pH value was determined on analytical equipment 720 KFS Titrino Methrom using combined micro pH electrode Methrom 6.0204.100 pH 14/0 70ºC.

1.4 Analysis of stability of the active substance in the pharmaceutical dosage form of Example 1 in different atmospheres

The influence of water/humidity and pharmaceutical excipients on occurrence of degradation products (lactone and oxidative degradation products) was assessed by testing film-coated tablets in the packages (HDPE plastic bottles) with different desiccants (without desiccant, silica gel, molecular sieves). Film-coated tablets were stored for 1 month under the conditions 40/75 (40°C ± 2°C, 75% RH ± 5%). The assay of degradation products of atorvastatin (lactone and oxidative degradation products) in tablets was determined by liquid chromatography. As reference sample the tablets stored in a refrigerator (2–8°C) were analyzed. The moisture content in the tablets was measured gravimetrically by determining loss on drying (LOD).

Table 5. Increase in the assay of degradation products of atorvastatin (lactone) in the film-coated tablets of said invention, stored 1 month under the conditions 40/75 (40°C ± 2°C, 75 % RH ± 5 %)

Desiccant	**LOD* (%)**	**Storage conditions**	**Increase of lactone assay in % to reference sample**
Reference sample	5.08	Refrigerator, 1 month (reference)	
without desiccant	5.17	40/75, 1 month	0.21
2 g silica gel	3.49	40/75, 1 month	0.05
4 g silica gel	2.73	40/75, 1 month	0.04
2 g molecular sieves	1.99	40/75, 1 month	0.03
4 g molecular sieves	1.55	40/75, 1 month	0.03
2 g silica gel + 2 g molecular sieves	1.73	40/75, 1 month	0.03

LOD* - loss on drying

After one month of testing under the condition of accelerated stability it was observed that due to smaller percent of moisture in the tablets with added desiccant, lactone in said tablets was formed in a considerably smaller percent (level 0.05%) compared to the tablets with no added desiccant (level 0.22%). Under the determined level of humidity, differences in the percents of formed lactone in the tablets, i.e. below 3.50% of moisture estimated as loss on drying were not significant.

Table 6. Increase in the assay of degradation products of atorvastatin (oxidative degradation products) in the film-coated tablets of said invention, stored 1 month under the conditions 40/75 (40°C ± 2°C, 75 % RH ± 5 %)

Desiccant	**LOD* (%)**	**Storage conditions**	**Increase in assay of oxidative degradation products in % to reference sample**	
			Uncoated tablets	Coated tablets according to Example 1
Reference sample	5.08	Refrigerator, 1 month (reference)		
without desiccant	5.17	40/75, 1 month	0.20	0.14
2 g silica gel	3.49	40/75, 1 month	0.42	0.12
4 g silica gel	2.73	40/75, 1 month	0.34	0.12
2 g molecular sieves	1.99	40/75, 1 month	0.43	0.15
4 g molecular sieves	1.55	40/75, 1 month	0.38	0.13
2 g silica gel + 2 g molecular sieves	1.73	40/75, 1 month	0.36	0.11

LOD* - loss on drying

After one month of testing under the condition of accelerated stability the increase of degradation products of atorvastatin (oxidative degradation products) in the coated tablet

of said invention was significantly smaller than in the uncoated tablet.

Example 2

Composition of one film-coated tablet

2.1. Tablet core

Table 7. Composition of the core

Ingredient	Weight (mg)
Atorvastatin (in the form of atorvastatin Ca)	40.00
Sodium lauryl sulfate	30.00
ProSolv HD 90	160.00
Pregelatinized starch	3.75
Cross-linked carboxymethylcellulose	12.50
Magnesium stearate	1.25
Talc	2.50

Preparation of the tablet core

Atorvastatin Ca, ProSolv HD 90, sodium lauryl sulfate, pregelatinized corn starch and crosslinked carboxymethylcellulose were homogeneously mixed. Magnesium stearate and talc were added, homogeneously mixed and compressed into tablets in the area with controlled low relative humidity, weight 250 mg.

2.2. Tablet coating

Table 8. Composition of the coating

Coating ingredients	Weight of coating to core weight (%) and weight of ingredients in a coating (mg)	
	6 %	8 %
Sodium carboxymenthylcellulose	12.275 mg	16.363 mg
Glycerol	1.225 mg	1.637 mg
Titanium dioxide	1.406 mg	1.875 mg
Pigment yellow	0.094 mg	0.125 mg

Preparation of the coating dispersion and coating of the tablet core

Sodium carboxymethylcellulose (Blanose CMC 7LF PH, Aqualon), (98.178 g) with

viscosity 25–50 mPas and glycerol (9.822 g) while mixing were dissolved in water (2230 g) and while mixing a colorant concentrate dispersion was added. The colorant concentration was prepared by grinding an aqueous dispersion of titanium dioxide (11.250 g) and pigment yellow (Sicopharm 10, BASF), (0.750 g). The resulting dispersion was sprayed onto the cores to obtain two different coatings 6% and 8% by weight to core weight. During the coating process the tablet weight was controlled and the coating film estimated. The film coated tablets with a 6% coating at convenient coating weight were taken from the coating drum during the coating process.

In said description of the invention, it is considered that the invention may be carried out within broad and equivalent ranges of the parameters, technical characteristics and conditions known to those of skill in the art wherein the examples and characteristics described, parameters and invention terms must not be interpreted as the limitation of the scope of the invention or any of its embodiments. All herein cited references are included in extenso.

CLAIMS

1. A stable pharmaceutical dosage form comprising one or more active substances, sensitive to pH of the environment, and one or more pharmaceutical excipients which provide stability of one or more active substances to pH of the environment wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof.

2. The stable pharmaceutical dosage form comprising one or more active substances, sensitive to pH of the environment, and one or more pharmaceutical excipients which afford stability of one or more active substances to pH of the environment and which are selected from the group consisting of different types of microcrystalline cellulose and modified form of microcrystalline cellulose wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof.

3. The stable pharmaceutical dosage form comprising one or more active substances, sensitive to pH of the environment, and one or more pharmaceutical excipients which afford stability of one or more active substances to pH of the environment and which are selected from the group of physical mixtures of microcrystalline cellulose and colloidal SiO_2 wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof.

4. The stable pharmaceutical dosage form comprising one or more active substances, sensitive to pH of the environment, and one or more pharmaceutical excipients which afford stability of one or more active substances to pH of the environment and which are selected from the group consisting of different types of microcrystalline cellulose such as, for example ProSolv™ SMCC® 90, ProSolv™ HD 90 and Avicel® PH 200 wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage

form and does not contain alkalizing or buffering substances or combinations thereof.

5. The stable pharmaceutical dosage form as defined in any of the preceding claims 1 to 4 wherein the active substance is selected from the group of HMG-CoA reductase inhibitors.

6. The stable pharmaceutical dosage form as defined in any of the preceding claims 1 to 5 wherein the active substance is preferably atorvastatin.

7. The stable pharmaceutical dosage form comprising:
   a) one or more uncoated particles of one or more active substances which are sensitive to pH of the environment, environmental humidity and/or oxidation;
   b) one or more pharmaceutical excipients which provide stability of the active substance to pH of the environment wherein said pharmaceutical dosage form has the water content below 3.5% by weight and preferably below 3% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof; and
   c) the coating which affords protection of one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity and where the coating comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

8. The stable pharmaceutical dosage form comprising:
   a) one or more uncoated particles of one or more active substances which are sensitive to pH of the environment, environmental humidity and/or oxidation and are selected from the group of HMG-CoA reductase inhibitors;
   b) one or more pharmaceutical excipients which provide stability of the active substance to pH of the environment wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof; and

c) the coating which affords protection of one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity and where the coating comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

9. The stable pharmaceutical dosage form comprising:
   a) one or more uncoated particles of one or more active substances which are sensitive to pH of the environment, environmental humidity and/or oxidation;
   b) one or more pharmaceutical excipients which provide stability of the active substance to pH of the environment and which are selected from the group consisting of different types of microcrystalline cellulose and modified forms of microcrystalline cellulose wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof; and
   c) the coating which affords protection of one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity and where the coating comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

10. The stable pharmaceutical dosage form comprising:
   a) one or more uncoated particles of one or more active substances which are sensitive to pH of the environment, environmental humidity and/or oxidation and are selected from the group of HMG-CoA reductase inhibitors;
   b) one or more pharmaceutical excipients which provide stability of the active substance to pH of the environment and which are selected from the group consisting of different types of microcrystalline cellulose and modified forms of microcrystalline cellulose wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire

pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof; and

c) the coating which affords protection of one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity and where the coating comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

11. The stable pharmaceutical dosage form comprising:

a) one or more uncoated particles of one or more active substances which are sensitive to pH of the environment, environmental humidity and/or oxidation;

b) one or more pharmaceutical excipients which afford stability of the active substance to pH of the environment and which are selected from the group of physical mixtures of microcrystalline cellulose and colloidal SiO_2 wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof; and

c) the coating which affords protection of one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity and where the coating comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

12. The stable pharmaceutical dosage form comprising:

a) one or more uncoated particles of one or more active substances which are sensitive to pH of the environment, environmental humidity and/or oxidation and are selected from the group of HMG-CoA reductase inhibitors;

b) one or more pharmaceutical excipients which provide stability of the active substance to pH of the environment and which are selected from the group of physical mixtures of microcrystalline cellulose and colloidal SiO_2

where said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof; and

c) the coating which affords protection of one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity and where the coating comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

13. The stable pharmaceutical dosage form comprising:

a) one or more uncoated particles of one or more active substances which are sensitive to pH of the environment, environmental humidity and/or oxidation;

b) one or more pharmaceutical excipients which afford stability of the active substance to pH of the environment and are selected from the group consisting of different types of microcrystalline cellulose such as, e.g. ProSolv™ SMCC® 90, ProSolv™ HD 90 and Avicel® PH 200 wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof; and

c) the coating which provides protection of one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity and where the coating comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

14. The stable pharmaceutical dosage form comprising:

a) one or more uncoated particles of one or more active substances which are sensitive to pH of the environment, environmental humidity and/or oxidation and are selected from the group of HMG-CoA reductase inhibitors;

b) one or more pharmaceutical excipients which afford stability of the active substance to pH of the environment and are selected from the group

consisting of different types of microcrystalline cellulose such as, e.g. ProSolv™ SMCC® 90, ProSolv™ HD 90 and Avicel® PH 200 wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof; and

c) the coating which affords protection of one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity and where the coating comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

15. The stable pharmaceutical dosage form comprising:

a) one or more coated particles of one or more active substances which are sensitive to pH of the environment, oxidation and/or environmental humidity wherein the particle of the active substance is coated with the coating which affords stability of the active substance from oxidation and/or environmental humidity and comprises one or more film-formers which are selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol; and

b) one or more pharmaceutical excipients which afford stability of the active substance to pH of the environment wherein said pharmaceutical dosage form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof.

16. The stable pharmaceutical dosage form comprising:

a) one or more coated particles of one or more active substances which are sensitive to pH of the environment, oxidation and/or environmental humidity wherein the particle of the active substance is coated with the coating which affords stability of the active substance to oxidation and/or environmental humidity; in

b) one or more pharmaceutical excipients which afford stability of the active substance to pH of the environment wherein said pharmaceutical dosage

form has the water content below 3.5% by weight to weight of the entire pharmaceutical dosage form and does not contain alkalizing or buffering substances or combinations thereof; and

c) the coating which affords protection of one or more active substances, one or more pharmaceutical excipients and the pharmaceutical dosage form from oxidation and/or environmental humidity and where the coating of coated particles and pharmaceutical dosage forms comprises one or more film-formers selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose and polyvinyl alcohol.

17. The stable pharmaceutical dosage form as defined in any of the preceding claims 7 to 16 wherein the active substance is preferably atorvastatin.

18. The stable pharmaceutical dosage form as defined in any of the preceding claims 7 to 14 and claim 15 wherein the coating of the pharmaceutical dosage form further comprises one or more pharmaceutical excipients selected from the group consisting of one or more plasticizers, one or more viscosity-increasing agents of a coating dispersion, one or more glidants, one or more colorants, one or more surfactants and other pharmaceutical excipients used for film coatings.

19. The stable pharmaceutical dosage form according to claim 16 wherein the coating of the pharmaceutical dosage form and/or coated active substance further comprises one or more pharmaceutical excipients selected from the group consisting of one of more plasticizers, one or more viscosity-increasing agents of the coating dispersion, one or more glidants, one or more colorants, one or more surfactants and other pharmaceutical excipients used for film coatings.

20. The stable pharmaceutical dosage form according to claim 18 or claim 19 wherein the plasticizer of the coating is selected from the group consisting of glycerol, diglycerol, ethanolamines, ethylene glycol, polyethylene glycols, glycerol α-monomethyl ether, glycerol monocloridine, 2,3-butylene glycol, 1,2,6-hexanetriol, 2-nitro-2-methyl-1,3-propanediol, propylene glycol, glyceryl triacetate, polyoxyethylene/polyoxypropylene copolymers, triethyl citrate, oleic acid, fractionated coconut oil and combinations thereof.

21. The stable pharmaceutical dosage form as defined in any of the preceding claims 18 to 20 wherein the viscosity-increasing agent of the coating is selected from the group consisting of carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, xanthan, chitosan, alginates and combinations thereof.

22. The stable pharmaceutical dosage form as defined in any of the preceding claims 18 to 21 wherein the glidant of the coating is selected from the group consisting of talc, magnesium stearate, calcium stearate and combinations thereof.

23. The stable pharmaceutical dosage form as defined in any of the preceding claims 18 to 22 wherein the colorant of the coating is selected from the group consisting of aluminium lakes, insoluble pigments, water-soluble dyes, titanium dioxide and talc.

24. The stable pharmaceutical dosage form as defined in any of the preceding claims 18 to 23 wherein the surfactant of the coating is selected from the group consisting ionic surfactants, nonionic surfactants or cationic surfactants or any combinations of said surfactants.

25. The stable pharmaceutical dosage form as defined in any of the preceding claims 1 to 24 which further comprises one or more pharmaceutical excipients selected from the group consisting of one or more binders, one or more disintegrants, one or more different glidants, one or more surfactants and the like.

26. The stable pharmaceutical dosage form as defined in any of the preceding claims 1 to 25 characterized in that it is the solid pharmaceutical dosage form.

27. The stable pharmaceutical dosage form according to claim 26 which is selected from the group consisting of powders, powders for suspensions, granules, tablets, capsules and the like.

28. The process for the preparation of the pharmaceutical dosage form as defined in any of the preceding claims 1 to 27.

29. Use of the active substance sensitive to pH of the environment, oxidation and/or environmental humidity for the preparation of the pharmaceutical dosage form as defined in any of the preceding claims 1 to 27 for the treatment of diseases selected from the group consisting of dyslipidemia, hyperlipidemia, hypercholesterolemia, atherosclerosis, arteriosclerosis, cardiovascular disease, coronary artery disease, coronary heart disease, vascular disorder, inflammatory disease, allergic disease, neurodegenerative disease, malignant disease, viral disease, abnormal bone states, amyloid-β precursor protein processing disorders such as Alzheimer's disease of Down's Syndrome.

30. The method of treating the diseases selected from the group consisting of dyslipidemia, hyperlipidemia, hypercholesterolemia, atherosclerosis, arteriosclerosis, cardiovascular disease, coronary artery disease, coronary heart disease, vascular disorder, inflammatory disease, allergic disease, neurodegenerative disease, malignant disease, viral disease, abnormal bone states, amyloid-β precursor protein processing disorders such as Alzheimer's disease of Down's Syndrome by using the pharmaceutical dosage form according to any of the preceding claims 1 to 27.