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(54) **Title**: NEW FORMULATION

(57) **Abstract**: The present invention relates to a hygroscopic matrix based composition, a process for the preparation thereof and its use in the treatment of diseases.

NEW FORMULATION

The present invention relates to a fixed dose combination formulation, a process for the preparation thereof and its use in the treatment of diseases.

Active pharmaceutical ingredients showing an ester, amide or thioester functionality, such as S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate, are often sensitive to moisture and frequently show chemical incompatibility with a wide range of commonly used pharmaceutical excipients, thus typical composition approaches such as lipid based drug delivery systems can not be considered. Incorporating the drug substance into a hygroscopic polymer matrix can be critical due to chemical as well as physical stability. The sorption of moisture by excipients in solid dosage forms can lead to considerable stability problems when the contained active pharmaceutical is instable in water due to the presence of a hydrolysis sensitive functional group. Though theoretically hygroscopic polymers are capable to bind moisture in the composition, thus protecting the active pharmaceutical ingredient from hydrolysis, a fairly high amount of polymer is needed to achieve this, what usually leads to capping or cracking of the immediate-release tablet composition. Thus, it is usually imperative to prevent moisture sorption during storage by both, a suitable composition and primary packaging.

The manufacturing of the composition according to the present invention shows surprisingly better flowability than past compositions comprising a hydrophobic, water instable compound with a waxy consistency. For instance, the composition according to the present invention does not demonstrate extreme funnel flow.

In a first aspect the present invention provides a composition comprising S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate (a hydrophobic, water instable compound with a waxy consistency), a super-disintegrant and atorvastatin.

In a second aspect the present invention provides a composition comprising S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate (a hydrophobic,

water instable compound with a waxy consistency), a super-disintegrant, atorvastatin and at least two diluents with a bulk density lower than 800g/L.

The invention also provides a method for treating or preventing a cardiovascular disorder in a mammal by administering to a mammal in need of such treatment a therapeutically effective amount of the composition provided by the invention.

The invention further provides a composition for treating or preventing a cardiovascular disorder. A composition according to the present invention for the use in the treatment or prevention of cardiovascular disorder is also part of the invention.

The hygroscopic matrix based composition is useful to chemically stabilize a hydrophobic and hydrolysis sensitive compound with a waxy consistency, such as S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate and to stabilize the physical properties of a tablet comprising said composition.

Brief description of the figures:

Figure 1 is a 3D reconstruction of all X-ray slices of a tablet produced according to example 1.

Figure 2 is a 3D reconstruction of all X-ray slices of a tablet according to placebo example A.

Figure 3 illustrates a X-ray powder diffraction pattern of S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate crystalline form, also known as Form A.

Figure 4 is a schematic drawing of the composition according to the present invention which comprises the core comprising dalcetrapib (A), the separation layer (B), the active coating comprising atorvastatin (C) and a seal coating or film coating (D).

Figure 5 is a schematic drawing of the composition according to the present invention which comprises the one layer comprising dalcetrapib (A), another layer comprising atorvastatin (B) and a seal coating or film coating (C).

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

The term "bulk density" refers to a density measurement of a loose, uncompacted substance, wherein the volume of the substance includes the air trapped between particles. The bulk density is measured in a graduated cylinder according to the European Pharmacopeia.

The term "diluent" refers to an excipient which fills out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. Suitable diluents include e.g. pharmaceutically acceptable fillers, such as microcrystalline cellulose (e.g. Avicel®), crospovidone micronized, cellulose powder, lactose spray-dried, lactose anhydrous, lactose monohydrate, dibasic calcium phosphate, sugars, sugar alcohols, corn starch, starch, pregelatinized starch, colloidal silicon dioxide, polysaccharides, and mixtures thereof.

The term "hydrophobic" means insoluble in water, not readily absorbing moisture, or being adversely affected by water; either incompatible with water or having little affinity for it. In other words the hydrophobic drug or compound would not spontaneously disperse in water. Specifically hydrophobic means logP > 3. The logP is measured or in the absence of experimental data calculated as clogP according to the model developed by Moriguchi (S. Moriguchi, S. Hirono, I. Nakagome, H. Hirano, (1994). "Comparison of reliability of log P values for drugs calculated by several methods" *Chem Pharm Bull* **1994**, **42** : 976–978)..

The term "hygroscopic polymeric excipient(s)" means polymeric excipient(s) which take(s) up moisture for example by absorption or adsorption even at relative humidity as low as 50%, at room temperature (e.g. about 25 °C). The moisture uptake is measured e.g by dynamic vapor sorption at room temperature. As an example the hygroscopicity can be measured in accordance with the method disclosed in the European Pharmacopoeia – 6th Edition (2008), Chapter 5.11. The dynamic vapor sorption technique measures the change in mass which is produced by varying the vapor concentration surrounding the product. Suitable "hygroscopic polymeric excipients" are hydroxypropyl methylcellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hydroxyethylmethyl

cellulose, carboxypolymethylene, methylcellulose, ethylcellulose, hydroxyethyl cellulose, celluloseacetate, polyvinylpyrrolidone crosslinked polyvinylpyrrolidone, micronized crosslinked polyvinylpyrrolidone, carboxymethylcellulose sodium, carboxymethylcellulose calcium, crosslinked carboxymethylcellulose, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powder, carboxymethyl starch, starch, pregelatinized starch or mixture thereof. In particular "hygroscopic polymeric excipients" refer to hydroxypropyl methylcellulose, carboxymethylcellulose sodium, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone. Examples of "water insoluble hygroscopic polymers" at room temperature (e.g. about 25 °C) include low-substituted hydroxypropyl cellulose, carboxypolymethylene, ethylcellulose, celluloseacetate, crosslinked polyvinylpyrrolidone, micronized crosslinked polyvinylpyrrolidone, carboxymethylcellulose calcium, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powder, and starch.

The term "Super-disintegrant" refers to disintegrants that very rapidly expand upon contact with water. Generally speaking, superdisintegrants are disintegration agents which can be used in a fractional amount of normal disintegrants to obtain the same effect. Examples of superdisintegrants include cross-linked carboxymethyl cellulose sodium (a.k.a. croscarmellose sodium), sodium starch glycolate, and cross-linked polyvinyl pyrollidone (a.k.a. crospovidone). Croscarmellose sodium is commercially available from FMC Corp. under the trade name Ac-Di-Sol® and from Avebe Corp. under the trade name Primellose®®. Sodium starch glycolate is commercially available from Penwest Pharmaceuticals Co. under the tradename Explotab® and from Avebe Corp. under the tradename Primojel®. Crospovidone is commercially available from BASF Corp. under the tradename Kollidon® CL and from International Specialty Chemicals Corp. under the tradename Polyplasdone®. Croscarmellose is also commercially available from Mingtai Chemical Co. Ltd under the tradename DISOLCEL® and from J. Rettenmaier & Söhne GmbH + Co (JRS) under the tradename Vivasol®. The most preferred superdisintegrants are croscarmellose sodium and crospovidone.

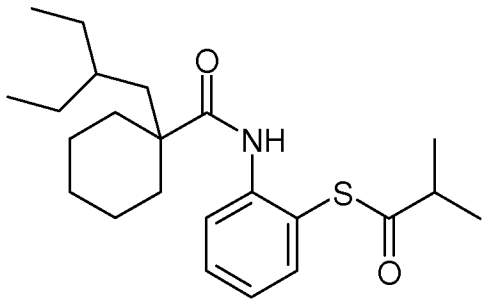
The term "water instable" means the presence of a hydrolysis sensitive functional group like an ester, amide or thioester.

The term "waxy consistency" means that the glass transition temperature (Tg) is lower than 25°C.

The term "pharmaceutical acceptable metal salt" refers to sodium, potassium, lithium, calcium, magnesium, aluminum, iron, or zinc salts.

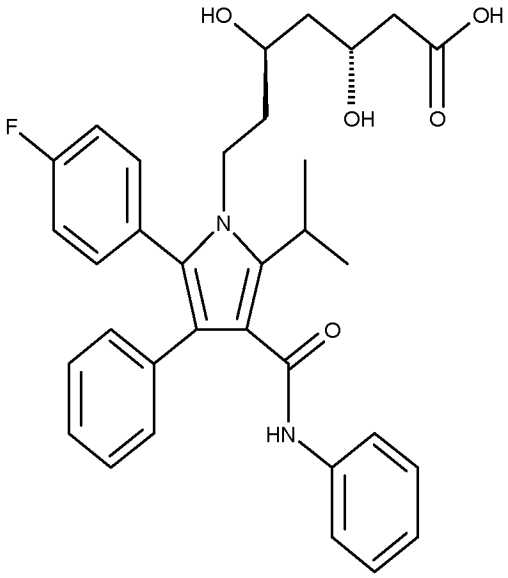
The term "PVA" and "PVOH" are interchangeable and refer to a polyvinyl alcohol which in particular are polyvinyl resins having hydroxyl groups and is obtained through saponification of polyvinyl acetate (polymerized vinyl acetate). More particularly the polyvinyl alcohol are obtained from Nippon-Gohsei (Gohsenol).

S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate is also known as thioisobutyric acid S-(2-{[1-(2-ethyl-butyl)-cyclohexanecarbonyl]-amino}-phenyl) ester, dalcetrapib or a compound of formula I



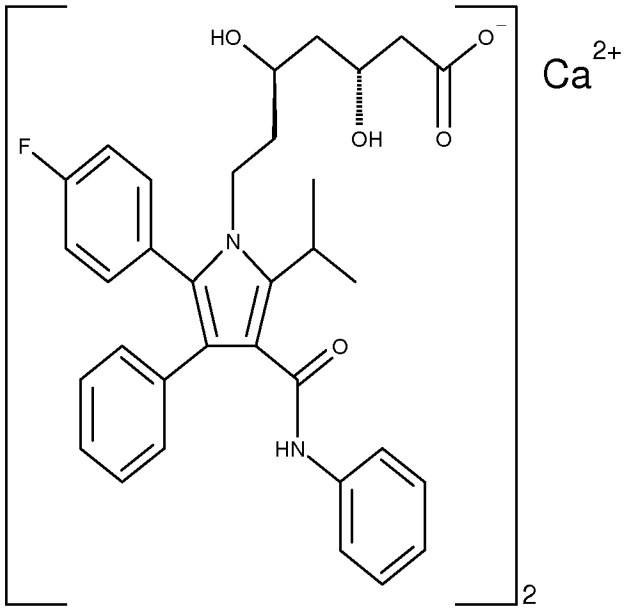
(I)

Atorvastatin refers to atorvastatin pharmaceutically acceptable salts and/or hydrates also known as [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, (2R-trans)5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2Hpyran-2-yl)ethyl-1H-pyrrole-3-carboxamide, atorvastatin acid or a compound of formula (II')



(II') pharmaceutical acceptable salts and/or hydrates. Atorvastatin refers in particular to [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid pharmaceutically acceptable salts and/or hydrate. The pharmaceutically salt is selected from monosodium salt, monopotassium salt, hemicalclium salt, N-methylglucamine salt, hemimagnesium salt or hemizinc salt, in particular hemicalclium salt or hemimagnesium salt, more particularly hemicalclium salt.More particularly atorvastatin refers to hemicalcium salt of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid also known [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt or [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1). Its chemical

structure may be represented by formula (II):



(II)

Even more particularly atorvastatin refers to [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate, most particularly in crystalline form I as disclosed in WO9703959. Form I is characterized by an X-ray powder diffraction pattern having peaks at about 9.2, 9.5, 10.3, 10.6, 11.9, 12.2, 17.2, 19.5, 21.6, 22.0, 22.7, 23.3, 23.7, 24.4, 28.9 and 29.2 ± 0.2 °, particularly by an XRPD peaks observed at an angle of diffraction 2Theta of 11.9, 17.1 and 21.6 (±0.2°).

Atorvastatin calcium is currently been sold as Lipitor®. Lipitor Atorvastatin has been described in EP1061073 B1, EP0409281 B1, EP0848705B1, EP 1148049 B1, EP0247633B1 and WO9416693.

Atorvastatin is a synthetic reversible inhibitor of the microsomal enzyme HMG-CoA reductase. Atorvastatin is usually administred orally as the calcium salt of the active hydroxyl acid in a dosage range of 10-80mg/day. Atorvastatin acid is converted to its lactone in vivo in humans, and these two forms appear to have approximately the same AUC (Area Under the Curve).

Lipitor® tablets for oral administration comprise 10mg, 20mg, 40mg or 80 mg atorvastatin and the following excipients: calcium carbonate, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, simethicone emulsion, talc, and titanium dioxide. In addition Lipitor ® may comprise candelilla wax.

Atorvastatin is unstable, as it is susceptible to heat, moisture, low pH environment and light. In acidic environment, atorvastatin will degrade to lactone. Furthermore, atorvastatin will decompose rapidly when exposed to UV or fluorescent lights. Atorvastatin may be destabilized by contact with molecular moieties of other components such excipients used in the core layer, dal layer or atv layer, or/and dalcetrapib. Therefore a stabilizing means may be required for effective pharmaceutical dosages.

In another embodiment of the present invention, at least one pharmaceutically acceptable stabilizing additive is present. In particular, the pharmaceutically acceptable stabilizing additive would be in close vicinity to atorvastatin. More particularly, the pharmaceutically acceptable stabilizing additive is present in the active coating comprising atorvastatin or in the atv layer. In particular the pharmaceutically acceptable stabilizing additive is selected from alkaline earth metal salts such as, calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate or aluminum magnesium hydroxide, or a mixture thereof. More particularly the pharmaceutically acceptable stabilizing additive is calcium carbonate.

In another embodiment of the invention, polyethylene glycol is not present in the active coating.

According to the present invention, the composition needs to maintain a good dissolution rate of atorvastatin and dalcetrapib, in particular similar to the mono-therapy compositions of atorvastatin and dalcetrapib. In particular, the composition according to the present invention produces similar exposures of dalcetrapib and atorvastatin to the mono-therapy reference tablets.

More particularly, according to a more particular embodiment of the present invention, the composition shows similar impurities profile to the mono-therapy reference tablets, atorvastatin and dalcetrapib.

Calcium carbonate has some incompatibilities with dalcetrapib and/or with some of the impurities of dalcetrapib. It increases the formation of iso-butyric acid which in turn increases the atorvastatin lactone formation.

When calcium carbonate is not present in the active coating, the dissolution rate of atorvastatin increases, which in turn increases the dalcetrapib dissolution.

Unless otherwise stated all percentages are given in weight percent of the total weight of the composition.

S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2- methylpropanethioate has been shown to be an inhibitor of CETP activity in humans (de Grooth et al., Circulation, 105, 2159-2165 (2002)) and rabbits (Shinkai et al., J. Med. Chem., 43, 3566-3572 (2000); Kobayashi et al., Atherosclerosis, 162, 131-135 (2002); and Okamoto et al., Nature, 406 (13), 203-207 (2000)). S-[2-([[1-(2- ethylbutyl) cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate has been shown to increase plasma HDL cholesterol in humans (de Grooth et al., supra) and in rabbits (Shinkai et al., supra ; Kobayashi et al., supra ; Okamoto et al., supra). Moreover, S-[2-([[1-(2- ethylbutyl) cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate has been shown to decrease LDL cholesterol in humans (de Grooth et al. , supra) and rabbits (Okamoto et al., supra). Additionally, S-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate inhibits the progression of atherosclerosis in rabbits (Okamoto et al., supra). S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate, as well as methods of making and using the compound, are described in EP patent EP1020439, Shinkai et al., J. Med. Chem. 43:3566-3572 (2000) or WO 2007/051714, WO 2008/074677 or WO2011/000793.

In a particular embodiment S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate is a solid in crystalline or amorphous form, more particularly in crystalline form. In a particular embodiment S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate is in crystalline form A.

Form A is characterized by an X-ray powder diffraction pattern having peaks at about 7.9°, 8.5°, 11.7°, 12.7°, 17.1°, 18.0°, 18.5°, 20.2°, 22.1°, 24.7° ± 0.2 °, particularly by an XRPD peaks observed at an angle of diffraction 2Theta of 7.9°, 11.7°, 17.1°, 18.5° (±0.2°).

The composition can be used to treat or prevent a cardiovascular disorder, including, but not limited to, atherosclerosis, peripheral vascular disease, dyslipidemia (e. g., hyperlipidimia), hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, cardiovascular disease, coronary heart disease, coronary artery disease, acute coronary syndrome, hyperlipidoproteinemia, vascular complications of diabetes, obesity or endotoxemia in a mammal, especially a human (i. e. , a male or female human). The composition can be used to reduce cardiovascular morbidity and mortality.

Accordingly, the invention provides a method for the treatment or prophylaxis of a cardiovascular disorder in a mammal, which method comprises administering to a mammal (particularly a mammal in need thereof) a therapeutically effective amount of the composition. The mammal particularly is a human (i. e. , a male or female human). The human can be of any race (e. g. , Caucasian or Oriental). The cardiovascular disorder particularly is selected from the group consisting of atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, and vascular complications of diabetes, obesity or endotoxemia in a mammal. More particularly, the cardiovascular disorder is selected from the group consisting of cardiovascular disease, coronary heart disease, coronary artery disease, acute coronary syndrome, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hyperlipidemia, atherosclerosis, hypertension, hypertriglyceridemia, hyperlipidoproteinemia, peripheral vascular disease, angina, ischemia, and myocardial infarction.

In particular embodiment of the invention, the composition comprises: a) a core comprising S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate and b) an active coating comprising atorvastatin or the composition comprises: a) one layer comprising S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate (herein referred as dal layer) and b) another layer comprising atorvastatin (herein referred as atv layer). In particular, the active coating

comprising atorvastatin would not be in contact with S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate.

In a particular embodiment of the invention, the composition is a fixed dose tablet, particularly in the form of a bilayer tablet or in an active coating tablet.

In certain embodiments of the present invention, the composition comprises: 10% to 69% by weight of the total weight of the core or dal layer, particularly 40% to 60% by weight of the total weight of the core or dal layer, more particularly 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate.

In certain embodiments of the present invention, the composition comprises: 1% to 10% by weight of the total weight of the core or dal layer, particularly 5% to 10% by weight of the total weight of the core or dal layer, more particularly 4% to 8% by weight of the total weight of the core or dal layer of a super-disintegrant.

In certain embodiments of the present invention, the composition comprises 30% to 70% by weight of the total weight of the core or dal layer, particularly 30% to 60% by weight of the total weight of the core or dal layer, more particularly 40% to 50% by weight of the total weight of the core or dal layer of at least two diluents with a bulk density lower than 800g/L.

In a particular embodiment, the present invention provides a composition comprising:

a) - 10% to 69% by weight of the total weight of the core or dal layer, particularly 40% to 60% by weight of the total weight of the core or dal layer, more particularly 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate

-1% to 10% by weight of the total weight of the core or dal layer, particularly 5% to 10% by weight of the total weight of the core or dal layer, more particularly 4% to 8% of the total weight of the core or dal layer by weight of a super-disintegrant, and

- 30% to 70% weight of the total weight of the core or dal layer, particularly 30% to 60% by weight of the total weight of the core or dal layer, more particularly 40% to 50% by weight of the total weight of the core or dal layer of at least two diluents with a bulk density lower than 800g/L; and

b) - atorvastatin.

In certain embodiments of the present invention as defined herein, the super-disintegrant is a hygroscopic polymeric excipient. In particular the hygroscopic polymeric excipient as superdisintegrant is croscarmellose sodium.

In a particular embodiment, the present invention provides a composition comprising:

a) - S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;
-croscarmellose sodium; and

b) atorvastatin.

In another embodiment, the present invention provides a composition comprising:

a) a core or a dal layer comprising:

- S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate; and

-croscarmellose sodium; and

b) an active coating or atv layer comprising atorvastatin.

In certain embodiments of the present invention as defined herein, the composition further comprises at least one additional hygroscopic polymeric excipient, in particular in the core or dal layer.

In certain embodiments of the present invention as defined herein, the composition further comprises at least two hygroscopic polymeric excipients, in particular in the core or dal layer.

In certain embodiments of the present invention as defined herein, the composition further comprises at least three hygroscopic polymeric excipients of which two are diluents with a bulk density lower than 800g/L, in particular in the core or dal layer.

In certain embodiments of the present invention as defined herein, the composition comprises 10% to 69% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate.

In certain embodiments of the present invention, the composition comprises: 10% to 69% by weight of the total weight of the core or dal layer, particularly 40% to 60% by weight of the total weight of the core or dal layer, more particularly 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate.

In certain embodiments of the present invention as defined herein, the composition comprises 1% to 10% by weight of the total weight of the core or dal layer, particularly 5% to 10% by weight of the total weight of the core or dal layer, more particularly 5% to 8% by weight of the total weight of the core or dal layer of croscarmellose sodium. More particularly, in a certain embodiment, the composition comprises 5% to 7% by weight of the total weight of the core or dal layer of croscarmellose sodium.

In certain embodiments of the present invention as defined herein, the composition comprises at least 30% by weight of the total weight of the core or dal layer of the hygroscopic polymeric excipients, in particular 44% to 50% by weight of the total weight of the core or dal layer, more particularly 46% to 48% by weight of the total weight of the core or dal layer, wherein the hygroscopic polymeric excipients are hydroxypropylmethyl cellulose, croscarmellose sodium, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone.

In certain embodiments of the present invention as defined herein, the composition comprises at least 30% by weight of the total weight of the core or dal layer of the hygroscopic polymeric excipients, particularly 34% to 44% by weight of the total weight of the core or dal layer, more particularly 40% to 44% by weight of the total weight of the core or dal layer.

In certain embodiments of the present invention as defined herein, the composition comprises at least 30% by weight of the total weight of the core or dal layer of the additional hygroscopic polymeric excipients, particularly 34% to 44% by weight of the total weight of the core or dal layer, more particularly 40% to 44% by weight of the total weight of the core or dal layer.

In a particular embodiment, the present invention provides a composition comprising:

a) - 10% to 69% by weight of the total weight of the core or dal layer, particularly 40% to 60% by weight of the total weight of the core or dal layer, more particularly 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;

-1% to 10% by weight of the total weight of the core or dal layer, particularly 5% to 10% by weight of the total weight of the core or dal layer, more particularly 4% to 8% by weight of the total weight of the core or dal layer of croscarmellose sodium, and

- 30% to 90% by weight of the total weight of the core or dal layer, particularly 34% to 44% by weight of the total weight of the core or dal layer, more particularly 40% to 44% by weight of the total weight of the core or dal layer of the hygroscopic polymeric excipients; and

b) atorvastatin.

wherein the hygroscopic polymeric excipients are selected from hydroxypropylmethyl cellulose, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone.

In certain embodiments of the present invention as defined herein, the composition comprises:

a) - 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;

-4% to 8% by weight of the total weight of the core or dal layer, of croscarmellose sodium

-32% to 41% by weight of the total weight of the core or dal layer of water insoluble hygroscopic polymer; and

- 4% to 5% by weight of the total weight of the core or dal layer of water soluble hygroscopic polymer; and

b) atorvastatin.

In certain embodiments of the present invention as defined herein, wherein the hygroscopic polymeric excipients are selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hydroxyethylmethyl cellulose, carboxypolymethylene, methylcellulose, ethylcellulose, hydroxyethyl cellulose, celluloseacetate, polyvinylpyrrolidone, crosslinked polyvinylpyrrolidone, micronized crosslinked polyvinylpyrrolidone, carboxymethylcellulose calcium, crosslinked carboxymethylcellulose, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powder, carboxymethyl starch, starch and pregelatinized starch.

In certain embodiments of the present invention as defined herein, wherein the hygroscopic polymeric excipients are hydroxypropylmethyl cellulose, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone.

In certain embodiments of the present invention as defined herein, the two diluents are hygroscopic polymeric excipients. In particular the hygroscopic polymeric excipients as diluents are ethylcellulose, micronized crosslinked polyvinylpyrrolidone, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powder, starch, pregelatinized starch.

In certain embodiments of the present invention as defined herein, at least two hygroscopic polymeric excipients are present.

In certain embodiments of the present invention as defined herein, the super-disintegrant and at least one of the diluents, or at least two diluents are hygroscopic polymeric excipients. More particularly, at least the super-disintegrant and one of the diluents are hygroscopic polymeric excipients.

In certain embodiments of the present invention as defined herein, the super-disintegrant and the two diluents are hygroscopic polymeric excipients.

In certain embodiments of the present invention as defined herein, there is at least 30% by weight of the total weight of the core or dal layer of hygroscopic polymeric excipients, particularly 44% to 50% by weight of the total weight of the core or dal layer.

In certain embodiments of the present invention, the super-disintegrant is croscarmellose sodium. In particular, the present invention comprises up to 6 % by weight of the total weight of the core or dal layer of croscarmellose sodium.

The invention provides a physically stable composition comprising a) at least S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, a hydrophobic and water instable cholesteryl ester transfer protein (CETP) inhibitor embedded in a chemically protective hygroscopic polymer matrix tablet consisting of at least one hygroscopic polymer e.g. hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), low-substituted hydroxypropyl cellulose (L-HPC), hydroxyethylmethyl cellulose (HEMC), carboxypolymethylene (Carbomer), methylcellulose (MC), ethylcellulose (EC), hydroxyethyl cellulose (HEC), celluloseacetate, polyvinylpyrrolidone(PVP), crosslinked polyvinylpyrrolidone (Crospovidone), micronized crosslinked polyvinylpyrrolidone (crospovidone micronized), carboxymethylcellulose sodium (croscarmellose sodium, CMC Na), carboxymethylcellulose calcium (croscarmellose calcium, CMC Ca), crosslinked carboxymethylcellulose (Crosslinked CMC), microcrystalline cellulose (MCC), silicified microcrystalline cellulose (silicified MCC), cellulose powder, carboxymethyl starch (sodium starch glycolate), starch (maize starch, potato starch, rize starch, wheat starch, tapioca starch), pregelatinized starch or a combination thereof in an amount of particularly 40% by weight or more of the total weight of the core or dal layer and b) atorvastatin.

The invention provides a physically stable composition comprising a) a core or dal layer comprising at least S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, a hydrophobic and water instable cholesteryl ester transfer protein (CETP) inhibitor embedded in a chemically protective hygroscopic polymer matrix tablet consisting of at least one hygroscopic polymer e.g. hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), low-substituted hydroxypropyl cellulose (L-

HPC), hydroxyethylmethyl cellulose (HEMC), carboxypolymethylene (Carbomer), methylcellulose (MC), ethylcellulose (EC), hydroxyethyl cellulose (HEC), celluloseacetate, polyvinylpyrrolidone(PVP), crosslinked polyvinylpyrrolidone (Crospovidone), micronized crosslinked polyvinylpyrrolidone (crospovidone micronized), carboxymethylcellulose sodium (croscarmellose sodium, CMC Na), carboxymethylcellulose calcium (croscarmellose calcium, CMC Ca), crosslinked carboxymethylcellulose (Crosslinked CMC), microcrystalline cellulose (MCC), silicified microcrystalline cellulose (silicified MCC), cellulose powder, carboxymethyl starch (sodium starch glycolate), starch (maize starch, potato starch, rize starch, wheat starch, tapioca starch), pregelatinized starch or a combination thereof in an amount of particularly 40% by weight or more of the total weight of the core or dal layer; and b) a second or out layer comprising atorvastatin.

In particular, the present invention provides a physically stable composition comprising: a) at least S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate embedded in a chemically protective hygroscopic polymer matrix tablet consisting of hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone; and b) atorvastatin.

The invention provides a physically stable composition comprising a) at least S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate embedded in a chemically protective hygroscopic polymer matrix tablet consisting of hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone in an amount of particularly 40% by weight or more of the total weight of the core or dal layer and b) atorvastatin.

Usually bringing a moisture sensitive active pharmaceutical ingredient in contact with a high amount of hygroscopic polymers such as HPMC, HPC, PVP , Crospovidone, CMC, crosslinked CMC and MC is considered critical to physical stability.

Surprisingly it was found that in case of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, a hydrophobic hydrolysis sensitive CETP inhibitor, a converse effect could be observed. It was possible to stabilize both, the

active pharmaceutical ingredient and the immediate release tablet by embedding the active in a hygroscopic polymeric matrix comprising of:

Ingredient	Relative amount of the total weight of the core or dal layer [%]
S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate	> 50%
Water insoluble, hygroscopic polymer	> 40%
Water soluble, hygroscopic polymer	> 4%
Other Excipients	< 6%

Furthermore, it was surprisingly found that increasing the amount of hydroscopic polymers from its usual range of 10 to 20% by weight to more than 30% by weight of the total weight of the core or dal layer in the presence of hydrophobic compound did not lead to capping or cracking of the immediate-release tablet composition as would have been expected. Therefore the hydrophobic compound prevents the formation of cracks of the immediate release tablet when more than 30% by weight of the total weight of the core or dal layer of the tablet consists of hygroscopic polymeric excipients.

In another embodiment, the present invention provides a composition comprising:

a) -48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate (a hydrophobic and water instable cholesteryl ester transfer protein (CETP) inhibitor); and

-at least 30% by weight of the total weight of the core or dal layer of hygroscopic polymeric excipients by composition weight, particularly 44% to 50% by weight of the total weight of the core or dal layer; and

b) atorvastatin

In another embodiment, the present invention provides a composition comprising:

a) - 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;

- 40% to 45% by weight of the total weight of the core or dal layer of water insoluble hygroscopic polymer; and

- 4% to 5% by weight of the total weight of the core or dal layer of water soluble hygroscopic polymer; and

b). atorvastatin.

In another embodiment, the present invention provides a composition comprising:

a) - 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate (a hydrophobic and water instable cholesteryl ester transfer protein (CETP) inhibitor); and

- at least 30% by weight, particularly 44% to 50% by weight of the total weight of the core or dal layer of hydroxypropylmethyl cellulose, croscarmellose sodium, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone; and

b) . atorvastatin.

In another embodiment, the present invention provides a composition comprising:

a) - 48% to 55% by weight o of the total weight of the core or dal layer f S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate (a hydrophobic and water instable cholesteryl ester transfer protein (CETP) inhibitor);

- 4% to 8% by weight of the total weight of the core or dal layer of croscarmellose sodium; and

- 35% to 44% by weight of the total weight of the core or dal layer of hydroxypropylmethyl cellulose, microcrystalline cellulose and crospovidone micronized; and

b) atorvastatin.

In another embodiment, the present invention provides a composition comprising:

a) - 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate (a hydrophobic and water instable cholesteryl ester transfer protein (CETP) inhibitor);

- less than 12% by weight of the total weight of the core or dal layer of crospovidone micronized; and

- 35% to 44% by weight of the total weight of the core or dal layer of hydroxypropylmethyl cellulose, microcrystalline cellulose and croscarmellose sodium; and

b) atorvastatin.

In another embodiment, the present invention provides a composition comprising:

a) - S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;
- croscarmellose sodium; and

b) atorvastatin.

In another embodiment, the present invention provides a composition comprising:

a) - S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;
- microcrystalline cellulose;
- crospovidone micronized;
- hydroxypropylmethyl cellulose;
- croscarmellose Sodium; and

b) atorvastatin

In another embodiment, the present invention provides a composition comprising:

a) - S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;
- mannitol;
- crospovidone micronized;
- hydroxypropylmethyl cellulose;

- croscarmellose Sodium; and

b) atorvastatin.

In another embodiment, the present invention provides a composition comprising:

a) - S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;
-mannitol;
- crospovidone micronized;
- hydroxypropylmethyl cellulose;
- croscarmellose Sodium;
-microcrystalline cellulose; and

b) atorvastatin.

In another embodiment the present invention provides a composition comprising:

a) - 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-ethylpropanethioate;
- 24% to 26% by weight of the total weight of the core or dal layer of microcrystalline cellulose;
- 11% to 12% by weight of the total weight of the core or dal layer of crospovidone micronized;
- 4% to 5% by weight of the total weight of the core or dal layer of hydroxypropylmethyl cellulose;
- 4% to 6 % by weight of the total weight of the core or dal layer of croscarmellose sodium; and

b) atorvastatin.

In another embodiment the present invention provides a composition comprising:

a) - 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-ethylpropanethioate;
- 24% to 26% by weight of the total weight of the core or dal layer of microcrystalline cellulose;
- 11% to 12% by weight of the total weight of the core or dal layer of crospovidone micronized;

- 4% to 5% by weight of the total weight of the core or dal layer of hydroxypropylmethyl cellulose;
- 4% to 6 % by weight of the total weight of the core or dal layer of croscarmellose sodium;
- 0 to 1% by weight of the total weight of the core or dal layer of magnesium stearate;
- 0 to 1% by weight of the total weight of the core or dal layer of colloidal silicon dioxide;
- 0 to 1% by weight of the total weight of the core or dal layer of sodium stearyl fumarate; and

b) atorvastatin.

In certain embodiment of the present invention, the active coating comprises:
- 3% to 55 % by weight of the total weight of the active coating of atorvastatin ;
- 10% to 50% by weight of the total weight of the active coating of a film forming polymer selected from polyvinyl alcohol, hydroxypropyl methylcellulose, hydroxyl propylcellulose, polyvinyl alcohol-poly ethylene glycol graft copolymer or copovidone (vinylpyrrolidone-vinylacetate copolymers) or a combination thereof;
- 0% to 50% by weight of the total weight of the active coating of a filler such as lactose monohydrate or microcrystalline cellulose;
- 0 to 5% by weight of the total weight of the active coating of a plasticizer such as triacetin, triethylcitrate or poly ethylene glycol;
- 0% to 45% by weight of the total weight of the active coating of an glidant/antisticking agent like talcum, glycerinmonostearate or others;
- 0% to 2% by weight of the total weight of the active coating of a thickener like Sodium carboxymethyl cellulose or hydroxyl ethylcellulose or others;
- 0% to 25 % by weight of the total weight of the active coating of a color like titandioxide, iron oxides or any other colour or mixture thereof;

In certain embodiment of the present invention, the active coating comprises:
- atorvastatin;
- Polyvinyl alcohol;
-croscarmellose sodium;
-triacetin;

- talcum; and
- simethicone.

In certain embodiment of the present invention, the active coating comprises:

- atorvastatin;
- Polyvinyl alcohol;
- croscarmellose sodium;
- triacetin;
- talcum; and
- simethicone.

In certain embodiment of the present invention, the active coating comprises:

- 45 % to 55 % by weight of the total weight of the active coating of atorvastatin;
- 10 % to 30 %by weight of the total weight of the active coating of polyvinyl alcohol;
- 0 % to 5% by weight of the total weight of the active coating of croscarmellose sodium;
- 0 % to 1 % by weight of the total weight of the active coating of Triacetin;
- 5 % to 40 %, more particularly 10% to 25%, most particularly between 18% to 22 % by weight of the total weight of the active coating of talcum; and
-3 % to 8%, more particularly between 4.5% and 5.5% by weight of the total weight of the active coating of simethicone.-

In certain embodiment of the invention, the composition comprises

a) - S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;
- microcrystalline cellulose;
- crospovidone micronized;
-hydroxypropylmethyl cellulose;
- croscarmellose sodium; and

b) - atorvastatin.;
-Polyvinyl alcohol;
-croscarmellose sodium;
-triacetin;
-calcum; and

- simethicone.-

In another embodiment according to the present invention, the active coating comprising atorvastatin comprises:

- 5.41, 10.82, 21.65 or 43.28 mg of atorvastatin;

- 0.6 to 4.8 mg (0.18 to 1.44mg)[1] of Simethicone Suspension USP (30% solids);

- 20.00 to 60.00 mg of PVA EG -05 PW;

-0.00 to 40.00 mg of Lactose monohydrate;

- 2.00 to 6.00 mg of Triacetin;

- 18.00 to 54.00 mg of Talcum; and

- 0.00 to 0.50 mg of Sodium Carboxymethyl cellulose.

In another embodiment according to the present invention, the atv layer comprising atorvastatin comprises:

- atorvastatin;
- Lactose;
- Microcrystalline Cellulose;
- Croscarmellose Sodium;
- Magnesium carbonate, calcium carbonate or magnesium oxide;
– hydroxypropyl cellulose (HPC);
- Polysorbate 80; and
- Magnesium stearate.

In certain embodiment of the present invention, the atv layer comprises:

- 1% to 18% by weight of the total weight of the atv layer of atorvastatin;
- 5% to 50% by weight of the total weight of the atv layer of lactose monohydrate,
- 10% to 55% by weight of the total weight of the atv layer of microcrystalline cellulose;
- 3 to 15% by weight of the total weight of the atv layer of croscarmellose sodium;
- 3% to 50% by weight of the total weight of the atv layer of a pharmaceutically acceptable stabilizing additive, in particular CaCO3 or MgCO3 or MgO;

- 0.3% to 5 % by weight of the total weight of the atv layer of hydroxyl propylcellulose;
- 0 to 1% by weight of the total weight of the atv layer of polysorbate 80; and
- 0 to 1.5% by weight of the total weight of the atv layer of magnesium stearate.

In a particular embodiment, the composition herein is film coated, in particular with a polymer coating, such as HPMC and HPC or polyvinyl alcohol-polyethylene glycol (Kollicoat® IR) or a polyvinyl alcohol based coat (PVA-based coat), particularly with 30 mg or less PVA-based coat, more particularly with 20 mg PVA-based coat.

In a particular embodiment, the composition herein is film coated with vinylpyrrolidone-vinyl acetatecopolymer (PVP VA 64 also known as Kollidon® VA 64), Triethylcitrate, Talcum and Titan dioxide.

Alternatively to the film forming polymer, the plasticizer, the filler and colours additives a ready to use mixture like Opadry II clear can be used.

In certain embodiment of the present invention, the core comprising dalcetrapib is separated from the active coating comprising atorvastatin by a separation layer. In particular, the separation layer comprises polyvinyl alcohol, triacetin and talcum. In another embodiment the separation layer comprises vinylpyrrolidone-vinyl acetatecopolymer (PVP VA 64 also known as Kollidon® VA 64) Triacetin and Talcum.

In certain embodiment of the present invention, the composition comprises a seal coat or a film coat as shown in figure 4. In particular, the seal coat comprises polyvinyl alcohol, triacetin, titan dioxide and talcum.

In certain embodiments of the present invention, the composition is a pharmaceutical composition.

The pharmaceutical composition can be, for example, in the form of a pill, capsule or tablet, each containing a predetermined amount of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate and atorvastatin and in particular coated for ease of swallowing, in the form of a powder or granules. In particular, the pharmaceutical composition is in the form of a tablet comprising S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, atorvastatin and the components of the tablet utilized and described therein. For oral administration, fine

powders or granules may contain diluting, dispersing and/or surface active agents and may be present, for example, in capsules or sachets in the dry state, or in tablets wherein binders and lubricants may be included. Components such as sweeteners, flavoring agents, preservatives, suspending agents, thickening agents, and/or emulsifying agents also may be present in the pharmaceutical composition.

In certain embodiments of the present invention, the composition comprises 100 mg to 600 mg of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate. In particular, the composition comprises 150 mg to 450 mg of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate. More particularly, the composition comprises 250 mg to 350 mg of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate. Most particularly, the composition comprises 250 mg to 350 mg of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate.

In certain embodiments of the present invention, the composition comprises 300 mg of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate and 5 mg, 10 mg, 20 mg or 40 mg of atorvastatin.

In another embodiment of the present invention, the composition comprises for pediatric use 25mg to 300mg of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate. In particular the pediatric composition comprises 75mg to 150mg of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate.

In another embodiment of the present invention, the composition comprises for pediatric use 150mg of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate and 5 mg, 10 mg or 20 mg of atorvastatin.

The CETP inhibitor can be administered to the mammal at any suitable dosage (e. g. , to achieve a therapeutically effective amount). For example, a suitable dose of a therapeutically effective amount of Compound I for administration to a patient will be between approximately 100 mg to about 1800 mg per day. A desirable dose is particularly about 300 mg to about 900 mg per day. A preferred dose is about 600 mg per day.

In another embodiment the invention provides a kit comprising a composition comprising a therapeutically effective amount of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate and atorvastatin and at least 30% by weight of hygroscopic polymeric excipients by composition weight, prescribing information also known as "leaflet", a blister package or bottle (HDPE or glass) and a container. The prescribing information particularly includes the advice to a patient regarding the administration of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate with food, especially to improve the bioavailability of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate. In more particular, the prescribing information includes the advice to a patient regarding the administration of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate and atorvastatin with food, especially to improve the bioavailability of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate .

In another embodiment the invention provides a kit comprising a composition as described herein, prescribing information also known as "leaflet", a blister package or bottle (HDPE or glass) and a container. The prescribing information particularly includes the advice to a patient regarding the administration of the S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate with food, especially to improve the bioavailability of the S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate. More particularly the prescribing information includes the advice to a patient regarding the administration of the S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate and atorvastatin with food, especially to improve the bioavailability of the S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate.

In another embodiment, the invention provides a kit comprising a composition comprising a therapeutically effective amount of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate and atorvastatin, and at least 30% by weight of hygroscopic polymeric excipients by composition weight, prescribing information, a blister package or bottle and a container. In particular embodiment the

invention provides the kit as described herein, wherein the prescribing information includes the advice to a patient regarding the administration of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate with food.

In another embodiment, the invention provides a tablet comprising the composition as herein described.

In another embodiment, the invention provides a composition as herein described for preparing a medicament for the treatment or prevention of cardiovascular disorder, in particular wherein the S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate is administered at a daily dose of 100mg to 1800mg, particularly 300mg to 900mg, more particularly 600mg, more particularly wherein S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate is administered with food.

In another embodiment, the invention provides a process for the preparation of the composition comprising the following steps:

a) Mixing and granulating, S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, crospovidone, microcrystalline cellulose, croscarmellose sodium and hydroxypropyl methylcellulose;

b) Spraying up to 0.5% by weight of HPMC in water or in 10%-30% ethanol by weight/70%-90% water by weight, onto the granulates obtained according to step a);

c) drying the granulates;

d) blending microcrystalline Cellulose, colloidal silicon dioxide and sodium stearylfumarate with the dry granulates obtained according to step c);

e) compressing the tablets;

f) aqueous film coating with the separation layer, in particular the separation layer comprises polyvinyl alcohol, triacetin and talcum;

g) aqueous film coating with the active coating, in particular the active coating comprises atorvastatin, polyvinyl alcohol, triacetin, talcum, simethicone and optionally croscarmellose sodium.

In another embodiment, the invention provides a process for the preparation of the composition comprising the following steps:

a) Mixing and granulating, S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, crospovidone, microcrystalline cellulose, croscarmellose sodium and hydroxypropyl methylcellulose;

b) Spraying up to 0.5% by weight of HPMC in water or in 10%-30% ethanol by weight/70%-90% water by weight, onto the granulates obtained according to step a);

c) drying the granulates;

d) blending microcrystalline Cellulose, colloidal silicon dioxide and sodium stearylfumarate with the dry granulates obtained according to step c);

e) compressing the tablets;

f) film coating with the separation layer, in particular the separation layer comprises polyvinyl alcohol, triacetin and talcum;

g) aqueous film coating with the active coating, in particular the active coating comprises atorvastatin, polyvinyl alcohol, triacetin, talcum, and optionally simethicone and/or optionally croscarmellose sodium; and-

h) aqueous film coating with a seal coating, in particular the seal coating comprises polyvinyl alcohol, triacetin and talcum, optionally titan dioxide and /or Colouring agent;

In another embodiment the present invention provides a process for the preparation of the composition as described herein, which comprises the following steps:

a) Mixing and granulating, S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, Crospovidone micronized,

microcrystalline Cellulose, Croscarmellose sodium and optionally with Hydroxypropylmethyl cellulose;

b) Spraying up to 0.5% by weight of Hydroxypropylmethyl cellulose in water or in 10%-30% ethanol by weight/70%-90% water by weight, more particularly in 20% Ethanol by weight/ 80% water by weight onto the granulates obtained according to step a);

c) drying the granulates;

d) blending microcrystalline Cellulose, colloidal silicon dioxide and sodium stearylfumarate with the dry granulates obtained according to step c);

e) compressing the tablets;

f) film coating with the separation layer, in particular the separation layer comprises polyvinyl alcohol, triacetin and talcum;

g) aqueous film coating with the active coating, in particular the active coating comprises atorvastatin, polyvinyl alcohol, croscarmellose sodium, triacetin, talcum and optionally simethicone and/or croscarmellose sodium;

h) aqueous film coating with a seal coating, in particular the seal coating comprises polyvinyl alcohol, triacetin and talcum, optionally titan dioxide and /or Colouring agent;

In another embodiment the present invention provides a process for the preparation of the composition as described herein, which comprises the following steps:

a) Mixing and granulating, S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, crospovidone micronized, mannitol, croscarmellose sodium and Hydroxypropylmethyl cellulose;

b) spraying up to 0.5% by weight of hydroxypropylmethyl cellulose in water or in 10%-30% ethanol by weight/70%-90% water by weight, more particularly in 20% Ethanol by weight/ 80% water by weight onto the granulates obtained according to step a);

c) drying the granulates; and

d) blending microcrystalline Cellulose, colloidal silicon dioxide and sodium stearylfumarate with the dry granulates obtained according to step c);

e) compressing the tablets;

f) film coating with the separation layer, in particular the separation layer comprises polyvinyl alcohol, triacetin and talcum;

g) aqueous film coating with the active coating, in particular the active coating comprises atorvastatin, polyvinyl alcohol, croscarmellose sodium, triacetin, talcum and optionally simethicone and/or croscarmellose sodium;

h) aqueous film coating with a seal coating, in particular the seal coating comprises polyvinyl alcohol, triacetin and talcum, optionally titan dioxide and /or Colouring agent.

In another embodiment the present invention provides a process for the preparation of the composition as described herein, which comprises the following steps:

a) Mixing and granulating, the water instable compound with a waxy consistency, crospovidone micronized, microcrystalline Cellulose and Croscarmellose sodium;

b) spraying the hydroxypropylmethyl cellulose in 10%-30% ethanol by weight/70%-90% water by weight, more particularly in 20% Ethanol by weight/ 80% water by weight onto the granulates obtained according to step a);

c) drying the granulates;

d) blending microcrystalline Cellulose, colloidal silicon dioxide and sodium stearylfumarate with the dry granulates obtained according to step c);

e) compressing the tablets;

f) film coating with the separation layer, in particular the separation layer comprises polyvinyl alcohol, triacetin and talcum;

g) aqueous film coating with the active coating, in particular the active coating comprises atorvastatin, polyvinyl alcohol, croscarmellose sodium, triacetin, talcum and optionally simethicone and/or croscarmellose sodium;

h) aqueous film coating with a seal coating, in particular the seal coating comprises polyvinyl alcohol, triacetin and talcum, optionally titan dioxide and /or Colouring agent.

In another embodiment, the invention provides a process for the preparation the dal layer comprising the following steps:

a) Mixing and granulating, S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, crospovidone, microcrystalline cellulose, croscarmellose sodium and hydroxypropyl methylcellulose;

b) Spraying up to 0.5% by weight of HPMC in water or in 10%-30% ethanol by weight/70%-90% water by weight, onto the granulates obtained according to step a);

c) drying the granulates;

d) blending microcrystalline Cellulose, colloidal silicon dioxide and sodium stearylfumarate with the dry granulates obtained according to step c);

In another embodiment, the invention provides a process for the preparation the atv layer comprising the following steps:

a) Sieving each of the following components, [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) trihydrate, lactose, microcrystalline cellulose, calcium carbonate, magnesium carbonate or magnesium oxide, and croscarmellose sodium and mixing them together to obtain a dry powder blend;

b) Granulating in a high shear granulator by spraying HPC and Polysorbate 80 in water, onto dry powder blend obtained according to step a);

c) wet sieving of the obtained granules and drying the granulates;

d) dry sieving of the granules through a 0.9 mm screen and blending microcrystalline Cellulose (for the 5 mg and 10mg dose strength of atorvastatin) , croscarmellose sodium, lactose (for the 5 mg and 10mg dose strength of atorvastatin) and magnesium stearate with the dry granulates obtained according to step c);

In another embodiment, the invention provides a process for the preparation the composition according to the present invention comprising the following steps:

a) compressing the blend obtained from dal layer step d) and the blend obtained from atv layer step d); and

b) film coating the compressed tablet obtain in step a)

Manufacturing process:

Herein, the API 1 refers to the active substance S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate which is a hydrophobic, water instable compound with a waxy consistency. The API 2 refers in examples 2 to 70 to the active substance [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. In the examples 1 to 70 the API 1 refers to S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate of formula (I') in crystalline form.

The composition of the present invention may be prepared according to any known process which results in keeping the API 1 substantially in crystalline form (the amount of the hydrophobic, API 1 in amorphous does not exceed 10% by weight). Furthermore, the composition of the present invention may be prepared according to any known process which results in keeping the API 1 substantially in crystalline form (the amount of the hydrophobic, water instable compound with a waxy consistency substantially in amorphous does not exceed 10% by weight).

The composition of the present invention may be prepared according to any known process which results in keeping the API 2 substantially in crystalline form (the amount of API 2 in amorphous does not exceed 10% by weight). Furthermore, the composition of the present invention may be prepared according to any known process which results in

keeping the API 2 substantially in crystalline form (the amount of API 2 in amorphous does not exceed 10% by weight).

The process for preparing the core or dal layer composition according to the invention may comprise the following steps:

1) dissolving Hydroxypropylmethyl cellulose (0.5% by weight of total Hydroxypropylmethyl cellulose) in 20% Ethanol by weight and 80% water by weight under constant stirring;

2) loading granulator (high shear mixer : e.g. Diosna®) vertical granulator with bottom driven impeller , with S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, Crospovidone micronized, microcrystalline Cellulose, Croscarmellose sodium and remainder of Hydroxypropylmethyl cellulose;

3) mixing the dry granulate components using impeller and chopper;

4) humidifying the granulate by spraying of the granulation fluid under constant mixing using impeller and chopper;

5) kneading the wetted granulate using impeller and chopper;

6) discharging the wet granulate, screening it over a conical mill [e.g. Frewitt ® (screening mill with rotating impeller));fitted with a 10mm square screen and loading it into the fluid bed dryer

7) drying the granulate in the fluid bed dryer (e.g Glatt®) with inlet air temperature ≤ 60°C until the final LOD (loss on drying) of ≤ 3.5% by weight is reached;

8) discharging the dried granulate and milling it using an impact mill fitted with a 1.5mm round perforation screen (e.g. Frewitt ® (impact mill with rotating hammer);

9) adding the components of the external phase (e.g. microcrystalline Cellulose, colloidal silicon dioxide and sodium stearylfumarate) over a sieve fitted with a 1mm round perforation screen to the granulate

10) blending all the components in a bin blender (e.g. Tumblemix® (tumble blending in bin blender));

11) compressing the tablets on a rotary tablet press with low compression force (around 6kN), (e.g. Korsch® (power assisted);

The process for preparing active coating composition according to the invention may comprise the following steps:

The process for preparing by layer tablet composition according to the invention may comprise the following steps:

12) preparing the coating suspension for the separation layer by dispersing the polyvinyl alcohol in a part of the water;

13) dispersing the talcum in another part of the water by homogeneization

14) preparing a mixture of PVA dissolved in water as obtained under 12), talcum suspended in water as obtained under 13), triacetin and any remaining water;

15) loading the tablets obtained under 11) into the perforated coating drum;

16) preheating the tablets in the perforated drum until an exhaust temperature of 40 to 45°C is reached;

17) spraying the coating suspension of the separation layer obtained under 14) onto the tablets under constant rotation of the perforated coating drum;

18) drying the film coated tablets under constant rotation of the perforated coating drum;

19) preparing the coating suspension for the active coating layer by dispersing the polyvinyl alcohol in a part of the water;

20) dispersing simethicone, atorvastatin and talcum in another part of the water by homogeneization

21) preparing a mixture of PVA dissolved in water as obtained under 19), the suspension containing atorvastatin as obtained under 20), triacetin and any remaining water;

22) spraying the coating suspension of the active coating layer obtained under 21) onto the tablets under constant rotation of the perforated coating drum;

23) drying the film coated tablets under constant rotation of the perforated coating drum;

24) preparing the coating suspension for the seal coat by dispersing the polyvinyl alcohol in a part of the water;

25) dispersing talcum, titan dioxide and/or any color in another part of the water by homogeneization

26) preparing a mixture of PVA dissolved in water as obtained under 24), the suspension as obtained under 25), triacetin and any remaining water;

27) spraying the coating suspension of the seal coat obtained under 26) onto the tablets under constant rotation of the perforated coating drum;

28) drying the film coated tablets under constant rotation of the perforated coating drum;

29) discharging the film coated tablets;

30) imprinting of the film coated tablets

Other features and embodiments of the invention will become apparent from the following examples which are given for illustration of the invention rather than for limiting its intended scope.

Examples 1 to 46 and placebo example A were prepared according to the above mentioned general processes, wherein the API 1 for example A has been replaced with mannitol. Examples 47 to 70 are prepared according to the above mentioned general processes. Examples 22 to 30, 36 to 46 and 62 to 70 were all film coated with 20 mg PVA-based coat (e.g. Opadry® e.g. Opadry II white 85F18422).

Example No 1

	Ingredient	Mass/Unit	Amount/Unit	hygroscopic polymer	
		[mg]	[%]	Water insoluble	Water soluble
Core or dal layer	API 1	300.00	52.54	N/A	N/A
	Microcrystalline Cellulose (Type 101)	66.00	11.56	+	
	Crospovidone micronized	66.00	11.56	+	
	HPMC (2910 3cp)	24.00	4.20		+
	CMC Na	34.00	5.95	+	
	Colloidal Silicon Dioxide	3.00	0.53	N/A	N/A
	Sodium stearylfumarate	3.00	0.53	N/A	N/A
	Microcrystalline Cellulose (Type 102)	75.00	13.35	+	
	Total core tablet	571.00	100.00		
	Amount hygroscopic polymers			42.21%	4.20%
	Total amount hygroscopic polymers			46.41%	

Example No 2

	Ingredient	Mass/Unit
		[mg]
Core	According to example 1	571.00
Separation Layer	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	triacetin	1.00
	talcum	9.00
Active Coating	API 2	5.41
	Triethylcitrate	0.25
	HPMC (2910 3cp)	1.25
	HPC (Klucel LF)	1.25
	Talcum	2.25
	Simethicone Suspension USP (30% solids)	0.60 (0.18)[1]

Seal Coat	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	triethylcitrate	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 3

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	triacetin	1.00
	talcum	9.00
Active Coating	API 2	43.30
	Triethylcitrate	2.00
	HPMC (2910 3cp)	10.00
	HPC (Klucel LF)	10.00
	Talcum	18.00
	Simethicone Suspension USP (30% solids)	4.80 (1.44)[1]
Seal Coat	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	triethylcitrate	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 4

	Ingredient	**Mass/Unit [mg]**

Core	According to example 1	571.00
Separation Layer	Kollidon ® VA 64	10. 00
	Triacetin	1.00
	Talcum	9.00
Active Coating	API 2	5.41
	Simethicone Suspension USP (30% solids)	0.60 (0.18)[1]
	Kollidon ® VA 64	2.50
	Triethylcitrate	0.25
	Talcum	2.25
Seal Coat	Kollidon ® VA 64	10.00
	Triethylcitrate	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 5

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	Kollidon ® VA 64	10. 00
	Triacetin	1.00
	Talcum	9.00
Active Coating	API 2	43.30
	Simethicone Suspension USP (30% solids)	4.80 (1.44)[1]
	Kollidon ® VA 64	20.00
	Triethylcitrate	2.00
	Talcum	18.00
S e	Kollidon ® VA 64	10.00

	Triethylcitrate	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 6

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	Kollicoat IR	10. 50
	Talcum	9.50
Active Coating	API 2	5.41
	Simethicone Suspension USP (30% solids)	0.60 (0.18)[1]
	Kollicoat IR	2.63
	Talcum	2.38
Seal Coat	Kollicoat IR	10.50
	Talcum	4.75
	Titan dioxide	4.75

[1] In suspension (solvent free)

Example No 7

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Sep arat	Kollicoat IR	10. 50

	Talcum	9.50
Active Coating	API 2	43.30
	Simethicone Suspension USP (30% solids)	4.80 (1.44)[1]
	Kollicoat IR	21.00
	Talcum	19.00
Seal Coat	Kollicoat IR	10.50
	Talcum	4.75
	Titan dioxide	4.75

[1] In suspension (solvent free)

Example No 8

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	triacetin	1.00
	talcum	9.00
Active Coating	API 2	5.41
	Triethylcitrate	0.25
	HPMC (2910 3cp)	1.25
	HPC (Klucel LF)	1.25
	Talcum	2.25
	Simethicone Suspension USP (30% solids)	0.60 (0.18)[1]
Seal Coat	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	triethylcitrate	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 9

	Ingredient	Mass/Unit [mg]
Core	According to example 1	571.00
Separation Layer	polyvinyl alcohol (PVA EG -05 PW)	10. 00
	triacetin	1.00
	talcum	9.00
Active Coating	API 2	5.41
	polyvinyl alcohol (PVA EG -05 PW)	2.50
	CMC Na	0.20
	Triacetin	0.25
	Talcum	2.25
	Simethicone Suspension USP (30% solids)	0.60 (0.18)[1]
Seal Coat	polyvinyl alcohol (PVA EG -05 PW)	10.00
	Triacetin	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 10

	Ingredient	Mass/Unit [mg]
Core	According to example 1	571.00
Separation Layer	polyvinyl alcohol (PVA EG -05 PW)	10. 00
	triacetin	1.00
	talcum	9.00
Active Coating	API 2	43.30
	polyvinyl alcohol (PVA EG -05 PW)	20.00
	CMC Na	---

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	Triacetin	2.00
	Talcum	18.00
	Simethicone Suspension USP (30% solids)	4.80 (1.44)[1]
Seal Coat	polyvinyl alcohol (PVA EG -05 PW)	10.00
	Triacetin	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 11

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	Opadry II white 85F18422	20. 00
Active Coating	API 2	5.40
	Opadry II clear 85F29116	19.95
	Calcium carbonate	16.2
	Simethicone Suspension USP (30% solids)	0.45 (0.14)[1]
Seal Coat	Opadry II brown 85F26792	15.00

[1] In suspension (solvent free)

Example No 12

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00

Separation Layer	Opadry II white 85F18422	20. 00
Active Coating	API 2	10.8
	Opadry II clear 85F29116	39.9
	Calcium carbonate	32.4
	Simethicone Suspension USP (30% solids)	0.9 (0.28)[1]
Seal Coat	Opadry II brown 85F26792	15.00

[1] In suspension (solvent free)

Example No 13

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	Opadry II white 85F18422	20. 00
Active Coating	API 2	21.6
	Opadry II clear 85F29116	79.8
	Calcium carbonate	64.8
	Simethicone Suspension USP (30% solids)	1.8 (0.56)[1]
Seal Coat	Opadry II brown 85F26792	15.00

[1] In suspension (solvent free)

Example No 14

	Ingredient	**Mass/Unit [mg]**

Core	According to example 1	571.00
Separation Layer	polyvinyl alcohol (PVA EG -05 PW)	10. 00
	Triacetin	1.00
	Talcum	9.00
Active Coating	API 2	5.41
	polyvinyl alcohol (PVA EG -05 PW)	2.50
	Triacetin	0.25
	Talcum	2.25
	Simethicone Suspension USP (30% solids)	0.6 (0.18)[1]
Seal Coat	polyvinyl alcohol (PVA EG -05 PW)	10.00
	Triacetin	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 15

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	polyvinyl alcohol (PVA EG -05 PW)	10. 00
	Triacetin	1.00
	Talcum	9.00
Active Coating	API 2	5.41
	polyvinyl alcohol (PVA EG -05 PW)	20.00
	Triacetin	2.00
	Talcum	18.00
	Simethicone Suspension USP (30% solids)	4.8 (1.44)[1]
Seal Coat	polyvinyl alcohol (PVA EG -05 PW)	10.00
	Triacetin	1.00

	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 16

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	26.09
	Microcrystalline Cellulose (PH 102)	28.6
	Croscarmellose Sodium	2.18
	Magnesium oxide	15
	HPC (Klucel LF)	1.45
	Polysorbate 80 (Tween 80)	0.29
	Lactose (Tablettose 70)	102.34
	Microcrystalline Cellulose (PH 102)	128.16
	Croscarmellose Sodium	15.26
	Magnesium stearate	2.59

Example No 17

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	10.82
	Lactose Pulvis	52.18
	Microcrystalline Cellulose (PH 102)	57.19
	Croscarmellose Sodium	4.35
	Magnesium oxide	30
	HPC (Klucel LF)	2.9

	Polysorbate 80 (Tween 80)	0.58
	Lactose (Tablettose 70)	86.77
	Microcrystalline Cellulose (PH 102)	66.9
	Croscarmellose Sodium	13.08
	Magnesium stearate	2.59

Example No 18

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	21.64
	Lactose Pulvis	104.36
	Microcrystalline Cellulose (PH 102)	114.38
	Croscarmellose Sodium	8.7
	Magnesium oxide	60.00
	HPC (Klucel LF)	5.8
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.73
	Magnesium stearate	1.61

Example No 19

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	36.09
	Microcrystalline Cellulose (PH 102)	28.6
	Croscarmellose Sodium	2.18
	Magnesium carbonate	17.5
	HPC (Klucel LF)	1.45
	Polysorbate 80 (Tween 80)	0.29

	Lactose (Tablettose 70)	117.2
	Microcrystalline Cellulose (PH 102)	150.81
	Croscarmellose Sodium	15.22
	Magnesium stearate	1.88

Example No 20

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	10.82
	Lactose Pulvis	72.18
	Microcrystalline Cellulose (PH 102)	57.19
	Croscarmellose Sodium	4.35
	Magnesium carbonate	35
	HPC (Klucel LF)	2.9
	Polysorbate 80 (Tween 80)	0.58
	Lactose (Tablettose 70)	100.7
	Microcrystalline Cellulose (PH 102)	77.97
	Croscarmellose Sodium	13.05
	Magnesium stearate	1.88

Example No 21

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	21.64
	Lactose Pulvis	144.36
	Microcrystalline Cellulose (PH 102)	114.38
	Croscarmellose Sodium	8.7
	Magnesium carbonate	70
	HPC (Klucel LF)	5.8

	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.7
	Magnesium stearate	1.88

Example No 22

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	3.34
	Microcrystalline Cellulose (PH 102)	5.93
	Croscarmellose Sodium	2.18
	Magnesium carbonate	13.86
	HPC (Klucel LF)	1.45
	Polysorbate 80 (Tween 80)	0.29
	Lactose (Tablettose 70)	32.73
	Microcrystalline Cellulose (PH 102)	58.12
	Croscarmellose Sodium	15.23
	Magnesium stearate	5.41

Example No 23

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	21.65
	Lactose Pulvis	13.36
	Microcrystalline Cellulose (PH 102)	23.72
	Croscarmellose Sodium	8.70
	Magnesium carbonate	55.45
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16

	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 24

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	43.30
	Lactose Pulvis	26.72
	Microcrystalline Cellulose (PH 102)	47.44
	Croscarmellose Sodium	17.40
	Magnesium carbonate	110.90
	HPC (Klucel LF)	11.60
	Polysorbate 80 (Tween 80)	2.32
	Croscarmellose Sodium	17.40
	Magnesium stearate	2.92

Example No 25

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	34.19
	Microcrystalline Cellulose (PH 102)	60.72
	Croscarmellose Sodium	8.70
	Magnesium carbonate	13.86
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16

Example No 26

	Ingredient	**Mass/Unit**

		[mg]
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	7.84
	Microcrystalline Cellulose (PH 102)	13.93
	Croscarmellose Sodium	2.18
	Magnesium carbonate	13.86
	HPC (Klucel LF)	1.45
	Polysorbate 80 (Tween 80)	0.29
	Lactose (Tablettose 70)	46.24
	Microcrystalline Cellulose (PH 102)	82.12
	Croscarmellose Sodium	15.23
	Magnesium stearate	1.46

Example No 27

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	21.65
	Lactose Pulvis	31.37
	Microcrystalline Cellulose (PH 102)	55.71
	Croscarmellose Sodium	8.70
	Magnesium carbonate	55.45
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 28

	Ingredient	**Mass/Unit [mg]**

Dal layer	According to example 1	571.00
Atv Layer	API 2	43.30
	Lactose Pulvis	62.74
	Microcrystalline Cellulose (PH 102)	111.42
	Croscarmellose Sodium	17.40
	Magnesium carbonate	110.90
	HPC (Klucel LF)	11.60
	Polysorbate 80 (Tween 80)	2.32
	Croscarmellose Sodium	17.40
	Magnesium stearate	2.92

Example No 29

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	52.20
	Microcrystalline Cellulose (PH 102)	92.70
	Croscarmellose Sodium	8.70
	Magnesium carbonate	13.86
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 30

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
	API 2	5.41

Atv Layer	Lactose Pulvis	12.35
	Microcrystalline Cellulose (PH 102)	21.92
	Croscarmellose Sodium	2.18
	Magnesium carbonate	13.86
	HPC (Klucel LF)	1.45
	Polysorbate 80 (Tween 80)	0.29
	Lactose (Tablettose 70)	59.75
	Microcrystalline Cellulose (PH 102)	106.11
	Croscarmellose Sodium	15.23
	Magnesium stearate	1.46

Example No 31

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	21.65
	Lactose Pulvis	49.38
	Microcrystalline Cellulose (PH 102)	87.70
	Croscarmellose Sodium	8.70
	Magnesium carbonate	55.45
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 32

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	43.30
	Lactose Pulvis	98.77

	Microcrystalline Cellulose (PH 102)	175.39
	Croscarmellose Sodium	17.40
	Magnesium carbonate	110.90
	HPC (Klucel LF)	11.60
	Polysorbate 80 (Tween 80)	2.32
	Croscarmellose Sodium	17.40
	Magnesium stearate	2.92

Example No 33

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	Atorvastatin Calcium Trihydrate	5.40
	Lactose Pulvis	16.09
	Microcrystalline Cellulose (PH 102)	28.61
	Croscarmellose Sodium	2.18
	Calcium carbonate	15.95
	HPC (Klucel LF)	1.45
	Polysorbate 80 (Tween 80)	0.29
	Lactose (Tablettose 70)	88.93
	Microcrystalline Cellulose (PH 102)	114.43
	Croscarmellose Sodium	15.23
	Magnesium stearate	1.46

Example No 34

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	10.80
	Lactose Pulvis	32.18
	Microcrystalline Cellulose (PH 102)	57.22

	Croscarmellose Sodium	4.35
	Calcium carbonate	31.90
	HPC (Klucel LF)	2.90
	Polysorbate 80 (Tween 80)	0.58
	Lactose (Tablettose 70)	76.28
	Microcrystalline Cellulose (PH 102)	59.29
	Croscarmellose Sodium	13.05
	Magnesium stearate	1.46

Example No 35

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	Atorvastatin Calcium Trihydrate	21.60
	Lactose Pulvis	64.36
	Microcrystalline Cellulose (PH 102)	114.44
	Croscarmellose Sodium	8.70
	Calcium carbonate	63.80
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 36

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	2.59
	Microcrystalline Cellulose (PH 102)	4.60
	Croscarmellose Sodium	2.18

	Calcium carbonate	15.95
	HPC (Klucel LF)	1.45
	Polysorbate 80 (Tween 80)	0.29
	Lactose (Tablettose 70)	32.73
	Microcrystalline Cellulose (PH 102)	58.12
	Croscarmellose Sodium	15.23
	Magnesium stearate	1.46

Example No 37

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	Atorvastatin Calcium Trihydrate	21.65
	Lactose Pulvis	10.35
	Microcrystalline Cellulose (PH 102)	18.38
	Croscarmellose Sodium	8.70
	Calcium carbonate	63.80
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 38

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	43.30
	Lactose Pulvis	20.70
	Microcrystalline Cellulose (PH 102)	36.76
	Croscarmellose Sodium	17.40
	Calcium carbonate	127.60

	HPC (Klucel LF)	11.60
	Polysorbate 80 (Tween 80)	2.32
	Croscarmellose Sodium	17.40
	Magnesium stearate	2.92

Example No 39

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	33.44
	Microcrystalline Cellulose (PH 102)	59.38
	Croscarmellose Sodium	8.70
	Calcium carbonate	15.95
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 40

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	7.09
	Microcrystalline Cellulose (PH 102)	12.59
	Croscarmellose Sodium	2.18
	Calcium carbonate	15.95
	HPC (Klucel LF)	1.45
	Polysorbate 80 (Tween 80)	0.29
	Lactose (Tablettose 70)	56.13

	Microcrystalline Cellulose (PH 102)	72.23
	Croscarmellose Sodium	15.23
	Magnesium stearate	1.46

Example No 41

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	21.65
	Lactose Pulvis	28.36
	Microcrystalline Cellulose (PH 102)	50.37
	Croscarmellose Sodium	8.70
	Calcium carbonate	63.80
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 42

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	43.30
	Lactose Pulvis	56.72
	Microcrystalline Cellulose (PH 102)	100.74
	Croscarmellose Sodium	17.40
	Calcium carbonate	127.60
	HPC (Klucel LF)	11.60
	Polysorbate 80 (Tween 80)	2.32
	Croscarmellose Sodium	17.40
	Magnesium stearate	2.92

Example No 43

	Ingredient	Mass/Unit [mg]
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	51.45
	Microcrystalline Cellulose (PH 102)	91.37
	Croscarmellose Sodium	8.70
	Calcium carbonate	15.95
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 44

	Ingredient	Mass/Unit [mg]
Dal layer	According to example 1	571.00
Atv Layer	API 2	5.41
	Lactose Pulvis	11.59
	Microcrystalline Cellulose (PH 102)	20.59
	Croscarmellose Sodium	2.18
	Calcium carbonate	15.95
	HPC (Klucel LF)	1.45
	Polysorbate 80 (Tween 80)	0.29
	Lactose (Tablettose 70)	72.53
	Microcrystalline Cellulose (PH 102)	93.33
	Croscarmellose Sodium	15.23
	Magnesium stearate	1.46

Example No 45

	Ingredient	Mass/Unit [mg]
Dal layer	According to example 1	571.00
Atv Layer	API 2	21.65
	Lactose Pulvis	46.37
	Microcrystalline Cellulose (PH 102)	82.36
	Croscarmellose Sodium	8.70
	Calcium carbonate	63.80
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 46

	Ingredient	Mass/Unit [mg]
Dal layer	According to example 1	571.00
Atv Layer	API 2	43.30
	Lactose Pulvis	92.74
	Microcrystalline Cellulose (PH 102)	164.72
	Croscarmellose Sodium	17.40
	Calcium carbonate	127.60
	HPC (Klucel LF)	11.60
	Polysorbate 80 (Tween 80)	2.32
	Croscarmellose Sodium	17.40
	Magnesium stearate	2.92

Not yet produced

Example No 47

	Ingredient	Mass/Unit

		[mg]
Core	According to example 1	571.00
Separation Layer	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	triacetin	1.00
	talcum	9.00
Active Coating	API 2	10.83
	Triethylcitrate	0.5
	HPMC (2910 3cp)	2.50
	HPC (Klucel LF)	2.50
	Talcum	4.5
	Simethicone Suspension USP (30% solids)	1.20 (0.36)[1]
Seal Coat	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	triethylcitrate	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 48

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	Triacetin	1.00
	Talcum	9.00
Acti	API 2	21.65

	Triethylcitrate	1.0
	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	Talcum	9.00
	Simethicone Suspension USP (30% solids)	2.40 (0.72)[1]
Seal Coat	HPMC (2910 3cp)	5.00
	HPC (Klucel LF)	5.00
	triethylcitrate	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 49

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	Polyvinyl alcohol (PVP VA 64 : Kollidon VA 64)	10. 00
	Triacetin	1.00
	Talcum	9.00
Active Coating	API 2	10.83
	Simethicone Suspension USP (30% solids)	1.20 (0.36)[1]
	Polyvinyl alcohol (PVP VA 64 : Kollidon VA 64)	5.00
	Triethylcitrate	0.50
	Talcum	4.50
Seal Coat	Polyvinyl alcohol (PVP VA 64 : Kollidon VA 64)	10.00
	Triethylcitrate	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 50

	Ingredient	Mass/Unit [mg]
Core	According to example 1	571.00
Separation Layer	Polyvinyl alcohol (PVP VA 64 : Kollidon VA 64)	10. 00
	Triacetin	1.00
	Talcum	9.00
Active Coating	API 2	21.65
	Simethicone Suspension USP (30% solids)	2.40 (0.72)[1]
	Polyvinyl alcohol (PVP VA 64 : Kollidon VA 64)	10.00
	Triethylcitrate	1.00
	Talcum	9.00
Seal Coat	Polyvinyl alcohol (PVP VA 64 : Kollidon VA 64)	10.00
	Triethylcitrate	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 51

	Ingredient	Mass/Unit [mg]
Core	According to example 1	571.00
Separation Layer	Kollicoat IR	10. 50
	Talcum	9.50
Active Coating	API 2	10.83
	Simethicone Suspension USP (30% solids)	1.20 (0.36)[1]
	Kollicoat IR	5.26
	Talcum	4.76

Seal Coatt	Kollicoat IR	10.50
	Talcum	4.75
	Titan dioxide	4.75

[1] In suspension (solvent free)

Example No 52

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	Kollicoat IR	10. 50
	Talcum	9.50
Active Coating	API 2	21.65
	Simethicone Suspension USP (30% solids)	2.40 (0.72)[1]
	Kollicoat IR	10.52
	Talcum	9.52
Seal Coat	Kollicoat IR	10.50
	Talcum	4.75
	Titan dioxide	4.75

[1] In suspension (solvent free)

Example No 53

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	polyvinyl alcohol (PVA EG -05 PW)	10. 00
	triacetin	1.00
	talcum	9.00

Active Coating	API 2	10.82
	polyvinyl alcohol (PVA EG -05 PW)	5.00
	CMC Na	0.10
	Triacetin	0.50
	Talcum	4.50
	Simethicone Suspension USP (30% solids)	1.20 (0.36)[1]
Seal Coat	polyvinyl alcohol (PVA EG -05 PW)	10.00
	Triacetin	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 54

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	polyvinyl alcohol (PVA EG -05 PW)	10. 00
	triacetin	1.00
	talcum	9.00
Active Coating	API 2	21.65
	polyvinyl alcohol (PVA EG -05 PW)	10.00
	CMC Na	0.05
	Triacetin	1.00
	Talcum	9.00
	Simethicone Suspension USP (30% solids)	2.40 (0.72)[1]
Seal Coat	polyvinyl alcohol (PVA EG -05 PW)	10.00
	Triacetin	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 55

	Ingredient	Mass/Unit [mg]
Core	According to example 1	571.00
Separation Layer	Opadry II white 85F18422	20. 00
Active Coating	API 2	43.2
	Opadry II clear 85F29116	159.6
	Calcium carbonate	129.6
	Simethicone Suspension USP (30% solids)	3.6 (1.08)[1]
Seal Coat	Opadry II brown 85F26792	15.00

[1] In suspension (solvent free)

Example No 56

	Ingredient	Mass/Unit [mg]
Core	According to example 1	571.00
Separation Layer	polyvinyl alcohol (PVA EG -05 PW)	10. 00
	Triacetin	1.00
	Talcum	9.00
Active Coating	API 2	10.82
	polyvinyl alcohol (PVA EG -05 PW)	5.00
	Triacetin	0.50
	Talcum	4.50
	Simethicone Suspension USP (30% solids)	1.2 (0.36)[1]
S e	polyvinyl alcohol (PVA EG -05 PW)	10.00

	Triacetin	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 57

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	polyvinyl alcohol (PVA EG -05 PW)	10. 00
	Triacetin	1.00
	Talcum	9.00
Active Coating	API 2	21.64
	polyvinyl alcohol (PVA EG -05 PW)	10.00
	Triacetin	1.00
	Talcum	9.00
	Simethicone Suspension USP (30% solids)	2.4 (0.72)[1]
Seal Coat	polyvinyl alcohol (PVA EG -05 PW)	10.00
	Triacetin	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 58

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation	polyvinyl alcohol (PVA EG -05 PW)	10. 00
	Triacetin	1.00

	Talcum	9.00
Active Coating	API 2	10.82
	polyvinyl alcohol (PVA EG -05 PW)	20.00
	Triacetin	2.00
	Talcum	18.00
	Simethicone Suspension USP (30% solids)	4.8 (1.44)[1]
Seal Coat	polyvinyl alcohol (PVA EG -05 PW)	10.00
	Triacetin	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 59

	Ingredient	**Mass/Unit [mg]**
Core	According to example 1	571.00
Separation Layer	polyvinyl alcohol (PVA EG -05 PW)	10. 00
	Triacetin	1.00
	Talcum	9.00
Active Coating	API 2	21.65
	polyvinyl alcohol (PVA EG -05 PW)	20.00
	Triacetin	2.00
	Talcum	18.00
	Simethicone Suspension USP (30% solids)	4.8 (1.44)[1]
Seal Coat	polyvinyl alcohol (PVA EG -05 PW)	10.00
	Triacetin	1.00
	Talcum	4.50
	Titan dioxide	4.50

[1] In suspension (solvent free)

Example No 60

	Ingredient	Mass/Unit [mg]
Dal layer	According to example 1	571.00
Atv Layer	API 2	43.28
	Lactose Pulvis	208.72
	Microcrystalline Cellulose (PH 102)	228.76
	Croscarmellose Sodium	17.40
	Magnesium oxide	120.00
	HPC (Klucel LF)	11.60
	Polysorbate 80 (Tween 80)	2.32
	Croscarmellose Sodium	17.46
	Magnesium stearate	5.18

Example No 61

	Ingredient	Mass/Unit [mg]
Dal layer	According to example 1	571.00
Atv Layer	API 2	43.28
	Lactose Pulvis	288.72
	Microcrystalline Cellulose (PH 102)	228.76
	Croscarmellose Sodium	17.4
	Magnesium carbonate	140
	HPC (Klucel LF)	11.6
	Polysorbate 80 (Tween 80)	2.32
	Croscarmellose Sodium	17.4
	Magnesium stearate	3.76

Example No 62

	Ingredient	Mass/Unit [mg]

Dal layer	According to example 1	571.00
Atv Layer	API 2	10.83
	Lactose Pulvis	6.68
	Microcrystalline Cellulose (PH 102)	11.86
	Croscarmellose Sodium	4.35
	Magnesium carbonate	27.73
	HPC (Klucel LF)	2.90
	Polysorbate 80 (Tween 80)	0.58
	Lactose (Tablettose 70)	34.14
	Microcrystalline Cellulose (PH 102)	26.43
	Croscarmellose Sodium	13.05
	Magnesium stearate	1.46

Example No 63

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	10.83
	Lactose Pulvis	15.69
	Microcrystalline Cellulose (PH 102)	27.85
	Croscarmellose Sodium	4.35
	Magnesium carbonate	27.73
	HPC (Klucel LF)	2.90
	Polysorbate 80 (Tween 80)	0.58
	Lactose (Tablettose 70)	48.23
	Microcrystalline Cellulose (PH 102)	37.34
	Croscarmellose Sodium	13.05
	Magnesium stearate	1.46

Example No 64

	Ingredient	**Mass/Unit**

		[mg]
Dal layer	According to example 1	571.00
Atv Layer	API 2	43.20
	Lactose Pulvis	128.72
	Microcrystalline Cellulose (PH 102)	228.88
	Croscarmellose Sodium	17.40
	Calcium carbonate	127.60
	HPC (Klucel LF)	11.60
	Polysorbate 80 (Tween 80)	2.32
	Croscarmellose Sodium	17.40
	Magnesium stearate	2.92

Example No 65

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	10.83
	Lactose Pulvis	5.18
	Microcrystalline Cellulose (PH 102)	9.19
	Croscarmellose Sodium	4.35
	Calcium carbonate	31.90
	HPC (Klucel LF)	2.90
	Polysorbate 80 (Tween 80)	0.58
	Lactose (Tablettose 70)	34.08
	Microcrystalline Cellulose (PH 102)	26.49
	Croscarmellose Sodium	13.05
	Magnesium stearate	1.46

Example No 66

	Ingredient	**Mass/Unit [mg]**

Dal layer	According to example 1	571.00
Atv Layer	API 2	10.83
	Lactose Pulvis	25.72
	Microcrystalline Cellulose (PH 102)	45.74
	Croscarmellose Sodium	8.70
	Calcium carbonate	31.90
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 67

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	10.83
	Lactose Pulvis	14.18
	Microcrystalline Cellulose (PH 102)	25.19
	Croscarmellose Sodium	4.35
	Calcium carbonate	31.90
	HPC (Klucel LF)	2.90
	Polysorbate 80 (Tween 80)	0.58
	Lactose (Tablettose 70)	48.15
	Microcrystalline Cellulose (PH 102)	37.42
	Croscarmellose Sodium	13.05
	Magnesium stearate	1.46

Example No 68

	Ingredient	**Mass/Unit [mg]**

Dal layer	According to example 1	571.00
Atv Layer	API 2	10.83
	Lactose Pulvis	43.72
	Microcrystalline Cellulose (PH 102)	77.74
	Croscarmellose Sodium	8.70
	Calcium carbonate	31.90
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No 69

	Ingredient	**Mass/Unit [mg]**
Dal layer	According to example 1	571.00
Atv Layer	API 2	10.83
	Lactose Pulvis	23.19
	Microcrystalline Cellulose (PH 102)	41.18
	Croscarmellose Sodium	4.35
	Calcium carbonate	31.90
	HPC (Klucel LF)	2.90
	Polysorbate 80 (Tween 80)	0.58
	Lactose (Tablettose 70)	62.21
	Microcrystalline Cellulose (PH 102)	48.36
	Croscarmellose Sodium	13.05
	Magnesium stearate	1.46

Example No 70

	Ingredient	**Mass/Unit [mg]**

Dal layer	According to example 1	571.00
Atv Layer	API 2	10.83
	Lactose Pulvis	61.72
	Microcrystalline Cellulose (PH 102)	109.74
	Croscarmellose Sodium	8.70
	Calcium carbonate	31.90
	HPC (Klucel LF)	5.80
	Polysorbate 80 (Tween 80)	1.16
	Croscarmellose Sodium	8.70
	Magnesium stearate	1.46

Example No A

Ingredient	**Mass/Unit**	**Amount/Unit**	**hygroscopic polymer**	
	[mg]	**[%]**	**Water insoluble**	**Water soluble**
Mannitol	300.00	52.54	N/A	N/A
Microcrystalline Cellulose	141.00	24.69	+	
Crospovidone micronized	66.00	11.56	+	
HPMC	24.00	4.20		+
CMC Na	34.00	5.95	+	
Colloidal Silicon Dioxide	3.00	0.53	N/A	N/A
Sodium stearylfumarate	3.00	0.53	N/A	N/A
Total tablet	571.00	100.00		
Amount hygroscopic polymers			42.21%	4.20%
Total amount hygroscopic polymers			46.41%	

Example B:

Two tablets produced according to example 1 and example A were sliced and their X-ray pictures were collected. Both figures represent an overlayed of all X-ray slices that were generated during the measurement to reconstruct the 3D tablet. While Figure 1 does not show any imperfection but a smooth surface, Figure 2 has lot of cracks. These cracks are also detectable by the human eye.

Example C:

XRPD patterns of S-[2-([[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate crystalline form A were recorded at ambient conditions in transmission geometry with a STOE STADI P diffractometer (Cu K alpha radiation source, primary monochromator, position sensitive detector, angular range 3° to 42° 2Theta, approximately 60 minutes total measurement time). The samples were prepared and analyzed without further processing (e.g. grinding or sieving) of the substance.

2theta / °	relative intensity / %
7.9	86.3
8.5	16.2
11.7	30.7
12.7	17.1
17.1	41.6

2theta / °	relative intensity / %
18	14.6
18.5	100
20.2	27.2
22.1	33.7
24.7	11.9

CLAIMS

1. A composition comprising:

a) - S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;
-croscarmellose sodium; and
b) atorvastatin.

2. A composition according to claim 1, comprising:

a) a core or one layer comprising :

- S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;

- croscarmellose sodium; and

b) an active coating or another layer comprising atorvastatin.

3. A composition according to claim 1 or 2, comprising:

a) a core comprising :

- S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;

- croscarmellose sodium; and

b) an active coating comprising atorvastatin.

4. A composition according to claim 1 or 2, comprising:

a) one layer comprising :

- S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;

- croscarmellose sodium; and

b) another layer comprising atorvastatin.

5. A composition according to any one of claims 1 to 4 further comprising at least one additional hygroscopic polymeric excipient, in particular wherein the hygroscopic polymeric excipient is in the core or dal layer.

6. A composition according to any one of claims 1 to 5, further comprising at least two hygroscopic polymeric excipients, in particular wherein the hygroscopic polymeric excipients are in the core or dal layer.

7. A composition according to any one of claims 1 to 6, further comprising at least three additional hygroscopic polymeric excipients of which two are diluents with a bulk density lower than 800g/L, in particular wherein the hygroscopic polymeric excipients are in the core or dal layer.

8. A composition according to any one of the claims 1 to 6, comprising:

a) - more than 50% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;

- more than 40% by weight of the total weight of the core or dal layer of water insoluble hygroscopic polymer;

- more than 4% by weight of the total weight of the core or dal layer of water soluble hygroscopic polymer;

- less than 6% of other excipients; and

b) atorvastatin.

9. A composition according to any one of the claims 1 to 3, comprising:

a) - 48% to 55% by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;

- 4% to 8% by weight of the total weight of the core or dal layer of croscarmellose sodium;

- 32% to 41% by weight of the total weight of the core or dal layer of water insoluble hygroscopic polymer;

- 4% to 5% by weight of the total weight of the core or dal layer of water soluble hygroscopic polymer; and

b) atorvastatin.

10. A composition according to any one of the claims 2 to 9, wherein the hygroscopic polymeric excipients are selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hydroxyethylmethyl cellulose, carboxypolymethylene, methylcellulose, ethylcellulose, hydroxyethyl cellulose, celluloseacetate, polyvinylpyrrolidone, crosslinked polyvinylpyrrolidone, micronized crosslinked polyvinylpyrrolidone, carboxymethylcellulose calcium, crosslinked carboxymethylcellulose, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powder, carboxymethyl starch, starch, pregelatinized starch.

11. A composition according to any one of the claims 1 to 10, wherein S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate is in crystalline form.

12. A composition according to any one of the claims 2 to 11, wherein the active coating comprises:

a) atorvastatin;

b)Polyvinyl alcohol;

c) croscarmellose sodium;

d)triacetin;

e) talcum; and

f) simethicone.-

13. A composition according to any one of the claims 2 to 12, wherein the active coating is separated by a separation layer from the core:

14. A composition according to any one of the claims 2 to 11, wherein another layer comprising atorvastatin comprises:

- atorvastatin;

- Lactose;
- Microcrystalline Cellulose;
- Croscarmellose Sodium;
- Magnesium carbonate, calcium carbonate or magnesium oxide;
– hydroxypropyl cellulose (HPC);
- Polysorbate 80; and
- Magnesium stearate.

15. A composition according to any one of the claims 1 to 14, wherein atorvastatin is [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate, most particularly in crystalline form I.

16. A composition according to any one of the claims 2 to 15, wherein the hygroscopic polymeric excipients are hydroxypropylmethyl cellulose, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone.

17. A composition according to any one of the claims 1 to 16, comprising:

b) - S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;
- microcrystalline cellulose;
- crospovidone micronized;
-hydroxypropylmethyl cellulose;
- croscarmellose sodium; and

b) atorvastatin.

18. A composition according to any one of the claims 1 to 17, comprising:

a) - 48% to 55% by weight of the total weight of the core or dal layer of -[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate;

-4% to 8% by weight of croscarmellose sodium;

- 35% to 44% by weight of hydroxypropylmethyl cellulose, microcrystalline cellulose and crospovidone micronized; and

b) atorvastatin.

19. A composition according to any one of the claims 1 to 18, wherein the composition is in the form of a tablet.

20. A composition according to any one of claims 1 to 7, comprising 10% to 69%, particularly 40% to 60%, more particularly 48% to 55% by w by weight of the total weight of the core or dal layer of S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate.

21. A composition according to any one of claims 1 to 8, comprising 1% to 10%, particularly 5% to 10% , more particularly 4% to 8% by weight of the total weight of the core or dal layer of croscarmellose sodium.

22. A composition according to any one of the claims 1 to 9, comprising 30% to 70%, particularly 30% to 60%, more particularly 40% to 50% of at least two diluents with a bulk density lower than 800g/L.

23. A composition according to any one of the claims 1 to 9, wherein there is at least 30%, particularly 34% to 44%, more particularly 40% to 44% by weight of the total weight of the core or dal layer of the hygroscopic polymeric excipients.

24. A composition according to any one of the claims 2 to 11, wherein the hygroscopic polymeric excipients are polymeric excipients which take up moisture by absorption or adsorption even at relative humidity as low as 50%, at room temperature.

25. A composition according to any one the claims 1 to 24 for treating or preventing cardiovascular disorder.

26. A composition according to any one the claims 1 to 24 for the use in the treatment or prevention of cardiovascular disorder.

27. A composition according to any one of the claims 25 or 26, wherein the cardiovascular disorder is atherosclerosis, peripheral vascular disease, dyslipidemia (e. g., hyperlipidimia), hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic

restenosis, hypertension, cardiovascular disease, coronary heart disease, coronary artery disease, acute coronary syndrome, hyperlipidoproteinemia, vascular complications of diabetes, obesity or endotoxemia.

28. A tablet comprising the composition of any one of claims 1 to 24.

29. Use of a composition of any one of claims 1 to 24 for preparing a medicament for the treatment or prevention of cardiovascular disorder.

30. The use according to claim 29, wherein the cardiovascular disorder is atherosclerosis, peripheral vascular disease, dyslipidemia (e. g., hyperlipidimia), hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, cardiovascular disease, coronary heart disease, coronary artery disease, acute coronary syndrome, hyperlipidoproteinemia, vascular complications of diabetes, obesity or endotoxemia.

31. The use according to claim 30, wherein S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate is administered at a daily dose of 100mg to 1800mg, particularly 300mg to 900mg, more particularly 600mg.

32. The use according to either claim 30 or 31, wherein S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate is administered with food.

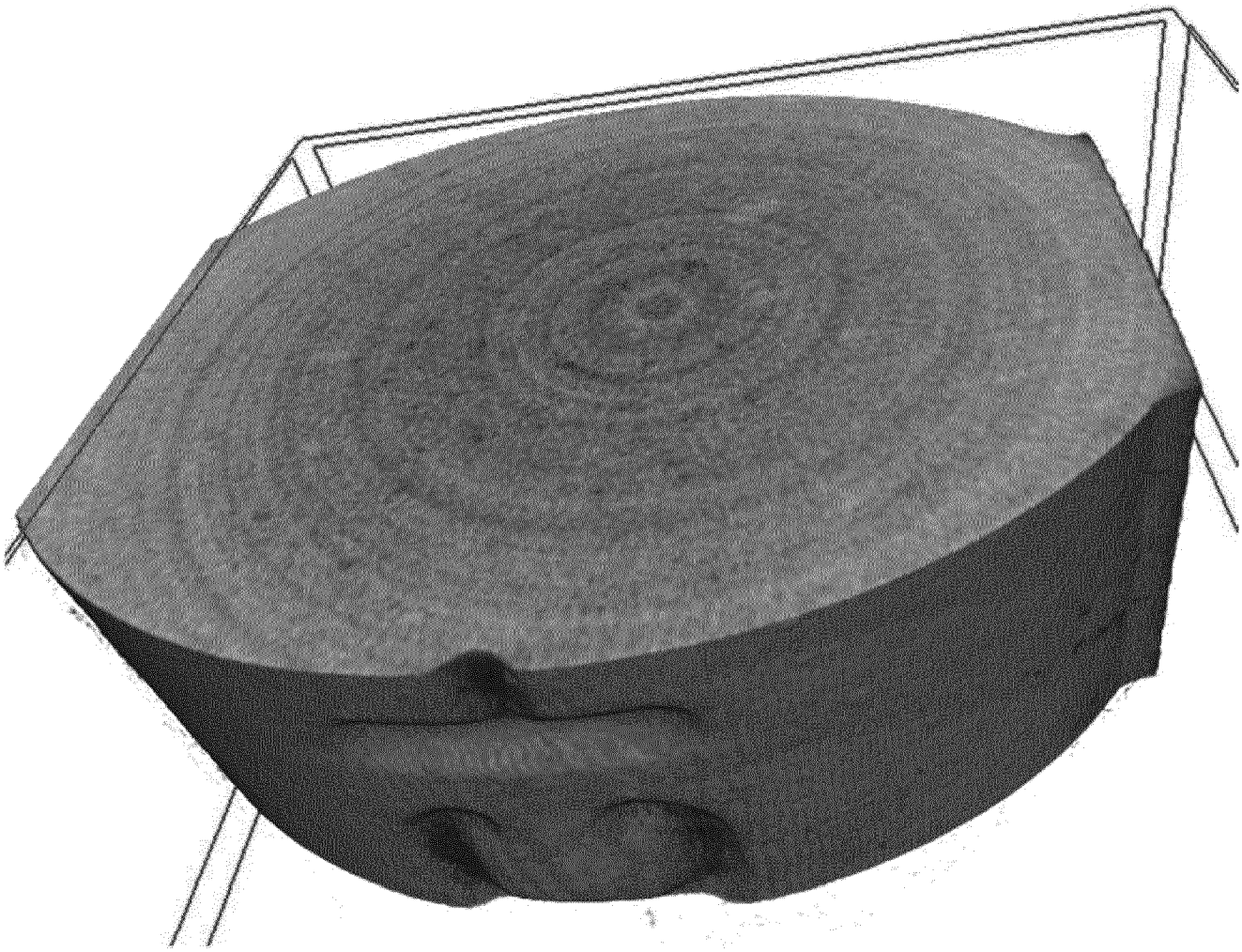

Figure 1

Figure 2

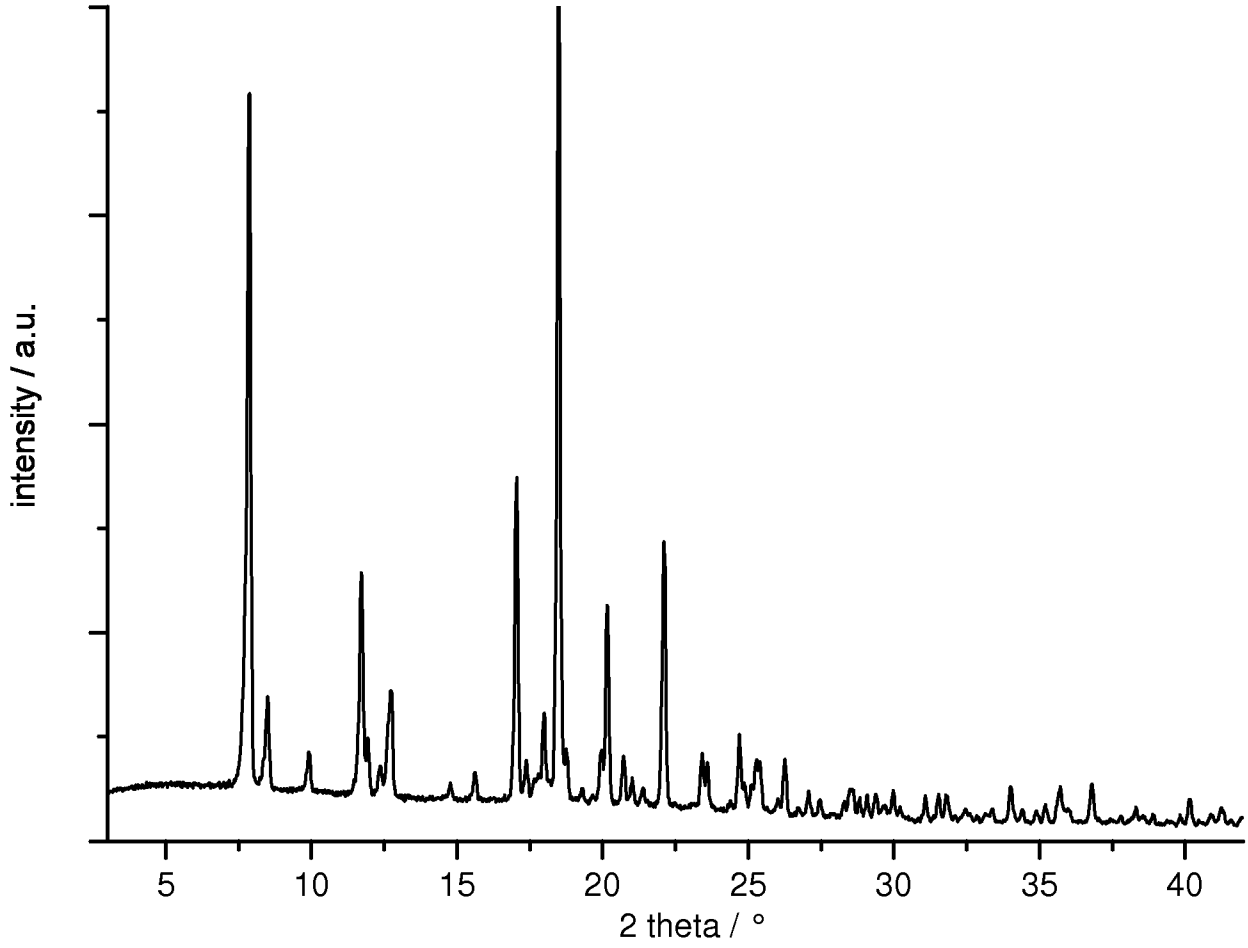

Figure 3

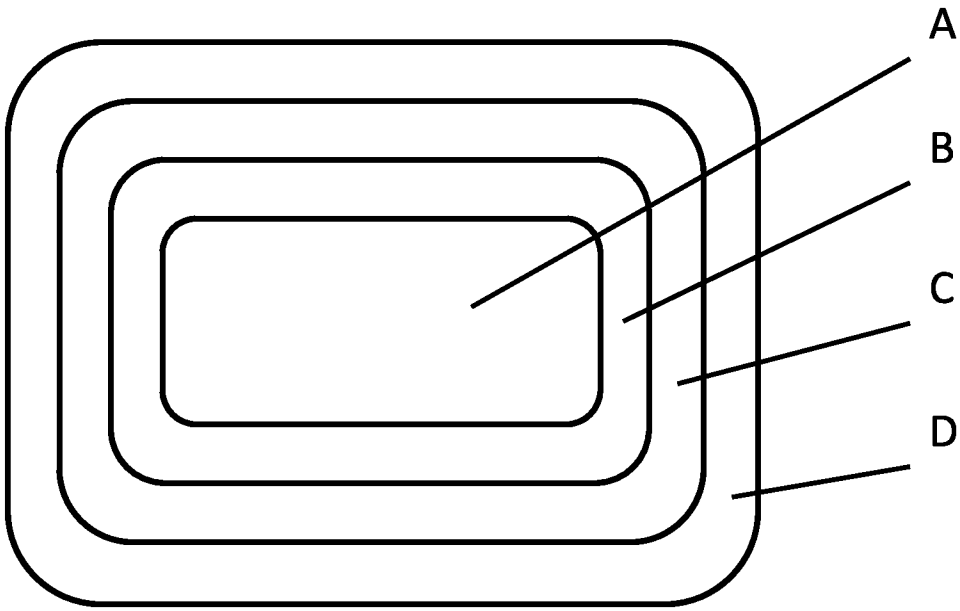

Figure 4

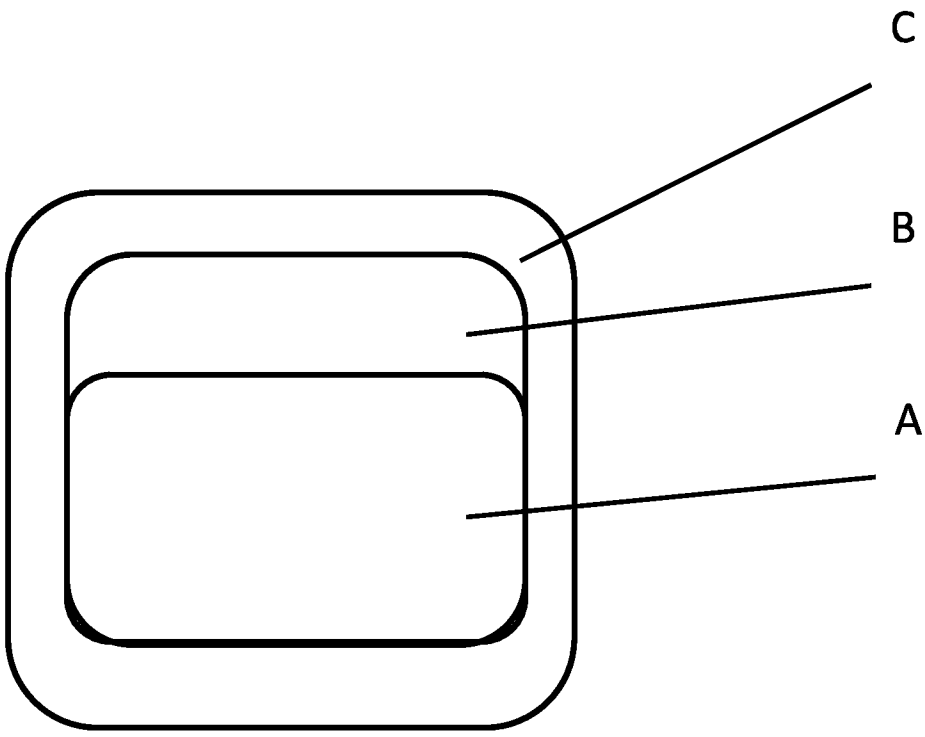

Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/058685

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/40 A61K9/20 A61K9/24 A61K31/167 A61K31/265
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/038007 A1 (CURATOLO WILLIAM J [US] ET AL) 17 February 2005 (2005-02-17) paragraph [0619]; example 1	1-32
A	US 2005/020668 A1 (URATA YASUO [JP] ET AL) 27 January 2005 (2005-01-27) paragraph [0069]; claim 7; example 1	1-32
A	US 2010/144853 A1 (GROSS GUENTER [DE] ET AL) 10 June 2010 (2010-06-10) table 1	1-32

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 July 2013	10/07/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Frelichowska, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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