(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 October 2008 (02.10.2008)

PCT

(10) International Publication Number
WO 2008/117154 A2

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 31/4422* (2006.01)
A61K 31/401 (2006.01)

(21) International Application Number:
PCT/IB2008/000678

(22) International Filing Date: 24 March 2008 (24.03.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
547/MUM/2007 26 March 2007 (26.03.2007) IN

(71) Applicant *(for all designated States except US)*: **TORRENT PHARMACEUTICALS LMITED** [IN/IN]; Torrent House,, Off Ashram Road,, Near Dinesh Hall, Ahmedabad, Gujarat 380 009 (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **VAYA, Navin, Ishwarlal** [IN/IN]; Torrent Pharmaceuticals Limited, Torrent Research Center,, P.O. BHAT, India, Gandhinagar, Gujarat 382 428 (IN). **DIXIT, Monesh, Pramod** [IN/IN]; Torrent Pharmaceuticals Limited, Torrent Research Center,, P.O. BHAT, India, Gandhinagar, Gujarat 382 428 (IN). **NAVALE, Suryakant, Vamanrao** [IN/IN]; Torrent Pharmaceuticals Limited, Torrent Research Center,, P.O. BHAT, India, Gandhinagar, Gujarat 382 428 (IN).

(74) Agents: **HARIHARAN, Rajeshwari** et al.; K & S Partners, B.K. House, Plot No.109, Sector - 44, Gurgaon 122 002 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2008/117154 A2

(54) **Title:** STABLE PHARMACEUTICAL COMPOSITIONS OF HMG-COA REDUCTASE INHIBITOR AND PROCESS FOR PREPARATION THEREOF

(57) **Abstract:** The present invention relates to stable pharmaceutical compositions of HMG-CoA reductase inhibitor and process for preparation thereof. More particularly, it relates to pharmaceutical compositions of HMG-CoA reductase inhibitor comprising polyethylene glycol (PEG), one or more alkalizing agents, and pharmaceutically acceptable excipients; and process for preparing such compositions.

STABLE PHARMACEUTICAL COMPOSITIONS OF HMG-COA REDUCTASE INHIBITOR AND PROCESS FOR PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to stable pharmaceutical compositions of HMG-CoA reductase inhibitor, and process for preparation thereof. More particularly, it relates to stable pharmaceutical compositions of HMG-CoA reductase inhibitor comprising polyethylene glycol (PEG), one or more alkalizing agents, and pharmaceutically acceptable excipients; and process for preparing such compositions.

BACKGROUND OF THE INVENTION

Atorvastatin, lovastatin, pravastatin, simvastatin, mevastatin, fluvastatin and cerivastatin, derivatives and analogs thereof are known as HMG-CoA reductase inhibitors and are used as antihypercholesterolemic agents.

Atorvastatin and pharmaceutically acceptable salts thereof are selective, competitive inhibitors of HMG-CoA reductase enzyme and are potent lipid-lowering compounds useful as hypolipidemic and/or hypocholesterolemic agents. The currently marketed composition of atorvastatin sold by Pfizer under the brand name Lipitor® comprise atorvastatin calcium, which is disclosed in US 5,273,995 and is chemical known as [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).

Atorvastatin can exist in crystalline and amorphous forms. Crystalline forms of atorvastatin calcium are disclosed in US 5,969,156, US 6,121,461 and US 6,605,729, all assigned to Warner-Lambert. Additionally, a number of published international patent applications have disclosed various crystalline forms of atorvastatin as well as process for preparing amorphous atorvastatin. These include: WO 00/71116; WO 01/28999; WO 01/36384; WO 01/42209; WO 02/41834; WO 02/43667; WO 02/43732; WO 02/051804; WO 02/057228; WO 02/057229; WO 02/057274; WO 02/059087; WO 02/083637; WO 02/083638; WO 03/011826; WO 03/050085; WO 03/070702 and WO 04/022053.

Atorvastatin is particularly sensitive to an acidic environment in which hydroxy acids are degraded into a lactone. Atorvastatin may also be degraded by environmental factors such as temperature, moisture, low pH or carbon dioxide from the air and light. While formulating compositions of atorvastatin, its degradation may also be accelerated by interactions with other pharmaceutical excipients, such as diluents, binders, lubricants, glidants and disintegrating agents. Various approaches are disclosed in the art to provide stable compositions of atorvastatin wherein degradation of atorvastatin is minimized.

US 5,686,104 and US 6,126,971, both assigned to Warner-Lambert, disclose solid oral compositions of atorvastatin wherein pharmaceutically acceptable salt of atorvastatin is stabilized by addition of an alkaline earth metal salt. In one of the preferred embodiments, the compositions are prepared by wet granulation using aqueous solution of a surfactant.

US 2004/247673 patent application assigned to Warner-Lambert discloses wet granulated pharmaceutical composition comprising atorvastatin or a pharmaceutically acceptable salt thereof with less than about 5 weight % of an alkaline earth metal salt additive and methods for preparing such compositions.

US 6,680,341 assigned to Lek Pharmaceuticals discloses stable solid pharmaceutical formulation containing a HMG-CoA reductase inhibitor and a buffering agent wherein the formulation is capable of providing a pH below 9. More particularly, the patent describes process for preparation of stable active substance containing a HMG-CoA reductase inhibitor and a low amount of a buffering agent.

There remains a need in the art for alternative pharmaceutical compositions of atorvastatin having minimal degradation of atorvastatin and low level of impurities. We have surprisingly found that stable pharmaceutical compositions of atorvastatin can be prepared by using polyethylene glycol and one or more alkalizing agents.

SUMMARY OF THE INVENTION

One embodiment discloses a stable pharmaceutical composition comprising

(i) an HMG-CoA reductase inhibitor;

(ii) 0.5 % to 25 % by weight of polyethylene glycol;

(iii) 0.1 to 50 % by weight of an alkalizing agent; and

(iv) at least one pharmaceutically acceptable excipient.

Another embodiment discloses a stable pharmaceutical composition comprising

(i) an HMG-CoA reductase inhibitor;

(ii) a calcium channel blocker;

(iii) 0.5 % to 25 % by weight of polyethylene glycol;

(iv) 0.1 to 50 % by weight of an alkalizing agent; and

(v) at least one pharmaceutically acceptable excipient.

Another embodiment discloses a stable pharmaceutical composition comprising

(i) atorvastatin;

(ii) 0.5 % to 25 % by weight of polyethylene glycol;

(iii) 0.1 to 50 % by weight of an alkalizing agent; and

(iv) at least one pharmaceutically acceptable excipient;

wherein the polyethylene glycol is coated on the atorvastatin and the composition provides a pH of more than 6.0.

Another embodiment discloses a stable pharmaceutical composition comprising

(i) atorvastatin;

(ii) amlodipine;

(iii) 0.5 % to 25 % by weight of polyethylene glycol;

(iv) 0.1 to 50 % by weight of an alkalizing agent; and

(v) at least one pharmaceutically acceptable excipient;

wherein the polyethylene glycol is coated on the atorvastatin and the composition provides a pH of more than 6.0.

Another embodiment discloses a process for preparation of a stable pharmaceutical composition, wherein the process comprises:

(i) mixing an HMG-CoA reductase inhibitor with at least one pharmaceutically acceptable excipient and optionally a calcium channel blocker and an alkalizing agent;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol;

(iii) drying the granules obtained in step (ii);

(iv) mixing the granules of step (iii) with the alkalizing agent and at least one pharmaceutically acceptable excipient;

(v) optionally lubricating the mixture of step (iv); and

(vi) compressing the mixture of step (iv) or (v) into a tablet or filling into a capsule.

Another embodiment discloses a process for preparation of a stable pharmaceutical composition, wherein the process comprises:

(i) mixing an HMG-CoA reductase inhibitor with at least one pharmaceutically acceptable excipient and optionally a calcium channel blocker and an alkalizing agent;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol;

(iii)drying the granules obtained in step (ii);

(iv)coating the granules obtained in step (iii) with the alkalizing agent;

(v) mixing the granules of step (iv) with the alkalizing agent and at least one pharmaceutically acceptable excipient,

(vi) optionally lubricating the mixture of step (v); and

(vii) compressing the mixture of step (v) or (vi) into a tablet or filling into a capsule.

Another embodiment discloses a process for preparation of a stable pharmaceutical composition, wherein the process comprises:

(ii) mixing atorvastatin with at least one pharmaceutically acceptable excipient and optionally a calcium channel blocker and an alkalizing agent;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol;

(iii) drying the granules obtained in step (ii);

(iv) mixing the granules of step (iii) with the alkalizing agent and at least one pharmaceutically acceptable excipient;

(v) optionally lubricating the mixture of step (iv); and

(vi) compressing the mixture of step (iv) or (v) into a tablet or filling into a capsule.

Another embodiment discloses a process for preparing a stable pharmaceutical composition, wherein the process comprises:

(i) mixing atorvastatin with at least one pharmaceutically acceptable excipient and optionally a calcium channel blocker and an alkalizing agent;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol;

(iii)drying the granules obtained in step (ii);

(iv)coating the granules obtained in step (iii) with the alkalizing agent;

(v) mixing the granules of step (iv) with the alkalizing agent and at least one pharmaceutically acceptable excipient;

(vi)optionally lubricating the mixture of step (v); and

(vii) compressing the mixture of step (v) or (vi) into a tablet or filling into a capsule.

Another embodiment discloses a process for preparation of a stable pharmaceutical composition, wherein the process comprises:

(i) mixing atorvastatin, amlodipine, at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant, and optionally an alkalizing agent;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol and optionally an antioxidant or a surfacant;

(iii)drying the granules obtained in step (ii);

(iv)coating the granules obtained in step (iii) with the alkalizing agent;

(v) mixing the granules of step (iv) with the alkalizing agent and at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant;

(vi) optionally lubricating the mixture of step (v); and

(vii) compressing the mixture of step (v) or (vi) into a tablet or filling into a capsule.

Yet another embodiment discloses a method for treating hypercholesterolaemia wherein the method comprises administering to a patient in need thereof a stable pharmaceutical composition comprising:

(i) atorvastatin;

(ii) 0.5 % to 25 % by weight of polyethylene glycol;

(iii) 0.1 to 50 % by weight of an alkalizing agent; and

(iv) at least one pharmaceutically acceptable excipient;

wherein the polyethylene glycol is coated on atorvastatin and the composition provides a pH of more than 6.0.

Still another embodiment discloses a method for prevention of cardiovascular disorder selected from myocardial infarction, stroke or angina, wherein the method comprises administering to a patient in need thereof a stable pharmaceutical composition comprising:

(i) atorvastatin;

(ii) 0.5 % to 25 % by weight of polyethylene glycol;

(iii) 0.1 to 50 % by weight of an alkalizing agent; and

(iv) at least one pharmaceutically acceptable excipient;

wherein the polyethylene glycol is coated on atorvastatin and the composition provides a pH of more than 6.0.

Further embodiment discloses a method for treating combined hypercholesterolaemia and hypertension, wherein the method comprises administering to a patient in need thereof a stable pharmaceutical composition comprising:

(i) atorvastatin;

(ii) amlodipine;

(iii) 0.5 % to 25 % by weight of polyethylene glycol;

(iv) 0.1 to 50 % by weight of an alkalizing agent; and

(v) at least one pharmaceutically acceptable excipient;

wherein the polyethylene glycol is coated on atorvastatin and the composition provides a pH of more than 6.0.

DETAILED DESCRIPTION OF THE INVENTION

The "HMG-CoA reductase inhibitor" as described herein may be selected from atorvastatin, pravastatin, simvastatin, lovastatin, mevastatin, fluvastatin, cerivastatin, and pharmaceutically acceptable salts thereof.

The term "atorvastatin" as described herein refers to free base of atorvastatin as well as pharmaceutically acceptable salts thereof. It also includes racemic mixture, enantiomer, hydrate and solvate of the base or pharmaceutically acceptable salts thereof; or mixtures thereof. The preferred salt is atorvastatin calcium. Atorvastatin may be present in crystalline form, amorphous form, or mixture thereof. In a preferred embodiment, atorvastatin is amorphous atorvastatin calcium. Atorvastatin may be present in an amount ranging from 1 % to 50 % by weight of the composition.

The term "stable" as described herein refers to pharmaceutical composition of atorvastatin wherein there is no significant increase in known or unknown impurities of atorvastatin, when stored at a temperature of 40 °C and 75 % relative humidity (RH) for a period of at least one month. For example, in stable compositions as described herein the amount of known impurities is not more than 0.2 % w/w after a period of one month when stored at a temperature of 40 °C and 75 % relative humidity (RH). Some of the known impurities of atorvastatin include: 5-(4-fluorophenyl)-1-[2-[(2R,4R)-4-hydroxy-6-oxotetrahydropyran-2-yl]ethyl]-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide ["lactone" impurity], (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrrol-1-yl]-3, 5-dihydroxyheptanoic acid tert-butyl ester ["tertiary butyl ester" impurity), 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) ["atorvastatin isomer" impurity] and β,δ-dihydroxy-2-(1-methylethyl)-4,5-diphenyl-3-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) ["desfluoro" impurity].

The term "polyethylene glycol" or "PEG" as described herein refers to polyethylene glycols having higher molecular weight, for example PEG's having molecular weight of more than 1000 daltons. Unless specified otherwise, the term "by weight

polyethylene glycol" refers to the amount of PEG on the basis of the weight of atorvastatin. PEG may be used in an amount ranging from 0.5 % to 25% by weight of atorvastatin. In compositions as described herein, atorvastatin is coated by PEG by granulating atorvastatin with a solution / dispersion of PEG in water or organic solvent, wherein the solution / dispersion may further comprise an anti-oxidant or a surfactant. Granulation may also be done by means of spraying in an apparatus like fluidized bed processor.

The term "alkalizing agent" as describe herein refers to excipients which provide basic or near-neutral micro-environment for atorvastatin. Alkalizing agent may be selected from meglumine, tromethamine, sodium carbonate, sodium bicarbonate, sodium citrate, potassium citrate, dibasic sodium phosphate, tribasic sodium phosphate, hydrogen phosphate, sodium hydroxide, potassium hydroxide; or mixtures thereof. The alkalizing agent may be present in an amount which provides a pH of more than 6, preferably pH of more than 9 to the pharmaceutical composition. More particularly, the alkalizing agent may be present in an amount ranging from 0.1 % to 50 %, more particularly 1 % to 40 % by weight of the composition.

The pharmaceutical compositions as described herein may comprise of one or more pharmaceutically acceptable excipients selected from diluent, disintegrant, anti-oxidant, surfactant or glidant / lubricant.

Diluent may be selected from powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, starch, dibasic sodium phosphate, tribasic sodium phosphate, dextrose, kaolin; sugars such as lactose or sucrose; sugar alcohols such as mannitol, sorbitol or erythritol; or mixtures thereof. The diluent may be present in an amount ranging from 10 % to 90 % by weight of the composition.

Disintegrant may be selected from croscarmellose sodium, sodium starch glycolate, pregelatinized starch, sodium carboxymethyl cellulose, microcrystalline cellulose, cross-linked polyvinylpyrrolidone and mixtures thereof. The disintegrant may be present in an amount ranging from 1 % to 15 % by weight of the composition.

Anti-oxidant may be selected from butylated hydroxanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, ascorbic acid; and mixtures thereof. The anti-oxidant may be present in an amount ranging from 0.01 to 3% by weight of the composition. In compositions as described herein, the anti-oxidant may be mixed with atorvastatin before the granulation step or it may be added to the dried granules before the compression step. Alternatively, anti-oxidant may be added to the solution / dispersion of PEG which is used to granulate atorvastatin.

Surfactant may be selected from one or more of non-ionic and ionic (i. e., cationic, anionic and Zwitterionic) surfactants suitable for use in pharmaceutical compositions. Suitable surfactants include mono fatty acid esters of polyoxyethylene sorbitan such as those sold under the brand name Tween® ; sodium lauryl sulfate, polyoxyethylene castor oil derivatives such as those sold under the brand name Cremophor®, polyethoxylated fatty acids and their derivatives, propylene glycol fatty acid esters, sterol and sterol derivatives; sorbitan fatty acid esters and their derivatives, sugar esters, polyoxyethylene-polyoxypropylene block copolymers such as those sold under the brand name Poloxamer®, soy lecithin, sodium stearyl fumarate, and mixtures thereof. The surfactant may be present in an amount ranging from 0.1 % to 5 % by weight of the composition. Sodium lauryl sulphate when used as a stabilizer may also act as a surfactant.

Lubricant / glidant may be selected from talc, metallic stearates such as magnesium stearate, calcium stearate, zinc stearate; colloidal silicon dioxide, finely divided silicon dioxide, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl monostearate, glyceryl behenate, sodium stearyl fumarate, magnesium trisilicate; and mixtures thereof. The lubricant / glidant may be present in an amount ranging from 0.1 % to 5 % by weight of the composition.

The pharmaceutical compositions as described herein may further comprise an additional therapeutic agent. In particular, a combination therapy of atorvastatin with a hypertensive agent may be desirable. Antihypertensive agent may be selected from a calcium channel blocker, an ACE inhibitor, an angiotensin receptor antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker. In

one embodiment, the antihypertensive agent is a calcium channel blocker selected from amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine, lercanidipine, or pharmaceutically acceptable salts thereof. In a preferred embodiment, the additional therapeutic agent is amlodipine. Amlodipine may be present as free base, or as pharmaceutically acceptable salt. Amlodipine as described herein also includes anhydrous form, hydrous form, different crystalline forms, amorphous form or enantiomers of amlodipine base or pharmaceutically acceptable salts thereof, or mixtures thereof. The preferred salt of amlodipine is amlodipine besylate. Amlodipine may be present in an amount such that the weight ratio of amlodipine to atorvastatin is between 0.1:1 to 2:1. The additional agent, such as amlodipine, may be combined with atorvastatin to form a stable pharmaceutical composition, for example, such as tablets or capsules. Such a combination may be useful in treating hypertension as well as treating or preventing hypercholesterolemia, hyperlipidemia and prophylaxis of conditions associated with hyperlipidemia such as myocardial infarction, stroke, angina and atherosclerosis.

The pharmaceutical composition as described herein may be in the form of a tablet, capsule or sachet. The composition may be prepared by techniques such as wet granulation. For example, a HMG-CoA reductase inhibitor such as atorvastatin may be mixed with pharmaceutically acceptable excipients such as diluent, disintegrant, anti-oxidant, surfactant and optionally an alkalizing agent. The atorvastatin may be coated with polyethylene glycol (PEG) by granulating the mixture of atorvastatin and excipients with a solution / dispersion of PEG in a solvent such as water or an organic solvent, wherein the solution / dispersion may also contain an antioxidant and/or a surfactant. The granulation may be achieved in a suitable apparatus such as a fluidized bed apparatus. In such an apparatus, it is desirable to spray the solution / dispersion of PEG using the "top-spray" technique. The granules obtained are dried. The dried granules may be coated further with a solution / dispersion of the alkalizing agent and dried. The dried granules may be mixed with the alkalizing agent and pharmaceutically acceptable excipients such as diluent, disintegrant, glidant and lubricant, and the mixture may be compressed in to a tablet or filled in a capsule or a sachet. In one embodiment, HMG-CoA reductase inhibitor may be mixed with another therapeutic

agent, such as a calcium channel blocker before the step of granulation and coating by the PEG dispersion. In a preferred embodiment, the calcium channel blocker is amlodipine.

In one embodiment, a stable tablet is prepared by

(i) mixing an HMG-CoA reductase inhibitor with at least one pharmaceutically acceptable excipient and optionally a calcium channel blocker and an alkalizing agent;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol;

(iii) drying the granules obtained in step (ii);

(iv) mixing the granules of step (iii) with the alkalizing agent and at least one pharmaceutically acceptable excipient;

(v) optionally lubricating the mixture of step (iv); and

(vi) compressing the mixture of step (iv) or (v) into a tablet.

In another embodiment, a stable tablet may be prepared by:

(i) mixing atorvastatin with at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant, and optionally an alkalizing agent selected from sodium carbonate, sodium bicarbonate, meglumine, or mixtures thereof;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol, antioxidant and optionally surfactant;

(iii)drying the granules obtained in step (ii);

(iv)mixing the granules of step (iii) with at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant, and the alkalizing agent;

(v) optionally lubricating the mixture of step (iv); and

(vi)compressing the mixture of step (iv) or (v) into a tablet.

In another embodiment, a stable tablet may be prepared by:

(i) mixing atorvastatin with at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant, and optionally

an alkalizing agent selected from sodium carbonate, sodium bicarbonate, meglumine, or mixtures thereof;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol and an antioxidant;

(iii)drying the granules obtained in step (iii);

(iv)coating the granules obtained in step (iii) with the alkalizing agent;

(v) mixing the granules of step (iv) with at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant, and the alkalizing agent;

(vi)optionally lubricating the mixture of step (v); and

(vii) compressing the mixture of step (v) or (vi) into a tablet.

In another embodiment, a stable tablet may be prepared by:

(i) mixing atorvastatin, amlodipine, at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant, and optionally an alkalizing agent selected from sodium carbonate, sodium bicarbonate, meglumine, or mixtures thereof;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol, antioxidant and optionally surfactant;

(iii)drying the granules obtained in step (ii);

(iv)coating the granules obtained in step (iii) with the alkalizing agent;

(v) mixing the granules of step (iv) with at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant, and the alkalizing agent;

(vi)optionally lubricating the mixture of step (v); and

(vii) compressing the mixture of step (v) or (vi) into a tablet.

The pharmaceutical compositions as described herein may be illustrated by way of the following examples which are not to be construed as limiting the scope of the invention:

EXAMPLE 1

Sr. No	Ingredients	Quantity (mg/tablet)
Core		
1	Atorvastatin Calcium	82.87
2	Lactose	750.00
3	Microcrystalline cellulose	241.13
4	Polyethylene glycol	4.00
5	Crospovidone	90.00
6	Sodium carbonate	20.00
7	Magnesium stearate	12.00
8	Purified water	q.s.
	Core Weight	**1200.00**
Coating		
9	Hydroxypropyl methylcellulose	13.34
10	Titanium dioxide	5.33
11	Talc	3.33
	Polyethylene glycol	2.00
12	Isopropyl alcohol + methylene chloride (1:1)	q.s.
	Total Weight	**1224.00**

PROCEDURE: Atorvastatin and lactose were mixed together and granulated with aqueous solution of polyethylene glycol by top spray in fluidized bed processor and the granules were dried. In a separate batch, microcrystalline cellulose and remaining quantity of lactose were mixed and granulated with aqueous solution of sodium carbonate by top spray in fluidized bed processor. The granules were dried, mixed with PEG-coated atorvastatin granules, crospovidone, and remaining quantity of microcrystalline cellulose, the mixture was lubricated by addition of magnesium stearate and compressed into tablets using appropriate tooling. The tablets were coated by a dispersion of hydroxypropyl methylcellulose, talc, polyethylene glycol and titanium dioxide in a mixture of isopropyl alcohol and methylene chloride.

EXAMPLE 2

Sr. No	Ingredients	Quantity (mg/tablet)
Core		
1	Atorvastatin Calcium	82.87
2	Lactose	750.00
3	Microcrystalline cellulose	240.13
4	Sodium lauryl sulphate	1.00
5	Polyethylene glycol	4.00
6	Crospovidone	90.00
7	Sodium carbonate	20.00
8	Magnesium stearate	12.00
9	Purified water	q.s.
	Core weight	**1200.00**
Coating		
10	Hydroxypropyl methylcellulose	13.34
11	Titanium dioxide	5.33
12	Talc	3.33
	Polyethylene glycol	2.00
13	Isopropyl alcohol + methylene chloride (1:1)	q.s.
	Total Weight	**1224.00**

PROCEDURE: Atorvastatin and lactose were mixed and granulated with aqueous solution of sodium lauryl sulphate and polyethylene glycol by top spray in fluidized bed processor and the granules were dried. In a separate batch, microcrystalline cellulose and remaining quantity of lactose were mixed and granulated with aqueous solution of sodium carbonate by top spray in fluidized bed processor. The granules were dried, mixed with PEG-coated atorvastatin granules, crospovidone and remaining quantity of microcrystalline cellulose, the mixture was lubricated by addition of magnesium stearate and compressed into tablets using appropriate tooling. The tablets were coated by dispersion of hydroxypropyl methylcellulose, talc, polyethylene glycol and titanium dioxide in a mixture of isopropyl alcohol and methylene chloride.

EXAMPLE 3

Sr. No.	Ingredients	Quantity (mg/tablet)
Core		
1	Atorvastatin calcium	82.87
2	Lactose	750.00
3	Butylated hydroxyanisole	0.24
4	Polyethylene glycol	6.00
5	Microcrystalline cellulose	240.89
6	Sodium carbonate	15.00
7	Methylene dichloride	q.s.
8	Purified water	q.s.
9	Crospovidone	90.00
10	Poloxamer	3.00
11	Methanol	q.s.
12	Magnesium stearate	12.00
	Core weight	**1200.00**
Coating		
13	Hydroxypropyl methylcellulose	14.40
14	Titanium dioxide	4.32
15	Talc	2.40
	Polyethylene glycol	2.88
16	Isopropyl alcohol + Methylene chloride (1:1)	q.s.
	Total weight	**1224.00**

PROCEDURE: Atorvastatin and lactose were mixed and granulated with solution of sodium lauryl sulphate and polyethylene glycol in methylene dichloride by top spray in fluidized bed processor, and the granules were dried. In a separate batch, microcrystalline cellulose and remaining quantity of lactose were mixed and granulated with aqueous solution of sodium carbonate by top spray in fluidized bed processor and the granules were dried. The granules were coated with a solution of poloxamer in methanol. The granules were dried, mixed with PEG-coated atorvastatin granules, crospovidone and remaining quantity of microcrystalline cellulose, the mixture was lubricated by addition of magnesium stearate and compressed into tablets using appropriate tooling. The tablets were coated by dispersion of hydroxypropyl methylcellulose, talc, polyethylene glycol and titanium dioxide in a mixture of isopropyl alcohol and methylene chloride.

EXAMPLE 4

Sr. No.	Ingredients	Quantity (mg/tablet)
Core		
1	Atorvastatin calcium	82.87
2	Lactose	50.00
3	Meglumine	24.00
4	Crospovidone	45.00
5	Butylated hydroxyanisole	3.60
6	Butylated hydroxytoluene	0.36
7	Polyethylene glycol	6.00
8	Methylene dichloride	q.s.
	Lactose	559.07
9	Microcrystalline cellulose	239.60
10	Sodium bicarbonate	132.50
	Crospovidone	45.0
11	Magnesium stearate	12.00
	Core Weight	**1200.00**
Coating		
12	Hydroxypropyl methylcellulose	14.40
13	Titanium dioxide	4.32
14	Talc	2.40
	Polyethylene glycol	2.88
15	Isopropyl alcohol + Methylene chloride (1:1)	q.s.
	Total Weight	**1224.00**

PROCEDURE: Atorvastatin, lactose, crospovidone and meglumine were mixed and granulated with solution of butylated hydroxyanisole, butylated hydroxytoluene and polyethylene glycol in methylene chloride by top spray in fluidized bed processor and the granules were dried. The granules were mixed with microcrystalline cellulose, sodium bicarbonate, and remaining quantity of lactose and crospovidone, the mixture was lubricated by addition of magnesium stearate and compressed into tablets using appropriate tooling. The tablets were coated by dispersion of hydroxypropyl methylcellulose, talc, polyethylene glycol and titanium dioxide in a mixture of isopropyl alcohol and methylene chloride.

EXAMPLES 5 AND 6

Sr. No.	Ingredients	Quantity (mg/tablet)	
Core			
		Example 5	**Example 6**
1	Atorvastatin Calcium	82.87	82.87
2	Lactose	50.00	50.00
3	Crospovidone	45.00	45.00
4	Butylated hydroxyanisole	3.60	3.60
5	Butylated hydroxytoluene	0.36	0.36
6	Polyethylene glycol	6.00	6.00
7	Methylene chloride	q.s.	q.s.
8	Meglumine	24.00	24.00
9	Purified Water	q.s.	q.s.
	Lactose	601.57	559.07
10	Microcrystalline cellulose	239.60	239.60
11	Sodium Bicarbonate	90.00	132.50
	Crospovidone	45.00	45.00
12	Magnesium Stearate	12.00	12.00
	Core weight	**1200.00 mg**	**1200.00 mg**
Coating			
13	Hydroxypropyl methylcellulose	24.00	24.00
14	Titanium dioxide	6.60	6.60
15	Talc	3.00	3.00
	Polyethylene glycol	2.40	2.40
16	Isopropyl alcohol + Methylene chloride (1:1)	q.s.	q.s.
	Total Weight	**1236.00 mg**	**1236.00 mg**

PROCEDURE: Atorvastatin, lactose and crospovidone were mixed together and granulated with solution of butylated hydroxyanisole, butylated hydroxytoluene and polyethylene glycol in methylene chloride by top spray in fluidized bed processor and the granules were dried. The granules were coated by spraying aqueous solution of meglumine in fluidized bed processor. The granules were dried, mixed with microcrystalline cellulose, sodium bicarbonate, and remaining quantity of lactose and crospovidone, the mixture was lubricated by addition of magnesium stearate and compressed into tablets. The tablets were coated by dispersion of hydroxypropyl methylcellulose, talc, polyethylene glycol 6000 and titanium dioxide in a mixture of isopropyl alcohol and methylene chloride. The pH of Example 6 was 8.9 when measured in water.

EXAMPLE 7

Sr. No	Ingredients
1	Fluvastatin
2	Lactose anhydrous
3	Microcrystalline cellulose
4	Sodium lauryl sulphate
5	Polyethylene glycol
6	Crospovidone
7	Tromethamine
8	Magnesium stearate
9	Purified water
10	Hydroxypropyl methylcellulose
11	Titanium dioxide
12	Talc
14	Isopropyl alcohol + methylene chloride (1:1)

PROCEDURE: The composition may be prepared by the process as described in Example 2.

EXAMPLE 8

Sr. No	Ingredients
1	Pravastatin sodium
2	Lactose
3	Microcrystalline cellulose
4	Polyethylene glycol
5	Crospovidone
6	Meglumine
7	Magnesium stearate
8	Purified water
9	Hydroxypropyl methylcellulose
10	Titanium dioxide
11	Talc
12	Isopropyl alcohol + methylene chloride (1:1)

PROCEDURE: The composition may be prepared by the process as described in Example 1.

EXAMPLE 9

Sr No	Ingredients	Quantity (in mg)
Core		
1	Atorvastatin calcium	82.87
2	Amlodipine besylate	13.87
3	Lactose	50.00
4	Crospovidone	45.00
5	Butylated hydroxyanisole	3.60
6	Butylated hydroxytoluene	0.36
7	Polyethylene glycol	6.00
8	Methylene chloride	q.s.
9	Meglumine	24.00
10	Purified Water	q.s.
	Lactose	587.70
11	Microcrystalline cellulose	239.60
12	Sodium bicarbonate	90.00
	Crospovidone	45.00
13	Magnesium stearate	12.00
	Core Weight	**1200.00**
Coating		
14	Hydroxypropyl methylcellulose	24.00
15	Titanium dioxide	6.60
18	Talc	3.00
19	Polyethylene glycol	2.40
20	Isopropyl alcohol + Methylene chloride (1:1)	q.s.
	Total Weight	**1236.00**

PROCEDURE: Atorvastatin, amlodipine, lactose and crospovidone were mixed and granulated with solution of butylated hydroxyanisole, butylated hydroxytoluene and polyethylene glycol in methylene chloride by top spray in fluidized bed processor and the granules were dried. The granules were coated by spraying aqueous solution of meglumine in a fluidized bed processor. The granules were dried, mixed with microcrystalline cellulose, sodium bicarbonate and remaining quantity of lactose and crospovidone, the mixture was lubricated by addition of magnesium stearate and compressed into tablets. The tablets were coated by dispersion of hydroxypropyl methylcellulose, talc, polyethylene glycol and titanium dioxide in a mixture of isopropyl alcohol and methylene chloride.

EXAMPLE 10

Sr No	Ingredients	Qty/tab (mg)
Core		
1	Atorvastatin calcium	82.87
2	Amlodipine besylate	13.87
3	Mannitol	50.00
4	Crospovidone	45.00
5	Butylated hydroxyanisole	3.60
6	Butylated hydroxytoluene	0.36
7	Polyethylene glycol	6.00
8	Methylene chloride	q.s.
9	Meglumine	24.00
10	Purified Water	q.s.
11	Lactose Monohydrate	187.70
12	Microcrystalline cellulose	239.60
13	Sodium bicarbonate	90.00
14	Crospovidone	45.00
15	Magnesium stearate	12.00
	Core Weight	**800.00**
Coating		
16	Hydroxypropyl methylcellulose	16.00
17	Titanium dioxide	4.40
18	Talc	2.00
19	Polyethylene glycol	1.60
20	Isopropyl alcohol + Methylene chloride (1:1)	q.s.
Total Weight		**824.00**

PROCEDURE: Atorvastatin, amlodipine, mannitol and crospovidone were mixed and granulated with solution of butylated hydroxyanisole, butylated hydroxytoluene and polyethylene glycol in methylene chloride by top spray in fluidized bed processor and the granules were dried. The granules were coated by spraying aqueous solution of meglumine in a fluidized bed processor. The granules were dried, mixed with lactose, microcrystalline cellulose, sodium bicarbonate and remaining quantity of crospovidone, the mixture was lubricated by addition of magnesium stearate and compressed into tablets. The tablets were coated by dispersion of hydroxypropyl methylcellulose, talc, polyethylene glycol and titanium dioxide in a mixture of isopropyl alcohol and methylene chloride.

The tablets of Example 5 were stored at a temperature of 40° C and 75% relative humidity (RH) for a period of one month. The impurity levels were measured as per the technique known in the art. The results are shown below in Table 1.

Table 1: Result of Stability studies for Example 5

Condition / Time	Amount of Impurity (% w/w)			
	Atorvastatin lactone	Tertiary butyl ester	Atorvastatin isomer	Desfluoro impurity
Initial	0.11	ND	0.06	0.01
After 1 Month (40°C/75% RH)	0.13	ND	0.06	0.01

The values in Table 1 show that there is no significant increase in the known impurities of atorvastatin, when the tablets are stored at a temperature of 40° C and 75% relative humidity (RH) for a period of one month.

WE CLAIM:

1) A stable pharmaceutical composition comprising

(i) an HMG-CoA reductase inhibitor;

(ii) 0.5 % to 25 % by weight of polyethylene glycol;

(iii) 0.1 to 50 % by weight of an alkalizing agent; and

(iv) at least one pharmaceutically acceptable excipient.

2) The composition of claim 1, wherein the composition further comprises a calcium channel blocker.

3) The composition of claim 1, wherein the polyethylene glycol is coated on the HMG-CoA reductase inhibitor and the composition provides a pH of more than 6.0.

4) A stable pharmaceutical composition comprising

(i) atorvastatin;

(ii) optionally amlodipine;

(ii) 0.5 % to 25 % by weight of polyethylene glycol;

(iii) 0.1 to 50 % by weight of an alkalizing agent; and

(iv) at least one pharmaceutically acceptable excipient;

5) The composition of claim 4, wherein the polyethylene glycol is coated on the atorvastatin and the composition provides a pH of more than 6.0.

6) The composition of claim 4, wherein the alkalizing agent is selected from the group consisting of meglumine, tromethamine, sodium carbonate, sodium bicarbonate, sodium citrate, potassium citrate, dibasic sodium phosphate, tribasic sodium phosphate, sodium hydroxide, potassium hydroxide; and mixtures thereof.

7) The composition of claim 4, wherein the pharmaceutically acceptable excipient is selected from diluent, disintegrant, antioxidant, surfactant, glidant or lubricant; or mixtures thereof.

8) The composition of claim 7, wherein the diluent is selected from powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, starch, dextrose, kaolin, lactose, sucrose, mannitol, sorbitol or erythritol; or mixtures thereof.

9) The composition of claim 7, wherein the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, pregelatinized starch, sodium carboxymethyl cellulose, microcrystalline cellulose or cross-linked polyvinylpyrrolidone; or mixtures thereof.

10) The composition of claim 7, wherein the antioxidant is selected from butylated hydroxanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid or ascorbic acid; or mixtures thereof.

11) The composition of claim 7, wherein the surfactant is selected from mono fatty acid esters of polyoxyethylene sorbitan, sodium lauryl sulfate, polyoxyethylene castor oil derivatives, polyethoxylated fatty acids and their derivatives, propylene glycol fatty acid esters, sterol and sterol derivatives, sorbitan fatty acid esters and their derivatives or polyoxyethylene-polyoxypropylene block copolymers; or mixtures thereof.

12) The composition of claim 7, wherein the glidant and/or lubricant is selected from talc, magnesium stearate, colloidal silicon dioxide, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl monostearate, glyceryl behenate, sodium stearyl fumarate, sodium benzoate or magnesium trisilicate; or mixtures thereof.

13) The composition of claim 4, wherein the composition is in the form of a tablet, or a capsule.

14) A process for preparing a stable pharmaceutical composition, wherein the process comprises:

(i) mixing an HMG-CoA reductase inhibitor with at least one pharmaceutically acceptable excipient and optionally a calcium channel blocker and an alkalizing agent;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol;

(iii) drying the granules obtained in step (ii);

(iv) coating the granules obtained in step (iii) with the alkalizing agent;

(v) mixing the granules of step (iv) with the alkalizing agent and at least one pharmaceutically acceptable excipient,

(vi) optionally lubricating the mixture of step (v); and

(vii) compressing the mixture of step (v) or (vi) into a tablet or filling into a capsule.

15) A process for preparing a stable pharmaceutical composition according to claim 14, wherein the process comprises:

(i) mixing atorvastatin, at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant, and optionally an alkalizing agent;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol and optionally an antioxidant or a surfacant;

(iii) drying the granules obtained in step (ii);

(iv) coating the granules obtained in step (iii) with the alkalizing agent;

(v) mixing the granules of step (iv) with the alkalizing agent and at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant;

(vi) optionally lubricating the mixture of step (v); and

(vii) compressing the mixture of step (v) or (vi) into a tablet or filling into a capsule.

16) A process for preparing a stable pharmaceutical composition according to claim 14, wherein the process comprises:

(i) mixing atorvastatin, amlodipine, at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant, and optionally an alkalizing agent;

(ii) granulating the mixture of step (i) with a solution or dispersion comprising polyethylene glycol and optionally an antioxidant or a surfacant;

(iii) drying the granules obtained in step (ii);

(iv) coating the granules obtained in step (iii) with the alkalizing agent;

(v) mixing the granules of step (iv) with the alkalizing agent and at least one pharmaceutically acceptable excipient selected from diluent, disintegrant, antioxidant and surfactant;

(vi) optionally lubricating the mixture of step (v); and

(vii) compressing the mixture of step (v) or (vi) into a tablet or filling into a capsule.

17) The composition according to any of the claims 14 to 16, wherein the alkalizing agent is selected from the group consisting of meglumine, tromethamine, sodium carbonate, sodium bicarbonate, sodium citrate, potassium citrate, dibasic sodium

phosphate, tribasic sodium phosphate, sodium hydroxide, potassium hydroxide; and mixtures thereof.

18) A method for treating hypercholesterolaemia wherein the method comprises administering to a patient in need thereof a stable pharmaceutical composition according to any of the claims 4 to 13.

19) A method for treating combined hypercholesterolaemia and hypertension, wherein the method comprises administering to a patient in need thereof a stable pharmaceutical composition according to any of the claims 14 to 17.