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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 September 2009 (24.09.2009)

PCT

(10) International Publication Number
WO 2009/116061 A2

(51) International Patent Classification:
A61K 31/20 (2006.01) *A61K 33/06* (2006.01)
A61K 31/4422 (2006.01)

(21) International Application Number:
PCT/IN2009/000009

(22) International Filing Date:
5 January 2009 (05.01.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
78/MUM/2008 10 January 2008 (10.01.2008) IN

(71) Applicant *(for all designated States except US)*: **ALKEM LABORATORIES LTD.** [IN/IN]; Devashish, Alkem House, Senapati Bapat Marg, Lower Parel, Mumbai 400 013 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MANOJ, Senapati** [IN/IN]; Plot No. 19A, M.S. Nagar, Unit IV, Bhuvaneshwar, Orissa 751 001 (IN). **MANAS, Ranjan** [IN/IN]; Ghantua, Vill: Singla, P.O. Ghantua, Dist: Balasore, Orissa 756 023 (IN). **UDIT, Agarwala** [IN/IN]; 3/517, Shreeji Krupa, 1st Floor, Block No. 3, H.R. Mahajani Marg, Matunga, Mumbai 400 019 (IN). **SATYANARAYANA, V.** [IN/IN]; 1004, Iris, Kesar Garden, Sector 20, Kharghar, Navi Mumbai 410 210, Maharashtra (IN). **RAMPAL, Ashok** [IN/IN]; C-943, Sushant Lok-1, Gurgaon 122 002 (IN).

(74) Agent: **ADVOCATE KHER SANJAY**; Clover Consulting, Clover House, 176-A, Vaishali, Sir-Bhalchandra Road, Hindu Colony, Dadar, Mumbai 400 014 (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, ST, 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, MK, 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).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2009/116061 A2

(54) Title: STABLE ORAL PHARMACEUTICAL COMPOSITION COMPRISING ATORVASTATIN

(57) Abstract: The present invention relates to a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt and alkaline aluminium salts in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

STABLE ORAL PHARMACEUTICAL COMPOSITION COMPRISING ATORVASTATIN

FIELD OF THE INVENTION

The present invention relates to a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt. More particularly it relates to a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt and suitable aluminium compounds in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

BACKGROUND OF THE INVENTION

Atorvastatin calcium, an HMG-CoA reductase inhibitor, disclosed in the U. S. Pat. No. 5,273,995, is currently sold in United States of America as Lipitor® having chemical name [R-(R*, R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. It is indicated for prevention of cardiovascular disease and hypercholesterolemia. Atorvastatin is susceptible to a low pH environment and can degrade to the corresponding lactone in an acidic environment.

Amlodipine besylate, a long-acting calcium channel blocker is chemically described as 3-Ethyl-5- methyl (±)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Amlodipine may readily be prepared as described in U.S. Pat. No. 4,572, 909. Amlodipine besylate, which is currently sold as Norvasc®, may be prepared as described in U.S. Pat. No. 4,879,303, which is incorporated herein by reference. Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers. A combination of amlodipine besylate and atorvastatin calcium tablets is available as CADUET® tablets in the United States of

America. This combination is indicated in treatment of cardiovascular disease, hypercholesterolemia, hypertension and Coronary Artery Disease (CAD).

U.S. Patent No. 5,686,104 discloses that HMG-CoA reductase inhibitors in an oral pharmaceutical composition for the treatment of hypercholesterolemia or hyperlipidemia are stabilized by combination with at least one alkaline earth metal salt such as calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate or aluminium magnesium hydroxide.

U.S. Patent No. 6,680,341 discloses a stabilized pharmaceutical formulation containing as an active ingredient an HMG-CoA reductase inhibitor, and a buffering agent, wherein the active composition has a pH in the range from 7 to 11; at least one constituent selected from the group consisting of a filler, a binder, a disintegrating agent and a glidant; and additional buffering agent, wherein the pharmaceutical formulation has a pH below 9.

U.S. Patent No. 6558659 discloses stabilized pharmaceutical composition for the treatment of dyslipidemia, comprising an active component consisting essentially of one or more compounds selected from the group consisting of (i) a ring-opened 7-substituted-3,5-dihydroxyheptafloic acid or a pharmaceutically acceptable acid salt thereof, and (ii) a ring-opened 7-substituted-3,5-dihydroxyheptenoic acid or a pharmaceutically acceptable acid salt thereof, and a stabilizing effective amount of at least one amido-group containing polymeric compound or at least one amino-group containing polymeric compound, or combination thereof, wherein said stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer or a combination of other stabilizers.

U.S. Patent No. 6531507 discloses a composition comprising a homogeneous mixture of a HMG-CoA reductase inhibitor with a buffering substance or a basifying substance in a finely distributed form, obtained by co-crystallization and/or co-precipitation of said HMG-CoA reductase inhibitor and said buffering substance or basifying substance. The

basifying substance used for co-crystallization and/or co-precipitation is selected from the group consisting of metal oxides, inorganic bases, organic bases and organic acids with basic character.

U.S. Patent Application No. 2003175338 discloses a pharmaceutical formulation comprising atorvastatin and an alkali metal salt additive, the alkali metal salt additive being present at a concentration of between approximately 1.2% and less than 5% by weight of the formulation.

PCT Application No. 2005011737 discloses combination of at least one therapeutic agent which is susceptible to degradation, and at least one stabilizing agent comprising at least one carbonate salt of an amino acid, wherein at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor, the stabilizing agent further comprises one or more saccharides, whereby said stabilizing agent can provide a protective stabilizing effect for said therapeutic agent susceptible to degradation when present in a pharmaceutical formulation.

PCT Application No. 2006006021A discloses a stabilized pharmaceutical composition comprising a therapeutically effective amount of one or more active pharmaceutical ingredients capable of degradation in a low pH environment and a stabilizing effective amount of one or more amino-group containing monomeric compounds and or amido-group containing monomeric compounds for the stabilization of the active pharmaceutical ingredient. The amino- group containing monomeric compound is selected from the group consisting of a hydrocarbyl amine, hydroxy substituted hydrocarbyl amine and mixtures thereof.

PCT Application No. 2006123358 discloses a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt and pharmaceutically acceptable carrier comprising about 0.5 % to about 3.0% by weight of tromethamine and an additional stabilizer in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

SUMMARY OF THE INVENTION

The present invention provides a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt and suitable aluminium compounds in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

The present invention also provides a stable oral pharmaceutical composition comprising a combination of atorvastatin or its pharmaceutically acceptable salt, amlodipine or its pharmaceutically acceptable salt and suitable aluminium compounds in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

Additionally, the present invention provides a process for preparing a stable oral pharmaceutical composition of atorvastatin or its pharmaceutically acceptable salt comprising mixing atorvastatin or its pharmaceutically acceptable salt with alkaline aluminium salts in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt; and other excipients and converting the mixture into a pharmaceutical composition.

The invention may be summarized as given below:

A. A stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt and alkaline aluminium salts in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

B. A stable oral pharmaceutical composition comprising a combination of atorvastatin or its pharmaceutically acceptable salt, amlodipine or its pharmaceutically acceptable salt and alkaline aluminium salts in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

C. A stable pharmaceutical composition as in A or B above, wherein the atorvastatin or a pharmaceutically acceptable salt thereof is used in amounts ranging from about 0.05 to about 70% w/w of the composition.

D. A stable pharmaceutical composition as in B above, wherein the amlodipine or a pharmaceutically acceptable salt thereof is used in amounts ranging from about 0.01 to about 60% w/w of the composition.

E. A stable pharmaceutical composition, as in A or B above, wherein the alkaline aluminium salts are used in amounts ranging from about 0.05 to about 70% w/w of the composition.

F. A stable pharmaceutical composition as in E above, wherein the alkaline aluminium salts are selected from the group comprising aluminium acetate; aluminium chlorhydroxy allantoinate; aluminium diacetate; aluminium hydroxide; aluminium hydroxide - sucrose, hydrated; aluminium oxide; aluminium monostearate; aluminium silicate; aluminium silicate pentahydrate; aluminium starch octenylsuccinate; aluminium stearate; aluminium sulfate; dihydroxyaluminium glycinate; dihydroxyaluminium sodium carbonate; magnesium aluminium silicate; starch aluminium octenyl succinate and the like or mixtures thereof.

G. A stable pharmaceutical composition as in A or B above, wherein the dosage form is a tablet.

H. A stable oral pharmaceutical composition as in A or B above, further comprising additional pharmaceutically acceptable excipients selected from the group comprising disintegrants, lubricants, glidants, fillers or diluents, wicking agents, carrier, colorant or coating material and the like or a mixture thereof.

I. A process for preparing a stable oral pharmaceutical composition of atorvastatin or its pharmaceutically acceptable salt comprising mixing atorvastatin or its pharmaceutically

acceptable salt with alkaline aluminium salts in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt; and other excipients and converting the mixture into a pharmaceutical composition.

DESCRIPTION OF THE INVENTION

Before the present formulations and methods are described, it is to be understood that this invention is not limited to particular compounds, formulas or steps described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a plurality of such compounds

and reference to "the step" includes reference to one or more step and equivalents thereof known to those skilled in the art, and so forth.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

The present invention provides a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt and suitable aluminium compounds in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

The present invention also provides a stable oral pharmaceutical composition comprising a combination of atorvastatin or its pharmaceutically acceptable salt, amlodipine or its pharmaceutically acceptable salt and suitable aluminium compounds in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

It has been surprisingly found that a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt can be obtained by providing, in a pharmaceutical composition, a stabilizing effective amount of suitable aluminium compounds.

The term "stable" indicates that when the composition is stored at 40°C at 75% relative humidity (RH) in closed containers with or without dessicant for extended period of time such as three months, there is no change in dissolution profile and total impurities percentages do not exceed 3% by weight to the atorvastatin or its pharmaceutically acceptable salt.

The present invention is particularly adapted to stable oral pharmaceutical compositions comprising atorvastatin or its pharmaceutically acceptable salt, as the active component

of the composition. Among the preferred pharmaceutically acceptable salts are metal and amine salts. The term "pharmaceutically acceptable salt" thus includes, but is not limited to sodium, potassium, lithium, calcium, magnesium, aluminium, iron and zinc salts of atorvastatin. Preferably, the atorvastatin is in the form of calcium salt. The atorvastatin or its pharmaceutically acceptable salt is used in a therapeutically effective amount in the stable oral pharmaceutical compositions of the present invention. The atorvastatin or its pharmaceutically acceptable salt will generally be present in an amount ranging from about 0.05 to about 70% w/w, preferably in an amount ranging from about 1.0 to about 60% w/w, and most preferably from about 1% to about 40% w/w of the composition. The therapeutic effective amount of atorvastatin or its pharmaceutically acceptable salt that may be used in the stable composition of the present invention is in the range from about 10 to about 100 mg, equivalent to the base.

The stable oral pharmaceutical compositions of the present invention may also include amlodipine or its pharmaceutically acceptable salt. The expression "pharmaceutically-acceptable acid addition salts" is intended to define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, besylate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts. Other acid addition salts of amlodipine may be prepared by reacting the free base form of amlodipine with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base of amlodipine and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent. A particularly preferred salt of amlodipine is the besylate salt. The amlodipine or its pharmaceutically acceptable salt is used in a therapeutically effective amount in the stable oral

pharmaceutical compositions of the present invention. The amlodipine or its pharmaceutically acceptable salt may generally be present in an amount ranging from about 0.01 to about 60% w/w, preferably in an amount ranging from about 0.05 to about 40% w/w, and most preferably from about 0.01% to about 20% w/w of the composition. The therapeutic effective amount of amlodipine or its pharmaceutically acceptable salt that may be used in the stable composition of the present invention is in the range from about 2.5 to about 20 mg, equivalent to the base.

Also present in the stable oral pharmaceutical composition of the present invention is a stabilizing effective amount of suitable aluminium compound(s). The suitable aluminium compounds are used in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt. The suitable aluminium compounds of the invention may be selected from the group comprising aluminium acetate; aluminium chlorhydroxy allantoinate; aluminium diacetate; aluminium hydroxide; aluminium hydroxide - sucrose, hydrated; aluminium oxide; aluminium monostearate; aluminium silicate; aluminium silicate pentahydrate; aluminium starch octenylsuccinate; aluminium stearate; aluminium sulfate; dihydroxyaluminium glycinate; dihydroxyaluminium sodium carbonate; magnesium aluminium silicate; starch aluminium octenyl succinate and the like or mixtures thereof. A preferred suitable aluminium compound of the invention is aluminium hydroxide. The amount of suitable aluminium compounds that may be used in the stable oral pharmaceutical composition of the subject invention ranges from about 0.1 to about 60 % w/w of the composition, more preferably, from about 1% to about 40% w/w of the total weight of the composition,.

The pharmaceutical composition of the present invention may further comprise conventional pharmaceutically acceptable excipients. Conventional pharmaceutical excipients include those which function in a dosage form, for example, as a disintegrant, lubricant, glidant, fillers or diluents, wicking agents, carrier, colorant or coating material

In preferred embodiments the composition of the present invention is formed into tablets. The fillers or diluents that may be used in the stable oral pharmaceutical composition of the present invention include microcrystalline cellulose, mannitol, dextrates, dextrins,

dextrose, fructose, lactose, lactitol, maltitol, maltodextrins, maltose and the like and mixtures thereof. A preferred filler is microcrystalline cellulose or lactose or a combination thereof. The diluents or fillers may be used in amounts ranging from about 0.1 to about 80% w/w. It is preferred that the fillers are used in amounts ranging from about 1 to about 70% w/w of the composition.

The disintegrants that may be used in pharmaceutical composition of the present invention include carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminium silicate, methylcellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate, and starch and the like or mixtures thereof. The disintegrants may be used in amounts ranging from about 0.1 to about 50% w/w. It is preferred that the fillers are used in amounts ranging from about 1 to about 20% w/w of the composition.

The lubricants used in the present invention may be selected from the group consisting of talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, polyethylene glycol and the like and mixtures thereof. Generally the amount of the lubricants used in the present invention may vary from about 0.001 to about 5 % w/w of the composition.

The typical glidants that may be included in the present invention include colloidal silicon dioxide, talc and the like. The amounts of glidants used in the present invention may vary from about 0.1 to about 5% w/w of the composition.

Examples of wicking agents that may be used in the present invention include colloidal silicon dioxide, kaolin, titanium dioxide, fumed silicon dioxide, m-pyrol, vinylpyrrolidone polymers such as povidone, or crosslinked polyvinylpyrrolidone such as crospovidone; cellulose and cellulose derivatives such as microcrystalline cellulose, methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropyl cellulose, carboxyalicyl celluloses and their alkali salts; sodium starch glycolate, starch and starch derivatives, ion-exchange resins and the like and mixtures thereof.

The binders used in the present invention may be selected from the group comprising of starch, gelatin, dextrin, maltodextrin, natural and synthetic gums like acacia, alginic acid, sodium alginate, guar gum, extract of fish moss, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, veegum, arabogalactan and the like and mixtures thereof.

The film forming polymer used in the the present invention may be selected from the group comprising opadry®, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone; and the like and mixtures thereof.

The composition of the present invention may also use solubilizers known in the art such as polysorbate 80 and the like; wetting agents known in the art such as sodium lauryl sulfate and the like; and antioxidants known in the art such as butylated hydroxyl anisol, butylated hydroxyl toluene and the like.

The term "pharmaceutical composition" as used herein includes solid oral dosage forms such as pellets, beads, granules and the like, which may be encapsulated or compressed into tablets. The pellets, beads, granules in turn may be prepared by conventional methods known to a person skilled in the art. The compressed tablets may optionally be coated with film-coat.

The pharmaceutical compositions of the present invention, maybe prepared by the conventional processes such as wet granulation, dry granulation or direct compression. In wet granulation, atorvastatin or its pharmaceutically acceptable salt is mixed with suitable aluminium compounds and various excipients and granulated, followed by screening and drying of the damp mass. The dried mass may be screened, lubricated and compressed. Dry granulation can be done by two processes: (1) slugging, which involves mixing the atorvastatin or its pharmaceutically acceptable salt with suitable aluminium compounds and the excipients, slugging, dry screening, lubrication and compression, or (2) roller compaction process. Direct compression involves compressing tablets directly from the physical mixture of atorvastatin or its pharmaceutically acceptable salt, suitable

aluminium compounds and the excipients. Alternatively the pharmaceutical compositions of the present invention may be obtained by preparing placebo granules comprising the suitable aluminium compounds and pharmaceutically acceptable excipients, and mixing these with atorvastatin to obtain a blend, which may be encapsulated or compressed into tablets. This method provides compositions of atorvastatin that are stable.

The following examples are intended to illustrate the scope of the present invention in all its aspects but not to limit it thereto.

EXAMPLE 1

The stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt may be prepared as given in Table 1.

Table 1

Name of Ingredients	Quantity (mg/Tablet)	%w/w
Atorvastatin calcium	80.00	6.54
Aluminium Hydroxide	264.00	21.57
Microcrystalline Cellulose	229.96	18.79
Lactose monohydrate	500.00	40.85
Croscarmellose sodium	75.00	6.13
Polysorbate 80	04.80	0.39
Butylated hydroxyl anisol	00.24	0.02
Purified water	q.s	
Extragranular		
Croscarmellose sodium	36.00	2.94
Magnesium stearate	10.00	0.82
Total wt	**1200.00**	
Coating		
Opadry AMB white	24.00	1.96
Purified water	q.s	
Total wt	**1224.00**	**100**

The atorvastatin calcium, aluminium hydroxide dry gel powder, microcrystalline cellulose, lactose monohydrate and Croscarmellose sodium were sifted through # 40 sieve and mixed for 10 minutes in a RMG. The binder solution was prepared by heating purified water to 40 - 50^{0}C and polysorbate 80 added to it with stirring. The Butylated

hydroxyl anisol (solution dissolved in IPA) was added to the above solution to get a clear solution. Then the previously prepared blend was granulated in RMG using the binder solution prepared above. The granules were dried in rapid drier at 50^0C till LOD below 5 % w/w was obtained and sifted through appropriate sieve. Then croscarmellose sodium was mixed with the above blend. Also magnesium stearate was added to the above blend and mixed. The blend was then compressed blend using suitable punches. The tablets were then coated with opadry white ready mix.

EXAMPLE 2

The stable oral pharmaceutical composition as prepared in example 1 was subjected to dissolution. The results are given in table 2

Media : 6.8 pH Phosphate buffer
Appratus : USP Type II
Agitation : 75 RPM
Volume : 900 ml

Table 2

S No	Time in min	% drug Dissolved
1	5	70.0
2	10	85.0
3	15	89.0
4	30	95.0

EXAMPLE 3-5

The stable oral pharmaceutical compositions comprising atorvastatin or its pharmaceutically acceptable salt may be prepared as given in Table 3.

Table 3

	Ingredient	%w/w		
		Example 3	Example 4	Example 5
01	Atorvastatin Calcium (Amorphous)	6.54	6.54	6.51
02	Aluminium Hydroxide	21.57	21.57	21.50
03	Microcrystalline Cellulose	39.38	39.38	19.05

04	Lactose monohydrate	21.81	22.63	40.72
05	Croscarmellose Sodium	2.94	4.08	6.11
06	Tween 80 (polysorbate 80)	0.39	0.39	0.39
07	Butylated hydroxyl anisol (dissolve in IPA)	0.02	0.02	0.02
08	Hydroxy propyl cellulose (Klucel LF)	1.96	1.96	1.96
09	Purified water			
	Extra-granular			
10	Croscarmellose sodium	2.94	2.94	2.93
11	Magnesium stearate	0.49	0.49	0.81
	Total wt			
	Coating			
12	Opadry AMB white	1.96	1.96	1.95
13	Purified water			
	Total wt			

The compositions were prepared as given as per the procedure given in example 1.

EXAMPLE 6

The stable oral pharmaceutical compositions comprising atorvastatin or its pharmaceutically acceptable salt and amlodipine or its pharmaceutically acceptable salt may be prepared as given in Table 4.

Table 4

Name of Ingredients	Quantity (mg/Tablet)	%w/w
Atorvastatin calcium	82.88	9.96
Aluminium Hydroxide	25.00	3.00
Pregelatinised starch	50.00	6.01
Colloidal silicon dioxide	8.0	0.96
Butylated hydroxyl anisol	4.7	0.56
Butylated hydroxyl toulene	0.4	0.05
Sodium lauryl sulfate	8.0	0.96
Hydroxy propyl cellulose	16.0	1.92
Isopropyl alcohol	q.s.	
Extragranular		
Amlodipine besylate	13.87	1.67
Mannitol	80.00	9.62

Croscarmellose sodium	48.00	5.77
Microcrystalline Cellulose	443.15	53.26
Colloidal silicon dioxide	8.0	0.96
Magnesium stearate	12.00	1.44
Coating		
Opadry AMB white	32.00	3.85
Purified water	q.s	
Total wt	**832.00**	**100**

The composition was prepared as given as per the procedure given in example 1.

EXAMPLE 7

The stable oral pharmaceutical compositions comprising atorvastatin or its pharmaceutically acceptable salt may be prepared as given in Table 5.

Table 5

Name of Ingredients	Quantity (mg/Tablet)	%w/w
Atorvastatin calcium	80.00	6.54
Dried aluminum Hydroxide	85.00	6.94
Microcrystalline Cellulose	308.96	25.24
Lactose monohydrate	200.00	16.34
Croscarmellose sodium	75.00	6.13
Polysorbate 80	04.80	0.39
Butylated hydroxyl anisol	00.24	0.02
Purified water	q.s	
Extragranular		
Croscarmellose sodium	36.00	2.94
Microcrystalline Cellulose	400.00	32.68
Magnesium stearate	10.00	0.82
Total wt	**1200.00**	
Coating		
Opadry white	24.00	1.96
Purified water	q.s	
Total wt	**1224.00**	100

The composition was prepared as given as per the procedure given in example 1.

EXAMPLE 8

The stable oral pharmaceutical composition as prepared in example 7 was subjected to dissolution. The results are given in Table 6 and Figure 1.

Media : 6.8 pH Phosphate buffer
Appratus : USP Type II
Agitation : 75 RPM
Volume : 900 ml

Table 6

Time in min	**Lipitor® 80 mg Tablet (% drug release)**	**Composition of example -7 (% drug release)**
5	85.63	81.23
10	94.08	90.90
15	96.70	94.96
30	98.73	99.73

EXAMPLE 9

The composition of the invention prepared in example 7 was subjected to accelerated studies for 3 months at 40°C/75%RH and dissolution studies for 3 months and the results are shown in Table 7 and Table 8.

Table 7

Condition	**Period**	**Description**	**LOD at 105°C % w/w**	**Dissolution in 30 min (%)**	**Assay (%)**
RT	**Initial**	White film coated oval shape tablet	4.48	99.73	100.30
40°C /75% RH	**1 M**	OK	5.38	94.96	99.80
	2 M	OK	5.24	92.13	99.20
	3M	OK	5.21	91.10	99.20

Table 8

Impurity profile

Condition		Desfluro	Oxoatorvast	Diastereomer	Methylester	Diepoxide	MSUI	Total
Initial		0.161	ND	0.056	ND	ND	0.135	0.934
40°C /75% RH	**1 M**	0.10	0.099	0.048	0.214	0.061	0.1300	0.876
	2 M	0.113	0.138	0.047	0.251	0.130	0.164	1.115
	3 M	0.111	0.196	0.046	0.308	0.237	0.180	1.379
Specification	**NMT**	0.5 %	0.5 %	0.5 %	0.5 %	0.5 %	0.2%	3.0%

- MSUI: maxium single unknown impurity
- NMT: Not More Than
- ND: Not Detected

Although the invention has been described in terms of particular embodiments and applications, one of ordinary skill in the art, in light of this teaching, can generate additional embodiments and modifications without departing from the spirit of or exceeding the scope of the claimed invention. It should be emphasized that the above-described embodiments of the present invention, particularly any "preferred" embodiments, are merely possible examples of the invention of implementations, merely set forth for a clear understanding of the principles of the invention. Accordingly, it is to be understood that the drawings and descriptions herein are proffered by way of example to facilitate comprehension of the invention and should not be construed to limit the scope thereof.

Claims:

1. A stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt and alkaline aluminium salts in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

2. A stable oral pharmaceutical composition comprising a combination of atorvastatin or its pharmaceutically acceptable salt, amlodipine or its pharmaceutically acceptable salt and alkaline aluminium salts in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

3. A stable pharmaceutical composition according to claim 1 or 2, wherein the atorvastatin or a pharmaceutically acceptable salt thereof is used in amounts ranging from about 0.05 to about 70% w/w of the composition.

4. A stable pharmaceutical composition according to claim 2, wherein the amlodipine or a pharmaceutically acceptable salt thereof is used in amounts ranging from about 0.01 to about 60% w/w of the composition.

5. A stable pharmaceutical composition according to claim 1 or 2, wherein the alkaline aluminium salts are used in amounts ranging from about 0.05 to about 70% w/w of the composition.

6. A stable pharmaceutical composition according to claim 5, wherein the alkaline aluminium salts are selected from the group comprising aluminium acetate; aluminium chlorhydroxy allantoinate; aluminium diacetate; aluminium hydroxide; aluminium hydroxide - sucrose, hydrated; aluminium oxide; aluminium monostearate; aluminium silicate; aluminium silicate pentahydrate; aluminium starch octenylsuccinate; aluminium stearate; aluminium sulfate; dihydroxyaluminium glycinate; dihydroxyaluminium sodium carbonate; magnesium aluminium silicate; starch aluminium octenyl succinate and the like or mixtures thereof.

7. A stable pharmaceutical composition according to claim 1 or 2, wherein the dosage form is a tablet.

8. A stable oral pharmaceutical composition according to claim 1 or 2, further comprising additional pharmaceutically acceptable excipients selected from the group comprising disintegrants, lubricants, glidants, fillers or diluents, wicking agents, carrier, colorant or coating material and the like or mixtures thereof.

9. A process for preparing a stable oral pharmaceutical composition of atorvastatin or its pharmaceutically acceptable salt comprising mixing atorvastatin or its pharmaceutically acceptable salt with alkaline aluminium salts in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt; and other excipients and converting the mixture into a pharmaceutical composition.