We Claim,

1. A pharmaceutical composition comprising:
   a) a first active ingredient having a HMG-CoA reductase inhibition activity, and;
   b) a surfactant selected from docusate sodium or salts and derivatives thereof;
   along with pharmaceutically acceptable exicipients.

2. A pharmaceutical composition as claimed in claim 1, wherein the HMG-CoA reductase inhibitor is a statin selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, as base form or as pharmaceutically acceptable salts or hydrates thereof.

3. A pharmaceutical composition as claimed in claim 2, wherein the statin is atorvastatin or pharmaceutically acceptable salt or hydrates thereof..

4. A pharmaceutical composition as claimed in claim 3, wherein atorvastatin is salt is calcium salt.

5. A pharmaceutical composition as claimed in claim 4, wherein mole fraction of atorvastatin is in range of 10mg to 80 mg.

6. The pharmaceutical composition as claimed in claim 1, wherein the of mole fraction docusate sodium is in range of 5mg to 400 mg per tablet

7. The pharmaceutical composition as claimed in claim 1, further comprises a stabilizing amount of meglumine

8. The pharmaceutical composition as claimed in claim 1 further comprises an additional stabilizing agent.

9. The pharmaceutical composition as claimed in claim 8, wherein the additional stabilizing agent is an antioxidant.

26 FEB 2010

10. The pharmaceutical composition as claimed in claim 9, wherein in the antioxidant is selected from butylated hydroxy anisole, butylated hydroxy toluene, DL-alpha-tocopherol, propyl gallate, octyl gallate, ethylenediamine tetraacetate, ascorbyl palmitate, acetyl cysteine, ascorbic acid, gluconolactone, sodium ascorbate, fumaric acid, lecithin and the like and mixtures thereof.

11. The pharmaceutical composition as claimed in claim 1 induces laxative and fecal softening activity in a mammal to whom such composition is administered.

Dated this 26th Day of February, 2010

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26 FEB 2010

Field of Invention:

The present invention is in the field of compositions of statins, more particularly present invention relates to pharmaceutical compositions having enhanced dissolution properties in acidic media, comprising a combination of statin and surfactant which also acts as fecal softener and acid solubilizer.

Background of Invention:

The statins (or HMG-CoA reductase inhibitors) are a class of drugs that lower cholesterol levels in people suffering from hypercholesterolemia.

They lower cholesterol by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. Inhibition of this enzyme, in the liver, results in decreased cholesterol synthesis along with increased synthesis of LDL receptors which results in an increased clearance of low-density lipoprotein (LDL) from the bloodstream. The first results can be seen after one week of use and the effect is maximal after four to six weeks.

Statins commonly used in medicine are atorvastatin (US5273995), cerivastatin (US5177080), fluvastatin (US4739073), lovastatin (US4231938), pravastatin (US4346227), rosuvastatin (US RE37314) and simvastatin (US4444784). They may be used in free form or as pharmaceutically acceptable salts thereof, generally alkaline or alkaline-earth salts, usually desirable to use the sodium or calcium salts, whether anhydrous or hydrated. For example, in clinical practice, atorvastatin is used as sodium (2:1) trihydrate salt. Cerivastatin, fluvastatin pravastatin and rosuvastatin as sodium salt, while, lovastatin and simvastatin are used as free form. A more recent compound, pitavastatin (EP304063), is currently under Phase III development in Europe.

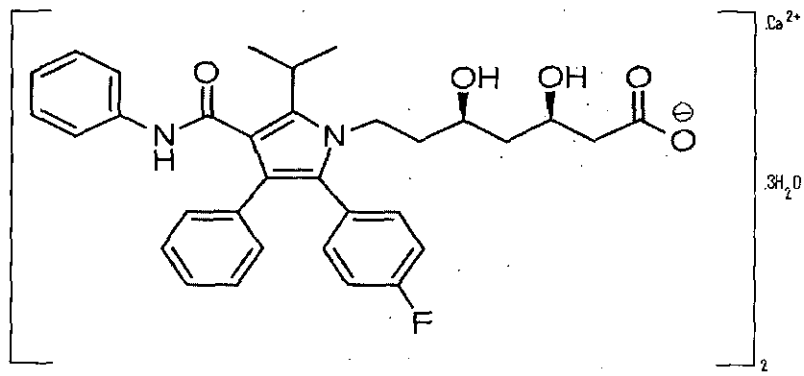
Among the most significant and frequent side effects of statins is flatulence (Bakker-Arkema et al, Atherosclerosis 2000 March, 149(1), 123-9 [PubMed 10704623]; Black et al, Arch Intern Med 1998 March 23, 158(6), 577-84 [PubMed 9521221]; Posvar et al, J Clin Pharmacol 1996 August, 36(8), 728-31 [PubMed 8877677]; Boccuzzi et al, Am J Cardiol 1991 November 1, 68(11), 1127-31 [Pubmed 1951069]; Zeller et al, Drug Intell Clin Pharm 1988 July-August, 22(7-8), 542-5 [PubMed 3046888]), which may be the

12 6 FEB 2010

cause of discomfort and symptomatological confusion, since its symptoms may be like those of coronary heart disease which is the aim of hypolipemic therapy by statins. Other side effects which are usually witnessed are muscle and joint aches, nausea, diarrhea and constipation.

Certain commercial products containing statins, like Lipitor (Atorvastatin as calcium 2:1 trihydrate), and formulations containing statins (WO 2004/021972) such as Pravastatin (WO 03/057195) have already been formulated with an antifoaming agent, that is, an emulsion of simethicone.

Atorvastatin calcium, a potent molecule from the "statin" family, is a lipid-lowering agent that acts by inhibiting the HMG-CoA reductase enzyme. Atorvastatin calcium has a chemical name [R—(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methyl ethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The chemical structure of atorvastatin is as below:



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol. Atorvastatin calcium is susceptible to heat, moisture, light and low pH, all causing degradation from the carboxylic form to the lactone form.

12 6 FEB 2010

A commercially available product containing atorvastatin is LIPITOR® oral tablets, manufactured by Pfizer. LIPITOR® tablets contain atorvastatin as its calcium salt trihydrate and are available in 10, 20, 40 and 80 mg atorvastatin acid equivalent strengths. LIPITOR® is indicated for prevention of cardiovascular diseases and hypercholesterolemia.

U.S. Patent Application Publication No. 2003/0175338 discloses a pharmaceutical composition of atorvastatin calcium and other salts, for example atorvastatin magnesium, etc. having particle sizes less than 150 μm, such composition having improved bioavailability.

U.S. Patent Application Publication No. 2005/0032880 discloses a composition of amorphous atorvastatin calcium wherein the amorphous atorvastatin is layered around a core.

WO 03/074034 describes pharmaceutical compositions with delayed release of anti-hypercholesterolemic drugs, e.g. statins. Stable tablets comprising simvastatin are described in WO 03/086387.

In view of above, the present inventor has formulated a novel pharmaceutical composition of statin or its pharmaceutically acceptable salts, solvates, hydrates, enantiomers, polymorphs or their mixtures along with a surfactant which also acts as fecal softener and acid solubilizer. The invention further also relates to processes for preparing the same and methods of use, treatment and administration thereof having a specific in-vitro release pattern in acidic and alkaline pH conditions of the gastrointestinal system, thus ensuring desired in-vivo profiles.

Summary of Invention:

Accordingly, the present invention provides a pharmaceutical composition comprising statin or pharmaceutically acceptable salts thereof along with at least, one surfactant with acid solubility enhancing activity and laxative and fecal softening activity and optionally other excipients. The said statin can be atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin.

26 FEB 2010

In another aspect, present invention provides a process for preparing the said oral pharmaceutical composition of atorvastatin or its pharmaceutically acceptable salt alongwith docusate salts in an amount sufficient to provide enhanced solubility and stability in gastric media of the atorvastatin or its pharmaceutically acceptable salt; and other excipients and converting the mixture into a pharmaceutical composition.

Detailed Description of Invention:

The invention will now be described in details in connection with certain preferred and optional embodiments so that various aspects thereof may be more fully understood and appreciated.

For purpose of this invention "an acid solubility enhancing and laxative and fecal softener agent" is an agent that effectively provides relief from constipation, a common side effect associated with the statins, in a suitable proportion

For the purposes of this invention, the term "pharmaceutical composition" 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 present invention describes a oral pharmaceutical composition comprising a statin in combination with a surfactant which acts as fecal softener and acid solubilizer alongwith at least one pharmaceutically acceptable excipient.

The compositions as described in the present invention comprise a statin preferably selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, either in base form or as pharmaceutically acceptable salts or hydrates thereof. Preferably, atorvastatin as calcium (2:1) trihydrate, cerivastatin, fluvastatin and pravastatin as sodium salt, rosuvastatin as calcium salt and lovastatin and simvastatin in free form.

26 FEB 2010

The present invention is particularly adapted to prepare 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 within the range of from about 0.05 to about 70%, and preferably an amount within the range of from about 1 to about 60% by weight of the composition, most preferably from about 5% to about 40% by weight of the composition. The therapeutically 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 80 mg, equivalent to the base.

Suitable surfactant of present invention selected from the group consisting of Docusate sodium and docusate salts. Docusate sodium and docusate salts are widely used as anionic surfactants in pharmaceutical formulations. Docusate sodium is mainly used in capsule and direct-compression tablet formulations to assist in wetting and dissolution. Docusate salts are also used in oral formulations as laxatives and fecal softeners.

In a preferred embodiment, the invention provides a oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt in combination with surfactant such as docusate sodium and docusate salts in an amount sufficient to provide enhanced solubility and stability in gastric media.

In another embodiment, the invention provides oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt in combination with surfactant such as docusate sodium and docusate salts alongwith at least one pharmaceutical excipient wherein about 15 to about 90 percent by weight of atorvastatin

26 FEB 2010

contained in w/w of formulation is present in intimate mixture with an acid solubility enhancing excipient..

The pharmaceutical composition of invention comprises the acid solubility enhancing, laxative and fecal softener agent is preferably docusate sodium in an amount in range of 10 to 400 mg/tablet. The effective amount of the docusate sodium depends on the amount of statin. Accordingly, the weight ratio of docusate sodium versus statin is at least 0.25, preferably at least 0.50, 0.75 or 1.00, and most preferably at least 1.25 or 1.50. Said ratios refer to the relative amounts to be administered, since the statin and the docusate salts are co-formulated, to the relative amounts that are present in the formulation. The maximum ratio of docusate salts versus statin is not particularly limited. However, it may be expedient that the amount of docusate salts does not exceed 50% by weight and preferably 30% by weight of the formulation.

In preferred embodiments of the present invention the solubility enhancing excipient comprises docusate sodium, and antioxidants.

In another embodiment, the composition of present invention further, comprises a stabilizing agent such as meglumine in an effective amount. Meglumine is an organic base commonly used as a pH-adjusting agent and solubilizing agent.

In an embodiment, the invention provides a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt, suitable docusate salts in an amount sufficient to provide enhanced solubility and stability *in vitro*, in gastric media of the atorvastatin or its pharmaceutically acceptable salt and a stabilizing effective amount of meglumine and an additional stabilizer.

In further embodiment, the invention provides a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier comprising a stabilizer, meglumine, wherein the amount of atorvastatin remains substantially unchanged upon storage at 40° C and 75% relative humidity in a closed container containing a desiccant for a period of three months.

26 FEB 2010

In an embodiment, the invention provides a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt and meglumine and an additional stabilizer in an amount sufficient to prevent degradation of the atorvastatin or its pharmaceutically acceptable salt.

In an embodiment, the invention provides a stable oral pharmaceutical composition comprising atorvastatin or its pharmaceutically acceptable salt and pharmaceutically acceptable carrier comprising about 0.5% to about 10.0% by weight of meglumine and an additional stabilizer in an amount sufficient to prevent degradation of atorvastatin or its pharmaceutically acceptable salt.

The compositions of the present invention may be administered orally in the form of solid compositions such as tablets, coated tablets, capsules, powder, granules or in the form of liquid compositions such as syrups, solutions, emulsions or the like. Preferably the composition is in form of coated tablets.

The pharmaceutical composition further comprises an additional stabilizer to improve stability of tablet. The said additional stabilizer that may be used in the present invention includes antioxidants selected from the group comprising butylated hydroxy anisole, butylated hydroxy toluene, DL-alpha-tocopherol, propyl gallate, octyl gallate, ethylenediamine tetraacetate, ascorbyl palmitate, acetyl cysteine, ascorbic acid, gluconolactone, sodium ascorbate, fumaric acid, lecithin and mixtures thereof.

The amounts of the antioxidants may vary from about 0.001% to about 0.01% w/w of the composition, preferably from about 0.005 to about 0.01%, most preferably 0.009% w/w of the composition.

The pharmaceutical composition of the present invention further comprises conventional pharmaceutically acceptable excipients that form the pharmaceutical carrier. Conventional pharmaceutical excipients include those which function in a dosage form, for example, an alkalizing agent, a fillers, disintegrants , lubricant, glidant, wicking agents, carrier, colorant or coating material.

26 FEB 2010

The pharmaceutical composition further comprises an alkalizing agent selected from sodium, potassium, magnesium, or calcium citrate, carbonate, bicarbonate, phosphate sulphate, sulphite, benzoate or ascorbate salt or combination thereof.

The pharmaceutical composition further comprises fillers selected from microcrystalline cellulose, mannitol, dextrates, dextrins, dextrose, fructose, lactose, lactitol, maltitol, maltodextrins, maltose and the like. Preferably the filler is mannitol, commercially available grade as Pearlitol SD 200.

The pharmaceutical composition further comprises disintegrants selected from colloidal silicon dioxide, croscarmellose, polyvinylpyrrolidone, starch, and its pregelatinized derivatives, e.g., Primojel®, which is sodium starch glycolate, and the like preferably Aerosil®, Acdisol® and polyvinylpyrrolidone.

The pharmaceutical composition further comprises lubricants selected form talc, magnesium stearate, stearic acid, sodium stearyl fumarate, high-molecular weight polyethyleneglycol (4000-8000), e.g., PEG 8000, and the like preferably sodium stearyl fumarate or talc or magnesium stearate.

The pharmaceutical composition of the present invention is provided with a light-resistant coating. The said coating consists of a layer constituted by cellulose derivatives, for example, sodium hydroxypropyl methylcellulose (HPMC), acrylic polymers, plasticizers, for example, diethyl citrate, opacifiers, for example titanium dioxide, talc and stearic acid. They may optionally contain pigments for tablet-colouring. As pigments, ferric oxide derivatives are preferred.

The pharmaceutical compositions of the present invention may be 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 tromethamine 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 docusate sodium and the

26 FEB 2010

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, docusate and the excipients.

Alternatively, the pharmaceutical compositions of the present invention may be obtained by preparing placebo granules comprising the docusate sodium 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 synergistic effect of the composition is exhibited by elimination of well known side effect of constipation associated with statins, by use of surfactant selected from docusate sodium and salts and derivatives, thereby inducing laxative and fecal softening activity in stain composition.

The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the present invention.

EXAMPLE 1:

200 mg tablet containing 20 mg of Atorvastatin and 60 mg of Docusate sodium.

Ingredient	Quantity (in gms)
Atorvastatin Calcium	20
Crosscarmellose Sodium	30
Sodium Hydrogen Carbonate	30
BHA	2
Dioctyl sodium sulphosuccinate	60
Mannitol (Pearlitol)	q.s to 200
Magnesium Stearate	5

EXAMPLE 2:

250 mg tablet containing 20 mg of Atorvastatin and 60 mg of Docusate sodium.

12 6 FEB 2010

Ingredient	Quantity (in gms)
Atorvastatin Calcium	20
Crosscarmellose Sodium	30
Sodium Hydrogen Carbonate	30
Meglumine	10
Dioctyl sodium sulphosuccinate	60
Mannitol (Pearlitol)	q.s to 250
Magnesium Stearate	5

EXAMPLE 3:

200 mg tablet containing 20 mg of Atorvastatin and 60 mg of Docusate sodium.

Ingredient	Quantity (in gms)
Atorvastatin Calcium (micronized)	20
Crosscarmellose Sodium	30
Sodium Hydrogen Carbonate	30
BHA	2
Dioctyl sodium sulphosuccinate	60
Mannitol (Pearlitol)	q.s to 200
Magnesium Stearate	5

EXAMPLE 4:

350 mg tablet containing 80 mg of Atorvastatin and 100 mg of Docusate sodium.

Ingredient	Quantity (in gms)
Atorvastatin Calcium	80
Crosscarmellose Sodium	50
Sodium Hydrogen Carbonate	30
Dioctyl sodium sulphosuccinate	100
Mannitol (Pearlitol)	q.s to 350
Magnesium Stearate	10

EXAMPLE 5:

400 mg tablet containing 80 mg of Atorvastatin and 100 mg of Docusate sodium.

12 6 FEB 2010

Ingredient	Quantity (in gms)
Atorvastatin Calcium	80
Crosscarmellose Sodium	50
Sodium Hydrogen Carbonate	30
Meglumine	30
Dioctyl sodium sulphosuccinate	100
Mannitol (Pearlitol)	q.s to 400
Magnesium Stearate	10

EXAMPLE 6:

860 mg tablet containing 80 mg of Atorvastatin and100 mg of Docusate sodium.

Ingredient	Quantity (in gms)
Atorvastatin Calcium	80
Crosscarmellose Sodium	200
Sodium Hydrogen Carbonate	120
Dioctyl sodium sulphosuccinate	100
Mannitol (Pearlitol)	q.s to 860
Magnesium Stearate	10

The stable pharmaceutical composition as prepared in above was subjected to dissolution in 900 ml of 6.8 pH phosphate buffer media at 75 RPM, in USP type II Apparatus:

Time in minutes	% drug release		
	Lipitor® (80 mg tablet)	Storvas® (80 mg tablet)	Composition of Example – 6
5	84	46.35	59.48
10	97	61.48	70.02
15	99	65.27	84.45
30	101	72.44	98.12

The stable pharmaceutical composition as prepared as above was subjected to dissolution in 900 ml of 0.1 N HCL media at 75 RPM, in USP type II Apparatus:

	% drug release

12 6 FEB 2010

Time in minutes	Lipitor® (80 mg tablet)	Storvas® (80 mg tablet)	Composition of Example – 6
5	35	29.32	34
10	39	31.83	37
15	46	34.92	42
30	52	35.20	49

26 FEB 2010

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2. A pharmaceutical composition as claimed in claim 1, wherein the HMG-CoA reductase inhibitor is a statin selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, as base form or as pharmaceutically acceptable salts or hydrates thereof.

3. A pharmaceutical composition as claimed in claim 2, wherein the statin is atorvastatin or pharmaceutically acceptable salt or hydrates thereof..

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6. The pharmaceutical composition as claimed in claim 1, wherein the of mole fraction docusate sodium is in range of 5mg to 400 mg per tablet

7. The pharmaceutical composition as claimed in claim 1, further comprises a stabilizing amount of meglumine

8. The pharmaceutical composition as claimed in claim 1 further comprises an additional stabilizing agent.

9. The pharmaceutical composition as claimed in claim 8, wherein the additional stabilizing agent is an antioxidant.

26 FEB 2010

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