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(54) Title: A PHARMACEUTICAL COMPOSITION COMPRISING ATORVASTATIN AND NIACIN

(57) Abstract: This invention relates to a pharmaceutical composition of atorvastatin and niacin comprising an immediate release component containing atorvastatin and a sustained release component containing niacin wherein the two components are not in intimate contact with each other.



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A PHARMACEUTICAL COMPOSITION COMPRISING ATORVASTATIN AND NIACIN

Field of the Invention

5 A pharmaceutical composition of atorvastatin and niacin comprising an immediate release component containing atorvastatin and a sustained release component containing niacin wherein the two components are not in intimate contact with each other is disclosed.

Background of the Invention

10 Atorvastatin, which is an inhibitor of the enzyme 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA reductase), is commercially available for the treatment of primary hypercholesterolemia, dysbetalipoproteinemia and homozygous familial hypercholesterolemia.

Nicotinic acid, also known as niacin, has been used for many years in the treatment of hyperlipidemia or hypercholesterolemia.

15 There have been several reports in literature on the combination of a HMG-CoA reductase with niacin. This pharmaceutical combination can be used to effectively treat, hyperlipidemia (*e.g.*, cholesterol-related cardiovascular disease) and atherosclerosis of multiple etiology.

20 U.S. Patent No. 6,090,830 discloses a pharmaceutical product for oral administration in a unit dosage form for treating hyperlipidemia comprising an immediate release lovastatin and a sustained release niacin component.

U.S. Patent No. 6,469,035 discloses a formulation of lovastatin and niacin wherein niacin core is coated with a coating comprising lovastatin.

25 Currently, bilayered tablets comprising an immediate release layer of atorvastatin and a second sustained release layer of niacin are being marketed in India by Nicholas and Lupin.

Niacin, being acidic in pH, may affect the stability of atorvastatin, if both of them come in direct contact with each other.

Summary of the Invention

Hence, we have now developed an alternate pharmaceutical formulation comprising atorvastatin and niacin wherein two active ingredients do not come in direct contact with each other.

5 According to one, there is provided a pharmaceutical composition of atorvastatin and niacin comprising:

 a) an immediate release component containing atorvastatin or pharmaceutically acceptable salts thereof; and

 b) a sustained release component containing niacin;

10 wherein the two components are not in intimate contact with each other.

In another aspect, there is provided a stabilized pharmaceutical composition of atorvastatin and niacin comprising:

 a) an immediate release component containing atorvastatin or pharmaceutically acceptable salts thereof; and

15 b) a sustained release component containing niacin;

 wherein the two components are not in intimate contact with each other.

In another aspect, there is provided a capsule formulation comprising an immediate release tablet containing atorvastatin or pharmaceutically acceptable salts thereof and a sustained release tablet containing niacin.

20 In another aspect, there is provided a pharmaceutical composition comprising an immediate release component containing atorvastatin or pharmaceutically acceptable salts thereof and a sustained release component containing niacin wherein at least one of the components further comprises a coating.

25 In another aspect, there is provided a process for the preparation of a pharmaceutical composition of atorvastatin and niacin comprising:

 a) an immediate release component containing atorvastatin or pharmaceutically acceptable salts thereof; and

 b) a sustained release component containing niacin;

wherein the two components are not in intimate contact with each other.

In another aspect, there is provided a method for treating hypercholesterolemia and dyslipidemia, comprising administering to a subject a pharmaceutical composition comprising an immediate release component containing atorvastatin or pharmaceutically acceptable salts thereof and a sustained release component containing niacin wherein the two components are not in intimate contact with each other.

Detailed Description of the Invention

As used herein the term "atorvastatin" refers to include atorvastatin and pharmaceutically acceptable salts thereof such calcium, magnesium, potassium etc.

Atorvastatin may exist in any of the solid state forms available such as amorphous or any other polymorphic form.

Niacin as used herein includes nicotinic acid and pharmaceutically acceptable salts thereof such as magnesium, potassium and ammonium.

The two components are not in intimate contact with each other to avoid any stability or incompatibility issues. These components may be separated by using coating or may exist as separate entities. Either a single component is coated or both may be coated.

Sustained release as used herein means that the therapeutically active medicament or drug is released from the formulation at a controlled rate such that therapeutically beneficial blood levels (but below toxic levels) of the medicament are maintained over an extended period of time. The term sustained release includes controlled release, prolonged action, extended release and slow release.

An "immediate release" as used herein means that at least 80% of the drug in the tablet is dissolved by 30 minutes under a dissolution test using USP Apparatus.

Pharmaceutical composition may be in the form of a tablet or a capsule.

The pharmaceutical composition may further comprise one or more "pharmaceutically acceptable excipients". They include sustained release polymers, surfactants, stabilizers, binders, diluents, lubricant/glidant, disintegrants, and coloring agents. These excipients may be present intragranularly or extragranularly.

Sustained release polymers may be selected from one or more of cellulose derivatives such as hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose and sodium carboxymethyl cellulose; gums selected from one or more of xanthan gum, karaya gum, locust bean gum, alginic acid and sodium alginate; and vinyl alcohol or vinylpyrrolidone based polymers selected from one or more of polyvinyl alcohol and polyvinylpyrrolidone and the like. In particular, HPMC of a specific grade providing desired release profile may be used such as Methocel K100 MCR[®], Methocel K4M[®], Methocel K15M[®] and the like.

The surfactant may be selected from anionic, cationic or non-ionic surface-active agents or surfactants. Suitable anionic surfactants include those containing carboxylate, sulfonate, and sulfate ions such as sodium lauryl sulfate (SLS), sodium laurate, dialkyl sodium sulfosuccinates particularly bis-(2-ethylhexyl) sodium sulfosuccinate, sodium stearate, potassium stearate, sodium oleate and the like. Suitable cationic surfactants include those containing long chain cations, such as benzalkonium chloride, bis-2-hydroxyethyl oleyl amine or the like. Suitable non-ionic surfactants include polyoxyethylene sorbitan fatty acid esters (polysorbate 80), fatty alcohols such as lauryl, cetyl and stearyl alcohols; glyceryl esters such as the naturally occurring mono-, di-, and tri-glycerides; fatty acid esters of fatty alcohols; polyglycolized glycerides such as gelucire; polyoxyethylene-polyoxypropylene block co-polymer such as Poloxamer and other alcohols such as propylene glycol, polyethylene glycol.

The term "stabilizer" as used herein means an agent that stabilizes a drug, for example alkalinizing agents, chelating agents, photoprotectants or antioxidants.

Examples of suitable antioxidants can include, for example, butylated hydroxyanisole (BHA), sodium ascorbate, butylated hydroxytoluene (BHT), sodium sulfite, propyl gallate, tocopherol, citric acid, malic acid, ascorbic acid or mixtures thereof. The antioxidants can be present at concentrations of, for example, from about 0.01% to about 5% by weight. The antioxidants may be dissolved in organic solvent such as ethanol, isopropanol, n-propanol, acetone, ethyl acetate and mixtures thereof and sprayed on to pharmaceutically acceptable inert excipients.

Examples of chelating agents can include, for example, disodium EDTA, edetic acid, citric acid, and combinations thereof. The chelating agents can be present at a

concentration of up to approximately 10% by weight of the composition, for example, from about 0.01 to about 5% by weight. The term “photoprotectant” as used herein means an agent for protection from the chemical or physical effects of light on a statin formulation. Examples can include metal oxides such as, for example, titanium oxide, ferric oxide or zinc oxide. The photoprotectant can be present at a concentration of up to approximately 10% by weight of the composition, for example, from about 0.01 to about 5% by weight.

The alkanizing agents as used herein can include alkali metal salt additives or alkaline earth metal salt additives. Alkali metal salt additives can be, for example, sodium carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate and other suitable alkali metal salts. In particular, the stabilizing alkali metal salt additive can be sodium carbonate or disodium hydrogen orthophosphate. Alkaline earth metal salt additives can include, for example, calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, or aluminum magnesium hydroxide. The amount of alkanizing agent may vary from about 1 to about 30% by weight of the composition.

Specific examples of “binders” include methyl cellulose, hydroxypropyl cellulose (HPC-L), hydroxyl propyl methylcellulose, polyvinylpyrrolidone, gelatin, ethyl cellulose, polyvinyl alcohol, pregelatinized starch, carboxymethyl cellulose, sodium alginate, microcrystalline cellulose or mixtures thereof.

The term “diluent” as used herein includes calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, cellulose powdered, dextrates, dextrans, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, sucrose and mixtures thereof.

Specific examples of lubricants/glidants include colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, and mixtures thereof.

Disintegrants may be selected from starches or modified starches such as starch, modified starch, croscarmellose sodium, crospovidone and sodium starch glycolate, cross linked sodium carboxymethylcellulose, hydroxypropyl cellulose (L- HPC) and mixtures thereof.

The pharmaceutical composition may be further film coated with functional or non functional layer. The coating may be selected from amongst one or more of those suitable coating materials known in the art. For example, the coating material can be Opadry or Opadry AMB. Coating may be performed by applying one or more film forming
5 polymers, with or without other pharmaceutically inert excipients, as a solution/suspension using any conventional coating technique known in the art, such as spray coating in a conventional coating pan or fluidized bed processor; or dip coating.

Coloring agent may be selected from FDA approved colorants and such as Iron Oxide, Lake of Tartrazine, Allura Red, Lake of Quinoline Yellow, Lake of Erythrosine,
10 Titanium Dioxide and the like.

According to one of the embodiments, there is provided a pharmaceutical composition in the form of capsule comprising an immediate release tablet of atorvastatin and a sustained release tablet of niacin.

According to another embodiment, there is provided a process for the preparation
15 of a capsule pharmaceutical composition comprising atorvastatin or pharmaceutically acceptable salts thereof and niacin, comprising the steps of:

- a) blending atorvastatin and one or more pharmaceutically acceptable excipients;
- b) optionally, granulating the blend step a);
- c) lubricating the blend of step a) or granules of step b);
- 20 d) compressing the blend of step c) to obtain tablets;
- e) coating the compressed tablet of step d);
- f) blending niacin with a sustained release polymer and one or more pharmaceutically acceptable excipients;
- g) optionally, granulating the blend of step f);
- 25 h) lubricating the blend of step f) or granules of step g);
- i) compressing the blend of step h) to obtain tablets;
- j) filling the atorvastatin tablet of step e) and niacin tablet of step i) into a capsule.

According to another embodiment, there is provided a pharmaceutical composition in the form of an inlay tablet comprising an immediate release inlay zone of atorvastatin and a sustained release base zone of niacin.

According to another embodiment, there is provided a process for the preparation of inlay tablets comprising atorvastatin or pharmaceutically acceptable salts thereof and niacin, wherein the process comprises the steps of:

- a) blending atorvastatin with other pharmaceutically acceptable excipients;
- b) optionally, granulating the blend of step a);
- c) lubricating the blend of step a) or granules of step b);
- 10 d) compressing the blend of step c) into suitable size tablet;
- e) coating the tablet of step d);
- f) blending niacin with a sustained release polymer and one or more pharmaceutically acceptable excipients;
- g) optionally, granulating the blend of step f);
- 15 h) lubricating the blend of step f) or granules of step g);
- i) compressing niacin blend of step h) and the atorvastatin tablet of step e) to form an inlay tablet.

According to another embodiment, there is provided a pharmaceutical composition in the form of compression coated tablet comprising an immediate release coat of atorvastatin over a sustained release core of niacin.

According to another embodiment, there is provided a process for the preparation of a compression coated tablet pharmaceutical composition comprising atorvastatin or pharmaceutically acceptable salts thereof and niacin, comprising the steps of

- a) blending atorvastatin and one or more pharmaceutically acceptable excipients;
- 25 b) optionally, granulating the blend step a);
- c) lubricating the blend of step a) or granules of step b);
- d) blending niacin with a sustained release polymer one and or more pharmaceutically acceptable excipients;

- e) optionally, granulating the blend of step d);
- f) lubricating the blend of step d) or granules of step e);
- g) compressing the blend of step f) into suitable size tablet;
- h) coating the tablet of step g);
- 5 i) compressing the atorvastatin blend of step c) and niacin tablet of step h) to form a compression coated tablet.

According to another embodiment, there is provided a pharmaceutical composition in the form of trilayer tablet comprising an immediate release layer of atorvastatin, an inert layer of pharmaceutically acceptable excipients and a sustained release layer of niacin
10 wherein the inert layer is present in between atorvastatin and niacin layer.

According to another embodiment, there is provided a process for the preparation of trilayer tablet comprising atorvastatin or pharmaceutically acceptable salts thereof and niacin, wherein the process comprises the steps of:

- a) blending atorvastatin with other pharmaceutically acceptable excipients;
- 15 b) optionally, granulating the blend of step a);
- c) lubricating the blend of step a) or granules of step b);
- d) blending niacin with a sustained release polymer and other pharmaceutically acceptable excipients;
- e) optionally, granulating the blend of step d);
- 20 f) lubricating the blend of step d) or granules of step e);
- g) blending pharmaceutically acceptable excipients for inert layer;
- h) compressing the blend of step c), f) and step g) into trilayer tablet;
- i) optionally, coating the compressed tablets.

According to another embodiment, there is provided a pharmaceutical composition
25 in the form of a capsule comprising an immediate release blend of atorvastatin and a sustained release tablet of niacin.

According to another embodiment, there is provided a process for the preparation of a capsule pharmaceutical composition comprising atorvastatin or pharmaceutically acceptable salts thereof and niacin, comprising the steps of:

- 5 a) blending niacin with a sustained release polymer and one or more pharmaceutically acceptable excipients;
- b) optionally, granulating the blend of step a);
- c) lubricating the blend of step a) or granules of step b);
- d) compressing the blend of step c) into suitable size tablet;
- e) coating tablet of step d);
- 10 f) blending atorvastatin and one or more pharmaceutically acceptable excipients;
- g) optionally, granulating the blend of step f);
- h) lubricating the blend of step f) or granules of step g);
- i) filling the niacin tablet of step e) and atorvastatin blend of step h) into a capsule.

- 15 Granules can be prepared by dry granulation or wet granulation. Wet granulation may be carried out using granulating fluid or binder solution. Dry granulation may be carried out by roller compaction or slugging.

The solvent used for granulation and coating may be selected from water, alcohols like methyl alcohol, ethyl alcohol or isopropyl alcohol, acetone, and mixture thereof.

- 20 The following examples illustrate the invention but do not limit the scope of the invention.

EXAMPLEExample 1:

Atorvastatin Tablets

Ingredients	Qty/tablet (mg)
Atorvastatin calcium	10.90
Calcium carbonate	7.50
Lactose monohydrate	50.00
Microcrystalline cellulose	66.60
Croscarmellose sodium	4.50
HPC-L	3.00
Polysorbate-80	1.50
Purified water	q.s
Croscarmellose sodium	4.50
Magnesium stearate	1.50
Total weight	150.00
Opadry white	4.50

5 Niacin Tablets

Ingredients	Qty/tablet (mg)
Niacin	500.00
Hydroxypropyl methylcellulose	110.00
Polyvinyl pyrrolidone	10.00
Purified water	q.s
Stearic acid	5.00
Total weight	625.00

I. Preparation of atorvastatin tablets

- a) atorvastatin calcium, calcium carbonate, lactose monohydrate, microcrystalline cellulose and croscarmellose sodium were sifted and blended together.
- 10 b) polysorbate-80 was dissolved in purified water.
- c) HPC-L was added to the solution of step b).
- d) blend of step a) was granulated with solution of step c).
- e) granules of step d) were dried and sifted.
- f) extragranular croscarmellose sodium and magnesium stearate were sifted and
15 added to granules of step e).

g) blend of step f) was then compressed into suitable size tablet.

h) tablet of step g) was coated using aqueous dispersion of Opadry.

II. Preparation of niacin tablets

5 a) niacin, hydroxypropyl methylcellulose and polyvinyl pyrrolidone were sifted and blended together.

b) blend of step a) was granulated with purified water.

c) granules of step b) were dried, sifted and lubricated using stearic acid.

d) lubricated granules of step c) were compressed into suitable tablets.

III. Tablets of step I) and step II) were filled in to a capsule.

10 **Comparative Example 1**

Atorvastatin layer

Ingredients	Qty/tablet (mg)
Atorvastatin calcium	10.90
Calcium carbonate	7.50
Lactose monohydrate	50.00
Microcrystalline cellulose	66.69
Croscarmellose sodium	4.50
HPC-L	3.00
Polysorbate-80	1.50
Purified water	q.s
Croscarmellose sodium	4.50
Magnesium stearate	1.52
OrangeLake	0.01
Total weight	150.00

Niacin layer

Ingredients	Qty/tablet (mg)
Niacin	500.0
Hydroxypropyl methylcellulose	57.5
Polyvinyl pyrrolidone	17.0
Purified water	q.s
Hydroxypropyl methylcellulose	120.0
Stearic acid	7.0
Tablet weight	701.5

Procedure:**I. Preparation of atorvastatin blend**

- a) atorvastatin calcium, calcium carbonate, lactose monohydrate, microcrystalline cellulose and croscarmellose sodium were sifted and blended together.
- 5 b) polysorbate 80 was dissolved in purified water.
- c) HPC-L was added to the solution of step b).
- d) Blend of step a) was granulated with solution of step c).
- e) granules of step d) were dried and sifted.
- 10 f) extragranular croscarmellose sodium and magnesium stearate were sifted and added to granules of step e).

II. Preparation of niacin blend

- a) niacin, hydroxypropyl methylcellulose and polyvinyl pyrrolidone were sifted and blended together.
- b) blend of step a) was granulated with purified water.
- 15 c) granules of step b) were dried and sifted.
- d) hydroxypropyl methyl cellulose and stearic acid was added to granules of step c).

III. Blend of atorvastatin step I and blend of niacin step II were compressed into a bilayer tablet.

We Claim:

1. A pharmaceutical composition of atorvastatin and niacin comprising
 - a) an immediate release component containing atorvastatin or pharmaceutically acceptable salts thereof; and
 - b) a sustained release component containing niacin;wherein the two components are not in intimate contact with each other.
2. The pharmaceutical composition according to claim 1 wherein pharmaceutical composition is a tablet or a capsule.
3. The pharmaceutical composition according to claim 2 wherein the tablet is a trilayered tablet or a coated tablet.
4. The pharmaceutical composition according to claim 2 or 3 wherein the tablet is coated.
5. The pharmaceutical composition according to claim 3 wherein the coated tablet is an inlay tablet or a compression coated tablet.
6. The pharmaceutical composition according to claim 2 wherein the capsule comprises an immediate release tablet containing atorvastatin and a sustained release tablet containing niacin
7. The pharmaceutical composition according to claim 1 wherein the pharmaceutical composition comprised pharmaceutically acceptable excipient selected from the group consisting of sustained release polymers, surfactants, stabilizers, binders, diluents, lubricant/glidant, disintegrants, and coloring agents.
8. The pharmaceutical composition according to claim 7 wherein the sustained release polymer is selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose and sodium carboxymethyl cellulose or mixture thereof.
9. The pharmaceutical composition according to claim 6 wherein the pharmaceutical composition is prepared by a process comprising the steps of:
 - I. Preparation of atorvastatin component
 - a) blending atorvastatin with one or more pharmaceutically acceptable excipients;

- b) optionally, granulating the blend of step a);
- c) compressing the blend of step a) or granules of step b) into a suitable size tablet;
- d) coating the tablet of step c);

II. Preparation of niacin component

- a) blending niacin with a sustained release polymer and one or more pharmaceutically acceptable excipients;
- b) optionally, granulating the blend of step a);
- c) compressing the blend of step a) or granules of step b) into a suitable size tablet;

III. Filing atorvastatin component and niacin component into a capsule.

10. The pharmaceutical composition according to claim 5 wherein the inlay tablet is prepared by a process comprising the steps of:

I. Preparation of atorvastatin component

- a) blending atorvastatin with one or more pharmaceutically acceptable excipients;
- b) optionally, granulating the blend of step a);
- c) compressing the blend of step a) or granules of step b) into a suitable size tablet;
- d) coating the tablet of step c); and

II. Preparation of niacin component

- a) blending niacin with a sustained release polymer and one or more pharmaceutically acceptable excipients;
- b) optionally, granulating the blend of step a);

III. Compressing the blend or granules of step ii) over the tablet of step i) to form an inlay tablet.

11. The pharmaceutical composition according to claim 5 wherein the compression coated tablet is prepared by a process comprising the steps of:

- a) Blending atorvastatin and one or more pharmaceutically acceptable excipients;
 - b) optionally, granulating the blend step a);
 - c) lubricating the blend of step a) or granules of step b);
 - d) blending niacin with a sustained release polymer and one or more pharmaceutically acceptable excipients;
 - e) optionally, granulating the blend of step d);
 - f) lubricating the blend of step d) or granules of step e);
 - g) compressing the blend of step f) into suitable size tablet;
 - h) coating the tablet of step g);
 - i) compressing the atorvastatin blend of step c) and niacin tablet of step h) to form a compression coated tablet.
12. The pharmaceutical composition according to claim 4 wherein said pharmaceutical composition is prepared by a process comprising the steps of:
- a) blending atorvastatin with other pharmaceutically acceptable excipients;
 - b) optionally, granulating the blend of step a);
 - c) lubricating the blend of step a) or granules of step b);
 - d) blending niacin with a sustained release polymer and other pharmaceutically acceptable excipients;
 - e) optionally, granulating the blend of step d);
 - f) lubricating the blend of step d) or granules of step e);
 - g) blending pharmaceutically acceptable excipients for inert layer;
 - h) compressing the blend of step c), f) and step g) into trilayer tablet;
 - i) optionally, coating the compressed tablets.
13. The pharmaceutical composition according to claim 1 for the treatment hypercholesterolemia and dyslipidemia.