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(54) Title: PHARMACEUTICAL COMPOSITION

(57) **Abstract:** The invention relates to a pharmaceutical composition comprising a core containing a HMG- CoA reductase inhibitor, and a film coating surrounding the core. In an embodiment, the core is substantially devoid of any binder, diluent or filler, which allows the composition to be made in relatively small size (eg unit dose of 200 mg) without compromising the dissolution properties of the composition. The invention also provides a method of manufacturing the pharmaceutical composition, and the therapeutic use of the composition.



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Pharmaceutical Composition

Technical field:

The present invention relates to a pharmaceutical composition comprising cholesterol lowering
5 agents, its process of preparation and use thereof.

Background:

Cholesterol is a chemical that can both benefit and harm the body. On the good side, cholesterol
plays important roles in the structure of cells and in the production of hormones. But too much
10 cholesterol in the blood can lead to heart and blood vessel disease. One type, of cholesterol
called high-density lipoprotein (HDL) cholesterol, or "good cholesterol," actually lowers the
risk of these problems but the other type, low-density lipoprotein (LDL) cholesterol, or "bad
cholesterol," is the type that threatens people's health.

15 Many factors may contribute to the fact that some people have higher cholesterol levels than
others. And some people have inherited disorders that prevent their bodies from properly using
and eliminating fats. This allows cholesterol to build up in the blood.

Treatment for high cholesterol levels usually begins with changes in daily habits. However,
some may need to use cholesterol-reducing drugs to reduce their risk of health problems.
20 Cholesterol-reducing drugs are medicines that lower the amount of cholesterol (a fat-like
substance) in the blood.

There are different types of cholesterol reducing agents that can be used .One such type is
HMG-CoA reductase inhibitors, often called "statins"; these are drugs that block an enzyme
called "3-hydroxy-3-methyl-glutaryl-coenzyme A reductase." This blocks one of the steps in
25 converting fat to cholesterol. These are the most effective cholesterol lowering agents available
and in recent years have received increased attention for their benefits beyond helping patients
with high cholesterol. Drugs in this group include: atorvastatin; cerivastatin; fluvastatin;
lovastatin; pravastatin; simvastatin; and rosuvastatin.

Formulations of various statins are available in the market. Most of them are in the form of tablets. But the drawback of these tablets is that as the strength of the tablet increases so does the size of the tablet: thus, a tablet containing 80mg of the active has a tablet weight of 800mg. Such large tablets are not acceptable from the patient compliance point of view since it may be
5 difficult for the geriatric or paediatric patients to swallow.. Hence there is a need to manufacture tablets having smaller size. But it has been observed that when the smaller tablets are manufactured according to the prior art process by reducing the tablet weight they have exhibited poor performance, because the dissolution of the smaller tablets is delayed, thereby delaying the availability of the medicament to the patient.

10

Thus there remains a need to provide tablets that are acceptable from the patient compliance point of view without affecting the performance of the tablet. The present invention provides a solution to the above problem of the prior art.

15 **Object:**

The object of the present invention is to provide a cholesterol lowering oral dosage composition having smaller size and lower unit dose weight than conventional tablets, in order to make it easier for patients to swallow, without compromising on efficacy and bio availability.

20 **Summary:**

We have unexpectedly found that the dissolution properties of a pharmaceutical composition containing a HMG-CoA reductase inhibitor can be improved by careful control of the manufacturing process to yield a novel pharmaceutical composition, which has a smaller size than has been practical in the prior art. This can be achieved by coating particles of the active
25 material prior to mixing the particles without adding any significant amount of binder, filler or diluent, and, in particular, without adding any significant amount of lactose to the particles themselves. The binder, filler and/or diluent can be placed in a carrier for the coated particles.

Broadly, the present invention provides an improved pharmaceutical composition comprising HMG-CoA reductase inhibitor(s). Such a pharmaceutical composition is useful in the treatment of conditions requiring the reduction of cholesterol.

- 5 The invention also provides a method of manufacturing a pharmaceutical composition according to the present invention.

Brief Description of the Drawings

- 10 Reference is now made to the accompanying drawings in which:

Fig. 1 is a schematic drawing of a tablet comprising a pharmaceutical composition according to the invention; and

- 15 Fig. 2 is a schematic drawing of an exemplary particle forming part of a pharmaceutical composition according to the invention.

Detailed Description of the Invention:

- Statin drugs are currently the most therapeutically effective drugs available for reducing the
20 level of LDL in the blood stream of a patient at risk for cardiovascular disease. This class of drugs includes lovastatin, simvastatin, pravastatin, compactin, fluvastatin and atorvastatin.

- According to the present invention various statins or HMG CoA reductase inhibitors that can be used including lovastatin, simvastatin, pravastatin, mevastatin, fluvastatin, cerivastatin,
25 pitavastatin, rosuvastatin, atorvastatin and combinations thereof. The preferred HMG CoA reductase inhibitor is simvastatin. The various available salts, solvates, derivatives, prodrugs, enantiomers, racemic mixtures, polymorphs thereof of the various HMG CoA reductase inhibitors mentioned above may be used.

The term HMG CoA reductase inhibitors and the various statins are mentioned in the description as well as the claims in a broad sense to include not only HMG CoA reductase inhibitors and the various statins per se but also their salts, solvates, derivatives, prodrugs, enantiomers, racemic mixtures, polymorphs thereof.

5

As described in the prior art, the problem with the existing dosage forms is that they are of a larger unit dose weight, especially for the unit dosages with higher strengths of the drug and this is undesirable from the patient compliance point of view. Further if the unit dose weight, for example, the tablet weight of the prior art tablets is reduced it results in a tablet that delays
10 disintegration, thus delaying dissolution and eventually delaying the availability of the medicament to the patient in need. Thus there is need of a formulation that is of smaller size, but does not delay the availability of the medicament to the patient in need.

According to the USP, for example, the simvastatin tablets should exhibit dissolution of not less
15 than 75% (Q) in 30 minutes (which is equivalent to 80% within 30 minutes). But it has been observed that the prior art tablets with reduced tablet weight fail the dissolution test according to the USP.

Surprisingly the inventors of the present invention have observed that the smaller tablets
20 manufactured according to the present invention have shown a dissolution profile which complies with the USP standard and thus the present invention has succeeded in solving the problems addressed in the prior art.

The present invention provides a pharmaceutical composition comprising coated HMG-CoA
25 reductase inhibitor(s) that is of smaller size and does not delay the dissolution.

Simvastatin is the common medicinal name of the chemical compound Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1 S-[1alpha,3alpha,7beta,8beta(2 S*,4
30 S*),8beta]]

Atorvastatin is the common medicinal name of the chemical compound [R-(R*, R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

5

Fluvastatin is the common medicinal name of the chemical compound [R*, S*-(E)]-($\pm$)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid.

Lovastatin is the common medicinal name of the chemical compound [1 S -[1 α (R*), 3 α , 7 β , 8 β (2 S*, 4 S*), 8 $\alpha\beta$]]-2-methylbutanoic acid 1,2,3, 7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2 H -pyran-2-yl)ethyl]-1-naphthalenyl ester

Pravastatin sodium is the common medicinal name of the chemical compound [1S-[1 α (β S*, δ S*), 2 α , 6 α , 8 β (R*), 8 $\alpha\alpha$]]-1,2,6,7,8,8a-hexahydro- β , δ , 6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)- 1-Naphthaleneheptanoic acid monosodium salt.

Rosuvastatin is the common medicinal name of the chemical compound bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl]](3R,5S)-3,5-dihydroxyhept-6-enoic acid]

20

Cerivastatin is the common medicinal name of the chemical compound [S-[R*, S'-(E)] -7-[4-(4-b fluorophenyl)-5-methoxymethyl)- 2,6bis(l-met ylethyl) 3-pyridinyl]-3,5-dihydroxy+ heptenoate

25 Mevastatin is the common medicinal name of the chemical compound [1 S -[1 α (R*), 7 β , 8 β (2 S*, 4 S*), 8 $\alpha\beta$]]-2-Methylbutanoic acid 1,2,3, 7,8,8a-hexahydro-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2 H -pyran-2-yl)ethyl]-1-naphthalenyl ester

Tablets comprising statins are generally made by mixing statins with excipients (inactive 30 ingredients) and compressing the mixture into tablets on a tablet press. Among ingredients most

commonly used as fillers and binders in pharmaceutical tablets are lactose (which may be either anhydrous lactose or lactose monohydrate) and cellulose. They are considered to be binders as well as fillers, because they usually enable compression into hard tablets, if they are the predominant ingredients.

5

According to the present invention there is provided a formulation having particles of coated HMG-CoA reductase inhibitor(s). The coated granules so obtained are then further mixed with other pharmaceutically acceptable excipients. The formulation is such that its final unit dose weight is preferably less than 800 mg, more preferably 150 – 400 mg, or 200 to 400 mg. The
10 smaller dosage units so manufactured do not exhibit problems with dissolution.

According to one aspect of the invention there is provided a pharmaceutical composition comprising a plurality of particles comprising a core of a HMG-CoA reductase inhibitor coated with a film, said particle core containing less than 10 wt% filler, binder and/or diluent, and said
15 particles being dispersed in a pharmaceutically acceptable carrier. Preferably, said particle core contains less than 5 wt% filler, binder and/or diluent, and most preferably said particle core contains substantially no filler, binder and/or diluent.

It is most preferred that the particle core contains substantially no filler, binder and diluent.
20

In an embodiment, the particle core contains substantially no other material except the active material, i.e., the HMG-CoA inhibitor, particularly simvastatin. However, we prefer that the core includes at least one other excipient, in particular an antioxidant. We also prefer that the core includes a lubricant and/or glidant.

25

According to another aspect of the invention there is provided a pharmaceutical composition comprising a plurality of particles comprising a core of a HMG-CoA reductase inhibitor coated with a film, said core containing less than 10 wt% lactose, and said particles being dispersed in a pharmaceutically acceptable carrier. Preferably, said core contains less than 5 wt% lactose,
30 and most preferably said core contains substantially no lactose.

It is preferred that the core contains less than 10% microcrystalline cellulose, more preferably less than 5% microcrystalline cellulose, and most preferably substantially no microcrystalline cellulose.

- 5 It is preferred that the core contains less than 10% hydroxypropyl cellulose, more preferably less than 5% hydroxypropyl cellulose, and most preferably substantially no hydroxypropyl cellulose.

It is preferred that the core contains less than 10% hydroxypropyl methylcellulose, more
10 preferably less than 5% hydroxypropyl methylcellulose, and most preferably substantially no hydroxypropyl methylcellulose.

In this specification the term "lactose" is used to refer equally to lactose anhydrous, lactose monohydrate and mixtures thereof. The term is also used to refer equally to α -lactose, β -
15 lactose and mixtures thereof. Further information about the grades of lactose is available in "Handbook of Pharmaceutical Excipients", Ed R..C. Rowe, 4th Edition, pages 323 to 332.

According to another aspect of the invention there is provided a pharmaceutical composition comprising a plurality of particles comprising a core of a HMG-CoA reductase inhibitor coated
20 with a film, said core containing at least 50% of said HMG-CoA reductase inhibitor, and said particles being dispersed in a pharmaceutically acceptable carrier.

Preferably, said core contains at least 60 wt% of said HMG-CoA reductase inhibitor. More preferably, said core contains from 60 to 70 wt% of said HMG-CoA reductase inhibitor. Most
25 preferably said core contains from 65 to 70wt% of said HMG-CoA reductase inhibitor.

It is preferred that said pharmaceutical composition contains at least 15 wt% of said HMG-CoA reductase inhibitor. More preferably, said pharmaceutical composition contains at least 20 wt% of said HMG-CoA reductase inhibitor. Still more preferably, said pharmaceutical composition
30 contains at least 30 wt% of said HMG-CoA reductase inhibitor. Still more preferably, said

pharmaceutical composition contains from 30 to 50 wt% of said HMG-CoA reductase inhibitor. Most preferably, said pharmaceutical composition contains from 35 to 45 wt% of said HMG-CoA reductase inhibitor, with 40 wt% of said of said HMG-CoA reductase inhibitor being especially preferred.

5

According to another aspect of the invention there is provided a pharmaceutical composition comprising a plurality of particles consisting of a core of a HMG-CoA reductase inhibitor in combination with one or more antioxidants, and, optionally one or more lubricants and/or glidants, said core being coated with a film, and said particles being dispersed in a
10 pharmaceutically acceptable carrier. Thus, in this aspect of the invention, the film coated particles contain a core of the active material, in combination with the antioxidant(s) and the optional lubricant(s)/glidant(s), and substantially nothing else.

If desired, the lubricant and/or glidant may be the same material.

15

The pharmaceutical compositions according to the invention are obtainable by mixing the particle ingredients to form particles; coating the particles; and mixing the coated particles with the carrier.

20 The pharmaceutical composition according to the invention may be formulated as various dosage forms but it is preferably formulated as a tablet, capsule, dry syrup for suspension, sachet.

In another aspect of the present invention there is provided a dosage unit preferably comprising from 5 mg to 80 mg, of simvastatin or any suitable HMG - CoA reductase inhibitor and
25 preferably a dosage amount selected from 10 mg, 20 mg, 40 mg and 80 mg. As mentioned above simvastatin is the preferred HMG-CoA reductase inhibitor and it may be used with advantage in these quantities.

Further the total weight of the single dosage unit may be dose similar for all strengths.

According to the present invention the film coating preferably comprises one or more polymers. Suitable polymers include, for example, comprise hydroxypropyl methyl cellulose (HPMC or hypromellose), hydroxypropyl cellulose (HPC), and other cellulose derivatives; polyvinyl pyrrolidone (PVP); polyvinyl acetate (PVA); gelatin; or a mixture thereof. Suitably the
5 polymers may be present in a range of 1 to 15% w/w of the total weight of the pharmaceutical composition. The preferred polymer is HPMC.

In addition, the coating may further include one or more antioxidants. The antioxidant(s) in the coating may be the same as, or different from, the antioxidant(s) in the particles.

10

The antioxidant provided in the particles and/or coating may comprise, for example, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, citric acid, malic acid, sodium ascorbate, sodium metabisulphite, or a mixture thereof. The preferred antioxidants are BHA, ascorbic acid and citric acid.

15

The pharmaceutically acceptable carrier contains one or more pharmaceutically acceptable excipients, including one or more diluents, one or more binders, one or more disintegrants, and/or one or more lubricants/glidants.

Suitable diluents may include, for example, calcium phosphate-dibasic, calcium sulfate,
20 cellulose-microcrystalline, cellulose powdered, dextrans, dextrans, dextrose excipients, fructose, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and equivalents thereof, and mixtures thereof. Suitably the diluents may be present in a quantity ranging from 15 to 90% w/w of the total weight of the pharmaceutical composition. The preferred diluent is microcrystalline cellulose.

25 Suitable binders may include, for example, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, polyvinyl alcohol, pullulan, starch, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, alginate and other cellulose derivatives and equivalents thereof, and mixtures thereof. Suitably the binders may be present in a quantity ranging from 1 to 15% w/w of the total weight of the

pharmaceutical composition. The preferred binders are hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone and mixtures thereof.

Suitable disintegrants may include, for example, hydroxypropyl cellulose, carboxymethylcellulose, calcium carboxymethylcellulose, sodium carboxymethylcellulose, 5 croscarmellose sodium, starch, crystalline cellulose, sodium starch glycolate, hydroxypropyl starch, partly pregelatinized starch, crospovidone and equivalents thereof, and mixtures thereof. Suitably the disintegrants may be present in a quantity ranging from 5 to 20% w/w of the total weight of the pharmaceutical composition. The preferred disintegrant is croscarmellose sodium.

10 Suitable lubricants/glidants may include, for example, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, colloidal silicon dioxide and equivalents thereof, and mixtures thereof. Suitably the lubricants may be present in a quantity ranging from 0.5 to 5% w/w of the total weight of the pharmaceutical composition. The preferred lubricant/glidants are magnesium stearate and 15 colloidal silicon dioxide.

Optionally the pharmaceutical composition may also include coloring agents, which would normally be provided in the carrier..

The invention also provides a method of manufacturing a pharmaceutical composition according to the present invention.

20

In a further aspect of the present invention particles containing an HMG- CoA reductase inhibitor and other optional excipients, such as one or more antioxidants, are coated, preferably using one or more polymers. Optionally one or more antioxidant may also be added to the coating agent.. The particles may be coated using suitable coating techniques known in the art.

25

The particles of HMG CoA reductase inhibitor and optionally excipients may also be granulated using techniques known in the art, prior to coating.

The coated granules so obtained are further mixed with suitable excipients and filled in capsules, sachets or may be compressed to form tablets.

5 As discussed above the total weight of the pharmaceutical dosage unit can be varied as desired, for reasons of practicability it may be preferable for the total weight of a single oral dosage unit to be less than 800mg, more preferably less than 700mg, still more preferably less than 600mg, We prefer that the total weight for a unit dosage of the tablet is preferably at least 150 mg, more preferably at least 200 mg. Thus, the weight of the dosage unit preferably ranges from 150 mg
10 to less than 800 mg, more preferably from 150 mg to 400 mg, and most preferably from 200 - 400mg. We prefer that the total amount of active material, especially simvastatin, in the dosage unit is from 20-40 wt%. More preferably the amount of the active material, especially simvastatin, is from 40 to 80 mg, and most preferably the amount of the active material is 40 mg or 80 mg; the total weight of the dosage unit is preferably from 150 to 400 mg, more
15 preferably from 200 - 400 mg.

The formulation of the present invention preferably exhibits dissolution of at least 80 % by weight of the pharmaceutical composition in about 30 minutes

20 The present invention further comprises a method of treatment which method comprises administering a pharmaceutical composition according to the present invention to person in need of reducing the cholesterol.

In the embodiments described above, the particle core does not include an binder, diluent or
25 filler, in particular lactose. It is preferred that the particle coating does not contain any of these materials either.

In a particularly advantageous embodiment, the pharmaceutical composition comprises a plurality of particles comprising a core of a HMG-CoA reductase inhibitor coated with a film,
30 said particles being dispersed in a pharmaceutically acceptable carrier, wherein the core

contains substantially no binder, filler or diluent, while the carrier contains one or more of a binder, a filler or a diluent. In particular, it is preferred that the core contains substantially no lactose, and that the carrier does contain lactose. It is especially preferred that the core contains the HMG-CoA reductase inhibitor in combination with one or more antioxidants, and one or more optional lubricants and/or glidants, and substantially nothing else. The core preferably contains 60-70 wt% of the HMG-CoA reductase inhibitor, and the composition preferably comprises 30 to 50 wt% of the HMG-CoA reductase inhibitor. The HMG-CoA reductase inhibitor is preferably simvastatin. The pharmaceutical composition is preferably provided in a unit dosage form having a total weight from 150 to 400 mg, or from 200 to 400 mg.

10

Referring to Fig. 1, a pharmaceutical composition according to the invention is provided in the form of a tablet 10. The tablet 10 comprises a plurality of particles 12 dispersed in a pharmaceutically acceptable carrier 14. The carrier 14 comprises one or more pharmaceutically acceptable excipients, such as one or more binders, one or more diluents, one or more disintegrants, one or more lubricants/glidants and one or more colorants.

15

The particles are shown in more detail in Fig. 2. Each particle 12 comprises a core 16 containing a HMG-CoA reductase inhibitor, especially simvastatin, surrounded by a film coating 18. The film coating 18 is a polymer film coating. The particle core does not contain any binder, diluent or filler, in particular lactose. It may, however, contain one or more antioxidants or one or more lubricants or one or more glidants. The coating 18 may also, or instead contain one or more antioxidants.

20

It will be clear from the foregoing that the present invention makes it possible to produce small tablets containing relatively large amounts of the active material, without prejudicing the dissolution properties of the pharmaceutical composition. In the prior art, the active material forms only a small percentage, e.g. typically 10 wt% or less, of the total weight of the composition, which means that very large tablets are required in order to produce unit dosage forms containing large amounts of the active material, such as 40 mg or 80 mg simvastatin. The present invention provides a method of making a pharmaceutical composition which solves this

30

problem, and allows the active material to be present as a relatively large percentage of the composition. The invention also provides new and useful pharmaceutical compositions. The objects of the invention are achieved in the preferred embodiment by coating particles of the active material prior to mixing the particles with excipients such as binders, fillers and diluents,
 5 in particular lactose and microcrystalline cellulose.

It should be noted that the drawings are not to scale, and are not intended to indicate the relative sizes or amounts of the various components.

10 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 invention.

Comparative Example 1

Ingredients	Qty (mg/tab)
Dry mix	
Simvastatin	80
Lactose monohydrate	526.6
Pregelatinized starch	80
Ascorbic acid	20
Microcrystalline cellulose	40
Binder	
Citric acid monohydrate	10
Lactose monohydrate	15
Purified water	q.s.
Extragranular	
Butylated hydroxy anisol	0.4
Pregelatinized starch	20
Magnesium stearate	8
Total	800

15

This is a composition from the prior art comprising an 800 mg tablet. The tablet was formed according to the following process steps:

14

Sift the simvastatin, lactose monohydrate, pregelatinized starch, ascorbic acid and microcrystalline cellulose through suitable sieves.

Load the above materials into a rapid mixer granulator.

Prepare the binder solution by dissolving lactose monohydrate and citric acid monohydrate in water.

Add the binder solution in to the dry mix in the rapid mixer granulator and prepare granules of proper consistency.

Dry the wet mass in a fluid bed dryer and sift the dried mass through suitable screen through multimill.

Sift the butylated hydroxy anisol, pregelatinized starch and magnesium stearate through suitable sieves.

Mix the dried granules, the butylated hydroxy anisol and the pregelatinized starch in octagonal blender.

Add the magnesium stearate to it and mix again in octagonal blender.

Compress the blend into tablets..

The dissolution data were as follows:

Time interval (min)	Drug release
10	78.4
15	94.6
20	99.8
30	100.1

The dissolution data were based on Dissolution: USP Type II / 900 ml 0.5% SLS in 0.01M NaH₂PO₄ / 50 RPM

This prior art tablet has a dissolution of 100% within a time of 30 minutes. Although the dissolution rate is satisfactory, the composition suffers from the disadvantage of a high mass.

Comparative Example 2**Simvastatin Tablets 80 mg**

Ingredients	Qty (mg/tab)
Dry mix	
Simvastatin	80
Lactose monohydrate	47.6
Pregelatinized starch	20
Ascorbic acid	20
Microcrystalline cellulose	10
Binder	
Citric acid monohydrate	10
Hypromellose 6 cps	5
Purified water	q.s.
Extragranular	
Butylated hydroxy anisol	0.4
Pregelatinized starch	5
Magnesium stearate	2
Total	200

This is a composition comprising a 200 mg tablet. The tablet was formed according to the
5 following process steps:

Sift the simvastatin, lactose monohydrate, pregelatinized starch, ascorbic acid and microcrystalline cellulose through suitable sieves.

Load the above materials into a rapid mixer granulator.

10 Prepare the binder solution by dissolving hypromellose and citric acid monohydrate in water.

Add the binder solution in to the dry mix in rapid mixer granulator and prepare granules of proper consistency.

15 Dry the wet mass in a fluid bed dryer and sift the dried mass through suitable screen through multimill.

Sift the butylated hydroxy anisol, pregelatinized starch and mangesium stearate through suitable sieves.

16

Mix the dried granules, the butylated hydroxy anisol and the pregelatinized starch in octagonal blender.

Add the magnesium stearate to it and mix again in octagonal blender.

Compress the blend into tablets..

5

The dissolution data were as follows:

Time interval (min)	Drug release
10	12.2
15	32.7
20	51.4
30	79.0

The dissolution data were based on Dissolution: USP Type II / 900 ml 0.5% SLS in 0.01M
10 NaH₂PO₄ / 50 RPM

Although this is a small tablet, the dissolution data are less satisfactory. In particular, the dissolution rate does not meet the USP standard of not less than 75% (Q) in 30 minutes

Example 1:**Simvastatin Tablets 80 mg**

Ingredients	Qty (mg/tab)
Dry mix	
Simvastatin	80
Ascorbic acid	20
Butylated hydroxy anisol	0.4
Colloidal silicon dioxide	2
Binder	
Citric acid monohydrate	10
Hypromellose 6 cps	5
Purified water	q.s.
Extragranular	
Microcrystalline cellulose	24.6
Pregelatinized starch	40
Croscarmellose sodium	10
Colloidal silicon dioxide	4
Magnesium stearate	4
Total	200

This is an example of a composition in accordance with the invention. The tablet was formed
5 according to the following process steps:

Sift the simvastatin, butylated hydroxy anisol, ascorbic acid and colloidal silicon
dioxide through suitable sieves.

Load the above materials into a rapid mixer granulator.

10 Prepare the binder solution by dissolving hypromellose and citric acid monohydrate in
water.

Add the binder solution in to the dry mix in the rapid mixer granulator and prepare
granules of proper consistency.

15 Dry the wet mass in a fluid bed dryer and sift the dried mass through suitable screen
through multimill.

Sift the microcrystalline cellulose, pregelatinized starch croscarmellose sodium,
colloidal silicon dioxide and magnesium stearate through suitable sieves.

18

Mix the dried granules, microcrystalline cellulose, pregelatinized starch croscarmellose sodium, colloidal silicon dioxide in octagonal blender.

Add the magnesium stearate to it and mix again in octagonal blender.

Compress the blend into tablets.

5

The dissolution data were as follows:

Time interval (min)	Drug release
10	98.7
15	102.4
20	103.0
30	103.1

The dissolution data were based on Dissolution: USP Type II / 900 ml 0.5% SLS in 0.01M

10 NaH₂PO₄ / 50 RPM.

It will be seen that the composition according to the invention has improved dissolution over comparative example 2

Example 2

This is an example of a further pharmaceutical composition in accordance with the invention.

Sr. No	Ingredients	mg/tab
1.	Simvastatin	40.0
2.	Ascorbic acid	10.0
3.	BHA	0.2
4.	Colloidal silicon dioxide	1.0
5.	HPMC	2.5
6.	Citric acid monohydrate	5.0
7.	Water	qs
8.	Microcrystalline cellulose	122.6
9.	Croscarmellose sodium	10.0
10.	Colloidal silicon dioxide	4.0
11.	Magnesium stearate	4.0
12.	Iron oxide red	0.2
13.	Iron oxide yellow	0.2
	Total	200

5

Simvastatin, ascorbic acid, BHA, colloidal silicon dioxide were sifted. This was granulated with a solution of HPMC, citric acid monohydrate in water. The granules so formed were then mixed with rest of the ingredients. The resulting blend was then compressed to form tablet. It may also be filed in capsules if desired.

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It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and

variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be falling within the scope of the invention.

CLAIMS:

1. A pharmaceutical composition comprising a plurality of particles comprising a core of a HMG-CoA reductase inhibitor coated with a film, said particle core containing less than 10 wt% filler, binder and/or diluent, and said particles being dispersed in a pharmaceutically acceptable carrier.
2. A pharmaceutical composition according to claim 1, wherein said core contains less than 10 wt% lactose.
3. A pharmaceutical composition according to claim 1 or 2, wherein said core contains at least 50 wt% of said HMG-CoA reductase inhibitor.
4. A pharmaceutical composition according to claim 1, 2 or 3, wherein said core further comprises one or more antioxidants, and, optionally one or more lubricants and/or glidants.
5. A pharmaceutical composition according to claim 1, 2 or 3, wherein said core consists of a HMG-CoA reductase inhibitor in combination with one or more antioxidants, and, optionally one or more lubricants and/or glidants.
6. A pharmaceutical composition according to claim 1, 2 or 3, wherein said core contains substantially no other components other than the HMG-CoA reductase inhibitor.
7. A pharmaceutical composition comprising a plurality of particles comprising a core of a HMG-CoA reductase inhibitor coated with a film, said core containing less than 10 wt% lactose, and said particles being dispersed in a pharmaceutically acceptable carrier.
8. A pharmaceutical composition according to claim 7, wherein said core contains at least 50 wt% of said HMG-CoA reductase inhibitor.

9. A pharmaceutical composition according to claim 7 or 8, wherein said core further comprises one or more antioxidants, and, optionally one or more lubricants and/or glidants.
10. A pharmaceutical composition according to claim 7 or 8, wherein said core consists of a
5 HMG-CoA reductase inhibitor in combination with one or more antioxidants, and, optionally one or more lubricants and/or glidants.
11. A pharmaceutical composition comprising a plurality of particles comprising a core of a HMG-CoA reductase inhibitor coated with a film, said core containing at least 50% of said
10 HMG-CoA reductase inhibitor, and said particles being dispersed in a pharmaceutically acceptable carrier.
12. A pharmaceutical composition according to claim 11, wherein said core contains less than 10 wt% filler, binder and/or diluent.
- 15 13. A pharmaceutical composition according to claim 11 or 12, wherein said core contains less than 10 wt% lactose.
14. A pharmaceutical composition according to claim 11 12 or 13, wherein said core further
20 comprises one or more antioxidants, and, optionally one or more lubricants and/or glidants.
15. A pharmaceutical composition according to claim 11, 12 or 13, wherein said core consists of a HMG-CoA reductase inhibitor in combination with one or more antioxidants, and, optionally one or more lubricants and/or glidants.
- 25 16. A pharmaceutical composition comprising a plurality of particles consisting of a core of a HMG-CoA reductase inhibitor in combination with one or more antioxidants, and, optionally one or more lubricants and/or glidants, said core being coated with a film, and said particles being dispersed in a pharmaceutically acceptable carrier.

17. A pharmaceutical composition according to claim 16, wherein said core contains at least 50 wt% of said HMG-CoA reductase inhibitor.
18. A pharmaceutical composition according to any one of claims 1 to 5, or 12, wherein
5 said core contains less than 5 wt% filler, binder and/or diluent.
19. A pharmaceutical composition according to any one of claims 1 to 5 or 12, wherein said core contains contain substantially no filler, binder and/or diluent.
- 10 20. A pharmaceutical composition according to any one of claims 1 to 10 or 13, wherein said core contains contain less than 5 wt% lactose.
21. A pharmaceutical composition according to any one of claims 1 to 10 or 13, wherein said core contains contain substantially no lactose.
- 15 22. A pharmaceutical composition according to any preceding claim wherein said core contains at least 60 wt% of said HMG-CoA reductase inhibitor.
23. A pharmaceutical composition according to any preceding claim wherein said core
20 contains from 60 to 70 wt% of said HMG-CoA reductase inhibitor.
24. A pharmaceutical composition according to any preceding claim wherein said core contains from 65 to 70 wt% of said HMG-CoA reductase inhibitor.
- 25 25. A pharmaceutical composition according to any preceding claim, which contains at least 15 wt% of said HMG-CoA reductase inhibitor.
26. A pharmaceutical composition according to any preceding claim, which contains at least 20 wt% of said HMG-CoA reductase inhibitor.

27. A pharmaceutical composition according to any preceding claim, which contains at least 30 wt% of said HMG-CoA reductase inhibitor.
28. A pharmaceutical composition according to any preceding claim, which contains from
5 30 to 50 wt% of said HMG-CoA reductase inhibitor.
29. A pharmaceutical composition according to any preceding claim, which contains from 35 to 45 wt% of said HMG-CoA reductase inhibitor.
- 10 30. A pharmaceutical composition according to any preceding claim, wherein the HMG-CoA reductase inhibitor comprises lovastatin, simvastatin, pravastatin, mevastatin, fluvastatin, cerivastatin, pitavastatin, rosuvastatin, atorvastatin or a combination of two or more thereof.
31. A pharmaceutical composition according to any preceding claim, wherein the HMG-
15 CoA reductase inhibitor comprises simvastatin.
32. A pharmaceutical composition according to any preceding claim, wherein an antioxidant is provided in the film coating.
- 20 33. A pharmaceutical composition according to any one of claims 4, 5, 9, 10, 14 to 17 or 32, wherein the antioxidant comprises butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, citric acid, malic acid, sodium ascorbate, sodium metabisulphite, or a mixture of two or more thereof.
- 25 34. A pharmaceutical composition according to claim 33, wherein the antioxidant is butylated hydroxyanisole (BHA), ascorbic acid and citric acid, or a mixture of two or more thereof.

35. A pharmaceutical composition according to any preceding claim, wherein the film coating is present in an amount from 1 to 15% w/w of the total weight of the pharmaceutical composition.
- 5 36. A pharmaceutical composition according to any preceding claim, wherein the film coating comprises a polymer film coating.
37. A pharmaceutical composition according to claim 36, wherein the polymer film coating comprises a cellulose derivative, polyvinyl pyrrolidone (PVP), polyvinyl acetate (PVA),
10 gelatin, or a mixture of two or more thereof.
38. A pharmaceutical composition according to claim 37, wherein the cellulose derivative comprises hydroxypropyl methyl cellulose (HPMC) and/or hydroxypropyl cellulose (HPC).
- 15 39. A pharmaceutical composition according to any preceding claim, wherein the pharmaceutically acceptable carrier comprises a diluent, a binder, a disintegrant, and/or a lubricant/glidant.
40. A pharmaceutical composition according to claim 39, wherein the diluent is calcium
20 phosphate-dibasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrans, dextrans, dextrose excipients, fructose, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners or a mixture thereof.
41. A pharmaceutical composition according to claim 40, wherein the diluent is
25 microcrystalline cellulose.
42. A pharmaceutical composition according to claim 39, 40 or 41, wherein the diluent is present in an amount ranging from 15 to 90% w/w of the total weight of the pharmaceutical composition.

43. A pharmaceutical composition according to claim 39, 40, 41 or 42, wherein the binder is methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, polyvinyl alcohol, pullulan, starch, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, alginate or a mixture thereof.
- 5
44. A pharmaceutical composition according to claim 43, wherein the binder is hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, or a mixture thereof.
- 10 45. A pharmaceutical composition according to any one of claims 39 to 44, wherein the binder is present in an amount ranging from 1 to 15% w/w of the total weight of the pharmaceutical composition.
- 15 46. A pharmaceutical composition according to any one of claims 39 to 45, wherein the disintegrant is hydroxypropyl cellulose, carboxymethylcellulose, calcium carboxymethylcellulose, sodium carboxymethylcellulose, croscarmellose sodium, starch, crystalline cellulose, sodium starch glycolate, hydroxypropyl starch, partly pregelatinized starch, crospovidone, or a mixture thereof.
- 20 47. A pharmaceutical composition according to claim 46, wherein the disintegrant is croscarmellose sodium.
- 25 48. A pharmaceutical composition according to any one of claims 39 to 47, the disintegrant is present in an amount ranging from 5 to 20% w/w of the total weight of the pharmaceutical composition.
49. A pharmaceutical composition according to any one of claims 39 to 48, wherein the lubricants/glidant is stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, colloidal silicon dioxide or a mixture thereof.

50. A pharmaceutical composition according to claim 49, wherein the lubricant/glidant is magnesium stearate, colloidal silicon dioxide or a mixture thereof.
51. A pharmaceutical composition according to any one of claims 39 to 50, wherein the lubricant/glidant is present in an amount ranging from 0.5 to 5% w/w of the total weight of the pharmaceutical composition.
52. A pharmaceutical composition according to any preceding claim, which is provided in the form of a capsule, sachet or tablet.
53. A pharmaceutical composition according to claim 52, which is provided in the form of a tablet.
54. A pharmaceutical composition according to claim 52 or 53, wherein the pharmaceutical composition is provided as a unit dosage form having a total weight less than 800mg.
55. A pharmaceutical composition according to claim 52 or 53, wherein the pharmaceutical composition is provided as a unit dosage form having a total weight less than or equal to 400mg.
56. A pharmaceutical composition according to claim 52 or 53, wherein the pharmaceutical composition is provided as a unit dosage form having a total weight greater than or equal to 150 mg.
57. A pharmaceutical composition according to any one of claims 52 to 56, wherein the HMG-CoA reductase inhibitor is present in an amount from 5 to 80 mg.
58. A pharmaceutical composition according to any one of claims 52 to 56, wherein the HMG-CoA reductase inhibitor is present in an amount from 10 to 50 mg.
59. A pharmaceutical composition according to any one of claims 52 to 56, wherein the HMG-CoA reductase inhibitor is present in an amount from 20 to 40 mg.

60. A pharmaceutical composition according to any preceding claim, which exhibits a dissolution of at least 75%(Q) in 30 minutes.
61. A method of reducing cholesterol levels in a mammal comprising administering an effective amount of a pharmaceutical composition according to any preceding claim to a patient
5 in need thereof.
62. A method according to claim 61, wherein the mammal is a human.
63. The use of a pharmaceutical composition according to any preceding claim in therapy.
64. The use of a pharmaceutical composition according to any preceding claim to reduce the cholesterol level of a patient in need thereof.
- 10 65. The use of a pharmaceutical composition according to any preceding claim in the treatment of cardiovascular disorders.
66. A method of making a pharmaceutical composition according to any one of claims 1 to 60, comprising forming said particles containing a HMG-CoA reductase inhibitor, coating said particles with the film, and combining said particles with the pharmaceutically acceptable
15 carrier.
67. A method of making a pharmaceutical composition comprising forming particles of a HMG-CoA reductase inhibitor optionally in combination with one or more pharmaceutically acceptable excipients, said excipients not including a filler, binder and/or diluent; forming a film coating on said particles; and combining said coated particles with a pharmaceutically
20 acceptable carrier.
68. A method according to claim 67, wherein said particles are formed of a combination comprising said HMG-CoA inhibitor and an antioxidant.
69. A method according to claim 67 or 68, wherein said HMG-CoA reductase inhibitor is simvastatin.

70. A method according to claim 66, 67, 68 or 69 further comprising compressing the film coated particles with the carrier to form a tablet.

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Fig.1.

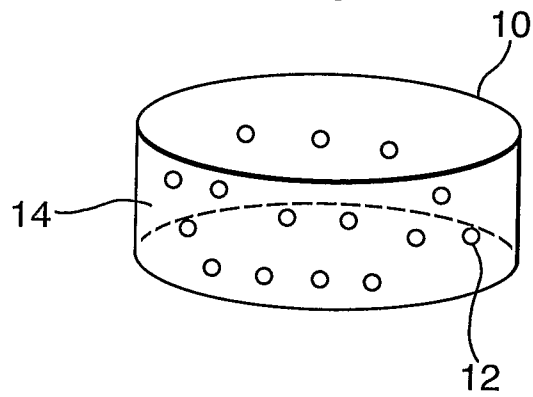


Fig.2.

