Pharmaceutical Compositions Comprising Fluvastatin

This invention is concerned with compositions, e.g. formulations for sustained release, of fluvastatin or a pharmaceutically acceptable salt thereof.

Fluvastatin is a member of a class of drugs commonly referred to as HMG CoA reductase inhibitors (sometimes called "statins"). The statins are used to reduce blood cholesterol levels in patients in need of such treatment. The site of action of the statins is the liver. Conventional rapid release forms of statins, e.g. which release the statin within about 2 hours have mild side effects associated with systemic delivery of the statin. The statins appear to enter systemic circulation because of the relatively high concentration of statin entering the liver in a relatively short space of time tends to flood the liver such that some of the statin is not metabolised on the first pass.

Fluvastatin may be used in the free acid form, in its ester form, or in form of a pharmaceutically acceptable salt. Such pharmaceutically acceptable salts include e.g. sodium salts, calcium salts, and ester salts. Fluvastatin sodium is preferably used.

Sustained release formulations have been suggested as a means of preventing or ameliorating the side effects associated with systemic entry of the statins - lovastatin, simvastatin and pravastatin (see EP 0 375 156).

Several methods of providing sustained release formulations have been proposed in the art. One such means is to use certain excipients in a matrix which modify the release of an active agent dispersed within said matrix. Hydroxypropyl methyl cellulose (HPMC) polymers have been suggested as release-modifying excipients, either alone or in combination with other materials, in sustained release formulations for use with a wide variety of active agents including the HMG CoA reductase inhibitors, see for example US 4,369,172, US 4,357,469, US 4,226,849 and US 4,389,393. It is thought that formulations containing HPMC polymers prolong drug release by forming a gelatinous matrix upon exposure to the aqueous medium of the stomach which prevents or delays ingress of the aqueous medium of the stomach into the dosage form and thereby preventing its rapid disintegration. The gel matrix is thought to form as a result of hydration of the HPMC polymer. However, the applicant could not find any suggestion that hydration of the HPMC occurred during storage of pharmaceutical compositions, e.g. oral dosage forms, containing HPMC. Furthermore, whether hydration occurs during storage or not, none of the aforementioned documents refer to any instability

problems associated with the use of HPMC and in particular colour instability.

The applicant was therefore surprised to find that pharmaceutical compositions comprising HPMC polymers formed gel-like domains upon storage over a prolonged period e.g. over more than 2 years which domains, still more surprisingly were highly coloured. Whereas this discolouration left the dosage forms with an unsightly, uneven mottled appearance, it was of no consequence for the safety and efficacy of the dosage forms. Nevertheless, the mottled appearance may be disturbing to patients and lead to poor patient compliance.

There is a need, therefore to provide pharmaceutical compositions of fluvastatin, e.g. for sustained release, which are colour-stable upon prolonged periods of storage, e.g. a storage over more than 2 years.

In accordance with the present invention there is provided pharmaceutical compositions, e.g. oral dosage forms, comprising fluvastatin, HPMC and optionally other pharmaceutical excipients which are colour-stable upon prolonged periods of storage, e.g. a storage over more than 2 years.

As used hereinabove, "colour-stable" used in connection with pharmaceutical compositions, e.g. oral dosage forms, is taken to mean said pharmaceutical composition in which the mottled discolouration hereinabove described is either substantially prevented or is present at levels not detectable by visual inspection, i.e. the mottled disclouration is either so faint as to be not apparent or it is capable of being masked by one or more excipients, e.g. colouring agents.

The presence of the gel-like domains may be detected by visual appearance alone. However, it may also be detected using known analytical techniques, for example microcalorimetry. Microcalorimetry may detect any heat flow, e.g. an exotherm as a result of excipient interactions, e.g. an exotherm associated with the hydration of HPMC. It is a characteristic of pharmaceutical compositions of the invention that they display a significant heat flow, i.e. a heat flow of greater than 5 micro Watts, e.g. up to 59 micro Watts, more particularly 19 to 59 micro Watts over a relatively long period of time, e.g. a period of 48 hours, when subjected to a stress test at 40 degrees centigrade and 75% relative humidity. The stress test may be carried out on an isothermal microcalorimeter (CSC Corporation, Provo. Utah) set to 40 degrees centigrade. The pharmaceutical composition may be subjected to an environment of 75% relative humidity, e.g. by preparing minihydrostats using a sodium chloride solution inside 250 microlitre polypropylene vial inserts.

As stated hereinabove, colour-stability may be achieved by substantially preventing or modulating the formation of HPMC gels. One means of achieving the object of colour stability may be to reduce the ambient moisture levels surrounding the pharmaceutical compositions during storage. Applicant has found that pharmaceutical compositions, e.g. oral dosage forms, stored under conditions such that the relative humidity does not exceed 75%, more preferably no more than 60%, e.g. 40 to 60% at a temperature of between 25°C and 40°C, display a markedly reduced tendency towards discolouration.

Accordingly, the present invention provides a method of preventing or substantially reducing the formation of gels of hydrated HPMC in pharmaceutical compositions comprising fluvastatin, HPMC and optionally other pharmaceutical excipients comprising the step of storing the pharmaceutical compositions at a relative humidity not exceeding 75% and at a temperature of between 25°C and 40°C.

The type of packaging employed may also reduce discolouration. Whereas conventional blister packaging may be employed, e.g. Triplex TPX blisters, it is preferred to use high density polyethylene (HDPE) bottles. Pharmaceutical compositions, e.g. oral dosage forms, as hereinabove described packaged in HDPE bottles may exhibit substantially no discolouration associated with the formation of HPMC gels. Pharmaceutical compositions, e.g. oral dosage forms, as hereinabove described packaged in HDPE bottles form another aspect of the present invention.

Pharmaceutical compositions, e.g. oral dosage forms, according to the invention may be formulated in any conventional form, e.g. powders, granules / granulates, capsules or tablets. Preferred pharmaceutical compositions may be in the form of tablets.
Pharmaceutical compositions, e.g. oral dosage forms, hereinabove described may be formed of a granulated mass comprising fluvastatin, HPMC and optionally other excipients commonly used in pharmaceutical composition, e.g. oral dosage forms, e.g. tablets. Surprisingly the applicant has found that the finer is the mean particle size of the granulated mass the less intense is the observed mottled disclouration. The applicant believes that the increased colour stability observed as the mean particle size is decreased may be due to the ability of the finer granules to form a tighter compact when compressed, thereby reducing the incidence and size of any voids in the compacted mass. As the HPMC gels are thought to form in these voids, the smaller their number and/or size, the less tendency there is for gels to form.

Preferred pharmaceutical compositions are tablets which are formed of granules having a mean granule particle size of less than about 200 microns, e.g. above 20 microns and less

than 125 microns, more particularly 100 to 125 microns, as determined by sieve analysis. However, the contribution to the art is the recognition of a correlation between granule size and the incidence and nature of the discolouration. It follows that the skilled artisan will understand that for different excipient mixtures, e.g. amounts of HPMC polymer, the incidence and nature of discolouration may vary within this preferred range, and in fact discolouration may be absent or visually insignificant outside of the aforementioned ranges. However, with no more than routine experimentation, the skilled person will be able to determine a suitable granule size for a given excipient mixture.

Granules as hereinabove described and pharmaceutical compositions, e.g. tablets made therefrom are further aspects of the present invention. Accordingly, the present invention provides for granules comprising fluvastatin, HPMC and optionally other pharmaceutical excipients and for pharmaceutical compositions comprising compressed granules comprising fluvastatin, HPMC and optionally other pharmaceutical excipients, wherein said granules have a mean granule particle size of less than about 200 microns, e.g. less than 125 microns, more particularly 100 to 125 microns.

In further aspect of the invention, it provides for a method of preventing or substantially reducing the formation of gels of hydrated HPMC in a pharmaceutical composition comprising a fluvastatin, HPMC and optionally other pharmaceutical excipients comprising the step of compressing granules comprising fluvastatin and HPMC, wherein said granules have a mean particle size of less than 200 microns.

In a further embodiment, applicants have found that the formation of gels of hydrated HPMC in granules as hereinabove described stored under conditions such that the relative humidity does not exceed 75%, more preferably no more than 60%, e.g. 40 to 60% at a temperature of between 25°C and 40°C, is prevented or substantially reduced. Granules are substantially colour-stable under these conditions. Accordingly, the present invention provides for a method of preventing or substantially reducing the formation of gels of hydrated HPMC in granules as hereinabove described comprising the step of storing the granules at a relative humidity not exceeding 75% and at a temperature of between 25°C and 40°C.

The reduction of moisture levels surrounding the granules or pharmaceutical compositions, e.g. oral dosage forms, upon storage and the use of fine granules as hereinabove described may be used alone or in combination to achieve the objects of the present invention.

As is clear from the definition provided above, granules and pharmaceutical compositions may be "colour-stable" notwithstanding that it may contain significant amounts of HPMC gel

such that the mottled discolouration would be quite apparent were it not for the presence of a colouring agent masking said discolouration.

Accordingly the invention provides in another of its aspects granules and pharmaceutical compositions comprising i) fluvastatin, HPMC and optionally other excipients, wherein the composition contains domains of HPMC gel, and ii) a colouring agent provided in sufficient amounts to mask any mottled discolouration associated with the HPMC gel domains.

Fluvastatin is known to exhibit a tendency towards photodegradation to give a highly coloured degradation product. Whereas this degradation is slight and has no consequence on the efficacy and safety of dosage forms containing fluvastatin, it is preferred to employ a colouring agent to mask any discolouration associated with this photo-degradation. However, as fluvastatin is typically dispersed essentially uniformly about granules or pharmaceutical compositions any discolouration of this type tends to be rather subtle and uniform. This subtle, dispersed discolouration may therefore be masked simply by using conventional colouring agents in relatively low amounts. This is fortunate, as the amounts of colouring agent, e.g. Iron oxides, that may be employed in pharmaceutical formulations are strictly controlled by regulatory authorities. For example in the case of iron oxide pigments, the amount of elemental iron acceptable for ingestion is currently set at 5 mg/day by the FDA.

However, in contrast to the discolouration associated with the photodegradation of fluvastatin, the discolouration associated with the formation of the HPMC gel tends to occur in discrete, random domains. The discolouration tends therefore to be more concentrated and therefore more intense, and patchy and as such is more difficult to mask. As such, conventional colouring agents employed in relatively small amounts do not provide adequate coverage.

The applicant was therefore faced with the problem of how to mask the unsightly, mottled appearance yet at the same time keeping the amount colouring agent, in particular iron-containing colouring material as small as possible.

Accordingly, the invention provides in another of its aspects granules and a pharmaceutical composition, e.g. an oral dosage form, comprising i) fluvastatin, HPMC and optionally other excipients, and ii) a coating wherein said coating comprises a colouring agent present in sufficient amounts to mask any mottled discolouration associated with the formation of HPMC gel.

The preceding paragraph provides that the colouring agent is contained in the coating. However, it is within the scope of the present invention that the colouring agent may be

employed in admixture with the active agent and other excipients. In such an embodiment a coating would be optional.

The colouring agent may be selected from any of those colouring agents known in the art, for example pigments, in particular any of the colouring agents known for use in pharmaceutical preparations are suitable for use in the present invention, see for example "Handbook of Pharmaceutical Excipients, 2nd Edition (1994), Eds. Wade and Weller", at pages 130-134. Suitable colouring agents include titanium dioxide, iron oxide (both ferrous and ferric), preferably Fe_2O_3 optionally in hydrated form. In a most preferred embodiment a combination of colouring agents may be used e.g. titanium dioxide and iron (II) oxide.

Having regard to the amount of colouring agent that may be employed in a unit dosage form, the maximum amount will be subject to the maximum daily limits of the given colouring agent permitted by regulatory authorities, and may vary below this limit according to the number of unit dosage forms to be taken per day, e.g. whether the dosage form is once- or twice-a-day, and the size of a given unit dosage form. With these considerations in mind, the skilled artisan would be able to determine an appropriate amount of colouring agent to effectively mask any mottled discolouration without undue burden. In a preferred embodiment the colouring agent may constitute up to 73% by weight based on the total weight of the coating, more particularly 17 to 30%, e.g. 22 to 25%. The percentages referred to represent the total colouring agent employed. I.e. the total colouring agent may be made composed of one colouring agent, e.g. iron (II) oxide, or a combination, e.g. titanium dioxide and iron (II) oxide.

Suitable coating materials include those materials conventionally used in coating tablets, granules and the like. Preferred coating materials are hydrophilic and permeable to, and/or at least to some extent soluble in, water and intestinal fluids. Any of the coating materials, in particular the elastic coatings described in the art are suitable for the purposes of the present invention.

Coating materials as hereinabove defined may be used in admixture with other excipients, conventional in coating formulations, for example talcum or silicon dioxide, for example synthetic amorphous silicic acid of the Syloid® type (Grace), for example SYLOID 244 FP, or wetting agents, for example the afore-mentioned polyethylene glycols or sorbates.

The coating materials may comprise additional excipients, for example plasticisers e.g. triethyl citrate, e.g. Citroflex® (Pfizer), triacetin, various phthalates, e.g. diethyl or dibutyl phthalate, mixed mono- or di-glycerides of the Myvacet® type (Eastman), for example MYVACET 9-40, the polyethylene glycols mentioned hereinbefore, for example having a

molecular weight of approximately from 6000 to 8000, and also ethylene oxide/propylene oxide block copolymers of the Pluronic® (BASF) or Syriperonic® (ICI) type, pulverulent mould release agents, for example magnesium trisilicate, starch or synthetic amorphous silicic acid of the SYLOID type, for example SYLOID 244 FP.

Coating weights employed in granules and pharmaceutical compositions according to the invention may vary within limits conventional in the art, and typically may be in the range of about 1 to about 4% by weight based on the total weight of the formulation, for example about 3% by weight.

In particularly preferred embodiments, for a 20 mg coated tablet the coat weight is about 2 to 2.5 mg, e.g. 2.44 mg; for a 40 mg coated tablet the coat weight is about 4.5 to 5.0 mg, e.g. 4.86 mg; for 80 mg coated tablets the coat weight is 9.5 to 10.0 mg, e.g. 9.75 mg; and for 160 mg coated tablets the coat weight is about 12.0 to 12.5 mg, e.g. 12.3 mg.

Granules and pharmaceutical compositions, e.g. oral dosage forms, according to the invention comprise but are not limited to any of the commercially available hydroxypropyl-methyl cellulose polymers that are suitable for the purpose of providing for sustained release of the active agent and include any of those materials referred to in EP 375156, US 4,369,172, US 4,357,469, US 4,226,849 and US 4,389,393 which are incorporated herein by reference.

A preferred HPMC polymer is available from Dow Corning under the trade name METHOCEL. Preferably the HPMC will have a hydroxypropyl (HP) degree of substitution of up to about 12, i.e. the HPMC will comprise up to about 12 percent HP functionality. More preferably the HPMC will have HP functionality of from 7 to 12 percent, most preferably 7 to 9 percent. The HPMC may have normal viscosity (2.0% HPMC in water) of from about 100 to 100,000 centipoise and a number average molecular weight of about 20,000 to about 170,000. A particularly preferred HPMC is METHOCEL K100LV, more preferably METHOCEL K100LVP CR, which has a number average molecular weight of about 20,000 to about 30,000. Methods of making such HPMC polymers are well known in the art.

HPMC polymers may be employed e.g. in amounts sufficient to ensure sustained release of the fluvastatin. By "sustained release" is meant that the fluvastatin is released from the pharmaceutical composition over an extended period of time, e.g. greater than about 6 hours. In a preferred pharmaceutical composition less than about 80% by weight of the fluvastatin is released in the first 8 hours after ingestion of the pharmaceutical composition, with the remaining fluvastatin being release thereafter. In more preferred compositions, less

than about 15 % by weight of the fluvastatin is released after 0.5 hour after ingestion, from about 10 to 50 % by weight is released within 2 hours after ingestion, and about 40 to 60% is released after 6 hours.

Preferably granules and pharmaceutical composition, e.g oral dosage forms, according to the invention comprise about 15 to about 50% by weight of HPMC based on the total weight of the composition, more preferably about 20 to 40%. The HPMC and a non-ionic hydrophilic polymer (discussed hereinbelow) preferably are present in a weight ratio of HPMC: non-ionic polymer of about 10:1 to about 3:1, more preferably 7:1 to 5:1, most preferably 6:1.

Whereas HPMC is a useful excipient to ensure sustained release of fluvastatin from pharmaceutical composition, applicant has found that conventional sustained release formulations containing HPMC alone as the rate-modifying excipient may nevertheless exhibit an initial drug burst or premature release of fluvastatin. By "premature release" is meant that a substantial amount of fluvastatin may be released in a short period of time after ingestion such that the amount of active agent delivered to the site of action is above the therapeutic level. Whereas this may not have any consequence for the efficacy of the drug substance there may be resultant toxic side effects associated with the greater than therapeutic dose. Surprisingly the applicant has discovered that the premature release may be avoided or ameliorated if the granules or pharmaceutical composition, e.g. oral dosage form, additionally comprises at least one non-ionic hydrophilic polymer.

Non-ionic hydrophilic polymers used in granules and pharmaceutical compositions according to the invention may be selected from the group consisting of hydroxyethylcellulose (HEC) having a number average molecular weight of from 90,000 to 1,300,000, preferably about 1,000,000 to about 1,300,000; hydroxypropyl cellulose (HPC) having a number average molecular weight of 370,000 to 1,500,000, preferably

850,000 to 1,500,000, more preferably 1,000,000 to 1,200,000 and poly(ethylene) oxide (PEO) having a number average molecular weight of about 100,000 to 500,000, preferably 150,000 to 300,000, more preferably 200,000.

Examples of HEC polymers are commercially available from Hercules Incorporated, Aqualon Division under the tradename NATROSOL 250H or NATROSOL 250L. Examples of HPC polymers are also available from Hercules Incorporation, Aqualon Division under the tradename KLUCEL or KLUCEL HXF, and examples of PEO polymers are available from Union Carbide Corporation under the tradename POLYOX. Methods of making the non-ionic hydrophilic polymers heretofore described are known to those skilled in the art. The non-ionic

hydrophilic polymers may be employed in granules and pharmaceutical compositions according to the invention in amounts ranging from about 1 to about 20% by weight, preferably about 3 to 12% by weight, more preferably about 4 to 7% by weight based on the total weight of the granules or pharmaceutical composition. The non-ionic hydrophilic polymer is present in an amount sufficient to prevent premature release of fluvastatin.

Pharmaceutical compositions, e.g. oral dosage forms, according to the invention may comprise other excipients which serve to facilitate processing and/or provide enhanced properties of the pharmaceutical compositions, including well known tabletting excipients such as binders, e.g. gelatin, sugars, natural and synthetic gums, polyvinyl pyroll idone), disintegrants (e.g. crosscarmelose, crospovidone, sodium starch glycolate), lubricants (e.g., magnesium stearate, hydrogenated vegetable oils, carnauba wax), flow agents (e.g. silicon dioxide), anti-adherents or glidants (e.g. talc) as well as sweeteners, fillers, flavourants and antioxidants.

As fluvastatin is sensitive to acidic media, it is conventional to include a basifying agent to impart a pH of at least about 9. Any basifying agent known for stabilising formulations containing HMG-CoA reductase inhibitors may be employed. Applicant has surprisingly found that in pharmaceutical compositions comprising a typical basifying agent, e.g. potassium carbonate or bicarbonate, and polyvinylpyrollidone and fluvastatin, there is a tendency for discolouration during storage. This discolouration, in the form of dark spots, is distinct from that hereinabove described and is thought to be a result of the action of in situ - generated carbonic acid on the active agent or excipients (the carbonic acid being formed as a degradation product of the potassium carbonate or bicarbonate in the presence of PVP and ambient moisture). In keeping with the discolouration associated with the HPMC, this discolouration does not affect the safety and efficacy of the pharmaceutical compositions and is likewise masked by adopting the same precautions as hereinabove described.

The structure and method of manufacture of fluvastatin is disclosed in European patent applications EP–A-114027 and EP-A-547000, which are incorporated herein by reference.

Pharmaceutical compositions, e.g. oral dosage forms, according to the invention may be manufactured according to any of the procedures known in the art. In the case of tablets they may be formed by a process which forms another aspect of this invention and which comprises the step of an aqueous high-shear granulation of the active agent and the tabletting excipients.

Granules are produced in a manner known per se, for example using aqueous granulation

methods known for the production of "built-up" granules or "broken-down" granules.

Methods for the formation of built-up granules operate continuously and comprise, for example, simultaneously spraying the granulation mass with granulation solution and drying, for example in a drum granulator, in pan granulators, on disc granulators, in a fluidised bed, by spray-drying or spray-solidifying, or operate discontinuously, for example in a fluidised bed, in a batch mixer or in a spray-drying drum.

Preferred are methods for the production of broken-down granules, which can be carried out discontinuously and in which the granulation mass first forms a wet aggregate with the granulation solution, which aggregate is then comminuted or formed into granules of the desired particle size using known granulation methods, the granules then being dried. Suitable granulators include, for example an Alexander granulator.

The granulation mass consists of comminuted, preferably ground, active ingredient and the excipients mentioned above. Depending on the method used, the granulation mass may be in the form of a premix or may be obtained by mixing the active ingredient into one or more excipients or mixing the excipients into the active ingredient. The wet granules are preferably dried, for example in the described manner by spray drying or in a fluidised bed.

Compression to form tablet cores may be carried out in conventional tabletting machines, for example eccentric, e.g. EK-0 Korsch, and rotary tabletting machines. The tablet cores may be of various shapes, for example round, oval, oblong, cylindrical etc., and various sizes, depending on the amount of active ingredient employed.

There now follows a series of example which serve to illustrate the invention.

Example 1

A portion of fluvastatin sodium is calculated and weighed. Potassium bicarbonate, microcrystalline cellulose, povidone, HPC, and HPMC are weighed and placed into individual separately labelled containers. A 20 weight percent excess of the batch quantity of OPADRY Yellow, YS-1-6347-G, is then placed into a labelled container. The microcrystalline cellulose, fluvastatin sodium, povidone, HPC, and HPMC are transferred, in that order, into a collette gral and mixed for 5 minutes with the plow at slow speed and the chopper off. The resulting mixture is passed through a 0.033 inch screen using a tornado mill with knives forward and at slow speed. The screened material is then mixed again in a collette gral with the plow at slow speed and the chopper off.

Potassium bicarbonate is dissolved into purified water until a clear homogenous solution is obtained. The potassium bicarbonate solution is then combined with the screened material, and the resulting mixture is granulated in a collette gral with the plow at fast speed and the chopper at slow speed. After adding the above solution, granulation should continue for 30 seconds with the plow at fast speed and the chopper at slow speed and for another 30 seconds with the plow at fast speed and the chopper at fast speed. The granulated mixture is then dried in a fluid bed dryer using a target inlet temperature of 50°C until an LOD of 2 percent to 3 percent is obtained.

The dried granules are then passed through a 1/16 inch screen using a tornado milt with knives forward and at slow speed. An amount of magnesium stearate based on the proportion of actual yield from the 1/16 inch screening step to the theoretical yield from the same step is calculated and weighed. The weighed magnesium stearate is then passed through a 60 mesh screen and blended with the dried granules in a free fall blender and the resulting granulation blend discharged into a plastic lined labelled drum. The granulation blend is then compressed into tablets and the tablets are dedusted, passed through a metal checker, and stored in a plastic, labelled drum.

To coat the tablets, the OPADRY Yellow is mixed with a required quantity of purified water to obtain a 10 w/w percent suspension. The tablets are transferred to a coating pan and warmed to a temperature of 40-45°C. The OPADRY Yellow suspension is then added, to spray coat the tablets until a 3 percent solid weight gain per tablet is achieved. The coating spray is shut off, and the tablets are cooled by shutting off the pan heat and jogging the pan for 5 minutes.

Example 2

A portion of fluvastatin sodium is calculated and weighed. Potassium bicarbonate, microcrystalline cellulose, povidone, HPC, and HPMC are weighed and placed into individual separately labelled containers. A 20 weight percent excess of the batch quantity of OPADRY Yellow, 00F12953, is then placed into a labelled container. The microcrystalline cellulose, fluvastatin sodium, povidone, HPC, and HPMC are transferred, in that order, into a collette gral and mixed for 5 minutes with the plow at slow speed and the chopper off. The resulting mixture is passed through a 0.9 mm screen using a Fitz Patrick mill with knives forward and at medium speed. The screened material is then mixed again in a collette gral with the plow at slow speed and the chopper off.

Potassium bicarbonate is dissolved into purified water until a clear homogenous solution is obtained. The potassium bicarbonate solution is then combined with the screened material,

and the resulting mixture is granulated in a collette gral with the plow at fast speed and the chopper at slow speed. After adding the above solution, granulation should continue for 30 seconds with the plow at fast speed and the chopper at slow speed and for another 30 seconds with the plow at fast speed and the chopper at fast speed. The granulated mixture is then dried in a fluid bed dryer using a target inlet temperature of 50°C until an LOD of 2.5 percent to 3.5 percent is obtained.

The dried granules are then passed through a 1.5 mm screen using a Fitz Patrick Mill with knives forward and at medium speed. An amount of magnesium stearate based on the proportion of actual yield from the 1.5mm screening step to the theoretical yield from the same step is calculated and weighed. The weighed magnesium stearate is then passed through a 1.5mm screen using a Fitz Patrick Mill with knives forward and at medium speed. and blended with the dried granules in a free fall blender and the resulting granulation blend discharged into a plastic lined labelled drum. The granulation blend is then compressed into tablets and the tablets are dedusted, passed through a metal checker, and stored in a plastic, labelled drum.

To coat the tablets, the OPADRY Yellow is mixed with a required quantity of purified water to obtain a 15 w/w percent suspension. The tablets are transferred to a coating pan and warmed to a temperature of 40-45°C. The OPADRY Yellow suspension is then added, to spray coat the tablets until a 3 percent solid weight gain per tablet is achieved. The coating spray is shut off, and the tablets are cooled by shutting off the pan heat and jogging the pan for 5 minutes.

Example 3

84.24 mg of fluvastatin sodium were combined with the following excipients according to the method described in Example 1 and 2 to provide a single dosage form described in Table 1:

TABLE 1 -

Fluvastatin sodium	84.24 mg
Potassium bicarbonate, USP	8.42 mg
Microcrystalline cellulose, NF, PH 101 (AVICEL)	111.26 mg
Povidone USP	4.88 mg
HPC,NF (KLUCEL HXF)	16.25 mg
HPMC, USP (METHOCEL K 100LVP CR)	97.50 mg
Magnesium Stearate	2.44 mg
OPADRY Yellow	9.75 mg

The OPADRY yellow (00F12953) consisted of HPMC 2910 3cps (72%ww); titanium dioxide (21.413%ww); PEG 8000 (4.0%ww); and iron oxide yellow (2.587%ww) (24% oxides TiO_2 + FeO_2).

The formulation of Table 1 produced pharmaceutical compositions and granules which showed no sign of the mottled discolouration.

When the OPADRY yellow (00F22737) consisted of HPMC 2910 3cps (80%ww); titanium dioxide (14.080% ww); PEG 8000 (4.0%ww); and iron oxide yellow (1.920%ww) (16% oxides TiO_2 + FeO_2), the pharmaceutical compositions displayed a mottled, uneven discolouration.

Claims

1. A pharmaceutical composition comprising compressed granules comprising fluvastatin, or a pharmaceutical acceptable salt thereof and HPMC wherein said granules have a mean particle size of less than 200 microns.

2. A pharmaceutical composition according to claim 1 wherein the pharmaceutical acceptable salt is a sodium salt

3. A pharmaceutical composition according to claims 1 to 2 wherein the granules have a mean particle size above 20 microns and less than 125 microns.

4. A pharmaceutical composition according to claim 3 wherein the granules have a mean particle size from 100 to 125 microns.

5. Pharmaceutical composition according to anyone of the preceding claims comprising a coating wherein the coating comprises up to 73% by weight of a colouring agent based on the total weight of the coating.

6. Pharmaceutical composition according to claim 5 wherein the coating comprises from 17 to 73% by weight of a colouring agent based on the total weight of the coating.

7. Pharmaceutical composition according to claim 6 wherein the coating comprises from 17 to 30% by weight of a colouring agent based on the total weight of the coating.

8. Pharmaceutical composition according to claim 7 wherein the coating comprises from 22 to 25% by weight of a colouring agent based on the total weight of the coating.

9. Pharmaceutical composition according to claim 8 wherein the coating comprises 24% by weight of a colouring agent based on the total weight of the coating.

10. A pharmaceutical composition according to anyone of the preceding claims in the form of an oral dosage form.

11. A pharmaceutical composition according to anyone of the preceding claims packaged in high density polyethylene (HDPE) bottles.

12. A pharmaceutical composition according to any of the preceding claims wherein the HPMC comprises up to 12 percent hydroxypropyl functionality and has a number average molecular weight of from 20,000 to 170,000.

13. A pharmaceutical composition according to any of the preceding claims wherein the HPMC is present in amounts of from 15 to 50% by weight based on the total weight of the composition.

14. A pharmaceutical composition according to any of the preceding claims additionally comprising a non-ionic hydrophilic polymer selected from hydroxyethyl celluiose or hydroxypropyl cellulose.

15. A pharmaceutical composition according to claim 14 wherein the ratio of HPMC to non-hydrophilic polymer is about 10:1 to 3:11.

16. Granules comprising fluvastatin and HPMC wherein the granules have a mean particle size of less than 200 microns.

17. Granules according to claim 16 wherein the granules have a mean particle size above 20 microns and less than 125 microns.

18. Granules according to claim 17 wherein the granules have a mean particle size from 100 to 125 microns.

19. Granules according to claims 16-18 wherein the HPMC is defined as in any one of claims 12-14.

20. A method of preventing or substantially reducing the formation of gels of hydrated HPMC in a pharmaceutical composition comprising fluvastatin and HPMC comprising the step of compressing granules comprising fluvastatin and HPMC, wherein said granules have a mean granule particle size of less than 200 microns.

21. A method according to claim 20 wherein the granules have a mean particle size above 20 microns and less than 125 microns.

22. A method according to claim 21 wherein the granules have a mean particle size from 100 to 125 microns.

23. The method according to claim 22 wherein the pharmaceutical composition is formed of compressed granules.