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(57) **Abrégé/Abstract:**

A process for the production of a composition comprising a water-insoluble statin which comprises the steps of: a) providing a mixture comprising: i) a water-insoluble statin ii) a water soluble carrier, iii) a solvent for each of the statin and the carrier, and b) spray-drying the mixture to remove the or each solvent and obtain a substantially solvent-free nano-dispersion of the statin in the carrier.



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(57) Abstract: A process for the production of a composition comprising a water-insoluble statin which comprises the steps of: a) providing a mixture comprising: i) a water-insoluble statin ii) a water soluble carrier, iii) a solvent for each of the statin and the carrier, and b) spray-drying the mixture to remove the or each solvent and obtain a substantially solvent-free nano-dispersion of the statin in the carrier.

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IMPROVEMENTS RELATING TO PHARMACEUTICAL COMPOSITIONS**Field of the Invention**

5

The present invention relates improvements relating to pharmaceutical compositions. In particular it relates to pharmaceutically active compositions and precursors therefor which contain a so-called "statin"

10

Background of the Invention

15

Statins are believed to reduce serum LDL cholesterol levels by inhibition of 3-hydroxy-3-methylglutaryl CoenzymeA reductatse (HMG-CoA Reductase). Several statins are known, including Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravavastatin, Rosuvastatin and Simvastatin.

20

Statins have been proposed for use in the treatment of coronary heart disease, myocardial infarction, stroke and peripheral artery disease and the statins appear to have favorable effect in the treatment of inflammation, dementia, neoplastic conditions, nuclear cataracts and pulmonary hypertension.

25

Many statins exhibit low water solubility and are practically insoluble in water. This hinders their effective use.

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Our co-pending international patent application PCT/GB03/03226 describes the formation of solid, porous beads comprising a three dimensional open-cell lattice of a water-soluble polymeric material. These are typically
5 'templated' materials formed by the removal of both water and a non-aqueous dispersed phase from a high internal phase emulsion (HIPE) which has a polymer dissolved in the aqueous phase. The beads are formed by dropping the HIPE emulsion into a low temperature fluid such as liquid nitrogen, then
10 freeze-drying the particles formed to remove the bulk of the aqueous phase and the dispersed phase. This leaves behind the polymer in the form of a 'skeletal' structure. The beads dissolve rapidly in water and have the remarkable property that a water-insoluble component dispersed in the
15 dispersed phase of the emulsion prior to freezing and drying can also be dispersed in water on solution of the polymer skeleton of the beads.

WO 2005/011636 discloses a non-emulsion based spray drying
20 process for forming 'solid amorphous dispersions' of drugs in polymers. In this method a polymer and a low-solubility drug are dissolved in a solvent and spray-dried to form dispersions in which the drug is mostly present in an amorphous form rather than in a crystalline form.

25

Our co-pending applications GB 0501835 and GB 0613925 (filed 13th July 2006) describe how materials which will form a nano-dispersion in water can be prepared, preferably by a spray-drying process. In the first of these applications the
30 water insoluble materials is dissolved in the solvent-phase

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of an emulsion. In the second, the water-insoluble materials are dissolved in a mixed solvent system and co-exist in the same phase as a water-soluble structuring agent. In both cases the liquid is dried above ambient
5 temperature (above 20 Celsius), such as by spray drying, to produce particles of the structuring agent, as a carrier, with the water-insoluble materials dispersed therein. When these particles are placed in water they dissolve, forming a nano-dispersion of the water-insoluble material with
10 particles typically below 300nm. This scale is similar to that of virus particles, and the water-insoluble material behaves as though it were in solution.

WO 2003/103640 (Elan Pharma International Ltd) discloses
15 nanoparticulate forms of statins (particularly Lovastatin or Simvastatin). Particle sizes are disclosed from 2000nm down to 50nm. Methods for the production of these nanoparticles include grinding, milling, homogenisation, and precipitation methods.

20 In the present application the term 'ambient temperature' means 20 degrees Celsius and all percentages are percentages by weight unless otherwise specified.

25 **Brief Description of the Invention**

We have now determined that both the emulsion-based and the single-phase method can be used to produce a water-soluble, nano-disperse form of a statin.

30

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Accordingly, the present invention provides a process for the production of a composition comprising a water-insoluble statin which comprises the steps of:

5 a) providing a mixture comprising:

i) a water-insoluble statin

10 ii) a water soluble carrier,

iii) a solvent for each of the statin and the carrier ,

and

15 b) spray-drying the mixture to remove the or each solvent and obtain a substantially solvent-free nano-dispersion of the statin in the carrier.

The preferred method of particle sizing for the dispersed
20 products of the present invention employs a dynamic light scattering instrument (Nano S, manufactured by Malvern Instruments UK). Specifically, the Malvern Instruments Nano S uses a red (633nm) 4mW Helium-Neon laser to illuminate a standard optical quality UV curvette containing a suspension
25 of material. The particle sizes quoted in this application are those obtained with that apparatus using the standard protocol. Particle sizes in solid products are the particle sizes inferred from the measurement of the particle size obtained by solution of the solid in water and measurement
30 of the particle size.

- 5 -

Preferably, the peak diameter of the water-insoluble statin is below 800nm. More preferably the peak diameter of the water-insoluble statin is below 500nm. In a particularly preferred embodiment of the invention the peak diameter of
5 the water-insoluble statin is below 200nm.

It is believed that reduction of the particle size in the eventual nano-dispersion has significant advantages in improving the availability of the otherwise water-insoluble
10 material. This is believed to be particularly advantageous where an improved bio-availability is sought, or, in similar applications where high local concentrations of the material are to be avoided. Moreover it is believed that nano-dispersions with a small particle size are more stable than
15 those with a larger particle size.

In the context of the present invention, "water insoluble" as applied to the statin means that its solubility in water is less than 10g/L. Preferably, the water insoluble statin
20 has solubility in water at ambient temperature (20 Celsius) less than 5g/L preferably of less than 1g/L, especially preferably less than 150mg/L, even more preferably less than 100mg/L. This solubility level provides the intended interpretation of what is meant by water-insoluble in the
25 present specification.

Preferred water-insoluble statins include Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravavastatin, Rosuvastatin, Simvastatin and
30 water insoluble derivatives thereof. For example, the range

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of solubilities of lovastatin, mevastatin and simvastatin lie between 0.0013-0.0015 mg/ml.

Preferred carrier materials are selected from the group
5 consisting of water-soluble inorganic materials, surfactants, polymers and mixtures thereof.

A further aspect of the present invention provides a process for preparing a statin composition comprising a water-
10 insoluble statin and a water-soluble carrier, which comprises the steps of:

a) forming an emulsion comprising:

15 i) a solution of the statin in a water-immiscible solvent for the same, and

ii) an aqueous solution of the carrier, and,

20 b) drying the emulsion to remove water and the water-immiscible solvent to obtain a substantially solvent-free nano-dispersion of the statin in the carrier

For convenience, this class of method is referred to herein as the "emulsion" method.

25

A further aspect of the present invention provides a process for preparing a statin composition comprising a water insoluble statin and a water-soluble carrier which comprises the steps of:

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a) providing a single phase mixture comprising:

i) at least one non-aqueous solvent

5 ii) optionally, water

iii) a water-soluble carrier material soluble in the mixture of (i) and (ii) and

10 iv) a water-insoluble statin which is soluble in the mixture of (i) and (ii), and,

b) drying the solution to remove water and the water miscible solvent to obtain a substantially solvent-free
15 nano-dispersion of the statin in the carrier.

For convenience, this class of method is referred to herein as the "single-phase" method.

20 In the context of the present invention substantially solvent free means that the free solvent content of the product is less than 15%wt, preferably below 10%wt, more preferably below 5%wt and most preferably below 2%wt.

25 In the context of the present invention it is essential that both the carrier material and the statin are essentially fully dissolved in their respective solvents prior to the drying step. It is not within the ambit of the present specification to teach the drying of slurries. For the
30 avoidance of any doubt, it is therefore the case that the solids content of the emulsion or the mixture is such that

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over 90%wt, preferably over 95%, and more preferably over 98% of the soluble materials present is in solution prior to the drying step.

5 In relation to the methods mentioned above, the preferred statin and the preferred carrier materials are as described above and as elaborated on in further detail below. Similarly the preferred physical characteristics of the material are as described above.

10

The 'single phase' method where both the statin and the carrier material are dissolved in a phase comprising at least one other non-aqueous solvent (and optional water) is preferred. This is believed to be more efficacious in
15 obtaining a smaller particle size for the nano-disperse statin. Preferably, the drying step simultaneously removes both the water and other solvents and, more preferably, drying is accomplished by spray drying at above ambient temperature.

20

The products obtainable by the process aspects of the present invention are suitable for use in the preparation of medicaments for treatment or prophylaxis of coronary heart disease, myocardial infarction, stroke, peripheral artery, inflammation, dementia, neoplastic conditions, nuclear
25 cataracts and/or pulmonary hypertension.

25

A further aspect of the present invention provides a method for the preparation of a medicament for use in the treatment or prophylaxis of coronary heart disease, myocardial
30 infarction, stroke, peripheral artery, inflammation,

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dementia, neoplastic conditions, nuclear cataracts and/or pulmonary hypertension which comprises the step of preparing a composition according to the present invention.

5

Detailed Description of the Invention

Various preferred features and embodiments of the present invention are described in further detail below.

10

Statins:

As noted above the preferred water-insoluble anti-parasitic drugs are water-insoluble anti-malarial drugs selected from the group consisting of Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravavastatin, Rosuvastatin, Simvastatin and derivatives and mixtures thereof. These can be present as the sole pharmaceutically active ingredient in compositions according to the present invention or be together with other drugs to provide a so-called 'combination therapy'. As an illustrative example, Simvastatin is also available in a combination formulation with Ezetimibe.

Water-Dispersible Product Form:

The present invention provides a method for obtaining a water-dispersible form of an otherwise water-insoluble material. This is prepared by forming a not wholly aqueous intermediate emulsion or solution in which both a water-soluble carrier material and the water insoluble statin are

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- 10 -

dissolved. On removal of solvents the insoluble statin is left dispersed through the water-soluble carrier material. Suitable carrier materials are described in further detail below.

5

The structure of the material obtained after the drying step is not well understood. It is believed that the resulting dry materials are not encapsulates, as discrete macroscopic bodies of the water-insoluble materials are not present in the dry product. Neither are the dry materials 'dry emulsions' as little or none of the volatile solvent comprising the 'oil' phase of the emulsion remains after the drying step. On addition of water to the dry product the emulsion is not reformed, as it would be with a 'dry emulsion'. It is also believed that the compositions are not so-called solid solutions, as with the present invention the ratios of components present can be varied without loss of the benefits. Also from X-ray and DSC studies, it is believed that the compositions of the invention are not solid solutions, but comprise nano-scale, phase-separated mixtures.

Preferably, the compositions produced after the drying step will comprise the statin and the carrier in a weight ratio of from 1:500 to 1:1 (as statin:carrier), 1:100 to 1:1 being preferred. Typical levels of around 10-30%wt water-insoluble statin and 90-70%wt carrier can be obtained by spray drying.

By the method of the present invention the particle size of the statin materials can be reduced to below 100nm and may

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be reduced to around 15nm. Preferred particle sizes are in the range 40-15nm.

'Emulsion' Preparation Method:

5

In one preferred method according to the invention the solvent for the water-insoluble statin is not miscible with water. On admixture with water it therefore can form an emulsion.

10

Preferably, the non-aqueous phase comprises from about 10 % to about 95 % v/v of the emulsion, more preferably from about 20 % to about 68 % v/v.

15

The emulsions are typically prepared under conditions which are well known to those skilled in the art, for example, by using a magnetic stirring bar, a homogeniser, a sonicator or a rotational mechanical stirrer. The emulsions need not be particularly stable, provided that they do not undergo

20

extensive phase separation prior to drying.

Homogenisation using a high-shear mixing device is a particularly preferred way to make an emulsion in which the aqueous phase is the continuous phase. It is believed that this avoidance of coarse emulsion and reduction of the droplet size of the dispersed phase of the emulsion, results in an improved dispersion of the 'payload' material in the dry product.

25

30

In a preferred method according to the invention a water-continuous emulsion is prepared with an average dispersed-

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phase droplet size (using the Malvern peak intensity) of
between 500nm and 5000nm. We have found that an 'Ultra-
Turrux' T25 type laboratory homogenizer (or equivalent)
gives a suitable emulsion when operated for more than a
5 minute at above 10,000 rpm.

There is a directional relation between the emulsion droplet
size and the size of the particles of the 'payload'
material, which can be detected after dispersion of the
10 materials of the invention in aqueous solution. We have
determined that an increase in the speed of homogenization
for precursor emulsions can decrease final particle size
after re-dissolution.

15 It is believed that the re-dissolved particle size can be
reduced by nearly one half when the homogenization speed
increased from 13,500 rpm to 21,500 rpm. The homogenization
time is also believed to play a role in controlling re-
dissolved particle size. The particle size again decreases
20 with increase in the homogenization time, and the particle
size distribution become broader at the same time.

Sonication is also a particularly preferred way of reducing
the droplet size for emulsion systems. We have found that a
25 Hert Systems Sonicator XL operated at level 10 for two
minutes is suitable.

It is believed that ratios of components which decrease the
relative concentration of the anti-parasitic to the solvents
30 and/or the carrier give a smaller particle size.

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'Single Phase' Preparation Method:

In an alternative method according to the present invention both the carrier and the statin are soluble in a non-aqueous solvent or a mixture of such a solvent with water. Both
5 here and elsewhere in the specification the non-aqueous solvent can be a mixture of non-aqueous solvents.

In this case the feedstock of the drying step can be a
10 single phase material in which both the water-soluble carrier and the water-insoluble statin are dissolved. It is also possible for this feedstock to be an emulsion, provided that both the carrier and the statin are dissolved in the same phase.

15

The 'single-phase' method is generally believed to give a better nano-dispersion with a smaller particle size than the emulsion method.

20 It is believed that ratios of components which decrease the relative concentration of the statin to the solvents and/or the carrier give a smaller particle size.

Drying:

25

Spray drying is well known to those versed in the art. In the case of the present invention some care must be taken due to the presence of a volatile non-aqueous solvent in the emulsion being dried. In order to reduce the risk of
30 explosion when a flammable solvent is being used, an inert gas, for example nitrogen, can be employed as the drying

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medium in a so-called closed spray-drying system. The solvent can be recovered and re-used.

We have found that the 'Buchi' B-290 type laboratory spray
5 drying apparatus is suitable.

It is preferable that the drying temperature should be at or above 100 Celsius, preferably above 120 Celsius and most preferably above 140 Celsius. Elevated drying temperatures
10 have been found to give smaller particles in the re-dissolved nano-disperse material.

Carrier Material:

15 The carrier material is water soluble, which includes the formation of structured aqueous phases as well as true ionic solution of molecularly mono-disperse species. The carrier material preferably comprises an inorganic material, surfactant, a polymer or may be a mixture of two or more of
20 these.

It is envisaged that other non-polymeric, organic, water-soluble materials such as sugars can be used as the carrier. However the carrier materials specifically mentioned herein
25 are preferred.

Suitable carrier materials (referred to herein as 'water soluble carrier materials') include preferred water-soluble polymers, preferred water-soluble surfactants and preferred
30 water-soluble inorganic materials.

- 15 -

Preferred polymeric carrier materials:

5 Examples of suitable water-soluble polymeric carrier materials include:

- 10 (a) natural polymers (for example naturally occurring gums such as guar gum, alginate, locust bean gum or a polysaccharide such as dextran;
- 15 (b) cellulose derivatives for example xanthan gum, xyloglucan, cellulose acetate, methylcellulose, methyl-ethylcellulose, hydroxy-ethylcellulose, hydroxy-ethylmethyl-cellulose, hydroxy-propylcellulose, hydroxy-propylmethylcellulose, hydroxy-propylbutylcellulose, ethylhydroxy-ethylcellulose, carboxy-methylcellulose and its salts (eg the sodium salt - SCMC), or carboxy-methylhydroxyethylcellulose and its salts (for example the sodium salt);
- 20 (c) homopolymers of or copolymers prepared from two or more monomers selected from: vinyl alcohol, acrylic acid, methacrylic acid, acrylamide, methacrylamide, acrylamide methylpropane sulphonates,
- 25 aminoalkylacrylates, aminoalkyl-methacrylates, hydroxyethylacrylate, hydroxyethylmethacrylate, vinyl pyrrolidone, vinyl imidazole, vinyl amines, vinyl pyridine, ethyleneglycol and other alkylene glycols, ethylene oxide and other alkylene oxides,
- 30 ethyleneimine, styrenesulphonates, ethyleneglycolacrylates and ethyleneglycol methacrylate

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(d) cyclodextrins, for example *beta*-cyclodextrin

(e) mixtures thereof

5

When the polymeric material is a copolymer it may be a statistical copolymer (heretofore also known as a random copolymer), a block copolymer, a graft copolymer or a hyperbranched copolymer. Co-monomers other than those listed above may also be included in addition to those listed if their presence does not destroy the water soluble or water dispersible nature of the resulting polymeric material.

15 Examples of suitable and preferred homopolymers include poly-vinylalcohol, poly-acrylic acid, poly-methacrylic acid, poly-acrylamides (such as poly-N-isopropylacrylamide), poly-methacrylamide; poly-acrylamines, poly-methyl-acrylamines, (such as polydimethylaminoethylmethacrylate and poly-N-morpholinoethylmethacrylate), polyvinylpyrrolidone, poly-styrenesulphonate, polyvinylimidazole, polyvinylpyridine, poly-2-ethyl-oxazoline poly-ethyleneimine and ethoxylated derivatives thereof.

25 Polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), poly(2-ethyl-2-oxazoline), polyvinyl alcohol (PVA) hydroxypropyl cellulose and hydroxypropyl-methyl cellulose (HPMC) and alginates are preferred polymeric carrier materials.

30

Preferred surfactant carrier materials:

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Where the carrier material is a surfactant, the surfactant may be non-ionic, anionic, cationic, amphoteric or zwitterionic.

5

Examples of suitable non-ionic surfactants include ethoxylated triglycerides; fatty alcohol ethoxylates; alkylphenol ethoxylates; fatty acid ethoxylates; fatty amide ethoxylates; fatty amine ethoxylates; sorbitan alkanoates; ethylated sorbitan alkanoates; alkyl ethoxylates; Pluronics™; alkyl polyglucosides; stearyl ethoxylates; alkyl polyglycosides.

10

Examples of suitable anionic surfactants include alkylether sulfates; alkylether carboxylates; alkylbenzene sulfonates; alkylether phosphates; dialkyl sulfosuccinates; sarcosinates; alkyl sulfonates; soaps; alkyl sulfates; alkyl carboxylates; alkyl phosphates; paraffin sulfonates; secondary n-alkane sulfonates; alpha-olefin sulfonates; isethionate sulfonates.

15

20

Examples of suitable cationic surfactants include fatty amine salts; fatty diamine salts; quaternary ammonium compounds; phosphonium surfactants; sulfonium surfactants; sulfonxonium surfactants.

25

Examples of suitable zwitterionic surfactants include N-alkyl derivatives of amino acids (such as glycine, betaine, aminopropionic acid); imidazoline surfactants; amine oxides; amidobetaines.

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Mixtures of surfactants may be used. In such mixtures there may be individual components which are liquid, provided that the carrier material overall, is a solid.

- 5 Alkoxylated nonionic's (especially the PEG/PPG Pluronic™ materials), phenol-ethoxylates (especially TRITON™ materials), alkyl sulphonates (especially SDS), ester surfactants (preferably sorbitan esters of the Span™ and Tween™ types) and cationics (especially
- 10 cetyltrimethylammonium bromide - CTAB) are particularly preferred as surfactant carrier materials.

Preferred inorganic carrier materials:

- 15 The carrier material can also be an water-soluble inorganic material which is neither a surfactant nor a polymer. Simple organic salts have been found suitable, particularly in admixture with polymeric and/or surfactant carrier materials as described above. Suitable salts include carbonate,
- 20 bicarbonates, halides, sulphates, nitrates and acetates, particularly soluble salts of sodium, potassium and magnesium. Preferred materials include, sodium carbonate, sodium bicarbonate and sodium sulphate. These materials have the advantage that they are cheap and physiologically
- 25 acceptable. They are also relatively inert as well as compatible with many materials found in pharmaceutical products.

- Mixtures of carrier materials are advantageous. Preferred
- 30 mixtures include combinations of surfactants and polymers. Which include at least one of:

- 19 -

- a) Polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl cellulose and hydroxypropyl-methyl cellulose (HPMC) , alginates and, at least one of;
- 5
- b) Alkoxyated nonionic's (especially the PEG/PPG Pluronic™ materials), phenol-ethoxylates (especially TRITON™ materials), alkyl sulphonates (especially SDS), ester surfactants (preferably sorbitan esters of the
- 10 Span™ and Tween™ types) and cationics (especially cetyltrimethylammonium bromide - CTAB)

The carrier material can also be a water-soluble small organic material which is neither a surfactant, a polymer

15 nor an inorganic carrier material. Simple organic sugars have been found to be suitable, particularly in admixture with a polymeric and/or surfactant carrier material as described above. Suitable small organic materials include mannitol, polydextrose, xylitol and inulin etc.

20

Non-aqueous solvent:

25 The compositions of the invention comprise a volatile, second non-aqueous solvent. This may either be miscible with the other solvents in pre-mix before drying or, together with those solvents may form an emulsion.

30 In one alternative form of the invention a single, non-aqueous solvent is employed in which can form a single phase

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with water in the presence of the statin and the carrier.
Preferred solvents for these embodiments are polar, protic
or aprotic solvents. Generally preferred solvents have a
dipole moment greater than 1 and a dielectric constant
5 greater than 4.5.

Particularly preferred solvents are selected from the group
consisting of haloforms (preferably dichloromethane,
chloroform), lower (C1-C10) alcohols (preferably methanol,
10 ethanol, isopropanol, isobutanol), organic acids (preferably
formic acid, acetic acid), amides (preferably formamide,
N,N-dimethylformamide), nitriles (preferably aceto-nitrile),
esters (preferably ethyl acetate) aldehydes and ketones
(preferably methyl ethyl ketone, acetone), and other water
15 miscible species comprising heteroatom bond with a suitably
large dipole (preferably tetrahydrofuran,
dialkylsulphoxide).

Haloforms, lower alcohols, ketones and dialkylsulphoxides
20 are the most preferred solvents.

In another alternative form of the invention the non-aqueous
solvent is not miscible with water and forms an emulsion.

The non-aqueous phase of the emulsion is preferably selected
25 from one or more from the following group of volatile
organic solvents:

- alkanes, preferably heptane, n-hexane, isooctane,
dodecane, decane;

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- cyclic hydrocarbons, preferably toluene, xylene, cyclohexane;
- halogenated alkanes , preferably dichloromethane, dichloroethane, trichloromethane (chloroform), fluoro-
5 trichloromethane and tetrachloroethane;
- esters preferably ethyl acetate;
- 10 • ketones preferably 2-butanone;
- ethers preferably diethyl ether;
- volatile cyclic silicones preferably either linear or
15 cyclomethicones containing from 4 to 6 silicon units. Suitable examples include DC245 and DC345, both of which are available from Dow Corning Inc.

Preferred solvents include dichloromethane, chloroform,
20 ethanol, acetone and dimethyl sulphoxide.

Preferred non-aqueous solvents, whether miscible or not have a boiling point of less than 150 Celsius and, more preferably, have a boiling point of less than 100 Celsius,
25 so as to facilitate drying, particularly spray-drying under practical conditions and without use of specialised equipment. Preferably they are non-flammable, or have a flash point above the temperatures encountered in the method of the invention.

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Preferably, the non-aqueous solvent comprises from about 10 % to about 95 % v/v of any emulsion formed, more preferably from about 20 % to about 80 % v/v. In the single phase method the level of solvent is preferably 20-100%v/v.

5

Particularly preferred solvents are alcohols, particularly ethanol and halogenated solvents, more preferably chlorine-containing solvents, most preferably solvents selected from (di- or tri- chloromethane).

10

Optional Cosurfactant:

In addition to the non-aqueous solvent an optional co-surfactant may be employed in the composition prior to the drying step. We have determined that the addition of a relatively small quantity of a volatile cosurfactant reduced the particle diameter of the material produced. This can have a significant impact on particle volume. For example, reduction from 297nm to 252nm corresponds to a particle size reduction of approximately 40%. Thus, the addition of a small quantity of co-surfactant offers a simple and inexpensive method for reducing the particle size of materials according to the present invention without changing the final product formulation.

25

Preferred co-surfactants are short chain alcohols or amine with a boiling point of <220°C.

Preferred co-surfactants are linear alcohols. Preferred co-surfactants are primary alcohols and amines.

30

Particularly preferred co-surfactants are selected from the

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group consisting of the 3-6 carbon alcohols. Suitable alcohol co-surfactants include n-propanol, n-butanol, n-pentanol, n-hexanol, hexylamine and mixtures thereof.

- 5 Preferably the co-surfactant is present in a quantity (by volume) less than the solvent preferably the volume ratio between the solvent and the co-surfactant falls in the range 100:40 to 100:2, more preferably 100:30 to 100:5.

10 Preferred Spray-Drying Feedstocks:

Typical spray drying feedstocks comprise:

- 15 a) a surfactant,
- b) at least one lower alcohol,
- c) more than 0.1% of at least one water-insoluble statin dissolved in the feedstock,
- 20 d) a polymer, and,
- e) optional water

25 Preferred spray-drying feedstocks comprise:

- a) at least one non-aqueous solvent selected from dichloromethane, chloroform, ethanol, acetone, and mixtures thereof,

30

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- b) a surfactant selected from PEG co-polymer nonionic's (especially the PEG/PPG Pluronic™ materials), alkyl sulphonates (especially SDS), ester surfactants (preferably sorbitan esters of the Span™ and Tween™ types) and cationics (especially cetyltrimethylammonium bromide - CTAB) and mixtures thereof,
- c) more than 0.1% of at least one water-insoluble statin,
- 10 d) a polymer selected from Polyethylene glycol (PEG), Polyvinyl alcohol (PVA), polyvinyl-pyrrolidone (PVP), hydroxypropyl cellulose and hydroxypropyl-methyl cellulose (HPMC) , alginates and mixtures thereof, and
- 15 e) optionally water.

The drying feed-stocks used in the present invention are either emulsions or solutions which preferably do not contain any solid matter and in particular preferably do not contain any undissolved statin.

20

It is particularly preferable that the level of the statin in the composition should be such that the loading in the dried composition is below 40%wt, and more preferably below 30%wt. Such compositions have the advantages of a small particle size and high effectiveness as discussed above.

25

Water-Dispersed Form:

30 On admixture of the water-soluble carrier material with water, the carrier dissolves and the water-insoluble statin

- 25 -

is dispersed through the water in sufficiently fine form that it behaves like a soluble material in many respects. The particle size of the water-insoluble materials in the dry product is preferably such that, on solution in water
5 the water-insoluble materials have a particle size of less than 1 micron as determined by the Malvern method described herein. It is believed that there is no significant reduction of particle size for the statin on dispersion of the solid form in water.

10

By applying the present invention significant levels of 'water-insoluble' materials can be brought into a state which is largely equivalent to true solution. When the dry product is dissolved in water it is possible to achieve
15 optically clear solutions comprising more than 0.1%, preferably more than 0,5% and more preferably more than 1% of the water-insoluble material.

20

It is envisaged that the solution form will be a form suitable for administration to a patient either 'as is' or following further dilution. In the alternative, the solution form of embodiments of the invention may be combined with other active materials to yield a medicament suitable for use in combination therapy.

25

EXAMPLES:

30

In order that the present invention may be further understood and carried forth into practice it is further described below with reference to non-limiting examples.

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A range of formulations were produced based on different excipients, different active loadings, and different process conditions.

5

The excipients were chosen from hydroxypropyl cellulose (Klucel EF, Herlus), polyvinyl pyrrolidone (PVP k30, Aldrich), hydroxypropyl methyl cellulose (HPMC, Mw 10k, 5cps, Aldrich), polyethylene glycol (PEG, Mw 6,000, Fluka),
10 Tween 80 (Aldrich), pluronic F68 (BASF), pluronic F127 (Aldrich), span 80 (Aldrich), cremphor RH40 (BASF), mannitol (Aldrich), and sodium alginate (Aldrich).

Active loadings varied from 10 wt% to 30 wt%, and the spray
15 dry temperature varied from 120 °C to 160 °C. Simvastatin particle size ranged from as small as 100 nm to 2 µm.

Details of these formulations are listed as below:

20 **Example 1: (20 wt% loadings)**

0.40 g Simvastatin, 1.00 g Klucel EF, 0.44 g HPMC, and 0.16 g Pluronic F68 were all dispersed into 100 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour before adding 60 ml
25 distilled water. A clear solution was obtained.

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 120 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

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20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 217 nm.

5 **Example 2: (20 wt% loadings)**

0.40 g Simvastatin, 1.00 g Klucel EF, 0.34 g HPMC, 0.16 g Pluronic F127, and 0.10 g Tween 80 were all dispersed into 100 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour before
10 adding 60 ml distilled water. A clear solution was obtained.

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 120 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

15

20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 125 nm.

20 Two dissolution tests based on a 20 mg simvastatin dose and an 80 mg simvastatin dose were carried out for formulation #15/39/28 following the standard USP2 test. The results are listed below;

25

Example 2a	Dissolution time, min								
20 mg API	5	10	15	20	25	35	50	Equilibrium	
% dissolution	25.6	66.9	71.4	85.9	83	89.3	92.5	100	
Example 2b	Dissolution time, min								
80 mg API	5	10	30	50	70	90	120	150	Equil- ibrium
% dissolution	15.1	31.8	51.8	63.4	69.6	80.4	92.8	95.8	100

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Example 3: (20 wt% loadings)

0.40 g Simvastatin, 1.00 g Klucel EF, and 0.60 g HPMC were all dispersed into 100 ml absolute ethanol. The ethanol
5 suspension was stirred intensively with a magnetic bar for about half hour before adding 60 ml distilled water. A clear solution was obtained.

The solution was then spray dried with a BUCHI Mini B-290
10 spray dryer at 160 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size
15 of 277 nm.

Example 4: (20 wt% loadings)

0.40 g Simvastatin, 1.44 g Klucel EF, and 0.16 g PEG 6000 were all dispersed into 100 ml absolute ethanol. The ethanol
20 suspension was stirred intensively with a magnetic bar for about half hour and a clear solution was obtained.

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 160 °C with the liquid feed rate at 2.5
25 ml/min. A white free flowing powder was obtained.

20 mg dried powder was dispersed into 10 ml distilled water, giving a translucent nanodispersion with a particle size of
467 nm.

30

Example 5: (20 wt% loadings)

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0.40 g Simvastatin, 1.00 g Klucel EF, 0.18 g HPMC, 0.16 g PEG 6000, 0.16 g Pluronic F127, and 0.10 g Tween 80 were all dispersed into 100 ml absolute ethanol. The ethanol suspension was stirred intensively with magnetic bar for
5 about half hour before adding 60 ml distilled water. A clear solution was obtained.

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 160 °C with the liquid feed rate at 2.5
10 ml/min. A white free flowing powder was obtained.

20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 105 nm.

15

Example 6: (20 wt% loadings)

0.40 g Simvastatin, 1.34 g Klucel EF, 0.16 g Pluronic F127, and 0.10 g Cremphor RH40 were all dispersed into 100 ml absolute ethanol. The ethanol suspension was stirred
20 intensively with a magnetic bar for about half hour before adding 60 ml distilled water. A clear solution was obtained.

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 160 °C with the liquid feed rate at 2.5
25 ml/min. A white free flowing powder was obtained.

20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 120 nm.

30

- 30 -

Two dissolution tests based on a 20 mg simvastatin dose and an 80 mg simvastatin dose were carried out for formulation #15/39/41 following the standard USP2 test. The results are given below.

5

Example 6a	Dissolution time, min						
20 mg API	5	10	15	20	25	Equilibrium	
% dissolution	40.6	54.3	80.8	79.8	102.8	100	
Example 6b	Dissolution time, min						
80 mg API	5	10	40	60	80	100	Equilibrium
% dissolution	61.1	75.7	85.0	89.5	93.2	100	100

10 **Example 7: (20 wt% loadings)**

0.40 g Simvastatin, 1.18 g Klucel EF, 0.16 g Pluronic F68, 0.16 g Pluronic F127, and 0.10 g Span 80 were all dispersed into 100 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour before adding 10 ml distilled water. A clear solution was obtained.

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 160 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

20

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20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 162 nm.

Example 8: (20 wt% loadings)

5 0.40 g Simvastatin, 1.40 g Klucel EF, 0.10 g Tween 80, and 0.10 g Span 80 were all dispersed into 100 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour and a clear solution was obtained.

10

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 160 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

15 20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 139 nm.

Example 9: (30 wt% loadings)

20 0.30 g Simvastatin, 0.57 g Klucel EF, 0.05 g PEG 6000, 0.05 g Pluronic F127, and 0.03 g Tween 80 were all dispersed into 50 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour before adding 30 ml distilled water. A clear solution was obtained.

25

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 160 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

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20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 202 nm.

Example 10: (30 wt% loadings)

5 0.30 g Simvastatin, 0.65 g Klucel EF, 0.025 g Tween 80, and 0.025 g Span 80 were all dispersed into 50 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour and a clear solution was obtained.

10

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 160 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

15 20 mg dried powder was dispersed into 10 ml distilled water, giving a translucent nanodispersion with a particle size of 328 nm.

Example 11: (20 wt% loadings)

20 0.20 g Simvastatin, 0.40 g Klucel EF, 0.10 g Pluronic F127, 0.10 g Tween 80, and 0.20 g Mannitol were all dispersed into 50 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour before added 30 ml distilled water. A clear solution was obtained.

25

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 140 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

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20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 151 nm.

5 A dissolution test based on a 20 mg simvastatin dose was carried out for formulation obtained from example 11 following the standard USP2 test. The results showed a fast dissolution formulation.

10

Example 11a	Dissolution time, min			
	5	10	15	Equilibrium
20 mg API				
% dissolution	90.2	96.3	99.2	100

Example 12: (20 wt% loadings)

15 0.20 g Simvastatin, 0.50 g Klucel EF, 0.10 g Pluronic F127, and 0.20 g Mannitol were all dispersed into 50 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour before adding 30 ml distilled water. A clear solution was obtained.

20

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 140 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

25 20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 211 nm.

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A dissolution test based on a 20 mg simvastatin dose was carried out for formulation #15/39/77 following the standard USP2 test. The results showed a very fast dissolution formulation.

5

Example 12a	Dissolution time, min			
20 mg API	5	10	15	Equilibrium
% dissolution	96.5	98.5	98.9	100

10 **Example 13 (20 wt% loadings)**

0.20 g Simvastatin, 0.60 g Klucel EF, 0.05 g Pluronic F127, 0.05 g Tween 80, and 0.10 g Mannitol were all dispersed into 50 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour before
15 adding 30 ml distilled water. A clear solution was obtained.

The solution was then spray dried with a BUCHI Mini B-290 spray dryer at 160 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

20

20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 145 nm.

25

Example 14: (20 wt% loadings)

- 35 -

0.20 g Simvastatin, 0.60 g Klucel EF, 0.10 g Pluronic F127, 0.025 g Tween 80, and 0.025 g Span 80 were all dispersed into 50 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour
5 and a clear ethanol solution was formed. 0.05 g Sodium alginate was dissolved into 30 ml distilled water. The ethanol solution and the aqueous solution were mixed together and a clear mixture was obtained.

10 The mixture was then spray dried with a BUCHI Mini B-290 spray dryer at 160 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

20 mg dried powder was dispersed into 10 ml distilled water,
15 giving a crystal clear nanodispersion with a particle size of 206 nm.

Example 15: (20 wt% loadings)

0.20 g Simvastatin, 0.60 g Klucel EF, 0.15 g Pluronic F127
20 were all dispersed into 50 ml absolute ethanol. The ethanol suspension was stirred intensively with a magnetic bar for about half hour. 0.05 g Sodium alginate was dissolved into 30 ml distilled water. The ethanol dispersion and the aqueous solution were mixed together and a clear mixture was
25 obtained.

The mixture was then spray dried with a BUCHI Mini B-290 spray dryer at 160 °C with the liquid feed rate at 2.5 ml/min. A white free flowing powder was obtained.

30

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20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 276 nm.

- 5 A dissolution test based on a 20 mg simvastatin dose was carried out for formulation Example 15 following the standard USP2 test. The results showed a very slow dissolution formulation.

Ex. 15	Dissolution time, min										
20 mg API	5	10	20	30	40	50	60	80	100	120	Equilibrium
% dissolution	57.1	61.8	75.8	83.5	87.6	92.5	95.5	92.7	99.8	101.3	100

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CLAIMS:

1. A process for the production of a composition
comprising a water-insoluble statin which comprises the
5 steps of:

a) providing a mixture comprising:

10 i) a water-insoluble statin

ii) a water soluble carrier,

15 iii) a solvent for each of the statin and the
carrier , and

b) spray-drying the mixture to remove the or each
solvent and obtain a substantially solvent-free
20 nano-dispersion of the statin in the carrier.

2. A process according to claim 1 which comprises the
steps of:

a) providing an emulsion comprising:

25 i) a solution of the water-insoluble statin in a
water-immiscible solvent for the same, and

30 ii) an aqueous solution of the carrier, and,

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- b) spray-drying the emulsion to remove water and the water-immiscible solvent to obtain a substantially solvent-free nano-dispersion of the statin in the carrier

5

- 3 A process according to claim 1 which comprises the steps of:

- a) providing a single phase mixture comprising:

10

i) at least one non-aqueous solvent

ii) optionally, water

15

iii) a water-soluble carrier material soluble in the mixture of (i) and (ii) and

iv) a water-insoluble statin which is soluble in the mixture of (i) and (ii), and,

20

- b) spray-drying the solution to remove water and the water miscible solvent to obtain a substantially solvent-free nano-dispersion of the statin in the carrier.

25

- 4 A process according to any of claims 1-3 wherein the spray drying process is conducted at a temperature at or above 120 Celsius.

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5. A process according to any of claims 1-4 in which the carrier material includes a polymer and/or a surfactant.

5 6. A process according to claim 6 wherein the carrier material includes at least one of polyethylene glycol, polyvinylpyrrolidone, poly(2-ethyl-2-oxazoline), polyvinyl alcohol, hydroxypropyl cellulose and hydroxypropyl-methyl cellulose and alginate.

10

7. A process according to claim 5 wherein the carrier material includes at least one of alkoxylated non-ionic surfactant, ether sulphate surfactant, cationic surfactant or ester surfactant.

15

8 A process according to any one of claims 1-7 wherein the non-aqueous solvent includes at least one of dichloromethane, chloroform, ethanol, acetone and dimethyl sulphoxide.

20

9. A process for the preparation of a medicament for use in the treatment or prophylaxis of coronary heart disease, myocardial infarction, stroke, peripheral artery, inflammation, dementia, neoplastic conditions, nuclear cataracts and/or pulmonary hypertension which comprises the step of preparing a composition by a process according to any one of claims 1-8.

25