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(54) **PROCESSES FOR PREPARING PHARMACEUTICAL COMPOSITIONS**

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(57) **ABSTRACT**

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

Fig. 1

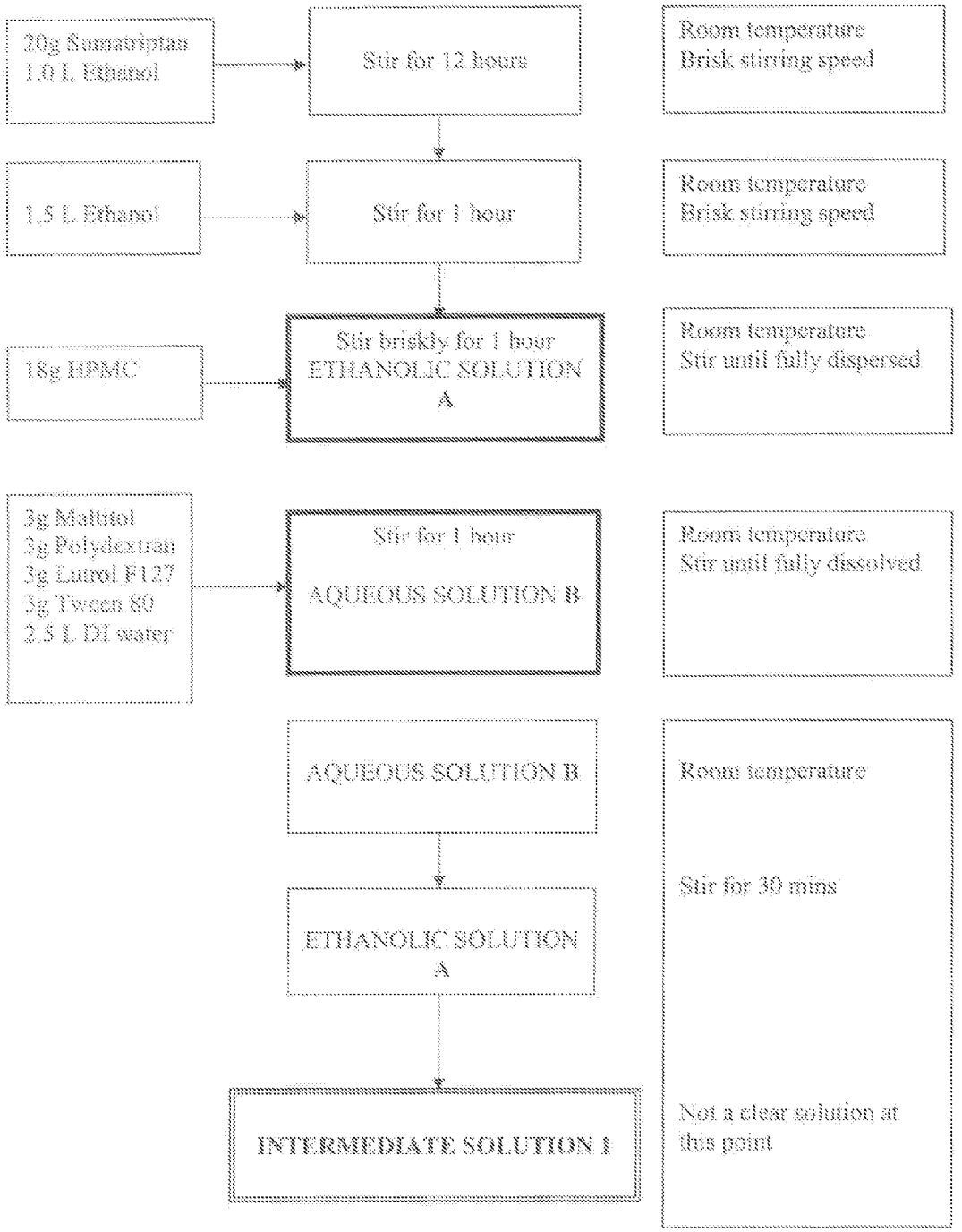

20g Sumatriptan
1.0 L Ethanol
Stir for 12 hours
Room temperature
Brisk stirring speed
1.5 L Ethanol
Stir for 1 hour
Room temperature
Brisk stirring speed
18g HPMC
Stir briskly for 1 hour
ETHANOLIC SOLUTION A
Room temperature
Stir until fully dispersed
3g Maltitol
3g Polydextran
3g Lutrol F127
3g Tween 80
2.5 L DI water
Stir for 1 hour
AQUEOUS SOLUTION B
Room temperature
Stir until fully dissolved
AQUEOUS SOLUTION B
ETHANOLIC SOLUTION A
INTERMEDIATE SOLUTION 1
Room temperature
Stir for 30 mins
Not a clear solution at this point

Fig. 1 continued

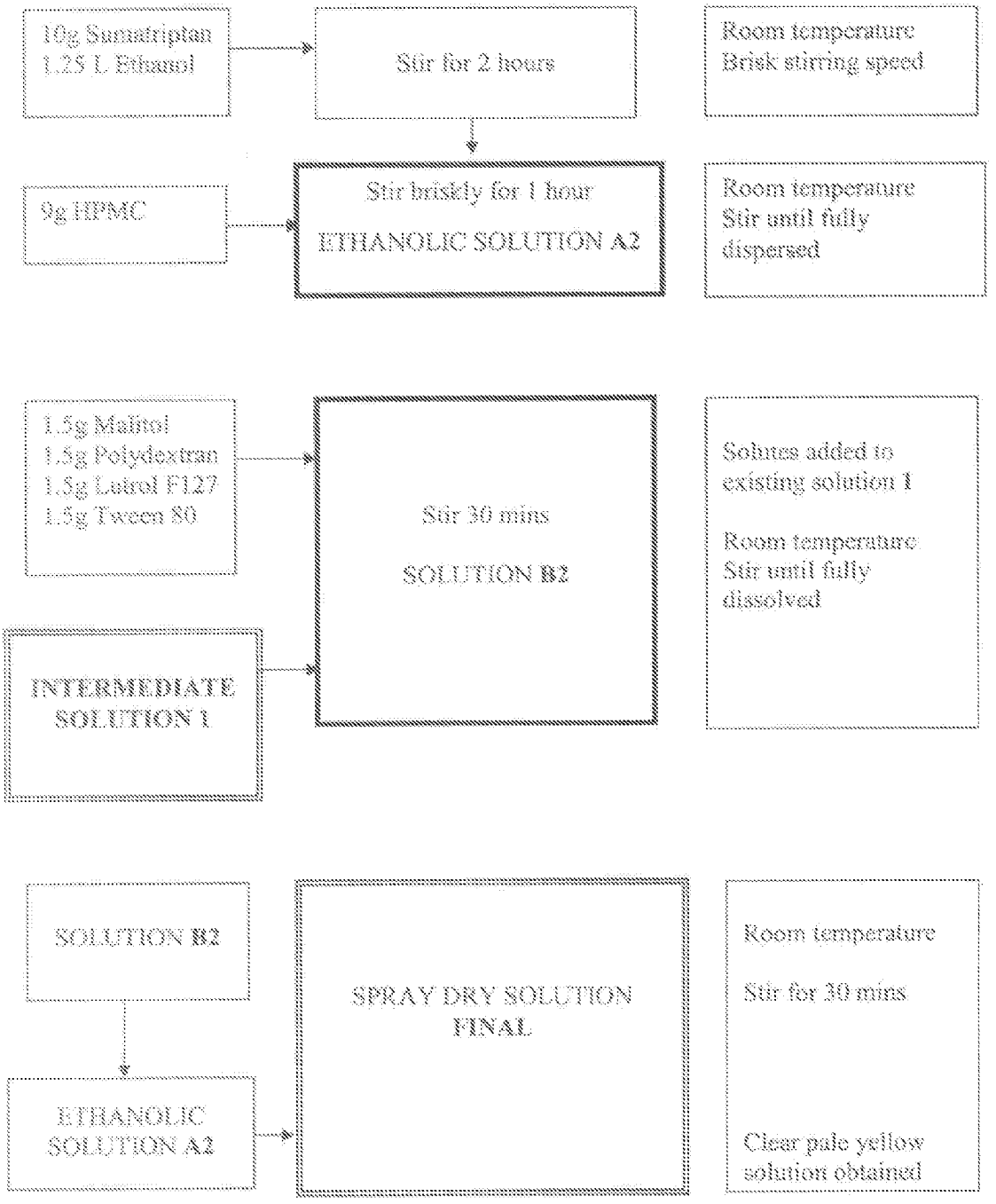
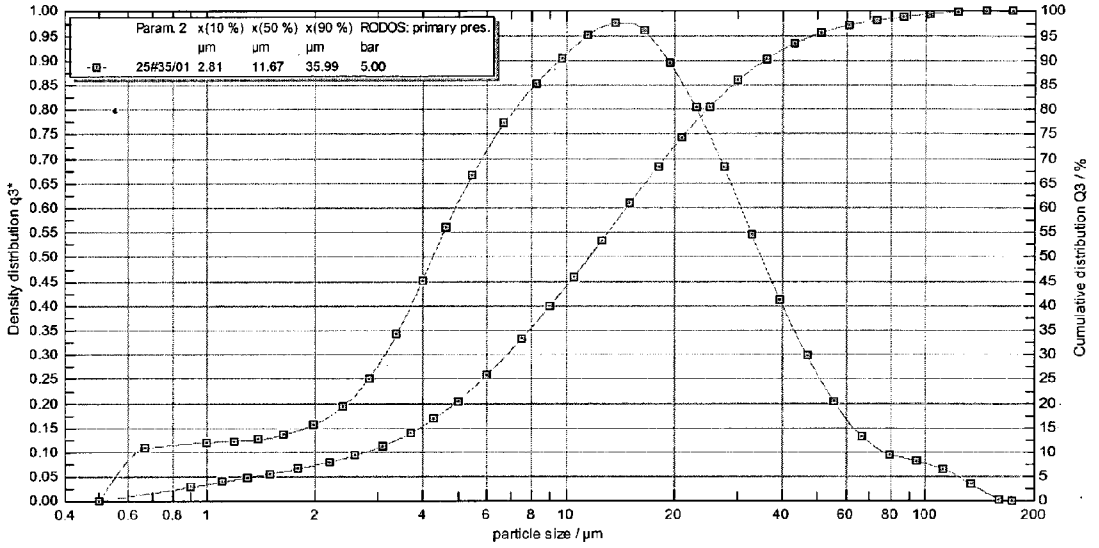


Fig. 2


Param. 2 x(10 %) x(50 %) x(90 %) RODOS: primary pres.
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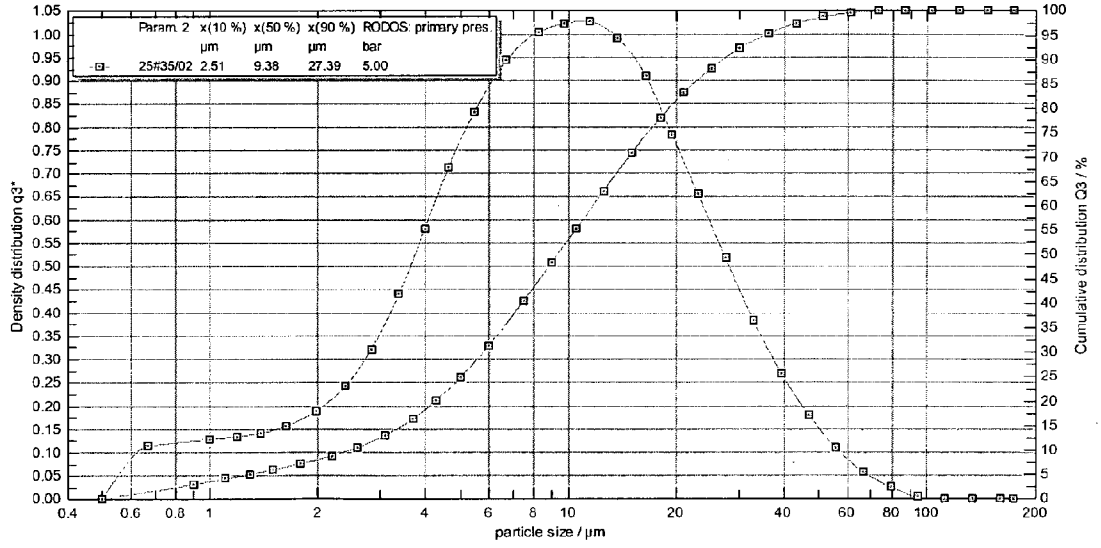
25#35/01 2.81 11.67 35.99 5.00
Density distribution q3*
Cumulative distribution Q3 / %
particle size / µm

Fig. 3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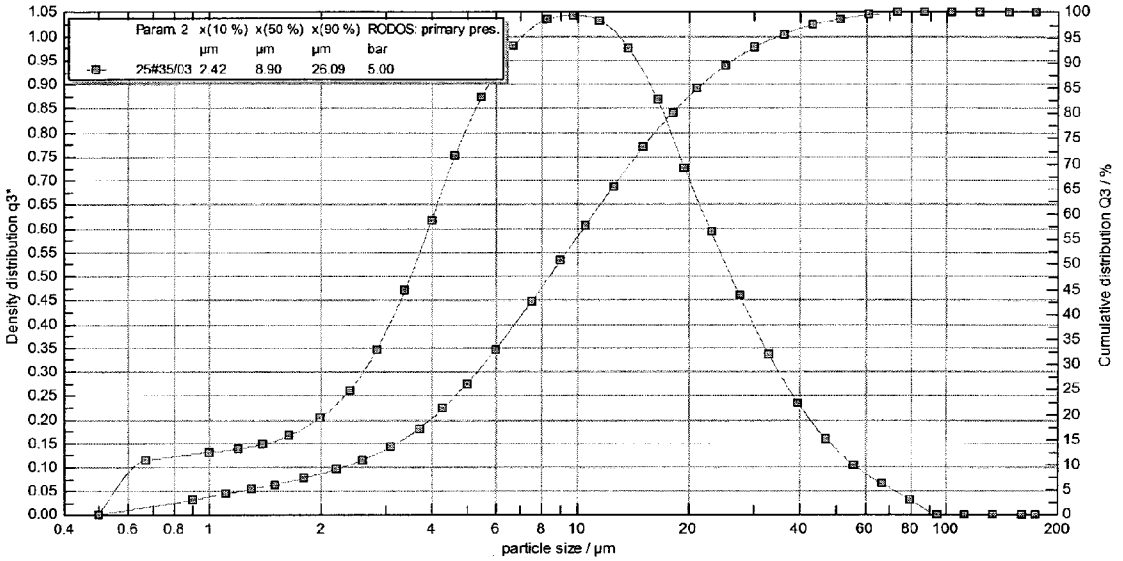
Density distribution q3*
Cumulative distribution Q3 / %
particle size / µm

Fig. 4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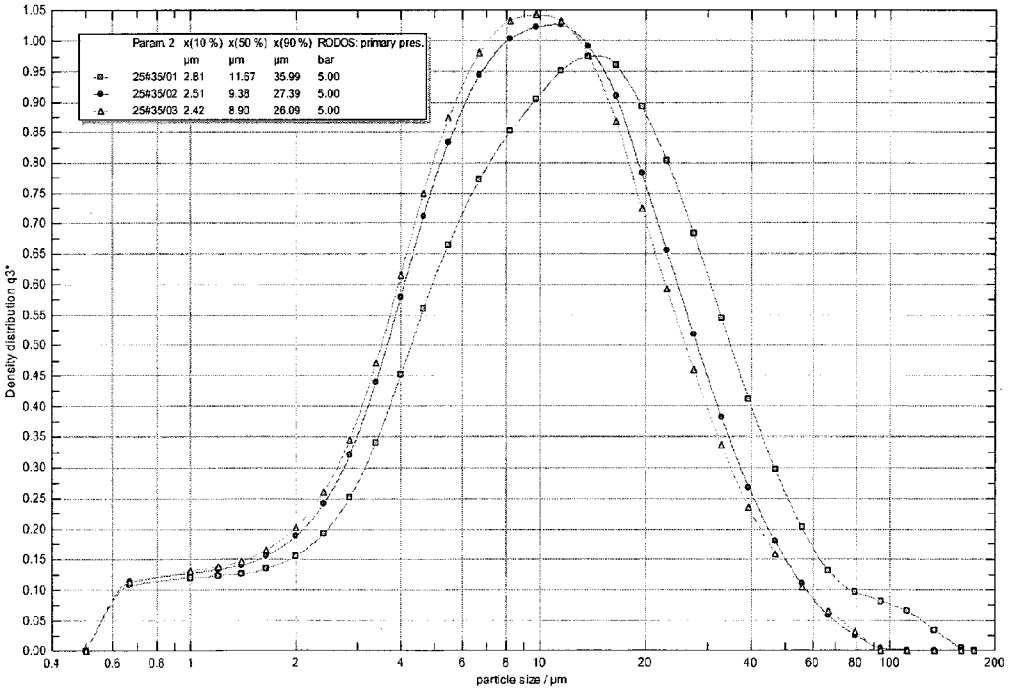
25#35/03 2.42 8.90 26.09 5.00
Density distribution q3*
Cumulative distribution Q3 / %
particle size / µm

Fig. 5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25#35/03 2.42 8.90 26.09 5.00
Density distribution q3*
particle size / µm

Fig. 6

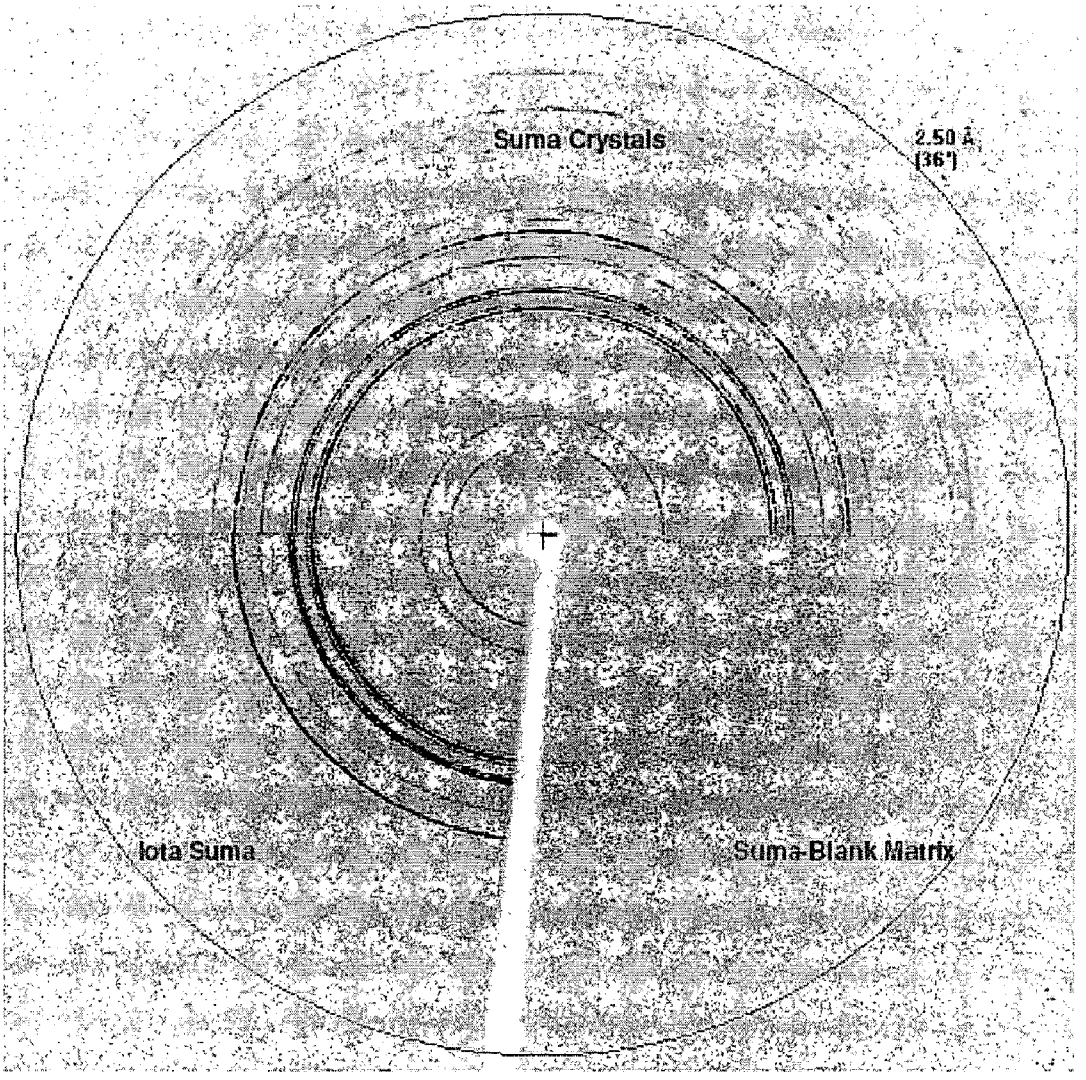
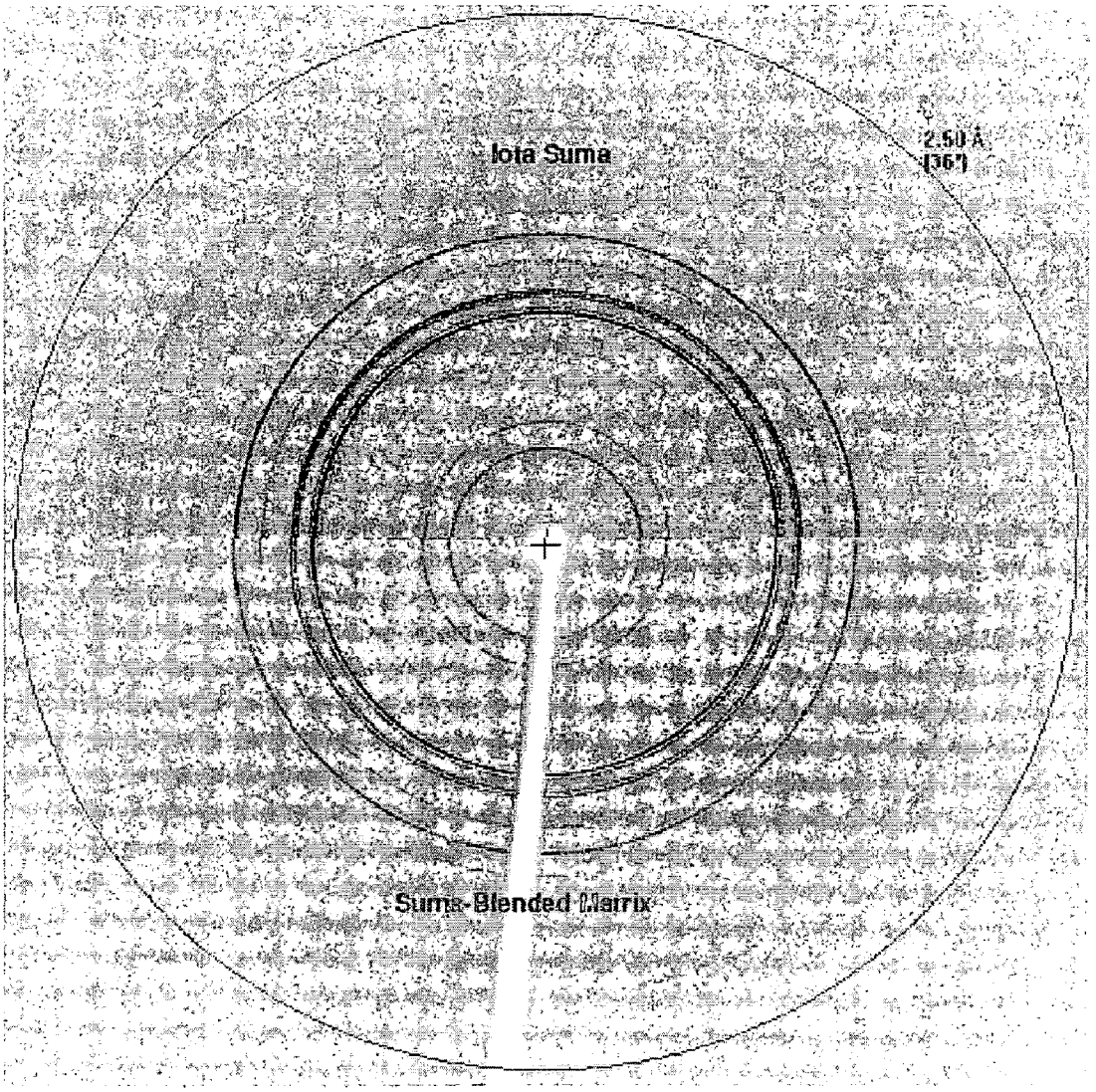


Fig. 7



PROCESSES FOR PREPARING PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

[0001] The present invention relates to improvements relating to pharmaceutical compositions. In particular it relates to pharmaceutically active compositions and precursors therefor which fall within the group of so-called "triptans".

BACKGROUND OF THE INVENTION

[0002] Triptans are a family of tryptamine-based drugs used, for example, in the treatment of migraine and cluster headaches. They are selective serotonin receptor agonists and their mechanism of action is attributed to their serotonin agonist activity at 5-HT_{1B} and 5-HT_{1D} receptors in the body, whether centrally, for example in the dorsal horn of the brain, and/or peripherally, for example at cranial blood vessels. Although other dosing regimes are possible, it is felt that triptans are preferably administered to a patient within twenty minutes of the onset of a headache.

[0003] Triptans include sumatriptan (Imitrex®, Imigran®), rizatriptan (Maxalt®), naratriptan (Amerge®, Natamig®), zolmitriptan (Zomig®), eletriptan (Relpax®), almotriptan (Axert®, Almogran®), and frovatriptan (Frova®, Migard®).

[0004] Many triptans exhibit low water solubility and are practically insoluble in water. This hinders their effective use, particularly for oral delivery in base form and water soluble salt forms are preferred, such as sumatriptan succinate, rizatriptan benzoate, naratriptan hydrochloride, eletriptan hydrobromide, almotriptan malate, frovatriptan succinate.

[0005] WO 2004/011537 describes the formation of solid, porous beads comprising a three dimensional open-cell lattice of a water-soluble polymeric material. These are typically "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 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 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.

[0006] WO 2005/011636 discloses a non-emulsion based spray drying 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.

[0007] Unpublished co-pending applications (GB 0501835 of 28 Jan. 2005 and GB 0613925 filed on 13 Jul. 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 water insoluble materials is dissolved in the solvent-phase 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 temperature (above 20° C.), 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 particles typically below 300 nm. This scale is similar to that of virus particles, and the water-insoluble material behaves as though it were in solution.

[0008] In the present application the term "ambient temperature" means 20° C. and all percentages are percentages by weight unless otherwise specified.

BRIEF DESCRIPTION OF THE INVENTION

[0009] 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 triptan.

[0010] Accordingly, the present invention provides a process for the production of a composition comprising a water-insoluble triptan which comprises the steps of:

[0011] a) providing a mixture comprising:

[0012] i) a water-insoluble triptan,

[0013] ii) a water soluble carrier, and

[0014] iii) a solvent for each of the triptan and the carrier; and

[0015] b) spray-drying the mixture to remove the or each solvent and obtain a substantially solvent-free nano-dispersion of the triptan in the carrier.

[0016] The preferred method of particle sizing for the dispersed 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 (633 nm) 4 mW Helium-Neon laser to illuminate a standard optical quality UV cuvette containing a suspension 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 of the particle size.

[0017] Preferably, the peak diameter of the water-insoluble triptan is below 1500 nm. More preferably the peak diameter of the water-insoluble triptan is below 1000 nm, most preferably below 800 nm. In a particularly preferred embodiment of the invention the median diameter of the water-insoluble triptan is in the range 400 to 1000 nm, more preferably 500 to 800 nm.

[0018] Advantageous compositions obtainable by the process of the present invention comprise a water-insoluble triptan and a water soluble carrier which comprises triptan particles of 750 nm average particle size dispersed in the carrier.

[0019] 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 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 those with a larger particle size.

[0020] In the context of the present invention, "water insoluble" as applied to the triptan means that its solubility in water is less than 25 g/L. "Water insoluble triptan" may also mean that the solubility of the triptan is less than 20 or less than 15 g/L. Preferably, the water insoluble triptan has solubility in water at ambient temperature (20° C.) less than 5 g/L

preferably of less than 1 g/L, especially preferably less than 150 mg/L, even more preferably less than 100 mg/L. This solubility level provides the intended interpretation of what is meant by water-insoluble in the present specification.

[0021] Preferred water-insoluble triptans include base forms of sumatriptan, rizatriptan, naratriptan, eletriptan, almotriptan, frovatriptan and zolmitriptan and water insoluble derivatives of these compounds.

[0022] Preferred carrier materials are selected from the group consisting of water-soluble organic and inorganic materials, surfactants, polymers and mixtures thereof.

[0023] A further aspect of the present invention provides a process for preparing a triptan composition comprising a water-insoluble triptan and a water-soluble carrier, which comprises the steps of:

[0024] a) forming an emulsion comprising:

[0025] i) a solution of the triptan in a water-immiscible solvent for the same, and

[0026] ii) an aqueous solution of the carrier; and

[0027] b) drying the emulsion to remove water and the water-immiscible solvent to obtain a substantially solvent-free nano-dispersion of the triptan in the carrier.

[0028] For convenience, this class of method is referred to herein as the "emulsion" method.

[0029] A further aspect of the present invention provides a process for preparing a triptan composition comprising a water insoluble triptan and a water-soluble carrier which comprises the steps of:

[0030] a) providing a single phase mixture comprising:

[0031] i) at least one non-aqueous solvent,

[0032] ii) optionally, water,

[0033] iii) a water-soluble carrier material soluble in the mixture of (i) and (ii), and

[0034] iv) a water-insoluble triptan which is soluble in the mixture of (i) and (ii); and

[0035] b) drying the solution to remove water and the water miscible solvent to obtain a substantially solvent-free nano-dispersion of the triptan in the carrier.

[0036] For convenience, this class of method is referred to herein as the "single-phase" method.

[0037] In the context of the present invention substantially solvent free means within limits accepted by international pharmaceutical regulatory bodies (eg FDA, EMEA) for residual solvent levels in a pharmaceutical product and/or 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.

[0038] In the context of the present invention it is essential that both the carrier material and the triptan 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 avoidance of any doubt, it is therefore the case that the solids content of the emulsion or the mixture is such that over 90% wt, preferably over 95%, and more preferably over 98% of the soluble materials present is in solution prior to the drying step.

[0039] In relation to the methods mentioned above, the preferred triptan 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.

[0040] The "single phase" method where both the triptan 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 obtaining a smaller particle size for the nano-disperse triptan. 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.

[0041] The products obtainable by the process aspects of the present invention are suitable for use in the preparation of medicaments for treatment of migraines and headaches, especially cluster headaches.

[0042] A further aspect of the present invention provides a method for the preparation of a medicament for use in the treatment of migraines and headaches, especially cluster headaches, which comprises the step of preparing a composition according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0043] Various preferred features and embodiments of the present invention are described in further detail below.

Triptans

[0044] As noted above the preferred water-insoluble triptans include sumatriptan, rizatripta, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan 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".

[0045] As an illustrative example, it would be beneficial to provide a combination of a triptan, such as Sumatriptan, and a further an agent, for example an NSAID such as diclofenac, ibuprofen or naproxen, paracetamol, or other analgesic agents such as for example, codeine or other anti-nausea agents such as for example, diphenhydramine or ondansetron.

Water-Dispersible Product Form

[0046] 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 triptan are dissolved. On removal of solvents the insoluble triptan is left dispersed through the water-soluble carrier material. Suitable carrier materials are described in further detail below.

[0047] 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. Further, from X-ray powder diffraction studies it is believed that the triptan nano-particle material produced is in crystalline form and not amorphous form and it is believed to be predominantly or entirely the same crystalline form as the starting material.

[0048] Preferably, the compositions produced after the drying step will comprise the triptan and the carrier in a weight ratio of from 1:500 to 1:1 (as triptan:carrier), 1:100 to 1:1 being preferred. Typical levels of around 10-50% wt water-insoluble triptan and 90-50% wt carrier can be obtained by spray drying.

[0049] By the method of the present invention the particle size of the triptan materials can be reduced to below 1000 nm and may be reduced to around 100 nm. Preferred particle sizes are in the range 400-800 nm.

"Emulsion" Preparation Method

[0050] In one preferred method according to the invention the solvent for the water-insoluble triptan is not miscible with water. On admixture with water it therefore can form an emulsion.

[0051] 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.

[0052] 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, or a rotational mechanical stirrer. The emulsions need not be particularly stable, provided that they do not undergo extensive phase separation prior to drying.

[0053] 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.

[0054] In a preferred method according to the invention a water-continuous emulsion is prepared with an average dispersed-phase droplet size (using the Malvern peak intensity) of between 500 nm and 5000 nm. We have found that an Ultra-Turrux T25 type laboratory homogenizer (or equivalent) gives a suitable emulsion when operated for more than a minute at above 10,000 rpm.

[0055] 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 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.

[0056] 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 with increase in the homogenization time, and the particle size distribution become broader at the same time.

[0057] Sonication is also a particularly preferred way of reducing the droplet size for emulsion systems. We have found that a Hert Systems Sonicator XL operated at level 10 for two minutes is suitable.

[0058] It is believed that ratios of components which decrease the relative concentration of the triptan to the solvents and/or the carrier give a smaller particle size.

"Single Phase" Preparation Method

[0059] In an alternative method according to the present invention both the carrier and the triptan are soluble in a non-aqueous solvent or a mixture of such a solvent with water. Both here and elsewhere in the specification the non-aqueous solvent can be a mixture of non-aqueous solvents.

[0060] In this case the feedstock of the drying step can be a single phase material in which both the water-soluble carrier and the water-insoluble triptan are dissolved. It is also possible for this feedstock to be an emulsion, provided that both the carrier and the triptan are dissolved in the same phase.

[0061] The "single-phase" method is generally believed to give a better nano-dispersion with a smaller particle size than the emulsion method.

[0062] It is believed that ratios of components which decrease the relative concentration of the triptan to the solvents and/or the carrier give a smaller particle size.

Drying

[0063] 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 explosion when a flammable solvent is being used, an inert gas, for example nitrogen, can be employed as the drying medium in a so-called closed spray-drying system. The solvent can be recovered and re-used.

[0064] We have found that the Buchi B-290 type laboratory spray drying apparatus is suitable.

[0065] It is preferable that the drying temperature should be at or above 100° C., preferably above 120° C. and most preferably above 140° C. Elevated drying temperatures have been found to give smaller particles in the re-dissolved nano-disperse material.

Carrier Material

[0066] 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 these.

[0067] 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 are preferred.

[0068] Suitable carrier materials (referred to herein as "water soluble carrier materials") include preferred water-soluble polymers, preferred water-soluble surfactants and preferred water-soluble inorganic materials.

Preferred Polymeric Carrier Materials

[0069] Examples of suitable water-soluble polymeric carrier materials include:

[0070] (a) natural polymers (for example naturally occurring gums such as guar gum, alginate, locust bean gum or a polysaccharide such as dextran;

[0071] (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 (e.g. the sodium salt—SCMC), or carboxy-methylhydroxyethylcellulose and its salts (for example the sodium salt);

[0072] (c) homopolymers of or copolymers prepared from two or more monomers selected from: vinyl alcohol, acrylic acid, methacrylic acid, acrylamide, methacrylamide, acrylamide methylpropane sulphonates, aminoalkylacrylates, aminoalkyl-methacrylates, hydroxyethylacrylate, hydroxyethylmethylacrylate, vinyl pyrrolidone, vinyl imidazole, vinyl amines, vinyl pyridine, ethyleneglycol and other alkylene glycols, ethylene oxide and other alkylene oxides, ethyleneimine, styrenesulphonates, ethyleneglycolacrylates and ethyleneglycol methacrylate;

[0073] (d) cyclodextrins, for example β-cyclodextrin; and

[0074] (e) mixtures thereof.

[0075] 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.

[0076] 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.

[0077] Polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), poly(2-ethyl-2-oxazaline), polyvinyl alcohol (PVA) hydroxypropyl cellulose and hydroxypropyl-methyl cellulose (HPMC) and alginates are preferred polymeric carrier materials.

Preferred Surfactant Carrier Materials

[0078] Where the carrier material is a surfactant, the surfactant may be non-ionic, anionic, cationic, amphoteric or zwitterionic.

[0079] 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; stearol ethoxylates; and alkyl polyglycosides.

[0080] 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; and isethionate sulfonates.

[0081] Examples of suitable cationic surfactants include fatty amine salts; fatty diamine salts; quaternary ammonium compounds; phosphonium surfactants; sulfonium surfactants; and sulfonxonium surfactants.

[0082] Examples of suitable zwitterionic surfactants include N-alkyl derivatives of amino acids (such as glycine, betaine, aminopropionic acid); imidazoline surfactants; amine oxides; and amidobetaines.

[0083] 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.

[0084] Alkoxylated nonionics (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 cetyltrimethylammonium bromide—CTAB) are particularly preferred as surfactant carrier materials.

Preferred Inorganic Carrier Materials

[0085] The carrier material can also be a 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, 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 acceptable. They are also relatively inert as well as compatible with many materials found in pharmaceutical products.

[0086] Mixtures of carrier materials are advantageous. Preferred mixtures include combinations of surfactants and polymers, which include at least one of:

[0087] a) polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl cellulose and hydroxypropyl-methyl cellulose (HPMC), and alginates; and at least one of:

[0088] b) alkoxylated nonionics (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 cetyltrimethylammonium bromide—CTAB).

[0089] The carrier material can also be a water-soluble small organic material which is neither a surfactant, a polymer 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, maltitol, dextrose, dextrins, dextrans, maltodextrin and inulin, etc.

Non-Aqueous Solvent

[0090] 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.

[0091] In one alternative form of the invention a single, non-aqueous solvent is employed in which can form a single phase with water in the presence of the triptan 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 greater than 4.5.

[0092] Particularly preferred solvents are selected from the group consisting of haloforms (preferably dichloromethane, chloroform), lower (C1-C10) alcohols (preferably methanol, 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 miscible species comprising heteroatom bond with a suitably large dipole (preferably tetrahydrofuran, dialkylsulphoxide).

[0093] Haloforms, lower alcohols, ketones and dialkylsulphoxides are the most preferred solvents.

[0094] In another alternative form of the invention the non-aqueous solvent is not miscible with water and forms an emulsion.

[0095] The non-aqueous phase of the emulsion is preferably selected from one or more from the following group of volatile organic solvents:

[0096] alkanes, preferably heptane, n-hexane, isooctane, dodecane, decane;

[0097] cyclic hydrocarbons, preferably toluene, xylene, cyclohexane;

[0098] halogenated alkanes, preferably dichloromethane, dichoroethane, trichloromethane (chloroform), fluoro-trichloromethane and tetrachloroethane;

[0099] esters, preferably ethyl acetate;

[0100] ketones, preferably 2-butanone;

[0101] ethers, preferably diethyl ether;

[0102] volatile cyclic silicones, preferably either linear or cyclomethicones containing from 4 to 6 silicon units. Suitable examples include DC245 and DC345, both of which are available from Dow Corning Inc.

[0103] Preferred solvents include dichloromethane, chloroform, ethanol, acetone and dimethyl sulphoxide.

[0104] Preferred non-aqueous solvents, whether miscible or not, have a boiling point of less than 150° C. and, more preferably, have a boiling point of less than 100° C., 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.

[0105] 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.

[0106] Particularly preferred solvents are alcohols, particularly ethanol and halogenated solvents, more preferably chlorine-containing solvents, most preferably solvents selected from (di- or trichloromethane).

Optional Cosurfactant

[0107] 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 297 nm to 252 nm 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.

[0108] Preferred co-surfactants are short chain alcohols or amine with a boiling point of <220° C.

[0109] Preferred co-surfactants are linear alcohols. Preferred co-surfactants are primary alcohols and amines. Particularly preferred co-surfactants are selected from the 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.

[0110] 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.

Preferred Spray-Drying Feedstocks

[0111] Typical spray drying feedstocks comprise:

[0112] a) a surfactant;

[0113] b) at least one lower alcohol;

[0114] c) more than 0.1% of at least one water-insoluble triptan dissolved in the feedstock;

[0115] d) a polymer; and,

[0116] e) optional water.

[0117] Preferred spray-drying feedstocks comprise:

[0118] a) at least one non-aqueous solvent selected from dichloromethane, chloroform, ethanol, acetone, and mixtures thereof;

[0119] b) a surfactant selected from PEG co-polymer nonionics (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;

[0120] c) more than 0.1% of at least one water-insoluble triptan;

[0121] 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

[0122] e) optionally, water.

[0123] 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 triptan.

[0124] The level of the triptan in the composition may be up to 95% wt, up to 90%, up to 85%, up to 80%, up to 75%, up to 70%, up to 65%, up to 60%, up to 55%, up to 50%, up to 45%, up to 40%, up to 35% or up to 30%. It is particularly preferable that the level of the triptan 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.

Water-Dispersed Form

[0125] On admixture of the water-soluble carrier material with water, the carrier dissolves and the water-insoluble triptan 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 the water-insoluble materials have a particle size of less than 1 μm as determined by the Malvern method described herein. It is believed that there is no significant reduction of particle size for the triptan on dispersion of the solid form in water.

[0126] 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 optically

clear solutions comprising more than 0.1%, preferably more than 0.5% and more preferably more than 1% of the water-insoluble material.

[0127] 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.

EXAMPLES

[0128] 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.

[0129] A range of formulations were produced based on different excipients, different active loadings, and different process conditions. The formulations include sumatriptan as an illustrative example of a triptan, but could equally have been prepared using one of the other available water insoluble triptans.

[0130] The excipients were chosen from hydroxypropyl cellulose (Klucel EF, Herlus), polyvinyl pyrrolidone (PVP k30, Aldrich), hydroxypropyl methyl cellulose (HPMC, Mw 10 k, 5 cps, Aldrich), polyethylene glycol (PEG, Mw 6,000, Fluka), Tween 80 (Aldrich), pluronic F68 (BASF), pluronic F127 (Aldrich), span 80 (Aldrich), cremphor RH40 (BASF), mannitol (Aldrich), and sodium alginate (Aldrich).

[0131] Details of these formulations are listed as below:

Example 1

20 wt % Loadings

[0132] 0.40 g Sumatriptan, 1.00 g Klucel EF, 0.44 g HPMC, and 0.16 g Pluronic F68 are all dispersed into 100 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bat for about half hour before adding 60 ml distilled water. A clear solution is obtained.

[0133] The solution is 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 is obtained.

[0134] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 100 and 500 nm.

Example 2

20 wt % Loadings

[0135] 0.40 g Sumatriptan, 1.00 g Klucel EF, 0.34 g HPMC, 0.16 g Pluronic F127, and 0.10 g Tween 80 are all dispersed into 100 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour before adding 60 ml distilled water. A clear solution is obtained.

[0136] 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 is obtained.

[0137] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 100 to 500 nm.

[0138] Two dissolution tests based on a 20 mg sumatriptan dose and an 80 mg sumatriptan dose are carried out using the standard USP2 test. 50% of the 20 rag dose is expected to dissolve within less than 10 minutes and 50% of the 80 mg dose within 30 minutes. 95% of the 20 mg dose is expected to dissolve within less than 60 minutes and 95% of the 80 mg dose within less than 150 minutes.

Example 3

20 wt % Loadings

[0139] 0.40 g Sumatriptan, 1.00 g Klucel EF, and 0.60 g HPMC are all dispersed into 100 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour before adding 60 ml distilled water. A clear solution is obtained.

[0140] The solution is 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 is obtained.

[0141] 20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 100 and 500 nm.

Example 4

20 wt % Loadings

[0142] 0.40 g Sumatriptan, 1.44 g Klucel EF, and 0.16 g PEG 6000 are all dispersed into 100 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour and a clear solution is obtained.

[0143] The solution is 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 is obtained.

[0144] 20 mg dried powder is dispersed into 10 ml distilled water, giving a translucent nanodispersion with a particle size of between 300 and 800 nm.

Example 5

20 wt % Loadings

[0145] 0.40 g Sumatriptan, 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 are all dispersed into 100 ml absolute ethanol. The ethanol suspension is stirred intensively with magnetic bar for about half hour before adding 60 ml distilled water. A clear solution is obtained.

[0146] The solution is 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 is obtained.

[0147] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of 100 to 200 nm.

Example 6

20 wt % Loadings

[0148] 0.40 g Sumatriptan, 1.34 g Klucel EF, 0.16 g Pluronic F127, and 0.10 g Cremphor RH40 are all dispersed into 100 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour before adding 60 ml distilled water. A clear solution is obtained.

[0149] The solution is 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 is obtained.

[0150] 20 mg dried powder was dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 100 and 200 nm.

[0151] Two dissolution tests based on a 20 mg sumatriptan dose and an 80 mg sumatriptan dose are carried out for formulations following the standard USP2 test. 50% of the 20

mg dose is expected to dissolve within less than 10 minutes and 50% of the 80 mg dose within less than 5 minutes. 95% of the 20 mg dose is expected to dissolve within less than 25 minutes and 95% of the 80 mg dose within less than 90 minutes.

Example 7

20 wt % Loadings

[0152] 0.40 g Sumatriptan, 1.18 g Klucel EF, 0.16 g Pluronic F68, 0.16 g Pluronic F127, and 0.10 g Span 80 are all dispersed into 100 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour before adding 10 ml distilled water. A clear solution is obtained.

[0153] The solution is 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 is obtained.

[0154] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 100 and 300 nm.

Example 8

20 wt % Loadings

[0155] 0.40 g Sumatriptan, 1.40 g Klucel EF, 0.10 g Tween 80, and 0.10 g Span 80 are all dispersed into 100 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour and a clear solution is obtained.

[0156] The solution is 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 is obtained.

[0157] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 100 and 300 nm.

Example 9

30 wt % Loadings

[0158] 0.30 g Sumatriptan, 0.57 g Klucel EF, 0.05 g PEG 6000, 0.05 g Pluronic F127, and 0.03 g Tween 80 are all dispersed into 50 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour before adding 30 ml distilled water. A clear solution is obtained.

[0159] The solution is 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 is obtained.

[0160] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 100 and 400 nm.

Example 10

30 wt % Loadings

[0161] 0.30 g Sumatriptan, 0.65 g Klucel EF, 0.025 g Tween 80, and 0.025 g Span 80 are all dispersed into 50 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour and a clear solution is obtained.

[0162] The solution is 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 is obtained.

[0163] 20 mg dried powder is dispersed into 10 ml distilled water, giving a translucent nanodispersion with a particle size of between 200 and 400 nm.

Example 11

20 wt % Loadings

[0164] 0.20 g Sumatriptan, 0.40 g Klucel EF, 0.10 g Pluronic F127, 0.10 g Tween 80, and 0.20 g Mannitol are all dispersed into 50 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour before added 30 ml distilled water. A clear solution is obtained.

[0165] The solution is 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 is obtained.

[0166] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 100 and 300 nm.

[0167] A dissolution test based on a 20 mg sumatriptan dose is carried out for formulation obtained from Example 11 following the standard USP2 test. 50% of the 20 mg dose is expected to dissolve within less than 5 minutes and 95% within less than 10 minutes.

Example 12

20 wt % Loadings

[0168] 0.20 g Sumatriptan, 0.50 g Klucel EF, 0.10 g Plutonic F127, and 0.20 g Mannitol are all dispersed into 50 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour before adding 30 ml distilled water. A clear solution is obtained.

[0169] The solution is 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 is obtained.

[0170] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 100 and 300 nm.

[0171] A dissolution test based on a 20 mg sumatriptan dose is carried out for following the standard USP2 test. 95% of the 20 mg dose is expected to dissolve within less than 5 minutes.

Example 13

20 wt % Loadings

[0172] 0.20 g Sumatriptan, 0.60 g Klucel EF, 0.05 g Pluronic F127, 0.05 g Tween 80, and 0.10 g Mannitol are all dispersed into 50 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour before adding 30 ml distilled water. A clear solution is obtained.

[0173] The solution is 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 is obtained.

[0174] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 100 and 300 nm.

Example 14

20 wt % Loadings

[0175] 0.20 g Sumatriptan, 0.60 g Klucel EF, 0.10 g Pluronic F127, 0.025 g Tween 80, and 0.025 g Span 80 are all

dispersed into 50 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour and a clear ethanol solution was formed. 0.05 g Sodium alginate is dissolved into 30 ml distilled water. The ethanol solution and the aqueous solution are mixed together and a clear mixture is obtained.

[0176] The mixture is 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 is obtained.

[0177] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 100 and 400 nm.

Example 15

20 wt % Loadings

[0178] 0.20 g Sumatriptan, 0.60 g Klucel EF, 0.15 g Pluronic F127 are all dispersed into 50 ml absolute ethanol. The ethanol suspension is stirred intensively with a magnetic bar for about half hour. 0.05 g Sodium alginate is dissolved into 30 ml distilled water. The ethanol dispersion and the aqueous solution are mixed together and a clear mixture is obtained.

[0179] The mixture is 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 is obtained.

[0180] 20 mg dried powder is dispersed into 10 ml distilled water, giving a crystal clear nanodispersion with a particle size of between 200 and 400 nm.

[0181] A dissolution test based on a 20 mg sumatriptan dose is carried out for the formulation prepared in Example 15 following the standard USP2 test. 50% of the mg dose is expected to dissolve within less than 5 minutes and 95% within less than 90 minutes.

Example 16

[0182] This example summarises the experimental conditions used to produce three consecutive batches of spray dried Sumatriptan USP formulation (containing 40% (w/w) sumatriptan). The batches were spray dried using a Niro Mobile Minor and the same spray drying conditions used for each batch. A single solution of the sumatriptan formulation was prepared and used to produce the batches, with spray drying occurring over a 2-day period.

[0183] All chemicals used for spray drying studies were sourced by Iota NanoSolutions. These include, for Sumatriptan Batches SMT/0706003 and SMT/0602002:

[0184] Tween 80 supplied by Croda Iota Batch E0028D

[0185] Mannitol supplied by Roquette Iota Batch E0010

[0186] Polydextran supplied by Danisco Iota Batch E0025

[0187] Lutrol F127 supplied by BASF Iota Batch E0014

[0188] HPMC supplied by Colorcon Iota Batch E0017

[0189] Ethanol (Absolute) supplied in bulk by VWR

Preparation of a Sumatriptan Solution for Spray Drying

Day 1:

[0190] The following quantities of powder were weighed out (to within 0.01 g): 19.9 g Sumatriptan Batch SMT/0706003 (required amount was 20 g). The sumatriptan was added to 1.0 L ethanol and left to stir overnight at room temperature in a capped bottle.

Day 2:

[0191] A further 1.5 L of ethanol was added to the suspension and stirred for 1 hour to fully dissolve the sumatriptan (total volume of ethanol was 2.5 L). A pale yellow solution was produced.

[0192] 18 g HPMC was then added to the ethanolic sumatriptan solution and stirred briskly for 1 hour to produce an even suspension.

[0193] The following aqueous solution was prepared separately by adding the following solutes to 2.5 L of de-ionised water and stirring for 1 hour: 3 g Mannitol, 3 g Polydextran, 3 g Lutrol F127, and 3 g Tween 80. The aqueous solution was then added to the sumatriptan/HPMC suspension and stirred for 30 mins. The resulting solution became "clear" but then became "cloudy" as the final amounts of aqueous solution were added. Total solids content at this stage was 50 g solids in 5.0 L 50% (v/v) ethanol/water solution (i.e. 1% (w/v))

[0194] To return to a "clear" solution a decision was made to adjust the solute concentrations and solvent concentrations such that the solids content remained at ~1% (w/v) but that the ethanol concentration was raised to 60% (v/v).

[0195] The following quantities of powder were weighed out (to within 0.01 g): 10 g Sumatriptan Batch SMT/0602002. The sumatriptan was added to 1.25 L ethanol and left to stir at room temperature for 2 hours. When the sumatriptan had dissolved, 9 g of HPMC was added and stirred for 1 hour to create a homogeneous suspension. Additional solutes were added to the existing 5 L volume of sumatriptan solution and the solution stirred for 30 mins, namely: 1.5 g Mannitol, 1.5 g Polydextran, 1.5 g Lutrol F127 and 1.5 g Tween 80. The aqueous solution was then added to the 1.25 L of ethanolic Sumatriptan/HPMC suspension and stirred for 30 mins. The resulting solution was clear, pale yellow.

[0196] The final solution contained 75 g solids in 6.25 L of 60% (v/v) ethanol/water i.e. 1.2% (w/v) solids.

[0197] The process for manufacturing the sumatriptan spray solution is summarised in the flowchart shown in FIG. **1**.

Spray Drying Process

[0198] A 2 L volume of the sumatriptan solution was spray dried using a Niro Mobile Minor fitted with a 2-fluid nozzle. The liquid feed was provided by a gear pump calibrated to provide a flow of 25 ml/minute. The following spray drying conditions were used:

Inlet temperature	100° C.
Outlet temperature (start)	57° C.
Liquid feed rate	25 ml/min
Atomisation pressure	0.5 bar

[0199] After all of the solution had been atomised, drying was halted and the spray dried powder recovered (Batch Number INS089-UT04). The spray dryer was then cleaned and dried prior to further use.

[0200] A 2 L volume of the sumatriptan solution was spray dried using a Niro Mobile Minor fitted with a 2-fluid nozzle.

The liquid feed was provided by a gear pump calibrated to provide a flow of 25 ml/minute. The following spray drying conditions were used:

Inlet temperature	100° C.
Outlet temperature (start)	59° C.
Liquid feed rate	25 ml/min
Atomisation pressure	0.5 bar

[0201] After all of the solution had been atomised, drying was halted and the spray dried powder recovered (Batch Number INS089-UT05). The spray dryer was then cleaned and dried prior to further use.

[0202] A 2 L volume of the sumatriptan solution was spray dried using a Niro Mobile Minor fitted with a 2-fluid nozzle. The liquid feed was provided by a gear pump calibrated to provide a flow of 25 ml/minute. The following spray drying conditions were used:

Inlet temperature	100° C.
Outlet temperature (start)	58° C.
Liquid feed rate	25 ml/min
Atomisation pressure	0.5 bar

[0203] After all of the solution had been atomised, drying was halted and the spray dried powder recovered (Batch Number INS089-UT06).

[0204] The recoveries obtained are shown in Table 1. Each spray drying run used 2.0 L of a 1.2% (w/v) solution i.e. 24 g spray dried.

TABLE 1

Recovery of Spray Dried Powders

Batch Number	Quantity of Material Recovered (% of starting material)
INS089-UT04	12.3 g (51%)
INS089-UT05	15.3 g (64%)
INS089-UT06	16.4 g (68%)

[0205] Size analysis of the three spray dried batches were carried out using a Sympatec Laser Sizer, fitted with a Rodos air dispenser. Powders dispersed at 5.0 bar.

[0206] FIG. **2** is a graph showing the size analysis of Sumatriptan Batch INS089-UT04, wherein:

x_{10} = 2.81 μm	x_{50} = 11.67 μm	x_{90} = 35.99 μm
SMD = 5.79 μm	VMD = 16.98 μm	
x_{16} = 4.17 μm	x_{84} = 28.41 μm	x_{99} = 96.35 μm
S_v = 1.04 m^2/cm^3	S_m = 7681.35 cm^2/g	

[0207] FIG. **3** is a graph showing the size analysis of Sumatriptan Batch INS089-UT05, wherein:

x_{10} = 2.51 μm	x_{50} = 9.38 μm	x_{90} = 27.39 μm
SMD = 5.16 μm	VMD = 12.79 μm	
x_{16} = 3.67 μm	x_{84} = 21.73 μm	x_{99} = 56.73 μm
S_v = 1.16 m^2/cm^3	S_m = 8619.08 cm^2/g	

[0208] FIG. **4** is a graph showing the size analysis of Sumatriptan Batch INS089-UT06, wherein:

x_{10} = 2.42 μm	x_{50} = 8.90 μm	x_{90} = 26.09 μm
SMD = 5.01 μm	VMD = 12.29 μm	
x_{16} = 3.52 μm	x_{84} = 20.55 μm	x_{99} = 57.62 μm
S_v = 1.20 m^2/cm^3	S_m = 8875.92 cm^2/g	

[0209] FIG. **5** is a graph showing the size analysis of Sumatriptan Batches INS089-UT04, INS089-UT05 and INS089-UT06.

Example 17

[0210] The following materials were used as purchased, without further purification:

[0211] 1-[3-(2-dimethylaminoethyl)-1H-indol-5-yl]-N-methyl-methanesulfonamide (Sumatriptan, 98%, MW 295.402 g/mol, supplied by PharmaKodex)

[0212] Hydroxypropyl methyl cellulose (HPMC, Mw 10,000, Aldrich)

[0213] Polyvinylpyrrolidone K30 (PVP, Mw 45,000, Aldrich)

[0214] Maltitol (MW 344.32 g/mol, Fluka)

[0215] Polydextrose (Litessse® II, Danisco)

[0216] Pluronic F-127 (Aldrich)

[0217] Tween 80 (MW 1309.68 g/mol, Aldrich)

[0218] Sumatriptan and the excipients were dissolved into water/ethanol co-solvent and the resulting solution was then spray dried on a Buchi B-290 Mini Spray Dryer. The spray drying was conducted with an inlet temperature of 100° C. and a pump rate of 2.5 ml/min. The make-up of each batch is set out in Table 2.

TABLE 2

Batch No.	Sumatriptan (wt %)	HPMC (wt %)	PVP (wt %)	Poly-dextrose (wt %)	Maltitol (wt %)	Pluronic F-127 (wt %)	Tween 80 (wt %)	Water:EtOH
39	20	24	24	8	8	8	8	1:1.6
42	40	18	18	6	6	6	6	1:1.2
54	40	36	—	6	6	6	6	1:1
55	40	—	36	6	6	6	6	1:1
58	40	42	—	6	6	—	6	1:1
60	40	40	—	6	6	—	8	1:1

[0219] In order to measure the sumatriptan particle size distribution (PSD), a 25 mg sample of the spray dried sumatriptan batches were dissolved into 26 ml distilled water with stirring (vortex) before measurements were taken using Malvern Nano-S particle sizer. The dispersions were corrected for viscosity.

[0220] To study the dissolution characterization, a 50 mg sample (equivalent to 20 mg sumatriptan) of the spray dried batches was dissolved into 1000 ml of distilled water at 37° C. with overhead paddle stirring at 50 rpm. Aliquots of each solution were taken at 5, 10, and 15 minutes. The dispersions were then diluted with 0.1 M HCl solution for UV characterization. The dissolution is expressed as a percentage of the initial sumatriptan concentration that has dissolved after specific time intervals, for each formulation.

TABLE 3

Batch No.	% Solids in solution	PSD (nm)	Dissolution In H_20 (5 min)	Dissoluton in H_20 (10 min)
39	1.5%	354	89	100
42	0.9%	306	98	100
54	0.8%	414	91	101
55	0.8%	598	99	99
58	0.8%	1030	76	99
60	0.8%	492	97	98

[0221] A UV calibration curve was also obtained by dissolving different amounts of sumatriptan into 0.1 M HCl solution.

[0222] FIGS. **6** and **7** show the X-ray powder diffraction results. These show that the sumatriptan nano-particle material produced is in crystalline form and not amorphous form and it is believed to be predominantly or entirely the same crystalline form as the starting material.

1. A process for the production of a composition comprising a water-insoluble triptan which comprises the steps of:
- a) providing a mixture comprising:
  - i) a water-insoluble triptan,
  - ii) a water soluble carrier, and
  - iii) a solvent for each of the triptan 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 triptan in the carrier.

2. A process according to claim **1**, which comprises the steps of:
- a) providing an emulsion comprising:
  - i) a solution of the triptan in a water-immiscible solvent for the same, and
  - ii) an aqueous solution of the carrier; and
- b) spray-drying the emulsion to remove water and the water-immiscible solvent to obtain a substantially solvent-free nano-dispersion of the triptan in the carrier.

3. A process according to claim **1**, which comprises the steps of:
- a) providing a single phase mixture comprising:
  - i) at least one non-aqueous solvent,
  - ii) optionally, water,
  - iii) a water-soluble carrier material soluble in the mixture of (i) and (ii), and
  - iv) a water-insoluble triptan which is soluble in the mixture of (i) and (ii); and
- b) spray-drying the solution to remove water and the water miscible solvent to obtain a substantially solvent-free nano-dispersion of the triptan in the carrier.

4. A process according to claim **1**, wherein the spray drying process is conducted at a temperature at or above 120° C.

5. A process according to claim **1**, in which the carrier material includes a polymer and/or a surfactant.

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

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.

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

9. A process according to claim **1**, wherein the water insoluble triptan is sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan or almotriptan.

10. A process for the preparation of a medicament for use in the treatment migraine or headache, which comprises the step of preparing a composition by a process according to claim **1**.

11. A composition comprising a water-insoluble triptan and a water soluble carrier which comprises triptan particles with an average particle size of between 100 and 1500 nm dispersed in the carrier.

12. A composition according to claim **11**, wherein the composition is obtained or obtainable by a process which comprises the steps of:
- a) providing a mixture comprising:
  - i) a water-insoluble triptan,
  - ii) a water soluble carrier, and
  - iii) a solvent for each of the triptan 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 triptan in the carrier.

13. A composition according to claim **11**, wherein the average particle size of the triptan particles is between 200 and 1000 nm, 400 and 1000 nm or 500 and 800 nm.

14. A composition according to claim **11**, wherein the triptan particles are substantially crystalline.

15. A composition according to claim **11**, wherein the triptan particles retain the crystallinity of the original triptan material used to prepare the composition.

16. A composition according to claim **11**, wherein the triptan particles are substantially free of amorphous material.

17. A composition according to claim **11**, further comprising one or more further therapeutically active agent.

18. A composition according to claim **17**, wherein the composition comprises an analgesic agent, an NSAID or paracetamol.

19. A composition according to claim **17**, wherein the composition comprises an anti-nausea agent, diphenhydramine or ondansetron.

20. A composition according to claim **11**, for use in treating migraine and/or headache.

21. A method of treating migraine and/or headache, comprising administering to a patient a therapeutically effective amount of a composition according to claim **11**.

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