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(54) Title: PROCESS FOR PREPARATION OF CRYSTALLINE NANO-PARTICLE SUSPENSIONS

(57) Abstract: A process for the preparation of a suspension comprising crystalline nano-particles ofa substantially water insoluble substance in an aqueous medium, involving inter alia dissolving a stabiliser in an aqueous phase and dispersing said substance therein, heating the suspension obtained to a temperature above the melting point of the substantially water insoluble substance until undissolved substance material is melted, or to a temperature where all particles are dissolved, cooling and sonicating or high pressure homogenizing to form a suspension of solid crystalline nano-particles.

PROCESS FOR PREPARATION OF CRYSTALLINE NANO-PARTICLE SUSPENSIONS

Field of the invention

The present invention relates to a process for the preparation of a suspension of crystalline nano-particles, particularly a suspension of crystalline nano-particles in an aqueous medium and more particularly to a process for the preparation of a suspension of crystalline nano-particles comprising a substantially water-insoluble pharmacologically active compound in an aqueous medium.

Background

Suspensions of a solid material in a liquid medium are useful in a number of applications including paints, inks, suspensions of pesticides and other agrochemicals, suspensions of biocides and suspensions of pharmacologically active compounds.

In the pharmaceutical field many pharmacologically active compounds have very low aqueous solubility that can result in low bioavailability when such compounds are administered to a patient. Generally, the bioavailability of such compounds is improved by reducing the particle size of the compound, particularly to a sub-micron size, because this improves dissolution rate and hence absorption of the compound.

The formulation of a pharmacologically active compound as an aqueous suspension, particularly a suspension with a sub-micron particle size, enables the compound to be administered intravenously thereby providing an alternative route of administration which may increase bioavailability compared to oral administration.

Production of suspensions of crystalline nanoparticles can be performed in different ways such as by suspending particles milled to the desired size or by precipitation of the crystalline nanoparticles. However, during milling processes milling beads of for example polystyrene, glass or zirconium oxide are used. Such milling beads may contaminate the nanoparticle product by small fragments of the beads formed by attrition in the process. These fragments will be left in the product, either in the isolated nanoparticles or in the

suspension. This contamination is highly undesired if the suspension is intended to be used for parenteral administration of a drug, for example intravenous or intramuscular administration.

Attempts to precipitate crystalline material by direct precipitation is generally difficult to control and results in the formation and growth of large (>1micron) crystals.

US 4,826,689 describes a process for the preparation of amorphous particles of a solid by infusing an aqueous precipitating liquid into a solution of the solid in an organic liquid under controlled conditions of temperature and infusion rate, thereby controlling the particle size. US 4,997,454 describes a similar process for the preparation of amorphous particles in which the precipitating liquid is non-aqueous. US 5,118,528 also describes a process for preparing a colloidal suspension of particles using a solvent/anti-solvent precipitation process.

US 5,780,062 describes a process for preparing small stable particles wherein a solution of a substance in an organic solvent is precipitated into an aqueous solution containing polymer/amphiphile complexes.

WO 98/23350 and WO 99/59709 describe processes in which a melt of an organic compound is dispersed in a liquid to form an emulsion. The emulsion is then subjected to ultrasound to give a crystalline suspension. The particles prepared using the process are of the order 2 to 10 microns.

Crystalline suspensions obtained directly by precipitation are known in the art to be influenced by agitation of the solutions. Various methods of agitation are known in the art (see for example, WO 01/92293), for example mechanical mixing, vibration, microwave treatment and sonication.

US 5,314,506 describes a crystallisation process in which a jet of a solution containing a substance is impinged with a second jet containing an anti-solvent for the substance. The rapid mixing produced by the impinging jets results in a reduction of the crystals so formed compared to conventional slow crystallisation processes. The smallest crystals disclosed are about 3 microns and the majority are in the range of from 3 to 20 microns.

WO 00/44468 describes a modification to the apparatus described in US 5,314,506 wherein ultrasound energy is applied at the point of impingement of the two jets to further

enhance localised mixing and is stated to give direct formation of small crystals with a diameter of less than 1 micron. Generally the crystalline particles described have an average size of 0.5 microns.

WO 00/38811 describes an apparatus and process wherein crystalline particles suitable for inhalation are prepared by precipitation of a substance from solution using an anti-solvent in a flow-cell mixing chamber in the presence of ultrasonic radiation at the point of mixing the solvent and anti-solvent system. This method results in the direct crystallisation of particles typically having an average particle size of from 4 to 10 microns. WO 02/00199 and WO 03/035035 describe modifications to the process described in WO 00/38811 that reduce crystal agglomeration and enable more efficient isolation of the crystals so formed.

EP 275 607 describes a process wherein ultrasound energy is applied to a suspension of crystals in a liquid phase, the ultrasound being used to fragment the pre-formed crystals. Generally the volume mean diameter of the resulting crystals was 10 to 40 microns.

An alternative approach to direct precipitation is to reduce the particle size of the material prior to suspension, for example by milling as described in US 5,145,684. However this can be disadvantageous as it may be difficult to achieve a sufficiently uniform crystal size.

Another alternative process of preparing submicron particle suspension is by precipitation and energy addition. Such processes are described in WO 2002/055059 and in WO 2004/009057.

A process for preparation of a stable suspension of solid amorphous particles of submicron size is described in WO 2007/02122, and also in WO 2008/097165. The active ingredient is combined with an inhibitor providing an oil phase and inhibiting the particle growth.

Previously, crystalline nano-particles have been produced by milling and precipitation.

It is particularly important that the particle size in a suspension of a pharmacologically active compound is as uniform as possible because a difference in particle size is likely to affect the bioavailability and hence the efficacy of the compound.

Furthermore, if the suspension is required for intravenous administration, large particles in the suspension may render the suspension unsuitable for this purpose, possibly leading to adverse or dangerous side effects. Preparing such suspensions by milling may lead to problems caused by unintended and undesired presence of fragment particles deriving from attrition of the milling bodies used.

The precipitation processes known have the disadvantage of only giving suspensions having low concentration of the precipitated compound.

There is therefore a need for alternative processes that enable nano-particles to be formed, particularly nano-particles having an average diameter of less than 1 micrometer, or even 500 nm, with a narrow particle size distribution.

Short description of the invention

We have surprisingly found that high concentration suspensions of nano-particles in an aqueous medium can be prepared in a process wherein conversion of a substantially water-insoluble substance in an amorphous/super cooled form into a crystalline form is induced by an input of high energy, for example by sonication or high pressure homogenisation, and wherein the obtained crystalline nanoparticles comprising a substantially water insoluble substance are of uniform size and have a narrow particle size distribution.

For some substances, the process can yield metastable crystal forms without the need of seeding, which is an advantage. The metastable forms are known to have an increased solubility, thereby providing an advantage in biopharmaceutical aspects.

In one embodiment of the invention there is provided a process for the preparation of a suspension of such crystalline nano-particles comprising a substantially water insoluble substance in an aqueous medium, comprising the following steps in the given order;

a) dissolving one or more stabiliser in an aqueous medium to obtain an aqueous phase.

b) dispersing a substantially water insoluble substance in the aqueous phase comprising one or more stabilisers;

c) heating the suspension obtained in step b) to a temperature above the melting point of the substantially water insoluble substance until undissolved substance material is melted, or to a temperature where all particles are dissolved;

d) cooling the suspension to near room temperature without preceding homogenization; and

e) sonicating or high pressure homogenizing the suspension for a sufficient period to form a suspension of solid crystalline nano-particles comprising a substantially water insoluble substance.

By the process described above, the substantially water insoluble substance is converted to crystalline nano-particles in a suspension which is comprising a high concentration of the substance.

The suspension obtained in the process above consisting of steps a)-e), is then in another embodiment, further passing through an additional process step f) wherein the aqueous medium is removed from the suspension to obtain crystalline nano-particles comprising a substantially water insoluble substance.

Brief Description of the Figures

Figure 1. X-ray diffractogram of Bicalutamide suspensions from Examle 1b before (upper curve) and after heating (lower curve), showing that different polymorphs are obtained.

Detailed description of the invention

In one embodiment of the invention there is provided a process for the preparation of a suspension of crystalline nano-particles of uniform size and having a narrow particle size distribution, comprising a substantially water insoluble substance, in an aqueous medium, the process comprising in the given order;

a) dissolving one or more stabiliser in an aqueous medium to obtain an aqueous phase.

b) dispersing a substantially water-insoluble substance in the aqueous phase comprising one or more stabilisers;
c) heating the suspension obtained in step b) to a temperature above the melting point of the substantially water-insoluble substance until undissolved substance material is melted, or to a temperature where all particles are dissolved;
d) cooling the suspension to near room temperature without preceding homogenization; and
e) sonicating or high pressure homogenizing the suspension for a sufficient period to form a suspension of solid crystalline nano-particles comprising a substantially water insoluble substance.

By the process described above, the substantially water insoluble substance is converted to crystalline nano-particles in a suspension which is comprising a high concentration of the substance.

The suspension obtained in the process above consisting of steps a)-e), is then in another embodiment, further passing through an additional process step f) wherein;
the aqueous medium is removed from the suspension to obtain crystalline nano-particles comprising a substantially water insoluble substance.

The process described herein is performed in an aqueous medium. Water is preferred as aqueous medium in perspective of environmental aspects. It is also suitable to use water if the product will be for parenteral administration, as the process can result in a product ready to use for, e.g. intramuscular administration.

In alternative embodiments of the invention the aqueous medium comprises water at a level selected from the group consisting of; above 90%, above 95%, above 99%, above 99.5% and above 99.9%, w/w.

In a further alternative embodiment of the invention the aqueous medium consists of practically 100% w/w of water.

A further aspect of the invention is crystalline nano-particles of a substantially water-insoluble substance made by the process of the present invention.

In this specification, by 'crystalline nano-particles' we mean crystalline particles with a mean particle size of less than one micron in diameter, i.e. less than one μm in diameter, unless otherwise specified.

By the process described herein, including the cooling of the melted substantially water-insoluble substance into a super cooled phase and applying high energy by sonication, the substantially water-insoluble substance is converted to crystalline nano-particles in a suspension which is comprising a high concentration of the substance. The unique conditions of constant super-saturation provided by the presence of the amorphous particle suspension in the present invention to a great extent acts as a driving force for the precipitation of crystals. This gives inter alia the advantage of having lesser aqueous medium to remove if so desired, which reduces costs and processing time for such a processing step.

In one embodiment of the invention the obtained crystalline nano-particles in the suspension have a mean particle size of less than 500 nm, preferably less than 400 nm, more particularly less than 300 nm, more particularly less than 270 nm, in diameter. In another embodiment the crystals in the suspension have a mean particle size in the range of from 10 to 500 nm, more particularly from 10 to 400 nm, more particularly from 10 to 300 nm, more particularly from 10 to 270 nm, more particularly from 30 to 270 nm, especially from 50 to 270 nm and still more especially from 100 to 250 nm, in diameter. By the term " mean particle size" used herein is meant the volume average particle diameter as measured using conventional techniques, for example by laser diffraction apparatus, using an assumed particle refractive index of 1.59 (for example with Malvern Mastersizer 2000).

In one embodiment of the invention the prepared crystalline nano-particles exhibit a narrow particle size distribution, by which is meant that in general that 99% (on a volume base) of the particles lie within ± 300nm of the volume average particle diameter.

In another embodiment of the invention the prepared crystalline nano-particles exhibit a narrow particle size distribution, by which is meant that in general that 99% (on a volume base) of the particles lie within ± 150 nm of the volume average particle diameter.

The crystalline nano-particles prepared according to the present process are substantially free from non-crystalline material, by which is meant that in one embodiment of the invention the nano-crystalline particles are at least 70% crystalline. In another embodiment of the invention the nano-crystalline particles are at least 80% crystalline. In still another embodiment of the invention the nano-crystalline particles are at least 85% crystalline. In a further embodiment of the invention the nano-crystalline particles are at least 90% crystalline. In an even further embodiment of the invention the nano-crystalline particles are at least 95% crystalline. In another alternative embodiment of the invention the nano-crystalline particles are 100% crystalline.

The degree of crystallinity can be determined using suitable known techniques, for example X-ray crystallography and/or differential scanning calorimetry (DSC) analysis and/or Raman spectroscopy.

Substantially water-insoluble substance

The substantially water-insoluble substance included in the suspension is in one embodiment of the invention a substantially water-insoluble organic substance.

In another embodiment of the invention the substantially water-insoluble substance is a substantially water-insoluble organic pharmacologically active substance (in the following also sometimes referred to as “active substance”).

In a further, other embodiment of the invention the substantially water-insoluble substance is a substantially water-insoluble organic pharmacologically active substance having a molecular weight of less than 800 Daltons (in the following also sometimes referred to as “active substance”).

In another further embodiment of the invention the substantially water-insoluble substance is a substantially water-insoluble organic pharmacologically active substance having a molecular weight of less than 700 Daltons (in the following also sometimes referred to as "active substance").

In an even further embodiment of the invention the substantially water-insoluble substance is a substantially water-insoluble organic pharmacologically active substance having a molecular weight of less than 600 Daltons (in the following also sometimes referred to as "active substance").

In an alternative further, other embodiment of the invention the substantially water-insoluble substance is a substantially water-insoluble organic pharmacologically active substance having a molecular weight of less than 500 Daltons (in the following also sometimes referred to as "active substance").

By substantially water-insoluble is meant a substance that has solubility in water at 25°C of less than 0.5 mg/ml. In an alternative embodiment of the invention the substantially water-insoluble substance has a solubility in water at 25°C of less than 0.1mg/ml. In a further alternative embodiment of the invention the substantially water-insoluble substance has a solubility in water at 25°C of less than 0.05 mg/ml.

The solubility of the substance in water may be measured using a conventional technique. For example, a saturated solution of the substance is prepared by adding an excess amount of the substance to water at 25°C and allowing the solution to equilibrate for 48 hours. Excess solids are removed by centrifugation or filtration and the concentration of the substance in water is determined by a suitable analytical technique such as HPLC.

In one embodiment of the invention the substantially water-insoluble substance, also sometimes referred to as "active substance", has a melting point below 300 °C at normal pressure.

In an alternative embodiment of the invention the substantially water-insoluble substance has a melting point below 250 °C at normal pressure.

In a further alternative embodiment of the invention the substantially water-insoluble substance has a melting point below 200 °C at normal pressure.

In another further embodiment of the invention the substantially water-insoluble substance has a melting point in the range of 100 °C to 300 °C (at normal pressure).

In another even further embodiment of the invention the substantially water-insoluble substance has a melting point in the range of 100 °C to 250 °C (at normal pressure).

In another alternative further embodiment of the invention the substantially water-insoluble substance has a melting point in the range of 110 °C to 250 °C (at normal pressure).

In another even further alternative embodiment of the invention the substantially water-insoluble substance has a melting point in the range of 110 °C to 200 °C (at normal pressure).

The process according to the present invention may be used to prepare aqueous suspensions of crystalline nano-particles of a wide range of substantially water-insoluble substances. Suitable substances include but are not limited to pigments, pesticides, herbicides, fungicides, industrial biocides, cosmetics and pharmacologically active substances.

Aqueous medium

With 'aqueous medium' is meant water or water mixed with a minor amount of water miscible organic solvent, which solvent is miscible with water in all proportions. It is preferred to use pure water as aqueous medium in the process.

Examples of water miscible organic solvents that may be present in minor amounts together with water in the aqueous medium include; a water-miscible alcohol, for example methanol, ethanol, n-propyl alcohol, isopropyl alcohol, tert-butyl alcohol, ethylene glycol or propylene glycol; dimethylsulfoxide; dimethylformamide; N-methylpyrrolidone; a water-miscible ether, for example tetrahydrofuran; a water-miscible nitrile, for example acetonitrile; a water-miscible ketone, for example acetone or methyl ethyl ketone; dimethylacetamide or a mixture of two or more of the above mentioned water-miscible organic solvents.

A minor amount of water miscible organic solvent is in one embodiment of the invention less than 10% w/w of the aqueous medium. In another embodiment of the invention a minor amount of water miscible organic solvent is less than 5% w/w of the aqueous medium. In still another embodiment of the invention a minor amount of water miscible organic solvent is less than 1% w/w of the aqueous medium. In a further embodiment of the invention a minor amount of water miscible organic solvent is less than 0.5% w/w of the aqueous medium. In an alternative embodiment of the invention a minor amount of water miscible organic solvent is less than 0.1% w/w of the aqueous medium.

In still another embodiment of the invention the aqueous medium is water. In still even another embodiment of the invention the aqueous medium is water, substantially free from organic solvent. In a further, still even another embodiment of the invention the aqueous medium is water, free from organic solvent.

Pharmacologically active substance

Numerous classes of pharmacologically active compounds are suitable for use in the present invention, including but not limited to, substantially water-insoluble anti-cancer agents, steroids, preferably glucocorticosteroids (especially anti-inflammatory

glucocorticosteroids, for example budesonide) antihypertensive agents (for example felodipine), beta-blockers (for example metoprolol, pindolol or propranolol), ACE inhibitors, angiotensin II receptor antagonists. Hypolipidaemic agents, anticoagulants, antithrombotics, antifungal agents (for example griseofulvin), antiviral agents, antibiotics, antibacterial agents (for example ciprofloxacin), antipsychotic agents, antidepressants, sedatives, anaesthetics, anti-inflammatory agents (for example ketoprofen), antihistamines, hormones (for example testosterone), immunomodifiers, or contraceptive agents.

In a further embodiment of the invention the substantially water-insoluble pharmacologically active substance is selected among bicalutamide, felodipine, 3,3,3-trifluoropropane-1-sulfonic acid, 4-[2-(2,4-dichlorophenyl)-5-methyl-4-(piperidin-1-ylcarbamoyl)imidazol-1-yl]phenyl ester and 1H-pyrrole-3-carboxamide, N-cyclopropyl-1-[[2-(1,1-difluoroethyl)-1-[(tetrahydro-2H-pyran-4-yl)methyl]-1H-benzimidazol-5-yl]sulfonyl].

Stabilisers

Stabilisers suitable for the prevention of particle aggregation in suspensions are well known to those skilled in the art. Suitable stabilisers include dispersants and surfactants which surfactants may be anionic, cationic or non-ionic.

Suitable dispersants according to above include, polymeric dispersants, for example polyvinylpyrrolidones, polyvinylalcohols or cellulose derivatives, particularly water-soluble or water-dispersible cellulose derivatives, for example hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethylhydroxyethyl cellulose or carboxymethyl cellulose. (Another cellulose derivative that specifically is excluded from use as stabiliser is Low-substituted hydroxypropyl cellulose, also known as L-HPC.) A preferred polymeric dispersant is polyvinylpyrrolidone (PVP). A wide range of PVP polymers may be used, for example a PVP with a molecular weight in the range of from 10,000 to 100,000 Daltons, such as 50,000 to 60,000, but excluding any cross-linked polyvinylpyrrolidone (e.g. PVP-XL or crospovidone) which may not be used.

Suitable surfactants include anionic surfactants exemplified by alkyl or aryl sulfates, more specifically exemplified by sodium dodecyl sulfate. Other suitable ionic surfactants include for example alkyl and aryl carboxylates for example, sodium or potassium myristate or sodium laurate; di-alkyl sulfosuccinates, particularly di-(C_4-C_{12})alkyl sulfosuccinates, such as sodium, calcium or potassium dioctyl sulfosuccinate (e.g. Docusate sodium, sold as Aerosol® OT) or sodium diamyl sulfosuccinate (sold as Aerosol® AY); or bile acid salts, such as salts of deoxycholic acid, taurocholic acid, or glycocholic acid, for example a sodium salt of a bile acid such as sodium taurocholate, sodium deoxycholate, salts of PEG-ylated phospholipids e.g. dipalmitoylphosphatidylethanolaminepolyethyleneglycol 2000, or sodium glycocholate.

Suitable cationic surfactants include quaternary ammonium compounds and fatty amines. Particular cationic surfactants include alkylammonium compounds (for example (C_8-C_{22})alkylammonium, particularly (C_8-C_{20})alkylammonium compounds, such as halides thereof) including, for example, laurylammonium chloride; alkyltrimethyl ammonium compounds (for example (C_8-C_{22}) alkyltrimethyl ammonium, particularly (C_8-C_{20})alkyltrimethyl ammonium compounds, such as halides thereof) for example cetyltrimethylammonium bromide (Cetramide), trimethyltetradecylammonium bromide (Myristamide) or lauryl trimethylammonium bromide (Lauramide); benzalkonium halides (such as (C_8-C_{20})alkylbenzyldimethylammonium halides, particularly (C_8-C_{18})alkylbenzyldimethylammonium halides and mixtures thereof), for example benzalkonium chloride; or alkylpyridinium compounds such as (C_8-C_{20})alkylpyridinium compounds, for example cetylpyridinium chloride or bromide.

Suitable non-ionic surfactants include, monoesters of sorbitan which may or may not contain polyoxyethylene residues (for example Polysorbat surfactants, e.g.Tween® surfactants such as Tween® 20 (Polysorbat 20), Tween® 40 (Polysorbat 40), Tween® 60 (Polysorbat 60) and Tween® 80 (Polysorbat 80)), ethers formed between fatty alcohols and polyoxyethylene glycols, polyoxyethylene-polypropylene glycols, a polyethoxylated castor oil (for example Cremophor® EL), a polyethoxylated hydrogenated castor oil (for example Cremophor® RH 40), polyethoxylated 12OH-stearic acid (for example Solutol® HS15).

Further suitable non-ionic surfactants include, for example ethylene oxide-propylene oxide co-polymers, particularly block co-polymers (poloxomers) such as Pluronic®, Tetronic® or Lutrol® surfactants such as Lutrol® F68 or Lutrol® F127.

Other suitable surfactants are well known to those skilled in the art and can be selected accordingly. Additional surfactants that may be suitable for use in the present invention include, for example, the surfactants listed in US 6,383,471, Table 1.

The aqueous phase may comprise a single stabiliser or a mixture of two or more stabilisers. In one embodiment of the invention the aqueous phase comprises a stabiliser that is a combination of a polymeric dispersant and a surfactant, which surfactant may be non-ionic, anionic or cationic. In a particular embodiment of the invention the stabiliser is a combination of a polymeric dispersant and an anionic surfactant.

In a further particular embodiment of the invention the stabiliser is a salt of dipalmitoylphosphatidylethanolaminepolyethyleneglycol 2000 or a combination of polyvinylpyrrolidone and sodium dioctyl sulfosuccinate.

In an even further particular embodiment of the invention the stabiliser is a combination of a polymeric dispersant which is polyvinylpyrrolidone and an anionic surfactant that is sodium dioctyl sulfosuccinate. In an alternative even further particular embodiment of the invention the stabiliser is a PEG-ylated phospholipid e.g. the sodium salt of dipalmitoylphosphatidylethanolaminepolyethyleneglycol 2000.

When the substantially water-insoluble substance is a pharmacologically active compound it is preferred that the stabiliser is a pharmaceutically acceptable material.

Generally it is desirable to minimise the quantity of stabiliser present, particularly when the substantially water-insoluble substance is a pharmacologically active substance, to minimise possible side effects associated with the stabiliser and/or to minimise interactions with the pharmacologically active substance that may be detrimental to the efficacy of the compound. Accordingly, it is generally preferred that the quantity of stabiliser should be the minimum that is required to stabilise amorphous particles and/or final suspension of crystalline nano-particles. Generally in the invention, the aqueous phase will contain from 0.001 to 4% by weight, particularly 0.01 to 3.5% by weight,

preferably from 0.05 to 3.0% by weight and especially from 0.1 to 2.5% by weight of stabiliser.

The Process

The active ingredient is dispersed in the aqueous phase. The concentration of the active substance in the suspension is preferably between 1 and 30 % (w/w). One or more stabilisers is/are present in the suspension. The amount of the stabiliser in relation to the active ingredient is in one embodiment of the invention in the range of from 1:2 to 1:10, w/w. In another embodiment of the invention the ratio of the stabiliser in relation to the active ingredient is in the range of from 1:3 to 1:9, w/w. In a further embodiment of the invention the ratio of the stabiliser in relation to the active ingredient is in the range of from 1:4 to 1:8, w/w.

After dispersing the active substance in the aqueous phase, the mixture obtained is then heated to the melting temperature of the active substance, or slightly below its melting temperature, alternatively slightly above the melting temperature, alternatively until all active substance particles are dissolved. For example the suspension is heated up to 10 centigrades above the melting temperature.

Therefore, active substance must be a substance that is chemically stable when heated to a temperature close to its melting temperature.

During the heating the active substance is melting, thus gradually transferred into the liquid state. The active substance combined with one or more stabiliser(s) appears as droplets in the aqueous phase, acting as reservoirs for the active substance.

If the melting temperature is above the boiling point of the aqueous phase, the process is performed under pressure.

The system wherein the active substance is transferred into the liquid state is then cooled, and the active substance is transferred into a super cooled state. A high-energy input is then performed, by for example sonication or high-pressure homogenisation. During the input of high energy the amorphous/super cooled component of the reservoirs are converted from their super-cooled state into crystalline state. In the aqueous phase the supersaturation of the compound is constant until all amorphous particles are dissolved.

In an embodiment of the present invention the concentration of substantially water-insoluble substance in the suspension is from 1 to 30% w/w. In another embodiment of the present invention the concentration of substantially water-insoluble substance in the suspension is from 3 to 15 % w/w. In a further embodiment of the present invention the concentration of substantially water-insoluble substance in the suspension is from 4 to 12 % w/w. In an even further embodiment of the present invention the concentration of substantially water-insoluble substance in the suspension is from 5 to 10 % w/w.

Sonication

By sonication, we mean application of ultrasound to the suspension.

The suspension is sonicated until crystallisation in the aqueous phase occurs. A sufficient period for sonicating the mixture after combination is therefore a period sufficient for substantially complete conversion of super cooled droplets/amorphous particles into crystalline particles (for example for conversion of more than 70, 80, 90, 95 or 95% by weight of the amorphous particles to crystalline nano-particles). A suitable sufficient period is for example at least 10 minutes, particularly at least 20 minutes, such as from 10 – 200 minutes, preferably 20 to 200 minutes, more preferably 10-120 minutes and especially 20-100 minutes. It will be appreciated that the time required may depend upon a number of factors, for example the nature of the sparingly-water soluble compound, the ultrasound frequency, the volume of the solutions used and energy output of the sonication equipment. This time may be determined by routine experimentation.

It is important that ultrasound is applied with a homogenous field. An example of an apparatus providing a homogenous field is Covaris S2, having focused acoustics. The intensity of the ultrasound energy may be adjusted between wide limits.

The ultrasound may be applied using well-known methods. Alternatives to the Covaris equipment are an ultrasonic probe or horn placed in the liquid medium, or an ultrasound reactor.

Suitable sonication equipment is well known to those skilled in the art and can be selected accordingly. Conveniently on a laboratory scale, sonication equipment such as the

earlier mentioned apparatus Covaris S2 can be used. On a non-laboratory scale also a sonoreactor, for example from AEA Technology (nowadays Prosonic) could be used, such as that described in GB 2,276,567.

The temperature during sonication is not considered to be critical and generally a temperature near room temperature, as below 50°C will be suitable. However, we have found that low temperatures generally favor the formation of smaller crystalline particles. Accordingly, in one embodiment of the present invention, the temperature during sonication of the suspension of amorphous particles is near room temperature, i.e. less than 50°C. In another embodiment of the invention near room temperature is less than 45 °C. In a further embodiment of the invention near room temperature is in the range of from 0 to 45 °C. In a special further embodiment of the invention near room temperature is in the range of from 1 to 35 °C. In an even further embodiment of the invention near room temperature is in the range of from 5 to 10 °C.

Without wishing to be bound by theory it is thought that lower temperatures result in a higher level of super-saturation during sonication and increases the degree of primary nucleation during sonication thereby giving a higher number of smaller crystalline particles.

High pressure homogenisation

The process according to this invention when utilising high-pressure homogenisation has a working range of pressure being from 3.5 MPa up to 200 MPa, range limits included.

An example of usable equipment is sold by the company Avestin Inc. under the product name of Emulsiflex C50.

If desired the suspension may be concentrated after crystallisation by removing excess water from the suspension, for example by evaporation. A high initial concentration facilitates such a process step.

This embodiment of the present invention provides suspensions of crystalline nano-particles of a solid substantially water-insoluble pharmacologically active substance in an

aqueous phase. Suitable process conditions for this embodiment are as hereinbefore described.

Optionally the aqueous phase can be removed from the suspension after the crystallisation. Suitable methods for removing the aqueous phase or medium are well known and include evaporation, for example by heating the suspension under vacuum, reverse osmosis, dialysis, ultra-filtration or cross-flow filtration.

If required, the crystalline nano-particles present in the suspension prepared according to the present invention may be isolated from the aqueous medium following crystallisation or removal of the aqueous medium. The crystalline nanoparticles may be separated using conventional techniques, for example by centrifuging, reverse osmosis, membrane filtration, lyophilisation or spray-drying. Isolation of the crystalline nanoparticles is useful when the particles comprise a substantially water-insoluble pharmacologically active compound because it allows the crystals to be washed and re-suspended in a sterile aqueous medium to give a suspension suitable for administration to a warm blooded mammal (especially a human), for example by oral or parenteral (e.g. intravenous) administration. It may be preferable not to isolate the crystals but instead use the suspension as formed, for example because isolation of crystals of a particular substance results in the formation of tightly bound aggregates. Thus, in one aspect of the invention, the suspension as such, comprising crystalline nanoparticles, formed by the inventive process is used for administration to humans.

In another aspect of the invention, the suspension obtained by the process steps a)-e) of the invention is used in a spray-granulation process. Such a spray-granulation process may be performed in a fluidized bed equipment, such as e.g. Glatt WSG, a rotogranulator such as e.g. Roto-Processor from Aeromatic, or centrifugal (CF) granulator from e.g. Freund. Such a spray-granulation process yields a granulate comprising (pharmacologically) active substance that can be either directly dispensed in sachets, gelatin capsules or HPMC capsules or, used for further processing e.g. for compression into tablets, either directly or after admixing of further tabletting excipients.

In another embodiment of the present invention the process is performed under sterile conditions, thereby providing a sterile suspension directly which can be

administered to a warm blooded mammal as described above without the need for additional purification or sterilisation steps. Alternatively, the suspension may be sterilized following crystallisation and optional removal of any water-miscible organic solvent present in the aqueous medium, to leave a sterile suspension.

According to a further aspect of the present invention there is provided an aqueous suspension comprising a continuous aqueous phase in which is dispersed crystalline nanoparticles of a substantially water-insoluble substance obtainable by the process according to the present invention.

In one embodiment of the invention the substantially water-insoluble substance is a substantially water-insoluble pharmacologically active substance as described above.

According to the invention, the concentration of the substantially water-insoluble substance present as crystalline nano-particles in the suspension is greater than 10 mM, for example from 10 to 1000 mM, from 10 to 500 mM, particularly from 20 to 300 mM. In weight percentage counted the concentration of the substantially water-insoluble substance in the suspension is 1-40% w/w. In a particular embodiment the concentration of the substantially water-insoluble substance in the suspension is 5-30% w/w.

The crystalline nanoparticle(s) of the substantially water-insoluble substance have a particle size as hereinbefore defined.

According to a further aspect of the present invention there is provided crystalline nano- particle(s) of a substantially water-insoluble substance obtained by the process according to the present invention. Preferably the substantially water-insoluble substance is a substantially water-insoluble pharmacologically active substance as described above. The crystalline nano- particle(s) of a substantially water-insoluble substance have a particle size as hereinbefore defined.

When the substantially water-insoluble substance is a pharmacologically active substance, it is foreseen to administer the suspensions according to the present invention to a warm blooded mammal (especially a human), for example by oral or parenteral (e.g. intravenous) administration.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising crystalline nano-particle(s) of a substantially

water-insoluble pharmacologically active substance in association with a pharmaceutically acceptable diluent or carrier.

According to an alternative further aspect of the present invention there is provided a pharmaceutical composition for parenteral administration comprising crystalline nano-particle(s) of a substantially water-insoluble pharmacologically active substance in association with a pharmaceutically acceptable diluent or carrier.

In an alternative embodiment the suspension obtained by the process steps a)-e) of the invention may be used as a granulation liquid in a wet granulation process followed by a drying step to prepare granules comprising the substantially water-insoluble pharmacologically active substance and one or more excipients. The resulting granules may then be used directly, for example by filling into capsules to provide a unit dosage containing the granules. Alternatively the granules may be optionally mixed with further excipients, disintegrants, binders, lubricants etc. and compressed into a tablet suitable for oral administration. If required, the tablet may be coated to provide control over the release properties of the tablet or to protect it against degradation, for example through exposure to light. Wet granulation techniques and excipients suitable for use in tablet formulations are well known in the art.

The crystalline nano-particles of a pharmacologically active substance prepared using the present process may also be used in other pharmaceutical formulations, including but not limited to, dry blended compositions such as capsules and direct compression tablet formulations; controlled or sustained release formulation wherein the particles are dispersed within a suitable matrix, for example in a water-swellable or water-erodible matrix or a biodegradable polymeric matrix.

According to a further aspect of the present invention there is provided crystalline nano- particle(s) of a substantially water-insoluble substance obtained by the process according to the present invention for use as a medicament.

The unique conditions of constant super-saturation provided by the presence of the amorphous particle suspension in the present invention may provide crystalline nano-particles of a material that could not be crystallised using known conventional crystallisation methods. The resulting crystalline nano-particles prepared using the present invention can then be used as seed crystals to promote crystallisation in more conventional

crystallisation processes. For example, the preparation of a crystalline pharmaceutical substance is often advantageous, because it may enable the compound to be prepared in a highly pure form. A crystalline form may also offer other advantages such as stability and material handling advantages.

According to a further aspect of the present invention there is provided the use of a crystalline nano-particle(s) of a substantially water-insoluble substance obtained by the process according to the present invention as seed crystal(s) in a crystallisation process. Suitable crystallisation processes in which the seed crystals may be used are well known in the art and include, for example systems that induce super-saturation by slow cooling, evaporation or the addition of an anti-solvent.

List of abbreviations	
Abbreviation	Meaning
Docusate sodium	Sodium dioctyl sulfosuccinate
DPPE-PEG 2000	Dipalmitoylphosphatidylethanolamine-polyethyleneglycol, wherein the covalently bound polyethyleneglycol has a molecular weight of 2000.
PEG-ylated molecule	Molecule having a covalently bound moitie or ”tail” of a polyethylene glycol
PVP K-30	Polyvinyl pyrrolidone K-30

EXAMPLES

In the following Examples, the mean particle diameter, determined as the volume average particle diameter (<d>v), was obtained by using a laser diffraction instrument from Malvern, i.e. Mastersizer 2000.

The present invention will be illustrated but not limited by the following examples.

Example 1

Comparative Example 1a - Preparation of microsuspension of Bicalutamide

A crude suspension of 10% (w/w) drug in a solution of 2.0% (w/w) PVP K30 and 0.3% (w/w) Docusate sodium in water was made by stirring for one hour. 2.67 ml of this suspension was transferred to a high-pressure 5ml glass vial and was thereafter closed with a cap and septum. The vial was put in the Covaris S2 and the suspension was sonicated for 20 minutes. The volume average particle size (diameter) of the obtained particles in the suspension was measured to 1.1μm.

Example 1b. Preparation of crystalline nanosuspension of Bicalutamide

A crude suspension of 10% (w/w) drug in a solution of 2.0% (w/w) PVP K30 and 0.3% (w/w) Docusate sodium in water was made by stirring for one hour. 2.67 ml of this suspension was transferred to a high-pressure 5 ml glass vial, a magnet was put inside and it was closed with a cap and septum. The vial was put in a glycerol bath using a specially designed holder with a teflon screw preventing the septum to come off at elevated pressures. The temperature was increased from 22°C to 194°C at a heating rate of 4.3°C/min under constant stirring at a rate of 220 rpm. The vial was thereafter immediately transferred to the Covaris S2 and the suspension was sonicated for 20 minutes at 18°C. The volume average particle size (diameter) of the obtained crystalline particles in the suspension was measured to 160 nm.

The X-ray diffractogram was determined for the suspensions obtained in Example 1b, both before and after heat treatment respectively. It is shown that Bicalutamide had changed into another, crystalline, polymorph after heat treatment and sonication, see figure 1.

Example 2 - Felodipine

Comparative Example 2a - Preparation of microsuspension of Felodipine

A crude suspension of 10% (w/w) drug in a solution of 1.33% (w/w) PVP K30 and 0.067% (w/w) Docusate sodium in water was made by stirring over night. 2.67 ml of this suspension was transferred to a high-pressure 5 ml glass vial and was thereafter closed with a cap and septum. The vial was placed in the Covaris S2 and the suspension was sonicated for 20 minutes. The volume average particle size (diameter) of the obtained particles in the suspension was measured to 5.5 μm.

Example 2b - Preparation of crystalline nanosuspension of Felodipine

A crude suspension of 10% (w/w) drug in a solution of 1.33% (w/w) PVP K30 and 0.067% (w/w) Docusate sodium in water was made by stirring over night. 2.67 ml of this suspension was transferred to a high-pressure 5 ml glass vial, a magnet was put inside and it was closed with a cap and septum. The vial was placed in a glycerol bath using a specially designed holder with a teflon screw preventing the septum to come off at elevated pressures. The temperature was increased from 22°C to 150°C at a heating rate of 4.7°C/min under constant stirring at a rate of 220 rpm. The vial was thereafter immediately transferred to the Covaris S2 and the suspension was sonicated for 20 minutes at 18°C. The volume average particle size (diameter) of the obtained crystalline particles in the suspension was measured to 248 nm.

Example 3

Comparative Example 3a - Preparation of microsuspension of 3,3,3-trifluoropropane-1-sulfonic acid, 4-[2-(2,4-dichlorophenyl)-5-methyl-4-(piperidin-1-ylcarbamoyl)imidazol-1-yl]phenyl ester

A crude suspension of 10% (w/w) drug in a solution of 2.0% DPPE-PEG 2000 sodium salt in water (w/w) was made by stirring over night. 2.67 ml of this suspension was transferred to a high-pressure 5 ml glass vial and was thereafter closed with a cap and septum. The vial

was put in the Covaris S2 and the suspension was sonicated for 20 minutes. The volume average particle size (diameter) of the obtained particles in the suspension was measured 3.0 μm.

Example 3b - Preparation of crystalline nanosuspension of 3,3,3-trifluoropropane-1-sulfonic acid, 4-[2-(2,4-dichlorophenyl)-5-methyl-4-(piperidin-1-ylcarbamoyl)imidazol-1-yl]phenyl ester

A crude suspension of 10% (w/w) drug in a solution of 2.0% DPPE-PEG 2000 sodium salt in water (w/w) was made by stirring over night. 2.67 ml of this suspension was transferred to a high-pressure 5 ml glass vial, a magnet was put inside and it was closed with a cap and septum. The vial was put in a glycerol bath using a specially designed holder with a teflon screw preventing the septum to come off at elevated pressures. The temperature was increased from 22°C to 193°C at a heating rate of 4.3°C/min under constant stirring at a rate of 220 rpm. The vial was thereafter immediately transferred to the Covaris S2 and the suspension was sonicated for 20 minutes at 18°C. The volume average particle size (diameter) of the obtained crystalline particles in the suspension was measured to 269 nm.

The X-ray diffractogram was determined for the both suspensions, before and after heat treatment respectively. It was shown that 3,3,3-trifluoropropane-1-sulfonic acid , 4-[2-(2,4-dichlorophenyl)-5-methyl-4-(piperidin-1-ylcarbamoyl)imidazol-1-yl]phenyl ester had changed into another polymorph after heat treatment.

Example 4

Comparative Example 4a - Preparation of microsuspension of 1H-pyrrole-3-carboxamide, N-cyclopropyl-1-[[2-(1,1-difluoroethyl)-1-[(tetrahydro-2H-pyran-4-yl)methyl]-1H-benzimidazol-5-yl]sulfonyl]

A crude suspension of 5% (w/w) drug in a solution of 1% (w/w) PVP K30 and 0.15% (w/w) Docusate sodium in water was made by stirring over night. 0.6ml of this suspension was transferred to a high-pressure 2 ml glass vial and was thereafter closed with a cap and septum. The vial was placed in the Covaris S2 and the suspension was sonicated for 20 minutes. The volume average particle size (diameter) of the obtained particles in the suspension was measured to 14μm.

Example 4b - Preparation of crystalline nanosuspension of 1H-pyrrole-3-carboxamide, N-cyclopropyl-1-[[2-(1,1-difluoroethyl)-1-[(tetrahydro-2H-pyran-4-yl)methyl]-1H-benzimidazol-5-yl]sulfonyl]

A crude suspension of 5% (w/w) drug in a solution of 1% (w/w) PVP K30 and 0.15% (w/w) Docusate sodium in water was made by stirring over night. 1ml of this suspension was transferred to a high-pressure 2 ml glass vial, a magnet was put inside and it was closed with a cap and septum. The vial was placed in a silicon oil bath using a specially designed holder with a teflon screw preventing the septum to come off at elevated pressures. The temperature in the bath was 190°C and the vial was kept in the bath for two minutes under constant stirring at a rate of 250 rpm. The vial was thereafter cooled at RT and transferred to the Covaris S2, all together three minutes before the suspension was sonicated for 20 minutes at 18°C. The volume average particle size (diameter) of the obtained crystalline particles in the suspension was measured to 130 nm.

CLAIMS

1. A process for the preparation of a suspension of crystalline nano-particles comprising a substantially water insoluble substance, in an aqueous medium, comprising the following steps in the given order;

a) dissolving one or more stabiliser in an aqueous medium to obtain an aqueous phase.

b) dispersing a substantially water-insoluble substance in the aqueous phase comprising one or more stabilisers;

c) heating the suspension obtained in step b) to a temperature above the melting point of the substantially water insoluble substance until undissolved substance material is melted, or to a temperature where all particles are dissolved;

d) cooling the suspension to near room temperature without preceding homogenization; and

e) sonicating or high pressure homogenizing the suspension for a sufficient period to form a suspension of solid crystalline nano-particles comprising a substantially water insoluble substance.

2. The process according to claim 1, with the additional step f) after steps a) – e), wherein the aqueous medium is removed from the suspension, to obtain crystalline nano-particles comprising a substantially water insoluble substance.

3. The process according to any one of claims 1- 2, wherein the substantially water-insoluble substance is a substantially water-insoluble pharmacologically active substance.

4. The process according to any of the preceeding claims wherein the stabiliser in the aqueous medium is a combination of a polymeric dispersant and a surfactant.

5. The process according to claim 4 wherein the stabiliser is a combination of a polymeric dispersant and an anionic surfactant.

6. The process according to claim 5 wherein the polymeric dispersant is polyvinylpyrrolidone and the anionic surfactant is sodium dioctyl sulfosuccinate.

7. The process according to any one of claims 1 to 6 wherein the near room temperature is less than 50°C.

8. The process according to any one of claims 1 to 7 wherein the step e) involves sonicating the suspension for a sufficient time to form solid crystalline nano-particles.

9. The process according to claim 8 wherein a sufficient time to form solid crystalline nano-particles is a period of from 10 – 200 minutes.

10. The process according to any one of claims 1 to 7 wherein the step e) involves high- pressure homogenisation for a sufficient time to form solid crystalline nano-particles.

11. The process according to claim 1 or 2 wherein the crystalline particles obtained have a mean particles size of less than 500 nm in diameter.

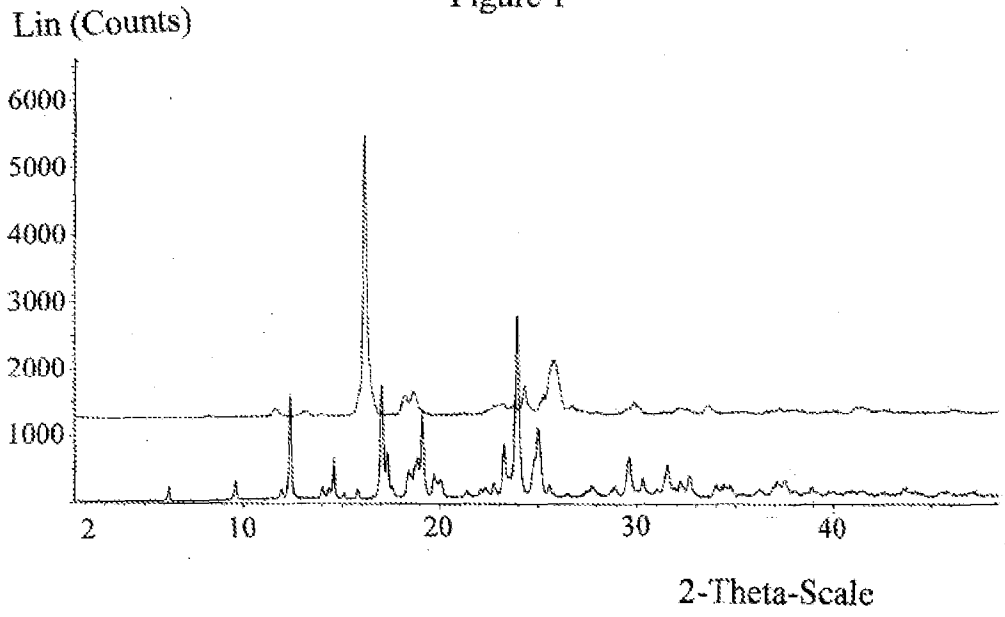
12. The process according to claim 1 or 2 wherein the crystalline particles obtained have a mean particles size of from 50 nm to 270 μm in diameter.

13. The use of the suspension obtained in accordance with the steps a) – e) in claim1, comprising a pharmacologically active substance, in a spray-granulation process to yield a granulate.

14. The process according to claim 1 or 2 performed under sterile conditions.

15. The process according to claim 1, wherein the concentration of the substantially water-insoluble substance in the suspension is from 1 to 30%, w/w.

Figure 1


Lin (Counts)
6000
5000
4000
3000
2000
1000
2
10
20
30
40
2-Theta-Scale

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2011/050161

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K, B01D, B01F, B01J, B82B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Lindfors L., Nanoparticle formulations of poorly soluble drug, Journal of Pharmacy and Pharmacology, 2004, 56, S, s109; abstract --	1-15
X	US 20020012704 A1 (PACE GARY W ET AL), 31 January 2002 (2002-01-31); claim 1; Examples 1-8 --	1-15
A	Van Eerdenbrugh B. et al., Top-down production of drug nanocrystals: nanosuspension stabilization, miniaturization and transformation into solid products, International journal of pharmaceutics, 2008, 364, 64-75; whole document -- --------	1-15

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17-05-2011	20-05-2011
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Continuation of: second sheet

International Patent Classification (IPC)

A61K 9/10 (2006.01)
A61K 9/14 (2006.01)

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US	20020012704	A1	31/01/2002	US	6682761	B2	27/01/2004