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(54) Title: SUSPENSION OF PARTICLES WITH DRUG

(57) Abstract: The invention relates to a suspension for therapeutic use of particles comprising a drug in a vehicle, to a method for preparing such suspension and to the use of such suspension for the treatment and/or prevention of a disease. The invention further relates to a drug delivery device for delivering such suspension and to the use of such drug delivery device for the treatment and/or prevention of a disease.

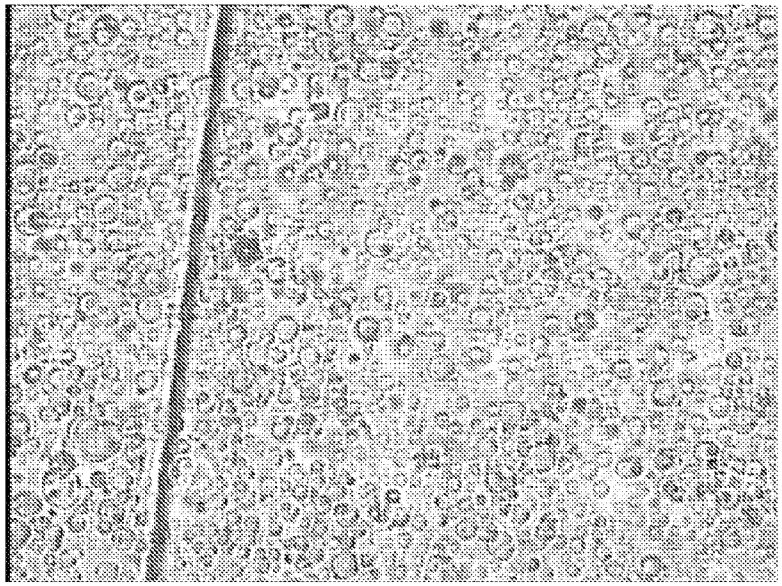

FIG. 4

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SUSPENSION OF PARTICLES WITH DRUG

FIELD OF THE INVENTION

The invention relates to a suspension for therapeutic use, to a method for preparing such suspension and to the use of such suspension for the treatment and/or prevention of a disease.

The invention further relates to a drug delivery device for delivering such suspension and to the use of such drug delivery device for the treatment and/or prevention of a disease.

BACKGROUND OF THE INVENTION

Most drugs are delivered orally, but an increasing number of therapeutics does not survive the gastrointestinal (GI) tract. Especially the class of biopharmaceuticals need to be administered by injection, either under the skin, into the muscles or directly into the circulation. There are biopharmaceuticals which effectiveness and toxicity would be significantly improved if they were administrated in a semi-continuous fashion, something that is practically not achievable with injections. Hence, for some diseases like multiple sclerosis, hemophilia and rheumatoid arthritis, a controlled delivery of the bioactive agent from an implantable device over prolonged periods of time would have various potential advantages. There are some implanted delivery devices applied in clinical practice, mainly in palliative care and oncology. The drugs that are administered comprise morphine, baclophen and floxuridine. See for example Fig. 1.

Any drug has, however, a limited shelf-live, which decreases considerably with increasing temperature. Therefore any drug to be applied in any kind of drug delivery device needs to be protected against deterioration. This especially applies to the controlled delivery of proteins, proteinaceous compounds and nucleic acids which biological molecules have in common that they have a high molecular weight with often a complex structure and that they are typically marginally stable in aqueous formulations, exhibiting at room temperature a shelf live stability ranging from minutes to at maximum a few days. In this respect it is observed that only inherently tough small molecule drugs can survive in aqueous

solution for a useful shelf life. The stabilization of biological complex molecules at ambient and physiological temperatures constitutes therefore a major challenge.

The most common manner to stabilize these complex biological molecules is the application of a freeze drying process which involves the complete removal of water from the molecule (that is often produced in an aqueous environment) and subsequent storage under cooled and completely dry conditions. Freeze drying processes are, however, expensive and time consuming processes and the end result is a product that needs reconstitution with an aqueous buffer prior to use. Moreover, the utility of freeze dried products for continuous use in a liquid form is constrained. An alternative method for the production of dry stable biological molecules is the use of a spray drying process. Spray drying precursor solutions containing the biopharmaceutical compound as well as stabilizing excipients result in the production of a fine powder comprised of a multiplicity of micrometer sized particles. One benefit of this powder over and above the production of a dry product obtained by freeze drying is that the particles can be suspended in an anhydrous liquid thereby creating an injectable formulation.

A problem associated to the use of suspensions that contain such micro particles in implantable pumps is the settling of the particles inside the device, which will strongly affect the safe and reliable functioning of the pump and thus the amount dosed per unit time. This means that within the timeframe the suspension is present inside the pump, the particles should not sediment. Known methods that are aimed to deal with this sedimentation problem include the decrease of the density difference that exists between the particles and the dispersion medium used in the suspension, and the increase of the viscosity of the dispersion medium. The decrease of the density difference has, for instance, been described in WO 2005/099669. A disadvantage of this approach is, however, that it relies on the use of perfluorocarbons and fluorinated ethers which may have the tendency not to result in stable dispersions, which is a strict requirement for accurately pumping suspensions out of a drug delivery device having a narrow orifice. The increase of the viscosity of the dispersion medium has, for example, been described in EP 1755650 B1. Ranges of 1 to 1000 kPoise (10^5 to 10^8 x the water viscosity) and more preferable ranges of 5-30 kPoise (5.10^5 to 3.10^6 x the water viscosity) are being mentioned. It is noted, however, that a disadvantage of increasing the viscosity of the dispersion medium is that the viscosity of the suspension as such will become extremely high at high particle loadings, which will hamper the pumpability of the suspension.

OBJECT OF THE INVENTION

It is therefore an object of the present invention to provide a suspension of particles that mitigate one or more of the above indicated drawbacks. In particular it is an object of the present invention to provide a suspension of particles wherein the particles feature a decreased tendency to sediment within the time frame of storage in the reservoir of a drug delivery device and wherein the suspension features an improved pumpability. Furthermore it is an object of the invention to develop a platform technology to stabilize vulnerable drugs like peptides and proteins in electronically controlled drug delivery devices like implantable pumps, transdermal devices, electronic pills and infusion pumps.

SUMMARY OF THE INVENTION

This object is achieved by providing a suspension for therapeutic use comprising

- particles, and
- a liquid non-aqueous biocompatible or biodegradable vehicle wherein the particles do not dissolve, aggregate or sediment

wherein the particles comprise

- a biocompatible or biodegradable matrix excipient forming an amorphous and chemically inert matrix,
- a drug preserved in the matrix,

wherein the particles have

- an average particle diameter in suspension of between 0.1 and 100 μm, wherein the term 'average' refers the the number average like being determined by e.g. scanning electron microscopy
- a particle size distribution such that at least 70 % of the particles is smaller than 10 times the average particle diameter.

and wherein the vehicle has

- a viscosity of between 1 and 25 mPa.s,
- a vapor pressure of between 0.005 and 0.06 bar,
- a boiling temperature of between 90 and 300 °C.

The matrix excipient is biocompatible or biodegradable and capable of forming a highly water soluble, amorphous and chemically inert (also over a period of one year) matrix. Said matrix is capable of immobilizing and stabilizing the drug molecules at

high temperatures (within relevant temperature range of say 36-41 degrees Celcius) for one year. Said dispersion medium is preferably capable of preventing water or oxygen to reach and chemically react with said particles. In the present invention use is made of an amorphous and chemically inert matrix. Suitably, use is made of a glass matrix. The matrix can suitably be made of a wide variety of glass forming compounds, optionally in the presence of a glass formation facilitator compound. The matrix can suitably be made of sugar glass, metal carboxylate glass or phosphate glass. Preferably, the matrix is made of sugar glass. Examples of matrix excipients forming a sugar glass include mannitol, inositol, trehalose, albumin and others. It is well known that such matrix excipients are an effective medium for the preservation of certain biological, proteinaceous, botanical and other organic materials. There is a considerable literature devoted to the theory of how sugar glasses exert this effect (e.g. Elbein, E. D et al., Glycobiology, 2003, 13, 17) and in particular in relation to vaccines (e.g. Maa, Y. F. et al., J Pharm Sci. 2003, 92, 319., Jiang, G et al., J Pharm Sci. 2006, 95, 80., Roser, B. Future Microbiol., 2006, 1, 21., Abdul-Fattah, A. M et al., Pharm Res. 2007, 24, 715).

The particles preferably contain a high loading of the drug, preferably between 1 and 75 wt%, more preferably between15 and 70 wt%, and in particular between 35 and 65 wt%. The drug is preferably a protein, peptide, proteinaceous compound, vaccine or nucleic acid. A wide variety of proteins and proteinaceous compounds can be applied in the present invention. Suitable examples of proteins and proteinaceous compounds include those proteins which have biological activity or which may be used to treat a disease or other pathological condition. They include, for instance, Factor VIII, Factor IX and other coagulation factors, chymotrypsin, trypsinogen, alpha-interferon, beta-interferon and other interferons, beta-galactosidase, lactate dehydrogenase, growth factors, clotting factors, enzymes, immune response stimulators, cytokines, lymphokines, immunoglobulins, interleukins, peptides, somatostatin, somatotropin analogues, somatomedin-C, Gonadotropic releasing hormone, follicle stimulating hormone, luteinizing hormone, LHRH, LHRH analogues such as leuprolide, nafarelin and goserelin, LHRH agonists and antagonists, growth hormone releasing factor, calcitonin, colchicine, gonadotropins such as chorionic gonadotropin, oxytocin, octreotide, somatotropin plus an amino acid, vasopressin, adrenocorticotrophic hormone, epidermal growth factor, prolactin, somatotropin plus a protein, cosyntropin, lypressin, polypeptides such as thyrotropin releasing hormone, thyroid stimulation hormone, secretin, pancreozymin, enkephalin, glucagon, endocrine agents secreted internally and distributed by way of the bloodstream, and the like. Further agents that may be delivered

include a, antitrypsin, insulin and other peptide hormones, adrenal cortical stimulating hormone, thyroid stimulating hormone, and other pituitary hormones erythropoietin, growth factors such as GCSF, GMCSF, insulin-like growth factor 1, tissue plasminogen activator, CF4, dDAVP, tumor necrosis factor receptor, pancreatic enzymes, lactase, interleukin-1 receptor antagonist, interleukin-2, tumor suppresser proteins, cytotoxic proteins, retroviruses and other viruses, viral proteins, antibodies, recombinant antibodies, and antibody fragments.

The drug is preferably selected from the group consisting of Factor IX, Factor VIII, interferon alpha, interferon beta, interferon omega, interferon gamma, beta-galactosidase, lactate dehydrogenase, chymotrypsin, trypsinogen, and (monoclonal) anibody, interleukin, insulin, coagulation factor, growth hormone, epoetin, anti-TNF-alpha, DNA, RNA, oligonucleotides, or any analogs thereof.

Interferons are a particularly preferred group of proteins to be used in the present invention. Interferons are glycoprotein cytokines which are produced by cells in response to various stimuli such as exposure to virus, bacterium, parasite or other antigen. Interferons display antiviral, immunomodulatory and antiproliferative activities, and they are used for treatments of viral hepatitis, multiple sclerosis and certain cancers. There is therefore a special interest to deliver interferons in a controlled manner over a prolonged period of time without intervention. The present invention provides a system which facilitates this.

In the context of the present invention the term "nucleic acid" means unbranched (linear or circular) chains of nucleotides in which the 5' phosphoric group of each nucleotide is esterified with the 3' hydroxyl of the adjoining nucleotide. The term includes ribonucleic acid (RNA), deoxyribonucleic acid (DNA) constructs, and single and double stranded molecules, oligonucleotides, gene expression constructs, mRNA molecules, ribozymes, and the like. The nucleic acid is suitably selected from the group consisting of DNA, RNA and oligonucleotides. Naturally-derived or purified, synthetically produced and recombinantly produced moieties are all included in said term. The term also includes analogs, derivatives, and constructs that include promoter, leader, signal, polyadenylation or intron sequences, locus control regions, markers, and the like. Nucleic acids containing modified, derivatized or non-naturally occurring nucleotide units as part of their structure are also included in the term.

Suitably, the nucleic acid is in the form of at least one selected from the group consisting of a nucleic acid/lipid complex, a nucleic acid-containing liposome, a ribozyme, a viral vector, a virosome, nucleic acid-containing dendrimers, nucleic acid-containing cationic polymers and nucleic acid-containing poly (lactic-co-glycolic)acid (PLGA) particles. The

term "nucleic acid/lipid complex" means a complex that forms between nucleic acids and small, cationic unilamellar vesicles held together by electrostatic interactions rather than by encapsulation of the nucleic acids in liposomes. A variety of topological arrangements can occur, such as DNA condensation, liposome aggregation and fusion. The term "liposome" means the multi- or unilamellar vesicles formed from phospholipids which are used as carriers for drugs and macromolecules, especially nucleic acids.

Suitably, the drug to be used in accordance with the present invention can be used in the form of a salt, preferably a pharmaceutically acceptable salt. Useful salts are known to those of skill in the art and include salts with inorganic acids, organic acids, inorganic bases or organic bases.

The particle size distribution is a very relevant parameter that was optimized based on the intended use of the suspension. It was found that the smaller the average particle the more preferable because of the following observations:

1) The attractive forces between the particles were further reduced resulting into non-aggregated dispersions

2) The dissolution kinetics of the biopharmaceutical compound in the beads once the non-aqueous suspension was pumped into a physiological aqueous medium increased; and

3) The sedimentation tendency of formulations in which the density of the particles was slightly unmatched strongly reduced

4) The clogging potential of particles due to confining geometries inside the delivery devices reduced

On the other hand:

1) The spray dry process bears limitations regarding particle size; the smaller the particle size the lower the spray drying efficiency.

2) When the size of the particle become sub-micrometer, the effect of inter-particle forces on the rheological behavior of the suspension also increases. It was found that for non-aggregated suspensions the smaller the particles the higher the suspension viscosity.

The relationships as given above has resulted in a preferable average diameter of the particles in suspension between of 0.5 – 10 micron, even more preferable is 0.5 – 5 micron and most preferable is an average diameter of 0.5 – 3 micron. The size distribution of the particles should be sufficiently narrow, avoiding the presence of too many particles with a diameter larger than 10 x the average particle diameter, but more preferable the 5x the average particle diameter and even more preferable 2x the average particle diameter.

Suitably, the suspension according to the present invention has a size distribution of the particles such that at least 70 %, preferably 90 % and more preferably at least 99 % of the particles has a diameter smaller than 10 times the average diameter. Preferably, the suspension has a size distribution of the particles such that at least 70 %, preferably 90 % and more preferably at least 99 % of the particles has a diameter smaller than 5 times the average diameter. More preferably, the suspension has a size distribution of the particles such that at least 70 %, preferably 90 % and more preferably at least 99 % of the particles has a particle diameter smaller than 2 times the average diameter.

Fig. 4 shows a microscopic image of a solution according to the invention.

Fig. 5 shows an image from an electron microscope of particles according to the invention. The particles have been in a suspension of the invention. They have been taken out of the suspension by attaching them to a grid prior to making the image.

The particles do not dissolve in the vehicle, aggregate or sediment within the time frame of storage in the reservoir of the implantable pump. On the other hand, the particles need to dissolve quickly, preferably within minutes when brought into contact with water, without leaving residual material that cannot be removed easily from the body.

The particles to be used in the present invention can, for instance, be made by means of a spray drying process or other processes which have been described in WO 02/32402, which entire document is hereby incorporated by reference.

The vehicle has a viscosity of between 1 and 25 mPa.s, preferably between 3 and 15 mPa.s, more preferably between 5 and 10 mPa.s.

The vehicle has a vapor pressure of between 0.005 and 0.06 bar, preferably between 0.02and 0.05 bar, more preferably between 0.005 and 0.01 bar vapor pressure water at 37C is 0.06 bar

The vehicle has a boiling temperature of between 90 and 300 °C, preferably between 130 and 300 °C, more preferably between 180 and 250 °C.

The vehicle has a density which is preferably between 0.5 and 1.5 g/mol, more preferably between 0.5 and 1.2 g/mol, in particular between 0.5 and 1.0 mol/g.

The solubility of water in the vehicle at 37 °C is preferably between 0 and 0.1 mass% , more preferably between 0 and 0.7 mass%, in particular between 0 and 0.5 mass%.

A preferred vehicle is non-aqueous, anhydrous, aprotic, non-polar, hydrophobic and has low reactivity.

Colloidal stability of the suspension is of high importance and can be realized by selecting a vehicle having the unique property of stabilizing the particles, giving also rise

to the lowest possible suspension viscosity. In order to overcome the problems inherent in the prior art, specifically the use of suspensions with high viscosities or high vapour pressures, the present invention requires the use of a vehicle with a very low viscosity. Such vehicles are known to those skilled in the art and comprise the class of liquids known as metabolisable oils. Such oils include vegetable derived materials such as safflower oil, olive oil, soybean oil and sesame oil, and lipid esters such as those derived from caprylic and capric acid triglycerides. Other metabolisable, biodegradable or biocompatible liquids which might be suitable belong to the class of saturated hydrocarbons, halogenated unsaturated ad saturated hydrocarbons and esters or ethers of these compounds.

Preferable vehicles are alkyl esters of oleic acid. A particularly preferred example is ethyl oleate (EO), the ethyl ester of oleic acid, which is an anhydrous liquid with pharmaceutical regulatory approval for administration by the intramuscular and sub-cutaneous routes. As well as having very low viscosity (5.5mPas at 25°C), ethyl oleate has other properties that make it a suitable vehicle for the application in question including a very high boiling point (~205°C) and thus a very low vapour pressure prolonged oxidative stability, very low residual moisture content and rapid absorption by body tissues. In addition it exhibits a low chemical reactivity with the materials used in the delivery devices that are mentioned in this disclosure. Dispersion of any of the formulations 1-5 described in the Examples (produced by spray drying) in ethyl oleate resulted in the production of generally monodisperse particles suspension of with minimal clumping or aggregation of the particles. This was demonstrated by thorough analysis of the suspensions with optical analytical techniques like in-situ microscopy.

The addition of calcium lactate as a stabilizing excipient to formulation 1 further improved the dispersability of the particles in the oil vehicle.

A complication associated with the use of metabolisable oils in general and more specifically ethyl oleate in the examples described here is the fact that they have low densities (less than 1.0 g/cm^3). This means that the particles have a tendency to sediment under the forces of gravity as they have a density higher than that of the surrounding liquid. In order to overcome this problem, the present invention recognises and adopts a method known to those skilled in the art and described in WO 2007/026180, which is incorporated herein by reference. This specification details a method of lowering the relative density of particles in a controllable fashion such that the average relative density of the particle population is sufficiently similar to that of the metabolisable oil, for example ethyl oleate (0.87g/cm^3 at 20°C) such that the particles neither float nor sink. The method for lowering

the density of the particles involves the incorporation of a gas generating compound into the aqueous formulation prior to spray drying. In the examples described here ammonium bicarbonate is the preferred excipient as it is pharmaceutically generally regarded as safe and has the desired characteristics required to perform the density controlling process. Other similar metal bicarbonate excipients are known and include sodium, calcium and potassium bicarbonate.

During the spray drying process, ammonium bicarbonate decomposes due to the heat of the process, liberating a mixture of carbon dioxide, water vapour and ammonium gasses in the approximate ratio of 56%, 23% and 21% respectively. Serendipitously, these gasses are produced at the exact same time that the particles are undergoing transition from a fluid liquid state to a viscous syrup state yet there is insufficient time for them to escape to the environment before the particles fully harden into the amorphous glass state. Thus the gasses are trapped within the rapidly drying particles forming enclosed gaseous voids within each particle. The amount of ammonium bicarbonate present in the original aqueous formulation directly correlates with the size of the gaseous void present in the resulting glass particle and therefore ultimately controls the final density of the particle population. Thus it is possible to match the density of the particles with the low density of metabolisable oils, for example ethyl oleate and therefore prevent sedimentation of the particles during long term storage. Long-term refers here to the period of time in which the drug reservoir is emptied which might range from a few weeks to 1 year. Sedimentation refers here to the displacement of particles under the action of gravity in which the distance of displacement is substantially smaller than the smallest dimension of the drug reservoir, which typically is 1 cm or smaller. The incorporation of this technology overcomes the issues of using high viscosity vehicles and gives full utility to the invention.

As mentioned earlier, a stable dispersion is a strict requirement for accurately pumping suspensions out of a drug delivery device having a narrow orifice. Therefore, in accordance with the present invention the suspension preferably also comprises a dispersant. Effective dispersants adsorb on the surface of the particles while other parts of the dispersant molecule protrude away from the surface into the surrounding liquid, thereby providing the so-called steric barrier. A wide variety of molecular structures is known that performs this task, for example homopolymers, block copolymers, graft copolymers, and surfactants. The dispersant is selected in function of the nature of the surface of the particles and the properties of the surrounding liquid. Suitable examples of dispersants for amorphous matrix particles in non-polar dispersion media often-used in medical formulations include

substances such as such as lecithin, liposomes, phospholipids, pegylated hydrophobic polymers, pegylated liposomes (stealth liposomes), and alkylated polar polymers (e.g. poly alkyl cyanoacrylates). ,. If more polar liquids are used as the fluid dispersion medium such as DMSO or glycols, preferred examples of dispersants include substances such as polyethylene oxide-polypropylene oxide (PEO-PPO) block copolymers (examples of commercial products: Poloxamer, Pluronic), popyvinylpyrrolidone (PVP), polysorbate, and poly(lactic-co-glycolic acid) (PLGA). The amount of dispersant needed to get the colloidal stability aimed at, is related to the specific surface area of the particles and suitably amounts to 0.1-10 mg/m^2.

The present invention also provides a drug delivery device for delivering to a patient in a controlled manner the suspension according to the present invention.

Accordingly, the present invention also relates to a drug delivery device which comprises a reservoir comprising the suspension according to the present invention and a means for releasing a discrete amount of the suspension from the drug delivery device.

Suitably, the present drug delivery device further comprises a pump system being arranged for ejecting the discrete amount of the suspension.

Suitably, the pump system used in accordance with the present invention is capable to provide delivery of the suspension at a flow rate of in the range of from 1-5000 micro liters per day. Preferably, the pump system used in accordance with the present invention is capable to provide delivery of the suspension at a flow rate of in the range of from 1-1000 micro liters per day. The volume fraction of particles ϕ in the suspension and the volume fraction of drugs in the particles μ needs to be such that, given the reservoir volume of the implant V, the following condition is fulfilled:

$$W = V \times \phi \times \mu \times \rho, \qquad [kg]$$

with W the amount (mass) of pharmaceutical ingredient that needs to be stored inside the device, which depends on the required daily dose and refill or explantation frequency if the device is non-refillable, and ρ the density of the pharmaceutical ingredient.

Suitable examples of the drug delivery systems in accordance with the present invention include implantable or insertable drug delivery devices, syringes, infusion sets, syringe pumps, modular ingestible drug delivery capsules (electronic pills), external infusion pumps, and transdermal reservoir systems.

Suitably, the pumping system to be used in the present drug delivery device comprises a dose compartment for comprising at least the discrete amount of fluid, a piston

for controlling a volume of the dose compartment and an actuator for controlling the piston. The piston and the actuator are arranged such that activating the actuator causes the piston to decrease the volume of the dose compartment for releasing the discrete amount of fluid. Another suitable pumping system is based on peristaltic fluid displacement. The applicability of the invention is however not limited to these pumping systems.

The present invention further relates to a method for preparing the suspension according to the present invention, which method comprises

- mixing the drug with the matrix excipient, resulting in a liquid formulation,
- spray drying the liquid formulation, resulting in particles, and
- mixing the particles with the vehicle.

In addition, the present invention relates to the use of the suspension according to the invention for the treatment and/or prevention of a disease.

Further, the present invention relates to the use of the drug delivery device according to the invention for the treatment and/or prevention of a disease.

Typical examples of such diseases include hophilia, and other blood disorders, growth disorders, diabetes, leukemia, hepatitis, renal failure, HIV infection, herediraty diseases such as cerebrosidase deficiency and adenosine deaminase deficiency, hypertension, septic shock, autoimmune diseases such as multiple sclerosis, Graves disease, systemic lupus erythematosus and rheumatoid arthritis, shock and wasting disorders, cystic fibrosis, lactose intolerance, Crohn's disease, inher cancers.flammatory bowel disease, gastrointestinal and other cancers.

BRIEF DESCRIPTION OF DRAWINGS

These and other aspects of the invention will be apparent from and elucidated with reference to the exemplary embodiments described hereinafter. In the drawing:

Fig. 1 shows an implanted pump delivering drugs intrathetically;

Fig. 2 shows the determined level of active Betaseron (interferon-beta, an example of a therapeutic agent) in an aqueous solution over time for a number of temperatures;

Fig. 3 shows the determined level of active Betaseron preserved in particles as well as particles in the vehicle ethyle oleate, according to the invention over time for a number of temperatures;

Fig. 4 shows an in-situ microscopic image of a suspension according to the invention; and

Fig. 5 shows an image from an electron microscope of particles according to the invention.

EXAMPLES

A number of formulations of particles according to the invention will be described below.

In these formulations, a Buchi B290 spray drier has been used. The drier has a number of ranges for the aspiration rate: 20-50 per m^3 of drying gas, more preferably 25-45 per m^3 drying gas, the drying gas being preferably Nitrogen. The outlet temperature of the drier has been varied in different experiments between 40 and 80 °C. The fluid pump rates ranged from 0.5 to 5 ml/min. Commercially available interferon-beta (IFN-β, Betaseron®) was obtained from Bayer and rehydrated according to the manufacturer's instructions immediately before use. In the formulations, low concentration of interferon has been used in order to reduce the required amount of interferon for the experiments. However, other experiments have shown that the advantages of the invention can easily be achieved with higher concentrations of the drug than the ones shown in the formulations below.

Formulation 1

Rehydrated Betaseron® was mixed with aqueous solutions of trehalose, mannitol and calcium lactate such that the final excipient ratios expressed as w/w% were trehalose: 79.5 w/w%, mannitol: 4.2 w/w% and calcium lactate: 16.3 w/w%. The interferon-beta concentration was 500 µg per gram powder. The resulting liquid formulation was spray dried. 89.6% of the total solid content contained within the aqueous liquid formulation was collected from the spray drier as a fine powder

Formulation 2

Rehydrated Betaseron® was mixed with aqueous solutions of trehalose and sucrose such that the final excipient ratios expressed as w/w % were trehalose: 80 w/w%, sucrose: 20 w/w%. The interferon-beta concentration was 100 µg per gram powder. The resulting liquid formulation was spray dried. 85.4% of the total solid content contained within the aqueous liquid formulation was collected from the spray drier as a fine powder.

Formulation 3

Rehydrated Betaseron® was mixed with aqueous solutions of trehalose and sucrose containing 0.02M ammonium bicarbonate such that the final excipient ratios expressed as w/w % were trehalose: 80 w/w%, sucrose: 20 w/w%. The interferon-beta concentration was 100 μg per gram powder. The resulting liquid formulation was spray dried. 87.5% of the total solid content contained within the aqueous liquid formulation was collected from the spray drier as a fine powder

Formulation 4

Rehydrated Betaseron® was mixed with aqueous solutions of trehalose and mannitol such that the final excipient ratios expressed as w/w% were trehalose: 95 w/w%, mannitol: 5 w/w%. The interferon-beta concentration was 100 μg per gram powder. The resulting liquid formulation was spray dried. 81.6% of the total solid content contained within the aqueous liquid formulation was collected from the spray drier as a fine powder.

Formulation 5

Rehydrated Betaseron® was mixed with aqueous solutions of trehalose and mannitol containing 0.02M ammonium bicarbonate such that the final excipient ratios expressed as w/w% were trehalose: 95 w/w%, mannitol: 5 w/w%. The interferon-beta concentration was 189 μg per gram powder. The resulting liquid formulation was spray dried. 82.4% of the total solid content contained within the aqueous liquid formulation was collected from the spray drier as a fine powder

Suspensions were prepared by suspending the spray dried powders into the vehicle under dry conditions, gently homogenizing powders in the vehcile by keeping them on roller bench for sufficient amount of time.

Analysis of formulations

The residual moisture content was determined. The results are listed in the below table.

Formulation	Residual moisture (% H_2O, w/w)
1	Not tested
2	2.8
3	3.2
4	3.2
5	2.7

Method for determination of stability IFN-β

The stability of IFN-β in the above formulations was determined using an enzyme-linked immunoassay (ELISA) that detects only bioactive IFN-β. The principle of ELISA is described in for example "Immunology", I. Roitt, J. Brostoff, D. Male, 5th Ed., 1998, p. 386-395. A commercially available version in kit form from Invitrogen Corporation (Reference KAC1201) was used.

In order to prepare a IFN-β reference solution for ELISA a known mass of micro-particulate powder containing a known mass of IFN-β was rehydrated with a known volume of aqueous diluent, for example water containing a defined concentration of an appropriate detergent, to create a solution with a known theoretical concentration of IFN-β . For powders presented as a suspension of particles in an oily anhydrous liquid, the particles must be exposed to an aqueous environment in order for them to dissolve. A process known in the art as phase partitioning can be usefully employed to achieve this. In the examples described here, powders suspended in oil-based anhydrous delivery vehicles were admixed with a 10-fold excess of aqueous extraction buffer, typically water containing a defined concentration of an appropriate detergent. The resultant oil/aqueous mixture is then gently mixed for a defined period of time at refrigerated temperatures (typically 2-8°C) in order for the oil and water phases to mix thoroughly. Upon cessation of the mixing, the oil and aqueous phases separate with the oil floating on top of the more dense aqueous liquid. The IFN-β is now to be found in the aqueous phase and can be used as if it were a powder sample simply rehydrated in an aqueous system.

In order to determine the thermal stability of the spray dried IFN-β prepared as described in Formulations 1 to 5, representative samples both of powders and of powders suspended in oil-based anhydrous liquids were dispensed and stored for a number of weeks at three different temperatures, 2-8°C, 25°C and 40°C. At each predetermined time point,

samples were removed from storage at each temperature, prepared for IFN-β analysis as described above and then subjected to analysis using the IFN-β-specific ELISA. Results are presented for some formulations along with relevant and appropriate control preparations of unformulated Betaseron®.

Fig. 2 shows the determined level of Betaseron (the interferon-beta) in an aqueous solution over time for a number of temperatures. One can clearly see the deterioration over the relative short indicated time, especially for the higher temperatures.

Fig. 3 shows the determined level of Betaseron preserved in the particles without being suspended, as well as particle suspended in ethyl oleate according to the invention over time for a number of temperatures. These experimental measurements clearly show the much better preservation for longer periods compared with the aqueous solution. The levels are normalized to the activity of unformulated, freshly reconstituated betaseron and are smaller than 1. This is due to betaseron losses that occur during the formulation, suspension and dissolution processes were was not yet optimised for minimum loss of betaseron.

CLAIMS:

1. Suspension for therapeutic use comprising
- particles, and
- a liquid non-aqueous biocompatible or biodegradable vehicle wherein the particles do not dissolve, aggregate or sediment,

wherein the particles comprise
- a biocompatible or biodegradable matrix excipient forming an amorphous and chemically inert matrix, and
- a drug preserved in the matrix,

wherein the particles have
- an average particle diameter of between 0.5 to 10 micron, and
- a particle size distribution such that at least 70 % of the particles is smaller than 10 times the average particle size,

and wherein the vehicle has
- a viscosity of between 1 and 25 mPa.s,
- a vapor pressure of between 0.005 and 0.06 bar, and
- a boiling temperature of between 90 and 300 °C.

2. Suspension of claim 1, wherein the vehicle has
- a density of between 0.5 and 1.5 g/ml, and
- a solubility of water of between 0 and 0.1 mass% at 37 °C.

3. The suspension of claim 1 or claim 2, wherein the vehicle a metabolisable oil selected from the group consisting of ethyl esters of fatty acids, soybean oil, safflower oil, glycols and other metabolisable oils belonging to the class of saturated hydrocarbons, halogenated unsaturated ad saturated hydrocarbons and esters or ethers of these compounds.

4. The suspension of any of the claims 1-3, wherein the vehicle is ethyl oleate.

5. The suspension of any of the claims 1-4, wherein the drug is a protein, peptide, proteinaceous compound, vaccine or nucleic acid.

6. The suspension of claim 5 wherein the drug is elected from the group consisting of Factor IX, Factor VIII, interferon alpha, interferon beta, interferon omega, interferon gamma, beta-galactosidase, lactate dehydrogenase, chymotrypsin, trypsinogen, and (monoclonal) anibody, interleukin, insulin, coagulation factor, growth hormone, epoetin, anti-TNF-alpha, DNA, RNA, oligonucleotides, or any analogs thereof.

7. The suspension of any of the claims 1 to 6, wherein the suspensing further comprises ammonium bicarbonate.

8. The suspension of any of the claims 1 to 7, wherein the matrix excipient comprises a disaccharide or a sugar alcohol.

9. A suspension comprising ethyl oleate and particles comprising
- one or more matrix excipients forming a glass matrix,
- a drug preserved in the matrix, and
- a stabilizing excipient for stabilizing a solution containing the particle.

10. A drug delivery device which comprises a reservoir comprising the suspension as defined in any one of claims 1-9 and a means for releasing a discrete amount of the suspension from the drug delivery device.

11. A drug delivery device according to claim 10 which further comprises a pump system being arranged for ejecting the discrete amount of the suspension.

12. A method for preparing a suspension as defined in any one of claims 1-9, which method comprises
- mixing the drug with the matrix excipients, resulting in a liquid formulation,
- spray drying the liquid formulation, resulting in particles, and
- mixing the particles with the vehicle.

13. Use of the suspension defined in any one of claims 1-9 for the treatment and/or prevention of a disease.

14. Use of the drug delivery device defined in any one of claims 10-11 for the treatment and/or prevention of a disease.

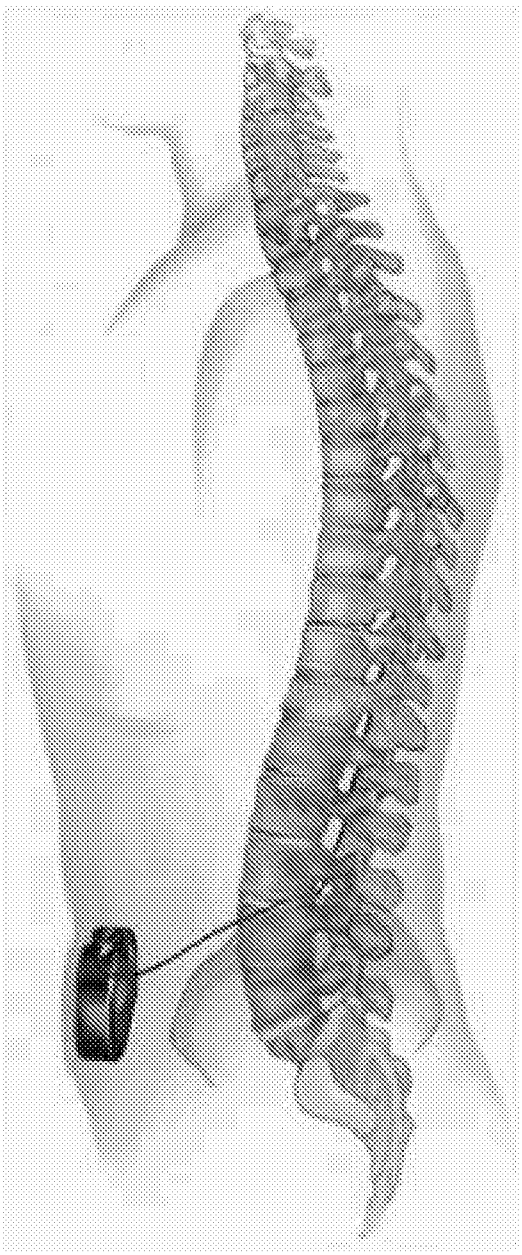

FIG. 1

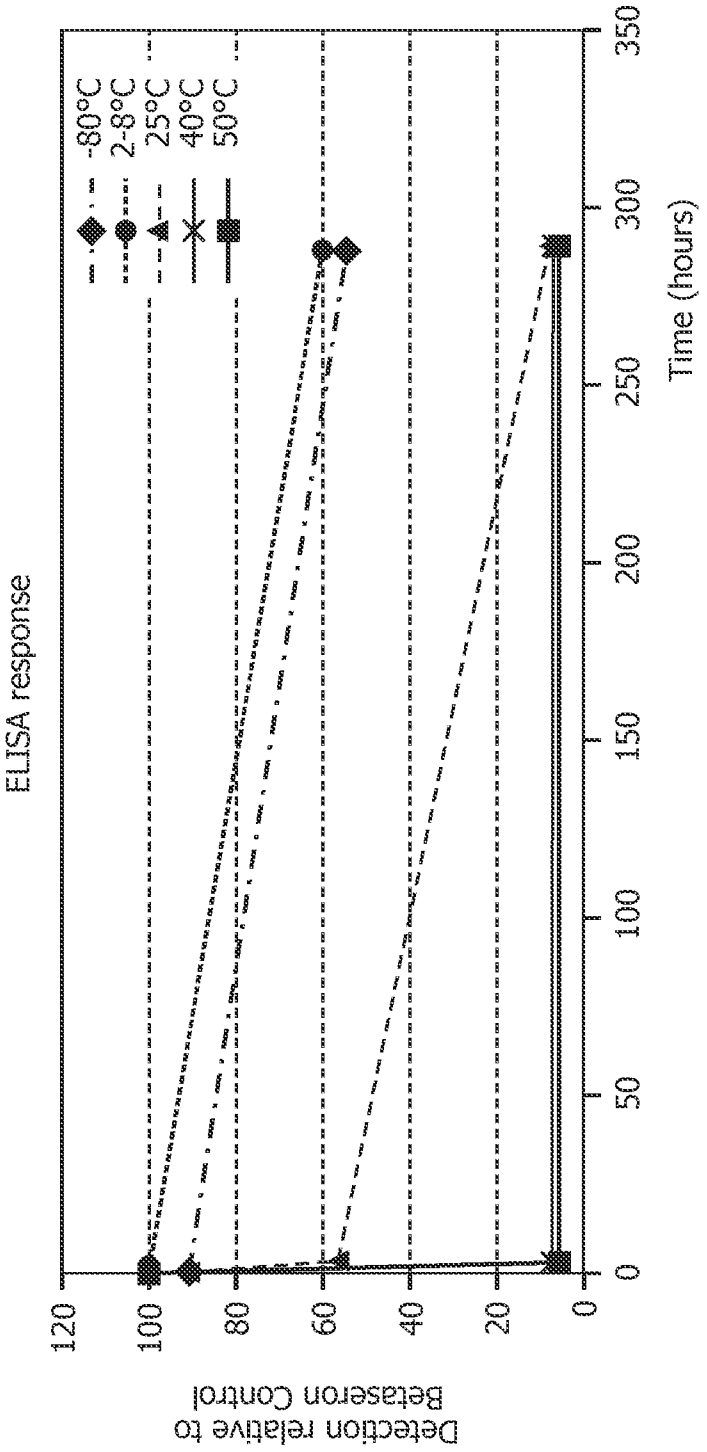
ELISA response
Detection relative to Betaseron Control
Time (hours)
-80°C
2-8°C
25°C
40°C
50°C
0
20
40
60
80
100
120
0
50
100
150
200
250
300
350

FIG. 2

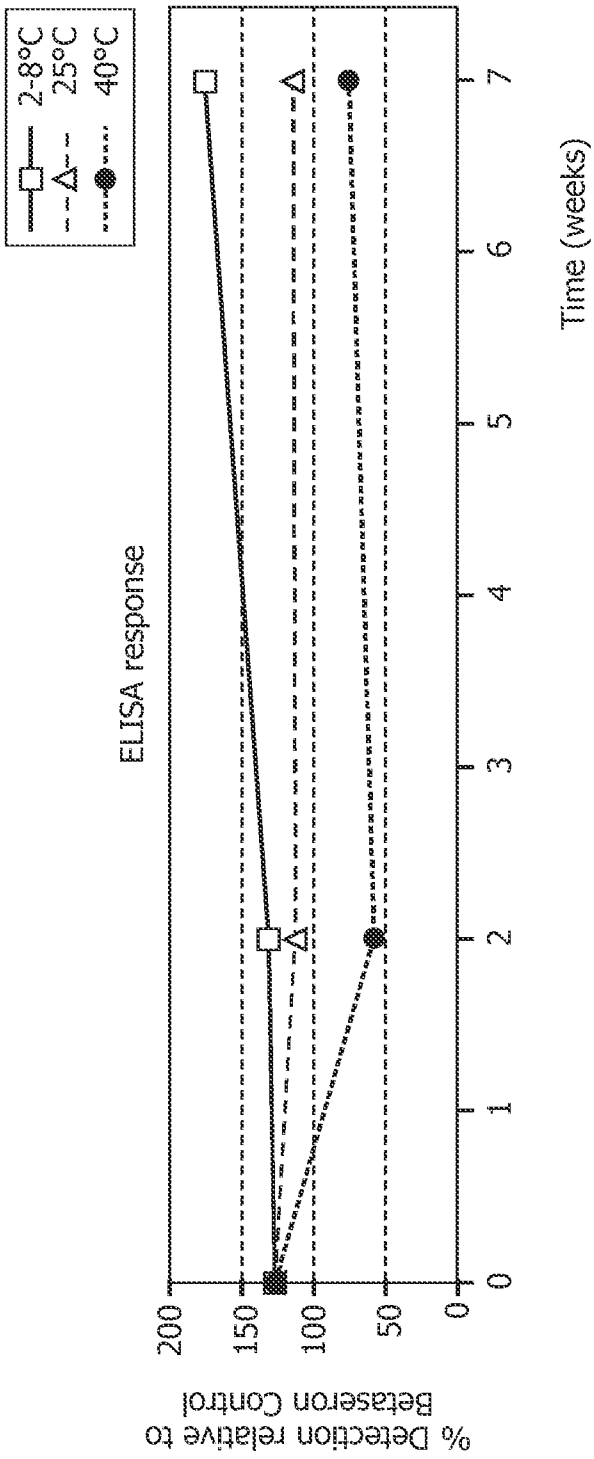
2-8°C
25°C
40°C
ELISA response
% Detection relative to Betaseron Control
200
150
100
50
0
0
1
2
3
4
5
6
7
Time (weeks)

FIG. 3

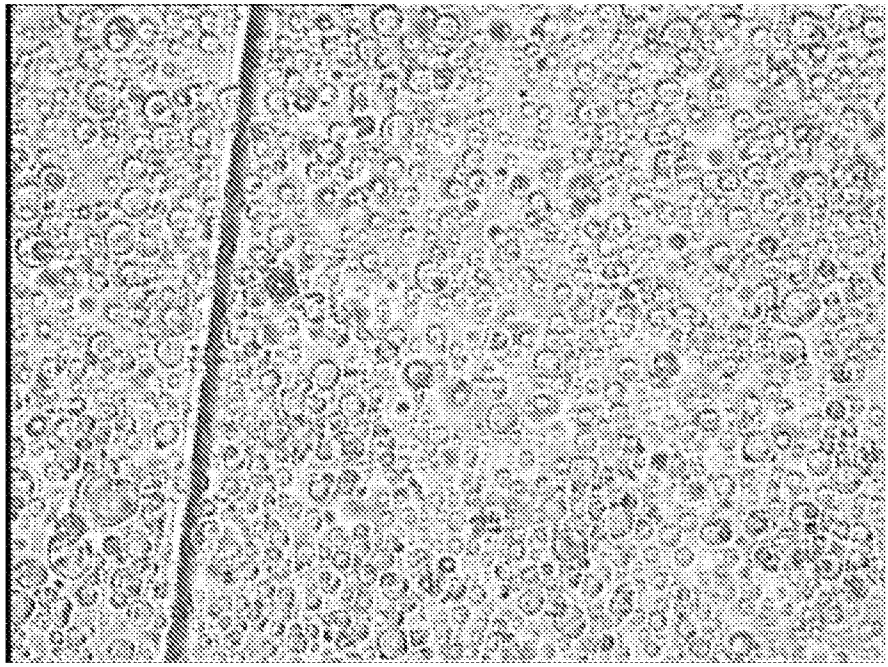

FIG. 4

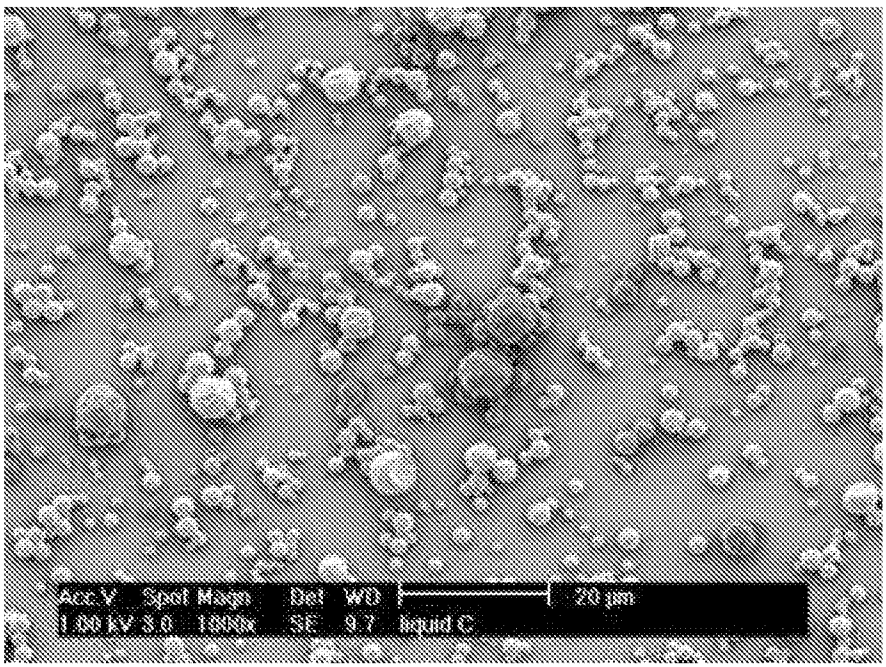

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/052676

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/10 A61K47/44 A61K31/00 A61K38/00
ADD.

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/251618 A1 (DENNIS PAULA [US] ET AL) 9 November 2006 (2006-11-09) the whole document claims 1-37; examples 1-12	1-14
X	WO 2006/083799 A2 (ALZA CORP [US]; ROHLOFF CATHERINE MANYA [US]; BERRY STEPHEN ANDREW [US) 10 August 2006 (2006-08-10) the whole document * abstract claims 1-32; examples 1-7	1-14
X	US 6 451 346 B1 (SHAH SUBODH [US] ET AL) 17 September 2002 (2002-09-17) the whole document claims 1-7; examples 1-11	1-14

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2010	02/11/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Felder, Christian

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/052676

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BOWEN P: "Particle Size Distribution Measurement from Millimeters to Nanometers and from Rods to Platelets" JOURNAL OF DISPERSION SCIENCE AND TECHNOLOGY, TAYLOR AND FRANCIS GROUP, NEW YORK, NY, US LNKD- DOI:10.1081/DIS-120015368, vol. 23, no. 5, 1 January 2002 (2002-01-01), pages 631-662, XP009102859 ISSN: 0193-2691 the whole document	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2010/052676

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		DE 69909519 T2	24-12-2003
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		JP 2002533377 T	08-10-2002
		PT 1143929 E	28-11-2003
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