Olanzapine is a yellow crystalline solid which is practically insoluble in water. The compound is disclosed and claimed in U.S. Patent No. 5,229,382 to Chakrabarti et al., which is incorporated herein by reference.

Olanzapine is an antagonist of dopamine at D-1 and D-2 receptors, and in addition has antimuscarinic, anti-cholinergic properties, and is an antagonist for 5HT-2 receptor sites. The compound also has antagonist activity at noradrenergic alpha-receptors. These properties indicate that the compound is a potential neuroleptic with relaxant, anxiolytic, or anti-emetic properties, and is useful in treating psychotic conditions such as schizophrenia, schizophreniform diseases, and acute mania. At lower doses the compound is indicated for use in the treatment of mild anxiety states.

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors serotonin 5HT $_{2A/2C}$ (K_I = 4 and 11nM, respectively), dopamine D $_{1-4}$ (K_I=11-31 $_I$ 25 nM), histamine H $_I$ (K_I =7nM), and adrenergic (alpha) $_1$ receptors (K_I= nM) GABA $_A$, BZD, and (beta) adrenergic receptors (K_I > 10 μM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia is unknown. However, it has been proposed that this drug's efficacy in schrizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT $_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with Bipolar 1 Disorder is unknown.

Antagonism at receptor other than dopamine and 5HT $_2$ with similar receptor affinities may explain some of the other therapeutic and side effect of olanzapine. Olanzapine's antagonism of muscorinic M $_{1-5}$ receptors explains its anticholinergic effects. Olanzapine's antagonism of histamine H $_1$ receptors may explain somnolence observed with this drug. Olanzapine's antagonism of adrenergic (alpha) receptors may explain orthostatic hypotension observed with this drug.

B. Background Regarding Nanoparticulate Drugs

Bioavailability is the degree to which a drug becomes available to the target tissue after administration. Many factors can affect bioavailability including the dosage form and various properties, e.g., dissolution rate of the drug. Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water. Poorly water soluble drugs tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with fully soluble drug substances.

It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. U.S. Patent No. 5,145,684 to Liversidge et. al., which is herein incorporated by reference, discloses particles of a drug substance having a non-crosslinked surface stabilizer absorbed on the surface thereof and methods for the preparation thereof. This patent does not teach or suggest nanoparticulate compositions of olanzapine.

Methods of making nanoparticulate compositions are described, for example, in U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." These patents do not describe methods of making nanoparticulate olanzapine.

Nanoparticulate compositions are also described, for example, in U.S. Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,336,507 for "Use of Charged

Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse

Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,428,814 for "Bioadhesive nanoparticulate compositions having cationic surface stabilizers;" 6,431,478 for "Small Scale Mill;" 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,582,285 for "Apparatus for sanitary wet milling;" 6,656,504 for "Nanoparticulate Compositions Comprising Amorphous Cyclosporine;" 6,742,734 for "System and Method for Milling Materials;" 6,745,962 for "Small Scale Mill and Method Thereof;" 6,811,767 for "Liquid droplet aerosols of nanoparticulate drugs;" and 6,908,626 for "Compositions having a combination of immediate release and controlled release characteristics;" all of which are specifically incorporated by reference. In addition, U.S. Patent Application No. 20020012675 A1, published on January 31, 2002, for "Controlled Release Nanoparticulate Compositions,"

and WO 02/098565 for "System and Method for Milling Materials," describe nanoparticulate active agent compositions, and are specifically incorporated by reference. None of these references describe nanoparticulate compositions of olanzapine.

Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter." These references do not describe nanoparticulate olanzapine.

There is a need in the art for nanoparticulate olanzapine formulations which overcome these and other problems associated with prior conventional olanzapine formulations. The present invention satisfies these needs.

SUMMARY OF THE INVENTION

The present invention relates to injectable nanoparticulate olanzapine compositions. The compositions comprise olanzapine and at least one surface stabilizer, which is preferably adsorbed on or associated with the surface of the olanzapine particles. The nanoparticulate olanzapine particles have an effective average particle size of less than about 5 microns. The surface stabilizer is present in an amount sufficient to maintain the olazapine at an effective average particle size that maintains the efficacy of the drug over a period of time, such as about one week or greater than about one week. The nanoparticle size of the olanzapine particles can be manipulated to give the desirable blood profile and

duration of action when administered by either intramuscular (IM) or subcutaneous (SC) routes.

Long acting anti-psychotics are preferred, as the patient population treated with such drugs can suffer from poor patient compliance, resulting in diminished therapeutic effect for the administered drug. Drugs requiring multiple daily administration, or even daily administration, are not preferred for this patient population. A simpler dosage form, such as a once-weekly dosage form, can result in dramatically improved patient compliance, and consequently improved quality of life. Advantages and properties of the compositions of the invention are described herein.

Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate olanzapine composition of the invention. The pharmaceutical compositions preferably comprise olanzapine, at least one surface stabilizer, and at least one pharmaceutically acceptable carrier, as well as any desired excipients.

The invention further discloses a method of making a nanoparticulate olanzapine composition. Such a method comprises contacting olanzapine and at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate olanzapine composition. The one or more surface stabilizers can be contacted with olanzapine either before, preferably during, or after size reduction of the olanzapine.

The present invention is also directed to methods of treatment using the injectable nanoparticulate olanzapine compositions of the invention for, for example, psychotropic therapy and the treatment of central nervous system disorders. In one embodiment of the invention, intramuscular or subcutaneous injection of olanzapine is utilized. The administration of the drug in this manner allows for the formation of an intramuscular or subcutaneous depot of olanzapine which slowly releases the drug into the patient's system over a longer period of

time than if administered orally. The period of time over which the drug is released is preferably up to about one week, from about two weeks to about six weeks, and from about two weeks to about twelve weeks. Additional time periods of efficacy are described herein. This allows for improved patient compliance with enhanced therapeutic outcomes. Moreover, injectable formulations of olanzapine result in a significantly shorter response time as compared to oral administration. While current conventional formulations of olanzapine can be formulated for injection (i.e., Zyprexa®), such conventional injectable olanzapine formulations are difficult to prepare due to the low water solubility of the drug.

In psychotropic therapy and the treatment of central nervous system disorders, it is important to provide an olanzapine dosage form that delivers the required therapeutic amount of the drug *in vivo* and renders the drug bioavailable in a rapid and consistent manner. The nanoparticulate olanzapine formulations of the present invention achieve those goals through the formation of a drug depot, preferably following intramuscular injection. The depot slowly releases the drug into the bloodstream at almost zero order kinetics for about one (1) to about twelve (12) weeks through control of the nanoparticle size of the drug. Different nanoparticle sizes will dissolve at different rates, and will therefore release the drug to the bloodstream from the depot at different release rates.

Both the foregoing general description and the following brief description of the drawings and detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1: Shows an electron micrograph of unmilled olanzapine.

Figure 2: Shows an electron micrograph of a milled nanoparticulate olanzapine formulation.

Figure 3: Shows an electron micrograph of a milled nanoparticulate olanzapine formulation.

Figure 4: Graphically shows the plasma concentration (ng/mL) of olanazpine over a six hour time period following intramuscular administration to six male dogs of a nanoparticulate olanzapine formulation.

Figure 5: Graphically shows the plasma concentration (ng/mL) of olanazpine over a six hour time period following intramuscular administration to six male dogs of a nanoparticulate olanzapine formulation.

Detailed Description of Invention

The invention provides injectable nanoparticulate olanzapine formulations that can comprise high drug concentrations in low injection volumes, with durations of action that can be controlled to give efficacious blood levels through manipulation of particle size and hence dissolution for periods of about one week or greater.

In other embodiments of the invention, compositions of the invention provide efficacious levels of drug from about one week to about two weeks, from about one week to about three weeks, from about one week to about four weeks, from about one week to about five weeks, from about one week to about six weeks, from about one week to about seven weeks, from about one week to about eight weeks, from about one week to about nine weeks, from about one week to about ten weeks, from about one week to about eleven weeks, from about one week to about twelve weeks, and any combination thereof, such as from about two weeks to about six weeks, from about three weeks to about four weeks, from about three weeks to about seven weeks, etc.

The composition of the invention is administered via injection, such as by intramuscular or subcutaneously, to form a drug depot. The drug depot results in efficacious levels of drug up to about one week or greater.

As taught in U.S. Patent No. 5,145,684, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. It was surprisingly discovered that stable, injectable, nanoparticulate olanzapine formulations can be made.

The current formulations of olanzapine suffer from the following problems: (1) the poor solubility of the drug results in a relatively low bioavailability; (2) dosing must be repeated several times each day; and (3) a wide variety of side effects are associated with the current dosage forms of the drug.

The present invention overcomes problems encountered with the prior art olanzapine formulations. Specifically, the nanoparticulate olanzapine formulations of the invention may offer the following advantages: (1) a decrease in the frequency of dosing and/or prolonged therapeutic levels of drug following dosing; (2) faster onset of action; (3) smaller doses of olanzapine required to obtain the same pharmacological effect; (4) increased bioavailability; (5) improved performance characteristics for intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller liquid dose volumes; (6) improved pharmacokinetic profiles, such as improved C_{max} and AUC profiles; (7) substantially similar or bioequivalent pharmacokinetic profiles of the nanoparticulate olanzapine compositions when administered in the fed versus the fasted state; (8) bioadhesive olanzapine formulations, which can coat the desired site of application and be retained for a period of time, thereby increasing the efficacy of the drug as well as eliminating or decreasing the frequency of dosing; (9) high redispersibility of the nanoparticulate olanzapine particles present in the compositions of the invention following administration;

(10) low viscosity liquid nanoparticulate olanzapine dosage forms can be made; (11) the nanoparticulate olanzapine compositions can be used in conjunction with other active agents; (12) the nanoparticulate olanzapine compositions can be sterile filtered; (13) the nanoparticulate olanzapine compositions are suitable for parenteral administration; and (14) the nanoparticulate olanzapine compositions do not require organic solvents or pH extremes.

A preferred dosage form of the invention is a liquid injectable formulation. However, the composition may also be formulated in a powder or solid for reconstitution prior to injectable administration, such as by lyophilization. The dosage form can be, for example, controlled release dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof.

The present invention is described herein using several definitions, as set forth below and throughout the application.

As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

"Conventional" or "non-nanoparticulate active agent" shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 5 microns. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 5 microns.

"Poorly water soluble drugs" as used herein means those having a solubility of less than about 30 mg/ml, preferably less than about 20 mg/ml, preferably less than about 10 mg/ml, or preferably less than about 1 mg/ml.

As used herein with reference to stable drug particles, 'stable' includes, but is not limited to, one or more of the following parameters: (1) that the olanzapine particles do not appreciably flocculate or agglomerate due to interparticle attractive forces, or otherwise significantly increase in particle size over time; (2) that the physical structure of the olanzapine particles is not altered over time, such as by conversion from an amorphous phase to crystalline phase; (3) that the olanzapine particles are chemically stable; and/or (4) where the olanzapine has not been subject to a heating step at or above the melting point of the olanzapine in the preparation of the nanoparticles of the invention.

'Therapeutically effective amount' as used herein with respect to a drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that 'therapeutically effective amount,' administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a 'therapeutically effective amount' by those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as injectable dosages.

Enhanced pK Profiles

The invention also preferably provides olanzapine compositions having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the olanzapine compositions preferably includes, but is not limited to: (1) a C_{max} for olanzapine, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the C_{max} for a non-nanoparticulate olanzapine formulation (*e.g.*, Zyprexa®), administered at the same dosage; and/or (2) an AUC for olanzapine, when assayed in the plasma of a mammalian subject following administration,

that is preferably greater than the AUC for a non-nanoparticulate olanzapine formulation (*e.g.*, Zyprexa®), administered at the same dosage. The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial injectable dose of olanzapine.

Conventional olanzapine (*e.g.*, Zyprexa®), reaches peak plasma levels in 5-8 hours, and has a half-life of about 35 hours, depending on metabolism.

A preferred injectable olanzapine composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate olanzapine formulation of (*e.g.*, Zyprexa®), administered at the same dosage, a C_{max} which is at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{max} exhibited by the non-nanoparticulate olanzapine formulation.

A preferred injectable olanzapine composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate olanzapine formulation (*e.g.*, Zyprexa®), administered at the same dosage, an AUC which is at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200%

greater than the AUC exhibited by the non-nanoparticulate olanzapine formulation.

Combination Pharmacokinetic Profile Compositions

In yet another embodiment of the invention, a first nanoparticulate olanzapine composition providing a desired pharmacokinetic profile is co-administered, sequentially administered, or combined with at least one other olanzapine composition that generates a desired different pharmacokinetic profile. More than two olanzapine compositions can be co-administered, sequentially administered, or combined. While the first olanzapine composition has a nanoparticulate particle size, the additional one or more olanzapine compositions can be nanoparticulate, solubilized, or have a microparticulate particle size.

The second, third, fourth, *etc.*, olanzapine compositions can differ from the first, and from each other, for example: (1) in the effective average particle sizes of olanzapine; or (2) in the dosage of olanzapine. Such a combination composition can reduce the dose frequency required.

If the second olanzapine composition has a nanoparticulate particle size, then preferably the olanzapine particles of the second composition have at least one surface stabilizer associated with the surface of the drug particles. The one or more surface stabilizers can be the same as or different from the surface stabilizer(s) present in the first olanzapine composition.

Preferably where co-administration of a "fast-acting" formulation and a "longer-lasting" formulation is desired, the two formulations are combined within a single composition, for example a dual-release composition.

A. Olanazpine Compositions

The invention provides compositions comprising nanoparticulate olanzapine particles and at least one surface stabilizer. The surface stabilizers are preferably adsorbed to or associated with the surface of the olanzapine particles. Surface stabilizers useful herein do not chemically react with the olanzapine particles or itself. Preferably, individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages. The compositions can comprise two or more surface stabilizers.

The present invention also includes nanoparticulate olanzapine compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous).

Olanzapine can be in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixtures thereof.

Illustrative but not limiting compositions comprise, based on % w/w:

Olanzapine	5 – 50%
Surface stabilizer	0.1 – 50%
preservatives (Optional)	0.05 - 0.25%
pH adjusting agent	pH about 6 to about 7
water for injection	q.s.

1. Surface Stabilizers

The choice of a surface stabilizer for olanzapine is non-trivial and required experimentation to realize a desirable formulation. Combinations of more than one surface stabilizer can be used in the invention. Useful surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and

surfactants. Surface stabilizers include nonionic, ionic, anionic, cationic, and zwitterionic surfactants.

Preferred surface stabilizers include, but are not limited to, a polysorbate, such as Tween 80, benzalkonium chloride, and combinations thereof.

Representative examples of useful surface stabilizers include but are not limited to Low viscosity hydroxypropyl cellulose (HPC or HPC-SL); hydroxypropyl methyl cellulose (HPMC); hydroxymethyl cellulose (HMC); ethycellulose; povidone; Pluronics; sodium deoxycholate; PEG-Phospholipids; Tyloxapol and other approved tritons, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.*, Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.*, Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation),

Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-lOG® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)$-$CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-derivatized phospholipid, PEG- derivatized cholesterol, PEG- derivatized cholesterol derivative, PEG- derivatized vitamin A, PEG- derivatized vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

Povidone Polymers

In one embodiment of the invention, a povidone polymer is utilized as a surface stabilizer. Povidone polymers for injectable compositions preferably have a molecular weight of less than about 40,000 daltons. Povidone polymers, also known as polyvidon(e), povidonum, PVP, and polyvinylpyrrolidone, are sold under the trade names Kollidon® (BASF Corp.) and Plasdone® (ISP Technologies, Inc.). They are polydisperse macromolecular molecules, with a chemical name of 1-ethenyl-2-pyrrolidinone polymers and 1-vinyl-2-pyrrolidinone polymers. Povidone polymers are produced commercially as a series of products having mean molecular weights ranging from about 10,000 to about 700,000 daltons. To be useful as a surface modifier for a drug compound to be administered to a mammal, the povidone polymer must have a molecular

weight of less than about 40,000 daltons, as a molecular weight of greater than 40,000 daltons would have difficulty clearing the body.

Povidone polymers are prepared by, for example, Reppe's process, comprising: (1) obtaining 1,4-butanediol from acetylene and formaldehyde by the Reppe butadiene synthesis; (2) dehydrogenating the 1,4-butanediol over copper at 200° to form γ-butyrolactone; and (3) reacting γ-butyrolactone with ammonia to yield pyrrolidone. Subsequent treatment with acetylene gives the vinyl pyrrolidone monomer. Polymerization is carried out by heating in the presence of H_2O and NH_3. *See The Merck Index*, 10th Edition, pp. 7581 (Merck & Co., Rahway, NJ, 1983).

The manufacturing process for povidone polymers produces polymers containing molecules of unequal chain length, and thus different molecular weights. The molecular weights of the molecules vary about a mean or average for each particular commercially available grade. Because it is difficult to determine the polymer's molecular weight directly, the most widely used method of classifying various molecular weight grades is by K-values, based on viscosity measurements. The K-values of various grades of povidone polymers represent a function of the average molecular weight, and are derived from viscosity measurements and calculated according o Fikentscher's formula.

The weight-average of the molecular weight, Mw, is determined by methods that measure the weights of the individual molecules, such as by light scattering. Table 1 provides molecular weight data for several commercially available povidone polymers, all of which are soluble.

TABLE 1

Povidone	K-Value	Mv (Daltons)**	Mw (Daltons)**	Mn (Daltons)**
Plasdone C-15®	17 ± 1	7,000	10,500	3,000
Plasdone C-30®	30.5 ± 1.5	38,000	62,500*	16,500
Kollidon 12 PF®	11-14	3,900	2,000-3,000	1,300
Kollidon 17 PF®	16-18	9,300	7,000-11,000	2,500
Kollidon 25®	24-32	25,700	28,000-34,000	6,000

*Because the molecular weight is greater than 40,000 daltons, this povidone polymer is not useful as a surface stabilizer for a drug compound to be administered parenterally (*i.e.*, injected).
**Mv is the viscosity-average molecular weight, Mn is the number-average molecular weight, and Mw is the weight average molecular weight. Mw and Mn were determined by light scattering and ultra-centrifugation, and Mv was determined by viscosity measurements.

Based on the data provided in Table 1, exemplary preferred commercially available povidone polymers for injectable compositions include, but are not limited to, Plasdone C-15®, Kollidon 12 PF®, Kollidon 17 PF®, and Kollidon 25®.

Cationic Surface Stabilizers

Depending upon the desired method of administration, bioadhesive formulations of nanoparticulate olanzapine can be prepared by selecting one or more cationic surface stabilizers that impart bioadhesive properties to the resultant composition. Useful cationic surface stabilizers are described below.

Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), polyvinylpyrrolidone-2-

dimethylaminoethyl methacrylate dimethyl sulfate, 1,2 Dipalmitoyl-sn-Glycero-3-Phosphoethanolamine-N-[Amino(Polyethylene Glycol)2000] (sodium salt) (also known as DPPE-PEG(2000)-Amine Na) (Avanti Polar Lipids, Alabaster, Al), Poly(2-methacryloxyethyl trimethylammonium bromide) (Polysciences, Inc., Warrington, PA) (also known as S1001), poloxamines such as Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.), lysozyme, long-chain polymers such as alginic acid, carrageenan (FMC Corp.), and POLYOX (Dow, Midland, MI).

Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl

ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

Nonpolymeric cationic surface stabilizers are any nonpolymeric compound, such as benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1-R_4 are CH_3;

(ii) one of R_1-R_4 is CH_3;

(iii) three of R_1-R_4 are CH_3;

(iv) all of R_1-R_4 are CH_3;

(v) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

(vi) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

(vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where $n>1$;

(viii) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

(ix) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

(x) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

(xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

(xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

While applicants do not wish to be bound by theoretical mechanisms, it is believed that the stabilizer hinders the flocculation and/or agglomeration of the olanzapine particles by functioning as a mechanical or steric barrier between the

particles, minimizing the close, interparticle approach necessary for agglomeration and flocculation.

2. Excipients

Exemplary preservatives include methylparaben (about 0.18% based on % w/w), propylparaben (about 0.02% based on % w/w), phenol (about 0.5% based on % w/w), and benzyl alcohol (up to 2% v/v). An exemplary pH adjusting agent is sodium hydroxide, and an exemplary liquid carrier is sterile water for injection. Other useful preservatives, pH adjusting agents, and liquid carriers are well-known in the art.

3. Nanoparticulate Olanzapine Particle Size

As used herein, particle size is determined on the basis of the weight average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, and disk centrifugation.

The compositions of the invention comprise olanzapine nanoparticles which have an effective average particle size of less than about 5 microns. In other embodiments of the invention, the olanzapine particles have a size of less than about 4900 nm, less than about 4800 nm, less than about 4700 nm, less than about 4600 nm, less than about 4500 nm, less than about 4400 nm, less than about 4300 nm, less than about 4200 nm, less than about 4100 nm, less than about 4 microns, less than about 3900 nm, less than about 3800 nm, less than about 3700 nm, less than about 3600 nm, less than about 3500 nm, less than about 3400 nm, less than about 3300 nm, less than about 3200 nm, less than about 3100 nm, less than about 3 microns, less than about 2900 nm, less than about 2800 nm, less than about 2700 nm, less than about 2600 nm, less than

about 2500 nm, less than about 2400 nm, less than about 2300 nm, less than about 2200 nm, less than about 2100 nm, less than about 2000 nm, less than about 1900 nm, less than less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100 nm, less than about 90 nm, less than about 80 nm, less than about 70 nm, less than about 60 nm, or less than about 50 nm, when measured by the above-noted techniques.

By "an effective average particle size of less than about 5 microns" it is meant that at least 50% of the nanoparticulate olanzapine particles have a weight average particle size of less than about 5 microns, when measured by the above-noted techniques. In other embodiments of the invention, at least about 70%, at least about 90%, at least about 95%, or at least about 99% of the nanoparticulate olanzapine particles have a particle size of less than the effective average, by weight, *i.e.,* less than about 5 microns, less than about 4900 nm, less than less than about 4800 nm, less than about 4700 nm, *etc.* (as listed in the paragraph above).

If the nanoparticulate olanzapine composition is combined with a microparticulate olanzapine or non-olanzapine active agent composition, then such a composition is either solubilized or has an effective average particle size of greater than about 5 microns. By "an effective average particle size of greater than about 5 microns" it is meant that at least 50% of the microparticulate olanzapine or non-olanzapine active agent particles have a particle size of greater than about 5 microns, by weight, when measured by the above-noted techniques.

In other embodiments of the invention, at least about 70%, at least about 90%, at least about 95%, or at least about 99%, by weight, of the microparticulate olanzapine or non-olanzapine active agent particles have a particle size greater than about 5 microns.

In the present invention, the value for D50 of a nanoparticulate olanzapine composition is the particle size below which 50% of the olanzapine particles fall, by weight. Similarly, D90 and D99 are the particle sizes below which 90% and 99%, respectively, of the olanzapine particles fall, by weight.

4. Concentration of Nanoparticulate Olanzapine and Surface Stabilizers

The relative amounts of olanzapine and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, upon the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, *etc.*

The concentration of olanzapine can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, from about 90% to about 0.5%, or from about 5.0% to about 50%, by weight, based on the total combined dry weight of the olanzapine and at least one surface stabilizer, not including other excipients.

The concentration of the at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, from about 10% to about 99.5%, or from about 0.1 to about 50%, by weight, based on the total combined dry weight of the olanzapine and at least one surface stabilizer, not including other excipients.

5. Additional Active Agents

The invention encompasses the nanoparticulate olanzapine compositions of the invention formulated or co-administered with one or more non-olanzapine active agents. Methods of using such combination compositions are also

encompassed by the invention. The non- olanzapine active agents can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

The compound to be administered in combination with a nanoparticulate olanzapine composition of the invention can be formulated separately from the nanoparticulate olanzapine composition or co-formulated with the nanoparticulate olanzapine composition. Where a nanoparticulate olanzapine composition is co-formulated with a second active agent, the second active agent can be formulated in any suitable manner, such as immediate-release, rapid-onset, sustained-release, or dual-release form.

Such non-olanzapine active agents can be, for example, a therapeutic agent. A therapeutic agent can be a pharmaceutical agent, including a biologic. The active agent can be selected from a variety of known classes of drugs, including, for example, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, such as NSAIDs and COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives (hypnotics and neuroleptics), astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates,

prostaglandins, radio-pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

Examples of secondary active agents particularly useful in the compositions of the invention include, but are not limited to, antidepressants. Examples of classes of useful antidepressants include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and monoamine oxidase Inhibitors (MAOI's). Examples of antidepressants include, but are not limited to, citalopram (Celexa®), escitalopram HB (Lexapro®), fluoxetine hydrochloride (Prozac®), paroxetine (Paxil®), fluvoxamine (Luvox®), sertraline (Zoloft®), venlafaxine (Effexor®), amitriptyline (Elavil®), desipramine, nortriptyline, duloxetine (Cymbalta®), mirtazepine (Remeron®), phenelzine (Nardil®), tranylcypromine (Parnate®), nefazodone (Serzone®), trazodone, and bupropion (Wellbutrin®). A particularly useful antidepressant is fluoxetine (Prozac®).

B. Methods of Making Injectable Olanzapine Formulations

In another aspect of the invention there is provided a method of preparing the injectable nanoparticulate olanzapine formulations of the invention. The method comprises of one of the following methods: attrition, precipitation, evaporation, or combinations of these. Exemplary methods of making nanoparticulate compositions are described in U.S. Patent No. 5,145,684. Methods of making nanoparticulate compositions are also described in U.S. Patent No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S.

Patent No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Patent No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

Following milling, homogenization, precipitation, *etc.*, the resultant nanoparticulate olanzapine composition can be utilized a liquid dosage formulation for injectable administration.

In one embodiment of the invention, the olanzapine particles are reduced to an effective average particle size of less than about 600 nm. Preferably, the effective average particle size of the nanoparticulate olanzapine is less than about 450 nm, more preferably less than about 300 nm, even more preferably less than about 250 nm, and most preferably less than about 100 nm. The pH of the liquid dispersion media is preferably maintained within the range of from about 3.0 to about 8.0, or about 5.0 to about 7.5, more preferably, at a pH of about 7.4, during the size reduction process. Preferably, the dispersion media used for the size reduction process is aqueous. However, any media in which olanzapine is poorly soluble and dispersible can be used as a dispersion media. Non-aqueous examples of dispersion media include, but are not limited to, aqueous salt solutions, safflower oil and solvents such as ethanol, t-butanol, hexane, and glycol.

Effective methods of providing mechanical force for particle size reduction of olanzapine include ball milling, media milling, and homogenization,

for example, with a Microfluidizer® (Microfluidics Corp.). Ball milling is a low energy milling process that uses milling media, drug, stabilizer, and liquid. The materials are placed in a milling vessel that is rotated at optimal speed such that the media cascades and reduces the drug particle size by impaction. The media used must have a high density as the energy for the particle reduction is provided by gravity and the mass of the attrition media.

Media milling is a high energy milling process. Drug, stabilizer, and liquid are placed in a reservoir and recirculated in a chamber containing media and a rotating shaft/impeller. The rotating shaft agitates the media which subjects the drug to impaction and sheer forces, thereby reducing the drug particle size.

Homogenization is a technique that does not use milling media. Drug, stabilizer, and liquid (or drug and liquid with the stabilizer added after particle size reduction) constitute a process stream propelled into a process zone, which in the Microfluidizer® is called the Interaction Chamber. The product to be treated is inducted into the pump, and then forced out. The priming valve of the Microfluidizer® purges air out of the pump. Once the pump is filled with product, the priming valve is closed and the product is forced through the interaction chamber. The geometry of the interaction chamber produces powerful forces of sheer, impact, and cavitation which are responsible for particle size reduction. Specifically, inside the interaction chamber, the pressurized product is split into two streams and accelerated to extremely high velocities. The formed jets are then directed toward each other and collide in the interaction zone. The resulting product has very fine and uniform particle or droplet size. The Microfluidizer® also provides a heat exchanger to allow cooling of the product. U.S. Patent No. 5,510,118, which is specifically incorporated by reference, refers to a process using a Microfluidizer® resulting in nanoparticulate particles.

Olanzapine can be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the olanzapine in the liquid

medium can vary from about 5 to about 60%, and preferably is from about 15 to about 50% (w/v), and more preferably about 20 to about 40%. The surface stabilizer can be present in the premix, it can be during particle size reduction, or it can be added to the drug dispersion following particle size reduction. The concentration of the surface stabilizer can vary from about 0.1 to about 50%, and preferably is from about 0.5 to about 20%, and more preferably from about 1 to about 10%, by weight.

The premix can be used directly by subjecting it to mechanical means to reduce the average olanzapine particle size in the dispersion to the desired size, preferably less than about 5 microns. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, olanzapine and the surface stabilizer can be dispersed in the liquid media using suitable agitation, *e.g.*, a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition.

The mechanical means applied to reduce the olanzapine particle size conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, and media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix is preferably from about 100 to about 1000 centipoise, and for ball milling the apparent viscosity of the premix is preferably from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal balance between efficient particle size reduction and media erosion but are in no way limiting

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills,

processing times of up to five days or longer may be required. Alternatively, processing times of less than 1 day (residence times of one minute up to several hours) are possible with the use of a high shear media mill.

The olanzapine particles must be reduced in size at a temperature which does not significantly degrade olanzapine. Processing temperatures of less than about 30° to less than about 40°C are ordinarily preferred. If desired, the processing equipment can be cooled with conventional cooling equipment. Control of the temperature, *e.g.*, by jacketing or immersion of the milling chamber with a cooling liquid, is contemplated. Generally, the method of the invention is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. Ambient processing pressures are typical of ball mills, attritor mills, and vibratory mills.

Grinding Media

The grinding media can comprise particles that are preferably substantially spherical in shape, *e.g.*, beads, consisting essentially of polymeric resin or glass or Zirconium Silicate or other suitable compositions. Alternatively, the grinding media can comprise a core having a coating of a polymeric resin adhered thereon.

In general, suitable polymeric resins are chemically and physically inert, substantially free of metals, solvent, and monomers, and of sufficient hardness and friability to enable them to avoid being chipped or crushed during grinding. Suitable polymeric resins include crosslinked polystyrenes, such as polystyrene crosslinked with divinylbenzene; styrene copolymers; polycarbonates; polyacetals, such as Delrin® (E.I. du Pont de Nemours and Co.); vinyl chloride polymers and copolymers; polyurethanes; polyamides; poly(tetrafluoroethylenes), *e.g.*, Teflon®(E.I. du Pont de Nemours and Co.), and

other fluoropolymers; high density polyethylenes; polypropylenes; cellulose ethers and esters such as cellulose acetate; polyhydroxymethacrylate; polyhydroxyethyl acrylate; and silicone-containing polymers such as polysiloxanes and the like. The polymer can be biodegradable. Exemplary biodegradable polymers include poly(lactides), poly(glycolide) copolymers of lactides and glycolide, polyanhydrides, poly(hydroxyethyl methacylate), poly(imino carbonates), poly(N-acylhydroxyproline)esters, poly(N-palmitoyl hydroxyproline) esters, ethylene-vinyl acetate copolymers, poly(orthoesters), poly(caprolactones), and poly(phosphazenes). For biodegradable polymers, contamination from the media itself advantageously can metabolize *in vivo* into biologically acceptable products that can be eliminated from the body.

The grinding media preferably ranges in size from about 0.01 to about 3 mm. For fine grinding, the grinding media is preferably from about 0.02 to about 2 mm, and more preferably from about 0.03 to about 1 mm in size.

The polymeric resin can have a density from about 0.8 to about 3.0 g/cm^3.

In one embodiment of the invention, the olanzapine particles are made continuously. Such a method comprises continuously introducing olanzapine into a milling chamber, contacting the olanzapine with grinding media while in the chamber to reduce the olanzapine particle size, and continuously removing the nanoparticulate olanzapine from the milling chamber.

The grinding media can be separated from the milled nanoparticulate olanzapine using conventional separation techniques, in a secondary process such as by simple filtration, sieving through a mesh filter or screen, and the like. Other separation techniques such as centrifugation may also be employed. Alternatively, a screen can be utilized during the milling process to remove the grinding media following completion of particle size reduction.

Sterile Product Manufacturing

Development of injectable compositions requires the production of a sterile product. The manufacturing process of the present invention is similar to typical known manufacturing processes for sterile suspensions. A typical sterile suspension manufacturing process flowchart is as follows:

Media Conditioning
↓
Compounding
↓
Particle Size Reduction
↓
Vial Filling
↓
Lyophilization and/or Terminal Sterilization

As indicated by the optional steps in parentheses, some of the processing is dependent upon the method of particle size reduction and/or method of sterilization. For example, media conditioning is not required for a milling method that does not use media. If terminal sterilization is not feasible due to chemical and/or physical instability, aseptic processing can be used.

C. Method of Treatment

Yet another aspect of the present invention provides a method of treating a mammal, including a human, of disorders of the central nervous system including, but not limited to psychiatric treatment. Such treatment comprises administering to the subject the injectable nanoparticulate olanzapine formulation of the invention. As used herein, the term "subject" is used to mean an animal,

preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

Examples of disorders that can be treated with olanzapine include, but are not limited to, schizophrenia and related psychoses, bipolar mania and/or bipolar disorder, seizures, obsessive/compulsive disorders, generalized anxiety disorder, post traumatic distress syndrome, extreme shyness, diabetic nerve pain, smoking cessation, and depression.

Particularly advantageous features of the present invention include that the pharmaceutical formulation of the invention exhibits a prolonged duration of action that can be controlled upon administration, and produces minimal or no pain or irritation upon administration. For example, compositions of the invention can provide efficacious levels of drug for up to about one week, from about two to about six weeks, or from about two to about twelve weeks. In addition, the injectable formulation of the invention can provide a high olanzapine concentration in a small volume to be injected. A general protocol for administration thereof comprises an intramuscular or subcutaneous bolus injection of olanzapine.

Conventional olanzapine (Zyprexa®) has a starting single evening dose of 10 mg. The usual maximum dose should be 20 mg. For treatment of psychoses, such as schizophrenia, the adult dosage is 5-10 mg/day initially, with a target dose of 10 mg/day within several days.

Olanzapine shows mesolimbic sensitivity, blocks conditioned avoidance at lower doses than those inducing catalepsy, substitutes for clozapine in a drug discrimination assay, produces a modest rise in prolactin, produces few extrapyramidal side effects, and reduces positive and negative symptoms of schizophrenia as efficaciously as clozapine. However, despite this 'atypical' profile, olanzapine has a weaker alpha-2 blockade than clozapine or risperidone. It has relatively high affinity for muscarinic, 5HT - 2, and D1, D2 and D4

receptors. Trials suggest a good response in schizophrenia with few extrapyramidal side effects (EPSEs).

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The nanoparticulate compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

One of ordinary skill will appreciate that effective amounts of olanzapine can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of olanzapine in the nanoparticulate compositions of the invention may be varied to obtain an amount of olanzapine that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired

therapeutic effect, the route of administration, the potency of the administered olanzapine, the desired duration of treatment, and other factors.

Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

The following examples are given to illustrate the present invention. It should be understood, however, that the spirit and scope of the invention is not to be limited to the specific conditions or details described in these examples but should only be limited by the scope of the claims that follow. All references identified herein, including U.S. patents, are hereby expressly incorporated by reference.

Example 1

The purpose of this example is to illustrate the procedure for identifying a suitable nanoparticulate formulation of olanzapine.

The study can be conducted by screening eleven surface stabilizers to identify the most suitable stabilizer for parenteral administration of olanzapine. The dispersions can be formulated at 40% solids to 2.4% surface stabilizer.

TABLE 2

Surface Stabilizer
Plasdone C15® (polyvinylpyrrolidone)
Kollidon 17PF® (a polyvinylpyrrolidone polymer)
Povidone K30® (a polyvinylpyrrolidone polymer)
Tyloxapol
Pluronic F68® (a high molecular weight polyoxyalkylene ether)
Pluronic F108® (a high molecular weight polyoxyalkylene ether)
Tween 80® (a polyoxyethylene sorbitan fatty acid ester)
dioctylsulfosuccinate (CAS No. 577-11-7; aka Docusate Sodium)
B20-5000® (a triblock copolymer surface modifier)
B20-5000-sulfonated (a triblock copolymer surface modifier)
lecithin (CAS No. 8002-43-5)
Povidone K30® and Pluronic F108®

Such combinations may produce stable dispersions of differing nanoparticulate size that will have differing durations of action when administered. Preclinical and clinical studies will identify the optimum formulation and size associated with the desired prolonged duration of action.

Example 2

The purpose of this example was to prepare a nanoparticulate formulation of olanzapine.

The particle size of olanzapine drug crystals was first measured prior to incorporation into a nanoparticulate formulation. The particle size, as measured using a Horiba LA 910 particle size analyzer (Horiba Instruments, Irvine, CA),

was a mean of 137.08 microns, and a D90 of less than 335.59 microns. See Fig. 1.

An aqueous dispersion of 10% olanzapine (Camida LLC, Newark, NJ), combined with 1% Tween 80, 0.1% benzalkonium chloride, and 20% dextrose, was milled in a NanoMill® 0.01 (Elan Drug Delivery), along with 500 micron PolyMill® grinding media (Dow Chemical) (50-89% media load). The mixture was milled at a speed of 1009 – 5500 rpms, at a temperature of 5-10°C, for about 30 min.

Following milling, the particle size of the milled olanzapine particles was measured, in deionized distilled water, using a Horiba LA 910 particle size analyzer. The median milled olanzapine particle size was 347 nm, with a mean size of 606 nm, a D90 of 1.28 microns, and a D83 of less than 1 micron. See Fig. 2.

Example 3

The purpose of this example was to prepare a nanoparticulate formulation of olanzapine.

An aqueous dispersion of 30% olanzapine (Camida LLC, Newark, NJ), combined with 2.5% Tween 80, was milled in a NanoMill® 0.01 (Elan Drug Delivery), along with 500 micron PolyMill® grinding media (Dow Chemical) (50-89% media load). The mixture was milled at a speed of 1009 – 5500 rpms, at a temperature of 5-10°C, for about 30 min.

Following milling, the particle size of the milled olanzapine particles was measured, in deionized distilled water, using a Horiba LA 910 particle size analyzer. The median milled olanzapine particle size was 990 nm, with a mean size of 1.136 nm, a D90 of 2.07 microns, and a D50 of less than 1 micron. See Fig. 3.

Example 4

The purpose of this example was to determine the *in vivo* characteristics of the nanoparticulate olanzapine formulation prepared in Example 2.

An *in vivo* study, utilizing male beagle dogs, was conducted to determine the therapeutic levels of olanazapine present *in vivo* over a period of time following intramuscular (IM) administration of the nanoparticulate olanazapine formulation prepared in Example 2. Six dogs were given a single intramuscular dose of 10 mg/kg (about 100 mg/animal), which is about 10x the daily dose in humans. Blood samples were taken at t = 0, 0.5, 1, 2, 4, 8, 24, and 49 hours post administration, and 4, 7, 14, and 28 days post administration. The plasma concentration (ng/ml) over a 168 hr period is shown in Fig. 4. As shown in Fig. 4, therapeutic levels of olanzapine, of 5 to 22 ng/ml, were present *in vivo* for over a 168 hr period. Fig. 5 further demonstrates that for all animals dosed, therapeutic levels of olanzapine, of 5to 22 ng/ml, were present *in vivo* for over a 168 hr period.

In addition to demonstrating that the injectable olazapine formulations of the invention produce measurable and detectable levels of drug in the plasma for more than seven days following administration, this example further demonstrates: (1) that the olanzapine formulation prepared as in Example 2 is syringeable with a 23 gauge needle; and (2) that the olanzapine formulation prepared as in Example 2 is well tolerated by mammals.

* * * *

It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention

provided they come within the scope of the appended claims and their equivalents.

What We Claim Is:

1. An injectable nanoparticulate olanzapine composition comprising:

(a) olanzapine nanoparticles having an effective average particle size that results in a therapeutic efficacy of about one week or greater;

(b) at least one surface stabilizer; and

(c) a pharmaceutically acceptable carrier.

2. The composition of claim 1, wherein the composition is administered via intramuscular or subcutaneous injection so as to form a depot.

3. The composition of claim 2, wherein the depot releases the olanzapine at therapeutic levels for a period of time from about two to about six weeks.

4. The composition of claim 1, wherein the depot releases the olanzapine at therapeutic levels for a period of time from about two to about twelve weeks.

5. The composition of claim 1, wherein the depot releases the olanzapine at therapeutic levels for a period of time selected from the group consisting of one week to about two weeks, from about one week to about three weeks, from about one week to about four weeks, from about one week to about five weeks, from about one week to about six weeks, from about one week to about seven weeks, from about one week to about eight weeks, from about one week to about nine weeks, from about one week to about ten weeks, from about one week to about eleven weeks, from about one week to about twelve weeks, and combinations thereof.

6. The composition of claim 1, wherein the olanzapine is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

7. The composition of claim 1, wherein the effective average particle size of the olanzapine particles is less than about 5 microns.

8. The composition of claim 7, wherein the effective average particle size of the olanzapine particles is selected from the group consisting of less than about 4900 nm, less than about 4800 nm, less than about 4700 nm, less than about 4600 nm, less than about 4500 nm, less than about 4400 nm, less than about 4300 nm, less than about 4200 nm, less than about 4100 nm, less than about 4 microns, less than about 3900 nm, less than about 3800 nm, less than about 3700 nm, less than about 3600 nm, less than about 3500 nm, less than about 3400 nm, less than about 3300 nm, less than about 3200 nm, less than about 3100 nm, less than about 3 microns, less than about 2900 nm, less than about 2800 nm, less than about 2700 nm, less than about 2600 nm, less than about 2500 nm, less than about 2400 nm, less than about 2300 nm, less than about 2200 nm, less than about 2100 nm, less than about 2000 nm, less than about 1900 nm, less than less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100 nm, less than about 90 nm, less than about 80 nm, less than about 70 nm, less than about 60 nm, and less than about 50 nm.

9. The composition of claim 1, wherein:

(a) the olanzapine is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, from about 90% to about 0.5%, and from about 5.0% to about 50%, by weight, based on the total combined weight of the olanzapine and at least one surface stabilizer, not including other excipients; and

(b) the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, from about 10% to about 99.5%, and from about 0.1 to about 50%, by weight, based on the total combined dry weight of the olanzapine and at least one surface stabilizer, not including other excipients.

10. The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of a non-ionic surface stabilizer, an ionic surface stabilizer, a anionic surface stabilizer, a cationic surface stabilizer, and a zwitterionic surface stabilizer.

11. The composition of claim 1, wherein at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose,

hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, random copolymers of vinyl acetate and vinyl pyrrolidone, cationic polymers, cationic biopolymers, cationic polysaccharides, cationic cellulosics, cationic alginates, cationic nonpolymeric compounds, cationic phospholipids, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl

ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

12. The composition of claim 1, comprising a surface stabilizer selected from the group consisting of a polysorbate, benzalkonium chloride, dextrose, and a combination thereof.

13. The composition of claim 1, further comprising at least one additional olanzapine composition having an effective average particle size which is different that the effective average particle size of the olanzapine composition of claim 1.

14. The composition of claim 1, additionally comprising one or more non-olanzapine active agents.

15. The composition of claim 14, wherein at least one non-olanzapine agent is an antidepressant.

16. The composition of claim 15, wherein the antidepressant is fluoxetine.

17. The composition of claim 1, wherein the composition is syringeable with a 23 gauge needle.

18. The composition of claim 1, which is well tolerated by a mammal.

19. A method of making an injectable nanoparticulate olanzapine composition that produces an intramuscular depot upon administration comprising:

contacting particles of olanzapine or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a

olanzapine composition having an effective average particle size that results in a therapeutic efficacy of about one week or greater.

20. The method of claim 19, wherein the contacting comprises grinding, wet grinding, homogenizing, or a combination thereof.

21. The method of claim 19, wherein the effective average particle size of the olanzapine particles is less than about 5 microns.

22. The composition of claim 21, wherein the effective average particle size of the olanzapine particles is selected from the group consisting of less than about 4900 nm, less than about 4800 nm, less than about 4700 nm, less than about 4600 nm, less than about 4500 nm, less than about 4400 nm, less than about 4300 nm, less than about 4200 nm, less than about 4100 nm, less than about 4 microns, less than about 3900 nm, less than about 3800 nm, less than about 3700 nm, less than about 3600 nm, less than about 3500 nm, less than about 3400 nm, less than about 3300 nm, less than about 3200 nm, less than about 3100 nm, less than about 3 microns, less than about 2900 nm, less than about 2800 nm, less than about 2700 nm, less than about 2600 nm, less than about 2500 nm, less than about 2400 nm, less than about 2300 nm, less than about 2200 nm, less than about 2100 nm, less than about 2000 nm, less than about 1900 nm, less than less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about

110 nm, less than about 100 nm, less than about 90 nm, less than about 80 nm, less than about 70 nm, less than about 60 nm, and less than about 50 nm.

23. A method for the treatment of a subject for disorders of the central nervous system comprising administering to the subject an effective amount of an injectable composition comprising:

(a) olanzapine nanoparticles having an effective average particle size of that results in a therapeutic efficacy of about one week or greater;

(b) at least one surface stabilizer;

(c) at least one pharmaceutically acceptable carrier.

24. The method of claim 23, wherein the effective average particle size of the olanzapine particles is less than about 5 microns.

25. The method of claim 24, wherein the effective average particle size of the olanzapine particles is selected from the group consisting of less than about 4900 nm, less than about 4800 nm, less than about 4700 nm, less than about 4600 nm, less than about 4500 nm, less than about 4400 nm, less than about 4300 nm, less than about 4200 nm, less than about 4100 nm, less than about 4 microns, less than about 3900 nm, less than about 3800 nm, less than about 3700 nm, less than about 3600 nm, less than about 3500 nm, less than about 3400 nm, less than about 3300 nm, less than about 3200 nm, less than about 3100 nm, less than about 3 microns, less than about 2900 nm, less than about 2800 nm, less than about 2700 nm, less than about 2600 nm, less than about 2500 nm, less than about 2400 nm, less than about 2300 nm, less than about 2200 nm, less than about 2100 nm, less than about 2000 nm, less than about 1900 nm, less than less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than

about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100 nm, less than about 90 nm, less than about 80 nm, less than about 70 nm, less than about 60 nm, and less than about 50 nm.

26. The method of claim 23, wherein the depot releases the olanzapine at therapeutic levels for a period of time from about two to about six weeks.

27. The method of claim 23, wherein the depot releases the olanzapine at therapeutic levels for a period of time from about two to about twelve weeks.

28. The method of claim 23, wherein the depot releases the olanzapine at therapeutic levels for a period of time selected from the group consisting of one week to about two weeks, from about one week to about three weeks, from about one week to about four weeks, from about one week to about five weeks, from about one week to about six weeks, from about one week to about seven weeks, from about one week to about eight weeks, from about one week to about nine weeks, from about one week to about ten weeks, from about one week to about eleven weeks, from about one week to about twelve weeks, and combinations thereof.

29. The method of claim 23, wherein the AUC of the olanzapine, when assayed in the plasma of a mammalian subject following injectable administration, is greater than the AUC for a non-nanoparticulate olanzapine formulation, administered at the same dosage.

30. The method of claim 29, wherein the AUC is selected from the group consisting of at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate formulation of olanzapine, administered at the same dosage.

31. The method of claim 23, wherein the method is used to treat an indication selected from the group consisting of schizophrenia and related psychoses, bipolar mania, bipolar disorder, seizures, obsessive/compulsive disorders, generalized anxiety disorder, post traumatic distress syndrome, extreme shyness, diabetic nerve pain, smoking cessation, and depression.

FIGURE 1: Olanzapine crystals prior to particle size reduction

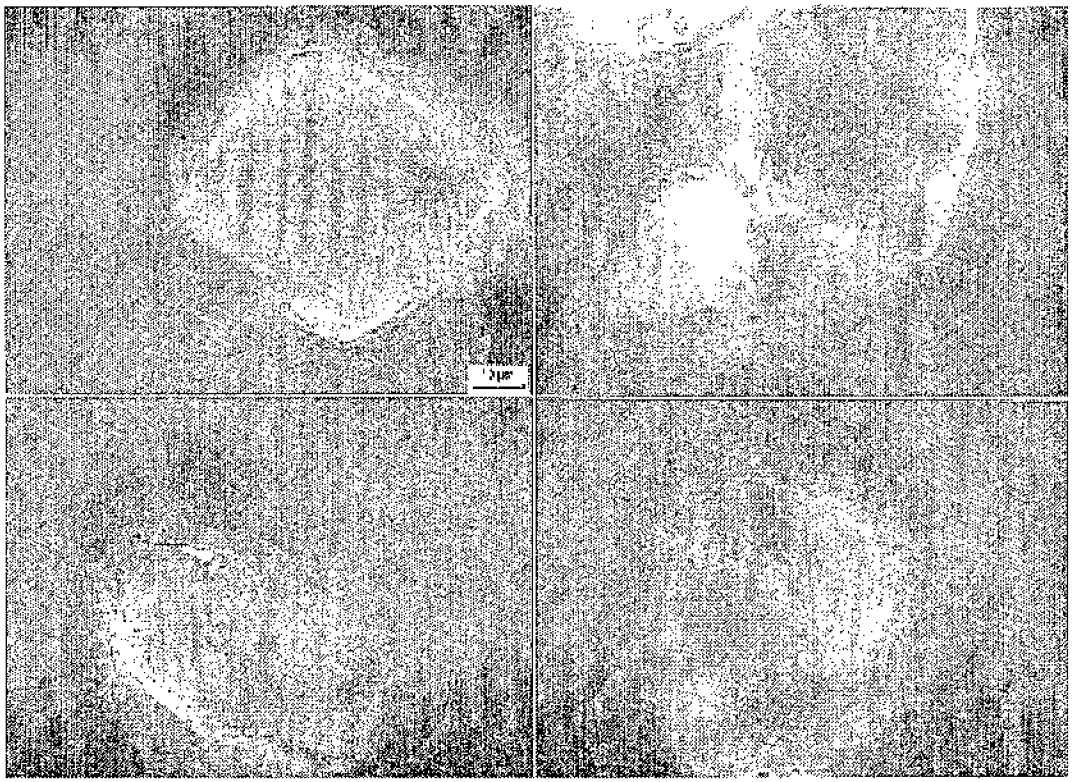


FIGURE 2: Olanzapine crystals following particle size reduction

FIGURE 3: Olanzapine crystals following particle size reduction

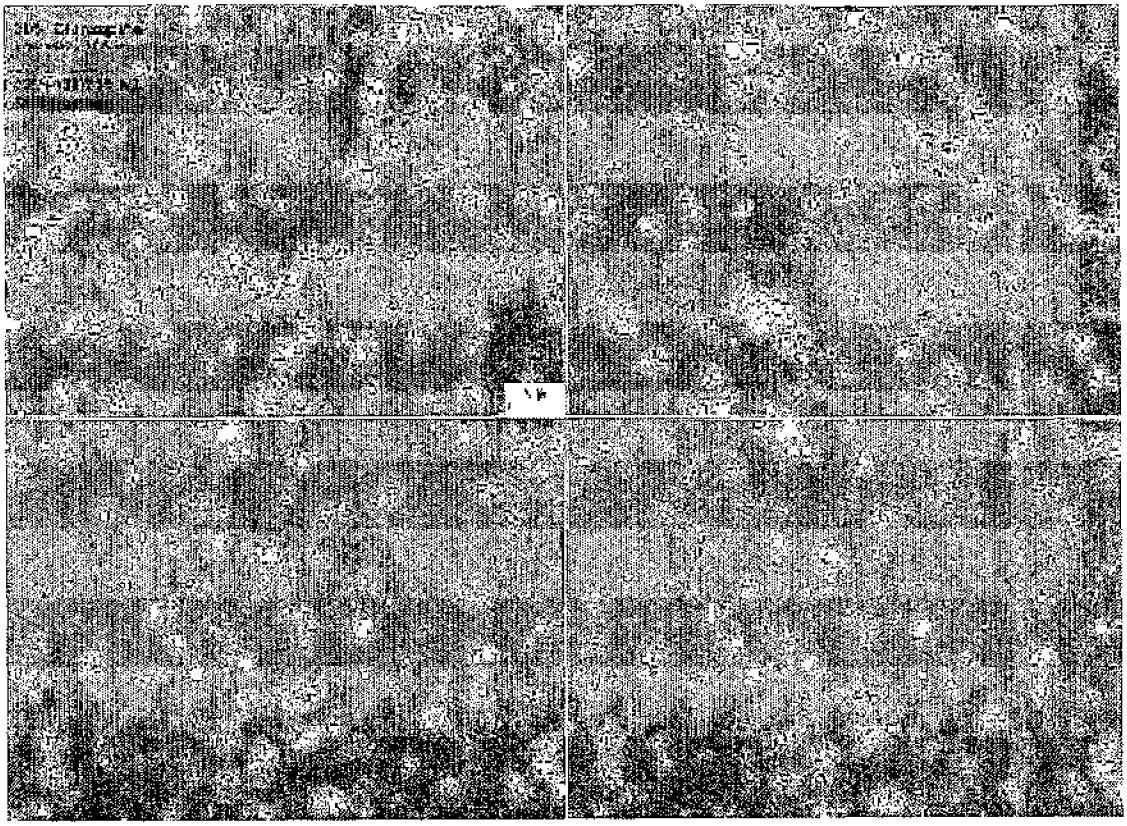


FIGURE 4

NanoOlanzapine Dog Study
Dosing (IM @ 10mg/kg ~100mg per animal)

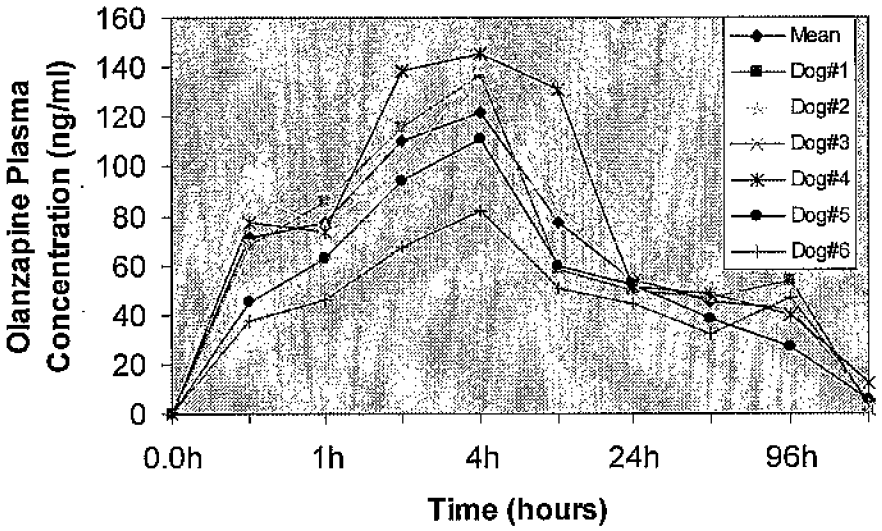
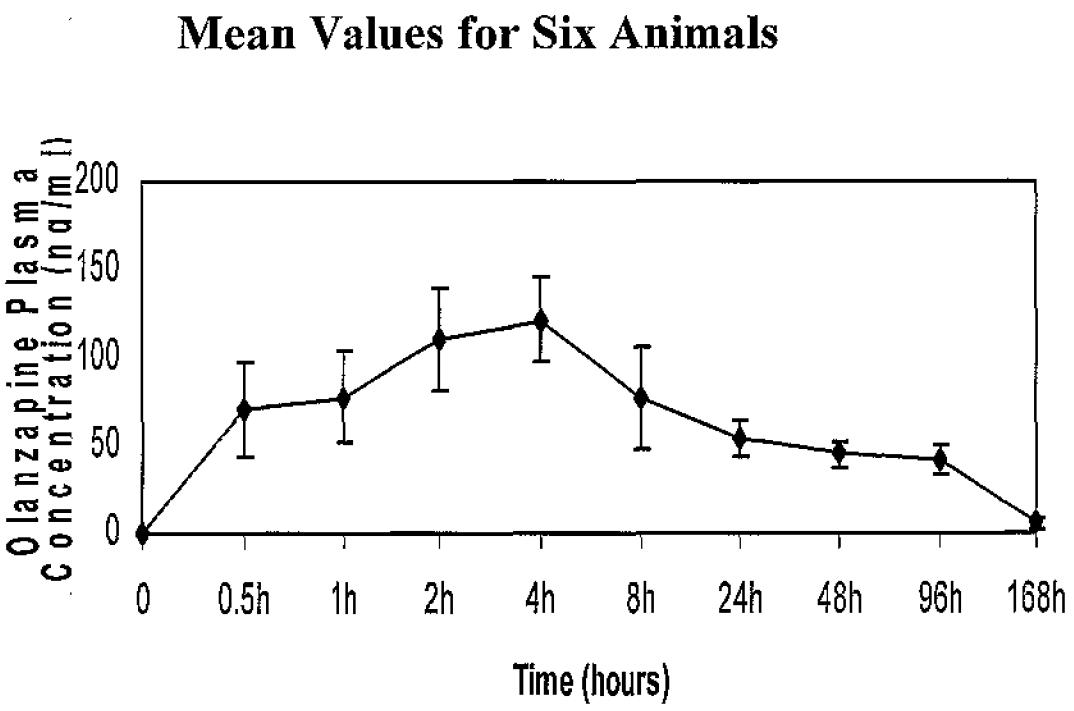


FIGURE 5

NanoOlanzapine Dog Study
Dosing (IM @ 10mg/kg ~100mg per animal)
Dose 10X the daily dose in man & well tolerated



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(54) Title: AEROSOL AND INJECTABLE FORMULATIONS OF NANOPARTICULATE BENZODIAZEPINE

(57) Abstract: Described are nanoparticulate formulations of a benzodiazepine, such as lorazepam, that does not require the presence of polyethylene glycol and propylene glycol as stabilizers, and methods of making and using such formulations. The formulations are particularly useful in aerosol and injectable dosage forms, and comprise nanoparticulate benzodiazepine, such as lorazepam, and at least one surface stabilizer. The formulations are useful in the treatment of status epilepticus, treatment of irritable bowel syndrome, sleep induction, acute psychosis, and as a pre-anesthesia medication.

WO 2006/088894 A2

AEROSOL AND INJECTABLE FORMULATIONS OF NANOPARTICULATE BENZODIAZEPINE

FIELD OF THE INVENTION

The present invention is directed to aerosol and injectable formulations of nanoparticulate benzodiazepine, and preferably, nanoparticulate lorazepam. The compositions of the invention are useful in treating status epilepticus, sleep induction, acute psychosis, irritable bowel syndrome, and for pre-anesthesia medication. Also encompassed by the invention are methods of making and using such compositions.

BACKGROUND OF THE INVENTION

I. Administration Routes for Drugs

The route of administration of a drug substance can be critical to its pharmacological effectiveness. Various routes of administration exist, and all have their own advantages and disadvantages. Oral drug delivery of tablets, capsules, liquids, and the like is the most convenient approach to drug delivery, but many drug compounds are not amenable to oral administration. For example, modern protein drugs which are unstable in the acidic gastric environment or which are rapidly degraded by proteolytic enzymes in the digestive tract are poor candidates for oral administration. Similarly, poorly water soluble compounds which do not dissolve rapidly enough to be orally absorbed are likely to be ineffective when given as oral dosage forms. Oral administration can also be undesirable because drugs which are administered orally are generally distributed to all tissues in the body, and not just to the intended site of pharmacological activity. Alternative types of systemic administration are subcutaneous or intravenous injection. This approach avoids the gastrointestinal tract and therefore can be an effective route for delivery of proteins and peptides. However, these routes of administration have a low rate of patient compliance, especially for drugs such as insulin which must be administered one or more times daily. Additional alternative methods of drug delivery have been developed including transdermal, rectal, vaginal, intranasal, and pulmonary delivery.

Nasal drug delivery relies on inhalation of an aerosol through the nose so that active drug substance can reach the nasal mucosa. Drugs intended for systemic activity can be absorbed into the bloodstream because the nasal mucosa is highly vascularized. Alternatively, if the drug is intended to act topically, it is delivered directly to the site of activity and does not have to distribute throughout the body; hence, relatively low doses may be used. Examples of such drugs are decongestants, antihistamines, and anti-inflammatory steroids for seasonal allergic rhinitis.

Pulmonary drug delivery relies on inhalation of an aerosol through the mouth and throat so that the drug substance can reach the lung. For systemically active drugs, it is desirable for the drug particles to reach the alveolar region of the lung, whereas drugs which act on the smooth muscle of the conducting airways should preferentially deposit in the bronchiole region. Such drugs can include beta-agonists, anti cholinergics, and corticosteroids.

A. Droplet/Particle Size Determines Deposition Site

In developing a therapeutic aerosol, the aerodynamic size distribution of the inhaled particles is the single most important variable in defining the site of droplet or particle deposition in the patient; in short, it will determine whether drug targeting succeeds or fails. *See* P. Byron, "Aerosol Formulation, Generation, and Delivery Using Nonmetered Systems," *Respiratory Drug Delivery*, 144-151, 144 (CRC Press, 1989). Thus, a prerequisite in developing a therapeutic aerosol is a preferential particle size. The deposition of inhaled aerosols involves different mechanisms for different size particles. D. Swift (1980); Parodi et al., "Airborne Particles and Their Pulmonary Deposition," in *Scientific Foundations of Respiratory Medicine*, Scaddings et al. (eds.), pp. 545-557 (W. B. Saunders, Philadelphia, 1981); J. Heyder, "Mechanism of Aerosol Particle Deposition," *Chest*, 80:820-823 (1981).

Generally, inhaled particles are subject to deposition by one of two mechanisms: impaction, which usually predominates for larger particles, and sedimentation, which is prevalent for smaller particles. Impaction occurs when the momentum of an inhaled particle is large enough that the particle does not follow the air stream and encounters a physiological surface. In contrast, sedimentation occurs primarily in the deep lung when very small particles which have traveled with the inhaled air stream encounter physiological surfaces as

a result of random diffusion within the air stream. For intranasally administered drug compounds which are inhaled through the nose, it is desirable for the drug to impact directly on the nasal mucosa; thus, large (ca. 5 to 100 μm) particles or droplets are generally preferred for targeting of nasal delivery.

Pulmonary drug delivery is accomplished by inhalation of an aerosol through the mouth and throat. Particles having aerodynamic diameters of greater than about 5 microns generally do not reach the lung; instead, they tend to impact the back of the throat and are swallowed and possibly orally absorbed. Particles having diameters of about 2 to about 5 microns are small enough to reach the upper- to mid-pulmonary region (conducting airways), but are too large to reach the alveoli. Even smaller particles, *i.e.*, about 0.5 to about 2 microns, are capable of reaching the alveolar region. Particles having diameters smaller than about 0.5 microns can also be deposited in the alveolar region by sedimentation, although very small particles may be exhaled.

B. Devices Used For Nasal And Pulmonary Drug Delivery

Drugs intended for intranasal delivery (systemic and local) can be administered as aqueous solutions or suspensions, as solutions or suspensions in halogenated hydrocarbon propellants (pressurized metered-dose inhalers), or as dry powders. Metered-dose spray pumps for aqueous formulations, pMDIs, and DPIs for nasal delivery are available from, for example, Valois of America or Pfeiffer of America.

Drugs intended for pulmonary delivery can also be administered as aqueous formulations, as suspensions or solutions in halogenated hydrocarbon propellants, or as dry powders. Aqueous formulations must be aerosolized by liquid nebulizers employing either hydraulic or ultrasonic atomization, propellant-based systems require suitable pressurized metered-dose inhalers (pMDIs), and dry powders require dry powder inhaler devices (DPIs) which are capable of dispersing the drug substance effectively. For aqueous and other non-pressurized liquid systems, a variety of nebulizers (including small volume nebulizers) are available to aerosolize the formulations. Compressor-driven nebulizers incorporate jet technology and use compressed air to generate the liquid aerosol. Such devices are commercially available from, for example, Healthdyne Technologies, Inc.; Invacare, Inc.; Mountain Medical Equipment, Inc.; Pari Respiratory, Inc.; Mada Medical, Inc.; Puritan-

Bennet; Schuco, Inc., DeVilbiss Health Care, Inc.; and Hospitak, Inc. Ultrasonic nebulizers rely on mechanical energy in the form of vibration of a piezoelectric crystal to generate inhalable liquid droplets and are commercially available from, for example, Omron Heathcare, Inc. and DeVilbiss Health Care, Inc.

A propellant driven inhaler (pMDI) releases a metered dose of medicine upon each actuation. The medicine is formulated as a suspension or solution of a drug substance in a suitable propellant such as a halogenated hydrocarbon. pMDIs are described in, for example, Newman, S. P., Aerosols and the Lung, Clarke et al., eds., pp. 197-224 (Butterworths, London, England, 1984).

Dry powder inhalers (DPIs), which involve deaggregation and aerosolization of dry powders, normally rely upon a burst of inspired air that is drawn through the unit to deliver a drug dosage. Such devices are described in, for example, U.S. Pat. No. 4,807,814 to Douche et al., which is directed to a pneumatic powder ejector having a suction stage and an injection stage; SU 628930 (Abstract), describing a hand-held powder disperser having an axial air flow tube; Fox et al., *Powder and Bulk Engineering*, pages 33-36 (March 1988), describing a venturi eductor having an axial air inlet tube upstream of a venturi restriction; EP 347 779, describing a hand-held powder disperser having a collapsible expansion chamber, and U.S. Pat. No. 5,785,049 to Smith et al., directed to dry powder delivery devices for drugs.

C. Problems With Conventional Aerosol And Injectable Compositions And Methods

Conventional techniques are extremely inefficient in delivering agents to the lung for a variety of reasons. Prior to the present invention, attempts to develop inhalable aqueous suspensions of poorly water soluble drugs have been largely unsuccessful. For example, it has been reported that ultrasonic nebulization of a suspension containing fluorescein and latex drug spheres, representing insoluble drug particles, resulted in only 1% aerosolization of the particles, while air-jet nebulization resulted in only a fraction of particles being aerosolized (Susan L. Tiano, "Functionality Testing Used to Rationally Assess Performance of a Model Respiratory Solution or Suspension in a Nebulizer," Dissertation Abstracts International, 56/12-B, pp. 6578 (1995)). Another problem encountered with nebulization of liquid formulations prior to the present invention was the long (4–20 min) period of time

required for administration of a therapeutic dose. Long administration times are required because conventional liquid formulations for nebulization are very dilute solutions or suspensions of micronized drug substance. Prolonged administration times are undesirable because they lessen patient compliance and make it difficult to control the dose administered. Lastly, aerosol formulations of micronized drug are not feasible for deep lung delivery of insoluble compounds because the droplets needed to reach the alveolar region (0.5 to 2 microns) are too small to accommodate micronized drug crystals, which are typically 2–3 microns or more in diameter.

Conventional pMDIs are also inefficient in delivering drug substance to the lung. In most cases, pMDIs consist of suspensions of micronized drug substance in halogenated hydrocarbons such as chlorofluorocarbons (CFCs) or hydrofluoroalkanes (HFAs). Actuation of the pMDI results in delivery of a metered dose of drug and propellant, both of which exit the device at high velocities because of the propellant pressures. The high velocity and momentum of the drug particles results in a high degree of oropharyngeal impaction as well as loss to the device used to deliver the agent. These losses lead to variability in therapeutic agent levels and poor therapeutic control. In addition, oropharyngeal deposition of drugs intended for topical administration to the conducting airways (such as corticosteroids) can lead to systemic absorption with resultant undesirable side effects. Additionally, conventional micronization (air-jet milling) of pure drug substance can reduce the drug particle size to no less than about 2-3 microns. Thus, the micronized material typically used in pMDIs is inherently unsuitable for delivery to the alveolar region and is not expected to deposit below the central bronchiole region of the lung.

Prior to the present invention, delivery of dry powders to the lung typically used micronized drug substance. In the dry powder form, micronized substances tend to have substantial interparticle electrostatic attractive forces which prevent the powders from flowing smoothly and generally make them difficult to disperse. Thus, two key challenges to pulmonary delivery of dry powders are the ability of the device to accurately meter the intended dose and the ability of the device to fully disperse the micronized particles. For many devices and formulations, the extent of dispersion is dependent upon the patient's inspiration rate, which itself may be variable and can lead to a variability in the delivered dose.

Delivery of drugs to the nasal mucosa can also be accomplished with aqueous, propellant-based, or dry powder formulations. However, absorption of poorly soluble drugs can be problematic because of mucociliary clearance which transports deposited particles from the nasal mucosa to the throat where they are swallowed. Complete clearance generally occurs within about 15–20 minutes. Thus, poorly soluble drugs which do not dissolve within this time frame are unavailable for either local or systemic activity.

As described below in the Background of Nanoparticulate Active Agent Compositions, several published U.S. patents and patent applications describe aerosols of nanoparticulate drugs. However, none of these documents describe aerosols of a nanoparticulate benzodiazepine, such as lorazepam.

II. Background Regarding Lorazepam

Lorazepam is a benzodiazepine. It is also known as 7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one. Its molecular formula is $C_{15}H_{10}Cl_2N_2O_2$, and it has a molecular weight of 321.16. Lorazepam has only slight solubility in water, *i.e.*, 0.08 mg/mL. United States Patent No. 6,699,849 to Loftsson et al., which is specifically incorporated by reference, refers to lorazepam and benzodiazepine. Lorazepam is a controlled substance. *Merck Index*, Thirteenth Ed., p. 999 (Merck & Co., Whitehouse Station, N.J. 2001). As pharmaceutically acceptable salts including organic salts or esters of lorazepam can be employed as a substitute for lorazepam, the references below to lorazepam are also intended to include lorazepam salts and esters and mixtures thereof.

Because of lorazepam's low water solubility, it is generally formulated for oral administration. However, oral administration of lorazepam has disadvantages. For example, lorazepam is susceptible to enzymatic degradation by glucuronyl transferase enzyme in the intestine or in the intestinal mucosa, as disclosed in United States Patent No. 6,692,766 to Rubinstein et al., which is incorporated by reference. Sterile lorazepam typically includes a preservative such as benzyl alcohol and requires refrigeration. Lorazepam delivered orally may have a slow absorption and onset of action.

Injectable formulations of lorazepam are preferable over oral administration doses because intravenous (IV) or intramuscular (IM) administration of a drug results in a significantly shorter response time as compared to oral administration. Moreover, injectable

formulations of pain medication are also preferable for post-operative health care, where oral administration may not be feasible. Injectable formulations of lorazepam are particularly preferred, as lorazepam is not addictive, in contrast to other injectable formulations of drugs, such as morphine and ketorolac (Toradol®).

However, injectable lorazepam formulations are difficult to formulate due to the low water-solubility of lorazepam. Moreover, current injectable formulations of lorazepam are undesirable because the formulations must include polyethylene glycol and propylene glycol as solubilizers, which can result in pain at the injection site.

III. Background Regarding Nanoparticulate Active Agent Compositions

Nanoparticulate compositions, first described in U.S. Pat. No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto or associated with the surface thereof a non-crosslinked surface stabilizer. The '684 patent also describes methods of making such nanoparticulate compositions but does not describe compositions comprising a benzodiazepine, such as lorazepam, in nanoparticulate form. Methods of making nanoparticulate compositions are described, for example, in U.S. Pat. Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Nanoparticulate compositions are also described, for example, in U.S. Pat. No. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" U.S. Pat. No. 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" U.S. Pat. No. 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" U.S. Pat. No. 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During

Sterilization;" U.S. Pat. No. 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" U.S. Pat. No. 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. Nos. 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" U.S. Pat. No. 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,518,738 for "Nanoparticulate NSAID Formulations;" U.S. Pat. No. 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No. 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,552,160 for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" U.S. Pat. No. 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" U.S. Pat. No. 5,580,579 for "Site-specific Adhesion Within the

GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" U.S. Pat. No. 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" U.S. Pat. No. 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" U.S. Pat. No. 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" U.S. Pat. No. 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" U.S. Pat. No. 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" U.S. Pat. No. 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" U.S. Pat. No. 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" U.S. Pat. No. 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" U.S. Pat. No. 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" U.S. Pat. No. 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,428,814 for "Bioadhesive

Nanoparticulate Compositions Having Cationic Surface Stabilizers;" U.S. Pat. No. 6,431,478 for "Small Scale Mill;" U.S. Pat. No. 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract;" U.S. Pat. No. 6,582,285 for "Apparatus for Sanitary Wet Milling;" and U.S. Pat. No. 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,656,504 for "Nanoparticulate Compositions Comprising Amorphous Cyclosporine;" 6,742,734 for "System and Method for Milling Materials;" 6,745,962 for "Small Scale Mill and Method Thereof;" 6,811,767 for "Liquid droplet aerosols of nanoparticulate drugs;" and 6,908,626 for "Compositions having a combination of immediate release and controlled release characteristics;" all of which are specifically incorporated by reference. In addition, U.S. patent application Ser. No. 20020012675 A1, published on Jan. 31, 2002, for "Controlled Release Nanoparticulate Compositions" and WO 02/098565 for "System and Method for Milling Materials," describe nanoparticulate compositions, and are specifically incorporated by reference.

In particular, documents referring to aerosols of nanoparticulate drugs include U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions" and U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions," and documents referring to injectable compositions of nanoparticulate drugs include U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen," and U.S. Pat. Nos. 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles." None of these documents describe injectable or aerosol compositions of a nanoparticulate benzodiazepine, such as lorazepam.

Amorphous small particle compositions are described, for example, in U.S. Pat. No. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" U.S. Pat. No. 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" U.S. Pat. No. 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" U.S. Pat. No. 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and U.S. Pat. No. 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter" all of which are specifically incorporated herein by reference.

There remains a need in the art for improved dosage forms of benzodiazepines, such

as lorazepam. The present invention satisfies this need.

SUMMARY OF THE INVENTION

The present invention is directed to the surprising and unexpected discovery of new aerosol and injectable dosage forms of a nanoparticulate benzodiazepine, such as lorazepam. The formulations comprises a nanoparticulate benzodiazepine, such as nanoparticulate lorazepam, having an effective average particle size of less than about 2000 nm. The nanoparticulate benzodiazepine, such as lorazepam, preferably has at least one surface stabilizer either adsorbed onto or associated with the surface of the benzodizepine. In one embodiment of the invention, the surface stabilizer is a povidone polymer. Because lorazepam is practically insoluble in water, significant bioavailability can be problematic.

In one embodiment there is provided an aerosol that delivers an optimal dosage of a benzodiazepine, such as lorazepam. The aerosols of the invention do not require a preservative such as benzyl alcohol, which affects lorazepam stability.

In another embodiment, a safe and effective injectable formulation of a benzodiazepine, such as lorazepam, is provided. The injectable formulation eliminates the need for propylene glycol and polyethylene glycol, such as polyoxyl 60 hydrogenated castor oil (HCO-60), as solubilizers for injectable lorazepam compositions, and solves the problem of the insolubility of lorazepam in water. This is beneficial, as in convention non-nanoparticulate injectable benzodiazepine formulations comprising polyoxyl 60 hydrogenated castor oil as a solubilizer, the presence of this solubilizer can lead to anaphylactic shock (i.e., severe allergic reaction) and death. The injectable dosage forms of the invention surprisingly deliver the required therapeutic amount of the drug *in vivo*, and render the drug bioavailable in a rapid and constant manner, which is required for effective human therapy. Moreover, the invention provides for compositions comprising high concentrations of a benzodiazepine, such as lorazepam, in low injection volumes, with rapid drug dissolution upon administration.

The present invention is also directed to aqueous, propellant-based, and dry powder aerosols of a nanoparticulate benzodiazepine, such as lorazepam, for pulmonary and nasal delivery, in which essentially every inhaled particle contains at least one nanoparticulate benzodiazepine, such as lorazepam, nanoparticle. The nanoparticulate benzodiazepine, such

as lorazepam, is highly water-insoluble. Preferably, the nanoparticulate benzodiazepine, such as lorazepam, has an effective average particle size of less than about 2 microns. Nanoparticulate aerosol formulations are described in U.S. Patent No. 6,811,767 to Bosch et al., specifically incorporated by reference. Non-aerosol preparations of submicron sized water-insoluble drugs are described in U.S. Pat. No. 5,145,684 to Liversidge et al., specifically incorporated herein by reference.

The invention also includes the following embodiments directed to aerosol formulations of a benzodiazepine, such as lorazepam. One embodiment of the invention is directed to aqueous aerosols of nanoparticulate dispersion of a benzodiazepine, such as lorazepam. Another embodiment of the invention is directed to dry powder aerosol formulations comprising a benzodiazepine, such as lorazepam, for pulmonary and/or nasal administration. Yet another embodiment of the invention is directed to a process and composition for propellant-based systems comprising a nanoparticulate benzodiazepine, such as lorazepam.

The nanoparticulate benzodiazepine, such as lorazepam, formulations of the invention may optionally include one or more pharmaceutically acceptable excipients, such as non-toxic physiologically acceptable liquid carriers, pH adjusting agents, or preservatives.

In another aspect of the invention there is provided a method of preparing the nanoparticulate benzodiazepine, such as lorazepam, injectable and aerosol formulations of the invention. The nanoparticulate dispersions used in making aerosol and injectable nanoparticulate benzodiazepine compositions can be made by wet milling, homogenization, precipitation, or supercritical fluid methods known in the art. An exemplary method comprises: (1) dispersing a benzodiazepine, such as lorazepam, in a liquid dispersion media; and (2) mechanically reducing the particle size of the benzodiazepine to the desired effective average particle size, e.g., less than about 2000 nm. At least one surface stabilizer can be added to the dispersion media either before, during, or after particle size reduction of the benzodiazepine. In one embodiment for the injectable composition, the surface stabilizer is a povidone polymer with a molecular weight of less than about 40,000 daltons. Preferably, the liquid dispersion media is maintained at a physiologic pH, for example, within the range of from about 3 to about 8, during the size reduction process. The nanoparticulate benzodiazepine dispersion can be used as an injectable formulation.

Dry powders comprising a nanoparticulate benzodiazepine, such as lorazepam, can be made by spray drying or freeze-drying aqueous dispersions of the nanoparticles. The dispersions used in these systems may or may not comprise dissolved diluent material prior to drying. Additionally, both pressurized and non-pressurized milling operations can be employed to make nanoparticulate benzodiazepine, such as lorazepam, compositions in non-aqueous systems.

In yet another aspect of the invention, there is provided a method of treating a subject in need with the injectable and/or aerosol nanoparticulate benzodiazepine, such as lorazepam, compositions of the invention. In an exemplary method, therapeutically effective amount of an injectable or aerosol nanoparticulate benzodiazepine composition of the invention is administered to a subject in need. The methods of the invention encompass treating a subject for status epilepticus, treatment of irritable bowel syndrome, sleep induction, acute psychosis, and pre-anesthesia medication. Diagnostic methods, comprising imaging of the administered dosage form, are also encompassed by the invention.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the invention encompass a nanoparticulate benzodiazepine, such as lorazepam, having an effective average particle size of less than about 2000 nm. For the injectable compositions, the nanoparticulate benzodiazepine, such as lorazepam, preferably has an effective average particle size of less than about 600 nm. For the aerosol compositions, the nanoparticulate benzodiazepine, such as lorazepam, has an effective average particle size of less than about 2000 nm. In one embodiment of the invention, the nanoparticulate benzodiazepine particles have at least one surface stabilizer either adsorbed onto or associated with the surface of the drug particles. The compositions are formulated into either an aerosol dosage form or an injectable dosage form. The aerosol dosage form can be either an aqueous aerosol or a dry powder aerosol.

Using the nanoparticulate benzodiazepine aerosol compositions of the invention, an essentially water-insoluble benzodiazepine, such as lorazepam, can be delivered to the deep lung. This is either not possible or extremely difficult using aerosol formulations of a micronized water-insoluble benzodiazepine. Deep lung delivery is necessary for benzodiazepine, such as lorazepam, compositions that are intended for systemic administration because deep lung delivery allows rapid absorption of the drug into the bloodstream by the alveoli, thus enabling rapid onset of action.

The present invention increases the number of benzodiazepine, such as lorazepam, particles per unit dose and results in distribution of a nanoparticulate benzodiazepine, such as lorazepam, over a larger physiological surface area as compared to the same quantity of a delivered micronized benzodiazepine, such as lorazepam. For systemic delivery by the pulmonary route, this approach takes maximum advantage of the extensive surface area presented in the alveolar region — thus producing more favorable benzodiazepine, such as lorazepam, delivery profiles, such as a more complete absorption and rapid onset of action.

Moreover, in contrast to micronized aqueous aerosol dispersions, aqueous dispersions of a water-insoluble nanoparticulate benzodiazepine, such as lorazepam, can be nebulized ultrasonically. Micronized drug is too large to be delivered efficiently by an ultrasonic nebulizer.

Droplet size determines *in vivo* deposition of a benzodiazepine, *i.e.*, very small particles, about <2 microns, are delivered to the alveoli; larger particles, about 2 to about 10 microns, are delivered to the bronchiole region; and for nasal delivery, particles of about 5 to about 100 microns are preferred. Thus, the ability to obtain very small benzodiazepine, such as lorazepam, particle sizes which can "fit" in a range of droplet sizes allows more effective and more efficient (*i.e.*, benzodiazepine uniformity) targeting to the desired delivery region. This is not possible using micronized benzodiazepine, as the particle size of benzodiazepine is too large to target areas such as the alveolar region of the lung. Moreover, even when micronized benzodiazepine is incorporated into larger droplet sizes, the resultant aerosol formulation is heterogeneous (*i.e.*, not all droplets contain benzodiazepine), and does not result in the rapid and efficient benzodiazepine delivery enabled by the nanoparticulate aerosol benzodiazepine, such as lorazepam, formulations of the invention.

The present invention also enables the aqueous aerosol delivery of high doses of benzodiazepine, such as lorazepam, in an extremely short time period, *i.e.*, 1–2 seconds (1 puff). This is in contrast to the conventional 4–20 min. administration period observed with pulmonary aerosol formulations of micronized drug. Furthermore, the dry aerosol nanoparticulate benzodiazepine, such as lorazepam, powders of the present invention are spherical and can be made smaller than micronized material, thereby producing aerosol compositions having better flow and dispersion properties, and capable of being delivered to the deep lung.

Finally, the aerosol benzodiazepine, such as lorazepam, compositions of the present invention enable rapid nasal delivery. Nasal delivery of such aerosol compositions will be absorbed more rapidly and completely than micronized aerosol compositions before being cleared by the mucociliary mechanism.

The dosage forms of the present invention may be provided in formulations which exhibit a variety of release profiles upon administration to a patient including, for example, an IR formulation, a CR formulation that allows once per day administration, and a combination of both IR and CR formulations. Because CR forms of the present invention can require only one dose per day (or one dose per suitable time period, such as weekly or monthly), such dosage forms provide the benefits of enhanced patient convenience and compliance. The mechanism of controlled-release employed in the CR form may be accomplished in a variety of ways including, but not limited to, the use of erodable formulations, diffusion-controlled formulations, and osmotically-controlled formulations.

Advantages of the nanoparticulate benzodiazepine formulations of the invention over conventional forms of a benzodiazepine, such as lorazepam (e.g., non-nanoparticulate or solubilized dosage forms) include, but are not limited to: (1) increased water solubility; (2) increased bioavailability; (3) smaller dosage form size due to enhanced bioavailability; (4) lower therapeutic dosages due to enhanced bioavailability; (5) reduced risk of unwanted side effects due to lower dosing; and (6) enhanced patient convenience and compliance. A further advantage of the injectable nanoparticulate benzodiazepine formulation of the present invention over conventional forms of injectable benzodiazepines, such as lorazepam, is the elimination of the need to use polyoxyl 60 hydrogenated castor oil (HCO-60) as a solubilizer. A further advantage of the aerosol nanoparticulate benzodiazepines, such as lorazepam, is a

reduced risk of unwanted side effects.

The present invention also includes nanoparticulate benzodiazepine, such as lorazepam, compositions, together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous) or aerosol delivery. The aerosols can be used for any suitable delivery, such as pulmonary or nasal delivery.

The present invention is described herein using several definitions, as set forth below and throughout the application.

The term "effective average particle size of less than about 2000 nm", as used herein means that at least 50% of the benzodiazepine, such as lorazepam, particles have a size, by weight, of less than about 2000 nm, when measured by, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, disk centrifugation, and other techniques known to those of skill in the art.

As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

As used herein with reference to a stable benzodiazepine, such as lorazepam, particle connotes, but is not limited to one or more of the following parameters: (1) benzodiazepine particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise significantly increase in particle size over time; (2) that the physical structure of the benzodiazepine particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) that the benzodiazepine particles are chemically stable; and/or (4) where the benzodiazepine has not been subject to a heating step at or above the melting point of the benzodiazepine in the preparation of the nanoparticles of the present invention.

The term "conventional" or "non-nanoparticulate" active agent or benzodiazepine, such as lorazepam, shall mean an active agent, such as lorazepam, which is solubilized or which has an effective average particle size of greater than about 2000 nm. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2000

nm.

The phrase "poorly water soluble drugs" as used herein refers to those drugs that have a solubility in water of less than about 30 mg/ml, preferably less than about 20 mg/ml, preferably less than about 10 mg/ml, or preferably less than about 1 mg/ml.

As used herein, the phrase "therapeutically effective amount" shall mean that drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that a therapeutically effective amount of a drug that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

The term "particulate" as used herein refers to a state of matter which is characterized by the presence of discrete particles, pellets, beads or granules irrespective of their size, shape or morphology. The term "multiparticulate" as used herein means a plurality of discrete, or aggregated, particles, pellets, beads, granules or mixture thereof irrespective of their size, shape or morphology.

The term "modified release" as used herein in relation to the composition according to the invention means release which is not immediate release and is taken to encompass controlled release, sustained release, and delayed release.

The term "time delay" as used herein refers to the duration of time between administration of the composition and the release of benzodiazepine, such as lorazepam, from a particular component.

The term "lag time" as used herein refers to the time between delivery of active ingredient from one component and the subsequent delivery of benzodiazepine, such as lorazepam, from another component.

I. Preferred Characteristics of the Nanoparticulate Benzodiazepine Compositions

There are a number of enhanced pharmacological characteristics of the nanoparticulate benzodiazepine, such as lorazepam, compositions of the present invention.

A. Increased Bioavailability

The benzodiazepine, such as lorazepam, formulations of the present invention exhibit increased bioavailability at the same dose of the same benzodiazepine, such as lorazepam, and require smaller doses as compared to prior conventional benzodiazepine, such as lorazepam, formulations.

Moreover, a nanoparticulate benzodiazepine, such as lorazepam, dosage form requires less drug to obtain the same pharmacological effect observed with a conventional microcrystalline benzodiazepine, such as lorazepam, dosage form. Therefore, the nanoparticulate benzodiazepine, such as lorazepam, dosage form has an increased bioavailability as compared to the conventional microcrystalline benzodiazepine, such as lorazepam, dosage form.

B. The Pharmacokinetic Profiles of the Benzodiazepine Compositions of the Invention are not Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

The compositions of the present invention encompass a benzodiazepine, such as lorazepam, wherein the pharmacokinetic profile of the benzodiazepine is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is little or no appreciable difference in the quantity of drug absorbed or the rate of drug absorption when the nanoparticulate benzodiazepine, such as lorazepam, compositions are administered in the fed versus the fasted state.

Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food. This is significant, as with poor subject compliance with a benzodiazepine, such as lorazepam,, an increase in the medical condition for which the drug is being prescribed may be observed.

The invention also preferably provides a benzodiazepine, such as lorazepam, compositions having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the benzodiazepine, such as lorazepam, compositions preferably includes, but is not limited to: (1) a C_{max} for benzodiazepine, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the C_{max} for a non-nanoparticulate benzodiazepine formulation administered at

the same dosage; and/or (2) an AUC for benzodiazepine, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate benzodiazepine formulation, administered at the same dosage; and/or (3) a Tmax for benzodiazepine, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the Tmax for a non-nanoparticulate benzodiazepine formulation, administered at the same dosage. The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of the benzodiazepine.

In one embodiment, a preferred benzodiazepine, such as lorazepam, composition exhibits in comparative pharmacokinetic testing with a non-nanoparticulate benzodiazepine, such as lorazepam, formulation, administered at the same dosage, a T_{max} not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the T_{max} exhibited by the non-nanoparticulate benzodiazepine, such as lorazepam, formulation.

In another embodiment, the benzodiazepine, such as lorazepam, composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate benzodiazepine, such as lorazepam, formulation, administered at the same dosage, a C_{max} which is at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{max} exhibited by the non-nanoparticulate benzodiazepine, such as lorazepam, formulation.

In yet another embodiment, the benzodiazepine, such as lorazepam, composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate benzodiazepine, such as lorazepam, formulation, administered at the same dosage, an AUC which is at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about

350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate benzodiazepine, such as lorazepam, formulation.

C. Bioequivalency of the Benzodiazepine Compositions of the Invention When Administered in the Fed Versus the Fasted State

The invention also encompasses a composition comprising a nanoparticulate benzodiazepine, such as lorazepam, in which administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

The difference in absorption of the compositions comprising the nanoparticulate benzodiazepine, such as lorazepam, when administered in the fed versus the fasted state, is preferably less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

In one embodiment of the invention, the invention encompasses nanoparticulate benzodiazepine, such as lorazepam, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular as defined by C_{max} and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMEA). Under U.S. FDA guidelines, two products or methods are bioequivalent if the 90% Confidence Intervals (CI) for AUC and C_{max} are between 0.80 to 1.25 (T_{max} measurements are not relevant to bioequivalence for regulatory purposes). To show bioequivalency between two compounds or administration conditions pursuant to Europe's EMEA guidelines, the 90% CI for AUC must be between 0.80 to 1.25 and the 90% CI for C_{max} must between 0.70 to 1.43.

D. Dissolution Profiles of the Benzodiazepine Compositions of the Invention

The benzodiazepine, such as lorazepam, compositions of the present invention have unexpectedly dramatic dissolution profiles. Rapid dissolution of an administered active agent is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. To improve the dissolution profile and bioavailability of benzodiazepine, such as lorazepam,, it is useful to increase the drug's dissolution so that it could attain a level close to 100%.

The benzodiazepine, such as lorazepam, compositions of the present invention preferably have a dissolution profile in which within about 5 minutes at least about 20% of the composition is dissolved. In other embodiments of the invention, at least about 30% or about 40% of the benzodiazepine, such as lorazepam, composition is dissolved within about 5 minutes. In yet other embodiments of the invention, preferably at least about 40%, about 50%, about 60%, about 70%, or about 80% of the benzodiazepine, such as lorazepam, composition is dissolved within about 10 minutes. Finally, in another embodiment of the invention, preferably at least about 70%, about 80%, about 90%, or about 100% of the benzodiazepine, such as lorazepam, composition is dissolved within about 20 minutes.

Dissolution is preferably measured in a medium which is discriminating. Such a dissolution media will produce two very different dissolution curves for two products having very different dissolution profiles in gastric juices, *i.e.*, the dissolution medium is predictive of *in vivo* dissolution of a composition. An exemplary dissolution medium is an aqueous medium containing the surfactant sodium lauryl sulfate at 0.025 M. Determination of the amount dissolved can be carried out by spectrophotometry. The rotating blade method (European Pharmacopoeia) can be used to measure dissolution.

E. Redispersibility Profiles of the Benzodiazepine Compositions of the Invention

An additional feature of the benzodiazepine, such as lorazepam, compositions of the present invention is that the compositions redisperse such that the effective average particle size of the redispersed benzodiazepine, such as lorazepam, particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate benzodiazepine, such as lorazepam, compositions of the invention did not redisperse to a nanoparticulate

particle size, then the dosage form may lose the benefits afforded by formulating the benzodiazepine, such as lorazepam, into a nanoparticulate particle size. A nanoparticulate size suitable for the present invention is an effective average particle size of less than about 2000 nm. In another embodiment, a nanoparticulate size suitable for the present invention is an effective average particle size of less than about 600 nm

Indeed, the nanoparticulate active agent compositions of the present invention benefit from the small particle size of the active agent; if the active agent does not redisperse into a small particle size upon administration, then "clumps" or agglomerated active agent particles are formed, owing to the extremely high surface free energy of the nanoparticulate system and the thermodynamic driving force to achieve an overall reduction in free energy. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall well below that observed with the liquid dispersion form of the nanoparticulate active agent.

Moreover, the nanoparticulate benzodiazepine, such as lorazepam, compositions of the invention exhibit dramatic redispersion of the nanoparticulate benzodiazepine, such as lorazepam, particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersion in a biorelevant aqueous media such that the effective average particle size of the redispersed benzodiazepine, such as lorazepam, particles is less than about 2 microns. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. *See e.g.*, Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res., 14* (4): 497-502 (1997).

It is believed that the pH and ionic strength of the test solution is more critical than

the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, *etc.*

Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 M HCl or less, about 0.01 M HCl or less, about 0.001 M HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts + sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

In other embodiments of the invention, the redispersed benzodiazepine, such as lorazepam, particles of the invention (redispersed in an aqueous, biorelevant, or any other suitable media) have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less

than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods. Such methods suitable for measuring effective average particle size are known to a person of ordinary skill in the art.

Redispersibility can be tested using any suitable means known in the art. *See e.g.,* the example sections of U.S. Patent No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate."

F. Benzodiazepine Compositions Used in Conjunction with Other Active Agents

The benzodiazepine, such as lorazepam, compositions of the invention can additionally comprise one or more compounds useful in the condition to be treated. Examples of such other active agents include, but are not limited to, antidepressants, steroids, antiemetics, antinauseants, spasmolytics, antipsychotics, opioids, carbidopa/levodopa or dopamine agonists, anesthetics, and narcotics.

Examples of antidepressants include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (tricyclics). SSRIs include drugs such as escitalopram (brand name: Lexapro) citalopram (brand name: Celexa), fluoxetine (brand name: Prozac), paroxetine (brand name: Paxil) and sertraline (brand name: Zoloft). Tricyclics include amitriptyline (brand name: Elavil), desipramine (brand name: Norpramin), imipramine (brand name: Tofranil) and nortriptyline (brand names: Aventyl, Pamelor). Other antidepressants exist that have different ways of working than the SSRIs and tricylics. Commonly used ones are venlafaxine (brand name: Effexor), nefazadone (brand name: Serzone), bupropion (brand name: Wellbutrin), mirtazapine (brand name: Remeron) and trazodone (brand name: Desyrel). Less commonly used are the monomine oxidase inhibitors (MAOIs), such as phenelzine (brand name: Nardil) and tranylcypromine (brand name: Parnate).

Examples of steroids include, but are not limited to, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone,

and triamcinolone.

Examples of antiemetics or antinauseants include, but are not limited to, promethazine (Phenergan®), metoclopramide (Reglan®), cyclizine (Merezine®), diphenhydramine (Benadryl®), meclizine (Antivert®, Bonine®), chlorpromazine (Thorazine®), droperidol (Inapsine®), hydroxyzine (Atarax®, Vistaril®), prochlorperazine (Compazine®), trimethobenzamide (Tigan®), cisapride; h2-receptor antagonists, such as nizatidine, ondansetron (Zofran®), corticosteriods, 5-Hydroxytryptamine antagonists, such as dolasetron (Anzemet®), granisetron (Kytril®), ondansetron (Zofran®), tropisetron; dopamine antagonists, such as domperidone (Motilium®), droperidol (Inapsine®), haloperidol (Haldol®), chlorpromazine (Thorazine®); Antihistamines (5HT2 receptor antagonists), such as cyclizine (Antivert®, Bonine®, Dramamine®, Marezine®, Meclicot®, Medivert®), diphenhydramine, dimenhydrinate (Alavert®, Allegra®, Dramanate®) dimenhydrinate (Driminate®); and cannabinoids, such as marijuana and marinol.

Examples of spasmolytics or antispasmodics include, but are not limited to, methocarbamol, guaifenesin, diazepam, dantrolene, phenytoin, tolterodine, oxybutynin, flavoxate, and emepronium.

Examples of antipsychotics include, but are not limited to, clozapine (Clozaril®), risperidone (Risperdal®), olanzapine (Zyprexa®), quetiapine (Seroquel®), ziprasidone (Geodon®), and aripiprazole (Abilify®).

Examples of opioids include, but are not limited to, (1) opium alkaloids, such as morphine (Kadian®, Avinza®), codeine, and thebaine; (2) semisynthetic opioid derivatives, such as diamorphine (heroin), oxycodone (OxyContin®, Percodan®, Percocet®), hydrocodone, dihydrocodeine, hydromorphine, oxymorphone, and nicomorphine; (3) synthetic opioids, such as (a) pheylheptylamines, including methadone and levo-alphacetylmethadol (LAAM), (b) phenylpiperidines, including pethidine (meperidine), fentanyl, alfentanil, sufentanil, remifentanil, ketobemidone, and carfentanyl, (c) diphenylpropylamine derivatives, such as propoxyphene, dextropropoxyphene, dextromoramide, bezitramide, and piritramide, (d) benzomorphan derivatives, such as pentazocine and phenzocine, (e) oripavine derivatives, such as buprenorphine, (f) morphinan derivatives, such as butorphanol and nalbufine, and miscellaneous other synthetic opioids, such as dezocine, etorphine, tilidine, tramadol, loperamide, and diphenoxylate (Lomotil®).

Examples of carbidopa/levodopa or dopamine agonists include, but are not limited to, ropinirole, pramipexole and cabergoline, bromocriptine mesylate (Parlodel®), pergolide mesylate (Permax®), pramipexole dihydrochloride (Mirapex®), and ropinirole hydrochloride (Requip™).

Examples of anesthetics include, but are not limited to, enflurane, halothane, isoflurane, methoxyflurane, nitrous oxide, etomidate, ketamine, methohexital, propofol, and thiopental.

II. Compositions

The invention provides compositions comprising nanoparticulate benzodiazepine, such as lorazepam, particles and at least one surface stabilizer. The surface stabilizers are preferably adsorbed to or associated with the surface of the benzodiazepine, such as lorazepam, particles. Surface stabilizers useful herein do not chemically react with the benzodiazepine, such as lorazepam, particles or itself. Preferably, individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages. In another embodiment, the compositions of the present invention can comprise two or more surface stabilizers.

The present invention also includes nanoparticulate benzodiazepine, such as lorazepam, compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous) or aerosol delivery. In certain embodiments of the invention, the nanoparticulate benzodiazepine, such as lorazepam, formulations are in an injectable form or an aerosol dosage form.

A. Benzodiazepine Particles

The invention is practiced with a benzodiazepine, such as lorazepam. The benzodiazepine, such as lorazepam, is preferably present in an essentially pure form, is poorly soluble, and is dispersible in at least one liquid media. By "poorly soluble," it is meant that the benzodiazepine, such as lorazepam, has a solubility in the liquid dispersion

media of less than about 10 mg/mL, and preferably of less than about 1 mg/mL. As noted above, the solubility of lorazepam in water is 0.08 mg/mL.

The drug can be selected from a variety of benzodiazepines for treatment of status epilepticus, treatment of irritable bowel syndrome, sleep induction, acute psychosis, and pre-anesthesia medications. Preferable drug classes are benzodiazepine, such as lorazepam, and pharmaceutically acceptable salts and esters of lorazepam. Benzodiazepines of particular interest are alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, and loprazolam. Particularly preferred benzodiazepines are alprazolam, midazolam, clonazepam, lorazepam, and triazolam. The preferred benzodiazepine is lorazepam. A description of these classes of benzodiazepines and a listing of species within each class can be found in Martindale, The Extra Pharmacopoeia, Twenty-ninth Edition (The Pharmaceutical Press, London, 1989), specifically incorporated by reference. The drugs are commercially available and/or can be prepared by techniques known in the art.

"Pharmaceutically acceptable" as used herein refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable salts and esters" as used herein refers to derivatives wherein the benzediazepine, such as lorazepam, is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quarternary ammonium salts of the benzodiazepine and preferably, lorazepam formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic,

benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

B. Surface Stabilizers

Suitable surface stabilizers can be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Preferred surface stabilizers include nonionic, ionic, cationic, anionic, and zwitterionic surfactants. A preferred surface stabilizer for an injectable nanoparticulate benzodiazepine formulation is a povidone polymer. Two or more surface stabilizers can be used in combination.

Representative examples of surface stabilizers include hydroxypropyl methylcellulose (now known as hypromellose), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens® such as e.g., Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (e.g., Carbowaxes 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also

known as Olin-lOG® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is C18H37CH2(CON(CH3)-CH2(CHOH)4(CH20H)2 (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl (-D-glucopyranoside; n-decyl (-D-maltopyranoside; n-dodecyl (-D-glucopyranoside; n-dodecyl (-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-(-D-glucopyranoside; n-heptyl (-D-thioglucoside; n-hexyl (-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl (-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-(-D-glucopyranoside; octyl (-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate. Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C12-15dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulfate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)4 ammonium chloride or bromide, N-alkyl (C12-18)dimethylbenzyl ammonium chloride, N-alkyl (C14-18)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C12-14) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt,

dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C12-14) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C12, C15, C17 trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336), POLYQUAT, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and distearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL and ALKAQUAT (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, Cationic Surfactants: Analytical and Biological Evaluation (Marcel Dekker, 1994); P. and D. Rubingh (Editor), Cationic Surfactants: Physical Chemistry (Marcel Dekker, 1991); and J. Richmond, Cationic Surfactants: Organic Chemistry, (Marcel Dekker, 1990).

Nonpolymeric surface stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary

ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula NR1R2R3R4(+). For compounds of the formula NR1R2R3R4(+):

(i) none of R1-R4 are CH3;

(ii) one of R1-R4 is CH3;

(iii) three of R1-R4 are CH3;

(iv) all of R1-R4 are CH3;

(v) two of R1-R4 are CH3, one of R1-R4 is C6H5CH2, and one of R1-R4 is an alkyl chain of seven carbon atoms or less;

(vi) two of R1-R4 are CH3, one of R1-R4 is C6H5CH2, and one of R1-R4 is an alkyl chain of nineteen carbon atoms or more;

(vii) two of R1-R4 are CH3 and one of R1-R4 is the group C6H5(CH2)n, where n>1;

(viii) two of R1-R4 are CH3, one of R1-R4 is C6H5CH2, and one of R1-R4 comprises at least one heteroatom;

(ix) two of R1-R4 are CH3, one of R1-R4 is C6H5CH2, and one of R1-R4 comprises at least one halogen;

(x) two of R1-R4 are CH3, one of R1-R4 is C6H5CH2, and one of R1-R4 comprises at least one cyclic fragment;

(xi) two of R1-R4 are CH3 and one of R1-R4 is a phenyl ring; or

(xii) two of R1-R4 are CH3 and two of R1-R4 are purely aliphatic fragments.

Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride (Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride,

meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated herein by reference.

Povidone Polymers

Povidone polymers are preferred surface stabilizers for use in formulating an injectable nanoparticulate benzodiazepine, such as lorazepam, formulations. Povidone polymers, also known as polyvidon(e), povidonum, PVP, and polyvinylpyrrolidone, are sold under the trade names Kollidon® (BASF Corp.) and Plasdone® (ISP Technologies, Inc.). They are polydisperse macromolecular molecules, with a chemical name of 1-ethenyl-2-pyrrolidinone polymers and 1-vinyl-2-pyrrolidinone polymers. Povidone polymers are produced commercially as a series of products having mean molecular weights ranging from about 10,000 to about 700,000 daltons. To be useful as a surface modifier for a drug compound to be administered to a mammal, the povidone polymer must have a molecular weight of less than about 40,000 daltons, as a molecular weight of greater than 40,000 daltons would have difficulty clearing the body.

Povidone polymers are prepared by, for example, Reppe's process, comprising: (1) obtaining 1,4-butanediol from acetylene and formaldehyde by the Reppe butadiene synthesis; (2) dehydrogenating the 1,4-butanediol over copper at 200° to form γ-butyrolactone; and (3) reacting γ-butyrolactone with ammonia to yield pyrrolidone. Subsequent treatment with acetylene gives the vinyl pyrrolidone monomer. Polymerization is carried out by heating in the presence of H_2O and NH_3. *See The Merck Index*, 10th Edition, pp. 7581 (Merck & Co., Rahway, NJ, 1983).

The manufacturing process for povidone polymers produces polymers containing molecules of unequal chain length, and thus different molecular weights. The molecular weights of the molecules vary about a mean or average for each particular commercially

available grade. Because it is difficult to determine the polymer's molecular weight directly, the most widely used method of classifying various molecular weight grades is by K-values, based on viscosity measurements. The K-values of various grades of povidone polymers represent a function of the average molecular weight, and are derived from viscosity measurements and calculated according to Fikentscher's formula.

The weight-average of the molecular weight, Mw, is determined by methods that measure the weights of the individual molecules, such as by light scattering. Table 1 provides molecular weight data for several commercially available povidone polymers, all of which are soluble.

TABLE 1

Povidone	K-Value	Mv (Daltons)**	Mw (Daltons)**	Mn (Daltons)**
Plasdone C-15®	17 ± 1	7,000	10,500	3,000
Plasdone C-30®	30.5 ± 1.5	38,000	62,500*	16,500
Kollidon 12 PF®	11-14	3,900	2,000-3,000	1,300
Kollidon 17 PF®	16-18	9,300	7,000-11,000	2,500
Kollidon 25®	24-32	25,700	28,000-34,000	6,000

*Because the molecular weight is greater than 40,000 daltons, this povidone polymer is not useful as a surface stabilizer for a drug compound to be administered parenterally (*i.e.*, injected).

**Mv is the viscosity-average molecular weight, Mn is the number-average molecular weight, and Mw is the weight average molecular weight. Mw and Mn were determined by light scattering and ultra-centrifugation, and Mv was determined by viscosity measurements.

Based on the data provided in Table 1, exemplary preferred commercially available povidone polymers include, but are not limited to, Plasdone C-15®, Kollidon 12 PF®, Kollidon 17 PF®, and Kollidon 25®.

C. Nanoparticulate Benzodiazepine Particle Size

As used herein, particle size is determined on the basis of the weight average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, and disk centrifugation.

Compositions of the invention comprise benzodiazepine, such as lorazepam, nanoparticles having an effective average particle size of less than about 2000 nm (*i.e.*, 2

microns). In other embodiments of the invention, the benzodiazepine, such as lorazepam, nanoparticles have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

In another embodiment, the nanoparticulate compositions of the present invention, and the injectable nanoparticulate compositions in particular, comprise benzodiazepine, such as lorazepam, nanoparticles that have an effective average particles size of less than about 600 nm. In other embodiments, the effective average particle size is less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm.

An "effective average particle size of less than about 2000 nm" means that at least 50% of the benzodiazepine, such as lorazepam, particles have a particle size less than the effective average, by weight, *i.e.*, less than about 2000 nm. If the "effective average particle size" is less than about 1900 nm, then at least about 50% of the benzodiazepine, such as lorazepam, particles have a size of less than about 1900 nm, when measured by the above-noted techniques. The same is true for the other particle sizes referenced above. In other embodiments, at least about 70%, at least about 90%, at least about 95%, or at least about 99% of the benzodiazepine, such as lorazepam, particles have a particle size less than the effective average, *i.e.*, less than about 2000 nm, about 1900 nm, about 1800 nm, *etc.*.

In the present invention, the value for D50 of a nanoparticulate benzodiazepine, such as lorazepam, composition is the particle size below which 50% of the benzodiazepine, such as lorazepam, particles fall, by weight. Similarly, D90 is the particle size below which 90% of the benzodiazepine, such as lorazepam, particles fall, by weight.

D. Concentration of Nanoparticulate Benzodiazepine and Surface Stabilizers

The relative amounts of benzodiazepine, such as lorazepam, and one or more surface stabilizers can vary widely. The optimal amount of the individual components depends, for example, upon physical and chemical attributes of the surface stabilizer(s) and benzodiazepine selected, such as the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer and benzodiazepine, *etc.*

Preferably, the concentration of benzodiazepine, such as lorazepam, can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined weight of the benzodiazepine and at least one surface stabilizer, not including other excipients. Higher concentrations of the active ingredient are generally preferred from a dose and cost efficiency standpoint.

Preferably, the concentration of surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of benzodiazepine, such as lorazepam, and at least one surface stabilizer, not including other excipients.

E. Other Pharmaceutical Excipients

Pharmaceutical compositions of the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients depending upon the route of administration and the dosage form desired. Such excipients are well known in the art.

Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring

agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, and quarternary compounds such as benzalkonium chloride.

Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

Examples of effervescent agents are effervescent couples, such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

F. Aerosol Formulations of Nanoparticulate Benzodiazepines

The compositions of the invention encompass aerosols comprising a nanoparticulate benzodiazepine, such as lorazepam. Aerosols can be defined as colloidal systems comprising very finely divided liquid droplets or dry particles dispersed in and surrounded by a gas. Both liquid and dry powder aerosol compositions are encompassed by the invention.

Aerosols intended for delivery to the nasal mucosa are inhaled through the nose. For optimal delivery to the nasal cavities, droplet or aggregate dry powder particle sizes of about 5 to about 100 microns are useful, with droplet or aggregate dry powder particle sizes of

about 30 to about 60 microns being preferred. The nanoparticulate benzodiazepine particles are either suspended in the liquid droplet for an aqueous dispersion aerosol, or comprised in the aggregate dry powder particles for a dry powder aerosol. For nasal delivery, a larger inhaled particle size is desired to maximize impaction on the nasal mucosa and to minimize or prevent pulmonary deposition of the administered formulation. Inhaled particles may be defined as (1) liquid droplets comprising a suspended benzodiazepine particle, such as lorazepam, (2) dry particles of a benzodiazepine, such as lorazepam, (3) dry powder aggregates of a nanoparticulate benzodiazepine, such as lorazepam, or (4) dry particles of a diluent which comprise an embedded benzodiazepine, such as lorazepam, nanoparticles.

For delivery to the upper respiratory region, inhaled particle sizes of about 2 to about 10 microns are preferred. More preferred is about 2 to about 6 microns. Delivery to the upper respiratory region may be desirable for a nanoparticulate benzodiazepine, such as lorazepam nanoparticles, that are to act locally. This is because a nanoparticulate benzodiazepine, such as lorazepam, deposited in the upper respiratory tract can dissolve and act on the smooth muscle of the airway, rather than being absorbed into the bloodstream of the patient. However, the goal for an inhaled benzodiazepine, such as lorazepam, is systemic delivery, such as in cases of a benzodiazepine, such as lorazepam, which are not amenable to oral administration. It is preferred that a benzodiazepine, such as lorazepam, which is intended for systemic administration, be delivered to the alveolar region of the lung because 99.99% of the available surface area for a benzodiazepine, such as lorazepam, absorption is located in the peripheral alveoli. Thus, with administration to the alveolar region, rapid absorption can be realized. For delivery to the deep lung (alveolar) region, inhaled particle sizes of less than about 2 microns are preferred.

1. Concentration of Nanoparticulate Benzodiazepine

For aqueous aerosol formulations, nanoparticulate benzodiazepine, such as lorazepam, nanoparticles are present at a concentration of about 0.05 mg/mL up to about 600 mg/mL. For dry powder aerosol formulations, nanoparticulate benzodiazepine, such as lorazepam, nanoparticles are present at a concentration of about 0.05 mg/g up to about 990 mg/g, depending on the desired dosage. Concentrated nanoparticulate aerosols, defined as comprising a nanoparticulate benzodiazepine, such as lorazepam, at a concentration of about

10 mg/mL up to about 600 mg/mL for aqueous aerosol formulations, and about 10 mg/g up to about 990 mg/g for dry powder aerosol formulations, are specifically encompassed by the present invention. More concentrated aerosol formulations enable the delivery of large quantities of a nanoparticulate benzodiazepine, such as nanoparticulate lorazepam, to the lung in a very short period of time, thereby providing effective delivery to appropriate areas of the lung or nasal cavities in short administration times, *i.e.*, less than about 15 seconds as compared to administration times of up to 4 to 20 minutes as found in conventional pulmonary nebulizer therapies.

2. Aqueous Aerosols

The present invention encompasses aqueous formulations comprising nanoparticulate benzodiazepine, such as lorazepam, nanoparticles. Aqueous formulations of the invention comprise colloidal dispersions of a poorly water-soluble nanoparticulate benzodiazepine, such as lorazepam, in an aqueous vehicle which are aerosolized using air-jet or ultrasonic nebulizers. The advantages of the invention can best be understood by comparing the sizes of nanoparticulate and conventional micronized benzodiazepine, such as lorazepam, particles with the sizes of liquid droplets produced by conventional nebulizers. Conventional micronized material is generally about 2 to about 5 microns or more in diameter and is approximately the same size as the liquid droplet size produced by medical nebulizers. In contrast, nanoparticulate benzodiazepine, such as lorazepam, are substantially smaller than the droplets in such an aerosol. Thus, aerosols comprising nanoparticulate benzodiazepine, such as lorazepam, improve drug delivery efficiency. Such aerosols comprise a higher number of nanoparticles per unit dose, resulting in each aerosolized droplet containing active benzodiazepine, such as lorazepam.

Thus, with administration of the same dosages of nanoparticulate and micronized benzodiazepine, such as lorazepam, more lung or nasal cavity surface area is covered by the aerosol formulation comprising a nanoparticulate benzodiazepine, such as lorazepam.

Another advantage of the invention is that the compositions of the invention permit a poorly water-soluble benzodiazepine, such as lorazepam, to be delivered to the deep lung. Conventional micronized drug substance is too large to reach the peripheral lung regardless of the size of the droplet produced by the nebulizer, but the present invention permits

nebulizers which generate very small (about 0.5 to about 2 microns) aqueous droplets to deliver a poorly water-soluble benzodiazepine, such as lorazepam, in the form of nanoparticles to the alveoli. One example of such devices is the Circular™ aerosol (Westmed Corp., Tucson, Ariz.).

Yet another advantage of the invention is that ultrasonic nebulizers can be used to deliver a poorly water-soluble benzodiazepine, such as lorazepam, to the lung. Unlike conventional micronized material, nanoparticulate benzodiazepine, such as lorazepam, are readily aerosolized and show good *in vitro* deposition characteristics. A specific advantage of the invention is that it permits poorly water-soluble benzodiazepine, such as lorazepam, to be aerosolized by ultrasonic nebulizers which require a nanoparticulate benzodiazepine, such as lorazepam, to pass through very fine orifices to control the size of the aerosolized droplets. While conventional drug material would be expected to occlude the pores, such nanoparticulates are much smaller and can pass through the pores without difficulty.

Another advantage of the invention is the enhanced rate of dissolution of a poorly water-soluble benzodiazepine, such as lorazepam, which is practically insoluble in water. Since dissolution rate is a function of the total surface area of a benzodiazepine, such as lorazepam, to be dissolved, a more finely divided benzodiazepine (*e.g.*, nanoparticles) have much faster dissolution rates than conventional micronized drug particles. This can result in more rapid absorption of an inhaled benzodiazepine, such as lorazepam. For a nasally administered benzodiazepine, such as lorazepam, it can result in more complete absorption of the dose, since with a nanoparticulate dose of the benzodiazepine, such as lorazepam, the nanoparticles can dissolve rapidly and completely before being cleared by the mucociliary mechanism.

3. Dry Powder Aerosol Formulations

Another embodiment of the invention is directed to dry powder aerosol formulations comprising a benzodiazepine, such as lorazepam, for pulmonary and/or nasal administration. Dry powders, which can be used in both DPIs and pMDIs, can be made by spray-drying an aqueous nanoparticulate dispersion of a benzodiazepine, such as lorazepam. Alternatively, dry powders comprising a nanoparticulate benzodiazepine, such as lorazepam, can be made by freeze-drying dispersions of the nanoparticles. Combinations of the spray-dried and

freeze-dried nanoparticulate powders can be used in DPIs and pMDIs. For dry powder aerosol formulations, a nanoparticulate benzodiazepine, such as lorazepam, may be present at a concentration of about 0.05 mg/g up to about 990 mg/g. In addition, the more concentrated aerosol formulations (*i.e.*, for dry powder aerosol formulations about 10 mg/g up to about 990 mg/g) have the additional advantage of enabling large quantities of a benzodiazepine, such as lorazepam, to be delivered to the lung in a very short period of time, *e.g.*, about 1 to about 2 seconds (1 puff).

The invention is also directed to dry powders which comprise nanoparticulate compositions for pulmonary or nasal delivery. The powders may comprise inhalable aggregates of a nanoparticulate benzodiazepine, such as lorazepam, or inhalable particles of a diluent which comprises at least one embedded benzodiazepine, such as lorazepam. Powders comprising a nanoparticulate benzodiazepine, such as lorazepam, can be prepared from aqueous dispersions of nanoparticles by removing the water by spray-drying or lyophilization (freeze drying). Spray-drying is less time consuming and less expensive than freeze-drying, and therefore more cost-effective. However, certain benzodiazepines, such as lorazepam, benefit from lyophilization rather than spray-drying in making dry powder formulations.

Dry powder aerosol delivery devices must be able to accurately, precisely, and repeatably deliver the intended amount of benzodiazepine, such as lorazepam. Moreover, such devices must be able to fully disperse the dry powder into individual particles of a respirable size. Conventional micronized drug particles of 2–3 microns in diameter are often difficult to meter and disperse in small quantities because of the electrostatic cohesive forces inherent in such powders. These difficulties can lead to loss of drug substance to the delivery device as well as incomplete powder dispersion and sub-optimal delivery to the lung. Many drug compounds, particularly a benzodiazepine, such as lorazepam, are intended for deep lung delivery and systemic absorption. Since the average particle sizes of conventionally prepared dry powders are usually in the range of 2–3 microns, the fraction of material which actually reaches the alveolar region may be quite small. Thus, delivery of micronized dry powders to the lung, especially the alveolar region, is generally very inefficient because of the properties of the powders themselves.

The dry powder aerosols which comprise nanoparticulate benzodiazepine, such as lorazepam, can be made smaller than comparable micronized drug substance and, therefore,

are appropriate for efficient delivery to the deep lung. Moreover, aggregates of nanoparticulate benzodiazepine, such as lorazepam, are spherical in geometry and have good flow properties, thereby aiding in dose metering and deposition of the administered composition in the lung or nasal cavities.

Dry nanoparticulate compositions can be used in both DPIs and pMDIs. (In this invention, "dry" refers to a composition having less than about 5% water.)

a. Spray-dried powders comprising a nanoparticulate benzodiazepine

Powders comprising a nanoparticulate benzodiazepine, such as lorazepam, can be made by spray-drying aqueous dispersions of a nanoparticulate benzodiazepine, such as lorazepam, and a surface stabilizer to form a dry powder which comprises aggregated nanoparticulate benzodiazpine, such as lorazepam. The aggregates can have a size of about 1 to about 2 microns which is suitable for deep lung delivery. The aggregate particle size can be increased to target alternative delivery sites, such as the upper bronchial region or nasal mucosa by increasing the concentration of a benzodiazepine, such as lorazepam, in the spray-dried dispersion or by increasing the droplet size generated by the spray dryer.

Alternatively, the aqueous dispersion of a nanoparticulate benzodiazepine, such as lorazepam, and surface stabilizer can comprise a dissolved diluent such as lactose or mannitol which, when spray dried, forms inhalable diluent particles, each of which comprises at least one embedded benzodiazepine, such as lorazepam, nanoparticle and surface stabilizer. The diluent particles with an embedded benzodiazepine, such as lorazepam, nanoparticles can have a particle size of about 1 to about 2 microns, suitable for deep lung delivery. In addition, the diluent particle size can be increased to target alternate delivery sites, such as the upper bronchial region or nasal mucosa by increasing the concentration of dissolved diluent in the aqueous dispersion prior to spray drying, or by increasing the droplet size generated by the spray dryer.

Spray-dried powders can be used in DPIs or pMDIs, either alone or combined with freeze-dried nanoparticulate active agent powder. In addition, spray-dried powders comprising a nanoparticulate benzodiazepine, such as lorazepam, can be reconstituted and used in either jet or ultrasonic nebulizers to generate aqueous dispersions having respirable

droplet sizes, where each droplet comprises at least one nanoparticulate benzodiazepine, such as lorazepam. Concentrated nanoparticulate dispersions may also be used in these aspects of the invention.

b. Freeze-Dried Powders Comprising a Nanoparticulate Benzodiazepine

Nanoparticulate benzodiazepine, such as lorazepam, dispersions can also be freeze-dried to obtain powders suitable for nasal or pulmonary delivery. Such powders may comprise aggregated nanoparticulate benzodiazepine, such as lorazepam, having a surface stabilizer. Such aggregates may have sizes within a respirable range, *i.e.*, about 2 to about 5 microns. Larger aggregate particle sizes can be obtained for targeting alternate delivery sites, such as the nasal mucosa.

Freeze dried powders of the appropriate particle size can also be obtained by freeze drying aqueous dispersions of benzodiazepine, such as lorazepam, and surface stabilizer, which additionally may comprise a dissolved diluent such as lactose or mannitol. In these instances the freeze dried powders comprise respirable particles of diluent, each of which comprises at least one embedded nanoparticulate benzodiazepine, such as lorazepam.

Freeze-dried powders can be used in DPIs or pMIs, either alone or combined with spray-dried nanoparticulate powder. In addition, freeze-dried powders containing a nanoparticulate benzodiazepine, such as lorazepam, can be reconstituted and used in either jet or ultrasonic nebulizers to generate aqueous dispersions having respirable droplet sizes, where each droplet comprises at least one nanoparticulate benzodiazepine, such as lorazepam. Concentrated nanoparticulate dispersions may also be used in these aspects of the invention.

c. Propellant-Based Aerosols

Yet another embodiment of the invention is directed to a process and composition for propellant-based systems comprising a nanoparticulate benzodiazepine, such as lorazepam. Such formulations may be prepared by wet milling the coarse benzodiazepine, and preferably, lorazepam particles and surface stabilizer in liquid propellant, either at ambient pressure or under high pressure conditions. Alternatively, dry powders comprising a

nanoparticulate benzodiazepine, such as lorazepam, may be prepared by spray-drying or freeze-drying aqueous dispersions of a nanoparticulate benzodiazepine, such as lorazepam, with the resultant powders dispersed into suitable propellants for use in conventional pMDIs. Such nanoparticulate pMDI formulations can be used for either nasal or pulmonary delivery. For pulmonary administration, such formulations afford increased delivery to the deep lung regions because of the small (*i.e.*, about 1 to about 2 microns) particle sizes available from these methods. Concentrated aerosol formulations can also be employed in pMDIs.

Another embodiment of the invention is directed to a process and composition for propellant-based MDIs containing nanoparticulate benzodiazepine, such as lorazepam. pMDIs can comprise either the discrete nanoparticles and surface stabilizer, aggregates of the nanoparticles and surface stabilizer, or diluent particles comprising the embedded nanoparticles. pMDIs can be used for targeting the nasal cavity, the conducting airways of the lung, or the alveoli. Compared to conventional formulations, the present invention affords increased delivery to the deep lung regions because the inhaled nanoparticles are smaller than conventional micronized material (<2 microns) and are distributed over a larger mucosal or alveolar surface area as compared to miconized drugs.

The nanoparticulate drug pMDIs of the invention can utilize either chlorinated or non-chlorinated propellants. Concentrated nanoparticulate aerosol formulations can also be employed in pMDIs.

In a non-aqueous, non-pressurized milling system, a non-aqueous liquid which has a vapor pressure of 1 atm or less at room temperature is used as a milling medium and may be evaporated to yield a dry nanoparticulate benzodiazepine, and preferably, lorazepam nanoparticles and surface modifier. The non-aqueous liquid may be, for example, a high-boiling halogenated hydrocarbon. The dry nanoparticulate benzodiazepine, and preferably, lorazepam nanoparticle composition thus produced may then be mixed with a suitable propellant or propellants and used in a conventional pMDI.

Alternatively, in a pressurized milling operation, a non-aqueous liquid which has a vapor pressure >1 atm at room temperature is used as a milling medium for making a nanoparticulate benzodiazepine, such as lorazepam, and surface stabilizer composition. Such a liquid may be, for example, a halogenated hydrocarbon propellant which has a low boiling point. The resultant nanoparticulate composition can then be used in a conventional pMDI

without further modification, or can be blended with other suitable propellants. Concentrated aerosols may also be made by such methods.

G. Injectable Nanoparticulate Benzodiazepine Formulations

The invention provides injectable nanoparticulate benzodiazepine, such as lorazepam, formulations that can comprise high drug concentrations in low injection volumes, with rapid drug dissolution upon administration. In addition, the injectable nanoparticulate benzodiazepine, such as lorazepam, formulations of the invention eliminate the need to use polyoxyl 60 hydrogenated castor oil (HCO-60) as a solubilizer. An exemplary injectable composition comprises, based on % w/w:

benzodiazepine (such as lorazepam)	5 – 50%
povidone polymer	0.1 – 50%
preservatives	0.05 - 0.25%
pH adjusting agent	pH about 6 to about 7
water for injection	q.s.

Exemplary preservatives include methylparaben (about 0.18% based on % w/w), propylparaben (about 0.02% based on % w/w), phenol (about 0.5% based on % w/w), and benzyl alcohol (up to 2% v/v). An exemplary pH adjusting agent is sodium hydroxide, and an exemplary liquid carrier is sterile water for injection. Other useful preservatives, pH adjusting agents, and liquid carriers are well-known in the art.

III. Methods Of Making the Benzodiazepine Formulations

Nanoparticulate benzodiazepine, such as lorazepam, compositions can be made using any suitable method known in the art such as, for example, milling, homogenization, precipitation, or supercritical fluid techniques. Exemplary methods of making nanoparticulate compositions are described in U.S. Patent No. 5,145,684. Methods of making nanoparticulate compositions are also described in U.S. Patent No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331 for "Co-

Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Patent No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated herein by reference.

The resultant nanoparticulate benzodiazepine, such as lorazepam, compositions or dispersions can be utilized in injectable, aerosol dosage formulations, controlled release formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, *etc.*

Consistent with the above disclosure, provided herein is a method of preparing the nanoparticulate benzodiazepine, such as lorazepam, formulations of the invention. The method comprises the steps of: (1) dispersing a benzodiazepine, such as lorazepam, in a liquid dispersion media; and (2) mechanically reducing the particle size of the benzodiazepine, such as lorazepam, to the desired effective average particle size, such as less than about 2000 nm or less than about 600 nm. A surface stabilizer can be added before, during, or after particle size reduction of the benzodiazepine, such as lorazepam. The liquid dispersion media can be maintained at a physiologic pH, for example, within the range of from about 3.0 to about 8.0 during the size reduction process; more preferably within the range of from about 5.0 to about 7.5 during the size reduction process. The dispersion media used for the size reduction process is preferably aqueous, although any media in which the benzodiazepine, such as lorazepam, is poorly soluble and dispersible can be used, such as safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol.

Effective methods of providing mechanical force for particle size reduction of a benzodiazepine, such as lorazepam, include ball milling, media milling, and homogenization, for example, with a Microfluidizer® (Microfluidics Corp.). Ball milling is a low energy

milling process that uses milling media, drug, stabilizer, and liquid. The materials are placed in a milling vessel that is rotated at optimal speed such that the media cascades and reduces the drug particle size by impaction. The media used must have a high density as the energy for the particle reduction is provided by gravity and the mass of the attrition media.

Media milling is a high energy milling process. Drug, stabilizer, and liquid are placed in a reservoir and recirculated in a chamber containing media and a rotating shaft/impeller. The rotating shaft agitates the media which subjects the drug to impaction and sheer forces, thereby reducing the drug particle size.

Homogenization is a technique that does not use milling media. Drug, stabilizer, and liquid (or drug and liquid with the stabilizer added after particle size reduction) constitute a process stream propelled into a process zone, which in the Microfluidizer® is called the Interaction Chamber. The product to be treated is inducted into the pump, and then forced out. The priming valve of the Microfluidizer® purges air out of the pump. Once the pump is filled with product, the priming valve is closed and the product is forced through the interaction chamber. The geometry of the interaction chamber produces powerful forces of sheer, impact, and cavitation which are responsible for particle size reduction. Specifically, inside the interaction chamber, the pressurized product is split into two streams and accelerated to extremely high velocities. The formed jets are then directed toward each other and collide in the interaction zone. The resulting product has very fine and uniform particle or droplet size. The Microfluidizer® also provides a heat exchanger to allow cooling of the product. U.S. Patent No. 5,510,118, which is specifically incorporated by reference, refers to a process using a Microfluidizer®.

Using a particle size reduction method, the particle size of benzodiazepine, such as lorazepam, is reduced to the desired effective average particle size, such as less than about 2000 nm for the aerosol formulation, and less than about 600 nm for the injectable formulation.

The benzodiazepine, such as lorazepam, can be added to a liquid media in which it is essentially insoluble to form a premix. The concentration of the benzodiazepine, such as lorazepam, in the liquid media can vary from about 5 to about 60%, and preferably is from about 15 to about 50% (w/v), and more preferably about 20 to about 40%. The surface stabilizer can be present in the premix or it can be added to the drug dispersion following

particle size reduction. The concentration of the surface stabilizer can vary from about 0.1 to about 50%, and preferably is from about 0.5 to about 20%, and more preferably from about 1 to about 10%, by weight.

The premix can be used directly by subjecting it to mechanical means to reduce the average benzodiazepine, such as lorazepam, particle size in the dispersion to less than about 2000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the benzodiazepine, such as lorazepam, and at least one surface stabilizer can be dispersed in the liquid media using suitable agitation, *e.g.*, a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition.

The mechanical means applied to reduce the benzodiazepine, such as lorazepam, particle size conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, and media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix is preferably from about 100 to about 1000 centipoise, and for ball milling the apparent viscosity of the premix is preferably from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal balance between efficient particle size reduction and media erosion.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. Alternatively, processing times of less than 1 day (residence times of one minute up to several hours) are possible with the use of a high shear media mill.

The benzodiazepine, such as lorazepam, particles can be reduced in size at a temperature which does not significantly degrade the benzodiazepine, such as lorazepam. Processing temperatures of less than about 30 to less than about 40°C are ordinarily preferred. If desired, the processing equipment can be cooled with conventional cooling equipment. Control of the temperature, *e.g.*, by jacketing or immersion of the milling chamber in ice water, is contemplated. Generally, the method of the invention is

conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. Ambient processing pressures are typical of ball mills, attritor mills, and vibratory mills.

Grinding Media

The grinding media can comprise particles that are preferably substantially spherical in shape, *e.g.*, beads, consisting essentially of polymeric resin. Alternatively, the grinding media can comprise a core having a coating of a polymeric resin adhered thereon. The polymeric resin can have a density from about 0.8 to about 3.0 g/cm^3.

In general, suitable polymeric resins are chemically and physically inert, substantially free of metals, solvent, and monomers, and of sufficient hardness and friability to enable them to avoid being chipped or crushed during grinding. Suitable polymeric resins include crosslinked polystyrenes, such as polystyrene crosslinked with divinylbenzene; styrene copolymers; polycarbonates; polyacetals, such as Delrin® (E.I. du Pont de Nemours and Co.); vinyl chloride polymers and copolymers; polyurethanes; polyamides; poly(tetrafluoroethylenes), *e.g.*, Teflon®(E.I. du Pont de Nemours and Co.), and other fluoropolymers; high density polyethylenes; polypropylenes; cellulose ethers and esters such as cellulose acetate; polyhydroxymethacrylate; polyhydroxyethyl acrylate; and silicone-containing polymers such as polysiloxanes and the like. The polymer can be biodegradable. Exemplary biodegradable polymers include poly(lactides), poly(glycolide) copolymers of lactides and glycolide, polyanhydrides, poly(hydroxyethyl methacylate), poly(imino carbonates), poly(N-acylhydroxyproline)esters, poly(N-palmitoyl hydroxyproline) esters, ethylene-vinyl acetate copolymers, poly(orthoesters), poly(caprolactones), and poly(phosphazenes). For biodegradable polymers, contamination from the media itself advantageously can metabolize *in vivo* into biologically acceptable products that can be eliminated from the body.

The grinding media preferably ranges in size from about 0.01 to about 3 mm. For fine grinding, the grinding media is preferably from about 0.02 to about 2 mm, and more preferably from about 0.03 to about 1 mm in size.

In a preferred grinding process the particles are made continuously. Such a method comprises continuously introducing a benzodiazepine, such as lorazepam, into a milling

chamber, contacting the benzodiazepine, such as lorazepam, with grinding media while in the chamber to reduce the benzodiazepine particle size, and continuously removing the nanoparticulate benzodiazepine from the milling chamber.

The grinding media is separated from the milled nanoparticulate benzodiazepine, such as lorazepam, using conventional separation techniques, in a secondary process such as by simple filtration, sieving through a mesh filter or screen, and the like. Other separation techniques such as centrifugation may also be employed.

Sterile Product Manufacturing

Development of injectable compositions requires the production of a sterile product. The manufacturing process of the present invention is similar to typical known manufacturing processes for sterile suspensions. A typical sterile suspension manufacturing process flowchart is as follows:

(Media Conditioning)
↓
Compounding
↓
Particle Size Reduction
↓
Vial Filling
↓
(Lyophilization) and/or (Terminal Sterilization)

As indicated by the optional steps in parentheses, some of the processing is dependent upon the method of particle size reduction and/or method of sterilization. For example, media conditioning is not required for a milling method that does not use media. If terminal sterilization is not feasible due to chemical and/or physical instability, aseptic processing can be used.

Aerosol Formulations

A nanoparticulate benzodiazepine, such as lorazepam, composition for aerosol administration can be made by, for example, by (1) nebulizing an aqueous dispersion of nanoparticulate benzodiazepine, such as lorazepam, obtained by milling, homogenization, precipitation, or supercritical fluid processes; (2) aerosolizing a dry powder of aggregates of nanoparticulate benzodiazepine, such as lorazepam, and surface modifier (the aerosolized composition may additionally contain a diluent); or (3) aerosolizing a suspension of a nanoparticulate benzodiazepine, such as lorazepam, aggregates in a non-aqueous propellant. The aggregates of nanoparticulate benzodiazepine, such as lorazepam, and surface stabilizer, which may additionally contain a diluent, can be made in a non-pressurized or a pressurized non-aqueous system. Concentrated aerosol formulations may also be made by such methods.

A. Aqueous Milling to Obtain Nanoparticulate Benzodiazepine Dispersions

In an exemplary aqueous milling process, benzodiazepine, such as lorazepam, particles are dispersed in a liquid dispersion media and mechanical means is applied in the presence of grinding media to reduce the particle size of the benzodiazepine, such as lorazepam, to the desired effective average particle size. The particles can be reduced in size in the presence of one or more surface stabilizers. Alternatively, the particles can be contacted with one or more surface stabilizer either before or after attrition. Other compounds, such as a diluent, can be added to the benzodiazepine, such as lorazepam, and surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

B. Precipitation to Obtain Nanoparticulate Benzodiazepine Compositions

Another method of forming the desired nanoparticle dispersion is by microprecipitation. This is a method of preparing stable dispersions of nanoparticulate benzodiazepine, such as lorazepam, in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example, (1) dissolving the benzodiazepine, such as lorazepam, in a suitable solvent with mixing; (2) adding the formulation from step (1) with mixing to a solution comprising at least one surface stabilizer

to form a clear solution; and (3) precipitating the formulation from step (2) with mixing using an appropriate nonsolvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means. The resultant nanoparticulate benzodiazepine, such as lorazepam, dispersion can be utilized in liquid nebulizers or processed to form a dry powder for use in a DPI or pMDI.

C. Non-Aqueous Non-Pressurized Milling System

In a non-aqueous, non-pressurized milling system, a non-aqueous liquid having a vapor pressure of about 1 atm or less at room temperature and in which the benzodiazepine, such as lorazepam, is essentially insoluble is used as a wet milling media to make a nanoparticulate benzodiazepine, such as lorazepam, composition. In such a process, a slurry of benzodiazepine, such as lorazepam, and surface stabilizer is milled in the non-aqueous media to generate nanoparticulate benzodiazepine, such as lorazepam. Examples of suitable non-aqueous media include ethanol, trichloromonofluoromethane, (CFC-11), and dichlorotetrafluoroethane (CFC-114). An advantage of using CFC-11 is that it can be handled at only marginally cool room temperatures, whereas CFC-114 requires more controlled conditions to avoid evaporation. Upon completion of milling the liquid medium may be removed and recovered under vacuum or heating, resulting in a dry nanoparticulate benzodiazepine, and preferably, lorazepam nanoparticle composition. The dry composition may then be filled into a suitable container and charged with a final propellant. Exemplary final product propellants, which ideally do not contain chlorinated hydrocarbons, include HFA-134a (tetrafluoroethane) and HFA-227 (heptafluoropropane). While non-chlorinated propellants may be preferred for environmental reasons, chlorinated propellants may also be used in this aspect of the invention.

D. Non-Aqueous Pressurized Milling System

In a non-aqueous, pressurized milling system, a non-aqueous liquid media having a vapor pressure significantly greater than 1 atm at room temperature is used in the milling process to make nanoparticulate benzodiazepine, such as lorazepam, compositions. If the milling media is a suitable halogenated hydrocarbon propellant, the resultant dispersion may be filled directly into a suitable pMDI container. Alternately, the milling media can be

removed and recovered under vacuum or heating to yield a dry benzodiazepine, such as lorazepam, nanoparticulate composition. This composition can then be filled into an appropriate container and charged with a suitable propellant for use in a pMDI.

E. Spray-Dried Powder Aerosol Formulations

Spray drying is a process used to obtain a powder comprising nanoparticulate drug particles following particle size reduction of the benzodiazepine, such as lorazepam, in a liquid media. In general, spray-drying is used when the liquid media has a vapor pressure of less than about 1 atm at room temperature. A spray-dryer is a device which allows for liquid evaporation and powder collection. A liquid sample, either a solution or suspension, is fed into a spray nozzle. The nozzle generates droplets of the sample within a range of about 20 to about 100 μm in diameter which are then transported by a carrier gas into a drying chamber. The carrier gas temperature is typically between about 80 and about 200 degrees C. The droplets are subjected to rapid liquid evaporation, leaving behind dry particles which are collected in a special reservoir beneath a cyclone apparatus.

If the liquid sample comprises an aqueous dispersion of a nanoparticulate benzodiazepine, such as lorazepam, and surface stabilizer, the collected product will comprise spherical aggregates of the nanoparticulate benzodiazepine, such as lorazepam. If the liquid sample comprises an aqueous dispersion of nanoparticles in which an inert diluent material was dissolved (such as lactose or mannitol), the collected product will comprise diluent (*e.g.*, lactose or mannitol) particles which comprise embedded nanoparticulate benzodiazepine, such as lorazepam. The final size of the collected product can be controlled and depends on the concentration of nanoparticulate benzodiazepine, such as lorazepam, and/or diluent in the liquid sample, as well as the droplet size produced by the spray-dryer nozzle. For deep lung delivery it is desirable for the collected product size to be less than about 2 microns in diameter, for delivery to the conducting airways it is desirable for the collected product size to be about 2 to about 6 microns in diameter, and for nasal delivery a collected product size of about 5 to about 100 microns is preferred. Collected products may then be used in conventional DPIs for pulmonary or nasal delivery, dispersed in propellants for use in pMDIs, or the particles may be reconstituted in water for use in nebulizers.

In some instances, it may be desirable to add an inert carrier to the spray-dried material to improve the metering properties of the final product. This may especially be the case when the spray dried powder is very small (less than about 5 microns) or when the intended dose is extremely small, whereby dose metering becomes difficult. In general, such carrier particles (also known as bulking agents) are too large to be delivered to the lung and simply impact the mouth and throat and are swallowed. Such carriers typically consist of sugars such as lactose, mannitol, or trehalose. Other inert materials, including polysaccharides and cellulosics, may also be useful as carriers.

Spray-dried powders comprising nanoparticulate benzodiazepine, such as lorazepam, may used in conventional DPIs, dispersed in propellants for use in pMDIs, or reconstituted in a liquid media for use with nebulizers.

F. Freeze-Dried Nanoparticulate Compositions

For a benzodiazepine that is denatured or destabilized by heat, such as having a low melting point (*i.e.*, about 70 to about 150 degrees C.), or, for example, biologics, sublimation is preferred over evaporation to obtain a dry powder nanoparticulate composition. This is because sublimation avoids the high process temperatures associated with spray-drying. In addition, sublimation, also known as freeze-drying or lyophilization, can increase the shelf stability of a benzodiazepine, particularly for biological products. Freeze-dried particles can also be reconstituted and used in nebulizers. Aggregates of freeze-dried nanoparticulate benzodiazepine, such as lorazepam, can be blended with either dry powder intermediates or used alone in DPIs and pMDIs for either nasal or pulmonary delivery.

Sublimation involves freezing the product and subjecting the sample to strong vacuum conditions. This allows for the formed ice to be transformed directly from a solid state to a vapor state. Such a process is highly efficient and, therefore, provides greater yields than spray-drying. The resultant freeze-dried product contains benzodiazepine, such as lorazepam, and at least one surface stabilizer. The benzodiazepine, such as lorazepam, is typically present in an aggregated state and can be used for inhalation alone (either pulmonary or nasal), in conjunction with diluent materials (lactose, mannitol, *etc.*), in DPIs or pMDIs, or reconstituted for use in a nebulizer.

IV

IV. Method of Treatment

In human therapy, it is important to provide a benzodiazepine, such as lorazepam, dosage form that delivers the required therapeutic amount of the drug *in vivo*, and that renders the drug bioavailable in a constant manner. Thus, another aspect of the present invention provides a method of treating a mammal, including a human, requiring status epilepticus treatment, irritable bowel syndrome treatment, sleep induction, acute psychosis, or pre-anesthesia medication using a nanoparticulate benzodiazepine, such as lorazepam, formulation of the invention. Such methods comprise the step of administering to a subject a therapeutically effective amount of a nanoparticulate benzodiazepine, such as lorazepam, formulation of the present invention. In one embodiment, the nanoparticulate benzodiazepine, such as lorazepam, formulation is an injectable formulation. In another embodiment, the nanoparticulate benzodiazepine, such as lorazepam, formulation is an aerosol formulation. Particularly advantageous features of the present invention include that the pharmaceutical formulation of the invention does not require the presence of polyethylene glycol and propylene glycol as stabilizers. In addition, the injectable formulation of the invention can provide a high lorazepam concentration in a small volume to be injected. A general protocol for injectable administration comprises a bolus injection of a benzodiazepine, such as lorazepam, with one continuous fast injection, rather than a slow infusion of the drug.

The benzodiazepine, such as lorazepam, compositions of the invention can be used for pulmonary or intranasal delivery. Pulmonary and intranasal delivery are particularly useful for the delivery of benzodiazepine, and preferably, lorazepam which is difficult to deliver by other routes of administration. Pulmonary or intranasal delivery is effective both for systemic delivery and for localized delivery to treat diseases of the air cavities.

The aerosols of the present invention, both aqueous and dry powder, are particularly useful in the treatment of respiratory-related illnesses such as asthma, emphysema, respiratory distress syndrome, chronic bronchitis, cystic fibrosis, chronic obstructive pulmonary disease, organ-transplant rejection, tuberculosis and other infections of the lung, fugal infections, respiratory illness associated with acquired immune deficiency syndrome, oncology, and systemic administration of an anti-emetic, analgesic, cardiovascular agent, *etc.*

The formulations and method result in improved lung and nasal surface area coverage by the administered benzodiazepine, such as lorazepam.

In addition, the aerosols of the invention, both aqueous and dry powder, can be used in a method for diagnostic imaging. Such a method comprises administering to the body of a test subject in need of a diagnostic image an effective contrast-producing amount of the nanoparticulate aerosol diagnostic image contrast composition. Thereafter, at least a portion of the body containing the administered contrast agent is exposed to x-rays or a magnetic field to produce an x-ray or magnetic resonance image pattern corresponding to the presence of the contrast agent. The image pattern can then be visualized.

"Therapeutically effective amount" is used herein with respect to a drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that 'therapeutically effective amount,' administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a "therapeutically effective amount" by those skilled in the art. "Therapeutically effective amount" also includes an amount that is effective for prophylaxis. It is to be further understood that drug dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

One of ordinary skill will appreciate that effective amounts of a benzodiazepine, such as lorazepam, can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of benzodiazepine, such as lorazepam, in the aerosol and injectable compositions of the invention may be varied to obtain an amount of benzodiazepine, such as lorazepam, that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered benzodiazepine, such as lorazepam,, the desired duration of treatment, and other factors.

Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or

composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, methods, and uses of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

The following prophetic example is given to illustrate the present invention. It should be understood, however, that the spirit and scope of the invention is not to be limited to the specific conditions or details described in this example but should only be limited by the scope of the claims that follow. All references identified herein, including U.S. patents, are hereby expressly incorporated by reference.

Example 1

The purpose of this example was to prepare a nanoparticulate benzodiazepine, such as lorazepam, formulation.

An aqueous dispersion of 10% (w/w) lorazepam, combined with 2% (w/w) polyvinylpyrrolidone (PVP) K29/32 and 0.05% (w/w) dioctylsulfosuccinate (DOSS), could be milled in a 10 ml chamber of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, PA; see e.g., U.S. Patent No. 6,431,478), along with 500 micron PolyMill® attrition media (Dow Chemical Co.) (89% media load). In an exemplary process, the mixture could be milled at a speed of 2500 rpms for 60 minutes.

Following milling, the particle size of the milled lorazepam particles can be measured, in deionized distilled water, using a Horiba LA 910 particle size analyzer. The initial mean milled lorazepam particle size is expected to be less than 2000 nm.

We Claim:

1. A nanoparticulate composition comprising:

(a) a benzodiazepine having an effective average particle size of less than about 2000 nm, wherein the benzodiazepine is selected from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, pharmaceutically acceptable salts and esters thereof, and mixtures thereof; and

(b) at least one surface stabilizer.

2. The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of a nonionic surfactant, an ionic surfactant, a cationic surfactant, an anionic surfactant, and a zwitterionic surfactant.

3. The composition of claim 1 or claim 2, wherein the surface stabilizer is selected from the group consisting of hypromellose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin, dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, tyloxapol, poloxamers, poloxamines, Tetronic 1508®, an alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), Crodestas SL-40® (Croda, Inc.); and SA9OHCO, decanoyl-N-methylglucamide; n-decyl (-D-glucopyranoside; n-decyl (-D-maltopyranoside; n-dodecyl (-D-glucopyranoside; n-dodecyl (-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-(-D-glucopyranoside; n-heptyl (-D-thioglucoside; n-hexyl (-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl (-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-(-D-glucopyranoside; octyl (-D-thioglucopyranoside; PEG-

phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, cationic polymers, cationic biopolymers, cationic polysaccharides, cationic cellulosics, cationic alginates, cationic phospholipids, cationic nonpolymeric compounds, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide, hexyldesyltrimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, cationic lipids, sulfonium, phosphonium, quarternary ammonium compounds, stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium bromide, C12-15dimethyl hydroxyethyl ammonium chloride, C12-15dimethyl hydroxyethyl ammonium bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulfate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)4 ammonium chloride, lauryl dimethyl (ethenoxy)4 ammonium bromide, N-alkyl (C12-18)dimethylbenzyl ammonium chloride, N-alkyl (C14-18)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C12-14) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C12-14) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C12, C15, C17 trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride, dimethyl ammonium chlorides, alkyldimethylammonium

halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL, ALKAQUAT, alkyl pyridinium salts, amines, alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, vinyl pyridine, amine salts, lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, alkylimidazolium salt, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

4. The composition of any one of claims 1 to 3, wherein the nanoparticulate benzodiazepine particles have an effective average particle size selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

5. The composition of any one of claims 1 to 4, wherein the composition is formulated into an aerosol of an aqueous dispersion of the composition of claim 1, wherein essentially each droplet of the aerosol comprises at least one nanoparticulate benzodiazepine particle, wherein:

(a) the benzodiazepine has a solubility in the aqueous dispersion of less than about 10 mg/mL; and

(b) the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 100 microns.

6. The aerosol composition of claim 5, wherein the benzodiazepine is present in a concentration selected from the group consisting of from about 0.05 mg/mL up to about 600 mg/mL, about 10 mg/mL or more, about 100 mg/mL or more, about 200 mg/mL or more, about 400 mg/mL or more, and about 600 mg/mL.

7. The aerosol composition of claim 5 or claim 6, wherein the composition is suitable for administration of the benzodiazepine dosage in about 15 seconds or less.

8. The aerosol composition of any one of claims 5 to 7, wherein the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) selected from the group consisting of about 2 to about 10 microns, about 2 to about 6 microns, less than about 2 microns, about 5 to about 100 microns, and about 30 to about 60 microns.

9. The composition of any one of claims 1 to 4, formulated into an injectable composition.

10. The injectable composition of claim 9, comprising as a surface stabilizer a povidone polymer.

11. The injectable composition of claim 10, wherein the povidone polymer has a molecular weight of about 40,000 daltons or less.

12. The injectable composition of any one of claims 9 to 11, wherein the effective average particle size of the benzodiazepine particles is less than about 600 nm.

13. A method of treating a subject in need comprising administering to the subject a nanoparticulate benzodiazepine composition comprising:

(a) a benzodiazepine having an effective average particle size of less than about 2000 nm, wherein the benzodiazepine is selected from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam,

nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, pharmaceutically acceptable salts and esters thereof, and mixtures thereof; and

(b) at least one surface stabilizer.

14. The method of claim 13, wherein the surface stabilizer is selected from the group consisting of a nonionic surfactant, an ionic surfactant, a cationic surfactant, an anionic surfactant, and a zwitterionic surfactant.

15. The method of claim 13 or claim 14, wherein the surface stabilizer is selected from the group consisting of hypromellose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin, dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, tyloxapol, poloxamers, poloxamines, Tetronic 1508®, an alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), Crodestas SL-40® (Croda, Inc.); and SA9OHCO, decanoyl-N-methylglucamide; n-decyl (-D-glucopyranoside; n-decyl (-D-maltopyranoside; n-dodecyl (-D-glucopyranoside; n-dodecyl (-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-(-D-glucopyranoside; n-heptyl (-D-thioglucoside; n-hexyl (-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl (-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-(-D-glucopyranoside; octyl (-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, cationic polymers, cationic biopolymers, cationic polysaccharides, cationic cellulosics, cationic alginates, cationic phospholipids, cationic nonpolymeric compounds, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide

bromide, hexyldesyltrimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, cationic lipids, sulfonium, phosphonium, quarternary ammonium compounds, stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium bromide, C12-15dimethyl hydroxyethyl ammonium chloride, C12-15dimethyl hydroxyethyl ammonium bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulfate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)4 ammonium chloride, lauryl dimethyl (ethenoxy)4 ammonium bromide, N-alkyl (C12-18)dimethylbenzyl ammonium chloride, N-alkyl (C14-18)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C12-14) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C12-14) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C12, C15, C17 trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride, dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL, ALKAQUAT, alkyl pyridinium salts, amines,

alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, vinyl pyridine, amine salts, lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, alkylimidazolium salt, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

16. The method of any one of claims 13 to 15, wherein the nanoparticulate benzodiazepine particles have an effective average particle size selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

17. The method of any one of claims 13 to 16, wherein the composition is formulated into an aerosol of an aqueous dispersion of the composition of claim 1, wherein essentially each droplet of the aerosol comprises at least one nanoparticulate benzodiazepine particle, wherein:

(a) the benzodiazepine has a solubility in the aqueous dispersion of less than about 10 mg/mL; and

(b) the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 100 microns.

18. The method of claim 17, wherein the benzodiazepine is present in a concentration selected from the group consisting of from about 0.05 mg/mL up to about 600 mg/mL, about 10 mg/mL or more, about 100 mg/mL or more, about 200 mg/mL or more, about 400 mg/mL or more, and about 600 mg/mL.

19. The method of claim 17 or claim 18, wherein the composition is suitable for administration of the benzodiazepine dosage in about 15 seconds or less.

20. The method of any one of claims 17 to 19, wherein the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) selected from the group consisting of about 2 to about 10 microns, about 2 to about 6 microns, less than about 2 microns, about 5 to about 100 microns, and about 30 to about 60 microns.

21. The method of any one of claims 13 to 16, wherein the composition is formulated into an injectable dosage form.

22. The method of claim 21, comprising as a surface stabilizer a povidone polymer.

23. The method of claim 22, wherein the povidone polymer has a molecular weight of about 40,000 daltons or less.

24. The method of any one of claims 21 to 23, wherein the effective average particle size of the benzodiazepine particles is less than about 600 nm.

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(54) Title: TOPICAL BIOADHESIVE FORMULATIONS

(57) Abstract: The present invention relates to topical bioadhesive formulations comprising low viscosity, non-liquid crystalline, mixtures of: a) at least one neutral diacyl lipid and/or at least one tocopherol; b) at least one phospholipid; c) at least one biocompatible, oxygen containing, low viscosity organic solvent; wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture and wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid. The invention additionally relates to a method of delivery of an active agent comprising administration of a preformulation of the invention, a method of treatment comprising administration of a preformulation of the invention and the use of a preformulation of the invention in a method for the manufacture of a medicament.

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Topical Bioadhesive Formulations

The present invention relates to formulation precursors (pre-formulations) for the *in situ* generation of controlled release lipid compositions. In particular, the invention relates to pre-formulations in the form of low viscosity mixtures (such as molecular solutions) of amphiphilic components and optionally at least one bioactive agent which undergo at least one phase transition upon exposure to aqueous fluids, such as body fluids, thereby forming a bioadhesive matrix.

Many bioactive agents including pharmaceuticals, nutrients, vitamins and so forth have a "functional window". That is to say that there is a range of concentrations over which these agents can be observed to provide some biological effect. Where the concentration in the appropriate part of the body (e.g. locally or as demonstrated by serum concentration) falls below a certain level, no beneficial effect can be attributed to the agent. Similarly, there is generally an upper concentration level above which no further benefit is derived by increasing the concentration. In some cases increasing the concentration above a particular level results in undesirable or even dangerous effects.

Some bioactive agents have a long biological half-life and/or a wide functional window and thus may be administered occasionally, maintaining a functional biological concentration over a substantial period of time (e.g. 6 hours to several days). In other cases the rate of clearance is high and/or the functional window is narrow and thus to maintain a biological concentration within this window regular (or even continuous) doses of a small amount are required. This can be particularly difficult where non-oral routes of administration (e.g. parenteral administration) are desirable. Furthermore, in some circumstances, such as in the fitting of implants (e.g. joint replacements or oral implants) the area of desired action may not remain accessible for repeated administration. In such cases a single administration must provide active agent at a therapeutic level over the whole period during which activity is needed.

Similarly, where the effect of a bioactive agent is required locally, it may be difficulty or undesirable to administer sufficient of that agent to achieve the effective level throughout the body of the subject. This may be due to undesirable effects of the agent itself (e.g. for steroid anti-inflammatory), or may be because the agent is

used to locally counter an undesirable feature of a systemic treatment (such as chemotherapy) but would undermine that primary treatment if used broadly.

A major difficulty with topically applied compositions is, however, their duration of action. These composition are, by their nature, applied to body surfaces which may be prone to abrasion, washing and flushing with bodily or applied fluids, such as tears, sweat or mucous. A particularly difficult situation for the use of topical preparations is in body cavities, such as the GI tract. This is because such cavities are typically coated in a mucous membrane which is non-adherent and turned over rapidly. In addition, thick, viscous preparations can be difficult to apply effectively to the mouth/throat or rectally to the lower GI tract and are difficult to manufacture due to high viscosity preventing sterile filtration. Existing compositions, however, are typically either low viscosity and short-lived or longer lived at the price of high viscosity. Furthermore, existing topical compositions are often capable of containing only a low level of active agent, due to poor compatibility between the base composition and the active agent. This results in a composition which rapidly loses effectiveness as it begins to dissipate from the site of action. It would therefore be of considerable value to provide topical formulations which were bioadherant, even to mucousal surfaces, and which could be formulated as a low viscosity preformulation which would become adherent upon contact with the desired surface. Furthermore it would be a significant advantage if the formulation was protective, non-irritant, and showed reasonable resistance to wear and exposure to aqueous ambient.

The present inventors have now established that by providing a pre-formulation comprising certain amphiphilic components, at least one bioactive agent and a biologically tolerable solvent, especially in a low viscosity phase such as molecular solution, the pre-formulation may be generated addressing many of the shortfalls of previous formulations. In particular, the pre-formulation is easy to manufacture, may be sterile-filtered, it has low viscosity (allowing easy and rapid administration), and/or allows a high level of bioactive agent to be incorporated (thus allowing a smaller amount of composition to be used and/or providing a long effective lifetime). The compositions are formed from materials that are non-toxic, biotolerable and biodegradable. They are suited for application at sensitive areas such as sensitive parts of the body and sites of inflammation, and comprising lipids which are part of natural protective surface linings, e.g. phospholipids. Furthermore,

due to the combination of bioadhesive properties and extremely low aqueous solubility of main constituents the compositions, the applied composition of the invention are stable to exposure to aqueous media and wear. The composition furthermore provides sustained release of a wide range of actives with a tuneable window of duration. The pre-formulation is therefore highly suitable for the formation of depot compositions following non-parenteral (e.g. topical) administration to body cavities and/or surfaces of the body or elsewhere and are formed from lipids which may provide inherent benefits in themselves in addition to forming highly effective carriers and topical depots for active agents.

In a first aspect, the present invention thus provides a pre-formulation comprising a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, (preferably oxygen containing) organic solvent;

optionally including at least one bioactive agent which is dissolved or dispersed in the low viscosity mixture, wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid and/or body surface.

Generally, the aqueous fluid will be a body fluid such as fluid from a mucosal surface, tears, sweat, saliva, gastro-intestinal fluid, extra-vascular fluid, extracellular fluid, interstitial fluid or plasma, and the pre-formulation will form a liquid crystalline phase structure when contacted with a body surface, area or cavity (e.g. *in vivo*) upon contact with the aqueous body fluid. The pre-formulation of the invention will generally not contain any significant quantity of water prior to administration.

In a second aspect of the invention, there is also provided a method of delivery of a bioactive agent to a human or non-human animal (preferably mammalian) body, this method comprising topically administering a pre-formulation comprising a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, (preferably oxygen containing) organic solvent;

and including at least one bioactive agent dissolved or dispersed in the low viscosity mixture; whereby to form at least one liquid crystalline phase structure upon contact with an aqueous fluid at a body surface following administration. Preferably, the pre-formulation administered in such a method is a pre-formulation of the invention as described herein.

The method of administration suitable for the above method of the invention will be a method appropriate for the condition to be treated and the bioactive agent used. A bioadhesive non-parenteral (e.g. topical) depot composition may be formed by administration to the surface of skin, mucous membranes and/or nails, to opthalmological, nasal, oral or internal surfaces or to cavities such as nasal, rectal, vaginal or buccal cavities, the periodontal pocket or cavities formed following extraction of a natural or implanted structure or prior to insertion of an implant (e.g a joint, stent, cosmetic implant, tooth, tooth filling or other implant).

In a further aspect, the present invention also provides a method for the preparation of a liquid crystalline composition (especially a depot composition) comprising exposing a pre-formulation comprising a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible (preferably oxygen containing), organic solvent;

and optionally at least one bioactive agent dissolved or dispersed in the low viscosity mixture, to an aqueous fluid at a body surface. Preferably the pre-formulation administered is a pre-formulation of the present invention as described herein. The exposure to a fluid may be internally within at an internal surface of a body cavity, or may be at an external body surface such as a skin surface, depending upon the nature of the composition and any active agent.

The liquid crystalline composition formed in this method is bioadhesive as described herein.

In a still further aspect the present invention provides a process for the formation of a pre-formulation suitable for the administration of a bioactive agent to a surface of a (preferably mammalian) subject, said process comprising forming a low viscosity mixture of

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible (preferably oxygen containing), organic solvent;

and optionally dissolving or dispersing at least one bioactive agent in the low viscosity mixture, or in at least one of components a, b or c prior to forming the low viscosity mixture. Preferably the pre-formulation so-formed is a formulation of the invention as described herein.

In a yet still further aspect the present invention provides the use of a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible (preferably oxygen containing), organic solvent;

wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture in the manufacture of a pre-formulation for use in the sustained local administration of said active agent, wherein said pre-formulation is capable of forming at least one liquid crystalline phase structure upon contact with an aqueous fluid.

In a further aspect, the present invention provides a method for the treatment of a human or animal subject comprising administration of a composition of the present invention, optionally including an active agent. In this aspect, the method of treatment is in particular a method for the treatment of inflammation and/or irritation, especially at a body surface and/or in a body cavity such as the gastrointestinal tract.

In a still further aspect, the present invention provides for the use of a composition of the present invention in therapy, and in particularly for the use of a composition of the present invention, optionally including an active agent, in the manufacture of a medicament for the treatment of inflammation and/or irritation, especially at a body surface and/or in a body cavity such as the gastrointestinal tract.

The use of non-lamellar phase structures (such as liquid crystalline phases) in the delivery of bioactive agents is now relatively well established. Such structures form when an amphiphilic compound is exposed to a solvent because the amphiphile has both polar and apolar groups which cluster to form polar and apolar regions. These regions can effectively solubilise both polar and apolar compounds. In addition,

many of the structures formed by amphiphiles in polar and/or apolar solvents have a very considerable area of polar/apolar boundary at which other amphiphilic compounds can be adsorbed and stabilised. Amphiphiles can also be formulated to protect active agents, to at least some extent, from aggressive biological environments, including enzymes, and thereby provide advantageous control over active agent stability and release.

The formation of non-lamellar regions in the amphiphile/water, amphiphile/oil and amphiphile/oil/water phase diagrams is a well known phenomenon. Such phases include liquid crystalline phases such as the cubic P, cubic D, cubic G and hexagonal phases, which are fluid at the molecular level but show significant long-range order, and the L3 phase which comprises a multiply interconnected bi-continuous network of bilayer sheets which are non-lamellar but lack the long-range order of the liquid crystalline phases. Depending upon their curvature of the amphiphile sheets, these phases may be described as normal (mean curvature towards the apolar region) or reversed (mean curvature towards the polar region).

The non-lamellar liquid crystalline and L3 phases are thermodynamically stable systems. That is to say, they are not simply a meta-stable state that will separate and/or reform into layers, lamellar phases or the like, but are the stable thermodynamic form of the lipid/solvent mixture.

As used herein, the term "low viscosity mixture" is used to indicate a mixture which may be readily administered to a subject and in particular readily administered by means of a standard syringe and needle or pump/aerosol spray arrangement. This may be indicated, for example by the ability to be dispensed from a 1 ml disposable syringe through a 22 awg (or a 23 gauge) needle by manual pressure. In a particularly preferred embodiment, the low viscosity mixture should be a mixture capable of passing through a standard sterile filtration membrane such as a 0.22 μm syringe filter. In other preferred embodiments, a similar functional definition of a suitable viscosity can be defined as the viscosity of a pre-formulation that can be sprayed using a compression pump or pressurized spray device using conventional spray equipment. A typical range of suitable viscosities would be, for example, 0.1 to 5000 mPas, preferably 1 to 1000 mPas at 20°C.

It has been observed that by the addition of small amounts of low viscosity solvent, as indicated herein, a very significant change in viscosity can be provided. As indicated in Figure 2, for example, the addition of only 5% solvent can reduce viscosity 100-fold and addition of 10% may reduce the viscosity up to 10,000 fold. In order to achieve this non-linear, synergistic effect, in lowering viscosity it is important that a solvent of appropriately low viscosity and suitable polarity be employed. Such solvents include those described herein infra.

Particularly preferred examples of low viscosity mixtures are molecular solutions and/or isotropic phases such as L2 and/or L3 phases. As describe above, the L3 is a non-lamellar phase of interconnected sheets which has some phase structure but lacks the long-range order of a liquid crystalline phase. Unlike liquid crystalline phases, which are generally highly viscous, L3 phases are of lower viscosity. Obviously, mixtures of L3 phase and molecular solution and/or particles of L3 phase suspended in a bulk molecular solution of one or more components are also suitable. The L2 phase is the so-called "reversed micellar" phase or microemulsion. Most preferred low viscosity mixtures are molecular solutions, L3 phases and mixtures thereof. L2 phases are less preferred, except in the case of swollen L_2 phases as described below.

The present invention provides a pre-formulation comprising components a, b, c and optionally and preferably at least one bioactive agent as indicated herein. One of the considerable advantages of the pre-formulations of the invention is that components a and b may be formulated in a wide range of proportions. In particular, it is possible to prepare and use pre-formulations of the present invention having a much greater proportion of phospholipid to neutral, diacyl lipid and/or tocopherol than was previously achievable without risking phase separation and/or unacceptably high viscosities in the pre-formulation. The weight ratios of components a:b may thus be anything from 5:95 right up to 95:5. Preferred ratios would generally be from 90:10 to 20:80 and more preferably from 85:15 to 30:70. In one preferred embodiment of the invention, there is a greater proportion of component b than component a. That is, the weight ratio a:b is below 50:50, e.g. 48:52 to 2:98, preferably, 40:60 to 10:90 and more preferably 35:65 to 20:80.

The amount of component c in the pre-formulations of the invention will be at least sufficient to provide a low viscosity mixture (e.g. a molecular solution, see above)

of components a, b and c and will be easily determined for any particular combination of components by standard methods. The phase behaviour itself may be analysed by techniques such as visual observation in combination with polarized light microscopy, nuclear magnetic resonance, and cryo-transmission electron microscopy (cryo-TEM) to look for solutions, L2 or L3phases, or liquid crystalline phases. Viscosity may be measured directly by standard means. As described above, an appropriate practical viscosity is that which can effectively be syringed and particularly sterile filtered and/or sprayed from a pump or pressurised spray. This will be assessed easily as indicated herein. The maximum amount of component c to be included will depend upon the exact application of the pre-formulation but generally the desired properties will be provided by any amount forming a low viscosity mixture (e.g. a molecular solution, see above) and/or a solution with sufficiently low viscosity.

Since the administration of unnecessarily large amounts of solvent to a subject is generally undesirable the amount of component c may, in one embodiment, be limited to no more than ten times (e.g. three times) the minimum amount required to form a low viscosity mixture, preferably no more than five times and most preferably no more than twice this amount.

Higher proportions of solvent may also be used for the non-parenteral (e.g. topical) applications of the invention, however, especially when applied to external body surfaces, where the solvent will be lost by evaporation rather than absorbed into the body. For such applications up to 100 times the minimum amount of solvent may be used (e.g. up to 95% by weight of the composition, preferably up to 80% by weight and more preferably up to 50% by weight), especially where a very thin layer of the resulting non-parenteral depot is desired.

Where the compositions of the invention are formulated as aerosol spray compositions (e.g. for topical or delivery of an active), the composition may also comprise a propellant. Such compositions may also include a high proportion of solvent component c), as considered above, since much of the solvent will evaporate when the composition is dispensed, particularly under the influence of the propellant.

Suitable propellants are volatile compounds which will mix with the composition of the invention under the pressure of the spray dispenser, without generating high

viscosity mixtures. They should evidently have acceptable biocompatibility. Suitable propellants will readily be identified by simple testing and examples include hydrocarbons (especially C_1 to C_4 hydrocarbons), carbon dioxide and nitrogen. Volatile hydrofluorocarbons such as HFCs 134, 134a, 227ea and/or 152a may also be suitable.

As a general guide, the weight of component c will typically be around 0.5 to 50% of the total weight of the a-b-c solution. This proportion may be limited to 2 to 30% or 5 to 20% by weight. As indicated above; however, in case of a spray composition, especially with a propellant, the amount of c may exceed 50%.

The formulations of the invention may additionally contain small proportions of other agent, such as polymers which are soluble in the precursor. Such polymers may act as a reinforcement of the swollen liquid crystalline phase so that a film attached to a mucosal surface is more strongly attached. A "reinforcement" along the same principle could also be obtained by soaking a matrix (paper, polymer net, or similar) with the precursor. Upon applying this "patch" to the skin the formulation may by itself act as the glue. In contrast to conventional adhesives for coating damaged tissue, whoever, the formulations of the invention are adhesive even to mucous membranes and are not irritant. In many cases, they are in fact soothing in themselves, as described herein, and may contain suitable active agent.

Component "a" as indicated herein is a neutral lipid component comprising a polar "head" group and also non-polar "tail" groups. Generally the head and tail portions of the lipid will be joined by an ester moiety but this attachment may be by means of an ether, an amide, a carbon-carbon bond or other attachment. Preferred polar head groups are non-ionic and include polyols such as glycerol, diglycerol and sugar moieties (such as inositol and glucosyl based moieties); and esters of polyols, such as acetate or succinate esters. Preferred polar groups are glycerol and diglycerol, especially glycerol.

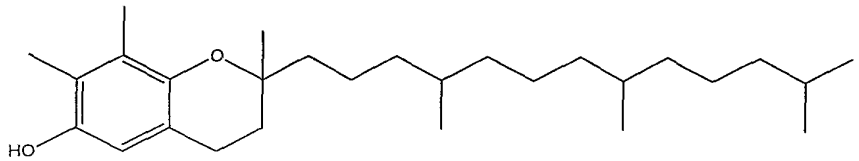
In one preferred aspect, component a is a diacyl lipid in that it has two non-polar "tail" groups. This is generally preferable to the use of mono-acyl ("lyso") lipids because these are typically less well tolerated *in vivo*. The two non-polar groups may have the same or a differing number of carbon atoms and may each independently be saturated or unsaturated. Examples of non-polar groups include

C_6-C_{32} alkyl and alkenyl groups, which are typically present as the esters of long chain carboxylic acids. These are often described by reference to the number of carbon atoms and the number of unsaturations in the carbon chain. Thus, CX:Z indicates a hydrocarbon chain having X carbon atoms and Z unsaturations. Examples particularly include caproyl (C6:0), capryloyl (C8:0), capryl (C10:0), lauroyl (C12:0), myristoyl (C14:0), palmitoyl (C16:0), phytanoly (C16:0), palmitoleoyl (C16:1), stearoyl (C18:0), oleoyl (C18:1), elaidoyl (C18:1), linoleoyl (C18:2), linolenoyl (C18:3), arachidonoyl (C20:4), behenoyl (C22:0) and lignoceroyl (C24:9) groups. Thus, typical non-polar chains are based on the fatty acids of natural ester lipids, including caproic, caprylic, capric, lauric, myristic, palmitic, phytanic, palmitolic, stearic, oleic, elaidic, linoleic, linolenic, arachidonic, behenic or lignoceric acids, or the corresponding alcohols. Preferable non-polar chains are palmitic, stearic, oleic and linoleic acids, particularly oleic acid.

The diacyl lipid, when used as all or part of component "a", may be synthetic or may be derived from a purified and/or chemically modified natural sources such as vegetable oils. Mixtures of any number of diacyl lipids may be used as component a. Most preferably this component will include at least a portion of diacyl glycerol (DAG), especially glycerol dioleate (GDO). In one favoured embodiment, component a consists of DAGs. These may be a single DAG or a mixture of DAGs. A highly preferred example is DAG comprising at least 50%, preferably at least 80% and even comprising substantially 100% GDO.

An alternative or additional highly preferred class of compounds for use as all or part of component a are tocopherols. As used herein, the term "a tocopherol" is used to indicate the non-ionic lipid tocopherol, often known as vitamin E, and/or any suitable salts and/or analogues thereof. Suitable analogues will be those providing the phase-behaviour, lack of toxicity, and phase change upon exposure to aqueous fluids, which characterise the compositions of the present invention. Such analogues will generally not form liquid crystalline phase structures as a pure compound in water. The most preferred of the tocopherols is tocopherol itself, having the structure below. Evidently, particularly where this is purified from a natural source, there may be a small proportion of non-tocopherol "contaminant" but this will not be sufficient to alter the advantageous phase-behaviour or lack of toxicity. Typically, a tocopherol will contain no more than 10% of non-tocopherol-

analogue compounds, preferably no more than 5% and most preferably no more than 2% by weight.



Tocopherol

In a further advantageous embodiment of the invention, component a) consists essentially of tocopherols, in particular tocopherol as shown above.

A preferred combination of constituents for component a) is a mixture of at least one DAG (e.g. GDO) with at least one tocopherol. Such mixtures include 2:98 to 98:2 by weight tocopherol:GDO, e.g.10:90 to 90:10 tocopherol:GDO and especially 20:80 to 80:20 of these compounds. Similar mixtures of tocopherol with other DAGs are also suitable.

Component "b" in the present invention is at least one phospholipid. As with component a, this component comprises a polar head group and at least one non-polar tail group. The difference between components a and b lies principally in the polar group. The non-polar portions may thus suitably be derived from the fatty acids or corresponding alcohols considered above for component a. It will typically be the case that the phospholipid will contain two non-polar groups, although one or more constituents of this component may have one non-polar moiety. Where more than one non-polar group is present these may be the same or different.

Preferred phospholipid polar "head" groups include phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol. Most preferred is phosphatidylcholine (PC). In a preferred embodiment, component b) thus consists of at least 50% PC, preferably at least 70% PC and most preferably at least 80% PC. Component b) may consist essentially of PC.

The phospholipid portion, even more suitably than any diacyl lipid portion, may be derived from a natural source. Suitable sources of phospholipids include egg, heart (e.g. bovine), brain, liver (e.g. bovine) and plant sources including soybean. Such

sources may provide one or more constituents of component b, which may comprise any mixture of phospholipids.

Since the pre-formulations of the invention may be administered to a subject for the controlled release of an active agent, it is preferable that the components a and b are biocompatible. In this regard, it is preferable to use, for example, diacyl lipids and phospholipids rather than mono-acyl (lyso) compounds. A notable exception to this is tocopherol, as described above. Although having only one alkyl chain, this is not a "lyso" lipid in the convention sense. The nature of tocopherol as a well tolerated essential vitamin evidently makes it highly suitable in biocompatibility.

The nature of the compositions of the invention as being suitable for soothing and healing irritation and inflammation at a body surface makes the need to well tolerated lipids highly important. In particular, the lipid composition will be present at high concentration in contact with tissue which may be damaged or inflamed. As a result, the very high level of compatibility of, for example, the diacyl lipids of the present invention, is significant in comparison with less well tolerated components such as mono-acyl lipids.

It is furthermore most preferable that the lipids and phospholipids of components a and b are naturally occurring (whether they are derived from a natural source or are of synthetic origin). Naturally occurring lipids tend to cause lesser amounts of inflammation and reaction from the body of the subject. Not only is this more comfortable for the subject but it may increase the residence time of the resulting depot composition, since less immune system activity is recruited to the administration site and there is less tendency for the subject to disturb the area. In certain cases it may, however, be desirable to include a portion of a non-naturally-occurring lipid in components a and/or b. This might be, for example an "ether lipid" in which the head and tail groups are joined by an ether bond rather than an ester. Such non-naturally-occurring lipids may be used, for example, to alter the rate of degradation of the resulting depot-composition by having a greater or lesser solubility or vulnerability to breakdown mechanisms present at the site of active agent release. Although all proportions fall within the scope of the present invention, generally, at least 50% of each of components a and b will be naturally occurring lipids. This will preferably be at least 75% and may be up to substantially 100%.

Two particularly preferred combinations of components a and b are GDO with PC and tocopherol with PC, especially in the region 30-90wt% GDO/tocopherol, 10-60 wt% PC and 1-30% solvent (especially ethanol, NMP and/or ispropanol). Most preferred combinations are 35-60% (e.g. 40-55) GDO with 20 to 50% (e.g. 25 to 45%) PC. These are especially suitable in combination with ethanol, particularly at 5 to 25% (e.g. 7 to 19%).

In addition to amphiphilic components a and b, the pre-formulations of the invention may also contain additional amphiphilic components at relatively low levels. In one embodiment of the invention, the pre-formulation contains up to 10% (by weight of components a and b) of a charged amphiphile, particularly an anionic amphiphile such as a fatty acid. Preferred fatty acids for this purpose include caproic, caprylic, capric, lauric, myristic, palmitic, phytanic, palmitolic, stearic, oleic, elaidic, linoleic, linolenic, arachidonic, behenic or lignoceric acids, or the corresponding alcohols. Preferable fatty acids are palmitic, stearic, oleic and linoleic acids, particularly oleic acid. It is particularly advantageous that this component be used in combination with a cationic peptide active agent (see below). The combination of an anionic lipid and a cationic peptide is believed to provide a sustained release composition of particular value. This may in part be due to increased protection of the peptide from the degradative enzymes present in vivo.

Component "c" of the pre-formulations of the invention is an oxygen containing organic solvent. Since the pre-formulation is to generate a depot/bioadhesive composition following administration (e.g. *in vivo),* upon contact with an aqueous fluid, it is desirable that this solvent be tolerable to the subject and be capable of mixing with the aqueous fluid, and/or diffusing or dissolving out of the pre-formulation into the aqueous fluid. Solvents having at least moderate water solubility are thus preferred.

A special case is where the composition of the invention is formulated as aerosol spray compositions. Here component c may be seen to comprise the propellant, having a low aqueous solubility. All mixing ratios from essentially pure propellant to mainly oxygen containing organic solvents may be considered. When dispensing the formulation the propellant will to a large degree evaporate. When c mainly constitutes propellant an instant increase of viscosity may be observed after spraying

the formulation. This is due to rapid evaporation of the propellant and may have the advantage of a more effective initial retention at the application site, and the potential disadvantage that the formulation has a low viscosity during "curing" (uptake of water and phase transformation to a liquid crystalline phase with high viscosity) is circumvented.

In a preferred version, the solvent is such that a relatively small addition to the composition comprising a and b, i.e. below 20%, or more preferably below 16%, e.g. up to 10% or even below give a large viscosity reductions of one order of magnitude or more., As described herein, the addition of 10% solvent can give a reduction of two, three or even four orders of magnitude in viscosity over the solvent-free composition, even if that composition is a solution or L_2 phase containing no solvent, or an unsuitable solvent such as water (subject to the special case considered below), or glycerol.

Typical solvents suitable for use as component c include at least one solvent selected from alcohols, ketones, esters (including lactones), ethers, amides and sulphoxides. Examples of suitable alcohols include ethanol, isopropanol and glycerol formal. Monools are preferred to diols and polyols. Where diols or polyols are used, this is preferably in combination with an at least equal amount of monool or other preferred solvent. Examples of ketones include acetone, n-methyl pyrrolidone (NMP), 2-pyrrolidone, and propylene carbonate. Suitable ethers include diethylether, glycofurol, diethylene glycol monoethyl ether, dimethylisobarbide, and polyethylene glycols. Suitable esters include ethyl acetate and isopropyl acetate and dimethyl sulphide is as suitable sulphide solvent. Suitable amides and sulphoxides include dimethylacetamide (DMA) and dimethylsulphoxide (DMSO), respectively. Less preferred solvents include dimethyl isosorbide, tetrahydrofurfuryl alcohol, diglyme and ethyl lactate. The most preferred solvent comprises ethanol and in particular consists of at least 80% ethanol, preferably at least 90% ethanol.

Since the pre-formulations are to be administered to a living subject, it is necessary that the solvent component c is sufficiently biocompatible. The degree of this biocompatibility will depend upon the application method and since component c may be any mixture of solvents, a certain amount of a solvent that would not be acceptable in large quantities may evidently be present. Overall, however, the solvent or mixture forming component c must not provoke unacceptable reactions

from the subject upon administration. Generally such solvents will be hydrocarbons or preferably oxygen containing hydrocarbons, both optionally with other substituents such as nitrogen containing groups. It is preferable that little or none of component c contains halogen substituted hydrocarbons since these tend to have lower biocompatibility. Where a portion of halogenated solvent such as dichloromethane or chloroform is necessary, this proportion will generally be minimised. Evidently, the range of suitable solvents will be greater in formulations for application to sound, external surfaces than to internal, sensitive and/or damaged surfaces, where only the most biocompatible will typically be acceptable. In addition, in the case of aerosol spray compositions also halogenated hydrocarbons may be considered as propellant, since it will evaporate to a large degree during dispensing.

Component c as used herein may be a single solvent or a mixture of suitable solvents but will generally be of low viscosity. This is important because one of the key aspects of the present invention is that it provides preformulations that are of low viscosity and a primary role of a suitable solvent is to reduce this viscosity. This reduction will be a combination of the effect of the lower viscosity of the solvent and the effect of the molecular interactions between solvent and lipid composition. One observation of the present inventors is that the oxygen-containing solvents of low viscosity described herein have highly advantageous and unexpected molecular interactions with the lipid parts of the composition, thereby providing a non-linear reduction in viscosity with the addition of a small volume of solvent.

The viscosity of the "low viscosity" solvent component c (single solvent or mixture) should typically be no more than 18 mPas at 20°C. This is preferably no more than 15 mPas, more preferably no more than 10 mPas and most preferably no more than 7 mPas at 20°C.

The solvent component c will generally be at least partially lost upon formation of the depot/bioadhesive composition on contact with a surface (e.g. a body surface or the surface of an implant), or diluted by absorption of water from the surrounding air and/or tissue. It is preferable, therefore, that component c be at least to some extent water miscible and/or dispersible and at least should not repel water to the extent that water absorption is prevented. In this respect also, oxygen containing solvents with relatively small numbers of carbon atoms (for example up to 10 carbons,

preferably up to 8 carbons) are preferred. Obviously, where more oxygens are present a solvent will tend to remain soluble in water with a larger number of carbon atoms. The carbon to heteroatom (e.g. N, O, preferably oxygen) ratio will thus often be around 1:1 to 6:1, preferably 2:1 to 4:1. Where a solvent with a ratio outside one of these preferred ranges is used then this will preferably be no more than 75%, preferably no more than 50%, in combination with a preferred solvent (such as ethanol). This may be used, for example to decrease the rate of evaporation of the solvent from the pre-formulation in order to control the rate of liquid crystalline depot formation.

A further advantage of the present pre-formulations is that a higher level of bioactive agent may be incorporated into the system. In particular, by appropriate choice of components a-c (especially c), high levels of active agent may be dissolved or suspended in the pre-formulations. Generally, the lipid components in the absence of water are relatively poorly solubilising but in the presence of water form phases too viscous to administer easily. Higher proportions of bioactive agent may be included by use of appropriate solvents as component c and this level will either dissolve in the depot composition as it forms *in situ* or may form microdrops or microcrystals which will gradually dissolve and release active agent. A suitable choice of solvent will be possible by routine experimentation within the guidelines presented herein. In particular, the present inventors have established that the combination of a low molecular weight alcohol solvent (such as ethanol or isopropanol) with the lipid components of the present invention is unexpectedly effective in solubilising a wide range of drugs and other active molecules.

The pre-formulations of the present invention typically do not contain significant amounts of water. Since it is essentially impossible to remove every trace of water from a lipid composition, this is to be taken as indicating that only such minimal trace of water exists as cannot readily be removed. Such an amount will generally be less than 1% by weight, preferably less that 0.5% by the weight of the pre-formulation. In one preferred aspect, the pre-formulations of the invention do not contain glycerol, ethylene glycol or propylene glycol and contain no more than a trace of water, as just described.

In some cases the composition may contain a trace of water (or a polar solvent with similar properties) such that it forms a rather low viscous L2 (reversed micellar)

phase. This can also help to solubilise certain actives in the formulation, particularly those which are only soluble in water.

There is, however, a certain embodiment of the present invention in which higher proportions of water may be tolerated. This is where water is present as a part of the solvent component in combination with an additional water-miscible component c (single solvent or mixture). In this embodiment, up to 10 wt% water may be present providing that at least 3 wt%, preferably at least 5% and more preferably at least 7 wt% component c is also present, that component c is water miscible, and that the resulting preformulation remains non-viscous and thus does not form a liquid crystalline phase. Generally there will be a greater amount of component c) by weight than the weight of water included in the preformulation. Most suitable solvents of use with water in this aspect of the invention include ethanol, isopropyl alcohol, NMP, acetone and ethyl acetate.

The pre-formulations of the present invention contain one or more bioactive agents (described equivalently as "active agents" herein). Active agents may be any compound having a desired biological or physiological effect, such as a protein, drug, antigen, nutrient, cosmetic, fragrance, flavouring, diagnostic, pharmaceutical, vitamin, or dietary agent and will be formulated at a level sufficient to provide an *in vivo* concentration at a functional level (this generally being a local concentration for topical compositions).

Drug agents that may be delivered by the present invention include drugs which act on cells and receptors, such as peripheral nerves, adrenergic receptors, and cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulation system, endocrine and hormone system, blood circulatory system, synoptic sites, neuroeffector junctional sites, the immunological system, the reproductive system, the skeletal system, autacoid system, the alimentary and excretory systems, the histamine system, and the central nervous system. Drug agents intended for local stimulatory or inhibitory effects on enzymes or proteins can also be delivered by the present invention. The effect of the delivered drug agent may also be associated with direct effects on DNA and/or RNA synthesis, such as on transcription, translation, or post-translational modification. Also these effects may be both stimulatory and inhibitory.

Examples of drugs which may be delivered by the composition of the present invention include, but are not limited to, antibacterial agents such as β-lactams or macrocyclic peptide antibiotics, anti fungal agents such as polyene macrolides (e.g. amphotericin B) or azole antifungals, anticancer and/or anti viral drugs such as nucleoside analogues, paclitaxel and derivatives thereof, anti inflammatorys, such as non-steroidal anti inflammatory drugs and corticosteroids, cardiovascular drugs such as blood-pressure lowing or raising agents (especially locally acting), analgesics, and prostaglandins and derivatives. Diagnostic agents include radionuclide labelled compounds and contrast agents including X-ray, ultrasound and MRI contrast enhancing agents (especially for application to an internal surface of a body cavity). Nutrients include vitamins, coenzymes, dietary supplements etc which may, for example, be used for local rescue from the effects of a systemic drug, such as rescue by folate from a folate analogue such as methotrexate.

Particularly suitable active agents include those which would normally have a short residence time in the body due to rapid breakdown or excretion and those with poor oral bioavailability, especially where their effect may be provided by topical treatment, thereby bypassing systemic absorption. These include peptide, protein and nucleic acid based active agents, hormones and other naturally occurring agents in their native or modified forms. By administering such agents in the form of a bioadhesive depot composition formed from the pre-formulation of the present invention, the agents are provided at a sustained level for an extended length of time in spite of having rapid systemic clearance rates. This offers obvious advantages in terms of stability and patient compliance over dosing multiple times each day for the same period. In one preferred embodiment, the active agent thus has a biological half life (upon entry into the blood stream) of less than 1 day, preferably less than 12 hours and more preferably less than 6 hours. In some cases this may be as low as 1-3 hours or less. Suitable agents are also those with poor oral bioavailability relative to that achieved by injection, for where the active agent also or alternatively has a bioavailability of below 0.1%, especially below 0.05% in oral formulations. Similarly, certain agents would be unsuitable or undesirable when administered sytemically but may be administered locally, particularly to external surfaces.

Peptide and protein based active agents are highly suitable for inclusion in the surface-applied depot compositions of the invention. Such agents may be included for their local effect, or may be applied at a surface for systemic action. Suitable

actives for local or systemic effect include human and veterinary drugs selected from the group consisting of adrenocorticotropic hormone (ACTH) and its fragments, angiotensin and its related peptides, antibodies and their fragments, antigens and their fragments, atrial natriuretic peptides, bioadhesive peptides, Bradykinins and their related peptides, calcitonins and their related peptides, cell surface receptor protein fragments, chemotactic peptides, cyclosporins, cytokines, Dynorphins and their related peptides, endorphins and P-lidotropin fragments, enkephalin and their related proteins, enzyme inhibitors, immunostimulating peptides and polyaminoacids, fibronectin fragments and their related peptides, gastrointestinal peptides, gonadotrophin-releasing hormone (GnRH) agonists and antagonist, glucagons like peptides, growth hormone releasing peptides, immunostimulating peptides, insulins and insulin-like growth factors, interleukins, luthenizing hormone releasing hormones (LHRH) and their related peptides, melanocyte stimulating hormones and their related peptides, nuclear localization signal related peptides, neurotensins and their related peptides, neurotransmitter peptides, opioid peptides, oxytocins, vasopressins and their related peptides, parathyroid hormone and its fragments, protein kinases and their related peptides, somatostatins and their related peptides, substance P and its related peptides, transforming growth factors (TGF) and their related peptides, tumor necrosis factor fragments, toxins and toxoids and functional peptides such as anticancer peptides including angiostatins, antihypertension peptides, anti-blood clotting peptides, and antimicrobial peptides; selected from the group consisting of proteins such as immunoglobulins, angiogenins, bone morphogenic proteins, chemokines, colony stimulating factors (CSF), cytokines, growth factors, interferons (Type I and II), interleukins, leptins, leukaemia inhibitory factors, stem cell factors, transforming growth factors and tumor necrosis factors.

A further considerable advantage of the depot compositions of the present invention is that active agents are released gradually over long periods without the need for repeated dosing. The composition are thus highly suitable for children or people who's lifestyle is incompatible with a reliable or repeated dosing regime. Also for "lifestyle" actives where the inconvenience of repeated dosing might outweigh the benefit of the active.

Cationic peptides are particularly suitable for use where a portion of the pre-formulation comprises an anionic amphiphile such as a fatty acid. In this

embodiment, preferred peptides include octreotide, lanreotide, calcitonin, oxytocin, interferon-beta and -gamma, interleukins 4, 5, 7 and 8 and other peptides having an isoelectric point above pH 7, especially above pH 8.

In one preferred aspect of the present invention, the composition of the invention is such that an I_2 phase, or a mixed phase including I_2 phase is formed upon exposure to aqueous fluids and a polar active agent is included in the composition. Particularly suitable polar active agents include peptide and protein actives, oligo nucleotides, and small water soluble actives, including those listed above. Of particular interest in this aspect are the peptide octreotide and other somatostatin related peptides, interferons alpha and beta, glucagon-like peptides 1 and 2 and their receptor agonists, luprorelin and other GnRH agonist, abarelix and other GnRH antagonists, interferon alpha and beta, zolendronate and ibandronate and other bisphosponates, and polar active chlorhexidine (e.g. chlorhexidine digluconate or chlorhexidine dihydrochloride). Consider to exclude. Most of those listed here as particularly interesting are for parenteral dosing, except chlorhexidine!

The amount of bioactive agent to be formulated with the pre-formulations of the present invention will depend upon the functional dose and the period during which the depot composition formed upon administration is to provide sustained release. Typically, the dose formulated for a particular agent will be around the equivalent of the normal single dose multiplied by the number times greater the expected duration of action the formulation is to provide. Evidently this amount will need to be tailored to take into account any adverse effects of a large dose at the beginning of treatment and so this will generally be the maximum dose used. The precise amount suitable in any case will readily be determined by suitable experimentation.

The formulations of the present invention may form non-parenteral depots where the active agent is slowly released at a body surface. It is particularly significant that the compositions generated from the preformulations are bioadhesive because this allows local release of the active agent over a sustained period. That is to say that the compositions should coat the surface to which they are applied and/or upon which they form as appropriate and should remain even when this surface is subject to a flow of air or liquid and/or rubbing. It is particularly preferable that the liquid crystalline depot compositions formed should be stable to rinsing with water. For example, a small volume (e.g. 100 µl) of depot precursor may be applied to a body

surface and be exposed to a flow of five hundred times its own volume of water per minute for 5 minutes. After this treatment, the composition can be considered bioadhesive if less than 50% of the composition or bioactive agent has been lost. Preferably this level of loss will be matched when water equalling 1000 times and more preferably 10 000 times the volume of the composition is flowed past per minute for five, or preferably 10, minutes.

Another advantageous property of the compositions of the invention is that the film generated following administration may not only act as a depot system. This film may also have the advantage of lowering evaporation of water from damaged areas or areas afflicted by a medical condition (where barrier properties of the skin is reduced). Thus, the compositions may have further advantageous properties in themselves and show additive and/or synergistic advantages in combination with active agents, for instance for the prophylaxis of inflammatory or allergic dermatoses and for the care and restoration of sensitive or stressed skin.

Although the non-parenteral depot compositions of the present invention may absorb some or all of the water needed to form a liquid crystalline phase structure from the biological surfaces with which they are contacted, some additional water may also be absorbed from the surrounding air. In particular, where a thin layer of high surface area is formed then the affinity of the composition for water may be sufficient for it to form a liquid crystalline phase structure by contact with the water in the air. The "aqueous fluid" referred to herein is thus, at least partially, air containing some moisture in this embodiment.

Non-parenteral depot compositions will typically be generated by applying the pre-formulation topically to a body surface (external or within a natural or artificially generated body cavity) and/or to the surface of an implant. This application may be by direct application of liquid such as by spraying, dipping, rinsing, application from a pad or ball roller, intra-cavity injection (e.g to an open cavity with or without the use of a needle), painting, dropping (especially into the eyes), applying in the form of a patch, and similar methods. A highly effective method is aerosol or pump spraying and evidently this requires that the viscosity of the pre-formulation be as low as possible and is thus highly suited to the compositions of the invention. Non-parenteral depots may, however, be used to administer systemic agents e.g. transmucosally or transdermally.

Where the formulation is administered in the form of a patch, this may rely on the "glue" function of the composition. This "glue property" may be beneficial for the tissue contacted by the formulation as the compositions can be soothing and rehydrating, as indicted herein. This is in contrast to previously known patches, where the adhesive is typically inert at best.

Conditions particularly suitable for causative or symptomatic treatment by topical bioadhesive depot compositions of the present invention include skin conditions (such as soreness resulting from any cause including chapping, scratching and skin conditions including eczema and herpes) eye conditions, genital soreness (including that due to genital infection such as genital herpes), infections and conditions for the finger and/or toe nails (such as bacterial or fungal infections of the nails such as onychomycosis or poronychia) and in particular imflammation and/or irritation at any body surface. Two particularly suitable conditions which may be improved by use of the compositions of the invention are oral mucositis and inflammatory bowel disease (e.g. crohn's disease or ulcerative collitus). Topical-type bioadhesive formulations may also be used to administer systemic active agents (e.g. medication), particularly by skin adsorption, oral, transdermal or rectal routes. Travel sickness medication is a preferred example, as is nicotine (e.g. in anti-smoking aids). Where context permits, "topical application" as referred to herein includes systemic agents applied non-parenterally to a specific region of the body.

Periodontal infections are particularly suitable for treatment by the compositions of the present invention. In particular, known compositions for treating periodontal infection are difficult to apply or are generally ineffective. The most widely used periodontal depot composition comprises insertion of a collagen "chip" into the periodontal space, from which an anti-infective agent is released. This chip is difficult to insert and does not form to match the shape and volume of the periodontal space, so that pockets of infection may remain untreated. In contrast to this, the compositions of the present invention, applied as a low viscosity preformulation, can be easily and quickly injected into the periodontal space and will flow to conform exactly to that space and fill the available volume. The compositions then quickly absorb water to form a robust gel which is resistant to aqueous conditions of the mouth. The only known previous attempt at such an injectible periodontal treatment relied on dispersions of relatively high viscosity

which were difficult to apply and were subject to undesirable phase separation. All of these drawbacks are now addressed in the compositions of the present invention as described herein. Highly suitable actives for periodontal administration are anti-antibacterial, antibiotic, anti-inflammatory, and local analgesic agents, in particular benzdamine, tramadol and particularly chlorhexidine.

Non-parenteral depot compositions are also of significant benefit in combination with non-pharmaceutical active agents, such as cosmetic actives, fragrances, essential oils etc. Such non-pharmaceutical depots will maintain the important aspects of bioadhesion and sustained release to provide prolonged cosmetic effects, but may easily be applied by spraying or wiping. This additionally applies to agents which have both cosmetic and medical (especially prophylactic) benefits such as sun-protective agents. Since the topical depot compositions provide robust, water resistant barriers which can solubilise high levels of actives, they are especially suitable for sunscreens and sunblocks in combination with ultra violet light (UV, e.g. UVa, UVb and/or UVc) absorbing and/or scattering agents, particularly where high levels of protection is desirable. The compositions are furthermore highly biocompatible and may act to moisten and soothe the skin during sun exposure. Compositions of the invention containing soothing agents such as aloe vera are also highly suitable for soothing and moistening application after exposure to sunlight, or to skin which is dry, inflamed or damaged due to, for example irritation, burning or abrasion.

Active agents particularly suited to non-parenteral (e.g. topical) depot administration, which includes intra oral, buccal, nasal, ophthalmic, dermal, rectal and vaginal delivery routes, include antibacterials such as chlorhexidine, chloramphenicol, triclosan, tetracycline, terbinafine, tobramycin, fusidate sodium, butenafine, metronidazole (the latter particularly for the (e.g. symtomatic) treatment of acne rosacea - adult acne or some vaginal infections), antiviral, including acyclovir, anti infectives such as bibrocathol, ciprofloxacin, levofloxacin, local analgesics such as benzydamine, lidocaine, prilocaine, xylocaine, bupivacaine, analgesics such as tramadol, fentanyl, sufentanyl, morphine, hydromorphone, methadone, oxycodone, codeine, asperine, acetaminophen, NSAIDS such as ibuprofen, flurbiprofen, naproxene, ketoprofen, fenoprofen, diclofenac, etodalac, diflunisal, oxaproxin, piroxicam, piroxicam, indomethansine, sulindac, tolmethin,

salysylic acids such as salisylamide and diflunisal, Cox1 or Cox2 inhibitors such as celecoxib, rofecoxib or valdecoxib, corticosteroids, anticancer and immuno stimulating agents (for instance ,metylaminolevulinat hydrocloride, interferon alpha and beta), anticonvulsants (for instance tiagabine topiramate or gabapentin), hormones (such as testosterone, and testosterone undecanoate, medroxyprogesterone, estradiol) growth hormones (like human growth hormone), and growth factors (like granulocyte macrophage colony-stimulating factor), immuno suppressants (cyclosporine, sirolimus, tacrolimus), nicotine and antivirals (e.g. acyclovir), vitamin D3 and derivatives thereof.

Other particularly suitable actives include:
Acetaminophen, Ibuprofen, Propoxyphene, Codeine, Dihydrocodein, Hydrocodone, Oxycodone, Nalbuphine, Meperidine, Leverorphanol, Hydromorphone, Oxymorphone, Alfentanil, Fentanyl and Sefentanil.

Some specific actives found by the inventors to form highly effective depots of the present invention include the following:

For topical bioadhesive, controlled release products for intraoral (including buccal & periodontal) administration;

i. benzydamine (local analgesic, anti inflammatory) or other local analgesic, analgesic, anti inflammatory, anti bacterial, anti fungal or combination thereof. Composition provides sustained effect at intraoral mucosa, in particular damaged, sensitised, infected mucosa e.g. in patients suffering from oral mucositis (induced by e.g. chemo- and radiotherapy). In particular for treatment of oral mucositis.

ii. tramadol (analgesic). Provides a composition with sustained systemic analgesic effect.

iii. chlorhexidine gluconate (antibacterial) for treatment of periodontal and topical infections. Particularly for long acting effect in periodontal pocket. Compositions result in depots releasing chlorhexidine over more than 1h, preferably more than 6h, most preferably more than 24 h when applied as a liquid, forming a bioadhesive gel *in situ.* Surface gel formation time observed to be between 1 second and 5 min.

Depots i to iii formable having high level of active agent incorporation and high degree of resistance to washing away. Preformulations in the form of a liquid administered as spray or liquid wash/rinse for i and ii and gel-forming liquid for iii, wherein liquid is applied to periodontal pocket, e.g. by injection.

For non-parenteral (e.g. topical or systemic) bioadhesive, controlled release products for nasal administration;

i. fentanyl (analgesic) provides rapid onset and sustained duration analgesia when administered as spray to the nasal or oral cavity

ii. diazepam (anti anxiety) provides non-parenteral, nasal or oral cavity depot with systemic effect giving rapid onset and sustained duration. Administered as a spray

For topical bioadhesive, controlled release products for ophthalmic administration;

i. diclofenac (NSAID) with sustained duration. Administered as in situ phase forming liquid

ii. pilocarpine (parasymptomimetic, cholinergic agonist) for treatment of glaucoma.

iii levocabastine hydrochloride, ketotifen fumarate providing liquid for eye-dropping to give long lasting relief from allergic conjunctivitis with long period between reapplication.

iv Pilocarpine hydrochloride for the treatment of Sjögrens syndrome.

v dexamethasone, (corticosteroid)

vi chloramphenicol (primarily bacteriostatic antiinfective)

vii indomethacin (NSAID)

Depots i to vii formulated as liquid spray or more preferably drops for direct application to eye surface and provide *in situ* depot formation with high resistance to washing out by tears and wear from blinking/eye rubbing. Composition of the invention show excellent compatibility ophthalmic application. Safety studies in rabbit models show no irritation and no blurring effects. Appropriate here?

Other actives suitable for ophthalmic compositions include Antihistamines, Mast cell stabilizers, Nonsteroidal anti-inflammatory drugs (NSAIDs), Corticosteroids (e.g. to treat allergic conjunctivitis), Anti-Glaucoma actives including inflow

suppressing/inhibiting agents (beta blocking agents: timolol, betaxolol, carteolol, levobunolol, etc., topical carbonic anhydrase inhibitors: dorzolamide, brinzolamide, sympathomimetics: epinephrine, dipivefrin, clonidine, apraclonidine, brimonidine), outflow facilitating agents (parasympathomimetics (cholinergic agonists): pilocarpine prostaglandin analogues and related compounds: atanoprost, travoprost, bimatoprost, unoprostone)

For non-parenteral (e.g. topical or systemic) bioadhesive, controlled release products for dermatological administration;

i. acyclovir (antiviral). Composition generates a bioadhesive, film forming product with sustained duration. Applied as spray or liquid

ii. testosterone undecanoate or testosterone enantate (hormone deficiency). Bioadhesive, film forming composition with sustained duration. May be applied as aerosol- or pump-spray, or as liquid.

Particularly suitable applications of dermatological formulations are anti-infective dermatological bioadhesive depots for protection in environments where contact with infective agents is likely (e.g. human or veterinary surgery, abattoir work, certain types of cleaning etc.). Bioadhesive depots generated from composition of the invention provide robust and sustained protection for the wearer. The compositions with antiinfective agents may also be used in situations where skin sterility of the wearer is important for the health of others, such as for nurses or doctors visiting multiple patients in hospital, where cross-infection must be avoided. A prior coating with a composition of the present invention may serve to provide resistance against picking up of infectives from one area and thus prevent transmission to another.

In the methods of treatment of the present invention, as well as in the corresponding use in therapy and the manufacture of medicaments, an active agent is not always necessary. In particular, lipids, particularly phospholipids such as PC have been implicated as highly beneficial in themselves for the treatment of certain conditions (including those described herein below). Without being bound by theory, it is believed that suitable lipids, such as those in the formulations of the present invention, are naturally present in the protective layers over and around many structures of the body, such as the linings of many body cavities and the contact surfaces of joints. These layers may serve as protection from adhesion and attack by

a wide variety of chemical and biological agents (such as on gastric surfaces and in the lining of the GI tract), may act as lubricants (particularly in joints but crucially also on the linings and membranes surrounding many internal structures such as heart and lungs), and may additionally contribute to cell wall repair by allowing lipid exchange and dilution of undesirable membrane-bound and membrane-soluble agents. The lipid nature of the compositions also forms a harmless substrate for unwanted inflammatory lipase enzymes including phospholipases such as phospholipase A_2 (PLA_2).

In an alternative embodiment of the methods of treatment and corresponding uses of the present invention, suitable actives may be included, either as the sole beneficial agent, or to complement the effect of suitable lipid components. Such actives will typically be suited for the treatment of inflammation and/or irritation, such as steroidal and non-steroidal anti-inflammatory drugs and local immune modulators. Examples of such agents are well known and many are mentioned herein elsewhere. They include, cis-urocanic acid, corticosteroids such as prednisone methylprednisolone and hydrocortisone, and derivatives of nonsteroidal anti-inflammatory compounds such as benzydamine, paracetamol, ibuprofen and salicylic acid derivatives including acetyl salicylate and 5-amino salicylates. Local inhibitors of inflammatory pathways are also suitable, including the antigen recognition suppressors methotrexate, azathioprine or 6-mercaptopurine and phospholipase inhibitors, such as PLA_2 inhibitors.

The pre-formulations of the present invention provide non-lamellar liquid crystalline depot compositions upon exposure to aqueous fluids, especially in contact with body surfaces. As used herein, the term "non-lamellar" is used to indicate a normal or reversed liquid crystalline phase (such as a cubic or hexagonal phase) or the L3 phase or any combination thereof. The term liquid crystalline indicates all hexagonal liquid crystalline phases, all cubic liquid crystalline phases and/or all mixtures thereof. Hexagonal as used herein indicates "normal" or "reversed" hexagonal (preferably reversed) and "cubic" indicates any cubic liquid crystalline phase unless specified otherwise. By use of the pre-formulations of the present invention it is possible to generate any phase structure present in the phase-diagram of components a and b with water. This is because the pre-formulations can be generated with a wider range of relative component concentrations than previous lipid depot systems without risking phase separation or resulting in highly viscous

solutions for injection. In particular, the present invention provides for the use of phospholipid concentrations above 50% relative to the total amphiphile content. This allows access to phases only seen at high phospholipid concentrations, particularly the hexagonal liquid crystalline phases.

For many combinations of lipids, only certain non-lamellar phases exist, or exist in any stable state. It is a surprising feature of the present invention that compositions as described herein frequently exhibit non-lamellar phases which are not present with many other combinations of components. In one particularly advantageous embodiment, therefore, the present invention relates to compositions having a combination of components for which an I_2 and/or L_2 phase region exists when diluted with aqueous solvent. The presence or absence of such regions can be tested easily for any particular combination by simple dilution of the composition with aqueous solvent and study of the resulting phase structures by the methods described herein.

In a highly advantageous embodiment, the compositions of the invention may form an I_2 phase, or a mixed phase including I_2 phase upon contact with water. The I_2 phase is a reversed cubic liquid crystalline phase having discontinuous aqueous regions. This phase is of particular advantage in the controlled release of active agents and especially in combination with polar active agents, such as water soluble actives because the discontinuous polar domains prevent rapid diffusion of the actives. Depot precursors in the L_2 phase are highly effective in combination with an I_2 phase depot formation. This is because the L_2 phase is a so-called "reversed micellar" phase having a continuous hydrophobic region surrounding discrete polar cores. L_2 thus has similar advantages with hydrophilic actives.

In transient stages after contact with body fluid the composition can comprise multiple phases since the formation of an initial surface phase will retard the passage of solvent into the core of the depot. Without being bound by theory, it is believed that this transient formation of a surface phase, especially a liquid crystalline surface phase, serves to dramatically reduce the "burst/lag" profile of the present compositions by immediately restricting the rate of exchange between the composition and the surroundings. Transient phases may include (generally in order from the outside towards the centre of the depot): H_{II} or L_α, I_2, L_2, and liquid (solution). It is highly preferred that the composition of the invention is capable

forming at least two and more preferably at least three of these phases simultaneously at transient stages after contact with water at physiological temperatures. In particular, it is highly preferred that one of the phases formed, at least transiently, is the I_2 phase.

It is important to appreciate that the preformulations of the present invention are of low viscosity. As a result, these preformulations must not be in any bulk liquid crystalline phase since all liquid crystalline phases have a viscosity significantly higher than could be administered by syringe or spray dispenser. The preformulations of the present invention will thus be in a non-liquid crystalline state, such as a solution, L_2 or L_3 phase, particularly solution or L_2. The L_2 phase as used herein throughout is preferably a "swollen" L_2 phase containing around 10 wt% or greater of solvent (component c) having a viscosity reducing effect. This is in contrast to a "concentrated" or "unswollen" L_2 phase containing no solvent, or a lesser amount of solvent, or containing a solvent (or mixture) which does not provide the decrease in viscosity associated with the oxygen-containing, low viscosity solvents specified herein.

In one embodiment, a small proportion (e.g.less than 5% by weight) of a reinforcing polymer may be added to the formulation.

Upon administration, the pre-formulations of the present invention undergo a phase structure transition from a low viscosity mixture to a high viscosity (tissue adherent) depot composition. Generally this will be a transition from a molecular mixture, swollen L_2 and/or L3 phase to one or more (high viscosity) liquid crystalline phases such as normal or reversed hexagonal or cubic liquid crystalline phases or mixtures thereof. As indicated above, further phase transitions may also take place following administration. Obviously, complete phase transition is not necessary for the functioning of the invention but at least a surface layer of the administered mixture will form a liquid crystalline structure. Generally this transition will be rapid for at least the surface region of the administered formulation (that part in direct contact with air, body surfaces and/or body fluids). This will most preferably be over a few seconds or minutes (e.g. up to 30 minutes, preferably up to 10 minutes, more preferably 5 minutes of less). The remainder of the composition may change phase to a liquid crystalline phase more slowly by diffusion and/or as the surface region disperses.

In one preferred embodiment, the present invention thus provides a pre-formulation as described herein of which at least a portion forms a hexagonal liquid crystalline phase upon contact with an aqueous fluid. The thus-formed hexagonal phase may gradually disperse, releasing the active agent, or may subsequently convert to a cubic liquid crystalline phase, which in turn then gradually disperses. It is believed that the hexagonal phase will provide a more rapid release of active agent, in particular of hydrophilic active agent, than the cubic phase structure, especially the I_2 and L_2 phase. Thus, where the hexagonal phase forms prior to the cubic phase, this will result in an initial release of active agent to bring the concentration up to an effective level rapidly, followed by the gradual release of a "maintenance dose" as the cubic phase degrades. In this way, the release profile may be controlled.

Without being bound by theory, it is believed that upon exposure (e.g. to body fluids), the pre-formulations of the invention lose some or all of the organic solvent included therein (e.g. by diffusion and/or evaporation) and take in aqueous fluid from the bodily environment (e.g. moist air close to the body or the *in vivo* environment) such that at least a part of the formulation generates a non-lamellar, particularly liquid crystalline phase structure. In most cases these non-lamellar structures are highly viscous and are not easily dissolved or dispersed into the *in vivo* environment and are bioadhesive and thus not easily rinsed or washed away. Furthermore, because the non-lamellar structure has large polar, apolar and boundary regions, it is highly effective in solubilising and stabilising many types of active agents and protecting these from degradation mechanisms. As the depot composition formed from the pre-formulation gradually degrades over a period of hours or days, or even weeks or months (depending upon the nature and site of application), the active agent is gradually released and/or diffuses out from the composition. Since the environment within the depot composition is relatively protected, the pre-formulations of the invention are highly suitable for active agents with a relatively low biological half-life (see above).

In an additional aspect of the invention, the topical compositions may be used to provide a physical barrier on body surfaces, in the absence of any active agent. In particular, because of the very high bioadherance of the compositions, "barrier" coatings formed by spraying or application of liquid may be formed from the present compositions so as to reduce contact with potential infective or irritant agents or to

reduce soiling of the body surfaces. The robust nature of the compositions and resistance to washing provide advantageous characteristics for such barriers, which could conveniently be applied as a liquid or by spraying. Without being bound to theory it is believed that the stability and wear resistance of applied topical compositions is due to the particular phase transitions of the composition on exposure to aqueous fluid/moisture and the bioadhesion thereof, in combination with the low aqueous solubility of the diacyl lipid building blocks.

The formulations, compositions and methods of the invention relating to the treatment of inflammation or irritation, are particularly suitable for addressing inflammation and/or irritation in a body cavity. Administration to a body cavity is thus highly suitable in this aspect and will be carried out by a method suitable for the cavity being treated. Mouthwashes, for example, may be suitable for oral or buccal cavities, while other parts of the GI tract may be suitably treated by oral formulations, including dispersions and dry pre-formulations, and rectal formulations such as enemas or suppositories. Rinses and pesseries are similarly suitable for vaginal delivery.

The compositions of the present invention are highly suitable for treating inflammation in a body cavity because of the highly bioadhesive nature of the non-lamellar phase and the resulting long-lasting effects. The inherently soothing and highly biocompatible nature of the constituents is also important and may pay a passive or active role in the treatment of inflammation.

The methods of treatment and corresponding uses of the present invention are thus most applicable to inflammatory diseases and inflammation caused by, for example, wounding, abrasion, or reaction to aggressive therapies such as irradiation and/or chemotherapy. Especially suitable are inflammatory diseases affecting at least one body cavity. Diseases of the GI tract are highly suitable for treatment with the compositions of the present invention, particularly inflammatory bowel disease including Crohn's disease and ulcerative collitus and oral inflammation such as oral mucositis. Similarly, application to a body cavity during surgery may also be used to take advantage of the properties of the formulations. They may thus be directly applied, for example by spraying or painting, to sooth inflammation resulting from or exposed during surgery and also to reduce the tendency of surgically manipulated tissue to "stick" and/or form adhesions/bridges at unwanted sites.

The invention thus particularly provides for a method of treatment of an inflammatory disease (e.g. Crohn's disease, ulcerative collitus or oral mucositis), said method comprising the administration of a preformulation of the present invention either in the absence of an active agent, or comprising at least one anti-inflammatory or anti-infective active agent such as one selected from corticosteroids such as prednisone methylprednisolone and hydrocortisone, and derivatives of nonsteroidal anti-inflammatory compounds such as benzydamine, paracetamol, ibuprofen and salicylic acid derivatives including acetyl salicylate and 5-amino salicylates. Local inhibitors of inflammatory pathways are also suitable, including the antigen recognition suppressors methotrexate, azathioprine or 6-mercaptopurine and phospholipase inhibitors, such as PLA_2 inhibitors. Other sutable actives include glutamine, antioxidants such as ascorbate, beta-carrotine, vitamin E, oxypentifylline, Azelastine hydrochloride, allopurinol, chlorhexadine, povidone iodine, nystatin, clotrimazole, polymixin E, tobramycin, amphotericin B, acyclovir, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage stimulating factor (GM-CSF), cytokines and cytokine inducers/supressors.

A particularly preferred method and corresponding use is a method for the treatment of oral mucositis in a human or animal subject (especially one in need thereof) by a composition of the present invention (especially comprising preferred combinations of components a), b) and c)) comprising at least one local analgesics or anti-inflammatory agent, especially benzydamine or a derivative thereof. Optionally these may be combined with one or more of the actives indicated above for the treatment of inflammation, and/or with a topical anaesthetic such as lignocaine, cocaine, diphendramine, or particularly dyclonine HCl.

The Invention will now be further illustrated by reference to the following non-limiting Examples and the attached Figures, in which;

Figure 1 shows the cumulative release of methylene blue (MB) from a depot formulation comprising PC/GDO/EtOH (45/45/10 wt%) when injected into excess water;

Figure 2 demonstrates the non-linear decrease of pre-formulation viscosity upon addition of N-methyl pyrolidinone (NMP) and EtOH;

Figure 3 displays the *in vitro* release in excess aqueous phase of chlorhexidine from a depot formulation comprising PC/GDO/EtOH (36/54/10 wt%) containing 50 mg chlorhexidine / g of formulation, corresponding to 5% drug load.

Examples:

Example 1

Availability of various liquid crystalline phases in the depot by choice of composition

Injectable formulations containing different proportions of phosphatidyl choline ("PC" - Epikuron 200) and glycerol dioleate (GDO) and with EtOH as solvent were prepared to illustrate that various liquid crystalline phases can be accessed after equilibrating the depot precursor formulation with excess water.

Appropriate amounts of PC and EtOH were weighed in glass vials and the mixture was placed on a shaker until the PC completely dissolved to form a clear liquid solution. GDO was then added to form an injectable homogenous solution.

Each formulation was injected in a vial and equilibrated with excess water. The phase behaviour was evaluated visually and between crossed polarizes at 25°C. Results are presented in Table 1.

TABLE 1

Formulation	PC (wt%)	GDO (wt%)	EtOH (wt%)	Phase in H_2O
A	22.5	67.5	10.0	L_2
B	28.8	61.2	10.0	I_2
C	45.0	45.0	10.0	H_{II}
D	63.0	27.0	10.0	H_{II}/L_α

L_2 = reversed micellar phase

I_2 = reversed cubic liquid crystalline phase

H_{II} = reversed hexagonal liquid crystalline phase

L_α = lamellar phase

Example 2

In vitro release of a water-soluble substance

A water-soluble colorant, methylene blue (MB) was dispersed in formulation C (see Example 1) to a concentration of 11 mg/g formulation. When 0.5 g of the formulation was injected in 100 ml water a stiff reversed hexagonal H_{II} phase was formed. The absorbency of MB released to the aqueous phase was followed at 664 nm over a period of 10 days. The release study was performed in an Erlenmeyer flask at 37°C and with low magnetic stirring.

The release profile of MB (see Figure 1) from the hexagonal phase indicates that this (and similar) formulations are promising depot systems. Furthermore, the formulation seems to give a low initial burst, and the release profile indicates that the substance can be released for several weeks; only about 50% of MB is released after 10 days.

Example 3

Viscosity in PC/GDO (6:4) or PC/GDO (3:7) on addition of solvent (EtOH, PG and NMP)

A mixture of PC/GDO/EtOH was manufactured according to the method in Example 1. All, or nearly all, of the EtOH was removed from the mixture with a rotary evaporator (vacuum, 40°C, 1h) and the resulting solid mixture were weighed in glass vial after which 2, 5, 10 or 20% of a solvent (EtOH, propylene glycol (PG) or n-methyl pyrrolidone (NMP)) was added. The samples were allowed to equilibrate several days before the viscosity was measured at a shear rate of $0.1s^{-1}$ with a Physica UDS 200 rheometer at 25°C.

This example clearly illustrates the need for solvent with certain depot precursors in order to obtain an injectable formulation (see Figure 2). The viscosity of solvent-free PC/GDO mixtures increases with increasing ratio of PC. Systems with low PC/GDO ratio (more GDO) are injectable with a lower concentration of solvent.

Example 4

Composition and in vitro phase study

The formulations were manufactured according to the method described in Example 1 with compositions according to Table 2. An active substance (peptide), salmon calcitonin (sCT), was added to each formulation to a concentration of 500 μg sCT/g formulation. The formulations were designed as homogenous suspensions for parenteral administration (mixing required shortly prior to use since the drug is not completely dissolved in the PC/GDO/EtOH system).

The phase study in this example is performed in excess of rat serum at 37°C in order to simulate an *in vivo* situation. Table 2 shows that the same phases as those in water are formed (compare Table 1).

TABLE 2

Formulation	PC (wt%)	GDO (wt%)	OA (wt%)	EtOH (wt%)	Phase in rat serum
E	18	72	-	10	L_2
F	36	54	-	10	I_2
G	34	51	5	10	I_2
H	54	36	-	10	H_{II}
I	72	18	-	10	H_{II}/L_α

OA = Oleic Acid

Example 5

Sterile filtration of formulations with reduced viscosity

To lower the viscosity with various solvents is sometimes necessary in order to obtain an injectable formulation and to be able to administrate the system with a regular syringe (see Example 3). Another important effect from the viscosity-lowering solvent is that the formulations can be sterile filtrated.

Formulations E to I in Example 4 were studied in a sterile filtration test by using a 0.22μm filter (before addition of the active substance). Formulations E to H were

successfully filtrated, but formulation I failed since the viscosity was too high. An aseptic manufacturing procedure was therefore needed for this formulation.

Example 6: Preparation of depot precursor compositions with various solvents.

Depending on composition of the formulation and the nature and concentration of active substance certain solvents may be preferable.

Depot precursor formulations (PC/GDO/solvent (36/54/10)) were prepared by with various solvents; NMP, PG, PEG400, glycerol/EtOH (90/10) by the method of Example 1. All depot precursor compositions were homogeneous one phase solutions with a viscosity that enabled injection through a syringe (23G - i.e. 23 gauge needle; 0.6mm x 30mm). After injecting formulation precursors into excess water a liquid crystalline phase in the form of a high viscous monolith rapidly formed with NMP and PG containing precursors. The liquid crystalline phase had a reversed cubic micellar (I_2) structure. With PEG400, glycerol/EtOH (90/10) the viscosification/solidification process was much slower and initially the liquid precursor transformed to a soft somewhat sticky piece. The difference in appearance probably reflects the slower dissolution of PEG400 and glycerol towards the excess aqueous phase as compared to that of EtOH, NMP and PG.

Example 7: Preparation of depot composition containing benzydamine.

Benzydamine is a non-steroidal antiinflammatory drug and is extensively used as a topical drug in inflammatory conditions.

1g of a depot formulation containing 1.5mg benzydamine was prepared by dissolving the active substance in a mixture of PC/GDO/EtOH (36/54/10) prepared as described in Example 1. The depot composition was stable against crystallization during storage at 25°C for at least two weeks. Equilibration of the formulation precursor with excess water resulted in a high viscous monolithic liquid crystalline phase (I_2 structure).

Example 8: Robustness of the behaviour of the formulation against variations in the excipient quality.

Depot precursor formulations were prepared with several different GDO qualities (supplied by Danisco, Dk), Table 3, using the method of Example 1. The final depot precursors contained 36%wt PC, 54%wt GDO, and 10%wt EtOH. The appearance of the depot precursors was insensitive to variation in the quality used, and after contact with excess water a monolith was formed with a reversed micellar cubic phase behaviour (I_2 structure).

Table 3. Tested qualities of GDO.

GDO quality	Monoglyceride (%wt)	Diglyceride (%wt)	Triglyceride (%wt)
A	10.9	87.5	1.6
B	4.8	93.6	1.6
C	1.0	97.3	1.7
D	10.1	80.8	10.1
E	2.9	88.9	8.2
F	0.9	89.0	10.1

Example 9: Preparation of depot composition containing saturated PC (Epikuron 200SH).

Depot precursor formulations were prepared with various amounts PC comprising saturated hydrocarbon chains by addition of Epikuron 200SH directly to a mixture of PC/GDO/EtOH, prepared as for Example 1. The formulations are shown in Table 4. All precursor formulations were homogenous one phase samples in RT, while they became more viscous with increasing amount Epikuron 200SH. Injecting the depot precursor into excess water gave a monolith comprising a reversed miceller cubic (I_2) structure. Monoliths formed from samples containing higher amounts of Epikuron 200SH became turbid, possibly indicating segregation between Epikuron 200SH and the other components upon exposure to water and formation of the I2 phase.

Table 4. Depot composition containing saturated PC

Formulation	Saturated PC, Epikuron 200SH (%wt)	PC (%wt)	GDO (%wt)	EtOH (%wt)
G1	3.9	34.6	51.9	9.6
G2	7.0	33.5	50.2	9.3
G3	14.3	30.8	46.3	8.6

Example 10: Bioadhesive spray of depot precursor formulation.

A pump spray bottle was found to be a convenient way to apply the formulation topically, e.g. to the skin or the oral mucosa.

A depot precursor formulation prepared as in Example 1 (36%wt PC, 54%wt GDO, and 10%wt EtOH) was sprayed with a pump spray bottle onto the skin and oral mucosa. A film with solid mechanical properties formed shortly after application.

Example 11: Robustness of a topical film.

After applying the depot precursor formulation, as described in Example 10, (36%wt PC, 54%wt GDO, and 10%wt EtOH) to the skin, the applied formulation was exposed to flushing water (10L/min) for 10 minutes. The formulation showed excellent bioadhesive properties and resistance against rinsing and no loss of the formulation could be discerned.

Example 12: Formation of cubic phase with solid properties after exposure of depot precursor formulation to air.

After exposing a depot precursor formulation prepared as described in Example 1 (36%wt PC, 54%wt GDO, and 10%wt EtOH) to air (RT, relative humidity 40%) for at least 3 hours, a solid cubic phase was formed. This formation of a cubic phase structure demonstrates that a topical film will acquire bulk non-lamellar depot properties after application without the need for direct exposure to excess aqueous fluid.

Example 13: Formulation to treat periodontitis or perimplantitis.

In order to treat periodontitis or perimplantitis an antibacterial formulation is injected in the periodontal pocket, and a prolonged effect of the formulation is normally desired.

100μL of a formulation as prepared in Example 1, with the addition of the antibiotic chlorohexidine (PC/GDO/EtOH/chlorhexidine (35/53/10/2)), is injected via a syringe into a rat peridontal pocket. The injected composition is observed to

transform from the low viscous formulation, and which initially spreads out to fill voids, to form a solid mass by uptake of gingival fluids. An antibacterial depot system is thus provided.

Chlorhexidine remains at clinically effective levels (MIC 125μg/ml) in the GCF of the periodontal pockets for over 1 week. The depot system is completely degraded by enzymes within 7 to 10 days and does not need to be removed.

Example 14: Alternate antibacterial formulation to treat periodontitis or perimplantitis.

An alternate antibacterial formulation was provided by a formulation prepared as described in Example 1 and containing the antibacterial detergent Gardol (Glycine, N-methyl-N-(1-oxododecyl)-, sodium salt) (PC/GDO/EtOH/Gardol (34/51/10/5)). This formulation is injected into the rat periodontal pocket.

Gardol is observed to remain at clinically effective levels in the GCF of the periodontal pockets for a prolonged period (several days). The depot system is completely degraded by enzymes within 7 to 10 days and did not need to be removed.

Example 15: Adhesion of the formulation to high energy surfaces.

In order to treat perimplantitis, adhesion not only to biological surfaces but also to high energy surfaces such as a gold or titanium implant is important. It is also important that the formulation adheres to ceramic and plastic surfaces.

A formulation (PC/GDO/EtOH (36/54/10)) as prepared in Example 1 was applied to various surfaces in the oral cavity. The composition showed excellent adhesion to ceramic, plastic, gold, as well as to a normal tooth surface and could not be rinsed away by excess aqueous fluid. The depot resulting from the composition stayed at the site in the oral cavity where it was applied for at least 6h.

Example 16: Bioadhesive sustained release formulation of sodium fluoride for use on the teeth.

Fluoride containing compounds are often needed to oppose caries attack and a bioadhesive formulation precursor with depot effect was prepared as indicated in Example 1 from a mixture of PC/GDO/EtOH/sodium fluoride (35/53/10/2). The formulation was a dispersion of sodium fluoride since it could not be dissolved in the precursor. The liquid formulation was applied to the teeth with the aid of a brush. By uptake of saliva the formulation solidified and formed a depot providing sustained release of sodium fluoride for an extended period (several hours).

Example 17: Oral Cavity Spray Depot Composition

To be suitable as a topical depot system in the oral cavity the mechanical properties of the system was adjusted by decreasing the PC/GDO ratio.

A mixture containing PC/GDO/EtOH (27/63/10) was prepared according to Example 1. A drop of patent blue was added to visualize the formulation after application. About 300µl of the formulation was sprayed into the oral cavity with pump spray bottle. Shortly after application the formulation viscosified/solidified since it underwent a phase transformation by uptake of aqueous fluid (saliva) and loss of solvent (EtOH). The formulation had excellent bioadhesion to keritinized surfaces such as the hard palate and the gum. Here the film lasted for several hours despite saliva secretion and mechanical wear by the tongue. At soft mucosal surfaces the duration was much shorter (minutes).

Example 18: Oral Cavity Liquid Depot Composition

To be suitable for application with a pipette to the oral cavity the solidification/ viscosification of the formulation has to be delayed relative to the spray formulation. This is to allow the formulation to be conveniently distributed with the tongue to a thin film in the oral cavity after application.

Propylene glycol (PG) and EtOH were added to a formulation prepared as in Example 1, to the final composition PC/GDO/EtOH/PG (24/56/10/10). 300µl of the formulation was conveniently applied with a pipette to the oral cavity and distributed with the tongue to a thin film in the oral cavity. After about 20 seconds the viscosification of the formulation started since it underwent a phase transformation by uptake of aqueous fluid (saliva) and loss of solvent (EtOH and PG). After about one minute the solidification/viscosification appeared to be

finished. The formulation had excellent bioadhesion to keritinized surfaces such as the hard palate and the gum. Here the film lasted for several hours despite saliva secretion and mechanical wear by the tongue. At soft mucosal surfaces the duration was much shorter (minutes).

Example 19 - Bioadhesive depot for nails

The mixture in Example 18 was sprayed to the nail bed and in between the toes. The formulation solidifies/viscosifies slowly by uptake of aqueous fluids (cf. sweat). The solidification can be speeded up by adding water after spray application. The formulation had excellent bioadhesive properties and had a duration for several hours.

Eample 20: Loading capacity of the bioactive agent benzydamine in the formulation precursors.

Formulations with compositions as specified in Table 5 were prepared using the method in Example 1. An excess amount of benzydamine (50mg) was added to 0.5 g of the formulations. The vials were placed on a shaker at 15 °C for three days after which the solutions were filtered through a filter (0.45μm) to get rid of crystals of undissolved benzydamine. The benzydamine concentration in each formulation was determined with reversed phase gradient HPLC and UV detection at 306nm and the results are given in Table 5.

Table 5

Composition GDO/PC(Lipoid S100)/EtOH	Benzydamine concentration in formulation
67.5/22.5/10	3.4%
63/27/10	3.2%
58.5/31.5/10	3.3%
60/20/20	4.0%
56/24/20	4.5%
52/28/20	4.3%

Example 21: Compositions containing PC and tocopherol

Depot precursor formulations were prepared with several different PC/α-tocopherol compositions using the method of Example 1 (PC was first dissolved in the appropriate amount of EtOH and thereafter α-tocopherol was added to give clear homogenous solutions).

Each formulation was injected in a vial and equilibrated with excess water. The phase behaviour was evaluated visually and between crossed polarizes at 25°C. Results are presented in Table 6.

Table 6

α-tocopherol	PC	Ethanol	Phase in excess H_2O
2.25g	2.25g	0.5g	H_{II}
2.7g	1.8g	0.5g	H_{II}/I_2
3.15g	1.35g	0.5g	I_2
3.6g	0.9g	0.5g	I_2/L_2

Example 22: In vitro release of water-soluble disodium fluorescein

A water-soluble colorant, disodium fluorescein (Fluo), was dissolved in a formulation containing PC/α-tocopherol/Ethanol (27/63/10 wt%) to a concentration of 5 mg Fluo/g formulation. When 0.1 g of the formulation was injected in 2 ml of phosphate buffered saline (PBS) a reversed micellar (I_2) phase was formed. The absorbency of Fluo released to the aqueous phase was followed at 490 nm over a period of 3 days. The release study was performed in a 3 mL vial capped with an aluminium fully tear off cap at 37°C. The vial was placed on a shaking table at 150 rpm.

The release of Fluo from the PC/α-tocopherol formulation (see Table 7) indicates that this (and similar) formulations are promising depot systems. Furthermore, the absence of a burst effect is noteworthy, and the release indicates that the substance can be released for several weeks to months; only about 0.4% of Fluo is released after 3 days.

Table 7

Formulation	% release (37°C)	
	24 h	72 h
PC/α-tocopherol/EtOH: 27/63/10 wt%	< 0.1*	0.43

* Release below detection limit of the absorbance assay

Example 23: Formulations of the analgesic/antiinflammatory benzydamine

Formulations were prepared as in Example 1 by mixing benzydamine with a mixture of GDO, PC, ethanol and optionally PG/AP in the following proportions.

Formulation	BZD	GDO	PC	EtOH	PG	AP
1	3.0	53.3	28.7	10.0	5.0	0.01
2	3.0	53.3	28.7	15.0	0	0.01
3	3.0	57.4	24.6	10.0	5.0	0.01
4	3.0	49.2	32.8	10.0	5.0	0.01

where BZD is benzydamine, EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, PG is propylene glycol, and AP is ascorbyl palmitate.

All formulations are low viscosity liquids which generate liquid crystalline phase compositions upon exposure to aqueous conditions.

Example 24: Fentanyl nasal formulation

Formulations were prepared as in Example 1 by mixing the narcotic analgesic fentanyl with a mixture of GDO, PC, ethanol and optionally PG in the following proportions.

Formulation	Fentanyl	PC	GDO	EtOH	PG
1	0.05	34	51	10	5
2	0.05	36	54	10	-
3	0.05	42	43	10	5
4	0.05	45	45	10	-
5	0.15	34	51	10	5
6	0.15	36	54	10	-
7	0.05	30	45	15	10

8	0.15	30	45	15	10

where EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, and PG is propylene glycol

All formulations are low viscosity liquids suitable for administration by nasal spray, which generate liquid crystalline phase compositions upon exposure to aqueous conditions.

Example 25: Diazepam nasal formulation

Formulations were prepared as in previous examples by mixing the benzodiazepine antianxiety agent diazepam with a mixture of GDO, PC, ethanol and optionally PG in the following proportions.

Formulation	Diazepam	PC	GDO	EtOH	PG
1	5	32	48	10	5
2	5	34	51	10	-
3	10	37	38	10	5
4	10	40	40	10	-
5	10	30	45	10	5
6	10	32	48	10	-
7	10	26	39	15	10
8	10	30	45	15	-

where EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, and PG is propylene glycol

All formulations are low viscosity liquids suitable for administration by nasal spray, which generate liquid crystalline phase compositions upon exposure to aqueous conditions.

Example 26: Acne formulations with Clindamycin

Formulations were prepared as in previous examples by mixing the semisynthetic antibiotic clindamycin (free base or salt) with a mixture of GDO, PC, ethanol and PG in the following proportions (by weight).

Formulation	Clindamycin HCl	PC	GDO	EtOH	PG
1	1	30	54	10	5
2	2	29	54	10	5
3	1	34	50	10	5
4	2	33	50	10	5

Formulation	Clindamycin base	PC	GDO	EtOH	PG
5	1	30	54	10	5
6	2	29	54	10	5
7	1	33	54	2	10
8	2	32	54	2	10

The resulting preformulations are low viscosity liquids which, after application resistant to water, sweat, etc. The formulation are applied locally on the skin as a gel or by spraying and are bioadhesive with good film-forming properties.

Example 27: Further examples of viscosity in PC/GDO mixtures on addition of co-solvent

Mixtures of PC/GDO and co-solvent were prepared according to the methods of Example 1 and Example 3 in the proportions indicated in the table below. The samples were allowed to equilibrate for several days before viscosity measurements were performed using a Physica UDS 200 rheometer at 25°C.

Sample	PC/GDO (wt/wt)	EtOH / wt%	Glycerol / wt%	H_2O / wt%	Viscosity / mPas
1	50/50	3	-	-	1900
2	50/50	5	-	-	780
3	50/50	7	-	-	430
4	50/50	8	-	-	300
5	50/50	10	-	-	210
6	50/50	15	-	-	100
7	45/55	3	-	-	1350
8	45/55	5	-	-	540
9	45/55	7	-	-	320
10	45/55	8	-	-	250
11	45/55	10	-	-	150
12	45/55	15	-	-	85
13	40/60	3	-	-	740
14	40/60	5	-	-	400
15	40/60	7	-	-	240
16	40/60	8	-	-	200
17	40/60	10	-	-	130
18	40/60	15	-	-	57
19	40/60	-	10	-	$8*10^6$
20	40/60	-	-	3	$2.5*10^8$
21	40/60	-	-	5	$4*10^7$

This example further illustrates the need for a solvent with viscosity lowering properties in order to obtain injectable formulations. The mixtures containing glycerol (sample 19) or water (samples 20 and 21) are too viscous to be injectable at solvent concentrations equivalent to the samples containing EtOH (compare with samples 13, 14 and 17).

Example 28: Sunscreen formulations

Formulations were prepared as in Example 1 by mixing each of several UV absorbing/scattering agents with a mixture of GDO, PC, and ethanol in the following proportions (by weight)

Formulation	PC	GDO	EtOH	Tioveil CM	Spectraveil FIN	Solaveil CT-100	Tioveil 50 MOTG
1	38	42	5	-	-	-	15
2	38	42	5	-	-	15	-
3	37	38	5	15	5	-	-

Where TIOVEIL CM (Uniqema) comprises Cyclomethicone (and) Titanium Dioxide (and) Dimethicone Copolyol (and) Aluminium Stearate (and) Alumina, SPECTRAVEIL FIN (Uniqema) comprises Zinc Oxide (and) C12-15 Alkyl Benzoate (and) Polyhydroxystearic Acid, SOLAVEIL CT-100 (Uniqema) comprises C12-15 Alkyl Benzoate (and) Titanium Dioxide (and) Polyhydroxystearic Acid (and) Aluminum Stearate (and) Alumina, and TIOVEIL 50 MOTG (Uniqema) comprises Titanium Dioxide (and) Caprylic/Capric Triglyceride (and) Mineral Oil (and) Polyhydroxystearic Acid (and) Aluminum Stearate (and) Alumina.

The resulting formulation precursors show low viscosity upon formulation and are readily applied by pump spray. Upon contact with body surfaces a resilient UV protective layer is formed.

Example 29: Chlorhexidine periodontal depots.

Formulations were prepared as in Example 1 by mixing the antiinfective agent chlorhexidine digluconate with a mixture of GDO, PC, and ethanol in the following proportions (by weight)

Table. Chlorhexidine digluconate depot formulation compositions.

Formulation	Chlorhexidine digluconate	PC	GDO	EtOH
A	5	34	51	10
B	5	36	54	5
C	7	33	50	10
D	10	32	48	10
E	15	30	45	10

The chlorhexidine depot preformulations have low viscosity and are easily administered to the periodontal pocket. The compositions provide better distribution and spreading of the active substance throughout the periodontal pocket when compared to current products, such as Periochip®.

The depot formed after application gives protection against re-infection of the pocket. The depot also has excellent bioadhesive properties and sticks to mucosal, teeth and bone surfaces.

Release of chlorhexidine digluconate from 250 mg Formulation A (see above) in 0.9% aqueous NaCl (500 ml) was studied. The formulation was held in a cylindrical metal cup which was placed in a teflon holder at the bottom of a standard USP release bath. The contact area between the formulation and surrounding saline solution was 2.4 cm^2, and the solution was stirred by paddle at 100 rpm.

The release curve shown in Figure 3 demonstrates the sustained and essentially uniform release of chlorhexidine from the formulation over a period of 24 hours.

Example 30, topical formulation with a NSAID

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID). It belongs to the phenylacetic acid group and is used in inflammatory conditions of various etiologies, degenerative joint disease and many other painful conditions.
A formulation for topical administration containing diclofenac sodium was prepared by first preparing a placebo formulation.

Composition of placebo formulation

Excipient	Abbreviation	Concentration (%)
Phosphatidyl choline (from soy bean)	SPC	45.0
Glycerol dioleate	GDO	45.0
Etanol 99,5 %	EtOH	10.0

Diclofenac sodium to a concentration of 5% was dissolved in the placebo formulation. The resulting oily liquid was slightly yellowish, transparent, and had a low viscosity.

Example 31, formation of liquid crystalline phase

One drop of the diclofenac sodium containing formulation in Example 30 was added to 3 ml aqueous saline solution with a pipette. A cohesive liquid crystalline phase formed.

Example 32, formation of rigid film *in situ*

One drop of the diclofenac sodium containing formulation in example 30 was applied to the skin on the arm of a healthy volunteer and smeared out to a thin film covering an area of about 2-4 cm^2. Shortly after application the liquid formulation

transformed to a much more rigid film by uptake of small amounts of water from the skin and/or the air.

Example 33, improving spray pattern by lowering viscosity
A placebo formulation with the composition as given in the Table in Example 30 was filled in a standard pump-spray bottle. After priming the pump with formulation the formulation could be applied to the skin with a sub-optimal spray-pattern. By diluting the formulation further with EtOH the viscosity of the formulation decreased and at an EtOH concentration corresponding to about 25% the formulation could be applied as a mist to the skin. Spaying the formulation to the skin on the arm of a healthy volunteer resulted in formation of a rigid film after evaporation of EtOH and uptake of small amounts of water from the skin and/or the air.

Example 34, improving spray pattern by using a compression pump device
A placebo formulation with the composition as given in the Table in Example 30 was filled in a standard compression pump bottle. This device gave a good mist/aerosol and spray pattern. Spaying the formulation to the skin on the arm of a healthy volunteer resulted in formation of a rigid film after uptake of small amounts of water from the skin and/or the air.

Example 35, use of pressure driven device
A placebo formulation with the composition as given in the Table in Example 30 was filled in a pressure driven spray-device either with a hydrocarbon propellant or with HFC-134a as propellant, respectively. Both propellants were found to form low-viscous homogeneous mixtures with the formulation. Spaying the formulation to the skin on the arm of a healthy volunteer resulted in rapid formation of a rigid film after uptake of small amounts of water from the skin and/or the air.

Example 36, spraying formulation with very low concentration of EtOH
A formulation with the composition as given in the table below was prepared by evaporating EtOH from the placebo formulation with the composition as given in the Table in Example 30 with the aid of a rotary evaporator (vacuum, 40°C). The resulting formulation had a high viscosity but when mixed with propellant (hydrocarbon propellant or HFC-134a) and filled in a spray bottle the formulation could be sprayed to the skin on the arm of a healthy volunteer where a rigid film formed after uptake of small amounts of water from the skin and/or the air.

Composition of placebo formulation

Excipient	Abbreviation	Concentration (%)
Phosphatidyl choline (from soy bean)	SPC	49.0
Glycerol dioleate	GDO	49.0
Etanol 99,5 %	EtOH	2.0

Example 37, targeting to different surfaces by varying the composition of the formulation

By varying the PC/GDO ratio in the formulation duration of the formulation at different places in the oral cavity could be adjusted. A formulation with the composition PC/GDO/EtOH (36/54/10) has a preference for adherance to hard surfaces, such as teeth, while a formulation with the composition PC/GDO/EtOH (27/63/10) was found to be better suited for the upper palate.

Example 38, formation of a liquid crystalline phase from precursors with various solvent mixtures

To improve solubility of active substance in the precursors it may be useful to change solvent in the formulation. A number of different solvent mixtures were used in the formulation precursors (see Table) and their ability to form a liquid crystalline phase after contacting them with excess aqueous solution was investigated. One drop of each formulation was added to 3 ml aqueous saline solution with a pipette. Independent of the solvent (mixture) used a cohesive liquid crystalline phase formed.

Composition of formulations

Excipients	Composition (wt%)
PC/GDO/EtOH	45/45/10
PC/GDO/EtOH/NMP	45/45/5/5
PC/GDO/EtOH/propylene-carbonate	45/45/5/5
PC/GDO/EtOH/dimethyl-isosorbide	45/45/5/5
PC/GDO/EtOH/dimethyl- acetamide	45/45/5/5
PC/GDO/EtOH/ethyl-acetate	45/45/5/5

Example 39 - topical formulation with testosterone enanthate

A topical formulation containing 2% testosterone enanthate was prepared by mixing the components in the Table below. Shortly after applying the liquid formulation to the skin it transformed to a much more rigid film by uptake of small amounts of water from the skin and/or the air.

Composition of topical formulation with testosterone enanthate

Component	Amount (g)	Composition (wt%)
Testosterone enanthate	0.060	2.00
Soy Phosphatidyl Choline	1.323	44.10
Glycerol Dioleate	1.323	44.10
Ethanol	0.294	9.80

Legends to Figures:

Figure 1. Cumulative release of MB from a depot forming a reversed hexagonal H_{II} phase.

Figure 2. Decrease in viscosity of the depot precursor on addition of solvents. PC/GDO (6/4) is a precursor to a reversed hexagonal H_{II} phase and PC/GDO (3/7) is a precursor to a reversed cubic I2 phase.

Figure 3: Release of Chlorhexidine from formulation A, see Example 33.

Claims:

1) a pre-formulation comprising a low viscosity mixture of:
a) at least one neutral diacyl lipid and/or a tocopherol;
b) at least one phospholipid;
c) at least one biocompatible, (preferably oxygen containing) organic solvent;
optionally including at least one bioactive agent is dissolved or dispersed in the low viscosity mixture, wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid and/or body surface.

2) A pre-formulation as claimed in claim 1 wherein said liquid crystalline phase structure is bioadhesive.

3) A pre-formulation as claimed in claim 1 or claim 2 wherein component a) consists essentially of diacyl glycerols, especially glycerol dioleate.

4) A pre-formulation as claimed in any of claims 1 to 3 wherein component b) is phosphatidylcholine.

5) A preformulation as claimed in any of claims 1 to 4 having a viscosity of 0.1 to 5000 mPas.

6) A preformulation as claimed in any of claims 1 to 5 having a molecular solution, L_2 and/or L_3 phase structure.

7) A preformulation as claimed in any of claims 1 to 6 having 35 to 60% by weight a), 20 to 50% by weight b) and 10 to 20% by weight c).

8) A preformulation as claimed in any of claims 1 to 10 wherein component c) is an alcohol.

9) A preformulation as claimed in any of claims 1 to 8 additionally comprising up to 10% by weight of a)+b) of a charged amphiphile.

10) A preformulation as claimed in any of claims 1 to 9 wherein said active agent is selected from corticosteroids nonsteroidal anti-inflammatory compounds, local inhibitors of inflammatory pathways phospholipase inhibitors, antioxidants, antiinfectives, cytokines and cytokine inducers/supressors.

11) A preformulation as claimed in any of claims 1 to 10 which is administrable by rinsing, spraying, gargling, as a patch, by suppository or by enema.

12) A preformulation as claimed in claim 11 comprising bezydamine

13) A topical formulation as claimed in any of claims 1 to 11 for intraoral administration which forms a bioadhesive, controlled release product, wherein said active agent comprises at least one selected from; benzydamine, tramadol, Acetaminophen, Ibuprofen, Propoxyphene, Codeine, Dihydrocodein, Hydrocodone, Oxycodone, Nalbuphine, Meperidine, Leverorphanol, Hydromorphone, Oxymorphone, Alfentanil, Fentanyl and Sefentanil.

14) A topical preformulation as claimed in any of claims 1 to 11 suitable for intraoral administration for treatment of periodontal and topical infections, wherein the active agent is chlorhexidine gluconate, and where the preformulation is applied as a liquid product which forms a surface gel *in situ* between 1 second. and 5 min after application.

15) A topical formulation as claimed in any of claims 1 to 11 suitable for ocular administration, wherein said active agent comprises at least one selected from diclofenac, pilocarpine, levocabastine hydrochloride, ketotifen fumarate, timolol, betaxolol, carteolol, levobunolol, dorzolamide, brinzolamide, epinephrine, dipivefrin, clonidine, apraclonidine, brimonidine, pilocarpine, atanoprost, travoprost, bimatoprost, unoprostone, pilocarpine hydrochloride, dexamethasone, chloramphenicol, and indomethacin.

16) A topical formulation as claimed in any of claims 1 to 11 for dermatological administration which forms a bioadhesive, controlled release product, wherein the active agent is selected from cosmetic agents, fragrances, flavourings, essential oils UV absorbing agents and mixtures thereof.

17) A method of delivery of a bioactive agent to a human or non-human animal (preferably mammalian) body, this method comprising administering a pre-formulation comprising a non-liquid crystalline, low viscosity mixture of:

a) at least one neutral diacyl lipid and/or at least one tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, oxygen containing, low viscosity organic solvent;

and at least one bioactive agent is dissolved or dispersed in the low viscosity mixture, whereby to form at least one liquid crystalline phase structure upon contact with an aqueous fluid *in vivo* following administration.

18) A method as claimed in claim 17 wherein said preformulation is a preformulation as claimed in any of claims 1 to 16.

19) The use of a non-liquid crystalline, low viscosity mixture of:

a) at least one neutral diacyl lipid and/or at least one tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, oxygen containing, low viscosity organic solvent;

wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture in the manufacture of a pre-formulation for use in the sustained local administration of said active agent, wherein said pre-formulation is capable of forming at least one liquid crystalline phase structure upon contact with an aqueous fluid.

20) The use as claimed in claim 19 wherein said preformulation is a preformulation as claimed in any of claims 1 to 16.

21) A method of treatment or prophylaxis of a human or non-human animal subject comprising administration of a preformulation as claimed in any of claims 1 to 16.

22) A method for the treatment of a human or animal subject comprising administration of a preformulation as claimed in any of claims 1 to 16.

23) A method as claimed in claim 22 for the treatment of inflammation and/or irritation at a body surface and/or in a body cavity.

24) The method as claimed in claim 23 wherein said inflammation is caused by Crohn's disease, ulcerative collitus or oral mucositis.

25) Use of a composition as claimed in any of claims 1 to 16 in the manufacture of a medicament for the treatment of inflammation and/or irritation at a body surface and/or in a body cavity.

26) Method for the treatment of oral mucositis in a human or animal subject comprising administration of a preformulation as claimed in claim 1, said composition comprising 40 to 60 wt% GDO, 20 to 35% PC, 5 to 25% ethanol, and 1 to 8% bezydamine, or a derivative thereof.

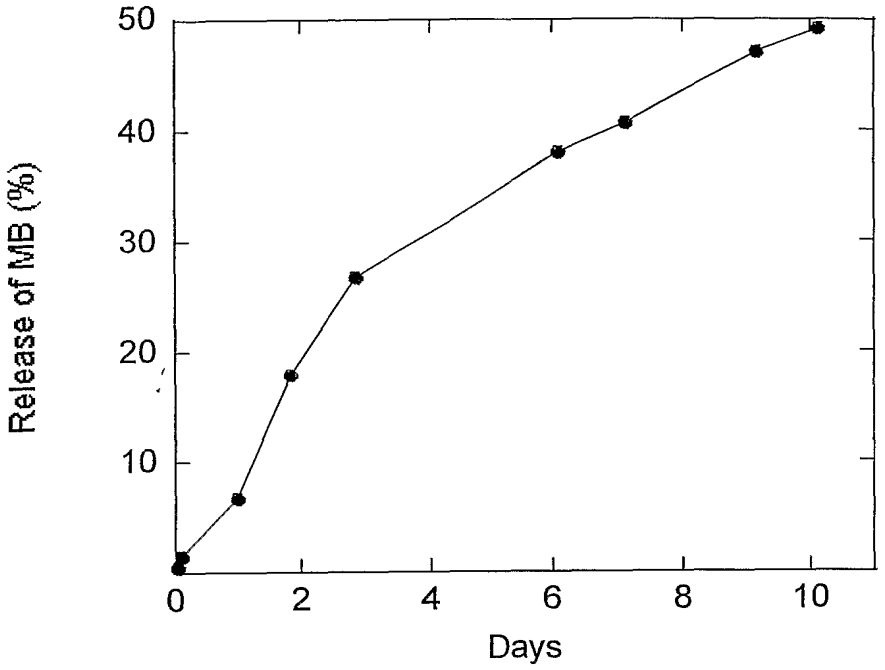


Figure 1. of MB from a depot forming a reversed hexagonal H_{II} phase.

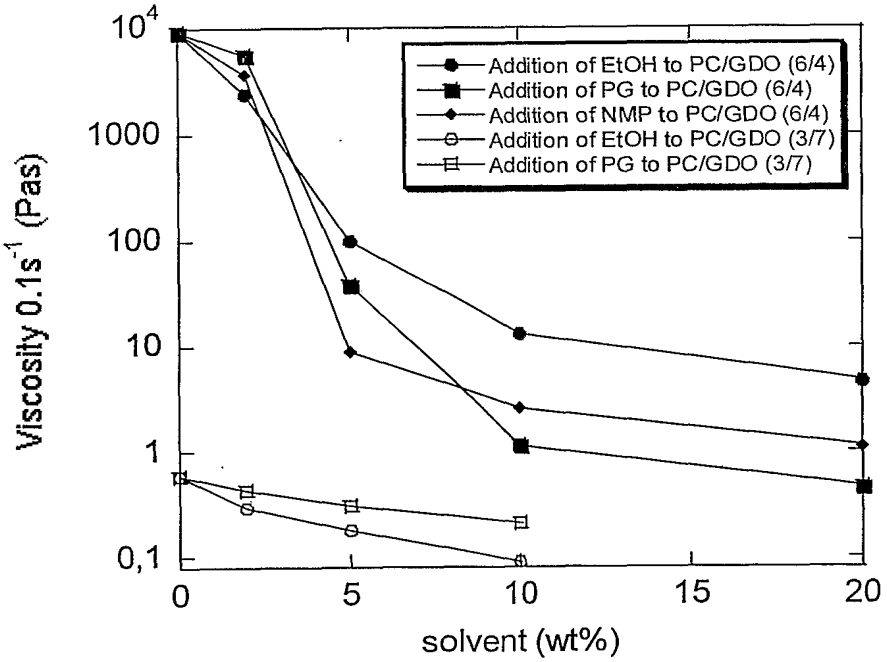


Figure 2.

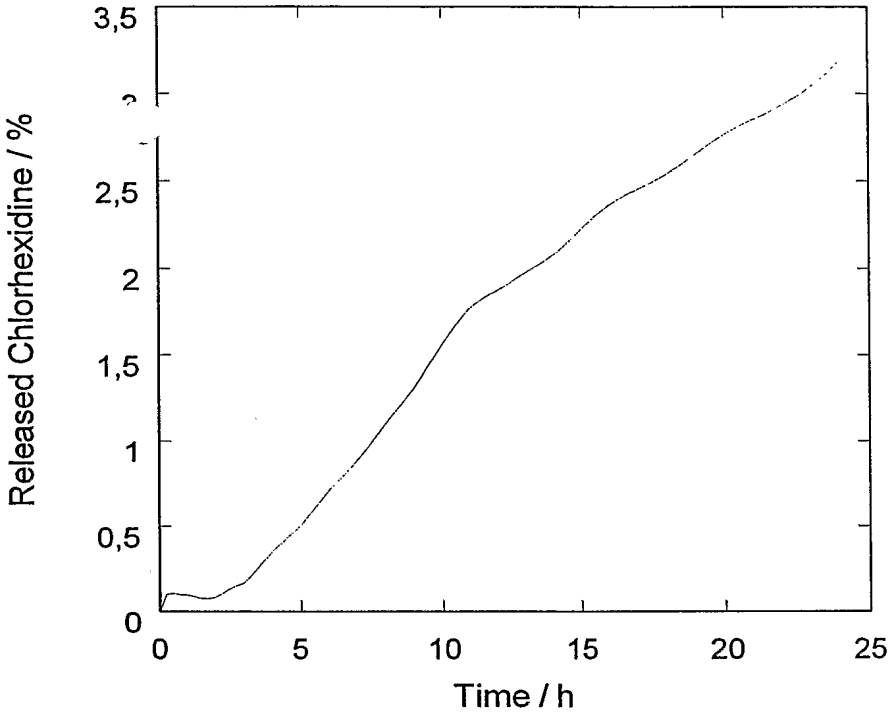


Figure 3

INTERNATIONAL SEARCH REPORT

Inter nal application No
PCT/GB2005/004746

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/10 A61K9/06 A61K9/12

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.
P,X	WO 2005/046642 A (CAMURUS AB; JOABSSON, FREDRIK; TIBERG, FREDRIK; GODDARD, CHRISTOPHER) 26 May 2005 (2005-05-26) page 13, last paragraph page 27, paragraph 3 - page 28, paragraph 3 examples 5,6 page 20	1-26
X	US 5 807 573 A (LJUSBERG-WAHREN ET AL) 15 September 1998 (1998-09-15) column 2, line 60 - line 64 column 4, line 4 - line 62 examples 1,3	1-26

-/--

[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
9 March 2006	16/03/2006

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Giménez Miralles, J

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

INTERNATIONAL SEARCH REPORT

Inter ıal application No
PCT/GB2005/004746

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/068562 A (THE PROCTER & GAMBLE COMPANY) 6 September 2002 (2002-09-06) page 10, last paragraph page 14	1-26
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Y	WO 98/47487 A (DUMEX-ALPHARMA A/S; NIELSEN, LISE, SYLVEST) 29 October 1998 (1998-10-29) the whole document	1-26
Y	US 6 464 987 B1 (FANARA DOMENICO ET AL) 15 October 2002 (2002-10-15) column 4, line 52 - line 65 claim 10 column 3	1-26
A	SHAH JAYMIN C ET AL: "Cubic phase gels as drug delivery systems" ADVANCED DRUG DELIVERY REVIEWS, AMSTERDAM, NL, vol. 47, no. 2-3, 25 April 2001 (2001-04-25), pages 229-250, XP002320651 ISSN: 0169-409X the whole document	1-26

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/004746

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17,18,21-24,26
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17, 18, 21-24 and 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ıal application No
PCT/GB2005/004746

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			JP	2002513748 T	14-05-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal application No
PCT/GB2005/004746

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— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS FOR NASAL DELIVERY

(57) Abstract: Use of phospholipids, one or more C2-C4 alcohols and water in the preparation of a vesicular composition adapted for intranasal administration of an active agent, wherein the concentrations of said phospholipids and said one or more alcohols in said composition are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

WO 2007/043057 A2

Compositions for Nasal Delivery

Nasal drug delivery is a popular way to treat local/respiratory ailments which has traditionally been restricted to administer drugs for sinus conditions, such as congestion and allergies. Recently, however, there has been increased interest in the nose as an alternative to oral and parenteral delivery for many systemic drugs and vaccines. The vastly vascularised and immunogenic nasal mucosa present potential benefits for systemic absorption in terms of quick action, avoidance of any degradation and/or unwanted entero-hepatic metabolism of the drug (improved bio-availability) and patient compliance as well as improved immune response for vaccines. The nasal route could also provide an attractive needle-free alternative for currently injectable drugs which may improve patient compliance and allow extended use of self-medication for many chronic diseases/acute conditions or vaccinations. Some systemically-acting drugs for the treatment of osteporosis, cardiovascular medications and painkillers are already on the market in nasal formulations.

However, although this route is beginning to be explored for systemic delivery of drugs the major limitation in nasal delivery is the insufficient permeation of drugs across the nasal mucosa. Furthermore, the anatomical and physiological features of the nose are not ideal for drug administration, since a relatively small surface area (150 cm^2) puts considerable constraints on formulations and drug candidates. Only very potent molecules can be used in this route. For example, for peptides there is the inverse relationship between bioavailability and molecular weight of the peptide which points toward, that

those peptides with more than 30-40 amino acids require penetration enhancers for attaining a sufficient bioavailability (in the range of 10%). There are two main pathways for absorption of the molecule from the nasal cavity: paracellular (driven by passive diffusion) or transcellular (driven by carrier or receptor mediated active transport). In the absence of active transport components, most peptides cross the nasal epithelium by the paracellular route, driven by passive diffusion. Due to hydrophilicity of peptides the transcellular route is mainly relevant for transport processes or for transcytosis. Both transcellular routes are energy dependent and are therefore designated as active transport processes.

The issue of improving nasal absorption is important. Several strategies have been investigated in the past decade such as chelators of calcium (EDTA), inhibition of nasal enzymes (boro-leucin, aprotinin), inhibition of muco-ciliar clearance (preservatives), solubilisation of nasal membrane (cyclodextrin, fatty acids, surfactants) and formation of micelles (surfactants). Many surfactants such as bile acids, Laureth 9 and taurodehydrofusidate (STDHF) turned out to be quite effective in enhancing nasal absorption, but caused local cytotoxic effects on ciliated cells. Therefore, enhancers with an acceptable safety profile under chronic treatment are still to be discovered. A greater permeability of drug through nasal mucosa has the potential to overcome the limitations of oral route and to approach the benefits of intravenous infusion. Safe and efficacious enhancers will be necessary for commercially successful products.

The delivery of biologically active materials to the skin and cell membranes by means of an aqueous vehicle that comprises the combination of lipid vesicles and water miscible organic solvents has been described in the art.

For example, an aqueous carrier system containing phospholipids and ethanol was described in EP 158441, with the weight ratio between the aforementioned components being from 40:1 to 1:20.

US 5,711,965 describes a solution comprising phospholipids, ethanol and water in a weight ratio of 10:16:74, respectively.

US 5,540,934, US 5,716,638 and WO 03/000174 describe an aqueous composition containing vesicles (ethosomes) in the presence of ethanol.

US 6,627,211 describes a carrier suitable for the administration of an anti-convulsive agent to the nasal mucous membranes. It appears that the content of organic solvents in said carrier is relatively high (30% to 60% ethanol and 30 to 60% propylene glycol).

It has now been found that an aqueous composition which contains phospholipids in a concentration of 0.2 to 10% by weight, in combination with one or more short chain alcohols, wherein the weight concentration of water is not less than 30% by weight and the weight concentration of said alcohol(s) is in the range between 12 to 30% by weight, may be adapted for use as an intranasal drug delivery vehicle.

Accordingly, in a first aspect, the present invention provides the use of phospholipid, one or more C2-C4 alcohols and water in the preparation of a vesicular composition adapted for intranasal administration of an active agent, wherein the concentrations of said phospholipid and said one or more alcohols in said composition are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, and the water content of said composition is not less than 30% by weight.

Preferably, the water content in the composition is not less than 35%, and more preferably not less than 45%. The weight ratio between the alcohol(s) and the phospholipids is not less than 2:1, and more preferably not less than 5:1.

Phospholipids suitable for use in the preparation of the composition according to the present invention include phosphatidylcholine (PC), hydrogenated phosphatidylcholine, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG) and phosphatidylinositol (PL). The chemical structure of phospholipids that may be used according to the present invention is described in US 4,614,730, which is incorporated herein by reference. Preferably, the phospholipids are present in the composition of the invention at a concentration of 0.5 to 5% by weight.

The term C2-C4 alcohols, as used herein, refers to alkanols containing two, three or four carbon atoms. The alcohols to be used according to the present invention

specifically include ethanol, 1-propanol, isopropyl alcohol and *tert*-butyl alcohol, with the former being especially preferred. The concentration of ethanol in the composition contemplated by the present invention for use as an intranasal drug delivery vehicle is preferably in the range of 15 to 27% by weight.

According to a particularly preferred embodiment of the invention, the composition further comprises one or more water miscible polyols, and especially glycols (1,2-diols, such as ethylene glycol and propylene glycol, with the latter being especially preferred), at a concentration of 1 to 30% by weight, and preferably 5 to 20 by weight.

The compositions of the present invention may be prepared by mixing together the various components, namely, water, phospholipids, one or more C2-C4 alcohols (and possibly also one or more polyols) and the active ingredient under conditions that allow the formation of vesicles. More specifically, the compositions of the present invention may be conveniently prepared by dissolving the phospholipids in the alcohol (or in the alcohol/glycol mixture), followed by the addition of the active ingredient, either in the form of an aqueous solution thereof or in a solid form, with a subsequent addition of water. The preparation of the composition is preferably carried out under stirring, typically at room temperature or at an elevated temperature, which is preferably not higher than 50°C.

Alternatively, a dispersion of the phospholipids and the active ingredient in water is prepared, into which the

alcohol, optionally together with polyol (e.g., a mixture of ethanol and propylene glycol) are added with stirring, possibly under heating.

It is also possible to first prepare freeze-dried lipid vesicles having the active ingredient encapsulated therein, and subsequently dispersing the same in a mixture of water, the C2-C4 alcohol and optionally polyol.

As mentioned above, the combination of phospholipids, water, and the water-miscible organic solvents (namely, the alcohol and the polyol) according to the concentrations and weight ratios specified above allows the formation of a non-irritant, vesicular composition, with the vesicles present therein, whose size ranging between 50 nm to few microns, and more specifically, up to 5μm, exhibiting good properties for enhanced nasal absorption. Figure 1 is TE (transmission electron) micrograph of a specific composition according to the present invention (containing insulin as the active agent; the exact composition is given in the Examples below - entry F in table 1A). It may be seen that in this specific system, the vesicular structures are multilamellar. The vesicles were visualized by transmission electron microscopy (TEM) and scanning electron microscopy. TEM analysis was carried out using a Philips TEM CM 12 electron microscope (TEM, Eindhoven, The Netherlands) with an accelerating voltage of 100kV.

Thus, the present invention concerns methods for intranasal administration, and compositions for intranasal administration comprising vesicular systems

formed from at least one active molecule, phospholipid, alcohol (C2-C4) and water. Optionally, the composition further comprises glycol (propylene glycol, transcutol, tetraglycol, etc).

We have found that pharmaceutical formulations including the above ingredients could deliver therapeutic amounts of agents to the systemic circulation or the brain of mammals and have efficient therapeutic or prophylaxis effect. The invention can be used for pharmaceutical, cosmetic, medical, veterinary, diagnostic and research applications. The present invention includes nasally administering to the mammal a therapeutically effective amount of active ingredient by means of compositions described above. The nasal delivery may be either for local purposes (to the mucosa of the nose), for systemic administration through the circulation or for CNS administration for curing brain disease.

It should be noted that the composition according to the present invention may include additional excipients that are well known in the art, such as surfactants, preservatives, thickening agents, co-solvents, adhesives, antioxidants, buffers, viscosity and absorption enhancing agents and agents capable of adjusting the pH and osmolarity of the formulation.

Suitable surfactants that can be used in accordance with the present invention include ionic, nonionic or amphoteric surface active agents. More specifically, hydrophilic surfactants (e.g. Tweens, Tween 80, Myrj, Brjs, Labrasol etc.) or lipophilic surfactants (eg. Span 20, Span 60, Myrj, Arlacel 83 and such) may be suitably

used, preferably at a concentration in the range of 0-25% by weight.

Suitable preservatives that can be used with the present formulations include, for example, benzyl alcohol, parabens, chlorobutanol, benzalkonium salts and combinations thereof. Some examples of antioxidants include tocopherols, butyl hydroxytoluene, sodium metabisulfite, potassium metabisulfite, ascorbyl palmitate and the like. These preservatives and antioxidants may be present in the formulations in a concentration of from about 0.001% up to about 5%w/w.

Regarding buffers, the nasal delivery system may include a buffer for maintaining the formulation at a pH of about 7.0. The particular buffer, of course, can vary depending upon the particular nasal delivery system used, as well as the specific active molecule selected. Buffers that are suitable for use in the present invention include, for example, acetate, citrate, prolamine, carbonate and phosphate buffers and combinations thereof. The pharmaceutical formulations of the present invention may include a pH adjusting agent.

Regarding thickening agents, the viscosity of the formulations of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. Thickening agents that can be added to the compositions of the present invention include for example, methyl cellulose, xanthan gum, tragacanth, adhesives, guar gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans, mucoadhesive polymer-

systems like poly(acrylates), cellulose derivatives, hyaluronic acid, hyaluronic acid derivatives, chitin, collagen, pectin, starch, poly(ethylene glycol), sulfated polysaccharides, carrageenan, Na-alginate, gelatine, pectin and combinations thereof. The desired concentration of the thickening agent will depend upon the agent selected and the viscosity desired.

The compositions may also comprise gel forming or bioadhesive compounds such as carbopols, alginates, scleroglucan, cellulose derivatives, starch, albumin, pluronic gels, diethyl aminoethyl (DEAE)-sephadex, polycarbophil, hyaluronic acid, hyaluronates, starch, gelatin, cholagen and others. Compositions can also be incorporated in the w/o cream, o/w cream, hydrophilic ointment or lipophilic ointment, gels, other semi-solid bases. The compositions could be delivered to the nasal cavity as drops, mists, aerosols, instillations, by use of pipetor, special devices, evaporators, vaporizators and such.

The formulations of the present invention may also include agents such as tolerance enhancers to reduce or prevent drying of the mucus membrane and to prevent irritation thereof.

The compositions according to the present invention may be applied to the nasal cavity as liquids, sprays, aerosols, nebulizaers or semi-solid preparations. Semisolid preparations may be on the base of gels, w/o or o/w creams or hydrophilic/lipophilic ointments. The compositions may contain molecularly dispersed (soluble, solubilized, etc.) active agent or the fine particles/crystals of the active agent. The compositions

could be administered from nasal sprays, metered-dose sprays, squeeze bottles, liquid droppers, disposable one-dose droppers, nebulizers, cartridge systems with unit-dose ampoules, single-dose pumps, bi-dose pumps, multiple-dose pumps or any other device. For example, the compositions of the invention may be stored in/delivered from a spray or aerosol device/container as described in details in Remington's Pharmaceutical Sciences (16th edition, Chapters 83 and 92).

Regarding spray devices, it should be noted that both single (unit) dose or multiple dose systems may be used. Typically, a spray device comprises a bottle and a pump; such devices are commercially available from various sources. Typically, the volume of liquid that is dispensed in a single spray actuation is in the range of from 5 to 250 microlitters/each nostril/single administration and the concentration of the active ingredient in the formulation may be readily adjusted such that one or more spray into the nostrils will comply with the dosage regimen.

The present invention also provides a spray device or a dose cartridge for use in a nasal delivery device loaded with a composition as described above.

In another aspect, the invention provides a method of administering an active pharmaceutical ingredient to a patient in need thereof, which method comprises the intranasal administration of a vesicular composition comprising a therapeutically effective amount of said ingredient, phospholipids, one or more C2-C4 alcohols and water, wherein the concentrations of said phospholipids and said one or more alcohols in said composition are in

the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 20%, and preferably not less than 30% by weight.

Mammals include humans, pet animals, laboratory animals, farm animals and wild animals.

The intranasal drug delivery vehicle according to the present invention may be adapted for the administration of active agents that can be used for medical, pharmaceutical, veterinary, research or diagnostic purposes. However, especially preferred active agents to be used according to the present invention include an anti-diabetic agent (e.g., insulin or derivative thereof), an anti-malaria agent (which is most preferably dihydroartemisinin); an anti-anxiety agent and an anticonvulsant (which is most preferably diazepam) and anti-emetic agent (which is most preferably granisetron hydrochloride); an anti-anxiety/anti-depressant (which is most preferably buspirone hydrochloride); an anti-multiple sclerosis agent (which is most preferably glatiramer acetate); an anti-depressant/ an anti-hot flashes agent (which is most preferably paroxetine or a pharmaceutically acid addition salt thereof); an anti-dementia/Alzheimer's agent (which is most preferably rivastigmine); and an anti-obesity agent (which is most preferably sibutramine).

More specifically, it has now been found that the intranasal drug delivery vehicle according to the present invention may be used for the intranasal administration of insulin. The term insulin or derivative thereof, as used herein, encompasses rapid acting (e.g. insulin

aspart, insulin glulisine, insulin lispro), short-acting (regular), intermediate-acting (NPH), intermediate and short acting mixtures and long-acting insulin (e.g. insulin glargine, insuline detemir) (according to FDA classification as appears in www.fda.gov/fdac/features/2002/chrt_insulin.html). Insulin is typically administered at daily dose of 1.5 to 150IU.

Accordingly, in another aspect, the present invention provides a pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of insulin or a derivative thereof together with water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight. Preferably, the composition further comprises a polyol, and more specifically, propylene glycol, at a concentration in the range of 1 to 30% by weight.

In another aspect, the present invention provides a method for treating diabetes in a mammal, which method comprises the intranasal administration of the aforementioned insulin-containing composition.

It has now been also found that the intranasal drug delivery vehicle according to the present invention may be used for the intranasal administration of diazepam. Diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzo-diazepin-2-one. A method for the synthesis of

diazepam has been described, for example by Sternbach LH, Reeder E, Keller O, & Metlesics W. [Quinazolines and 1,4-benzodiazepines III substituted 2-amino-5-phenyl-3H-1,4-benzodiazepine 4-oxides. J Org Chem, 26: 4488-4497, 1961]. Diazepam is typically administered at a daily dose of 0.2 to 100 mg.

Accordingly, in another aspect, the present invention provides a pharmaceutical composition, which comprises a therapeutically effective amount of diazepam together with water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight. Preferably, the composition further comprises a polyol, and more specifically, propylene glycol, at a concentration in the range of 1 to 30% by weight.

In another aspect, the present invention provides a method for preventing and/or treating epileptic seizures in a mammal, which method comprises the intranasal administration of the aforementioned diazepam-containing composition.

It has now been also found that it is possible to prepare a pharmaceutical composition of Granisetron [an anti-emetic agent, which is chemically named: endo-1-methyl-N-(9-methyl-9-azabicycle[3.3.1]non-3-yl)-1H-indazole-3-carboxamide] that is suitable for the intranasal administration of said drug. Granisetron is described in EP 200444; methods for preparing granisetron are also

described in WO03/080606. Granisetron is typically administered at a daily dose of 0.1 to 10 mg.

Accordingly, in another aspect, the present invention provides a pharmaceutical composition, which comprises a therapeutically effective amount of granisetron or a pharmaceutically acceptable salt thereof together with water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight. Preferably, the composition further comprises a polyol, and more specifically, propylene glycol, at a concentration in the range of 1 to 30% by weight.

In another aspect, the present invention provides a method for treating and/or preventing emesis in a mammal, which method comprises the intranasal administration of the aforementioned granisetron-containing composition.

Other compositions for intranasal administration contemplated by the present invention comprise:
(i) a therapeutically effective amount of an a pharmaceutically active ingredient selected from the group consisting of buspirone, glatiramer, paroxetine, rivastigmine and sibutramine and a pharmaceutically acceptable salt thereof, together with:
(ii) water;
(iii) phospholipids; and
(iv) one or more C2-C4 alcohols;
wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and

12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight. Preferably, the composition further comprises a polyol, and more specifically, propylene glycol, at a concentration in the range of 1 to 30% by weight.

In another aspect, the present invention provides a method for preventing and/or treating obesity in a mammal, which method comprises the intranasal administration of the aforementioned sibutramine-containing composition. Sibutramine is typically administered at a daily dose of 1 to 30 mg. Its preparation is described by Jeffery et al., [Synthesis of Sibutramine, A Novel Cyclobutylalkylamine Useful in the Treatment of Obesity and its Major Human Metabolites, J. Chem. Soc. Perkin. Trans. 1, 2583-2589 (1996)] and also in US Patent Nos. 4,746,680; 4,929,629; and 5,436,272.

In another aspect, the present invention provides a method for preventing and/or treating dementia, and specifically, Alzheimer disease in a mammal, which method comprises the intranasal administration of the aforementioned rivastigmine-containing composition. Rivastigmine may be administered as its hydrogen tartrate salt at a daily dose of 1 to 20 mg.

In another aspect, the present invention provides a method for treating multiple sclerosis in a mammal, which method comprises the intranasal administration of the aforementioned glatiramer-containing composition. Glatiramer is typically administered at a daily dose of 1 to 60 mg. Glatiramer acetate is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine

in a molar ratio of approximately 4.6:1.5:3.6:1.0, respectively, which is synthesized by chemically polymerizing the four amino acids, forming products with average molecular weights ranging from about 4000 to about 13,000 daltons. The corresponding molar fractions are approximately 0.427 for alanine, 0.141 for glutamic acid, 0.337 for lysine and 0.093 for tyrosine, and may vary by about +/-10%.

In another aspect, the present invention provides a method for treating depression and/or hot flushes in a mammal, which method comprises the intranasal administration of the aforementioned paroxetine-containing composition. Paroxetine is typically administered at a daily dose of 5 to 100 mg. Its preparation is described, for example, in US 6,956,121 and US 6,686,473.

An especially important aspect of the present invention is related to the treatment of malaria. In malaria prevalent regions of the world, Plasmodium infections is the reason for a very high mortality rates (hundreds of thousands of deaths), especially among children. Many patients with acute malaria are unable to tolerate oral therapy and parenteral treatment, which could only be available at hospitals, is necessary. However, these amenities are usually inaccessible.

It has now been found that anti-malaria drug administered intranasally is effective at least as or even more that i.p. administration. This finding paves the way to the formulation of a pharmaceutical composition for intra-nasal administration comprising a carrier and at least one anti-malaria agent.

Examples of anti-malaria drugs are artemisinin derivatives, dihydroartemisinin, artemotil, chloroquine, primaquine, doxycillin, quinine, aminoquinolines, cinchona alkaloids, antifolates, quinidine, melfoquine, halofantrine, lumefantrine, amodiaquine, pyronaridine, tafenoquine, artesunates, artemether, artemotil, biguanides, proguanil, chloproguanil, diaminopyrimidines, pyremethamine, trimethoprim, dapsone, sulfonamides, atovaquone, sulfadoxine-pyrimethamine, N-acetyl cysteine, piperaquine, DHA-piperaquine, lumefantrine, dermaseptins, bisphosphonates, quercitin etc.

The present invention is thus also concerned with a pharmaceutical composition for intra-nasal administration comprising a carrier and at least one anti-malaria drug, wherein said carrier is most preferably a vesicular carrier (namely, a carrier that contain vesicles suspended therein), and also with the use of an anti-malaria agent in the preparation of a medicament for intra-nasally treating malaria.

The intranasal composition may comprise any carrier or combination of carriers known to be suitable for intranasal administration. Preferably, however, the composition in accordance with this aspect of the invention comprises at least one anti malaria agent in combination with the intranasal drug delivery vehicle as described above, which vehicle comprises not less than 30% by weight water, from 12 to 30% by weight C2-C4 alcohol(s), from 1 to 30% by weight water-miscible polyol(s), from 0.2 to 10% phospholipids arranged in a vesicular structure. Other preferred features of the

anti-malaria composition are as described above in connection with said intranasal drug delivery vehicle.

By another aspect the present invention provides a method for treating malaria (including cerebral malaria) comprising: administering intra-nasally to a subject in need of such treatment a therapeutically effective amount of at least one anti-malaria drug. Preferably, the anti-malaria drug is dihydroartemisinin, which is typically administered at the following dosage regimen:
Adults: 40-120mg/day in divided doses for 6-7 days;
Children: 2-4 mg/kg in a divided loading dose on the first day followed by 1-2 mg/kg daily for 6 days.
Dihydroartemisinin can be prepared by reduction of artemisinin with sodium borohydride; [A. Brossi et al., Arteether, a New Antimalarial Drug: Synthesis and Antimalarial Properties, J. Med. Chem. 31, 645-650 (1988)].

As used herein, nasally administering or nasal administration includes administering the compositions into naristilles of the nose to the mucous membranes of the nasal passage or nasal cavity of the mammal. Such formulations can be administered, for example, as a nasal spray, nasal inhaler, nasal drop, aerosol, propellants, pressured dispersion, aqueous aerosol, nebulizer, nasal suspension, instillation, nasal gel, nasal ointment and nasal cream by aid of any new or old type device. Administration of compositions of the present invention may also take place using a nasal tampon or nasal sponge containing the compositions.

Active ingredient can also be brought into a viscous base by adding to the above delivery systems conventionally used ingredients such as natural gums, cellulose and derivatives, acrylic polymers (eg.carbopol) and vinyl polymers (polyvinylpyrrolidone), scleroglucans, xylan, alginates, calcium alginate, hyaluronates, collagenates, starch gells, gelatine systems, kitosan carriers.

It should be understood that the intranasal drug delivery vehicle according to the present invention is not limited for the administration of the specific active ingredients mentioned above. It should be noted that the active agent can be a chemically defined synthetic molecule, a naturally derived or synthetic peptide, a protein, a polysaccharide, or a nucleic acid such as RNA or DNA. The active agent may also be referred to as active compound, drug, drug substance, medicinal substance, therapeutic agent, and the like. The active agents that could be delivered by means of the above compositions alone or in combinations are without being limited:

-Antimalarial agents (e.g. artemisinin derivatives, dihydroartemisinin, artemotil, chloroquine, primaquine, doxycillin, quinine, aminoquinolines, cinchona alkaloids, antifolates, quinidine, melfoquine, halofantrine, lumefantrine, amodiaquine, pyronaridine, tafenoquine, artesunates, artemether, artemotil, biguanides, proguanil, chloproguanil, diaminopyrimidines, pyremethamine, trimethoprim, dapsone, sulfonamides, atovaquone, sulfadoxine-pyrimethamine, N-acetyl cysteine, piperaquine, DHA-piperaquine, lumefantrine, dermaseptins, bisphosphonates, quercitin etc. The drugs could be used alone or in combinations.)

-OTC drugs (e.g. antipyretics, anesthetics, cough suppressants, etc.)

-Antiinfective agents

Anti-malaria agents (such as dihydroartemisinin, etc.)

-Antibiotics (e.g. penicillins, cephalosporins, macrolids, tetracyclines, aminoglycosides, anti-tuberculosis agents, doxycycline, ciprofloxacine, moxifloxacine, gatifloxacine, carbapenems, azithromycine, clarithromycine, erythromycine, ketolides, penems, tobramyicin, filgrastim, pentamidine, microcidin, clerocidin; amikacine, etc.)

-Antifungal/Antimycotic (metronidazole, ketoconazole, itraconazole, voriconazole, clotrimazole, bifonazole, fluconazole, amphotericine B, natamycine, nystatine, ciclopiroxolamine, etc.)

-Genetic molecules (e.g. Anti-sense oligonucleotides, nucleic acids, oligonucleotides, DNA, RNA,

-Anti-cancer agents (e.g. anti-proliferative agents, anti-vascularization agents, taxol, etopside, cisplatin, etc.)

-Anti-protozoal agents

-Antivirals (e.g. acyclovir, gancyclovir, ribavirin, anti-HIV agents, anti-hepatitis agents, famciclovir, valaciclovir, didanosine, saquinavir, ritonavir, lamivudine, stavudine, zidovudine, etc.)

-Anti-inflammatory drugs (e.g. NSAIDs, steroidal agents, cannabinoids, leukotriene-antagonists, tacrolimus, sirolimus, everolimus, etc.)

-Anti-allergic molecules (e.g. antihistamines, fexofenadine)

-Bronchodilators

-Vaccines and other immunogenic molecules (e.g. tetanus toxoid, reduced diphtheria toxoid, acellular pertussis

vaccine, mums vaccine, smallpox vaccine, anti-HIV vaccines, hepatitis vaccines, pneumonia vaccines, influenza vaccines, TNF-alpha-antibodies etc.)

-Anesthetics, local anesthetics.

-Antipyretics (e.g. paracetamol, ibuprofen, diclofenac, aspirin, etc.)

-Agents for treatment of severe events such cardiovascular attacks, seizures, hypoglycemia, etc.

-Afrodisiacs from plants or synthetics

-Anti-nausea and anti-vomiting.

-Immunomodulators (immunoglobulins, etc.)

-Cardiovascular drugs (e.g. beta-blockers, alpha-blockers, calcium channel blockers, etc.)

-Peptide and steroid hormones (eg. insulin, insulin derivatives, insulin detemir, insulin monomeric, oxytocin, LHRH, LHRH analogues, adreno-corticotropic hormone, somatropin, leuprolide, calcitonin, parathyroid hormone, estrogens, testosterone, adrenal corticosteroids, megestrol, progesterone, sex hormones, growth hormones, growth factors, etc.)

-Peptide and protein related drugs (e.g. amino acids, peptides, polypeptides, proteins)

-Vitamins (e.g. Vit A, Vitamins from B group, folic acid, Vit C, Vit D, Vit E, Vit K, niacin, derivatives of Vit D, etc.)

- Autonomic Nervous System Drugs

-Fertilizing agents

-Antidepressants (e.g. buspirone, venlafaxine, benzodiazepins, selective serotonin reuptake inhibitors (SSRIs), sertraline, citalopram, tricyclic antidepressants, paroxetine, trazodone, lithium, bupropion, sertraline, fluoxetine, etc.)

-Agents for smoking cessation (e.g. bupropion, nicotine, etc.)

-Agents for treating alcoholism and alcohol withdrawal

-Lipid-lowering agents (eg. inhibitors of 3 hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, simvastatin, atrovastatin, etc.)

-Drugs for CNS or spinal cord (benzodiazepines, lorazepam, hydromorphone, midazolam, Acetaminophen, 4'-hydroxyacetanilide, barbiturates, anesthetics, etc.)

- Anti-epilepsic agents (e.g. valproic acid and its derivatives, carbamazepin, etc.)

-Angiotensin antagonists (e.g. valsartan, etc.)

-Anti-psychotic agents and anti-schizophrenic agents (e.g. quetiapine, risperidone)

-Agents for treatment of Parkinsonian syndrome (e.g. L-dopa and its derivatives, trihexyphenidyl, etc.)

-Anti-Alzheimer drugs (e.g. cholinesterase inhibitors, galantamine, rivastigmine, donepezil, tacrine, memantine, N-methyl D-aspartate (NMDA) antagonists).

-Agents for treatment of non-insulin dependent diabetes (e.g. metformine,

-Agents against erectile dysfunction (e.g. sildenafil, tadalafil, papaverine, vardenafil, PGE1, etc.)

-Prostaglandins

-Agents for bladder dysfunction (e.g. oxybutynin, propantheline bromide, trospium, solifenacin succinate etc.)

-Agents for treatment menopausal syndrome (e.g estrogens, non-estrogen compounds, etc.)

-Agents for treatment hot flashes in postmenopausal women

-Agents for treatment primary or secondary hypogonadism (e.g. testosterone, etc.)

-Cytokines (e.g. TNF, interferons, IFN-alpha, IFN-beta, interleukins etc.)

-CNS stimulants

-Muscle relaxants

-Anti paralytic gas agents

-Appetite stimulators/depressors (e.g. cannabinoids, etc.)

-Gastrointesinal absorption modifiers

-Narcotics and Antagonists (e.g. opiates, oxycodone etc.)

-Painkillers (opiates, endorphins, tramadol, codein, NSAIDs, gabapentine etc.)

-Hypnotics (Zolpidem, benzodiazepins, barbiturates, ramelteon, etc.)

-Histamines and Antihistamines

-Antimigraine Drugs (e.g. imipramine, propranolol, sumatriptan, eg.)

-Diagnostic agents (e.g. Phenolsulfonphthalein, Dye T-1824, Vital Dyes, Potassium Ferrocyanide, Secretin, Pentagastrin, Cerulein, etc.)

- Topical decongestants or anti-inflammatory drugs

-Anti-acne agents (e.g. retinoic acid derivatives, doxicillin, minocyclin, etc.)

-ADHD related medication (e.g. methylphenidate, dexmethylphenidate, dextroamphetamine, d- and l-amphetamin racemic mixture, pemoline, etc.)

-Diuretic agents

-Anti-osteoporotic agents (e.g. bisphosphonates, aledronate, pamidronate, tirphostins, etc.)

-Drugs for treatment of asthma

-Anti-Spasmotic agents (e.g. papaverine, etc.)

-Agents for treatment of multiple sclerosis and other neurodegenerative disorders (eg. mitoxantrone, glatiramer acetate, interferon beta-1a, interferon beta-1b, etc.)

-Plant derived agents from leave, root, flower, seed, stem or branches extracts.

In the drawings

Figure 1 is a TE micrograph of insulin vesicles in a Composition F according to the invention.

Figure 2 is a graph showing Blood glucose levels (% of initial) in mice following intranasal administration of 25µL of insulin composition G (aqueous control containing 58IU/ml) versus untreated mice.

Figure 3 is a graph showing Blood glucose levels (% of initial) in mice following intranasal administration of 25µL of human insulin compositions C (a composition of the invention containing 58IU/ml insulin) and D (placebo) versus untreated mice.

Figure 4 is a graph showing Blood glucose levels (% of initial) in mice following intranasal administration of 25µL of insulin composition F (a composition of the invention containing 20IU/ml insulin) versus untreated mice.

Figure 5 is a graph showing Blood glucose levels (% of initial) in mice following intranasal administration of 25µL of insulin compositions N and O (compositions of the invention containing 58IU/ml insulin) versus untreated mice.

Figure 6 is a bar diagram showing the results of Writhing test in mice following administration of diazepam

vesicular composition prior to writhing induction with acetic acid versus untreated control.

Figure 7 is a bar diagram showing the results of Writhing test in mice following administration of diazepam vesicular carrier(drug dose 5mg/kg) simultaneously with writhing induction with acetic acid solution versus untreated control.

Figure 8 is a bar diagram showing the results of Writhing test in mice following intranasal (IN) administration of diazepam phospholipid ethanolic vesicles Composition (5mg/kg) and subcutaneous (SC) injection of diazepam simultaneously with writhing induction with acetic acid solution versus untreated control.

Figure 9 is a graph depicting the changes in the weight of rats following administration of ipecac syrup and inducing Pica syndrome on day 3. Animals intranasally treated with granisetron HCl Composition B (IN-GR, 1.5mg drug/kg rat, n=5) versus untreated control (n=5).

Figure 10 is a graph showing the changes in the food consumption in rats following administration of ipecac syrup and inducing Pica syndrome on day 3. Animals intranasally treated with granisetron HCl Composition B (IN-GR, 1.5mg drug/kg rat, n=5) versus untreated control (n=5).

Figure 11 is a graph showing the changes in the kaolin consumption in rats following administration of ipecac syrup and inducing Pica syndrome on day 3. Animals intranasally treated with granisetron HCl Composition B

(IN-GR, 1.5mg drug/kg rat, n=5) versus untreated control (n=5).

Figure 12 is a CLS (confocal laser scanning) micrograph showing the transport of Rhodamine B across the nasal mucosa from the composition of the invention applied for 0.5h to the rat nostril. White means the highest fluorescent intensity.

Figure 13 is a graph showing Blood glucose levels (% of initial) in mice following intranasal administration of 25µL of insulin compositions in a comparative study. The concentration of human insulin in all Compositions is 63 IU/mL. Composition I is a composition of the invention; Composition II is a control composition having only 10% EtOH; Composition III is a liposomal control composition.

Examples

Materials

Insulin solution used for preparation of the Compositions C-V is Biosynthetic Human Insulin aqueous solution 100IU/mL (Actrapid, Novartis).

Example 1

Insulin-containing composition

20 mg of phospholipids (Phospholipon 90, Natterman were dissolved in 0.3g ethanol (J.T. Baker) and to this solution 0.1g propylene glycol was added. The obtained solution was added slowly to the 0.58 g of the aqueous solution of human insulin (100IU/mL) under constant stirring at room temperature. The composition is stirred for additional 5 min. It is also possible to introduce

the aqueous human insulin solution into the phospholipid solution in ethanol and propylene glycol. The final composition contains 58 IU insulin/ g.

Example 2

Insulin-containing composition

15 mg of phospholipids (Phospholipon 90) were dissolved in a mixture of 225mg ethanol and 75mg propylene glycol. To the obtained solution, 685 mg of aqueous solution of insulin (100IU/mL) were added slowly under constant stirring at 40C temperature. The composition is stirred for additional 5 min. The final composition contains 68.5 IU insulin/g. This composition is also prepared at room temperature.

Example 3

Insulin-containing composition

To freeze-dried liposomes containing 40 mg phospholipid and 116 IU human insulin a mixture of 0.6g EtOH, 0.2g PG and 1.16g DDW was added in aliquots under constant stirring at room temperature. The composition is stirred for additional 5 min. The final composition containes 58IU insulin/ g (1.45 IU insulin/25 microliter).

Example 4

Insulin-containing composition

To a liposomal dispersion containing 30mg phospholipid, 137 IU insulin and 685mg DDW, 225mg EtOH and 75mg

Propylene glycol were added under constant stirring at room temperature. The composition is stirred for additional 5 min. The final composition contains 68.5IU insulin/g.

Example 5

Insulin-containing composition

0.05g Carbopol 974P was dispersed in 1mL of insulin aqueous solution (100IU/mL). In a separate container 0.5 g of Phospholipon 90 and 0.15g cholesterol were dissolved in 1.85g ethanol and to this solution 0.95g propylene glycol were added. To this mixture 0.65g Tween 20 were added. To the obtained system 4.8mL of insulin aqueous solution (100IU/mL) were added slowly under constant stirring at room temperature in Heidolph mixer (650rpm). The composition was stirred for additional 5 min. This phase was slowly added to Carbopol dispersion in insulin aqueous solution under constant mixing at 400rpm. To the obtained system 0.05g triethanolamine (TEA) were added slowly under constant mixing at 400rpm.

Example 6

Insulin-containing composition

0.01g Carbopol 974P was dispersed in 1.18 mL of DDW. In a separate container 0.5 g of phospholipids (Phospholipon 90) and 0.02g ceramide were dissolved in 1.48g ethanol and to this solution 1g propylene glycol were added. To the obtained system 5.8mL of insulin aqueous solution (100IU/mL) were added slowly under constant stirring at room temperature in Heidolph mixer (650rpm). The composition was stirred for additional 5 min. This phase

was slowly added to Carbopol dispersion in DDW under constant mixing at 400rpm. To the obtained system 0.01g triethanolamine (TEA) were added slowly under constant mixing at 400rpm.

Example 7

Dihydroartemisinin-containing compositions

Dihydroartemisinin	23-350mg
Phospholipid	70-250mg
Ethanol	750-1050mg
Propylene glycol	350-1000mg
Water to	3.5g

Preparation: Phospholipid was dissolved in ethanol and to this solution propylene glycol was added. To the obtained solution DHA was added and the mixture was left at room temperature for 3-4 days. Then DDW was added to the composition slowly under constant stirring. The composition was stirred for additional 15 min.

Example 8

Diazepam-containing composition

1 g soy phospholipid was dissolved in a mixture of 3 g ethanol and 9.8 g propylene glycol and to this solution 400mg of diazepam and 2.4 g Labrasol was added. Water (3.4 g) preheated to 40C was added slowly with constant stirring in Heidolph mixer (650rpm). The composition is stirred for additional 15min. The final composition contains 2%w/w diazepam.

Example 9

Granisetron HCl-containing composition

50 mg of soy phospholipids were dissolved in 150 mg ethanol. To this solution, 200 mg of propylene glycol and 10mg Labrasol were added and mixed. To the obtained mixture 15 mg of granisetron were added and dissolved. 575 microlitter of DDW (at room temperature) were added very slowly under constant vortexing. The composition is stirred for additional 5 min.

Example 10

Granisetron HCl-containing composition

70mg of Phospholipon 90 were dissolved in 150 mg ethanol. To this solution, 230mg propylene glycol were added and mixed. To the obtained mixture, 20mg of granisetron HCl were added and dissolved. 530 microlitter of DDW (preheated to 40C) were added very slowly under constant vortexing. The composition is stirred for additional 15 min.

Example 11

Hypoglycemic effect (reduced blood glucose levels) by intranasal administration of insulin

Tables IA and IB detail various compositions of human insulin, which were prepared according to the procedures described in Examples 1-6 above.

Table IA

Component, %w/w	*C*	*D*	*E*	*F*	*G*	*H*
Insulin aqueous soln.	58	-	68.5	20	58	58
Phospholipon 90	2	2	1.5	2	-	2
Ethanol	30	30	22.5	30	-	10
Propylene Glycol	10	10	7.5	10	-	10
Water (double distilled)	-	58	-	38	42	20
Final insulin dose administered to mice IU/25µL of Composition	1.45	0	1.71	0.5	1.45	1.45

Table IA (continuation):

Component, %w/w	*H*	*I*	*J*	*K*	*L*	*M*
Insulin aqueous soln.	58	-	58	58	58	58
Phospholipon 90	2	2	1	0.25	0.5	5
Ethanol	12	12	15	15	15	12.5
Propylene Glycol	10	10	5	10	12	5
Water (double distilled)	18	76	21	16.75	14.5	19.5
Final insulin dose administered to mice IU/25µL of Composition	1.45	0	1.45	1.45	1.45	1.45

Table IB

Component, % w/w	*N*	*O*	*P*	*Q*	*R*	*S*	*T*	*U*	*V*
Insulin aqueous soln.	58	58	58	58	58	58	58	58	58
Phospholipon 90	5	2	9	10	8	1	5	5	1
Cholesterol	-	-	1	-	-	0.1	1.5	-	-
Ceramide	-	-	-	1	-	-	-	0.2	-
Tween 20	-	-	-	1.8	-	-	6.5	-	-
Ethanol	15	15	20	20	20	20	18.5	14.8	12
Propylene Glycol	10	10	12	9	10	10	10	10	15
Water (double distilled)	12	15	-	-	3.9	9.8	-	11.9	13.5
Hydroxy-propyl cellulose	-	-	-	0.2	0.1	-	-	-	0.5
Carbopol	-	-	-	-	-	0.1	0.5	0.1	-

The effect of nasal administration of insulin to mice by means of the compositions described in Tables IA and IB was tested as follows.

Experiments were carried out on C75/bl male mice (weight 22-28g). 25 µL of the Compositions (see Figures and Table) were applied to the nasal cavity of the animal under short isofluran anesthesia. The mice have not received food during the experiment. Blood glucose levels were measured by glucose oxidase method using Glucometer Elite (disposable strips). The measurements were performed starting from one hour prior to intranasal administration of Compositions up to a maximum of 8 hours from the administration. Compositions D and I were used as Placebo controls for the Compositions C and H,

respectively. Composition G served as the insulin aqueous solution control.

Figures 2-5 present the Blood Glucose Levels (BGL) profiles following administration of various insulin compositions. Administration of compositions D and I (placebo controls), or composition G (aqueous control) had no effect on BGL (Figures 2 and 3). Compositions C, F, N and O significantly improved intranasal insulin absorption reducing the BGL.

Example 12

Treatment and prophylaxis of malaria by intranasal administration of dihydroartemisinin (DHA)

Table II details compositions of dihydroartemisinin, which were prepared according to the procedure described in Example 7 above.

Table II:

Component, %w/w	*A*	*B*	*C*	*D*	*E*
Dihydroartemisinin (DHA)	0.66	0.66	0.33	0.40	10
Phospholipon 90	2	2	5	2	5
Ethanol	27	20	17	22	28
Propylene Glycol	10	20	20	15	25
Tween 20	-	10	-	5	2
Water (double distilled)	54.34	47.34	57.67	55.6	30

The compositions described in Table II were tested as follows.

Experiments were carried out in vivo in ICR female mice infected with 10^6 erythrocytes parasitized Plasmodium berghei anka, a model of cerebral malaria with striking similarities to the human disease. Infections were monitored using giemsa-stained thin blood smears prepared from tail blood. The animals were treated under isoflurane anesthesia with 10mg DHA/kg/day in a two divided daily doses by two dosage regimens: prophylaxis regimen- starting at 2 days before the infection for a total of 6 days; treatment regimen- starting on day 2 after infection (parasitemia first detected) for a total of 4 days. Mice were either treated by the intranasal administration or by the i.p. injection containing the same DHA doses. Controls included placebo (delivery carrier only) and untreated infected animals. Experiments were conducted in accordance with institutional guidelines for animal care.

Results show that parasites were not detected in the prophylaxis regimen animal group treated with intranasal administration of DHA in the enhancing permeation carrier, but appeared in 74% of mice treated in the same regimen by i.p. DHA injection. In the treatment regimen, 75% of mice which received intranasal DHA survived, in comparison with only 19% in the i.p. treatment group. Isoflurane anesthesia and the administration of the placebo carrier did not affect the development of the disease. All mice in the control groups succumbed to the parasitemia.

In conclusion, it has been shown that DHA intranasal administration from an enhancing permeation carrier, was

effective for prophylaxis and treatment of anemic and cerebral malaria in mice.

Example 13

Intranasal administration of diazepam

The efficacy of the intranasal administration of the diazepam-containing composition prepared according to Example 8 was tested by means of the following experiments.

Experiment 1: The experiments were carried out on Female Balb/c mice (21-26g). Two experimental groups were used: control (untreated) (n=6) and treated group (n=6). The animals in active treatment group were administered with the Diazepam intranasal Phospholipid ethanolic vesicular compositions 2.9µl in each nose (5mg/kg animal). Half an hour after nasal application, each animal in treated and control groups was IP administered with acetic acid 0.6% (10 ml/kg) and individually housed in cage with a smooth flat floor. Antinociception effect was recorded by counting the number of writhes 5 minutes after injection of acetic acid for period of 10 minutes. A writhe is indicated by abdominal constriction and stretching of at least one hind limb.

Figure 6 is a bar diagram illustrating the results obtained, which show that intranasal administration of diazepam from the vesicular composition, 0.5 h before acetic acid injection efficiently prevented writhing episodes.

Experiment 2: The experiment was carried out on Female Balb/c mice (21-26g). Two experimental groups were used: control (untreated) (n=6) and treated group (n=6). The

animals in active treatment group were administered with the Diazepam intranasal vesicular composition 2.9µl in each nose (5mg/kg animal). Immediately after nasal application (t=0), each animal in treated and control groups was IP administered with acetic acid 0.6% (10 ml/kg) and individually housed in cage with a smooth flat floor. Antinociception was recorded by counting the number of writhes 5 minutes after injection of acetic acid for period of 10 minutes.

Figure 7 is a bar diagram illustrating the results obtained, which show that intranasal administration of diazepam from the vesicular composition simultaneously with injection of acetic acid solution was efficient in treating writhing episodes.

Experiment 3: The experiments were carried out on Female Balb/c mice (21-26g). Three experimental groups were used: control (untreated) (n=4), mice intranasally administered with the Diazepam IN vesicular composition (2.8µl in each nostril = diazepam dose of 5mg/kg animal) (n=4) and mice subcutaneously administered with the Diazepam solution 0.125 % at dose of 5mg/kg animal (n=4). The animals in active treatment groups were administered with the Diazepam intranasal composition and subcutaneous diazepam. Simultaneously, each animal in treated and control groups was IP administered with acetic acid 0.6% (10 ml/kg) and individually housed in cage with a smooth flat floor. Antinociception was recorded by counting the number of writhes 5 minutes after injection of acetic acid for period of 10 minutes.

Figure 8 is a bar diagram illustrating the results obtained, which show that intranasal administration of

diazepam from the vesicular composition, was significantly more efficient in treating writhing episodes as compared to the same dose of the drug administered subcutaneously.

Example 14

Intranasal administration of granisetron HCl

Table III details compositions of granisetron, which were prepared according to the procedures described in Examples 9-10 above.

Table III

Component %w/w	*A*	*B*	*C*	*D*	*E*
Granisetron HCL	1.5	1.5	2	3	4
Phospholipon 90	5	5	5	5	2
Ethanol	10	15	18	25	27
Propylene Glycol	20	20	12	5	20
Labrasol	-	1	1	1	1
Water (DDW)	63.5	57.5	62	61	46

Table III (continuation)

Component %w/w	*F*	*G*	*H*	*I*	*J*	*K*
Granisetron HCL	5	1.5	2	1.5	2	1
Phospholipon 90	5	0.5	7	10	5	5
Ethanol	10	10	15	12	10	10
Propylene Glycol	20	20	23	15	20	20
Labrasol	1	1	-	2	12	6
Water (DDW)	59	67	53	59.5	51	58

The compositions detailed in Table III were used for the intranasal administration of granisetron hydrochloride to rats and the pharmacodynamic response thereof was evaluated as follows.

Experiments were carried out on Male SD/H rats weighing 200-240 g. The animals were housed individually in cages (23×23×20 cm) in a room with a 12-h light/12-h dark cycle (lights on between 06:00 and 18:00 h) at a constant temperature (27±1 °C) and humidity (50±5%). Pelleted food and water was available ad libitum. Each cage had a wire-mesh floor to permit collection of spilt kaolin and food. Kaolin pellets were prepared according to the methods described Takeda et al. (1993). Briefly, gum Arabic and hydrated aluminum silicate (kaolin- China clay) were mixed together (1:100 on a weight: weight basis) with distilled water to form a thick paste. Pellets of the resulting kaolin mixture were shaped to resemble the dimensions of the rats' normal laboratory diet. The pellets were dried completely at room temperature.

The kaolin pellets were introduced into the cages 3 days prior to drug administration. They were held in identical stainless-steel containers (7×8×3 cm, attached to the side of the cage) to the food pellets. The kaolin and food containers were removed each day (at 10:00 h) and the spilt kaolin and food collected, to determine the rats' consumption, during each 24-h period, up to a total 72 h observation time. Rat weight was also recorded on a daily basis.

Ipecac syrup 5ml/kg was administrated orally and animals returned to the experiment cages. Rats were administrated

with intranasal Granisetron HCl Composition B (at a dose of 1.5mg granisetron HCl/kg rat). One hour after intranasal administration of granisetron, Ipecac syrup was given orally using a gavage to treated (n=5) and untreated (control, n=5) animals. Immediately after Ipecac syrup, the animals in the treatment group were administered with an additional dose of intranasal Granisetron hydrochloride followed by drug intranasal administration at regular 12-h intervals for additional 2.5 days. Kaolin and food intake as well as rat weights were measured at 24, 48 and 72 h post- Ipecac.

The results collected are represented in Figures 9 to 11. The Results show that intranasal administration of granisetron HCl from composition B, was efficient in preventing weight loss (Fig. 9), stimulating food consumption (Fig. 10) and preventing kaolin consumption (Fig. 11) in rats with Pica syndrome (equivalent to emesis and vomiting in humans).

Example 15

Transport of fluorescent probe across nasal mucosa following in vivo administration

Visualization of Rhodamine B (hydrophilic probe, MW 479) permeation across the nasal mucosa using the composition of the invention (containing 0.05% (0.5mg/mL) Rhodamine B) was carried out as follows.

A stock solution of Rhodamine B (2mg/mL) was prepared in water. 50mg of phospholipid were dissolved in 200 mg ethanol. To this solution 100 mg propylene glycol and 10 mg Labrasol were added and mixed. To the obtained mixture

250 microliter of the aforementioned aqueous Rhodamine B solution (2mg/ml) were added slowly with constant stirring. The residual 390 microlitter of DDW were added slowly to the obtained system with constant vortexing. The composition is stirred for additional 5 min. The composition is described in Table IV.

Table IV

Component	*Rhodamine B composition %w/w*
Rhodamine B stock aqueous soln.	25
Phospholipon 90	5
Ethanol	20
Propylene Glycol	10
Labrasol	1
Water (DDW)	39

The composition was applied intranasally to the right nostril of SD/H male 220-250g rats (application volume 100µL) anesthetized i.p. with Ketamine-Xylazine mixture
The animals were sacrificed 1/2 hour from the application and the nasal septum with the adjunct epithelial membrane from each animal were carefully removed from the bone. The harvested septum was fixed with 3.8% Formalin in PBS (pH 7.4) for 1 hour in room temperature. The untreated epithelia on the left side of the septum were separated from the septum. The septum with right side epithelia was placed on the slide, covered with cover glass, fixed with tape and observed under CLS microscope (10-40X/0.6 plan Neofluor lens, Zeiss LSM 410 confocal system with an Axiovert 135 inverted microscope).

Figure 12 is a photograph showing that the composition of the invention efficiently delivered rhodamine B across the nasal mucosa (White means the highest fluorescent intensity).

Example 16

Granisetron HCL-containing composition in the form of a viscous liquid

700mg of Phospholipon 90 were dissolved in 1500 mg ethanol. To this solution 2300mg of propylene glycol were added and mixed. To the obtained mixture 200mg of granisetron were added and dissolved. 5280 microlitter of DDW (preheated to 40C) were added very slowly under constant mixing in Heidolph mixer (650rpm). The composition was mixed for additional 15 min. To the obtained system 20mg of hydroxypropylcellulose were added slowly and mixed for additional 15 min in Heidolph mixer (650rpm). The resulting composition was left for 30min in room temperature and than mixed for additional 5min.

Example 17

Insulin-containing composition in the form of a semi-solid

0.2 g of phospholipon 90 were dissolved in 3g ethanol and to this solution 0.94g propylene glycol were added. The obtained solution was added slowly to 5.8 mL of the aqueous insulin solution (100IU/mL) under constant stirring at room temperature in Heidolph mixer (650rpm). The composition was stirred for additional 5

min. To the obtained system 60 mg of hydroxypropylcellulose were added slowly and mixed for additional 15 min in Heidolph mixer (650rpm). The resulting composition was left for 30min in room temperature and than mixed for additional 10 min. The final semi-solid composition contains 58IU insulin/ g.

Example 18

Insulin-containing composition in the form of a gel

0.2g of Carbopol 980 was dispersed in 2.48g DDW in Heidolph mixer (400rpm) followed by a slow addition of 0.2 g of TEA. The mixture was left for 10min in room temperature to obtain the gel phase.

In another container 0.2g of Phospholipin 90 were dissolved in 2g EtOH to this solution 1g of propylene glycol and 0.02g of Vitamin E were added and mixed to obtain clear system in Heidolph mixer (700rpm). The obtained system was stirred for additional 5 min and added slowly to the gel phase under constant mixing at 400rpm. To the obtained semi-solid preparation 3.9mL of insulin aqueous solution containing 250 IU/mL (prepared from dissolving 40.6mg of human insulin powder containing 24IU/mg (Sigma) in DDW) was added. The obtained composition was mixed for additional 5 min. It is notable that insulin solution could be added in each stage of the preparation. The final semi-solid composition contains 97.5IU insulin/ g.

Example 19 (comparative)

Insulin-containing compositions were prepared, as described in Table V below:

Table V

	Compositions, , %w/w		
Component	*I*	*II*	*III*
Insulin aqueous solution 100IU/ml	63	63	63
Phospholipon 90	2	2	2
Ethanol	25	10	2
Propylene Glycol	10	-	-
DDW	-	25	33
Final insulin dose administered to mice IU/25µL of Composition	1.575 IU	1.575 IU	1.575 IU

Experimental protocol:

Nasal absorption experiments with insulin compositions I, II (control composition containing 10% EtOH) and III (control liposomal composition containing 2% EtOH) were performed in ICR/male mice (7-10Weeks) obtained from (Harlan/Israel). The animals were fasted 1 h prior to an insulin administration and during the experiment time, with free access to water. Compositions were intranasally administered to the animals (12.5µl in each nostril, a total of 25 µl per animal- each nose side), using a pipette with a disposable plastic tip. The nasal insulin formulations were administered at time=0h following a short isofluran anesthesia. The total amount of insulin delivered nasally to each animal, was 1.575 IU. Blood glucose levels were measured by glucose oxidase method using Glucometer Elite (disposable strips). The

measurements were performed starting from one hour prior to intranasal administration of Compositions up to 6 hours from the administration.

The results presented in Figure 13 show that Composition I efficiently reduced blood glucose levels, while administration of Compositions II and III (controls) had no effect on BGL.

Example 20

Buspirone HCl-containing composition

The following compositions were prepared:

Component, %w/w		
	A	*B*
Buspirone HCL	1	2
Phospholipon 90	2	2
Ethanol	20	25
Propylene Glycol	10	-
Vitamin E	0.2	0.2
Carbopol 980	1	-
Triethanolamine (TEA)	1	-
Water (DDW)	64.8	70.8

Preparation method for Buspirone Composition A:

0.1g of Carbopol 980 was dispersed in 2.48g DDW in Heidolph mixer (400rpm) to this dispersion 1g of EtOH was added under constant mixing followed by a slow addition of 0.1 g of TEA. The mixture was left for 10min in room temperature to obtain the gel phase.

In another container 0.2g of Phospholipin 90 were dissolved in 1g EtOH to this solution 1g of propylene glycol and 0.02g of Vitamin E were added and mixed to obtain clear system. To this system 0.1g of buspirone HCl

dissolved in 4g DDW were slowly added under constant stirring at room temperature in Heidolph mixer (700rpm). The obtained system was stirred for additional 5 min and added slowly to the gel phase under constant mixing at 400rpm. The obtained composition A was mixed for additional 5 min.

Preparation method for Buspirone Composition A:

0.2g of Phospholipin 90 were dissolved in 2.5g EtOH; to this solution 0.02g of Vitamin E were added and mixed to obtain clear system. To this system, 0.2g of buspirone HCl dissolved in 7.08g DDW were slowly added under constant stirring at room temperature in Heidolph mixer (700rpm). The obtained system was stirred for additional 5 min.

Example 21

Insulin-containing composition

0.2g mg of phospholipids (Phospholipon 90) were dissolved in 1.5g ethanol and to this solution 0.5g propylene glycol were added.

Insulin aqueous solution containing 250 IU/mL insulin was prepared by dissolving 81.25mg of human insulin powder containing 24IU/mg (Sigma) in 7.8 mL DDW. The obtained insulin aqueous solution was added slowly under constant stirring at room temperature to the previously prepared phospholipid solution. The composition is stirred for additional 5 min. The final composition contains 195 IU insulin/g.

Example 22

Glatiramer acetate -containing composition

The following compositions were prepared:

Component, %w/w			
	A	*B*	*C*
Glatiramer acetate	1	2	2
Soy phospholipids	2	2	3
Ethanol	20	25	15
Propylene Glycol	10	-	10
Vitamin E	0.2	0.2	0.2
Carbopol 980	1	-	0.1
Triethanolamine (TEA)	1	-	0.1
Water (DDW)	64.8	70.8	69.6

Example 23

Paroxetine -containing composition

The following compositions were prepared:

Component, %w/w		
	A	*B*
Paroxetine	0.5	1
Phosphatydylcholine	2.5	3
Ethanol	23	15
Propylene Glycol	10	15
Vitamin E	0.2	0.2
Labrasol	1	-
Water (DDW)	62.8	65.8

Example 24

Rivastigmine -containing composition

The following compositions were prepared:

Component, %w/w		
	A	*B*
Rivastigmine tartrate	0.5	0.75
Soy Phospholipid	2	5
Ethanol	12	20
Propylene Glycol	10	15
Water (DDW)	75.5	59.25

Example 25

Sibutramine -containing composition

The following compositions were prepared:

Component, %w/w		
	A	*B*
Sibutramine	1	1.5
Phospholipon 90	5	2
Ethanol	14	22
Propylene Glycol	15	-
Vitamin E	0.2	-
Labrasol	1	-
Water (DDW)	63.8	74.5

Claims:

1) Use of phospholipids, one or more C2-C4 alcohols and water in the preparation of a vesicular composition adapted for intranasal administration of an active agent, wherein the concentrations of said phospholipids and said one or more alcohols in said composition are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

2) Use of phospholipids, one or more C2-C4 alcohols, one or more water-miscible polyols and water in the preparation of a vesicular composition adapted for the intranasal administration of an active agent, wherein the concentrations of said phospholipids, said one or more alcohols and said one or more polyols in said composition are in the ranges of 0.2 to 10%, 12 to 30% and 1 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

3) Use according to claim 2, wherein the C2-C4 alcohol is ethanol and the polyol is propylene glycol.

4) Use of a carrier comprising not less than 30% by weight water, from 12 to 30% by weight C2-C4 alcohol(s), from 1 to 30% by weight water-miscible polyol(s), from 0.2 to 10% phospholipids arranged in a vesicular structure and therapeutically effective amount of a pharmaceutically active ingredient, in the preparation of a pharmaceutical composition suitable for intranasal administration.

5) Use according to any one of claims 1 to 4, wherein the weight ratio between the C2-C4 alcohol and the phospholipids is not less than 2:1.

6) Use according to any one of claims 1 to 5, wherein said composition is a composition for treating and/or preventing emesis, diabetes, malaria, depression, Alzheimer's disease, multiple sclerosis, hot flushes symptoms and obesity.

7) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-emetic agent.

8) Use according to claim 7, wherein the anti-emetic agent is granisetron or a pharmaceutically acceptable salt thereof.

9) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of granisetron or a pharmaceutically acceptable salt thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

10) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-diabetic agent.

11) Use according to claim 10, wherein the anti-diabetic agent is insulin or a derivative thereof.

12) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of insulin or a derivative thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

13) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-malaria agent.

14) Use according to claim 13, wherein the anti-malaria agent is dihydroartemisinin.

15) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of dihydroartemisinin, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

16) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-anxiety and/or anticonvulsant agent.

17) Use according to claim 16, wherein the anti-anxiety and/or anticonvulsant agent is diazepam.

18) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of diazepam, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

19) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-obesity agent.

20) Use according to claim 19, wherein the anti-obesity agent is sibutramine or a pharmaceutically acceptable salt thereof.

21) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of sibutramine or a pharmaceutically acceptable salt thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

22) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an antidepressant or anti-hot flashes agent.

23) Use according to claim 22, wherein the antidepressant or anti-hot flashes agent is paroxetin or a pharmaceutically acceptable salt thereof.

24) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of paroxetine or a pharmaceutically acceptable salt thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

25) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-multiple sclerosis agent.

26) Use according to claim 25, wherein the anti-multiple sclerosis agent is glatiramer acetate.

27) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of glatrimer or a pharmaceutically acceptable salt thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

28) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-dementia agent.

29) Use according to claim 28, wherein the anti-dementia agent is rivastigmine or a pharmaceutically acceptable salt thereof.

30) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of rivastigmine or a pharmaceutically acceptable salt thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

31) A method of administering an active pharmaceutical ingredient to a patient in need thereof, which method comprises the intranasal administration of a composition comprising a therapeutically effective amount of said ingredient, phospholipids, one or more C2-C4 alcohols and water, wherein the concentrations of said phospholipids and said one or more alcohols in said composition are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight, said phospholipids forming vesicles in said composition.

32) A method for preventing and/or treating emesis in a mammal, which method comprises the intranasal

administration of a granisetron-containing composition according to claim 9.

33) A method for treating diabetes in a mammal, which method comprises the intranasal administration of the insulin-containing composition according to claim 12.

34) A method for treating malaria in a mammal, which method comprises the intranasal administration of the dihydroartemisinin-containing composition according to claim 15.

35) A method for treating epileptic seizures in a mammal, which method comprises the intranasal administration of a diazepam-containing composition according to claim 18.

36) A method for preventing and/or treating obesity in a mammal, which method comprises the intranasal administration of a sibutramine-containing composition according to claim 21.

37) A method for treating depression and/or hot flushes in a mammal, which method comprises the intranasal administration of a paroxetine-containing composition according to claim 24.

38) A method for treating multiple sclerosis in a mammal, which method comprises the intranasal administration of a glatiramer acetate-containing composition according to claim 27.

39) A method for preventing and/or treating dementia in a mammal, and specifically, Alzheimer disease, which method comprises the intranasal administration of a rivastigmine-containing composition according to claim 30.

40) Use of an anti-malaria agent and a vesicular carrier in the preparation of a medicament for the intranasal treatment of malaria.

41) A method for preventing and/or treating malaria in a mammal, which method comprises the intranasal administration of a therapeutically effective amount of an anti-malaria drug in a pharmaceutically acceptable carrier.

42) A method according to claim 41, wherein the pharmaceutically acceptable carrier contains vesicles.

43) A method according to claim 42, wherein the carrier comprises not less than 30% by weight water, from 12 to 30% by weight C2-C4 alcohol(s), from 1 to 30% by weight water-miscible polyol(s) and from 0.2 to 10% phospholipids arranged in a vesicular structure.

44) A method according to claim 42, wherein the anti-malaria drug is dihydroartemisinin.

45) A method according to claim 41, wherein the anti-malaria drug is an artemisinin derivative.

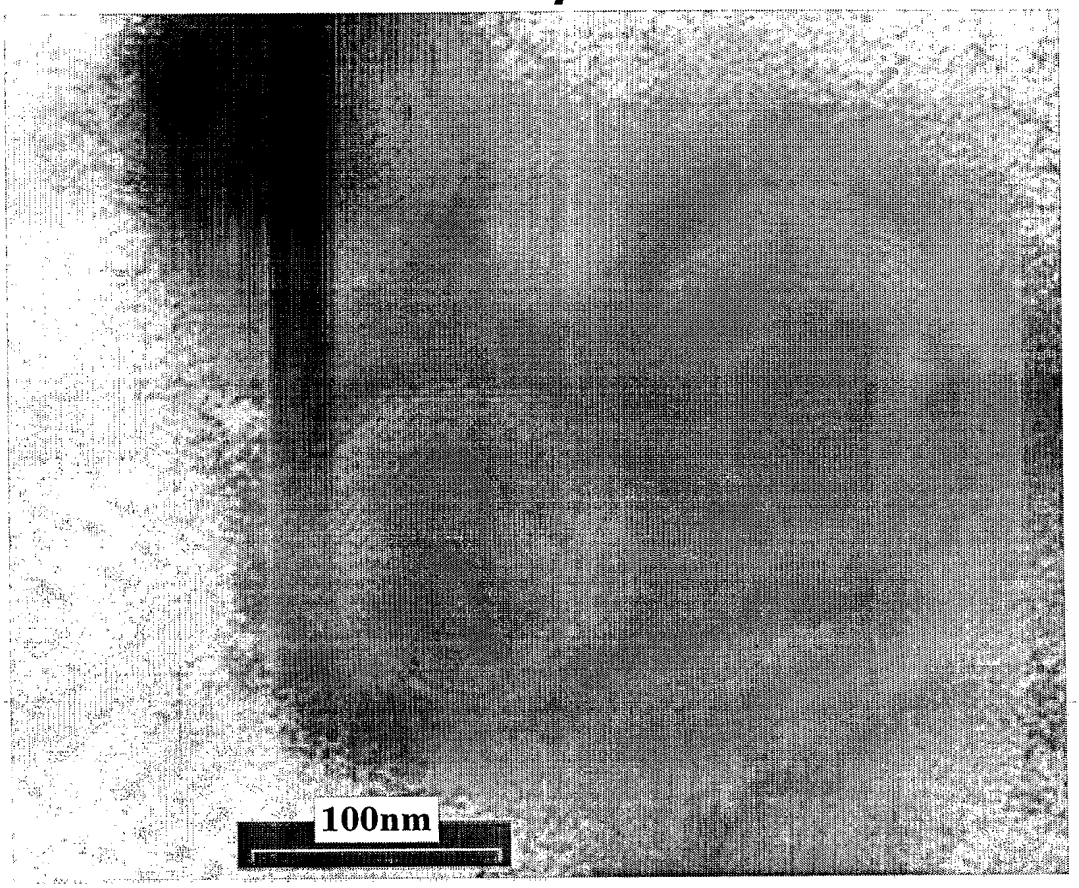
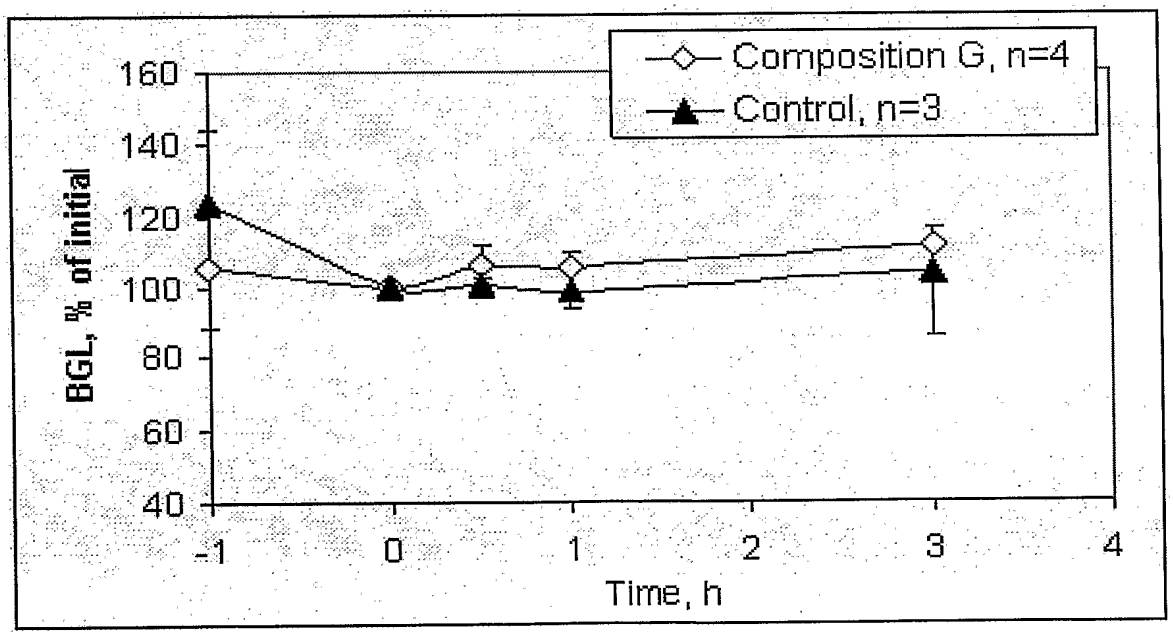

100nm

Fig. 1


Composition G, n=4
Control, n=3
BGL, % of initial
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140
120
100
80
60
40
-1
0
1
2
3
4
Time, h

Fig. 2

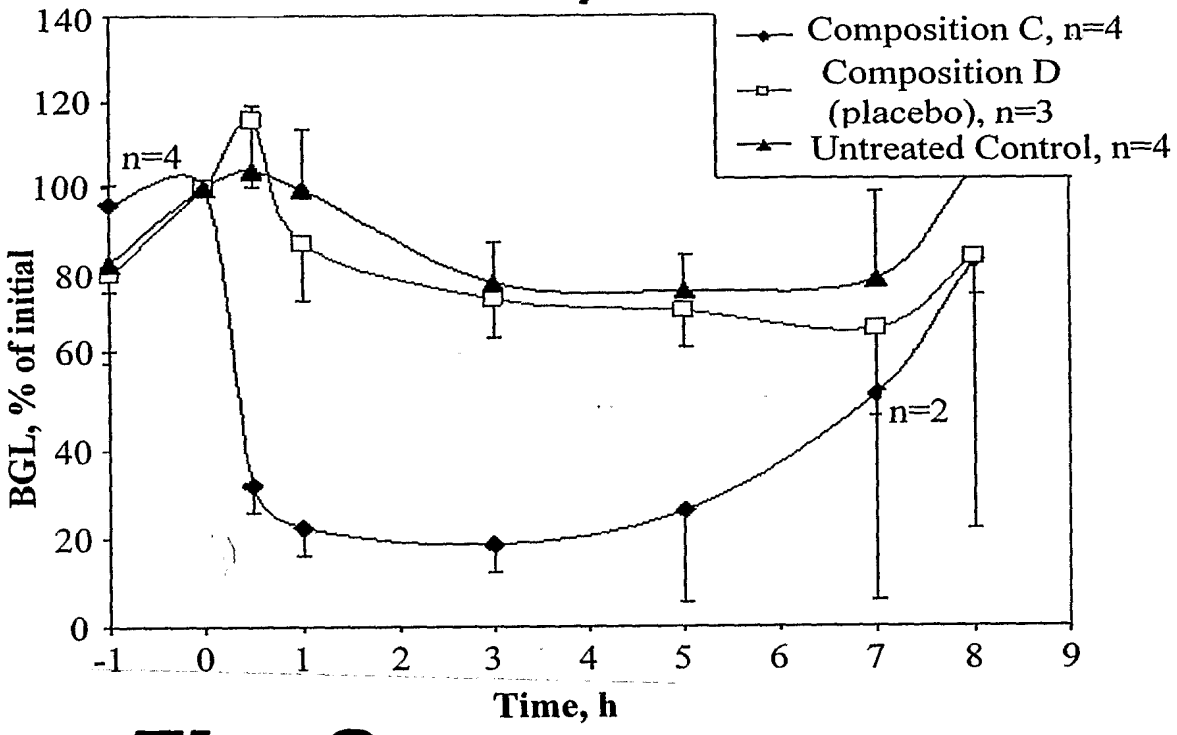
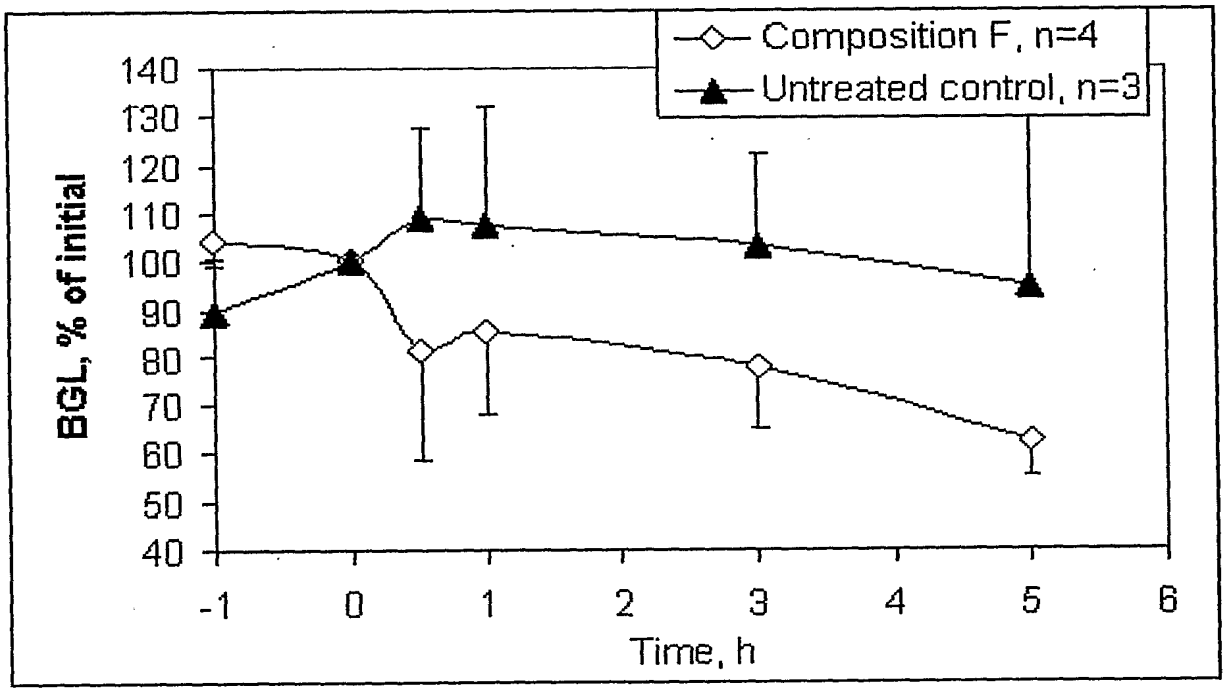

Composition C, n=4
Composition D (placebo), n=3
Untreated Control, n=4
n=4
n=2
BGL, % of initial
Time, h
140
120
100
80
60
40
20
0
-1
0
1
2
3
4
5
6
7
8
9

Fig. 3


Composition F, n=4
Untreated control, n=3
BGL, % of initial
Time, h
140
130
120
110
100
90
80
70
60
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-1
0
1
2
3
4
5
6

Fig. 4

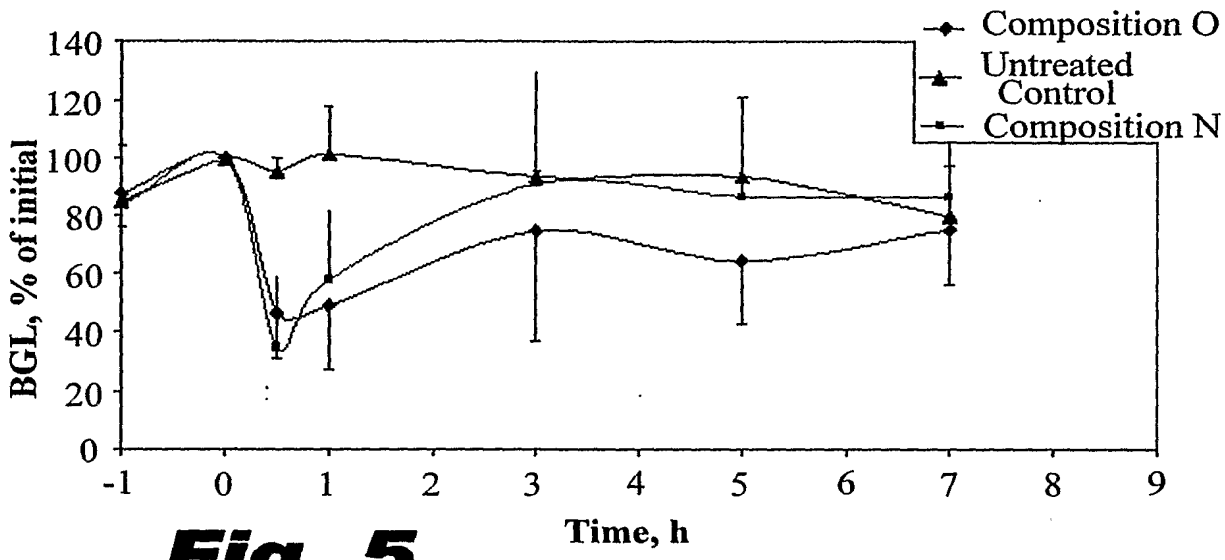
Composition O
Untreated Control
Composition N
BGL, % of initial
140
120
100
80
60
40
20
0
-1
0
1
2
3
4
5
6
7
8
9
Time, h

Fig. 5

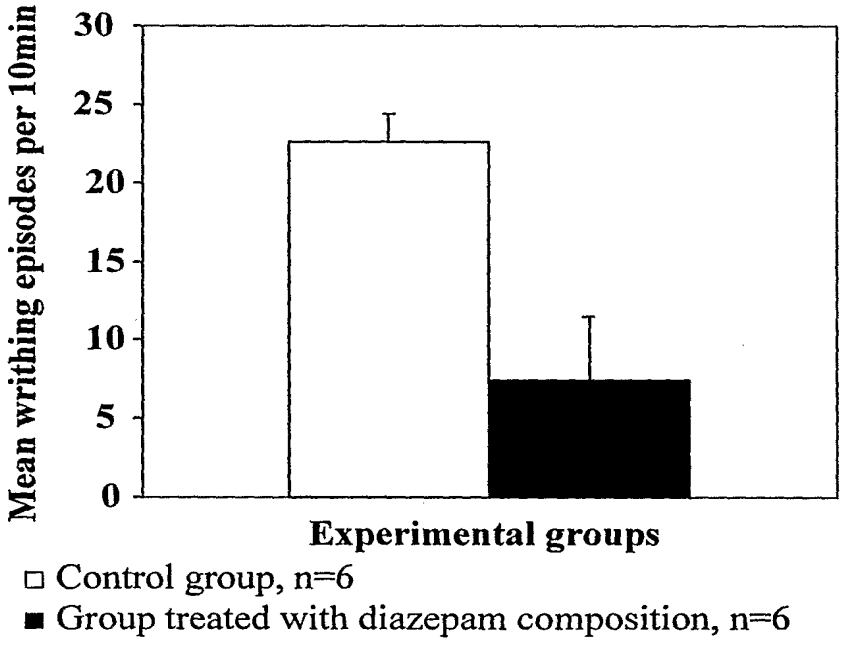
Mean writhing episodes per 10min
30
25
20
15
10
5
0
Experimental groups
□ Control group, n=6
■ Group treated with diazepam composition, n=6

Fig. 6

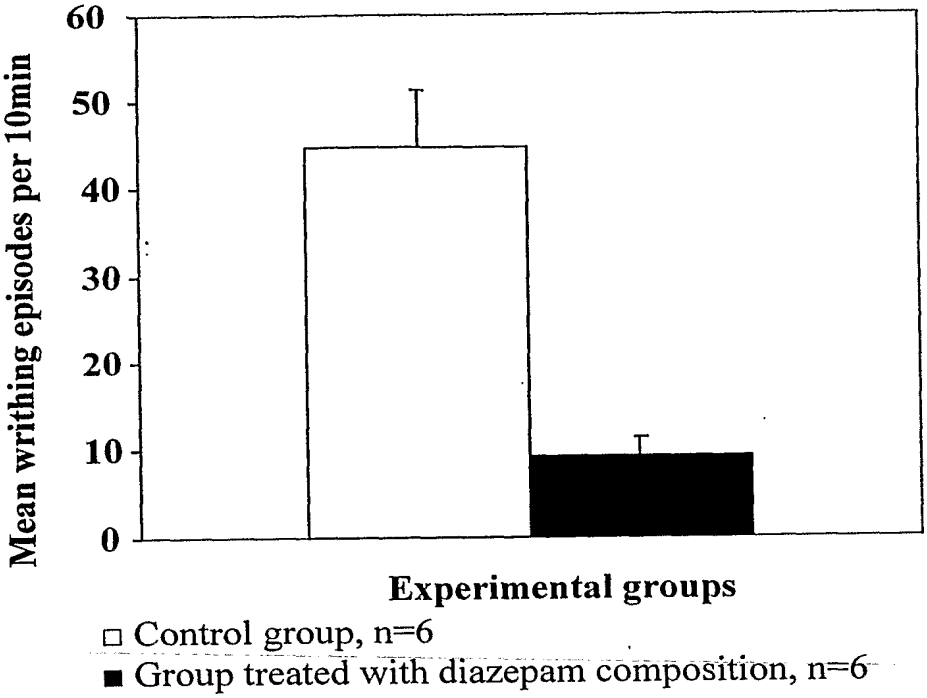
60
50
40
30
20
10
0
Mean writhing episodes per 10min
Experimental groups
□ Control group, n=6
■ Group treated with diazepam composition, n=6

Fig. 7

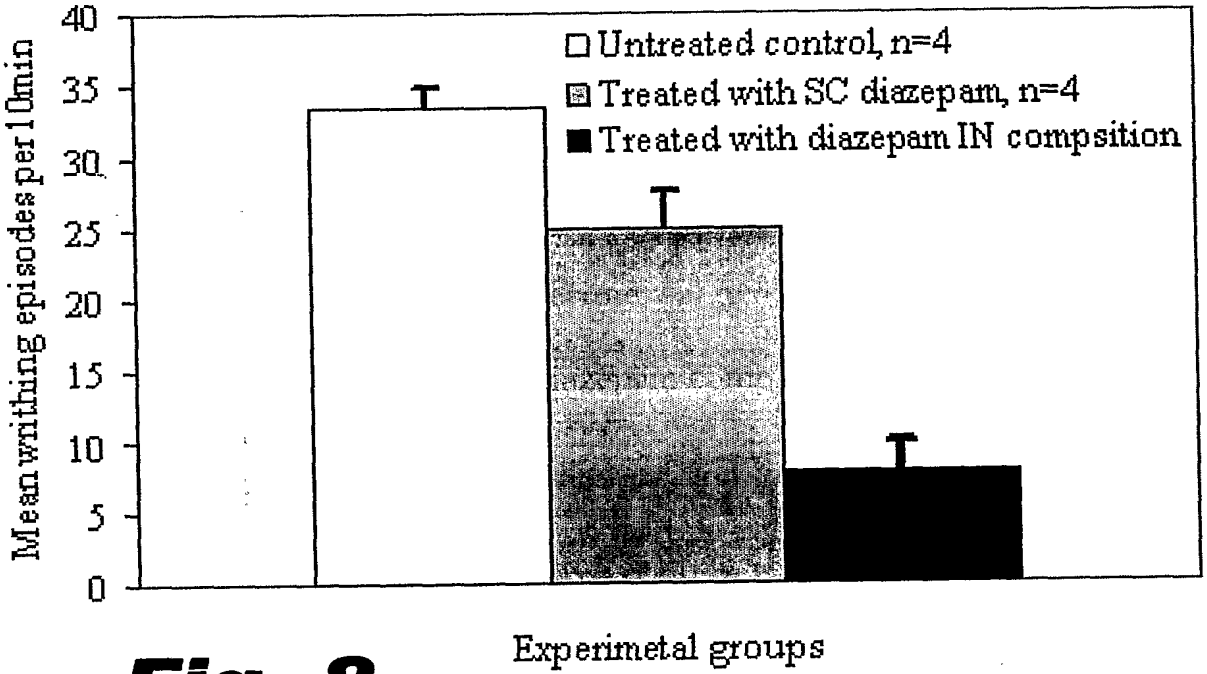
40
35
30
25
20
15
10
5
0
Mean writhing episodes per 10min
□ Untreated control, n=4
▨ Treated with SC diazepam, n=4
■ Treated with diazepam IN compsition
Experimetal groups

Fig. 8

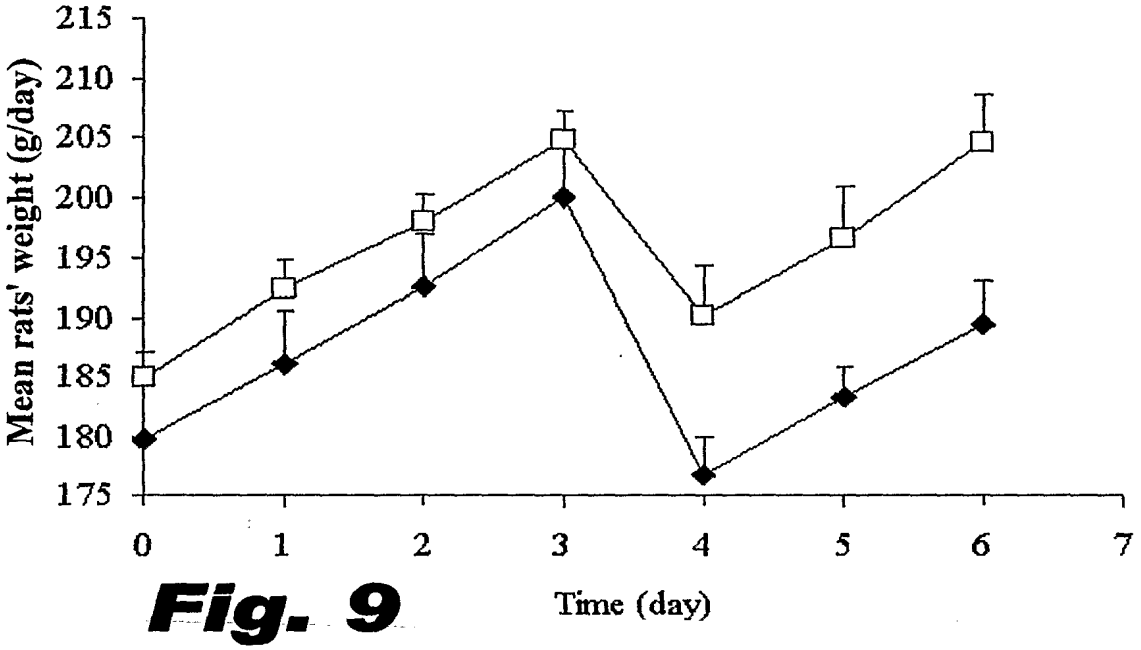
Mean rats' weight (g/day)
215
210
205
200
195
190
185
180
175
0
1
2
3
4
5
6
7
Time (day)

Fig. 9

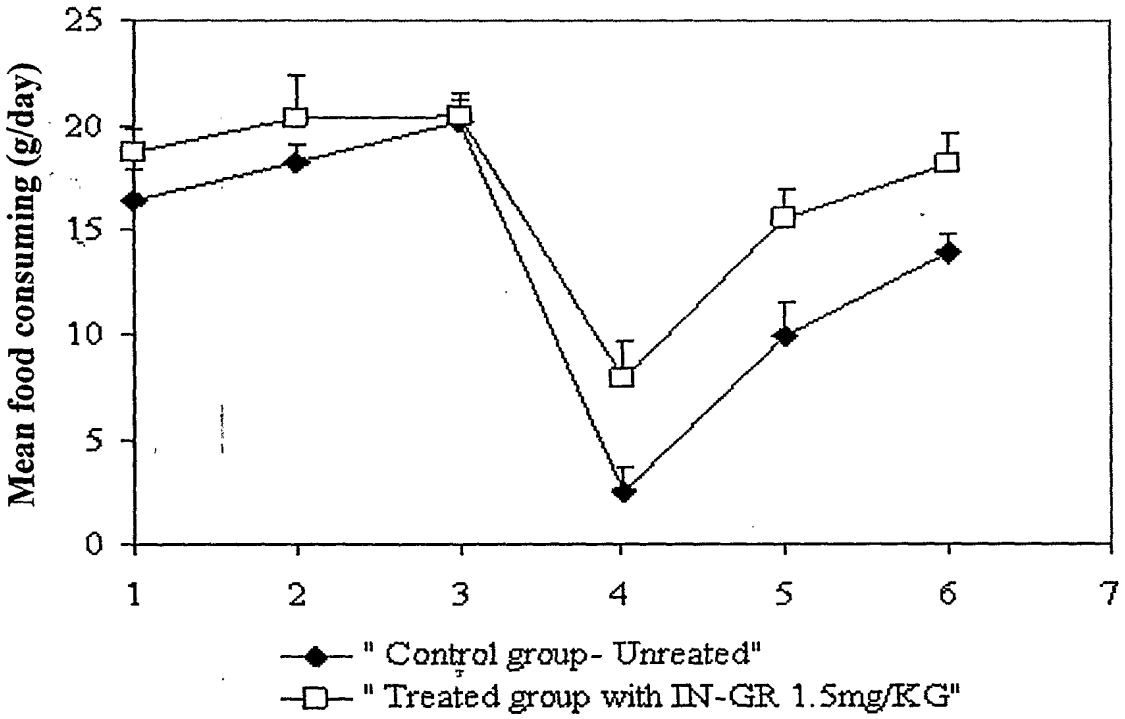
Mean food consuming (g/day)
25
20
15
10
5
0
1
2
3
4
5
6
7
" Control group- Unreated"
" Treated group with IN-GR 1.5mg/KG"

Fig. 10

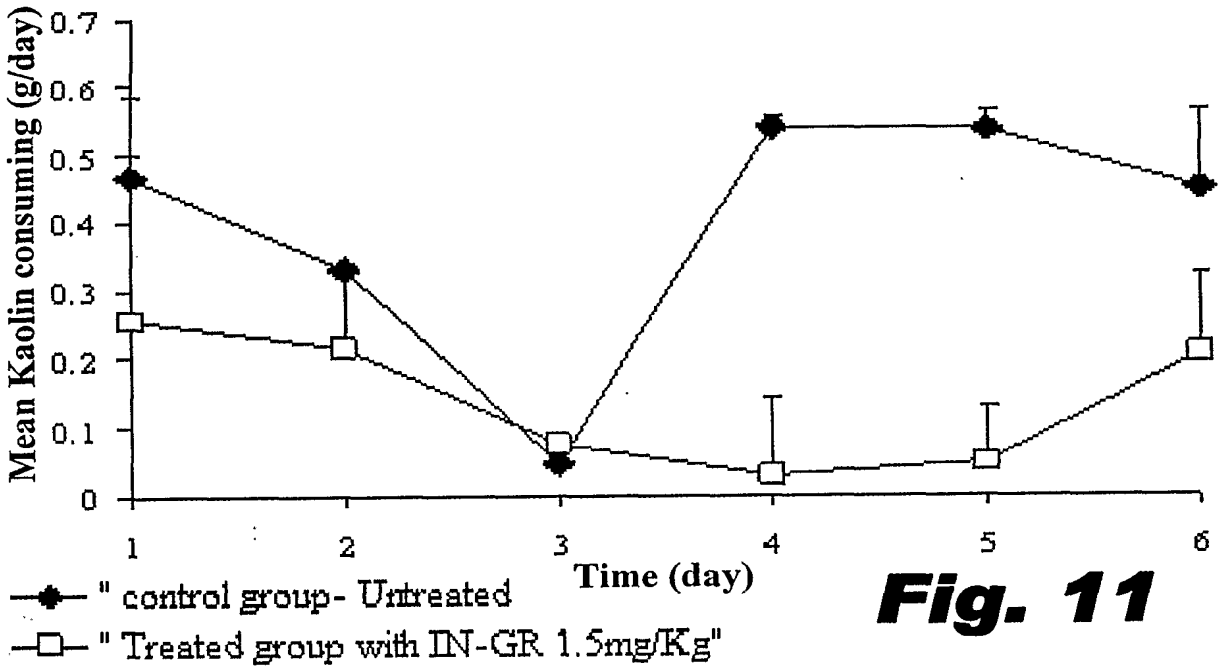
Mean Kaolin consuming (g/day)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
5
6
Time (day)
" control group- Untreated
" Treated group with IN-GR 1.5mg/Kg"

Fig. 11

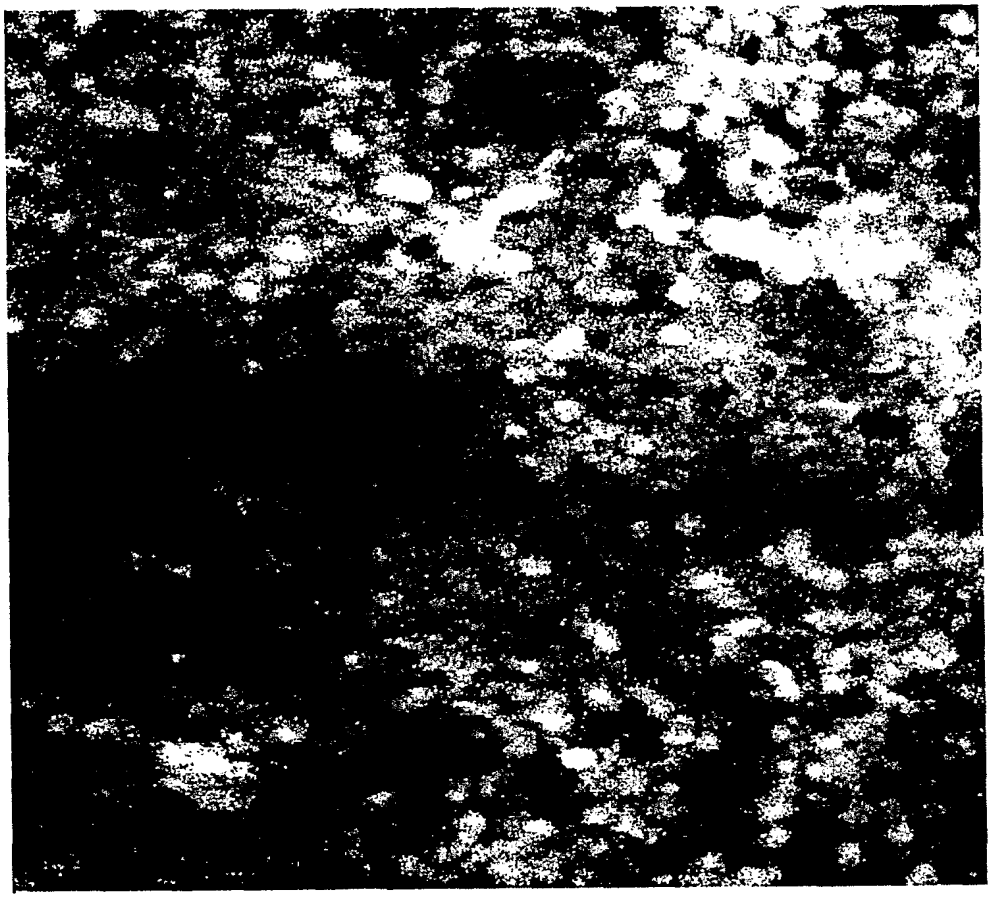

Fig. 12

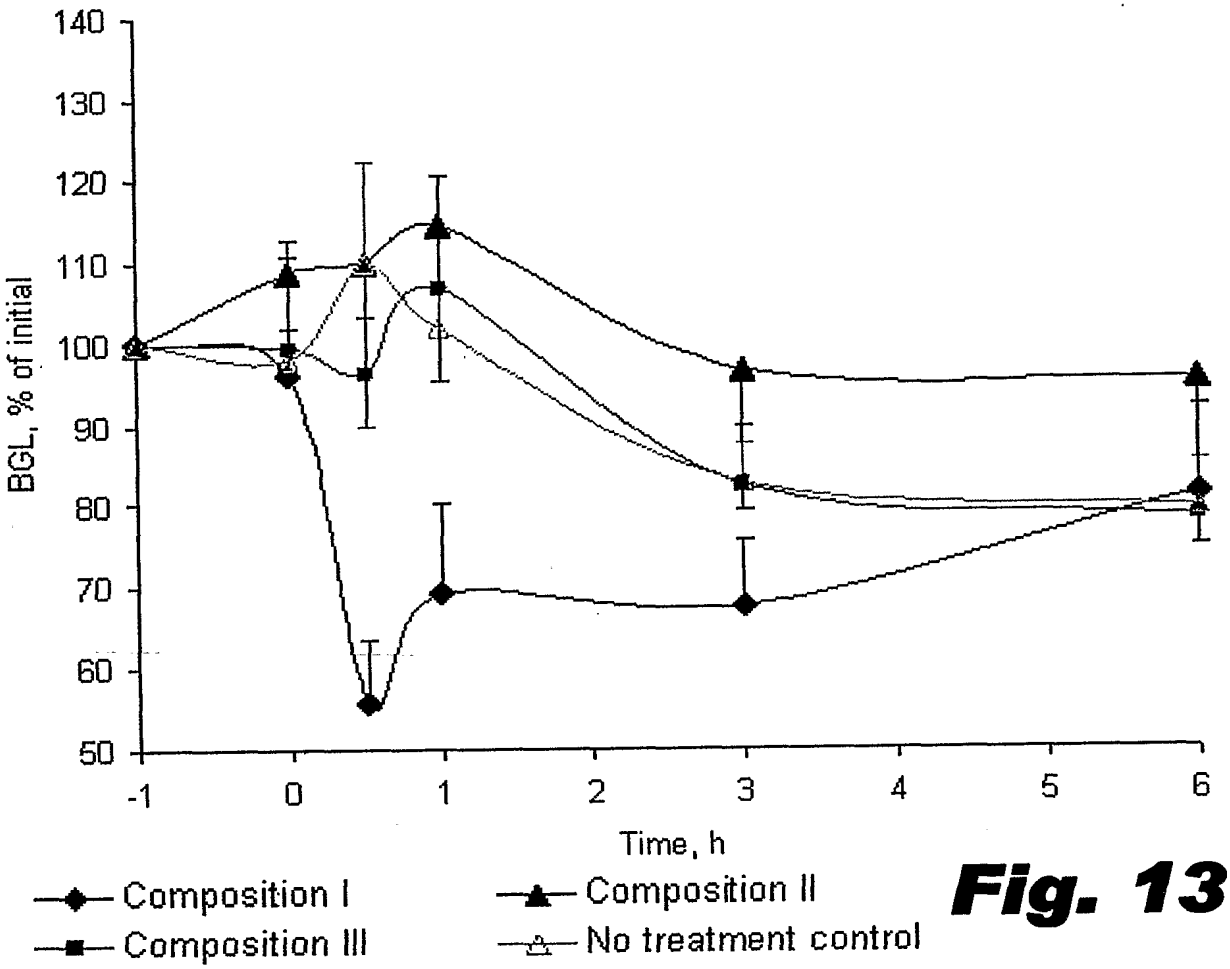
140
130
120
110
100
90
80
70
60
50
BGL, % of initial
-1
0
1
2
3
4
5
6
Time, h
Composition I
Composition II
Composition III
No treatment control

Fig. 13

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

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Erklärungen gemäß Regel 4.17:
— *hinsichtlich der Berechtigung des Anmelders, ein Patent zu beantragen und zu erhalten (Regel 4.17 Ziffer ii)*
— *Erfindererklärung (Regel 4.17 Ziffer iv)*

Veröffentlicht:
— *ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** SMOKING WITHDRAWAL COMBINATION WAFER

(54) **Bezeichnung:** RAUCHERENTWÖHNUNGS-KOMBINATIONSWAFER

(57) **Abstract:** The present invention relates to a quickly decomposing oral drug preparation, for the application of active ingredient combinations for smoking withdrawal, which contains nicotine, a nicotine salt, a nicotine derivative, or a substance that reacts to nicotine, in combination with another active ingredient, and the use of such a drug preparation for the treatment of smoking withdrawal, and the use of nicotine, and/or nicotine salts or derivatives, for the production of medications for the treatment of smoking withdrawal. The active ingredient that is to be administered, in combination, for this purpose is a centrally active ingredient, preferably an antidepressant for the fighting of psychic dependency in terms of a smoking withdrawal therapy. The administration of the active ingredient combination to the patient should be handled in a simple and reliable way and should exclude side effects to a large extent.

(57) **Zusammenfassung:** Die vorliegende Erfindung betrifft schnell zerfallende orale Darreichungsformen zur Applikation von Wirkstoffkombinationen zur Raucherentwöhnung mit einem Gehalt an Nikotin, einem Nikotinsalz, einem Nikotinderivat oder einem Stoff mit nikotinerger Wirkung, in Kombination mit einem weiteren Wirkstoff sowie die Verwendung solcher Darreichungsformen zur Behandlung der Nikotinabhängigkeit, zur Nikotinsubstitution oder zur Raucherentwöhnung und die Verwendung von Nikotin bzw. seiner Salze oder Derivate zur Herstellung von Arzneiformen zur Behandlung der Nikotinabhängigkeit. Der in Kombination zu verabreichende Wirkstoff ist dabei ein zentral wirkender Stoff , vorzugsweise ein Antidepressivums zur Bekämpfung der psychischen Abhängigkeit im Rahmen einer Raucherentwöhnungs-Therapie. Die Verabreichung der Wirkstoffkombination soll für den Patienten auf einfache und zuverlässige Weise erfolgen und Nebenwirkungen weitgehend ausschließen.

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Raucherentwöhnungs-Kombinationswafer

Die vorliegende Erfindung betrifft schnell zerfallende orale Darreichungsformen zur Applikation von Wirkstoffkombinationen zur Raucherentwöhnung mit einem Gehalt an Nikotin, einem Nikotinsalz, einem Nikotinderivat oder einem Stoff mit nikotinerger Wirkung, in Kombination mit einem weiteren Wirkstoff.
Die Erfindung betrifft ferner die Verwendung solcher Darreichungsformen zur Behandlung der Nikotinabhängigkeit, zur Nikotinsubstitution oder zur Raucherentwöhnung, sowie die Verwendung von Nikotin bzw. seiner Salze oder Derivate zur Herstellung von Arzneiformen zur Behandlung der Nikotinabhängigkeit.

Ca. 30 % der Weltbevölkerung rauchen und konsumieren dabei jährlich etwa 6 Billionen Zigaretten. Rauchen gehört wie der Alkoholgenuss zu den gesellschaftlich akzeptierten und weit verbreiteten Arten des Drogenkonsums, wobei das im Tabak hauptsächlich vorkommende Alkaloid Nikotin eine anderen Rauschmitteln vergleichbare suchterzeugende Wirkung besitzt, die zu einer physischen Abhängigkeit führt. Die toxischen Effekte des Nikotins, das ein starkes Nervengift ist, werden dabei bei Rauchern durch Gewöhnung zurückgedrängt.

Nikotin erreicht bereits kurz nach der Inhalation das Gehirn und wirkt dort an Acetylcholinrezeptoren, wobei es eine Reihe physiologischer Reaktionen auslöst. Dadurch kommt es zur Zunahme der Herzfrequenz, Verengung der Blut-

gefäße mit einhergehendem Blutdruckanstieg und einer deutlichen Abnahme der Hauttemperatur. Darüber hinaus werden über zentrale Effekte die psychomotorische Leistungsfähigkeit sowie Aufmerksamkeits- und Gedächtnisleistungen gesteigert.

Das hohe Suchtpotential wird neben der direkten Wirkung auf die nikotinergen Acetylcholinrezeptoren vor allem der Beeinflussung des Dopaminsystems zugeschrieben, von dem angenommen wird, das es maßgeblich für den Belohnungseffekt des Rauchens verantwortlich ist.

Da durch regelmäßigen Nikotinkonsum eine Vermehrung der zentralen nikotinergen Acetylcholinrezeptoren eintritt, führt ein Ausbleiben der Nikotinzufuhr zu Entzugserscheinungen.

Neben Nikotin konnten im Tabakrauch bisher mehr als 4000 Verbindungen identifiziert werden, von denen viele eine cancerogene Wirkung aufweisen oder zumindest im Verdacht stehen, krebserzeugend zu sein.

Nikotinkonsum ist eine wesentliche Ursache für Gefäßerkrankungen, Bluthochdruck, Krebs und Asthma sowie die damit einhergehenden Spätfolgen wie Schlaganfall, Herzinfarkt, chronische Bronchitis, COPD (chronisch obstruktive Lungenerkrankungen), Raucherbein, Arteriosklerose und Sehstörungen.

Statistiken zeigen, daß bestimmte schwerwiegende Erkrankungen unmittelbar ursächlich auf das Rauchen zurückzuführen

sind. So betreffen z.B. 90 % bis 95 % der Lungenkrebserkrankungen, 90 % der Amputationen sowie nahezu alle Herzinfarkte vor dem 40. Lebensjahr Raucher. Insgesamt werden sogar 30 % aller Krebserkrankungen dem Zigarettenkonsum zugeschrieben. Es hat sich weiterhin gezeigt, daß das Thromboserisiko bei Einnahme oraler Kontrazeptiva bei Raucherinnen 10-fach höher ist, während neuere Studien zeigen sollen, daß erektile Dysfunktion bei rauchenden Männern deutlich häufiger auftritt.

Insgesamt liegt die Lebenserwartung von Rauchern in Deutschland um ca. 10 % unter der von Nichtrauchern und nahezu ein Viertel aller "vorzeitigen" Todesfälle ist auf Folgeerkrankungen des Rauchens zurückzuführen. Darüber hinaus wird die Zahl der vorzeitigen Invaliden durch Rauchen auf 70.000 bis 100.000 pro Jahr geschätzt und die Zahl derer, die an den Folgen des "Passivrauchens" sterben, auf ca. 500 bis 3500.

Die gesamten durch das Rauchen verursachten Kosten belaufen sich nach Schätzungen der Deutschen Gesellschaft für Nikotinforschung auf ca. 75 Milliarden Euro jährlich.

Aufgrund der einleitend diskutierten negativen Folgen und der gesundheitlichen Risiken ist das Rauchen vermehrt in den Fokus der gesundheitspolitischen Diskussion geraten. Nicht zuletzt auch deshalb, weil mittlerweile nachgewiesen wurde, daß auch Passivrauchen zu ernsthaften Erkrankungen führen kann.

Der Raum für Raucher wird zunehmend eingeschränkt und Rauchen ist an vielen öffentlichen Plätzen und am Arbeitsplatz weitgehend verboten. In den USA, Italien und Irland ist das Rauchverbot in Restaurants und Gaststätten bereits durch entsprechende Gesetze bestätigt.

Hinzu kommt, daß die Kosten für Tabakwaren in Deutschland in den letzten Jahren stark angestiegen sind und weitere Kosten auf Raucher, z.B. durch einen erhöhten Krankenkassenbeitrag zur Deckung der durch das Rauchen verursachten zusätzlichen Kosten im Gesundheitswesen, zukommen werden. Tabakgenuß wird somit zunehmend ein Luxus mit nicht zu vernachlässigenden finanziellen Aspekten. So verbrennt ein Raucher beispielsweise bei ca. 20 Zigaretten am Tag bei einem Preis von ca. 20 Cent pro Zigarette runde 1.500 Euro pro Jahr.

Angesichts der zuvor genannten Zahlen und der bekannten gesundheitsschädlichen Auswirkungen des Tabakrauchens gibt es demnach viele gute Gründe, außer den ohnehin offenkundigen finanziellen Aspekten, nicht zu rauchen oder aufzuhören.

Dennoch ist für die meisten Nikotinabhängigen eine Beendigung der Abhängigkeit nur schwer möglich. Der Hauptgrund dafür liegt in den Entzugserscheinungen, welche sich nach Beendigung des Tabakkonsums einstellen.

Der Ausstieg aus dieser Suchtabhängigkeit wird deshalb erleichtert, wenn der Nikotinbedarf zumindest während einer Entwöhnungsphase auf andere Weise gedeckt wird, z. B. im

Rahmen einer Nikotin-Substitutionstherapie. Dies kann beispielsweise mittels sogenannter Nikotinpflaster erfolgen, die Nikotin über die Haut an den menschlichen Organismus abgeben und so die Nikotin-Entzugserscheinungen unterdrücken, wodurch die Raucherentwöhnung erleichtert wird. Nachteilig an diesen transdermalen therapeutischen Systemen (TTS) ist aber, daß diese über einen langen Zeitraum auf der Haut verbleiben und als störend empfunden werden. In ungünstigen Fällen können sowohl durch das Nikotin als auch durch den Kleber Reizungen der Haut und allergische Reaktionen hervorgerufen werden. Darüber hinaus wird über die TTS zwar kontinuierlich Nikotin an den Organismus abgegeben, Spitzenkonzentrationen, wie sie beim Rauchen auftreten und die für die Belohnungseffekte verantwortlich sein können, bleiben aber aus.

Es hat sich weiterhin gezeigt, daß bei vielen Rauchern neben der wirkstoffbezogenen, d. h. nikotinbezogenen, physischen Abhängigkeit zusätzlich eine psychische Abhängigkeit vorliegt, die durch Nikotinsubstitution alleine nicht behandelt werden kann.

Dieses wird insbesondere deutlich, wenn man die kurze Halbwertzeit des Nikotins berücksichtigt, die zwischen 30 min und 120 min liegt. Demnach müßten Raucher zumindest morgens starke Entzugssymptome zeigen. Die Erfahrung zeigt aber, daß das Bedürfnis nach einer Zigarette und der Zeitraum bis zur nächsten Zigarette oft stark von äußeren Faktoren wie Streß, Sport, Gesellschaft und dergleichen abhängt und nicht von echten physischen Symptomen bestimmt wird. So können sowohl der Tabakkonsum als auch seine Frequenz in

Abhängigkeit von der psychischen Verfassung stark schwanken.

Vielfach ist auch die psychische Abhängigkeit verantwortlich für das Auftreten von Rückfällen.

In diesem Zusammenhang ist es erwähnenswert, daß sich in klinischen Studien gezeigt hat, daß insbesondere die Kombination von Nikotin mit einem Antidepressivum die Erfolgsraten bei der Raucherentwöhnung verbessern kann.
Allerdings ist die unterstützende Verabreichung von Psychopharmaka wegen des Nebenwirkungsrisikos und der Gefahr von Über- bzw. Unterdosierungen nicht unproblematisch.

Die Kombination von Nikotin oder nikotinerg wirkender Stoffe mit einem Antidepressivum in einer Arzneimittelform ist deshalb wünschenswert, da so die Einnahme für den Patienten erleichtert und auch das Risiko fehlerhafter Anwendungen minimiert wird.

Weil Raucher in vielen Situationen des täglichen Lebens das Bedürfnis nach einer Zigarette haben, sollte für diese Art der Therapie eine Applikationsform gewählt werden, die eine einfache und unauffällige Applikation gewährleistet und möglichst nicht an die klassische Arzneiform Tablette erinnert, da die Raucherentwöhnung keine Krankheit im klassischen Sinn darstellt, so daß sichergestellt ist, daß die Darreichungsform eine gute Compliance aufweist.

Zudem sollte die Verabreichung an den Patienten so einfach wie möglich erfolgen und der Patient keine Vorbehalte gegen

die Einnahme der Medikation, z.B. aufgrund der Größe der Darreichungsform oder dergleichen haben. Die Nachteile bekannter Darreichungsformen sollten dabei vermieden werden.

Es war deshalb die Aufgabe der vorliegenden Erfindung, Nikotinhaltige pharmazeutische Darreichungsformen bereitzustellen, die gleichzeitig die Verabreichung eines zusätzlichen Wirkstoffs, vorzugsweise eines Antidepressivums, zur Bekämpfung der psychischen Abhängigkeit im Rahmen einer Raucherentwöhnungs-Therapie ermöglichen. Bei der Verabreichung dieses zusätzlichen Wirkstoffs sollten Nebenwirkungen weitgehend ausgeschlossen werden, und die Anwendung sollte für den Patienten auf einfache und zuverlässige Weise erfolgen können.

Es hat sich gezeigt, daß diese Aufgabe durch flächenförmige Darreichungsformen aus einem hydrophilen Polymerfilm, der in der Mundhöhle zerfällt, gelöst wird, in den mindestens zwei Wirkstoffe eingearbeitet sind, wobei mindestens einer der Wirkstoffe Nikotin, ein Nikotinsalz, ein Nikotinderivat oder ein Stoff mit nikotinerger Wirkung ist, und mindestens ein weiterer Wirkstoff enthalten ist, wobei dieser weitere Wirkstoff zur Gruppe der psychisch wirksamen Substanzen gehört.

Demgemäß enthalten die erfindungsgemäßen Darreichungsformen eine Kombination des Wirkstoffs Nikotin, oder eines Nikotinsalzes, eines Nikotinderivates oder eines Stoffes mit nikotinerger Wirkung, zusammenfassend auch als nikotinerge Wirkstoffe bezeichnet, mit mindestens einem weiteren auf das zentrale Nervensystem wirkenden Stoff.

Die Kombination der Wirkstoffe in der erfindungsgemäßen Darreichungsform erleichtert dem Patienten die Einnahme beider Wirkstoffe.

Zudem wird das Risiko von Medikationsfehlern verringert, da der Patient nur ein Medikament für beide Wirkstoffe einnehmen muss. Dadurch werden Compliance und Therapieerfolg verbessert.

Infolge der Möglichkeit der direkten Resorption bestimmter Wirkstoffe über die Schleimhaut wird außerdem die Zeit bis zum Wirkungseintritt deutlich verringert, so daß der Patient innerhalb kürzester Zeit eine Linderung der Entzugssymptome spürt.

Durch die Kombination nikotinerg wirkender Substanzen, zu denen selbstverständlich auch Nikotin, Nikotinsalze und Nikotinderivate zählen, mit einem zentral wirkenden Wirkstoff, z.B. einem Antidepressivum, können sowohl die physischen als auch die psychischen Entzugserscheinungen wirksam unterdrückt werden. Darüber hinaus bietet die erfindungsgemäße Darreichungsform gegenüber den TTS den Vorteil, daß die Wirkstoffe so gering dosiert werden können, daß der unter Entzug Leidende immer dann, wenn er zur Zigarette greifen würde, eine Darreichungsform appliziert. Auf diese Weise wird auch der Drang, etwas aktiv gegen den Entzug zu unternehmen, der sich unter normalen Umständen im Anzünden einer Zigarette manifestiert, befriedigt. Die Befriedigung dieses Dranges ist bei der Raucherentwöhnung eine nicht zu unterschätzende Komponente, da das Rauchen nicht nur mit

der Aufrechterhaltung des Nikotinspiegels, sondern auch immer mit einer als entspannend empfundenen Tätigkeit verbunden war.

Darüber hinaus werden bei Applikation des Wafers Konzentrationsspitzen von Nikotin im Blut erzeugt, so daß im Gegensatz zur kontinuierlichen Abgabe von Nikotin aus einem TTS mit einem konstanten Plasmaspiegel ein dem Rauchen analoger Konzentrationsverlauf erhalten wird.

Um die Applikation der Darreichungsform zusätzlich mit einem Belohnungseffekt zu verbinden, können dieser besonders angenehm empfundene Geschmacks- oder Aromastoffe zugesetzt sein.

Da die Applikation der Darreichungsform die Entzugssymptome unterdrückt und die Stimmung verbessert, kann eine gute Compliance und eine optimale Wirksamkeit gewährleistet werden.

Die Verabreichung dieser Wirkstoffkombinationen in flächenförmigen Darreichungsformen (Wafern) ermöglicht nicht nur, wie bereits dargelegt, eine einfache Einnahme, sondern auch eine exakte Abstimmung der Wirkstoffkomponenten untereinander, so daß Fehldosierungen durch vergessenene oder doppelte Einnahme nur eines Wirkstoffs und somit eine unzureichende Therapie einer Suchtkomponente unterbleiben.

Durch die Variation des Verhältnisses der Wirkstoffe zueinander können zudem die Dosierungen an die jeweiligen Bedürfnisse angepaßt werden. So kann z.B. der Nikotingehalt

im Laufe der Entwöhnung langsam gesenkt werden, so daß sich die Zahl nikotinerger Acetylcholinrezeptoren wieder den normalen physiologischen Gegebenheiten anpaßt. Ebenso können die zur Unterdrückung der psychischen Abhängigkeit gegebenen Antidepressiva ausschleichend dosiert werden.

Aufgrund der einfachen und kostengünstigen Herstellung der Wafer ist es möglich, eine große Anzahl von Arzneimitteln mit unterschiedlichen Wirkstoffkonzentrationen bereitzustellen.
Ist der Wafer aus einem Laminat aufgebaut, so kann bei der Herstellung z.B. nur die Schichtdicke einer wirkstoffhaltigen Schicht oder die Konzentration des Wirkstoffes verändert werden.
Andererseits können Arzneimittel mit unterschiedlichem Wirkstoffgehalt aber gleichem Wirkstoffverhältnis einfach über unterschiedliche Flächenzuschnitte der Darreichungsform hergestellt werden.

Darüber hinaus können die erfindungsgemäßen Wafer mit den Wirkstoffkombinationen aufgrund ihrer flachen Form leicht mitgeführt werden, z.B. in der Brieftasche, und sind auch unterwegs sofort verfügbar und einfach einzunehmen.

Als wasserlösliche oder quellfähige Polymere für den hydrophilen wasserlösliche und/oder quellfähige Polymerfilm eignen sich als Grundpolymer Polymere aus der Gruppe, die Dextran, Polysaccharide, einschließlich der Stärke und Stärkederivate, Cellulosederivate, wie Carboxymethylcellulose, Ethyl- oder Propylcellulose, Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Natrium-Carboxymethyl-

cellulose (z. B. Walocel), Methylcellulose, Hydroxyethylcellulose und Hydroxypropylethylcellulose, Polyvinylalkohole, Polyethylenglykole, Polyacrylsäuren, Polyacrylate, Polyvinylpyrrolidone, Alginate, Pektine, Gelatine, Alginsäure, Kollagen, Chitosan, Arabinogalactan, Galactomannan, Agar-Agar, Agarose, Carrageen natürliche Gummen, Tragant, hochdisperses Siliziumdioxid, Bentonit, sowie Derivate der vorgenannten hydrophilen Polymere bzw. Kombinationen aus zwei oder mehreren dieser Polymere umfaßt. Alternativ kann der Polymerfilm auch aus einem Polyvinylalkohol-Polyethylenglycol-Pfropfcopolymer hergestellt sein.

Der Polymeranteil an einer erfindungsgemäßen Darreichungsform beträgt vorzugsweise 5 bis 95 Gew.-%, besonders bevorzugt 15 bis 75 Gew.-%, bezogen auf die Trockenmasse der Darreichungsform.

Bei dem in den erfindungsgemäßen Darreichungsformen zusätzlich zu Nikotin enthaltenen, auf das zentrale Nervensystem wirkenden Stoff handelt es sich vorzugsweise um einen Wirkstoff aus der Gruppe der Psychopharmaka, welche die Wirkstoffgruppen der Antidepressiva, Tranquilizer, Nootropika, Neuroleptika, Psychotonika oder Psychomimetika umfaßt.

Besonders bevorzugt sind dabei Wirkstoffe aus der Gruppe der Antidepressiva, da sie sich hinsichtlich der Überwindung der psychischen Abhängigkeit als sehr geeignet erwiesen haben. Die Erfindung umfaßt ferner auch nikotinhaltige Darreichungsformen der genannten Art, welche zwei oder mehrere Psychopharmaka aus den genannten Wirkstoffgruppen als zusätzliche Wirkstoffe enthalten.

Insbesondere kann der zusätzliche, auf das Zentralnervensystem wirkende Stoff ausgewählt sein aus der Gruppe, die Phenothiazine, Azaphenothiazine, Thioxanthene, Butyrophenone, Diphenylbutylpiperidine, Iminodibenzylderivate, Iminostilbenderivate, Dibenzocycloheptadienderivate, Dibenzodiazepinderivate, Dibenzoxepinderivate, Benzodiazepine, Indolderivate, Phenylethylaminderivate und Hypericinderivate sowie pharmazeutisch akzeptable Salze oder Derivate dieser Verbindungen umfaßt, wobei der Wirkstoff aus der Gruppe, die Chlorpromazin, Perphenazin, Sulpirid, Clozapin, Risperidon, Reserpin, Lorazepam, Mirtazapin, Maprotilin, Mianserin, Tranylcypromin, Moclobemid, Oxitriptan, Viloxazin, Reboxetin, Meprobamat, Hydroxyzin, Buspiron, Coffein, Fenetyllin, Methylphenidat, Prolintan, Fenfluramin, Meclofenoxat, Nicergolin, Piracetam, Pyritinol sowie pharmazeutisch akzeptable Salze dieser Wirkstoffe umfaßt, ausgewählt ist.

Bevorzugt werden Brotizolam, Triazolam und Buprion als Antidepressiva eingesetzt.

Als Nikotinsalze bzw. Nikotinderivate können in den erfindungsgemäßen Darreichungsformen vorzugsweise Nikotinhydrochlorid, Nikotindihydrochlorid, Nikotinsulfat, Nikotinbitartrat, Nikotin-Zinkchlorid und Nikotinsalicylat eingesetzt werden, entweder einzeln oder in Kombination, oder auch in Kombination mit Nikotin.

Als Substanzen mit nikotinerger Wirkung, d. h. Substanzen mit Wirkung am Nikotin-Rezeptor, werden neben Nikotin

selbst bevorzugt Lobelin, Succinylcholin und andere periphere Muskelrelaxantien eingesetzt.

Die für eine Behandlung der psychischen Abhängigkeit geeigneten Wirkstoffdosen und Plasmaspiegel sind dem Fachmann bekannt. Vorzugsweise wird die Dosis des auf das Zentralnervensystem wirkenden Stoffes auf die in der Darreichungsform vorhandene Nikotindosis abgestimmt, derartig, daß beide Wirkstoffe möglichst den jeweils therapeutisch günstigen Plasmaspiegel aufbauen.

In einer bevorzugten Darreichungsform enthält die erfindungsgemäße Arzneimittelzubereitung eine Kombination aus zwei Wirkstoffen, nämlich Nikotin, einem Nikotinsalz, einem Nikotinderivat oder einem Stoff mit nikotinerger Wirkung, sowie als weitere Wirkstoffkomponente zusätzlich einen auf das Zentralnervensystem wirkenden Stoff, welcher aus den oben genannten Stoffen oder Stoffgruppen ausgewählt werden kann.

In einer anderen Ausführungsform enthält die Arzneimittelzubereitung zwei nikotinerge Wirkstoffe, wobei diese auch Nikotin, ein Nikotinsalz oder ein Nikotinderivat sein können, und einen der vorhergehend definierten zentral wirkenden Stoffe, wobei die maximale Anzahl der kombinierten Wirkstoffe fünf nicht überschreitet.

In einer anderen Ausführungsform enthält die Arzneimittelzubereitung einen nikotinergen Wirkstoff, wobei dieser auch Nikotin, ein Nikotinsalz oder ein Nikotinderivat sein kann, und mindestens zwei der vorhergehend definierten zentral

wirkenden Stoffe, wobei die maximale Anzahl der kombinierten Wirkstoffe fünf nicht überschreitet.

Die erfindungsgemäßen Darreichungsformen ermöglichen nicht nur eine Nikotinsubstitution, sondern sie gestatten gleichzeitig eine Behandlung der psychischen Abhängigkeitskomponente der Nikotinsucht.

Zur Verbesserung der physiko-chemischen Eigenschaften, z.B. Verringerung der Brüchigkeit oder Versprödung, können dem Film Feuchthaltemittel zugesetzt sein, wie z.B. Glycerin, Propylenglycol, Sorbitol, Mannitol, Polyethylenglycol, Polyglycerinester und dergleichen.

In einer weiteren Ausführungsform können dem Wafer zur Stabilisierung des Films und der Wirkstoffe Antioxidantien zugesetzt sein, z.B. Vitamin C (Ascorbinsäure), Ascorbylpalmitat, Vitamin E (Tocopherolacetat), Hydroxybenzoesäurederivate. Weiterhin können auch saure und basische Ionentauscher als Stabilisatoren verwendet werden.

In weiteren Ausführungsformen können dem Film weitere Inhaltsstoffe wie Farbstoffe, Pigmente, Geschmacksstoffe, natürliche und/oder synthetische Aromastoffe, Süßstoffe, puffernde Systeme zugesetzt sein. Insbesondere Geschmacks- und Aromastoffe können dabei den oft schlechten Eigengeschmack oder Geruch der Wirkstoffe überdecken und/oder der Darreichungsform einen angenehmen Geschmack verleihen, so daß die Bereitschaft zur Einnahme der Medikation durch den Patienten deutlich verbessert wird.

Der Zusatz von puffernden Systemen dient zum einen der Stabilisierung des Films und der Wirkstoffe gegen äußere Einflüsse und bei der Lagerung, zum anderen kann so der pH-Wert der Darreichungsform auf einen physiologisch akzeptablen pH-Wert eingestellt werden, so daß Schleimhautreizungen vermieden werden. Durch ein Puffersystem kann auch die Löslichkeit von aciden oder basischen Wirkstoffen in der Matrix verbessert werden.

Die erfindungsgemäßen Darreichungsformen sind dünn, beispielsweise in Form einer Oblate gestaltet. Die Dicke der Darreichungsform beträgt vorzugsweise 0,1 bis 5 mm, besonders bevorzugt 0,5 bis 1 mm. Die untere Grenze für die Dicke der Darreichungsformen liegt bei etwa 50 µm. Die Fläche der Darreichungsform beträgt dabei zwischen 0,09 cm^2 und 12 cm^2, bevorzugt zwischen 1 cm^2 und 8 cm^2, und besonders bevorzugt zwischen 3 cm^2 und 6 cm^2.

In einer weiteren Ausführungsform enthalten die Wafer der vorliegenden Erfindung ein Sprengmittel oder ein Dochtmittel, z.B. ein Bicarbonat-Säure-Gemisch oder ein Aerosil, daß durch Kontakt mit Flüssigkeit aktiviert wird und den Zerfall des Wafers nach Applikation und somit auch die Wirkstofffreisetzung beschleunigt.

In einer bevorzugten Ausführungsform liegt der Wafer als Schaum vor, so daß die Wirkstoffabgabe aufgrund der vergrößerten Oberfläche noch schneller erfolgt. Hierbei können in den Hohlräumen des Schaums auch einer oder mehrere der Wirkstoffe in flüssiger Form vorliegen.

Zur Verbesserung der Resorption der Wirkstoffe durch die Schleimhaut können in dem Film auch Permeationsförderer, z.B. Stoffe aus den Gruppen der Fettalkohole, Fettsäuren, Polyoxyethylenfettalkoholether, Polyoxyethylenfettsäureester, Fettalkoholester und Fettsäureester, insbesondere Sorbitanmonolaurat oder Ester von langkettigen Fettsäuren mit Methyl-, Ethyl- oder Isopropylalkohol, oder Ester von Fettalkoholen mit Essigsäure oder Milchsäure, oder auch Stoffe wie DMSO (Dimethylsulfoxid) und Ölsäurediethanolamin zugesetzt sein. Der Mengenanteil dieser Stoffe beträgt 0,1 bis 25 Gew.-%, vorzugsweise von 1 bis 10 Gew.-%, jeweils bezogen auf das Gesamtgewicht der Wirkstoffmatrix.

Darüber hinaus können in der Zusammensetzung des Wafers Verbindungen enthalten sein, die die Wirkstofffreisetzung verzögern (z.B. Mikroverkapselung).

In einer weiteren Ausführungsform besitzt der Wafer mukoadhäsive Eigenschaften, so daß dieser an der Schleimhaut bis zur vollständigen Auflösung haftet.

In einer bevorzugten Ausführungsform ist mindestens einer der Wirkstoffe an einen Ionentauscher gebunden, so daß das hydrophile Polymer schnell im Mundraum zerfällt, die Freisetzung des Wirkstoffes aber erst verzögert oder bei verändertem pH-Wert, z.B. im Gastrointestinaltrakt erfolgt. Auf diese Weise können Wirkstoffe mit unterschiedlichem Wirk- und Resorptionsmechanismus in einer Darreichungsform verabreicht werden, d.h. mindestens einer der freigesetzten Wirkstoffe wird entweder am Applikationsort resorbiert,

z.B. über die Mundschleimhaut oder er wird weitertransportiert und an einem anderen Ort resorbiert.

Der Wafer kann auch als Laminat mit unterschiedlichen Schichten aufgebaut sein, wobei die Wirkstoffe in diskreten Schichten enthalten sind, die räumlich voneinander getrennt sind und sich in ihrem Aufbau voneinander unterscheiden. Die Wirkstoffe können so an unterschiedlichen Wirkorten oder aber auch verzögert freigesetzt werden, wenn sich die Zerfallszeit der unterschiedlichen Schichten das Wafers unterscheidet.

Ebenso können die Wirkstoffe in Schichten angeordnet sein, die unterschiedlich schnell zerfallen, so daß die gesamte Zubereitung einen Retardeffekt aufweist.

In einer weiteren Ausführungsform kann eine der äußeren Schichten mukoadhäsiv sein, um das Anhaften der Darreichungsform auf der Schleimhaut zu begünstigen und die Wirkstoffresorption über die Schleimhaut durch den direkten Kontakt zu vereinfachen.

Der Zerfall in wäßrigem Medium der erfindungsgemäßen Darreichungsform erfolgt vorzugsweise im Bereich von 1 s bis 5 min, stärker bevorzugt im Bereich von 5 s bis 1 min, und am meisten bevorzugt im Bereich von 10 s bis 30 s.

Die erfindungsgemäßen Darreichungsformen eignen sich in vorteilhafter Weise für die Verabreichung von Medikamenten in der Mundhöhle oder zur rektalen, vaginalen oder intra-

nasalen Verabreichung. Sie können in der Humanmedizin wie auch in der Veterinärmedizin eingesetzt werden.

Die vorliegende Erfindung ist weiterhin auf die Verwendung einer der erfindungsgemäßen Wirkstoffkombination zur Herstellung einer oralen Darreichungsform zur Raucherentwöhnung gerichtet, wobei die Darreichungsform bevorzugt als Wafer formuliert wird.

Weiterhin ist die vorliegende Erfindung auf ein Verfahren zur therapeutischen Raucherentwöhnung gerichtet, wobei die Verabreichung einer zuvor beschriebenen Wirkstoffkombination von Nikotin und zentral wirkendem Stoff mittels einer oral applizierbaren Darreichungsform mit transmukosaler Resorption erfolgt.

Schließlich ist die vorliegende Erfindung auch auf ein Verfahren zur Herstellung einer flächenförmigen Darreichungsform gerichtet, das die folgenden Schritte umfaßt:

- Herstellen einer Lösung, die zumindest ein Polymer und mindestens zwei Wirkstoffe, von denen einer Nikotin, ein Nikotinsalz, ein Nikotinderivat oder eine nikotinerg wirkende Substanz und der andere ein Psychopharmakon ist, enthält;
- Ausstreichen der Lösung auf eine Beschichtungsunterlage; und
- Verfestigen der ausgestrichenen Lösung durch Trocknen und Entzug des Lösemittels.

Ansprüche

1. Flächenförmige, bei Kontakt mit Feuchtigkeit schnell zerfallende Arzneimittelzubereitung auf Basis hydrophiler Polymere zur Freisetzung einer Wirkstoffkombination zur Raucherentwöhnung, dadurch gekennzeichnet, daß die Arzneimittelzubereitung eine Wirkstoffkombination aus mindestens zwei Wirkstoffen enthält, von denen mindestens einer aus der Gruppe der nikotinergen Wirkstoffe ausgewählt ist.

2. Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß die Gruppe der nikotinergen Wirkstoffe Nikotin, Nikotinderivate, die korrespondierenden pharmazeutisch akzeptablen Salze von Nikotin und Nikotinderivaten sowie Verbindungen mit nikotinerger Wirkung umfaßt.

3. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß ein zweiter Wirkstoff aus der Gruppe ausgewählt ist, die die Psychopharmaka umfaßt.

4. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Psychopharmaka aus der Gruppe ausgewählt sind, die die Antidepressiva, Tranquilizer, Nootropika, Neuroleptika, Psychotonika und Psychomimetika umfaßt.

5. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß mindestens einer der Wirkstoffe neben Nikotin aus der Gruppe ausgewählt ist, die Phenothiazine, Azaphenothiazine, Thioxanthene, Butyropheno-

ne, Diphenylbutylpiperidine, Iminodibenzylderivate, Iminostilbenderivate, Dibenzocycloheptadienderivate, Dibenzodiazepinderivate, Dibenzoxepinderivate, Benzodiazepine, Indolderivate, Phenylethylaminderivate und Hypericinderivate sowie pharmazeutisch akzeptable Salze oder Derivate dieser Verbindungen umfaßt.

6. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß mindestens einer der Wirkstoffe neben Nikotin aus der Gruppe ausgewählt ist, die Chlorpromazin, Perphenazin, Sulpirid, Clozapin, Risperidon, Reserpin, Lorazepam, Mirtazapin, Maprotilin, Mianserin, Tranylcypromin, Moclobemid, Oxitriptan, Viloxazin, Reboxetin, Meprobamat, Hydroxyzin, Buspiron, Coffein, Fenetyllin, Methylphenidat, Prolintan, Fenfluramin, Meclofenoxat, Nicergolin, Piracetam, Pyritinol, Brotizolam, Triazolam und Buprion sowie ihre pharmakologisch akzeptablen Salze umfaßt.

7. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Nikotinsalze und Nikotinderivate aus der Gruppe ausgewählt sind, die Nikotinhydrochlorid, Nikotindihydrochlorid, Nikotinsulfat, Nikotinbitartrat, Nikotin-Zinkchlorid und Nikotinsalicylat sowie Kombinationen dieser Verbindungen umfaßt.

8. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Substanzen mit nikotinerger Wirkung aus der Gruppe ausgewählt sind, die Nikotin, Lobelin, Succinylcholin und andere periphere

Muskelrelaxantien sowie Kombinationen dieser Substanzen umfaßt.

9. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das hydrophile Polymer ausgewählt ist aus der Gruppe, die Dextran, Polysaccharide, einschließlich der Stärke und Stärkederivate, Cellulosederivate, wie Carboxymethylcellulose, Ethyl- oder Propylcellulose, Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Natrium-Carboxymethylcellulose (z. B. Walocel), Methylcellulose, Hydroxyethylcellulose und Hydroxypropylethylcellulose, Polyvinylalkohole, Polyethylenglykole, Polyacrylsäuren, Polyacrylate, Polyvinylpyrrolidone, Alginate, Pektine, Gelatine, Alginsäure, Kollagen, Chitosan, Arabinogalactan, Galactomannan, Agar-Agar, Agarose, Carrageen natürliche Gummen, Tragant, hochdisperses Siliziumdioxid, Bentonit, sowie Derivate der vorgenannten hydrophilen Polymere bzw. Kombinationen aus zwei oder mehreren dieser Polymere umfaßt.

10. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Polymerfilm aus einem Polyvinylalkohol-Polyethylenglycol-Pfropfcopolymer hergestellt ist.

11. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung ein Feuchthaltemittel, ausgewählt aus der Gruppe, die Glycerin, Propylenglycol, Sorbitol, Mannitol, Polyethylenglycol und Polyglycerinester umfaßt, enthält.

12. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung ein Antioxidans enthält, ausgewählt aus der Gruppe, die Vitamin C (Ascorbinsäure), Ascorbylpalmitat, Vitamin E (Tocopherolacetat) und Hydroxybenzoesäurederivate umfaßt.

13. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Wirkstoff der Zubereitung zur Geschmacksmaskierung an einen sauren oder basischen Ionentauscher gebunden ist.

14. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung Farbstoffe und/oder Pigmente enthält.

15. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung natürliche und/oder synthetische Aromastoffe enthält.

16. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung ein Sprengmittel oder Dochtmittel enthält.

17. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der pH-Wert der Zubereitung über ein Puffersystem eingestellt ist.

18. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das hydrophile Polymer in weniger als 5 min, bevorzugt in weniger als 3 min, weiter bevorzugt in weniger als 1 min, und besonders bevor-

zugt in weniger als 30 s nach Applikation im Mundraum zerfällt.

19. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das hydrophile Polymer schnell im Mundraum zerfällt, der Wirkstoff aber an einen Ionentauscher gebunden bleibt, der den Wirkstoff erst im Gastrointestinaltrakt freisetzt.

20. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Wirkstoffe in diskreten Schichten enthalten sind, die räumlich voneinander getrennt sind und sich in ihrem Aufbau voneinander unterscheiden.

21. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung als Schaum vorliegt und mindestens einer der Wirkstoffe in flüssiger Form in den Hohlräumen des Schaums vorliegt.

22. Arzneimittelzubereitung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß sie eine Kombination aus einem nikotinergen Wirkstoff und einem Antidepressivum enthält.

23. Verwendung einer Darreichungsform nach einem oder mehreren der Ansprüche 1 bis 22 zur rektalen, vaginalen oder intranasalen Verabreichung von pharmazeutischen Wirkstoffen an Menschen oder Tiere.

24. Verwendung einer Wirkstoffkombination aus nikotinergem Wirkstoff und Psychopharmakon zur Herstellung einer oralen

Darreichungsform nach einem der vorhergehenden Ansprüche zur Raucherentwöhnung.

25. Verwendung einer Wirkstoffkombination aus nikotinergem Wirkstoff und Antidepressivum zur Herstellung einer oralen Darreichungsform nach einem der vorhergehenden Ansprüche zur Raucherentwöhnung.

26. Verwendung nach einem oder mehreren der Ansprüche 23 - 26, dadurch gekennzeichnet, daß das Arzneimittel als Wafer formuliert wird.

27. Verfahren zur therapeutischen Behandlung einer unter Entzugserscheinungen der Raucherentwöhnung leidenden Person, dadurch gekennzeichnet, daß die Verabreichung der Wirkstoffkombination aus nikotinergem Wirkstoff und Psychopharmakon mittels einer oral applizierbaren Darreichungsform mit transmukosaler Resorption erfolgt.

28. Verfahren zur Herstellung einer flächenförmigen Darreichungsform nach einem der Ansprüche 1 bis 22, gekennzeichnet durch das

- Herstellen einer Lösung, die zumindest ein Polymer und mindestens zwei Wirkstoffe enthält, von denen einer Nikotin, ein Nikotinsalz, ein Nikotinderivat oder eine nikotinerg wirkende Substanz und der andere ein Psychopharmakon ist;
- Ausstreichen der Lösung auf eine Beschichtungsunterlage und
- Verfestigen der ausgestrichenen Lösung durch Trocknen und Entzug des Lösemittels.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/5513(2006.01)i, A61K 31/355(2006.01)i, A61K 9/16(2006.01)i, A61K 47/10(2006.01)i, A61P 25/22(2006.01)i

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)

IPC8 as above

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 practicable, search terms used)

eKOMPASS, Google scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007043057 A2 (TOUITOU, ELKA et. al.) 19 April 2007 See claims 18 and 35, p. 6 (line 1-3), 8 (line 3-11)	1-19
A	WO 2005117830 A1 (CAMURUS AB, SWED) 15 December 2005 See whole document	1-19
A	WO 2006075123 A1 (CAMURUS AB, SWED) 20 July 2006 See whole document	1-19
A	WO 2007144081 A2 (LTS LOHMANN THERAPIE-SYSTEM A.-G.) 21 December 2007 See whole document ----------//	1-19

☐ Further documents are listed in the continuation of Box C.

☒ 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 application or patent 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 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

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"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
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Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	KIM, YONG Telephone No. 82-42-481-8164

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 514/220; 514/221

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/58; 514/219; 514/220; 536/103; 536/46; 540/569

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Google: nasal; nose; nostril; NEAR3 administ$; composition; particle size; benzodiazepine; (coat$; active agent); particle size distribution; multimodal; distribution; greater than NEAR3 nm; plasma concentration maximum; Csubmax; particulate; heterogen$

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2003/0181411 A1 (Bosch, et. al.) 25 Sep 2003 (25.09.2003); claims 1, 6, 12, 17; para [0033], [0037], [0043], [0070]-[0074], [0116], [0117], [0140], [0147], [0187]	1, 4, 5, 7-9, 14-16 --- 2, 3, 6, 10-13, 17-26, 46-60
X -- Y	US 2006/0198896 A1 (Liversidge, et. al.) 7 Sep 2006 (07.09.2006); claims 1-4, 5, 8, 13, 16, 17, 20; para [0001], [0032], [0033], [0036], [0067], [0068], [0074], [0091], [0154], [0209]	27-45 and 61-65 --- 2, 3, 6, 10-13, 17-26, 46-60

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
25 July 2008 (25.07.2008)	04 AUG 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/42311

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/62; A61K 31/55 (2012.01)
USPC - 514/220-221
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)
USPC-514/220-221

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-424/400, 434 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PUBWEST, Google Scholar, Google, Intranasal, nasal, inhalation, mucosal, drug, delivery, denzodazepine, diazepam, tocopherol, tocotrienol, Vitamin E, alcohol, ethanol, benzyl alcohol, alkyl glycoside

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/0258865 A1 (Cartt et al.) 15 October 2009 (15.10.2009) para [0010]-[0021], [0024]-[0030], [0035]-[0039], [0047], [0138], [0142]-[0143], [0147], [0161]-[0162], [0180]-[0181], [0196]-[0204]	1-62
A	US 2009/0130216 A1 (Cartt et al.) 21 May 2009 (21.05.2009) entire document	1-62
A	US 2008/0279784 A1 (Cartt et al.) 13 November 2008 (13.11.2008) entire document	1-62
A	US 2009/0304801 A1 (Liversidge et al.) 10 December 2009 (10.12.2009) entire document	1-62

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
10 August 2012 (10.08.2012)	31 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

Electronic Acknowledgement Receipt

EFS ID:	15524608
Application Number:	13495942
International Application Number:	
Confirmation Number:	7399
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Melanie O'Donnell
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.501
Receipt Date:	15-APR-2013
Filing Date:	13-JUN-2012
Time Stamp:	21:31:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	35401_716_501_Tran_04_15_2013.pdf	270342 898d581983539873 0f78494d6cb2da63b0626a8b	no	4

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	35401_716_501_IDS_04_15_2013.pdf	270318 660bf9063146ff8976954ae6531098e94030943e	no	6
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Other Reference-Patent/App/Search documents	USProvAppl60148464.pdf	4216678 e3e77c38c70677ba3787ffeac27e3fe3d1b32ba8	no	93
Warnings:					
Information:					
4	Foreign Reference	EP780386.pdf	7346493 64aa58aa2f1137f726ff8788544b92fd3caa70d4	no	86
Warnings:					
Information:					
5	Foreign Reference	EP818442.pdf	1148513 08774915e8a186879aab67908f8069af53bb079f	no	22
Warnings:					
Information:					
6	Foreign Reference	EP945485.pdf	1225922 e3ae956dd39f84eb0216ef8d024db50f251edf4f	no	26
Warnings:					
Information:					
7	Foreign Reference	EP1004578.pdf	2457315 677cae9be5f6bfdaf20556b94b45bf6a88d503c0	no	26
Warnings:					
Information:					
8	Foreign Reference	EP606046.pdf	5415758 a23f0e58e0785d0b17089d7eec2f0242c968b0cd	no	43
Warnings:					
Information:					
9	Foreign Reference	EP931788.pdf	1166301 7fc9455ce921384b1c7b0edcb07c2b31d52b9f4e	no	25
Warnings:					
Information:					
10	Foreign Reference	JP2003_505403.pdf	1045392 f14baf9d05bdc34cdf2a5bcb53a5df29767db222	no	73

Warnings:					
Information:					
11	Foreign Reference	JP2005_508939.pdf	1567369 4c0e038db5fb6034d4086f83b7cbbdca50350a18	no	76
Warnings:					
Information:					
12	Foreign Reference	JP2007_510722.pdf	2206873 52352de018ecb0950de7da4bca65b310ccd7651c	no	110
Warnings:					
Information:					
13	Foreign Reference	WO90_05719.pdf	2689362 17218eca0467a2b4ebb50bd7122c895d47c758cd	no	84
Warnings:					
Information:					
14	Foreign Reference	WO96_27583.pdf	2520695 fbc0453fded7e011fcf884125b197d0a5f35d1a6	no	71
Warnings:					
Information:					
15	Foreign Reference	WO96_33172.pdf	1740185 89915dc892ae1a11c67e0268ec6baa28d2bf81c2	no	50
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Information:					
16	Foreign Reference	WO97_014407A1.pdf	1013800 683536ca4877198ee7c064b3462a8b543a4f880e	no	32
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Information:					
17	Foreign Reference	WO98_03516.pdf	1615821 5f42696aade44e3922a3e35a94787bfaa64996b4	no	48
Warnings:					
Information:					
18	Foreign Reference	WO98_07697.pdf	2089211 5e165ce9d3900921df70ad9d47f87296e8db60d0	no	51
Warnings:					
Information:					
19	Foreign Reference	WO98_30566.pdf	1155452 [illegible]ef04	no	27

Warnings:					
Information:					
20	Foreign Reference	WO98_33768.pdf	1459018 9999224d627410dfbbe363d945ac937361cfb68e	no	34
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Information:					
21	Foreign Reference	WO98_34915.pdf	2284898 910c823a80be23803bb2f04438fb5a23c7370c1b	no	50
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Information:					
22	Foreign Reference	WO98_34918.pdf	2393044 c692249a3c2265012f51699bc29461db8e30bcf0	no	63
Warnings:					
Information:					
23	Foreign Reference	WO1999_007675.pdf	1035577 84d15cf9ad60d750f2df9245d14234aa5e57d114	no	26
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Information:					
24	Foreign Reference	WO99_29667.pdf	5674289 d0b4257062859b327e9f083c0cd6afd5aa15a33f	no	149
Warnings:					
Information:					
25	Foreign Reference	WO99_52889.pdf	1755491 751d474d43e0c65013ba7f6c5e1f76b2239e17cd	no	36
Warnings:					
Information:					
26	Foreign Reference	WO99_52910.pdf	2399490 77a59da608ac54f2645a0d58f4a1f517f72b02b	no	52
Warnings:					
Information:					
27	Foreign Reference	WO2000_74681.pdf	4935004 ffbe67d8b3aafa4aaedb49fa795e38ec9db18fd7	no	141
Warnings:					
Information:					
28	Foreign Reference	WO05_044234A2.pdf	3809020 [illegible]	no	68

Warnings:					
Information:					
29	Foreign Reference	WO2005_089768.pdf	1430921 02db9db78198e981667f7a669801fa552a30221d	no	47
Warnings:					
Information:					
30	Foreign Reference	WO05_117830A1.pdf	3458643 f9e4c7c7570a2d177faf00589f9616a35e6ec517	no	69
Warnings:					
Information:					
31	Foreign Reference	WO2006_055603.pdf	1748085 547f3b66e2629c303b07b619edf3d3bcd544dc98	no	58
Warnings:					
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32	Foreign Reference	WO2006_088894.pdf	2498937 a965c46f0e9b53d3c06a380b36d2eb8982fa31fd	no	65
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33	Foreign Reference	WO2006_075123.pdf	5620634 315663aef55ccda966a7a402b7a93b6b5b03f3ef	no	62
Warnings:					
Information:					
34	Foreign Reference	WO2007_043057.pdf	4736531 058fb2520a116d3c5c07180232c60268022a8156	no	63
Warnings:					
Information:					
35	Foreign Reference	WO2007_144081.pdf	1836909 49827b9fb26659e7ae1302d3187142a5a28da65d	no	25
Warnings:					
Information:					
36	Non Patent Literature	Wermeling.pdf	1190828 707b6c75f9dcaef86494580d4723e7ca72ba4d70	no	6
Warnings:					
Information:					
37	Non Patent Literature	EP087478137SuppSrchRpt_2June2010.pdf	612546 [illegible]9221	no	8

Warnings:					
Information:					
38	Non Patent Literature	PCT_US09_038696_ISR_28Sept 2009.pdf	34728 548174406b3b2c5b8d0943ac71626cc8f7d2565d	no	1
Warnings:					
Information:					
39	Non Patent Literature	PCT_US08_62961SrchRpt_25July2008.pdf	58571 31b4ab2b3a5fb309e8264f8f4f9ca099833446ba	no	1
Warnings:					
Information:					
40	Non Patent Literature	PCT_US12_42311_ISR_31Aug2012.pdf	38141 7a99b9ea862f5c3947435e677508e64fd0d4d109	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	90173105		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Steve Cartt	Group Art Unit: 1612
Serial Number: 13/495,942	Examiner: Adam Milligan
Filing Date: 06/13/2012	**CONFIRMATION NO: 7399**
Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

FILED ELECTRONICALLY ON: April 15, 2013

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Madam:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

A. ☒ *37 CFR §1.97(b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;

-- OR --

☒ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

B. ☐ *37 CFR §1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97(e) provided concurrently herewith;

-- OR --

☐ a fee of $180.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR §1.97(d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in §1.97(e);

-- AND --

ii. a fee of $180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97(e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e)(1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the

requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98(a)(2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☒ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner, for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.35401-716.501).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: April 15, 2013

By: /Matthew V. Grumbling/
Matthew V. Grumbling
Registration No. 44,427

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/495,942	06/13/2012	Steve Cartt	35401-716.501	7399

21971 7590 05/08/2013

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
MILLIGAN, ADAM C	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
05/08/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 13/495,942	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-65* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-65* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1-22 and 57-59, drawn to a pharmaceutical solution for nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside, in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient., classified in class 424, subclass 465.

Group II. Claims 23-56 and 60-65, drawn to a method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside, classified in class 514, subclass 221.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the invention of Group I can be used for administration or the oral or buccal mucosa, which is distinct from nasal administration. Note that the pharmaceutical solution, while being intended for nasal administration, is suitable for other forms of administration (i.e. oral). Language, such as

intended use, that suggests or makes optional but does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation. See MPEP 2103. Here, the phrases “for nasal administration” and “for administration to one or more nasal mucosal membranes of a patient” are interpreted as mere intended uses that do not limit the scope of a claim.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because at least the following reasons apply:

--the inventions have acquired a separate status in the art in view of their different classification

--the inventions require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search strategies or search queries).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time

of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product

claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADAM MILLIGAN whose telephone number is (571)270-7674. The examiner can normally be reached on M-F 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ADAM C MILLIGAN/
Examiner, Art Unit 1612

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Steve Cartt, et al. Serial No.: 13/495,942 Filing Date: June 13, 2012 Title: **Administration of Benzodiazepine Compositions**	Group Art Unit: 1629 Confirmation No.: 7399 Examiner: Milligan, Adam C. Customer No.: 21971 Certificate of Electronic Filing I hereby certify that the attached **Preliminary Amendment** and all marked attachments are being deposited by Electronic Filing on September 6, 2013 by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. By: /Linda Anders/ Linda Anders

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT

Dear Madam:

We are filing this paper in response to the Restriction Requirement mailed May 8, 2013, setting an initial deadline of June 8, 2013. Accordingly, Applicants petition for a three-month extension of time, and submit the appropriate fee. Applicants respectfully request entry of the following response and examination of the pending claims.

Amendments to the Claims begin on page 2.

Remarks begin on page 8.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in this application.

1. (Previously Presented) A Pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);

(c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and

(d) an alkyl glycoside,

in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient.

2. (Previously Presented) The pharmaceutical solution of claim 1, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).

3. (Previously Presented) The pharmaceutical solution of claim 2, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

4. (Previously Presented) The pharmaceutical solution of claim 3, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

5. (Previously Presented) The pharmaceutical solution of claim 1, containing about 1 to about 20 % (w/v) of benzodiazepine.

6. (Previously Presented) The pharmaceutical solution of claim 5, containing about 1 to about 20 % (w/v) of diazepam.

7. (Previously Presented) The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

8. (Previously Presented) The pharmaceutical solution of claim 1, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof.

9. (Previously Presented) The pharmaceutical solution of claim 1, containing two or more alcohols.

10. (Previously Presented) The pharmaceutical solution of claim 1, containing ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)).

11. (Previously Presented) The pharmaceutical solution of claim 1, containing ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).

12. (Previously Presented) The pharmaceutical solution of claim 11, wherein the benzodiazepine is present in the pharmaceutical solution in a concentration from about 20 mg/mL to about 200 mg/mL.

13. (Previously Presented) The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w).

14. (Previously Presented) The pharmaceutical solution of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w).

15. (Previously Presented) The pharmaceutical solution of claim 1, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w).

16. (Previously Presented) The pharmaceutical solution of claim 15, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 25% to about 40% (w/w).

17. (Previously Presented) The solution of claim 1, consisting of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).

18. (Previously Presented) The solution of claim 1, wherein the pharmaceutically-acceptable formulation comprises at least about 0.01% (w/w) of an alkyl glycoside.

19. (Previously Presented) The solution of claim 18, wherein the pharmaceutically-acceptable formulation about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside.

20. (Previously Presented) The solution of claim 1, consisting essentially of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

21. (Previously Presented) The solution of claim 20, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

22. (Previously Presented) The solution of claim 21, consisting of about 56.47% (w/v) vitamin E, about 10.5 % (w/v) benzyl alcohol, about 10 % (w/v) diazepam, about 0.25 % (w/v) dodecyl maltoside, q.s. dehydrated ethanol.

23. (Withdrawn) A method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside.

24. (Withdrawn) The method of claim 23, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).

25. (Withdrawn) The method of claim 24, wherein the natural or synthetic tocopherols or tocotrienols is Vitamin E.

26. (Withdrawn) The method of claim 23, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

27. (Withdrawn) The method of claim 26, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

28. (Withdrawn) The method of claim 23, wherein the solution contains about 1 to about 20 % (w/v) of benzodiazepine.

29. (Withdrawn) The method of claim 28, wherein the solution contains about 1 to about 20 % (w/v) of diazepam.

30. (Withdrawn) The method of claim 23, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

31. (Withdrawn) The method of claim 23, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof.

32. (Withdrawn) The method of claim 23, wherein the solution contains two or more alcohols.

33. (Withdrawn) The method of claim 23, wherein the solution contains ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)).

34. (Withdrawn) The method of claim 33, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.

35. (Withdrawn) The method of claim 34, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.

36. (Withdrawn) The method of claim 23, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w).

37. (Withdrawn) The method claim 36, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w).

38. (Withdrawn) The method of claim 23, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w).

39. (Withdrawn) The method of claim 38, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w).

40. (Withdrawn) The method of claim 23, wherein the solution contains ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).

41. (Withdrawn) The method of claim 23, wherein the solution is in a pharmaceutically-acceptable spray formulation.

42. (Withdrawn) The method of claim 41, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.

43. (Withdrawn) The method of claim 42, wherein said pharmaceutical solution is in a pharmaceutically-acceptable spray formulation having volume from about 10 μL to about 200 μL.

44. (Withdrawn) The method of claim 43, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril.

45. (Withdrawn) The method of claim 43, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.

46. (Withdrawn) The method of claim 45, wherein the administration of the pharmaceutical solution comprises spraying a first quantity of the pharmaceutical solution into the first nostril, spraying a second quantity of the pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical solution into the first nostril.

47. (Withdrawn) The method of claim 46, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical solution to the second nostril.

48. (Withdrawn) The method of claim 46, wherein nasal administration of the pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical solution.

49. (Withdrawn) The method of claim 23, wherein the solution contains at least about 0.01% (w/w) of an alkyl glycoside.

50. (Withdrawn) The method of claim 24, wherein the solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.

51. (Withdrawn) The method of claim 50, wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside.

52. (Withdrawn) The method of claim 23, wherein the solution consists essentially of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

53. (Withdrawn) The method of claim 23, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

54. (Withdrawn) The method of claim 23, wherein the solution consists of about 56.47% (w/v) vitamin E, about 10.5 % (w/v) benzyl alcohol, about 10 % (w/v) diazepam, about 0.25 % (w/v) dodecyl maltoside, q.s. dehydrated ethanol.

55. (Withdrawn) The method of claim 23, wherein the solution consists of diazepam, alkyl glycoside, vitamin E, ethanol, and benzyl alcohol.

56. (Withdrawn) The method of claim 23, wherein the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).

57. (Previously Presented) The solution of claim 17, consisting of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).

58. (Previously Presented) The solution of claim 17, consisting of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).

59. (Previously Presented) The solution of claim 17, consisting of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

60. (Withdrawn) The method of claim 23, wherein the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).

61. (Withdrawn) The method of claim 23, wherein the solution consists of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).

62. (Withdrawn) The method of claim 23, wherein the solution consists of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

63. (Withdrawn) The method of claim 23, wherein said treatment achieves bioavailability that is from about 80-125% of that achieved with the same benzodiazepine administered intravenously.

64. (Withdrawn) The method of claim 63, wherein said treatment achieves bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously.

65. (Withdrawn) The method of claim 64, wherein said treatment achieves bioavailability that is from about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously.

REMARKS

Responsive to the restriction requirement of May 8, 2013, Applicants hereby elect group I, claims 1-22 and 57-59. No new matter has been added by the foregoing amendment. Claims 1-65 are pending and presented for examination. Favorable action is respectfully requested.

CONCLUSION

Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned attorney at (858) 350-2332. The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415, referencing Attorney Docket No. 35401-716.501.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: September 6, 2013

By: /Matthew V. Grumbling/
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REMARKS

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CONCLUSION

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Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: September 6, 2013

By: /Matthew V. Grumbling/
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Electronic Patent Application Fee Transmittal

Application Number:	13495942
Filing Date:	13-Jun-2012
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/Linda Anders
Attorney Docket Number:	35401-716.501

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	700	700

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**700**

Electronic Acknowledgement Receipt

EFS ID:	16789142
Application Number:	13495942
International Application Number:	
Confirmation Number:	7399
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Linda Anders
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.501
Receipt Date:	06-SEP-2013
Filing Date:	13-JUN-2012
Time Stamp:	17:29:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$700
RAM confirmation Number	5106
Deposit Account	232415
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		35401-716-501-responseRR.pdf	142983 dd79815b2fbc4250e30d69a157f7c6d7bb281379	yes	10

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Response to Election / Restriction Filed	1	1
Claims	2	9
Applicant Arguments/Remarks Made in an Amendment	10	10

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30537 8c49418e1ecb7fedd5570416ae1c7682fd2e90e7	no	2

Warnings:

Information:

Total Files Size (in bytes):	173520

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/495,942	Filing Date 06/13/2012	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT

09/06/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 65	Minus	** 65	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

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LIE
/TERRY MALLOY/

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
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				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	1	of	1	Attorney Docket Number	35401-716.501

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2004-141923 A1	07/22/2004	Dugger et al.	
	2.	US-8,530,463	09/10/2013	Cartt	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	3.	WO-2009-120933 A2	10/01/2009	Particle Sciences Inc.		
	4.	WO-95-31217 A1	11/23/1995	Dumex Ltd.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	5.	AU application 2009228093 First exam report dated July 19, 2013	
	6.	EP application 09723906.5 Extended European search report dated June 3, 2013	
	7.	JP application 2010-507633 Decision of refusal dated July 9, 2013.	

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**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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(54) **Title**: PHARMACEUTICAL SOLUTIONS AND METHOD FOR SOLUBILIZING THERAPEUTIC AGENTS

(57) **Abstract**: Pharmaceutical solutions containing hydrophobic or lipophilic therapeutic agents and methods for producing the same are provided. Pharmaceutical solutions of the invention are produced by dissolving the therapeutic agent in one or more tocopherols or tocotrienols and one or more alcohols or glycols. These solutions are used to produce pharmaceutical compositions.

WO 2009/120933 A2

PHARMACEUTICAL SOLUTIONS AND METHOD FOR SOLUBILIZING THERAPEUTIC AGENTS

This patent application claims the benefit of priority from U.S. Application Serial No. 61/040,281, filed March 28, 2008, teachings of which are herein incorporated by reference in their entirety.

Background of the Invention

A vast number of potential therapeutic agents are discovered each year, many of which are water insoluble or poorly water soluble. For such hydrophobic compounds, direct injection may be impossible or highly dangerous, and can result in hemolysis, phlebitis, hypersensitivity, organ failure and/or death. Such compounds are termed by pharmacists as "lipophilic", "hydrophobic", or in their most insoluble form, "amphiphobic".

A few examples of therapeutic agents in these categories are ibuprofen, diazepam, griseofulvin, cyclosporin, cortisone, proleukin, etoposide and paclitaxel. (Kagkadis et al. *PDA J. Pharm. Sci. Tech.* 1996 50(5):317-323; Dardel *Anaesth. Scand.* 1976 20:221-24; Sweetana and Akers *PDA J. Pharm. Sci. Tech.* 1996 50(5):330-342).

Administration of chemotherapeutic agents is particularly problematic. Most of these agents are poorly soluble and thus are difficult to deliver in aqueous solvents and to supply at therapeutically effective levels. Further, water-soluble, chemotherapeutic agents are generally taken up by both cancer and non-cancer cells, making such agents non-specific and oftentimes unacceptably toxic.

For therapeutic agents that cannot be formulated as an aqueous solution, emulsions have oftentimes provided a cost-effective and therapeutically acceptable alternative. However, it is difficult to render emulsions sterile and/or

endotoxin free for intravenous injection. Oils typically used for pharmaceutical emulsions include saponifiable oils from the family of triglycerides, for example, soybean oil, sesame seed oil, cottonseed oil, safflower oil and the like (Hansrani, et al. *J. Parenter. Sci. Technol.* 1983 37:145-150). One or more surfactants are used to stabilize the emulsion, and excipients are added to render the emulsion more biocompatible, stable and less toxic. Lecithin from egg yolks or soybeans is a commonly used surfactant. Sterile manufacturing can be accomplished by sterilization of all the components before manufacture, followed by aseptic technique in all stages of manufacture. Improved ease of manufacture and assurance of sterility is obtained by terminal sterilization following sanitary manufacture, either by heat or by filtration. However, terminal sterilization by heat or filtration treatments is not suitable for all emulsions.

Vitamin E emulsions have been disclosed. For example, injectable vitamin E emulsions are described by Hidiroglou and Karpinski (*Brit. J. Nutrit.* 1988 59:509-518) for dietary supplementation in sheep and for research on the pharmacokinetics of vitamin E and its derivatives. An injectable form of vitamin E for mice was prepared by Kato et al. (*Chem. Pharm. Bull.* 1993 41(3):599-604). Micellar solutions were formulated with TWEEN 80, BRIJ 58 and HCO-60. Isopropanol was used as a co-solvent, and was then removed by vacuum evaporation; the residual oil glass was then taken up in water with vortexing as a micellar suspension. An emulsion was also prepared by dissolving vitamin E with soy phosphatidycholine (lecithin) and soybean oil. Water was added and the emulsion prepared with sonication. Ethanol-free emulsions of alpha-tocopherol, stabilized by biocompatible surfactants, as a vehicle or carrier for

therapeutic drugs is also disclosed in U.S. Patent Nos. 6,667,048 and 6,660,286.

E-Ferol, a vitamin E emulsion for vitamin E supplementation and therapy in neonates was also disclosed by Alade et al. (*Pediatrics* (1986) 77(4):593-597). The surfactant mixture used to emulsify the 25 mg/mL vitamin E in E-Ferol was composed of 9% TWEEN 80 and 1% TWEEN 20. However, this supplement was not safe.

An alternative means of solubilizing low solubility compounds is direct solubilization in a non-aqueous milieu, for example, alcohols (such as ethanol), dimethylsulfoxide, and/or triacetin. For example, WO 95/11039 describes the use of vitamin E (100 mg), lecithin (20 mg), ethanol (100 mg) and EUTANOL (500 mg) as an injectable formulation of the immunosuppressant molecule cyclosporine (50 mg). U.S. Patent No. 5,689,846 discloses various alcohol solutions of paclitaxel. U.S. Patent No. 5,573,781 discloses the dissolution of paclitaxel in ethanol, butanol and hexanol and an increase in the antitumor activity of paclitaxel when delivered in butanol and hexanol as compared to ethanol.

WO 95/31217 discloses that tocopherols can be used as solvents and/or emulsifiers of drugs that are substantially insoluble in water, in particular for the preparation of topical formulations. The use of vitamin E-TPGS as an emulsifier in formulations containing high levels of α-tocopherol is mentioned and formulations for topical administration composed of a lipid layer (α-tocopherol), the drug and vitamin E-TPGS as an emulsifier in quantities of less than 25% w/w of the formulation.

WO 97/03651 discloses lipid vehicle drug delivery compositions that contain at least five ingredients: a therapeutic drug, vitamin E, an oil in which the drug and vitamin E are dissolved, a stabilizer (either phospholipid,

a lecithin, or a poloxamer which is a polyoxyethylene-polyoxypropylene copolymer) and water.

Similarly, U.S. Patent No. 6,962,691 teaches topical compositions composed of at least ten ingredients: alendronate sodium, povidone, povidone vinyl acetate, vitamin E, menthol, dimethyl isosorbide, acetone, ethanol, tetrafluroroethane and, dichlorodifluoromethane.

U.S. Patent No. 4,393,073 also suggests vitamin E as an active ingredient in pharmaceutical compositions containing ethanol.

Summary of the Invention

An aspect of the present invention relates to a pharmaceutical solution comprising a therapeutic agent dissolved in one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof and one or more alcohols or glycols, or any combinations thereof. In some embodiments, the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w) and the alcohol(s) and/or glycol(s) is in an amount from about 1% to about 70% (w/w).

Another aspect of the present invention relates to methods for producing these pharmaceutical solutions.

Another aspect of the present invention relates to methods of treatment of a patient with these pharmaceutical solutions.

Detailed Description of the Invention

The present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents.
Advantageously, the resulting pharmaceutical solution is not

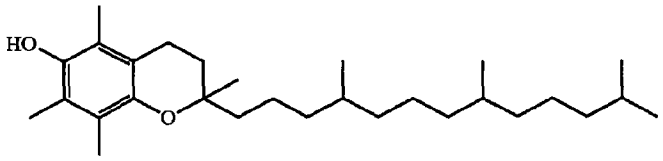
an emulsion or vesicle, and can be used directly in the production of pharmaceutical compositions. Moreover, the combination of a tocopherol and/or a tocotrienol and an alcohol and/or glycol is much less irritating to the skin and/or mucous membranes than pure alcohol solutions and generally provides higher loading of a therapeutic agent than emulsions, liposomes, encapsulations, or cyclodextrins.

A solution in the context of the present invention is a homogeneous mixture composed of three or more substances. In such a mixture, a solute is dissolved in another substance, known as a solvent. In accordance with the present invention, a pharmaceutical solution is formed by dissolving a therapeutic agent in a tocopherol and/or a tocotrienol and an alcohol and/or glycol as solvents. In one embodiment of the present invention, the therapeutic agent is dissolved completely in the tocopherol and/or a tocotrienol and the alcohol and/or glycol solvents. In another embodiment of the present invention, the therapeutic agent may not be completely solubilized and thus is partially dissolved in the tocopherol and/or a tocotrienol and the alcohol and/or glycol solvents. In this embodiment, particulates of therapeutic agent may be present in the pharmaceutical solution. The resulting pharmaceutical solutions of either embodiment can be used in a variety of pharmaceutical compositions with various modes of administration.

The combination of tocopherol and/or a tocotrienol and alcohol and/or glycol is also useful in solubilizing at least in part amphiphobic therapeutic agents. In this embodiment, the solution acts as a transport phase through partial solubilization to increase the bioavailability of the amphiphobic therapeutic agent from a finely divided suspension of the agent.

Tocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and

synthetic compounds, also known by the generic names tocols or vitamin E. Alpha-tocopherol is the most abundant and active form of this family of compounds, and it has the following chemical structure:



Other members of this family include beta-, gamma-, and delta-tocopherol, alpha-, beta-, gamma-, and delta-tocotrienols, tocopsoralen, alpha-tocopherol derivatives and/or analogs such as tocopherol acetate, phosphate, succinate, nicotinate and linoleate, as well as isomers thereof and esters thereof. Use of the phrase tocopherol(s) and/or tocotrienol(s) herein is meant to be inclusive of any member of this family alone or in combination. In one embodiment of the present invention the tocopherol(s) and/or tocotrienol(s) employed is alpha-tocopherol.

Examples of alcohol(s) for use in the present invention include, but are not limited to ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof. Examples of glycols for use in the present invention include, but are not limited to ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, and any isomers thereof, and any combinations thereof. In one embodiment of the present invention the alcohol is ethanol (ethyl alcohol). Preferred is use of an ethanol that is biocompatible in the sense that it is not toxic and does not cause any physiological or pharmacological effects. In this regard, the ethanol is desirably 180 to 200 proof ethanol, *i.e.*, in the range of 90-100% ethanol. Advantageously, diluting a tocopherol or tocotrienol with an alcohol or glycol dramatically reduces

the inherent viscosity of the tocopherol or tocotrienol thereby allowing for generation of sprayable formulations.

In accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent. In some embodiments, the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w) and the alcohol(s) and/or glycol(s) is in an amount about 1% to about 70% (w/w).

As a non-limiting example, the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol. However, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol:30% ethanol (200 proof), Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol:5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%.

Accordingly, preferred for some embodiments is that alpha-tocopherol and ethanol constitute 60% to 99% and 1% to 40%, respectively, of the pharmaceutical solution. In other embodiments, the alpha-tocopherol and ethanol constitute approximately 70% to 90% and 10% to 30%, respectively, of the pharmaceutical solution. In still other embodiments, the tocopherol and ethanol are used at ratios of approximately 95:5, 90:10, 85:15, 80-20, 75:25, 70:30, 65:35, or 60:40, respectively.

Pharmaceutical solutions of the present invention can be produced by dissolving any difficult to solubilize therapeutic agent (*i.e.*, hydrophobic or lipophilic therapeutic agents) in one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents. By therapeutic agents

it is meant to be inclusive of, but is not limited to, small organic molecules, therapeutic peptides, non-peptides and nucleotides. Hydrophobic derivatives of water-soluble molecules such as lipid conjugates/prodrugs are also within the scope of therapeutic agents.

Exemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with the present invention include, but are in no way limited to, steroids such as Dexamethasone, 17-beta-Estradiol; benzodiazepenes such as Diazepam, alpraxolam, bromazepam, chlordiazepoxidem, clonazepam, estazolam, flunitrazepam, flurazepam, lorazepam, lormetazepam, mexazolam, nitrazepam, oxazepam, temazepam, and triazolam; Rapamycin and analogues; Taxol (paclitaxel) and analogues; Actinomycin D; Prostaglandins (PGE1); Vitamin A; Probucol; Batimastat; Statins (HMG-CoA Reductase Inhibitors; Trapidil (and other anti-proliferative Growth Factor Inhibitors); Cytochalasin B; and microtubule binding agents such as epothilones, elutherobin and discodermolide. Pharmaceutical solutions and compositions formulated from the solutions may comprise one or more therapeutic agents in solution. Further, pharmaceutical compositions formulated from the pharmaceutical solutions of the present invention may further comprise one or more additional therapeutic agents in encapsulated or micronized (not dissolved) forms.

The present invention also provides for use of a combination of tocopherol and/or a tocotrienol and alcohol and/or glycol to solubilize at least in part amphiphobic therapeutic agents. In this embodiment, the solution acts as a transport phase through partial solubilization to increase the bioavailability of the amphiphobic therapeutic agent from a finely divided suspension of the agent.

Pharmaceutical solutions of the invention can be formulated into pharmaceutical compositions for administration to animals, preferably humans, via

intravascular, oral, intramuscular, cutaneous and subcutaneous routes. Specifically, pharmaceutical compositions of the present invention can be administered by any of the following nonlimiting exemplary routes, intraabdominal, intraarterial, intraarticular, intracapsular, intracervical, intracranial, intraductal, intradural, intralesional, intralocular, intralumbar, intramural, intranasal, intraocular, intraoperative, intraparietal, intraperitoneal, intrapleural, intrapulmonary, intraspinal, intrathoracic, intratracheal, intratympanic, intrauterine, and intraventricular. The pharmaceutical compositions of the present invention can be nebulized using mechanical nebulizers or suitable aerosol propellants which are known in the art for pulmonary delivery of lipophilic compounds. The most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular therapeutic agent which is being used.

Pharmaceutical solutions of the instant invention are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means. For many therapeutic agents, administration via the nasal route provides for faster attainment of therapeutic levels of the therapeutic agent systemically. However, many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve hydrophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes. Such solutions can be administered

via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer.

The instant pharmaceutical solutions comprising a therapeutic agent, one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols can also be formulated into a pharmaceutical composition for injection by combining the instant pharmaceutical solution with, *e.g.*, saline solution or water and a Vitamin E solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

For oral therapeutic administration, the instant pharmaceutical solutions can be combined with one or more carriers and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, foods and the like. Such compositions and preparations should contain at least 0.1% of active compound. Tablets, troches, pills, capsules, and the like can also contain one or more of the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. The above listing is merely representative and one skilled in the art could envision other binders, excipients, sweetening agents and the like. When the unit dosage form is a capsule, it can

contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials can be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules can be coated with gelatin, wax, shellac or sugar and the like.

A syrup or elixir can contain the instant pharmaceutical solution, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be substantially non-toxic in the amounts employed.

In addition, the instant pharmaceutical solution can be formulated into sustained-release preparations and devices including, but not limited to, those relying on osmotic pressures to obtain a desired release profile.

Formulations suitable for parenteral administration can be aqueous or non-aqueous injection solutions, which are generally isotonic with the blood of the intended recipient. These preparations can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions can include suspending agents and thickening agents. The formulations can be presented in unit\dose or multi-dose containers, for example sealed ampoules and vials.

Formulations suitable for topical application to the skin can take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, oil or other pharmaceutical formulation which accomplishes direct contact between the therapeutic agent and the skin. Topical formulations can also be prepared which are suitable for occlusive therapy.

Formulations in the forms of ointments, creams, lotions and pastes can generally have carriers in the forms of

oleaginous bases (*e.g.*, White Petrolatum and White Ointment); absorption bases formed by adding a water-in-oil emulsifying agent to an oleaginous base (*e.g.*, Hydrophilic Petrolatum, AQUABASE, and AQUAPHOR); water-in-oil emulsion bases, prepared by adding water to an absorption base (*e.g.*, HYDROCREAM, EUCERIN, NIVEA, and Cold Cream); oil-in-water emulsion bases (*e.g.*, DERMABASE, UNIBASE, VELVACHOL, and hydrophilic ointment); and water soluble bases (*e.g.*, polyethylene glycol ointment such as PEG 400-600 G or PEG 3350-400 G). Suitable carriers to produce a spray, gel, or aerosol are well-known in the art.

A carrier for topical application can also contain additional ingredients such as other carriers, moisturizers, penetration enhancers, humectants, emollients, dispersants, radiation blocking compounds, cleansing agents, anti-infective agents (*e.g.*, antibiotics, fungicides, scabicides, or pediculicides), anti-inflammatory agents (*e.g.*, corticosteroids), keratolytics (agents that soften, loosen, and facilitate exfoliation of the squamous cells of the epidermis), as well as other suitable materials that do not have a significant adverse effect on the activity of the topical composition. Additional ingredients can include, for example a sodium acid phosphate moisturizer, witch hazel extract, glycerine humectant, apricot kernal oil emollient, or corn oil dispersant. Other materials which can optionally be included in a topical composition include inositol or B-complex vitamins.

Formulations suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration can also be delivered by iontophoresis (*see*, for example, *Pharmaceutical Research* 3 (6):318 (1986)) and typically take the form of an optionally

buffered aqueous solution. Formulations of the present invention are also suitable for delivery via microneedle delivery technology for cutaneous administration.

What is claimed is:

1. A pharmaceutical solution comprising one or more therapeutic agents dissolved in one or more tocopherols or tocotrienols and one or more alcohols or glycols.

2. The pharmaceutical solution of claim 1 wherein the one or more tocopherol or tocotrienol is 30% to 99% and the one or more alcohol or glycol is 1% to 70% of the volume of the pharmaceutical solution.

3. The pharmaceutical solution of claim 1 wherein the one or more tocopherols or tocotrienols is alpha-tocopherol.

4. The pharmaceutical solution of claim 1 wherein the one or more alcohols or glycols is ethanol.

5. A pharmaceutical solution consisting of a therapeutic agent dissolved in alpha-tocopherol and ethanol.

6. A pharmaceutical composition comprising the pharmaceutical solution of any of claims 1 through 5.

7. The pharmaceutical composition of claim 6 further comprising one or more additional therapeutic agents in encapsulated or micronized forms.

8. The pharmaceutical solution of any of claims 1 through 5 wherein the one or more therapeutic agents is partially dissolved in one or more tocopherols or tocotrienols and one or more alcohols or glycols.

9. A method for solubilizing a therapeutic agent comprising dissolving a therapeutic agent in one or more

tocopherols or tocotrienols and one or more alcohols or glycols to form a pharmaceutical solution.

10. The method of claim 9, wherein the one or more tocopherol or tocotrienol is 30% to 99% and the one or more alcohol or glycol is 1% to 70% of the volume of the pharmaceutical solution.

11. The method of claim 9 wherein the one or more tocopherols or tocotrienols is alpha-tocopherol.

12. The method of claim 9 wherein the one or more alcohols or glycols is ethanol.

13. The method of any of claims 9 through 12 wherein the therapeutic agent is partially dissolved in one or more tocopherols or tocotrienols and one or more alcohols or glycols.

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(54) Title: TOCOPHEROL COMPOSITIONS FOR DELIVERY OF BIOLOGICALLY ACTIVE AGENTS

(57) Abstract

The present invention provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions. Such compositions are particularly suitable for transmucosal, and especially intranasal or rectal administration, or administration via the oral cavity.

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Tocopherol compositions for delivery of biologically active agents

The present invention is directed to new pharmaceutical compositions for delivery of biologically active agents. More particularly, the invention concerns the use of a tocopherol or a derivative thereof to prepare compositions having low irritability suitable for administration to mucosal membranes and which may be used efficiently to administer drugs, which are substantially insoluble or only sparingly soluble in water.

For systemic action, drugs are normally administered by mouth and are then absorbed in the gastrointestinal tract. However, this mode of administration is not suitable in all circumstances, for example in the case of drugs which are metabolised to any significant degree by the liver or which are poorly absorbed. In other cases, the oral route may be impractical, for example in patients suffering from nausea or who are unconscious. Before surgery, oral administration is not advisable because of the risk of vomiting and in many cases, a more rapid effect may be required than can be achieved by the oral route.

In these circumstances the parenteral route is frequently used, most notably intravenous or intramuscular injection. However, whilst this provides a convenient way of achieving a strong and rapid systemic effect, it has a number of disadvantages including the requirement for sterile equipment and trained personnel. It is also unpleasant to the patient.

Moreover, in cases where a systemic effect is not required, local administration may be preferable, for example to avoid side effects, to reduce the dosage, or

simply to facilitate the administration.

Such problems have lead in recent years to an increasing interest in developing formulations for the topical administration of drugs, and in particular for topical administration involving absorption from mucous membranes.

Topical administration has the advantage that drugs may be administered readily and simply to achieve a systemic or dermal, regional or localised effect, as required. However, topical absorption of drugs through the skin can be slow, and in many cases transmucosal routes of delivery are preferred. Since it may be performed by untrained personnel and permits therapeutic plasma levels of drugs rapidly to be achieved, intranasal administration has received particular attention in this regard.

For topical delivery, biologically active drugs are normally administered in the form of aqueous solutions. However, many biologically active compounds are substantially insoluble or only sparingly soluble in water and in such cases, organic solvents are required to dissolve these agents. The problem here is that mucosal tissues are generally very sensitive and such solvents are frequently too irritant to be of clinical use. Thus for example, Lau and Slattery [Int. J. Pharm. 1989, p. 171-74] attempted to administer the benzodiazepines diazepam and lorazepam by dissolving these compounds in a range of solvents including: triacetin, DMSO, PEG 400, Cremophor EL, Lipal-9-LA, isopropyladipate and azone dodecyle-aza-cycloheptane-2-one. Whilst many of the solvents dissolved diazepam and lorazepam in the desired concentrations, when administered to the nose they were too irritant to be of use. Thus, Cremophor EL was found to be the least irritative for mucosal tissue, but nasal absorption using this solvent is rather slow and peak concentration is low relative to that found after iv. administration.

Triglycerides such as vegetable oils are generally non-irritant, but usually these oils are too poor as solvents to be of any use.

Attempts have been made to develop various other vehicles for transmucosal delivery of drugs, such as benzodiazepines, having limited water solubility. Thus, for example WO 86/04233 of Riker discloses a pharmaceutical composition wherein the drug (eg. diazepam) is dissolved in a mixture of propellant and co-solvent eg. glycerolphosphatide. The composition requires a pressurized system and at least one halogenated hydrocarbon aerosol propellant.

In US Patent 4,863,720 of Burghardt, a sublingual sprayable pharmaceutical preparation is disclosed, in which the active drug can be a benzodiazepine, optionally comprising polyethylene glycol (PEG) and requiring ethanol, di- and/or triglyceride of fatty acids and a pharmaceutically acceptable propellant gas.

US Patent 4,950,664 of Rugby-Darby describes the nasal administration of benzodiazepines in a pharmaceutically acceptable nasal carrier. The carrier may be a saline solution, an alcohol, a glycol, a glycol ether or mixtures thereof.

In PCT WO 91/16929 of Novo Nordisk, glycofurols or ethylene glycols are suggested as carriers for a variety of drugs, including benzodiazepines, which may be used on mucous membranes.

Another solution proposed to this problem, has been the use of micelles or liposomes, but these are frequently difficult to produce on a technical scale.

A further constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to administer more than about 0.1 ml per dose per nostril. Therefore, a great need exists for solvents, in which, on the one hand the solubility of the active drug is high, and which, on the other hand, are non-irritating to the

mucosa.

The aim of the present invention is to provide a solution to the above mentioned problems.

Tocopherols and their derivatives such as esters for example, are widely used in vitamin supplementation and as antioxidants in the food industry and in many pharmaceutical compositions. However, although in a few cases, a potential use in formulating pharmaceutical compositions has been reported, tocopherols and derivatives thereof have not generally previously been proposed as drug carriers.

Thus for example, European Patent Application No. 539,215 of Stafford-Miller suggests a possible use of Vitamin E and its derivatives as penetration enhancers in topical compositions.

WO 89/03689 of The Liposome Co., describes a liposome system based on acid derivatives of α-tocopherol in a low pH aqueous medium for delivery of drugs which tolerate, or require, acid conditions.

The present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues.

As will be described in more detail below, it has also been found that certain tocopherol derivatives are efficient, non-irritant emulsifiers for such drugs, when dissolved in a tocopherol-based solvent.

In one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions.

A further aspect of the invention provides a composition for delivery of a substantially insoluble or

sparingly soluble biologically active agent, comprising said agent dissolved in a tocopherol or a derivative thereof.

Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol (chemical name: 2,5,7,8-tetramethyl-2-(4',8',12'-trimethyldecyl)-6-chromanole) is the most active and widely distributed in nature, and has been the most widely studied. Other members of the class include beta, gamma, and delta tocopherols but these are not used in pure form in therapeutics, although they are present in foodstuffs. Tocopherols occur in a number of isomeric forms, the D and DL forms being most widely available.

As used herein, the term "tocopherol" includes all such natural and synthetic tocopherol or Vitamin E compounds.

The melting point of natural α-tocopherol is between 2.5 and 3.5°C. α-Tocopherol is a viscous oil at room temperature, is soluble in most organic solvents, but insoluble in water.

Although tocopherols are available naturally in foodstuffs and may be extracted from plants, α-tocopherol is now mainly produced synthetically.

Any of the forms or isomers of tocopherols and their derivatives, eg. esters may be used according to the present invention. Thus for example, α-tocopherol can be used as such or in the form of its esters such as α-tocopherol acetate, linoleate, nicotinate or hemi succinate-ester, many of which are available commercially.

A special article of commerce is called Tenox GT-2 and consists of 70% tocopherol of natural origin, which has been concentrated from vegetable oil. This oil has a mild odour and a gentle taste.

The compositions of the present invention are particularly suited for application to mucous membranes

in animals or humans, to deliver systemically substantially insoluble or sparingly soluble biologically active agents in a manner which ensures that a clinical effect is reached at least as rapidly as by conventional oral administration, with for instance tablets.

Thus, the compositions of the invention may be used for controlled release delivery of bioactive agents to achieve a beneficial or therapeutic effect over a prolonged period of time.

The compositions of the invention may also be applied to achieve a local effect, where desired, on the mucous membranes or the underlying tissue.

However, whilst the beneficial effects of the invention are particularly apparent in transmucosal delivery, the utility of the invention is not limited and compositions according to the invention may also be administered topically to all body surfaces, including the skin and all other epithelial or serosal surfaces, as well as parenterally or enterally, eg. as implants or by intravenous, intramuscular or subcutaneous injection, by infusion, or orally.

Transmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes for example in the nose, vagina, rectum, ears, eyes, oral cavity, lungs, genito-urinary tracts, and gastro-intestinal tract. Nasal, rectal and oral cavity administrations are particularly preferred.

The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent. However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application.

Viscosity can be reduced by addition of co-solvents such as ethanol, but this is less desired, since

solutions of this kind tend to be irritating to certain mucosal tissues.

Alternatively, the tocopherol solutions may be emulsified, to obtain formulations of lower viscosity. This may be achieved in known manner, by mixing the tocopherol-based "oil phase" containing the dissolved bioactive agent with an appropriate aqueous phase, eg. water, saline or buffer solutions.

Methods and appropriate aqueous media for obtaining emulsions are well known in the art and described in the literature. Emulsions according to the invention may be oil-in-water (O/W) or water-in-oil (W/O) emulsions. Generally speaking, O/W emulsions may be achieved when the oil phase contains up to about 70% lipids. W/O emulsions are formed when the oil phase exceeds c.a. 70%.

For nasal administration, due to the small administration volume required, it has generally been found that a high concentration of the oil (or lipid) phase is required. Emulsions with high lipid content are technically difficult to achieve and may be unstable. It may therefore be necessary to employ an emulsifier in order to form a stable emulsion. A wide range of emulsifiers are well known, both in the food and pharmaceutical arts, and are widely described in the literature. However, stability and viscosity may still be a problem, where very high contents of the oil phase are required. Moreover, some of the more widely available commercial emulsifiers, eg. phospholipids, polysorbates or various sorbitan esters of fatty acids may be irritating to the more sensitive mucosal tissues, such as those of the nose.

The inventors have surprisingly found however that tocopherol derivatives, particularly certain esters, may themselves form efficient, non-irritating emulsifiers to enable stable emulsions to be formed, even where high lipid levels are involved eg. about 50-70%. Particular

mention may be made in this regard of Vitamin E TPGS which is a water soluble derivative of Vitamin E and consists of α-tocopherol, which is esterified with succinic acid, the other acidic group of the latter being esterified with polyethylene glycol 1000. Vitamin E TPGS is an almost odourless waxy amphiphilic substance with a molecular weight about 1513. The melting point is about 36°C and its solubility in water is about 20%.

Stable emulsions may readily be achieved according to the invention using a range of tocopherols or derivative compounds as solvents, with Vitamin E TPGS as emulsifier, and any suitable aqueous medium.

A further aspect of the invention thus provides a composition suitable for delivery of substantially insoluble or sparingly soluble biologically active agents, comprising a tocopherol or a derivative thereof, and Vitamin E TPGS as emulsifier.

The tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers.

It has furthermore surprisingly been shown that various other solvents may be used in the emulsion system described above, without compromising the stability of the emulsion.

When the emulsion according to the present invention is of the oil-in-water type, it is desirable that the droplet size is as small as possible. It has been shown that by using systems according to the invention, for example, α-tocopherol, water, Vitamin E TPGS and bioactive agent, it is possible to form stable emulsions with an initial droplet size in the range 0.01-100 μm, preferably 0.01-50 μm, most preferably 0.1-20 μm.

The compositions which may be prepared according to the present invention, may contain any biologically

active agent which is insoluble or sparingly soluble in water, ie. with a solubility in water (w/v) which is 3% or less. For example such agents may include any bioactive agent which has less than 1% (w/v) solubility in water. Representative active agents from a range of different therapeutic groups are listed below, by way of exemplification.

Hormones and hormone-like substances of the steroid-group:

Corticosteroids such as cortisone, hydrocortisone, prednolone, prednisolone, triamcinolone acetonide, dexamethasone, flunisolide, budesonide, toxicorole pivalate, betametasone, beclomethasone dipropionate, fluticasone etc;

Sex-hormones such as: estradiol, progesterone, testosterone etc;

Antibiotics: Tetracyclines such as tetracycline, doxycycline, oxytetracycline, chloramphenicol etc; Macrolides such as erythromycin and derivatives, etc;

Antivirals: such as acyclovir, idoxuridine, tromantadine etc;

Antimycotics: Miconazole, ketoconazole, fluconazole, itraconazole, econazole, terconazole, griseofulvin, and polyenes such as amphotericin B or nystatine etc;

Anti-amoebics: Metronidazole, metronidazole benzoate and tinidazole etc;

Anti-inflammatory drugs: NSAID's such as indomethacin, ibuprofen, piroxicam, diclofenac etc;

Anti-allergics: Disodium cromoglycate etc;

Immunosuppressive agents: cyclosporins etc;

Coronary drugs: including vasodilators such as nitroglycerin, isosorbide dinitrate, Calcium-antagonists such as verapamile, nifedipine and diltiazem, Cardiac-glycosides such as digoxine.

Analgesics: eg. morphine, buprenorphine, etc;

Local anaesthetics: eg. lidocaine, etc;

Anxiolytics, sedatives & hypnotics: diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lormetazepam, brotizolam, clobazam, clonazepam, lorazepam, oxazepam, buspirone, etc;

Migraine relieving agents: sumatriptan, ergotamines and derivatives etc;

Drugs against motion sickness: eg. cinnarizine, anti-histamines, etc;

Anti-emetics: eg. ondansetron, tropisetron, granisetrone, metoclopramide, etc.

Others: such as disulfiram, vitamin K, etc.

The emulsions according to the present invention are especially suitable for nasal application because of their low index of irritability and are therefore particularly well suited to the delivery of biologically active drugs influencing the central nervous system (CNS).

Other biologically active agents which may be used include peptides, hormones, etc. The active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w).

Generally speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative solvent. The emulsion used in compositions of the invention may contain 1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w).

As mentioned above, the emulsions of the present invention can be prepared by conventional means, by heating the oil and aqueous phases separately, and then mixing the two phases. The active ingredient can be dissolved in the lipid fraction of the tocopherol solvent and other solvents may be added if desired. The emulsifier, eg. Vitamin E TPGS, and optionally other emulsifiers, can be added to either the oil and/or the water phase. The water phase is then vigorously mixed with the oil phase. Mixing, eg. stirring may be continued as required eg. for up to 2 hours. Depending on the viscosity of the emulsion, a magnetic stirrer, a low shear mixer or the like can be used. If necessary, the emulsion can be processed by a low shear mixer and a high pressure homogenizer to achieve the desired droplet size. The formulations may be inspected microscopically to measure the droplet size and to be sure that no precipitation has taken place. The type of emulsion formed may be determined readily by a colour test using an oil- and/or water-soluble dye. To confirm the result, it may be examined whether the emulsion is easy to wash off with water or not. An O/W emulsion is coloured with the water-soluble dye and is very easy to wash off with water. A W/O emulsion is coloured with

the oil-soluble dye and is very difficult to wash off with water.

In a further aspect, the present invention thus provides a method of preparing a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising dissolving said agent in an amount of a tocopherol or a derivative thereof, sufficient to dissolve said agent.

In a preferred aspect, the method of the invention further comprises forming an emulsion of said tocopherol/biologically active agent solution, by mixing with an aqueous phase, optionally in the presence of an emulsifier, preferably vitamin E TPGS.

The compositions of the invention may take any of the conventional pharmaceutical forms known in the art, and may be formulated in conventional manner, optionally with one or more pharmaceutically acceptable carriers or excipients. Thus for example the compositions may take the form of ointments, creams, solutions, salves, emulsions, lotions, liniments, aerosols, sprays, drops, pessaries, suppositories, tablets, capsules or lozenges.

In a still further aspect, the present invention provides the use of a tocopherol or a derivative thereof for the preparation of a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent to a human or non-human animal subject.

Alternatively viewed, the invention can be seen to provide a method of treatment of a human or non-human animal subject by delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising administering to said subject a composition of the invention as hereinbefore defined.

The formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added:

Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin.

To optimize the stability of the emulsions, it may be appropriate to add surfactants such as Vitamin E TPGS poloxamers (eg. Pluronic®), cetearyl glucoside, polysorbates or sorbitan esters of fatty acids, or any of the other surfactants well known in the art, or other stabilisers such as xanthan gum, or propylene glycol alginate.

It is also possible to enhance the bioadhesive properties of the formulations according to the present invention by addition of bioadhesive polymers such as:

- polyacrylic polymers such as carbomer and carbomer derivatives, eg. Polycarbophil or Carbopol etc;
- cellulose derivatives such as hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropyl-cellulose or sodium carboxymethylcellulose etc;
- natural polymers like gelatin, sodium alginate, pectin etc;
- more generally, any physiologically acceptable polymer showing bioadhesive characteristics may be used.

To ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives such as benzalkonium chloride, sodium edetate, sorbic acid, potassium sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable.

The invention will now be described in more detail in the following non-limiting Examples, with reference to the drawings in which:

Figure 1 is a graph showing mean serum concentrations (ng/ml) against time (minutes) after intranasal administration of 2.5 mg diazepam

(Formulation C) -▲- Desmethyldiazepam -■- Diazepam;

Figure 2 is a graph showing mean serum concentrations (ng/ml) against time (minutes) after oral administration of 2.0 mg diazepam (Formulation D) -■- Desmethyldiazepam -♦- Diazepam;

EXAMPLES

As already mentioned, administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 µl). The first example has a very high concentration of diazepam, and it is possible to administrate diazepam to the nose and to achieve a rapid clinical effect.

Example 1

A diazepam nosedrop preparation is made as follows: (100 g)

5 g of diazepam is mixed with 44 g of Tenox GT2, and 22 g of triacetin, and 5 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.45 g of Pluronic F-68 (poloxamer 188) and 0.01 g of benzalkonium chloride are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed into the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion was a pale yellow o/w emulsion, where the mean droplet size was about 1-2 µm.

This formulation (1) was tested in 8 rabbits in a randomized cross-over study compared with a commercially available diazepam formulation, Stesolid® 5mg/ml for

injection, (2).

Formulation 1 was given intranasally (i.n.) with a Eppendorf Multipette ® 4780. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits receive a volume that equals 2 mg diazepam, 40μl of formulation 1. After each administration the actual dose received is estimated by visual inspection of the pipette tip and the rabbit nostrils. Only applications volumes estimated to 80% are accepted.

Formulation 2 was given as an ear-vein infusion during ½ minute. The rabbits received 0.4 ml Stesolid® 5mg/ml (equals 2 mg diazepam). The rabbits were placed in a supine position for half a minute to attain the same experimental conditions as for i.n. dosing.

The rabbits were then tested with respect to pharmacodynamic response in the following way:

- Hind legs to one side and the rabbit must stay in this position even after a firm tip with a finger on the hip. The test is immediately repeated with both legs placed on the other side.

The rabbits were tested approximately once per minute until positive pharmacodynamic response, and thereafter tested every 2 minutes. Total test period is 20 minutes. The same person has dosed and tested all the rabbits in the present study.

The time to pharmacodynamic response is 4.4 minutes (mean, n=8) using formulation 1 and 1.6 minutes (mean, n=8) using formulation 2.

Example 2

A diazepam nosedrop preparation is made as follows: (100 g)

5 g of diazepam is mixed with 45.4 g of Tenox GT2, and 22.7 g of triacetin, and 15 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.45 g of Pluronic F-68 (poloxamer 188) and 0.01 g of benzalkonium chloride are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a clear orange w/o emulsion.

A less concentrated formulation of diazepam is required for the rectal administration, but still it can be very difficult to find an acceptable vehicle with low irritation.

Example 3

A diazepam enema preparation is made as follows: (100 g)

1 g of diazepam is mixed with 40 g of α-tocopherol, and 15 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. 5 g of ethanol is added to the oil phase immediately before mixing with the water phase. To the water phase, 2.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the

magnetic stirrer. The emulsion is a white o/w emulsion.

Cinnarizine is used for motion sickness. Like diazepam, the drug has a very low water solubility. It will be a great advantage if the patient can administer the drug easily and have a rapid effect.

Example 4

A cinnarizine nosedrop formulation is made as follows: (100 g)

5 g of cinnarizine is mixed with 64 g of α-tocopherol, and 8 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a white o/w emulsion.

Miconazole is used for the local treatment of infections caused by fungi. The next two formulations show formulations for use in the oral cavity and the vagina.

Example 5

A miconazole preparation for the oral cavity is made as follows: (100 g)

20 g of miconazole is mixed with 58.8 g of α-tocopherol, and 13 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. 5 g of ethanol is added to the oil phase immediately before

mixing with the water phase. To the water phase, 1.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is added very slowly to the oil phase under vigorously mixing by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a yellow to brown w/o emulsion.

Example 6

A miconazole vaginal cream is made as follows: (100 g)

5 g of miconazole is mixed with 38 g of α-tocopherol, and 38 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 2.5 g of Pluronic F-681 (poloxamer 188) and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a low shear mixer. Thereafter, the emulsion is cooled to room temperature still mixed by the low shear mixer. The emulsion is a glossy, beige w/o emulsion. The emulsion has a consistency as an ointment and is very sticky.

The following Examples are divided into three subsections covering 1) Solubility; 2) Compositions and 3) Pharmacology/toxicology.

Example 7

SOLUBILITY

For the following, non-limiting, sparingly soluble drugs in water, the solubility in α-tocopherol and sesame oil are listed in Table 1:

Sesame oil was chosen as the reference, because it is a very commonly used and well tolerated vegetable oil. The solubilities in sesame oil and α-tocopherol were investigated by visual inspection of the saturation point.

TABLE 1.

Active agent	g drug in 100 g of α-tocopherol	g drug in 100 g of sesame oil
Diazepam	12	2
Alprazolam	4 < x < 6	< 0.2
Midazolam	> 13	1 < x < 2
Cinnarizine	11 < x < 18	2 < x < 4
Metoclopramide	2 < x < 4	< 2
Budesonide	1 < x < 2	< 0.1
Miconazole	60	5 < x < 10
Metronidazole benzoate	12 < x < 14	< 2
Lidocaine	> 45	> 18
Disulfiram	5	3 < x < 4
Progesterone	> 30	2 < x < 4
Testosterone	16 < x < 18	0.6 < x < 1

All the investigated biologically active agents show a surprisingly high solubility in α-tocopherol.

COMPOSITIONS

In the following, non-limiting Examples, several drugs are shown in a number of different types of

administration forms.

The emulsions were prepared as follows:

The oil and the water phase were heated slowly until homogeneous phases were achieved.
The warm water phase was vigorously mixed into the oil phase. Then, the emulsion was slowly cooled to room temperature while stirring. The emulsion may be homogenized.

The preparation of the solutions was made as simple solution, in which the preparations were stirred until the drug was completely dissolved.

As already mentioned, administration of drugs with low water solubility to the nose is very difficult, because of the limited acceptable volume for the nose (about 100 µl). The following examples have very high concentration of diazepam, so it was possible to administer diazepam to the nose and to get a fast clinical effect.

Example 8

An O/W emulsion of diazepam as a nosedrop (100g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	59.000 g
	Vitamin E TPGS.	5.000 g
Water phase:	Disodium edetate	0.050 g
	Potassium sorbate	0.200 g
	Xanthan gum	0.025 g
	purified water to	100.000 g

The water phase was adjusted to pH 4.7 by 1N HCl.

Example 9

An O/W emulsion of diazepam as nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	58.000 g
	Sorbitan trioleate	0.500 g
	Fractionated coconut oil	5.000 g
Water phase:	Potassium sorbate	0.200 g
	Poloxamer 188	1.000 g
	Xanthan gum	0.030 g
	Polysorbate 80	0.500 g
	Purified water to	100.000 g.

The water phase was adjusted to pH 4.5 by 2N HCl.

Example 10:

An O/W emulsion of diazepam as nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	50.000 g
	Triacetin	10.000 g
	Cetearyl glucoside	2.000 g
	Methylparahydroxybenzoate (MPHB)	0.080 g
	Propylparahydroxybenzoate (MPHB)	0.040 g
Water phase:	Poloxamer 188	3.000 g
	Xanthan gum	0.030 g
	Purified water to	100.000 g.

Example 11:

A solution of diazepam, eg. as nosedrop, (25 g):

	Diazepam	1.250 g

α-Tocopherol	10.000 g
Triacetin	13.750 g

A less concentrated formulation of diazepam is needed for the rectal administration, but still it can be very difficult to find an acceptable vehicle with low irritation.

Example 12:

A solution of cinnarizine, eg. as drops for administration to the oral cavity (25g):

Cinnarizine	1.250 g
α-tocopherol	17.500 g
ethanol	1.250 g
fractionated coconut oil	5.00 g

A study has shown, that cinnarizine has a higher oral bioavailability, if it is dissolved in a vehicle before administration, [J. Pharm. Sci., vol 76, no. 4, p. 286-288, 1987], an example of such a vehicle could be α-tocopherol.

Example 13:

A solution of cinnarizine, eg. for oral administration in capsules, (25 g):

Cinnarizine	0.750 g
α-Tocopherol	24.250 g

Miconazole is used locally for treatment of infections caused by fungi. The following examples show formulations for the oral cavity and the vagina.

Example 14

A solution of miconazole e. g. as drops for administration to the oral cavity (25g).

Miconazole	6.250 g
α-Tocopherol	16.875 g
Ethanol	1.875 g

Budesonide is a very potential drug, and is used as a local corticoid, e. g. for rhinitis.

Example 15

An O/W emulsion of budesonide as nosedrop or nasal spray (50g).

Oily phase:	Budesonide	0.025 g
	α-tocopherol	12.500 g
	Vitamin E TPGS	5.000 g
Water phase:	Potassium sorbate	0.100 g
	Xanthan gum	0.020 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Example 16

A solution of budesonide as nosedrop (25g).

Budesonide	0.025 g
α-tocopherol	10.000 g
Sesame oil	14.975 g

Alprazolam is a benzodiazepine which is used for the treatment of e. g. anxiety, therefore a rapid effect is

desired in a easy way.

Example 17

An o/w emulsion of alprazolam as nosedrop or nasal spray (100g).

Oily phase:	Alprazolam	0.500 g
	α-tocopherol	20.000 g
	Vitamin E TPGS	10.00 g
Water phase:	Potassium sorbate	0.200 g
	Xanthan gum	0.050 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Example 18

A solution of alprazolam, e. g. as drops for administration in the oral cavity (25g).

alprazolam	0.125 g
α-tocopherol	13.750 g
sesame oil	11.125 g

Midazolam is a benzodiazepine tranquiliser with a sedative effect e.g., and is used for the treatment of anxiety and tension states, and as a sedative and for premedication. Midazolam has a very high first-pass effect after oral administration.

Example 19

An O/W emulsion of midazolam as nosedrop (50g).

Oily phase:	Midazolam	1.250 g

	α-Tocopherol	29.500 g
	Vitamin E TPGS	2.500 g
Water phase:	Potassium sorbate	0.100 g
	Xanthan gum	0.013 g
	Poloxamer 188	0.750 g
	Disodium edetate	0.025 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Disulfiram is used in the treatment of chronic alcoholism.

Example 20

A solution of disulfiram, e. g. as an oral solution or for oral administration by capsules (25g).

Disulfiram	1.125 g
α-Tocopherol	23.875 g

Example 21

An O/W emulsion of lidocaine for treatment of e.g. insect bites (100 g).

Oily phase:	Lidocaine	5.000 g
	α-Tocopherol	40.000 g
	Cetearyl glucoside	4.000 g
	MPHB	0.080 g
	PPHB	0.040 g
Water phase:	Poloxamer 188	3.000 g
	Xanthan gum	0.030 g
	Purified water to	100.000 g