2000 amino acids residues. The mean molecular weight of an amino acid residue is about 110 daltons, and so the molecular weights of most polypeptide chains are between 5500 and 220,000. *See e.g.*, L. Stryer, *Biochemistry,* 3rd Edition, p. 22 (W.H. Freeman & Co., NY, 1988).

A protein is a large macromolecule composed of one or more polypeptide chains. In the context of the present invention, a "peptide" refers to a peptide or a polypeptide, but not a protein.

Preferably, the peptide surface stabilizers of the invention are water soluble. By "water soluble," it is meant that the peptide has a water solubility of greater than about 1 mg/mL, greater than about 10 mg/mL, greater than about 20 mg/mL, or greater than about 30 mg/mL. This is in contrast to prior art compositions teaching the use of a peptide as an active agent in a nanoparticulate active agent composition. *See e.g.*, U.S. Patent Nos. 6,270,806; 6,592,903; 6,428,814; and 6,375,986. In such prior art references, when a peptide is utilized as an active agent in a nanoparticulate composition, the peptide is *poorly water soluble.*

There is an extensive catalog of commercially available peptides that can be used in the compositions of the invention. For example, the on-line peptide catalog http://www.peptide-catalog.com/PC/Peptides provides a list of hundreds of commercially available peptides, along with their structure and molecular weight. In addition, to the many commercially available peptides, custom peptides can be made and utilized in the compositions of the invention.

A preferred peptide surface stabilizer is poly(Lysine, Tryptophan)) 4:1 hydrobromide.

**B. Secondary or Auxiliary Surface Stabilizers**

The compositions of the invention can also include one or more auxiliary non-peptide surface stabilizers in addition to the at least one peptide surface stabilizer.

The auxiliary surface stabilizers of the invention are preferably adsorbed on, or associated with, the surface of the active agent particles. The auxiliary surface



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stabilizers especially useful herein preferably do not chemically react with the active agent particles or itself. Preferably, individual molecules of the auxiliary surface stabilizer are essentially free of intermolecular cross-linkages.

Two or more auxiliary surface stabilizers can be employed in the compositions and methods of the invention.

Suitable surface stabilizers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Preferred auxiliary surface stabilizers include nonionic, anionic, cationic, zwitterionic, and ionic surfactants.

Representative examples of secondary surface stabilizers include 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, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropyl celluloses (e.g., HPC, HPC-SL, and HPC-L), hydroxypropyl methylcellulose (HPMC), hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), 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), dialkylesters of sodium sulfosuccinic acid (*e.g.*, Aerosol OT®, which is a dioctyl ester of sodium sulfosuccinic acid (DOSS) (American Cyanamid)); Duponol P®, which is a sodium lauryl sulfate (DuPont); 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 $C_{18}H_{37}CH_2C(O)N(CH_3)$-$CH_2(CHOH)_4(CH_2OH)_2$ (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; lysozyme, PEG-derivatized phospholipid, PEG-derivatized cholesterol, PEG- derivatized cholesterol derivative, PEG-derivatized vitamin A, PEG-derivatized vitamin E, 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, a charged phospholipid such as dimyristoyl phophatidyl glycerol, 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, dodecyl trimethyl ammonium 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).

Particularly preferred nonpolymeric primary 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 immonium 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, 1986), specifically incorporated by reference. The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

### C. Active Agents

The nanoparticles of the invention comprise at least one active, therapeutic, or diagnostic agent, collectively referred to as a "drug." A therapeutic agent can be a pharmaceutical agent, including biologics such as proteins, peptides, and nucleotides, or a diagnostic agent, such as a contrast agent, including x-ray contrast agents.

The active agent exists as a crystalline phase, an amorphous phase, a semi-amorphous phase, a semi-crystalline phase, or mixtures thereof. The crystalline phase differs from a non-crystalline or amorphous phase which results from precipitation techniques, such as those described in EP Patent No. 275,796.

The invention can be practiced with a wide variety of active agents. The active agent is preferably present in an essentially pure form, is poorly soluble, and is dispersible in at least one liquid dispersion media. By "poorly soluble" it is meant that the active agent has a solubility in a liquid dispersion media of less than about 30 mg/mL, less than about 20 mg/mL, less than about 10 mg/mL, or less than about 1 mg/mL. Useful liquid dispersion medias include, but are not limited to, water, aqueous salt solutions, safflower oil, and solvents such as ethanol, t-butanol, hexane, and glycol. A preferred liquid dispersion media is water.

Two or more active agents can be used in combination.

#### 1. Active Agents Generally

The active agent can be selected from a variety of known classes of drugs, including, for example, nutraceuticals, COX-2 inhibitors, retinoids, anticancer agents, NSAIDS, proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, 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, 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 representative active agents useful in this invention include, but are not limited to, acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

Exemplary nutraceuticals and dietary supplements are disclosed, for example, in Roberts et al., *Nutraceuticals: The Complete Encyclopedia of Supplements, Herbs, Vitamins, and Healing Foods* (American Nutraceutical Association, 2001), which is specifically incorporated by reference. A nutraceutical or dietary supplement, also known as a phytochemical or functional food, is generally any one of a class of dietary supplements, vitamins, minerals, herbs, or healing foods that have medical or

pharmaceutical effects on the body. Exemplary nutraceuticals or dietary supplements include, but are not limited to, lutein, folic acid, fatty acids (*e.g.*, DHA and ARA), fruit and vegetable extracts, vitamin and mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids (*e.g.*, iso-leucine, leucine, lysine, methionine, phenylanine, threonine, tryptophan, and valine), green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics. Nutraceuticals and dietary supplements also include bio-engineered foods genetically engineered to have a desired property, also known as "pharmafoods."

Active agents to be administered in an aerosol formulation are preferably selected from the group consisting of proteins, peptide, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

### 2. Anticancer Active Agents

Useful anticancer agents are preferably selected from alkylating agents, antimetabolites, natural products, hormones and antagonists, and miscellaneous agents, such as radiosensitizers.

Examples of alkylating agents include: (1) alkylating agents having the bis-(2-chloroethyl)-amine group such as, for example, chlormethine, chlorambucile, melphalan, uramustine, mannomustine, extramustinephoshate, mechlore-thaminoxide, cyclophosphamide, ifosfamide, and trifosfamide; (2) alkylating agents having a substituted aziridine group such as, for example, tretamine, thiotepa, triaziquone, and mitomycine; (3) alkylating agents of the alkyl sulfonate type, such as, for example,

busulfan, piposulfan, and piposulfam; (4) alkylating N-alkyl-N-nitrosourea derivatives, such as, for example, carmustine, lomustine, semustine, or streptozotocine; and (5) alkylating agents of the mitobronitole, dacarbazine and procarbazine type.

Examples of antimetabolites include: (1) folic acid analogs, such as, for example, methotrexate; (2) pyrimidine analogs such as, for example, fluorouracil, floxuridine, tegafur, cytarabine, idoxuridine, and flucytosine; and (3) purine derivatives such as, for example, mercaptopurine, thioguanine, azathioprine, tiamiprine, vidarabine, pentostatin, and puromycine.

Examples of natural products include: (1) vinca alkaloids, such as, for example, vinblastine and vincristine; (2) epipodophylotoxins, such as, for example, etoposide and teniposide; (3) antibiotics, such as, for example, adriamycine, daunomycine, doctinomycin, daunorubicin, doxorubicin, mithramycin, bleomycin, and mitomycin; (4) enzymes, such as, for example, L-asparaginase; (5) biological response modifiers, such as, for example, alpha-interferon; (6) camptothecin; (7) taxol; and (8) retinoids, such as retinoic acid.

Examples of hormones and antagonists include: (1) adrenocorticosteroids, such as, for example, prednisone; (2) progestins, such as, for example, hydroxyprogesterone caproate, medroxyprogesterone acetate, and megestrol acetate; (3) estrogens, such as, for example, diethylstilbestrol and ethinyl estradiol; (4) antiestrogens, such as, for example, tamoxifen; (5) androgens, such as, for example, testosterone propionate and fluoxymesterone; (6) antiandrogens, such as, for example, flutamide; and (7) gonadotropin-releasing hormone analogs, such as, for example, leuprolide.

Examples of miscellaneous agents include: (1) radiosensitizers, such as, for example, 1,2,4-benzotriazin-3-amine 1,4-dioxide (SR 4889) and 1,2,4-benzotriazine-7-amine 1,4-dioxide (WIN 59075); (2) platinum coordination complexes such as cisplatin and carboplatin; (3) anthracenediones, such as, for example, mitoxantrone;

(4) substituted ureas, such as, for example, hydroxyurea; and (5) adrenocortical suppressants, such as, for example, mitotane and aminoglutethimide.

In addition, the anticancer agent can be an immunosuppressive drug, such as, for example, cyclosporine, azathioprine, sulfasalazine, methoxsalen, and thalidomide.

The anticancer agent can also be a COX-2 inhibitor.

### 3. Analgesic Active Agents

An analgesic can be, for example, an NSAID or a COX-2 inhibitor.

Exemplary NSAIDS that can be formulated in compositions of the invention include, but are not limited to, suitable nonacidic and acidic compounds. Suitable nonacidic compounds include, for example, nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, and dapsone. Suitable acidic compounds include, for example, carboxylic acids and enolic acids. Suitable carboxylic acid NSAIDs include, for example: (1) salicylic acids and esters thereof, such as aspirin, diflunisal, benorylate, and fosfosal; (2) acetic acids, such as phenylacetic acids, including diclofenac, alclofenac, and fenclofenac; (3) carbo- and heterocyclic acetic acids such as etodolac, indomethacin, sulindac, tolmetin, fentiazac, and tilomisole; (4) propionic acids, such as carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, and pirprofen; and (5) fenamic acids, such as flufenamic, mefenamic, meclofenamic, and niflumic. Suitable enolic acid NSAIDs include, for example: (1) pyrazolones such as oxyphenbutazone, phenylbutazone, apazone, and feprazone; and (2) oxicams such as piroxicam, sudoxicam, isoxicam, and tenoxicam.

Exemplary COX-2 inhibitors that can be formulated in combination with the nanoparticulate nimesulide composition of the invention include, but are not limited to, celecoxib (SC-58635, CELEBREX®, Pharmacia/Searle & Co.), rofecoxib (MK-966, L-748731, VIOXX®, Merck & Co.), meloxicam (MOBIC®, co-marketed by Abbott Laboratories, Chicago, IL, and Boehringer Ingelheim Pharmaceuticals), valdecoxib (BEXTRA®, G.D. Searle & Co.), parecoxib (G.D. Searle & Co.),

etoricoxib (MK-663; Merck), SC-236 (chemical name of 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)] benzenesulfonamide; G.D. Searle & Co., Skokie, IL); NS-398 (N-(2-cyclohexyloxy-4-nitrophenyl)methane sulfonamide; Taisho Pharmaceutical Co., Ltd., Japan); SC-58125 (methyl sulfone spiro(2.4)hept-5-ene I; Pharmacia/Searle & Co.); SC-57666 (Pharmacia/Searle & Co.); SC-558 (Pharmacia/Searle & Co.); SC-560 (Pharmacia/Searle & Co.); etodolac (Lodine®, Wyeth-Ayerst Laboratories, Inc.); DFU (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl 2(5H)-furanone); monteleukast (MK-476), L-745337 ((5-methanesulphonamide-6-(2,4-difluorothio-phenyl)-1-indanone), L-761066, L-761000, L-748780 (all Merck & Co.); DUP-697 (5-Bromo-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl; DuPont Merck Pharmaceutical Co.); PGV 20229 (1-(7-tert.-butyl-2,3-dihydro-3,3-dimethylbenzo(b)furan-5-yl)-4-cyclopropylbutan-1-one; Procter & Gamble Pharmaceuticals); iguratimod (T-614; 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1- benzopyran-4-one; Toyama Corp., Japan); BF 389 (Biofor, USA); CL 1004 (PD 136095), PD 136005, PD 142893, PD 138387, and PD 145065 (all Parke-Davis/Warner-Lambert Co.); flurbiprofen (ANSAID®; Pharmacia & Upjohn); nabumetone (FELAFEN®; SmithKline Beecham, plc); flosulide (CGP 28238; Novartis/Ciba Geigy); piroxicam (FELDANE®; Pfizer); diclofenac (VOLTAREN® and CATAFLAM®, Novartis); lumiracoxib (COX-189; Novartis); D 1367 (Celltech Chiroscience, plc); R 807 (3 benzoyldifluoromethane sulfonanilide, diflumidone); JTE-522 (Japan Tobacco, Japan); FK-3311 (4'-Acetyl-2'-(2,4-difluorophenoxy)methanesulfonanilide), FK 867, FR 140423, and FR 115068 (all Fujisawa, Japan); GR 253035 (Glaxo Wellcome); RWJ 63556 (Johnson & Johnson); RWJ 20485 (Johnson & Johnson); ZK 38997 (Schering); S 2474 ((E)-(5)-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide indomethacin; Shionogi & Co., Ltd., Japan); zomepirac analogs, such as RS 57067 and RS 104897 (Hoffmann La Roche); RS 104894 (Hoffmann La Roche); SC 41930 (Monsanto); pranlukast (SB 205312, Ono-1078, ONON®, ULTAIR®; SmithKline Beecham); SB 209670 (SmithKline Beecham); and APHS (heptinylsulfide).

### D. Nanoparticulate Active Agent Particle Size

The compositions of the invention contain nanoparticulate active agent particles which have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns). In other embodiments of the invention, the active agent particles have a 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 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 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% by weight of the active agent particles have a particle size less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.*, 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 active agent particles have a particle size less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.*

If the nanoparticulate active agent composition is combined with a conventional active agent composition, then such a composition is either solubilized or has an effective average particle size greater than about 2 microns. By "an effective average particle size of greater than about 2 microns" it is meant that at least 50% of the microparticulate active agent particles have a particle size greater than about 2 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 active agent particles have a particle size greater than about 2 microns.

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

### 5. Concentration of Nanoparticulate Active Agent and Peptide Stabilizer

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

The concentration of the peptide 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 the at least one active agent and at least one peptide surface stabilizer, not including other excipients.

The concentration of the at least one active agent 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 dry weight of the active agent and at least one peptide surface stabilizer, not including other excipients.

## B. Methods of Making Nanoparticulate Active Agent Formulations

The nanoparticulate active agent compositions of the invention, comprising at least one peptide as a surface stabilizer, can be made using, for example, milling, homogenization, or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in the '684 patent. Methods of making nanoparticulate active agent 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.

The resultant nanoparticulate active agent compositions can be utilized in any desired dosage form.

### 1. Milling to obtain Nanoparticulate Active Agent Dispersions

Milling the active agent to obtain a nanoparticulate dispersion comprises dispersing active agent particles in a liquid dispersion media in which the active agent is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the active agent to the desired effective average particle size. The dispersion media can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. Water is a preferred dispersion media.

The active agent particles are preferably reduced in size in the presence of at least one peptide surface stabilizer. Alternatively, the active agent particles can be contacted with at least one peptide surface stabilizer either during or after attrition. One or more secondary surface stabilizers may also be added before, during, or after attrition. Other compounds, such as a diluent, can be added to the active agent/peptide surface stabilizer composition before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

### 2. Precipitation to Obtain Nanoparticulate Active Agent Compositions

Another method of forming the desired nanoparticulate active agent composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more peptide 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 poorly soluble active agent in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one peptide surface stabilizer and optionally one or more secondary surface stabilizers, to form a clear solution; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. 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.

### 3. Homogenization to Obtain Nanoparticulate Active Agent Compositions

Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Such a method comprises dispersing active agent particles in a liquid dispersion media in which the active agent is poorly soluble, followed by subjecting the dispersion to homogenization to reduce the particle size of the active agent to the desired effective average particle size. The active agent particles can be reduced in size in the presence of at least one peptide surface stabilizer and, if desired, one or more additional surface stabilizers. Alternatively, the active agent particles can be contacted with at least one peptide surface stabilizer and, if desired, one or more additional surface stabilizers, either during or after attrition. Other compounds, such as a diluent, can be added to the active agent/peptide surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

### C. Methods of Using Nanoparticulate Active Agent Formulations

The nanoparticulate active agent compositions of the present invention can be administered to humans and animals via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (powders, ointments or drops), or as a buccal or nasal spray.

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 active agent 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.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carrier), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium

carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active agent, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Actual dosage levels of active agent in the nanoparticulate compositions of the invention may be varied to obtain an amount of active agent 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 active agent, 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

including the body weight, general health, sex, diet, time and route of administration, potency of the administered active agent, rates of absorption and excretion, combination with other active agents, and the severity of the particular disease being treated.

* * * * *

The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

The formulations in the examples that follow were also investigated using a light microscope. Here, "stable" nanoparticulate dispersions (uniform Brownian motion) were readily distinguishable from "aggregated" dispersions (relatively large, nonuniform particles without motion).

**Example 1**

The purpose of this example was to prepare a nanoparticulate nystatin composition having a peptide surface stabilizer.

Nystatin is a poorly water-soluble antimycotic polyene antibiotic obtained from *Streptomyces noursei.* It is an antifungal agent indicated for oral, gastrointestinal, and vaginal candidiasis. Oral candidiasis, in particular, is a common affliction of immunocompromised patients. Nystatin is indicated in the therapy of all infections caused by susceptible microorganisms in those patients in whom candidal (monilial) infections are most likely to complicate therapy.

A slurry of 2% (w/w) nystatin (Sigma-Aldrich Co.) and 1% (w/w) poly(Lysine, Tryptophan) 4:1 hydrobromide ("Poly(Lys,Trp)") (Sigma; St. Louris, MO), which is a cationic random co-polyamino acid having a molecular weight of 38,000, in water was

milled for 1 day using low energy (ball milling) techniques in the presence of ceramic YTZ grinding media.

The mean size of the nystatin particles following milling was 149 nm, with a D90 of 270 nm, as determined by static light scattering using a Horiba LA-910 light-scattering particle size analyzer (Horiba Instruments, Irvine, CA). The composition had a zeta potential of 47.7 mV, as measured by electrophoresis in $5x10^{-4}$ M NaCl (Malvern ZetaSizer). Dispersibility was verified by phase contrast microscopy.

Figure 1 shows representative photomicrographs of the nystatin crystals before (Fig. 1A) and after (Fig. 1B) milling.

Particle size stability under controlled conditions was monitored over time. Figure 2 shows the results of monitoring the nystatin particle size stability over time at 5°C (solid line), 25°C (dashed line), and 40°C (dotted line) for the nanoparticulate nystatin/peptide composition.

These results demonstrate that a peptide surface stabilizer can be successfully used to stabilize an active agent at a nanoparticulate particle size. Moreover, such a peptide surface stabilizer may confer additional therapeutic advantages to the final formulation. For example, the peptide surface stabilizer Poly(Lys,Trp) is cationic and, therefore, nanoparticulate active agent compositions utilizing this surface stabilizer will be bioadhesive.

The resultant composition exhibited a mean particle sizes of 149 nm and were free of agglomeration. Moreover, the nanoparticulate nystatin/peptide composition exhibited virtually no particle size growth at all three temperatures tested.

**Example 2**

The purpose of this example was to determine whether a cationic surface charge, such as that obtained with the use of a cationic peptide surface stabilizer, enhances the adhesion of small particles to cells.

Cell-binding experiments were performed with polystyrene latex microspheres as a model. A positive surface charge would be expected to enhance the interaction of particles with cell-surface macromolecules, which have a net negative charge.

Cationic microspheres with a mean zeta-potential (51.5 mV) comparable to the nanoparticulate nystatin/peptide composition of Example 1 were tested against anionic microspheres (mean zeta-potential = -50.9 mV). The microspheres were incubated with NIH/3T3 fibroblasts, washed thoroughly, fixed, and subjected to SEM analysis.

Figure 3 shows representative micrographs of cells with anionic particles (Fig. 3A) and cationic particles (Fig. 3B).

The results indicate that positively-charged particles interact more strongly with the cell surface than negatively-charged particles, and it is believed that nanoparticulate active agent compositions having a cationic peptide as a surface stabilizer with comparable zeta potentials will follow the same trend.

**Example 3**

The purpose of this example was to determine if milling of an active agent, such as nystatin, having a peptide surface stabilizer affects the active agent's activity.

The minimum inhibitory concentration (MIC) of a milled nystatin composition having as a peptide surface stabilizer Poly(Lys, Trp) was compared to the MIC of two unmilled nystatin compositions. Nystatin for the milled nanoparticulate composition was obtained from Sigma-Aldrich Co. and the two unmilled nystatin compositions were obtained from Sigma-Aldrich Co. and Paddock Laboratories, Inc. Details regarding the milled and unmilled nystatin compositions are given in Table 1 below, including particle size of the milled nanoparticulate nystatin/Poly(Lys, Trp) composition and the potency (USP U/ml) and MIC for each nystatin composition.

| TABLE 1 | | | | |
|---|---|---|---|---|
| **Nystatin Concentration** | **Surface Stabilizer and Concentration** | **Mean Particle Size (nm)** | **Potency (USP U/ml)** | **MIC** |
| 2% (Sigma) | 1% Poly(Lys, Trp) [1] | 129 | 101,200 | 1:10,000 |
| | | | | |
| 5% (Sigma) | N/A – unmilled | N/A | 253,000 | 1:10,000 |
| 4% (Paddock) | N/A – unmilled | N/A | 253,000 | 1:100,000 |

[1]Poly(Lysine, Tryptophan) is a cationic random co-polyamino acid.

The nanoparticulate sample was ball milled for 26 hours with ceramic YTZ milling media.

The minimum inhibitory concentration (MIC) of the milled nystatin/peptide composition and the two unmilled samples were determined in cultures of *C. albicans*. MIC as reported here is the maximum dilution of formulation in culture broth which inhibits growth of *C albicans*. As shown in Table 1, above, the milled nystatin/peptide composition did not exhibit any significant differences in MIC, and surprisingly, was more active than at least one of the unmilled nystatin samples. These data confirm that the milling process does not decrease the activity of nystatin.

**Example 4**

The purpose of this example was to prepare a nanoparticulate composition of a diuretic, Compound A, utilizing a peptide surface stabilizer. Diuretics can be used to reduce the swelling and fluid retention caused by various medical problems, including heart or liver disease. They are also is used to treat high blood pressure.

A slurry of 2% (w/w) Compound A and 1% (w/w) poly(Lysine, Tryptophan) 4:1 hydrobromide as a peptide surface stabilizer in water was milled for 3 days in an aqueous environment in a low energy mill, in the presence of 0.8 mm yttrium-stabilized ceramic media.

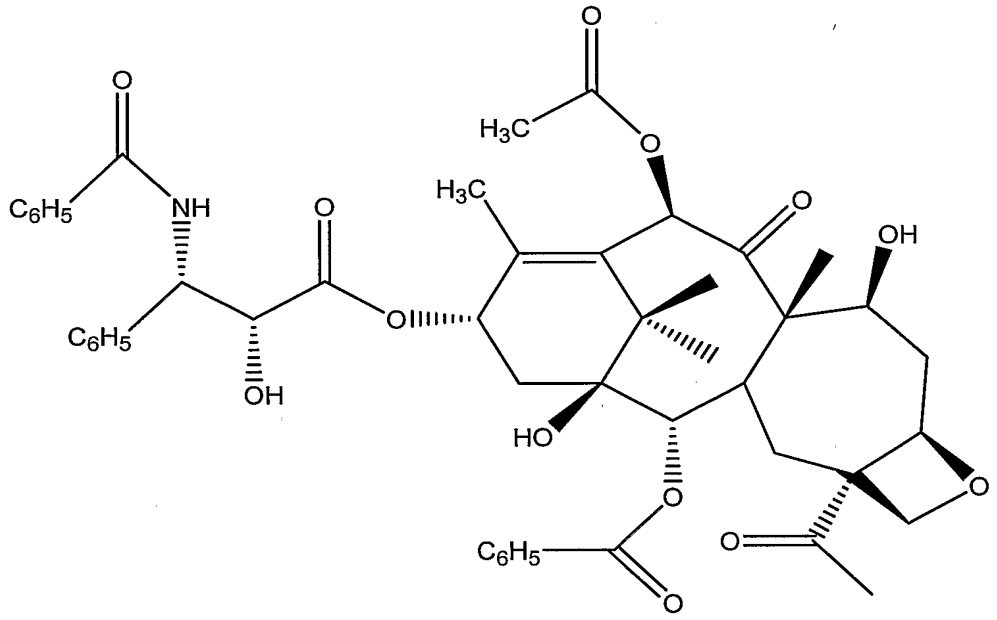
Particle size analysis of the resulting Compound A dispersion was conducted via laser light diffraction using the Horiba LA 910 particle size analyzer (Horiba Instruments, Irvine, CA) and water as a diluent. The mean particle size of the milled

Compound A dispersion was 99 nm, with a D90 of 138 nm. The composition was stable.

**Example 5**

The purpose of this example was to prepare a nanoparticulate composition of paclitaxel utilizing a peptide surface stabilizer. Paclitaxel belongs to the group of medicines called antineoplastics. It is used to treat cancer of the ovaries, breast, certain types of lung cancer, and a cancer of the skin and mucous membranes more commonly found in patients with acquired immunodeficiency syndrome (AIDS). It may also be used to treat other kinds of cancer.

Paclitaxel has the following chemical structure:




A slurry of 2% (w/w) paclitaxel and 1% (w/w) poly(Lysine, Tryptophan) 4:1 hydrobromide as a peptide surface stabilizer in water was milled for 3 days in an aqueous environment in a low energy mill, in the presence of 0.8 mm yttrium-stabilized ceramic media.

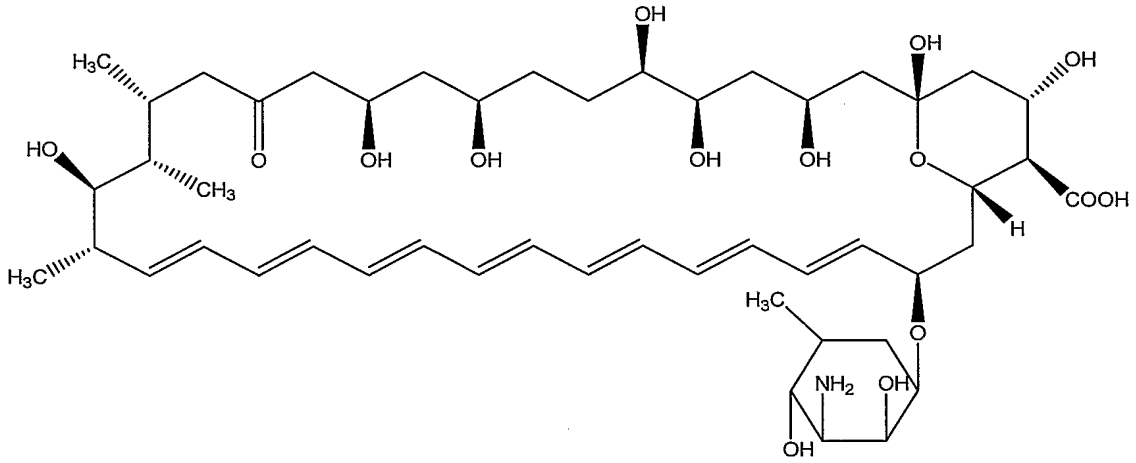
Particle size analysis of the resulting paclitaxel dispersion was conducted via laser light diffraction using the Horiba LA 910 particle size analyzer (Horiba Instruments, Irvine, CA) and water as a diluent. The mean particle size of the milled

paclitaxel dispersion was 139 nm, with a D90 of 185 nm. The composition was stable.

**Example 6**

The purpose of this example was to prepare a nanoparticulate composition of amphotericin B utilizing a peptide surface stabilizer. Amphotericin B is a poorly water soluble antifungal agent. Topically, it is used to treat skin yeast infections; intravenously, it is used to treat a variety of life-threatening fungal infections.

Amphotericin B has the following chemical structure:




In this experiment, amphotericin B was milled with Poly (Lys, Trp) 4:1 Hydrobromide as a peptide surface stabilizer. A 2% (w/w) slurry of amphotericin B (Sigma) in water was prepared with 1% (w/w) poly (Lys, Trp) (Sigma). The composition was ball-milled for 24 hours with 0.8 mm ceramic YTZ milling media. The particle size of the resulting amphotericin B dispersion was characterized by static laser light scattering on a Horiba LA-910 particle size distribution analyzer. The results are shown in Table 2, below.

**TABLE 2**

| Drug and Concentration | Surface Stabilizer and Concentration | Mean Particle Size (nm) | D50 (nm) | D90 (nm) |
|---|---|---|---|---|
| 2% Amphotericin B | 1% Poly(Lys, Trp) | 121 | 96 | 230 |

These results demonstrate that amphotericin B dispersions can be successfully stabilized by a peptide surface stabilizer, such as the random copolypeptide poly (Lys, Trp) 4:1 Hydrobromide.

* * * *

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.

We claim:

1. A composition comprising:
   (a) particles of at least one active agent having an effective average particle size of less than about 2000 nm; and
   (b) at least one water soluble peptide surface stabilizer.

2. The composition of claim 1, wherein the peptide surface stabilizer is poly(Lysine, Tryptophan) 4:1 hydrobromide.

3. The composition of claim 1 or claim 2, further comprising at least one secondary surface stabilizer.

4. The composition of any one of claims 1 to 3, wherein the secondary surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

5. The composition of claim 3 or claim 4, wherein the secondary 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, and random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a 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.

6. The composition of any one of claims 1 to 5, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

7. The composition of any one of claims 1 to 6 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, tablets, capsules, sachets, lozenges, powders, pills, granules, controlled release formulations, fast melt formulations, lyophilized

formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

8. The composition of any one of claims 1 to 7, wherein:

(a) the active agent 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%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the active agent and at least one peptide surface stabilizer, not including other excipients; or

(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, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the active agent and at least one peptide surface stabilizer, not including other excipients.

9. The composition of any one of claims 1 to 8, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

10. The composition of any one of claims 1 to 10, wherein the effective average particle size of the active agent particles is 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 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 100 nm, less than about 75 nm, and less than about 50 nm.

11. The composition of any one of claims 1 to 10, wherein at least about 70%, at least about 90%, at least about 95%, or at least about 99% of the active agent particles have a particle size less than the effective average particle size.

12. The composition of any one of claims 1 to 11, further comprising at least one additional active agent composition having an effective average particle size which is different that the effective average particle size of the active agent composition of claim 1.

13. The composition of any one of claims 1 to 12, wherein the active agent is selected from the group consisting of nystatin, paclitaxel, amphotericin B, a diuretic, a dermal agent, nutraceuticals, COX-2 inhibitors, retinoids, anticancer agents, NSAIDS, proteins, peptides, nucleotides, anti-obesity drugs, dietary supplements, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole,

loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

14. The composition of claim 13, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics.

15. The composition of claim 13, wherein the anticancer agent is selected from the group consisting of alkylating agents, antimetabolites, anthracenediones, natural products, hormones, antagonists, radiosensitizers, platinum coordination complexes, adrenocortical suppressants, immunosuppressive agent, substituted ureas, and COX-2 inhibitors.

16. The composition of claim 15, wherein:

(a) the alkylating agent is selected from the group consisting of chlormethine, chlorambucile, melphalan, uramustine, mannomustine, extramustinephoshate, mechlore-thaminoxide, cyclophosphamide, ifosfamide, trifosfamide, tretamine, thiotepa, triaziquone, mitomycine, busulfan, piposulfan, piposulfam, carmustine, lomustine, semustine, streptozotocine, mitobronitole, dacarbazine and procarbazine; or

(b) the antimetabolite is selected from the group consisting of methotrexate, fluorouracil, floxuridine, tegafur, cytarabine, idoxuridine, flucytosine, mercaptopurine, thioguanine, azathioprine, tiamiprine, vidarabine, pentostatin, and puromycine; or

(c) the natural product is selected from the group consisting of vinblastine, vincristine, etoposide, teniposide, adriamycine, daunomycine, doctinomycin, daunorubicin, doxorubicin, mithramycin, bleomycin, mitomycin, L-asparaginase, alpha-interferon, camptothecin, taxol, and retinoic acid; or

(d) the hormone or antagonist is selected from the group consisting of prednisone, hydroxyprogesterone caproate, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, ethinyl estradiol, tamoxifen, testosterone propionate, fluoxymesterone, flutamide, leuprolide; or

(e) the anticancer agent is selected from the group consisting of cisplatin, carboplatin, mitoxantrone, hydroxyurea, mitotane, aminoglutethimide, cyclosporine, azathioprine, sulfasalazine, methoxsalen, and thalidomide.

17. The composition of claim 13, wherein the NSAID is selected from the group consisting of nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, dapsone, aspirin, diflunisal, benorylate, fosfosal, diclofenac, alclofenac, fenclofenac, etodolac, indomethacin, sulindac, tolmetin, fentiazac, tilomisole, carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, pirprofen, flufenamic, mefenamic, meclofenamic, niflumic, oxyphenbutazone, phenylbutazone, apazone, feprazone, piroxicam, sudoxicam, isoxicam, and tenoxicam.

18. The composition of claim 13, wherein the COX-2 inhibitor is selected from the group consisting of nimesulide, celecoxib, rofecoxib, meloxicam, valdecoxib, parecoxib, etoricoxib, flurbiprofen, nabumetone, etodolac, iguratimod, flosulide, piroxicam, diclofenac, lumiracoxib, monteleukast, pranlukast, heptinylsulfide, SC-236, SC-58125, SC-57666, SC-558, SC-560, SC 41930, NS-398, DFU, L-745337, L-

761066, L-761000, L-748780, DUP-697, PGV 20229, BF 389, CL 1004, PD 136005, PD 142893, PD 138387, PD 145065, D 1367, R 807, JTE-522, FK-3311, FK 867, FR 140423, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, S 2474, RS 57067, RS 104897, RS 104894, and SB 209670.

19. The composition of any one of claims 1 to 18, wherein upon administration to a mammal the active agent particles redisperse such that the particles have an effective average particle size selected from the group consisting of less than about 2 microns, 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 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 100 nm, less than about 75 nm, and less than about 50 nm.

20. The composition of any one of claims 1 to 19, wherein the composition redisperses in a biorelevant media such that the active agent particles have an effective average particle size selected from the group consisting of less than about 2 microns, 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 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 100 nm, less than about 75 nm, and less than about 50 nm.

21. The composition of claim 20, wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a

salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

22. The composition of any one of claims 1 to 21, wherein:

(a) the $T_{max}$ of the active agent, when assayed in the plasma of a mammalian subject following administration, is less than the $T_{max}$ for a non-nanoparticulate composition of the same active agent, administered at the same dosage; or

(b) the $C_{max}$ of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the $C_{max}$ for a non-nanoparticulate composition of the same active agent, administered at the same dosage; or

(c) the AUC of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate composition of the same active agent, administered at the same dosage.

23. The composition of claim 22, wherein the $T_{max}$ is selected from the group consisting of 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%, and not greater than about 5% of the $T_{max}$ exhibited by a non-nanoparticulate composition of the same active agent, administered at the same dosage.

24. The composition of claim 22, wherein the $C_{max}$ is selected from the group consisting of 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 a non-nanoparticulate composition of the same active agent, administered at the same dosage.

25. The composition of claim 22, 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 composition of the same active agent, administered at the same dosage.

26. The composition of any one of claims 1 to 25 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

27. The composition of claim 26, wherein the difference in absorption of the active agent composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of 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 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

28. The composition of any one of claims 1 to 27, wherein administration of the composition to a human in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

29. The composition of claim 28, wherein "bioequivalency" is established by:

(a) a 90% Confidence Interval of between 0.80 and 1.25 for both $C_{max}$ and AUC; or

(b) a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for $C_{max}$.

30. The composition of any one of claims 1 to 29, formulated into a liquid dosage form and having a viscosity at a shear rate of 0.1 (1/s), measured at 20°C, selected from the group consisting of less than about 2000 mPa·s, from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

31. The composition of claim 30, wherein the viscosity of the dosage form is:

(a) selected from the group consisting of less than about 1/200, less than

about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a liquid dosage form of a non-nanoparticulate composition of the same active agent, at about the same concentration per ml of active agent; or

(b) selected from the group consisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, and less than about 90% of the viscosity of a liquid dosage form of a non-nanoparticulate composition of the same active agent, at about the same concentration per ml of active agent.

32. The composition of any one of claims 1 to 31, further comprising one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

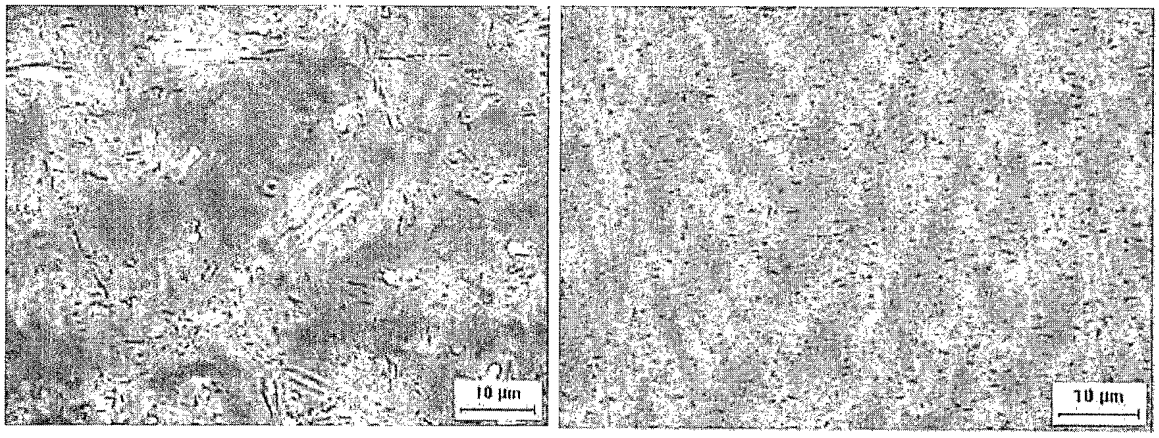
33. The composition according to any one of claims 1 to 32, wherein the composition is bioadhesive.

34. The use of a composition according to any one of claims 1 to 33 for the manufacture of a pharmaceutical medicament.

35. A method of making a composition according to any one of claims 1 to 33, comprising contacting particles of at least one active agent with at least one water-soluble peptide surface stabilizer for a time and under conditions sufficient to provide an active agent composition having an effective average particle size of less than about 2000 nm.

# FIGURE 1

A B



# FIGURE 2

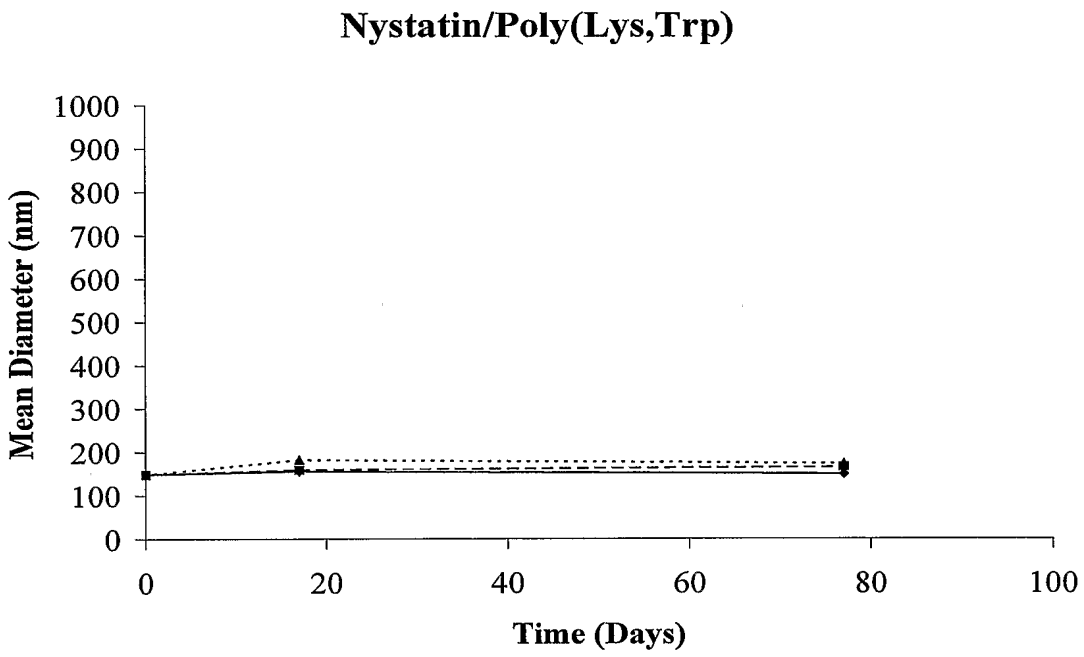
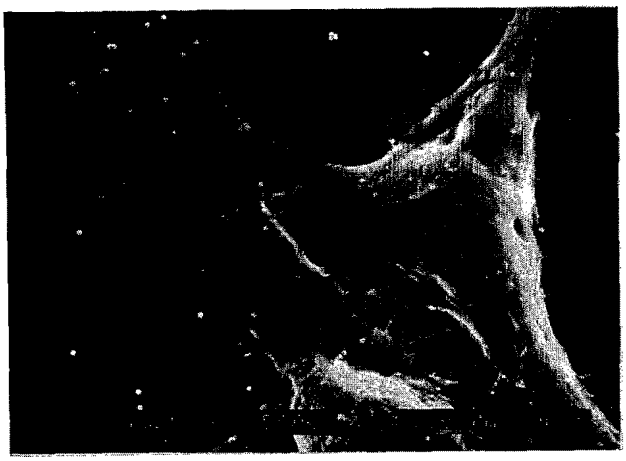

Nystatin/Poly(Lys,Trp)
Mean Diameter (nm)
1000
900
800
700
600
500
400
300
200
100
0
0
20
40
60
80
100
Time (Days)

FIGURE 3

A



B

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 8164419 |
| **Application Number:** | 12413439 |
| **International Application Number:** | |
| **Confirmation Number:** | 9049 |
| **Title of Invention:** | ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS |
| **First Named Inventor/Applicant Name:** | Steve Cartt |
| **Customer Number:** | 21971 |
| **Filer:** | Peter R. Munson./Ann Lygas/Matthew V. Grumbling |
| **Filer Authorized By:** | Peter R. Munson. |
| **Attorney Docket Number:** | 35401-716.201 |
| **Receipt Date:** | 05-AUG-2010 |
| **Filing Date:** | 27-MAR-2009 |
| **Time Stamp:** | 16:42:41 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

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|---|---|
| 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 | 35401-716-201SIDSTransmittal.pdf | 306505<br>b4ef21ed0cd2f75f9226fd5f8e38e3c58bf52101 | no | 4 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Information Disclosure Statement (IDS) Filed (SB/08) | 35401-716-201SIDSFiled.pdf | 97849<br>ce3d3562c648409a8010fd03b8d5745ee8200b12 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| This is not an USPTO supplied IDS fillable form | | | | | |
| 3 | Foreign Reference | WO05044234A2.pdf | 3809020<br>8f09d7e30775765bff4e769262b7ab8b01abf1f0 | no | 68 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | NPL Documents | Wermeling.pdf | 1190828<br>707b6c75f9dcaef86494580d4723e7ca72ba4d70 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | NPL Documents | EP087478137SuppSrchRpt.pdf | 612546<br>5c0f50397c3670d2aad60e2a907fd3feafb89221 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 6016748 | | |

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**<u>New Applications Under 35 U.S.C. 111</u>**
**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.**

**<u>National Stage of an International Application under 35 U.S.C. 371</u>**
**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.**

**<u>New International Application Filed with the USPTO as a Receiving Office</u>**
**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 et al. | Group Art Unit: 1612 |
| Serial Number: 12/413,439 | Examiner: Adam C. Milligan |
| Filing Date: March 27, 2009 | **CONFIRMATION NO: 9049** |
| Title: Administration of Benzodiazepine Compositions | |

Certificate of Electronic Filing

I hereby certify that the attached Information Disclosure Statement and all marked attachments are being deposited by Electronic Filing on AUGUST 5, 2010 by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Ann Lygas
Ann Lygas

Date: August 5, 2010

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Sir:

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 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.35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: 8/5/2010

By: _____
Matthew V. Grumbling
Reg. No. 44,427

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Palo Alto, CA 94304-1050
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Customer No. 021971

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/413,439 | 03/27/2009 | Steve Cartt | 35401-716.201 | 9049 |

21971 7590 12/08/2010
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 |
|---|---|
| 12/08/2010 | 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. | Applicant(s) | |
|---|---|---|---|
| | 12/413,439 | CARTT ET AL. | |
| | Examiner | Art Unit | |
| | ADAM MILLIGAN | 1612 | |

*-- 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 _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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**

4)☒ Claim(s) 1-47 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-47 are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**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).

a)☐ All b)☐ Some * c)☐ None of:

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.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Phone Call*

A telephone call was made to Matthew Grumbling on 11/29/2010 to request an oral election to the following restriction requirement, but did not result in an election being made.

### *Election/Restrictions*

Restriction to one of the following inventions is required under 35 U.S.C. 121:

**Group I.** Claims 1-19, drawn to a pharmaceutical composition, classified in class 424, subclass 465.

**Group II.** Claims 20-45, drawn to a method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, classified in class 514, subclass 221

Note, claims 46 and 47 will be assigned a group upon amendment. Currently, the claims are drawn to a composition, but depend from a claim drawn to a method of treating. Thus, it is currently unclear which group the claims properly belong to.

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 administered orally. Moffett (U.S. 3,609,145) teaches that benzodiazepine compounds can be administered orally (col. 2, lines 65-76). Oral administration is materially different from nasal administration insofar as mucosal absorption is different than gastrointestinal absorption.

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 reason(s) apply:

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

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).

***Election of Species***

This application contains claims directed to the following patentably distinct species:

Please elect a single species for each of the following:

a) *Benzodiazepine drug:* such as recited in claims 3 and 23.

b) *One or more natural or synthetic tocopherols or tocotrienols, or any combination thereof:* such as recited in claims 7 and 27.

c) *One or more alcohols or glycols, or any combinations thereof:* such as recite in claims 8, 9, 28 and 29.

d) *Alkyl glycoside:* such as taught by the instant specification.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-19 of Group I are generic as to the above disclosed species and claims 20-45 of Group II are generic as to the above disclosed species.

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a

claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve 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 election of species 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 on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species 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 species 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 species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

## ***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.

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612

/A. M./
Examiner, Art Unit 1612

| Notice of References Cited | Application/Control No. 12/413,439 | Applicant(s)/Patent Under Reexamination CARTT ET AL. | |
|---|---|---|---|
| | Examiner ADAM MILLIGAN | Art Unit 1612 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-3,609,145 | 09-1971 | Moffett, Robert B. | 540/513 |
| | B | US- | | | |
| | C | US- | | | |
| | D | US- | | | |
| | E | US- | | | |
| | F | US- | | | |
| | G | US- | | | |
| | H | US- | | | |
| | I | US- | | | |
| | J | US- | | | |
| | K | US- | | | |
| | L | US- | | | |
| | M | US- | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
|---|---|---|---|---|---|---|
| | N | | | | | |
| | O | | | | | |
| | P | | | | | |
| | Q | | | | | |
| | R | | | | | |
| | S | | | | | |
| | T | | | | | |

**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| In re the Patent Application of: | Confirmation No.: 9049 |
|---|---|
| Applicant: Steve Cartt | Group Art Unit: 1612 |
| Serial No.: 12/413,439 | Examiner: Milligan, Adam C. |
| Filed: 03/27/2009 | Certificate of Electronic Filing |
| Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS | I hereby certify that the attached Response to Restriction Requirement and all marked attachments are being deposited by Electronic Filing on January 5, 2011 by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.<br>By: Linda Anders<br>Linda Anders |

Dear Sir/Madam:

## RESPONSE TO RESTRICTION REQUIREMENT DATED DECEMBER 9, 2010

Applicant hereby submits a timely response to the Restriction Requirement mailed December 8, 2010, in the above referenced application. No fees are believed to be due. However, in the event any additional fees are due, please charge to Deposit Account No. 23-2415, referencing Docket No. 35401-716.201.

**Amendments to the claims** begin on page 2 of this paper.
**Remarks** begin on page 8 of this paper.

## CLAIMS

**Amendments to the Claims**

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicants reserve the right to pursue the subject matter of the withdrawn claim in this or any other appropriate patent application.

1. (Withdrawn) A pharmaceutical composition for nasal administration comprising:

(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); and

(c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w),

in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient.

2. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The pharmaceutical composition 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, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

4. (Withdrawn) The pharmaceutical composition of claim 3, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

5. (Withdrawn) The pharmaceutical composition of claim 1, wherein the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof.

6. (Withdrawn) The pharmaceutical composition of claim 5, wherein the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm.

7. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The pharmaceutical composition of claim 1, wherein the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.

10. (Withdrawn) The pharmaceutical composition of claim 1, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 1 mg/mL to about 600 mg/mL.

11. (Withdrawn) The pharmaceutical composition of claim 1, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 10 mg/mL to about 250 mg/mL.

12. (Withdrawn) The pharmaceutical composition of claim 11, wherein the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 50 mg/mL.

13. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The pharmaceutical composition of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 60% to about 75% (w/w).

15. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The composition of one of claims 1 - 16, further comprising at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

18. (Withdrawn) The composition of claim 1, wherein the pharmaceutically-acceptable formulation comprises at least about 0.01% (w/w) of an alkyl glycoside.

19. (Withdrawn) The composition of claim 18, wherein the pharmaceutically-acceptable formulation about 0.01% to 1% (w/w) of an alkyl glycoside.

20. (Original) A method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising:

(a) administering to one or more nasal mucosal membranes of a patient a pharmaceutical composition for nasal administration comprising 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), and one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).

21. (Original) The method of claim 20, 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).

22. (Original) The method of claim 21, wherein said patient is a human.

23. (Original) The method of claim 20, 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, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

24. (Original) The method of claim 23, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

25. (Original) The method of claim 20, wherein the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof.

26. (Original) The method of claim 25, wherein the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm.

27. (Original) The method of claim 20, 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.

28. (Original) The method of claim 20, 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.

29. (Original) The method of claim 20, wherein the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.

30. (Original) The method of claim 20, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 1 mg/mL to about 600 mg/mL.

31. (Original) The method of claim 30, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration of from about 10 mg/mL to about 250 mg/mL.

32. (Original) The method of claim 31, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration of from about 20 mg/mL to about 50 mg/mL.

33. (Original) The method of claim 20, wherein the pharmaceutical composition 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).

34. (Original) The method claim 33, wherein the pharmaceutical composition 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).

35. (Original) The method of claim 20, wherein the pharmaceutical composition comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w).

36. (Original) The method of claim 35, wherein the pharmaceutical composition comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w).

37. (Original) The method of claim 20, wherein the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

38. (Original) The method of claim 20, wherein the composition is in a pharmaceutically-acceptable spray formulation.

39. (Original) The method of claim 38, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.

40. (Original) The method of claim 39, wherein said pharmaceutical composition is in a pharmaceutically-acceptable spray formulation having volume from about 10 $\mu$L to about 200 $\mu$L.

41. (Original) The method of claim 40, wherein the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril.

42. (Original) The method of claim 40, wherein the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.

43. (Original) The method of claim 42, wherein the administration of the pharmaceutical composition comprises spraying a first quantity of the pharmaceutical composition into the first nostril, spraying a second quantity of the pharmaceutical composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical composition into the first nostril.

44. (Original) The method of claim 43, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical composition to the second nostril.

45. (Original) The method of claim 43, wherein nasal administration of the pharmaceutical composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical composition.

46. (Currently Amended) The ~~composition~~ method of claim 20, wherein the pharmaceutically-acceptable formulation comprises at least about 0.01% (w/w) of an alkyl glycoside.

47. (Currently Amended) The ~~composition~~ method of claim 21, wherein the pharmaceutically-acceptable formulation about 0.01% to 1% (w/w) of an alkyl glycoside.

## REMARKS

**Amendment**

By the foregoing amendment, claims 46 and 47 have been amended to correct an informality noted in the Office Action mailed December 8, 2010 (Restriction Requirement). No new matter has been added with this Response. Applicant reserves the right to pursue the subject matter of the withdrawn claim in this or any other appropriate patent application.

**Restriction Requirement**

In the Restriction Requirement the Examiner required restriction to one of the two following inventions:

Group I: Claims 1-19, drawn to a pharmaceutical composition, classified in class 424, subclass 465.

Group II: Claims 20-45, drawn to a method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, classified in class 514, subclass 221.

Claims 46-47 were not assigned to a group, as they were formally recited compositions but were dependent from method claims. By the foregoing amendment, claims 46-47 have been amended to recite methods. Applicants submit that they are properly placed with group II.

Applicants were further required to elect a single disclosed species for each of the following:

a) Benzodiazepine drug: such as recited in claims 3 and 23;

b) One or more natural or synthetic tocopherols or tocotrienols, or any combination thereof, such as recited in claims 7 and 27;

c) One or more alcohols or glycols, or any combinations thereof; such as recited in claims 8, 9, 28 and 29;

d) Alkyl glycoside: such as taught by the instant specification.

**Applicants' Election**

Applicants hereby elect group II, drawn to methods, claims 20-47, without traverse.

Regarding the election of species requirement, Applicants provisionally elect the species of:

a) Benzodiazepine drug: **diazepam.**

b) One or more natural or synthetic tocopherols or tocotrienols: **Vitamin E** (alpha tocopherol.

c) One or more alcohols or glycols, or any combinations thereof; such as recited in claims 8, 9, 28 and 29: **Benzyl alcohol.**

d) Alkyl glycoside: **Dodecyl maltoside.**

## CONCLUSION

Applicant timely submits these remarks in response to the Office Communication dated December 8, 2010. In the event that fees are due in connection with the filing of this response, please charge the necessary fees to Deposit Account No. 23-2415 referencing Docket No. 35401-716.201. Should the examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (858) 350-2332.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: January 5, 2011

By: Matthew V. Grumbling
Registration No. 47,664

650 Page Mill Road
Palo Alto, CA 94304
(858) 350-2306
Customer No. 021971

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 9173524 |
| **Application Number:** | 12413439 |
| **International Application Number:** | |
| **Confirmation Number:** | 9049 |
| **Title of Invention:** | ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS |
| **First Named Inventor/Applicant Name:** | Steve Cartt |
| **Customer Number:** | 21971 |
| **Filer:** | Peter R. Munson./Linda Anders/MG |
| **Filer Authorized By:** | Peter R. Munson. |
| **Attorney Docket Number:** | 35401-716.201 |
| **Receipt Date:** | 05-JAN-2011 |
| **Filing Date:** | 27-MAR-2009 |
| **Time Stamp:** | 19:35:47 |
| **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 | | 35401-716-201-responseRR.pdf | 4141224<br>cce7e5c42474f673535c32f0f3f8b0e5f5f5a6e8 | yes | 9 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Response to Election / Restriction Filed | 1 | 1 |
| | Amendment Copy Claims/Response to Suggested Claims | 2 | 7 |
| | Applicant Arguments/Remarks Made in an Amendment | 8 | 9 |
| **Warnings:** | | | |
| **Information:** | | | |
| | **Total Files Size (in bytes):** | 4141224 | |

**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 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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 | Filing Date | ☐ To be Mailed |
|---|---|---|
| 12/413,439 | 03/27/2009 | |

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY ☒ RATE ($) | SMALL ENTITY FEE ($) | OR | OTHER THAN SMALL ENTITY RATE ($) | OTHER THAN SMALL ENTITY FEE ($) |
|---|---|---|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | | | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | | | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | | OR | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | | | 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 $250 ($125 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 | | | TOTAL | |

## APPLICATION AS AMENDED – PART II

| AMENDMENT 01/05/2011 | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE ($) | SMALL ENTITY ADDITIONAL FEE ($) | OR | OTHER THAN SMALL ENTITY RATE ($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * 62 | Minus | ** 62 | = 0 | X $26 = | 0 | OR | X $ = | |
| Independent (37 CFR 1.16(h)) | * 2 | Minus | ***3 | = 0 | X $110 = | 0 | OR | X $ = | |
| ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | 0 | OR | TOTAL ADD'L FEE | |

| AMENDMENT | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) | | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | | OR | X $ = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | | OR | X $ = | |
| ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/SHANDA ROSS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/413,439 | 03/27/2009 | Steve Cartt | 35401-716.201 | 9049 |

21971 7590 03/18/2011
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 |
|---|---|
| 03/18/2011 | 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. | Applicant(s) | |
|---|---|---|---|
| | 12/413,439 | CARTT ET AL. | |
| | Examiner | Art Unit | |
| | ADAM C. MILLIGAN | 1612 | |

***-- 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 3 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 *05 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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**

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *1-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**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).

a)☐ All b)☐ Some * c)☐ None of:

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.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :3pgs(9/16/2009), 1pg(11/17/2009), 1pg(8/5/2010).

**DETAILED ACTION**

***Election/Restrictions***

Applicants' election without traverse of Group II, claims 20-45, in the reply filed on 1/5/2011 is acknowledged.

**Claims 1-19** are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant's election of diazepam as the benzodiazepine drug, Vitamin E as the natural or synthetic tocopherol or tocotrienol, benzyl alcohol as the one or more alcohols or glycols, and dodecyl maltoside as the alkyl glycoside is also acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The restriction is made FINAL.

***Claim Rejections - 35 USC § 112 - Written Rejection***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 20-47** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. However, a showing of possession alone does not cure the lack of a written description. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 969-70, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002)(emphasis added). An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). See also Ariad

Pharmaceuticals Inc. v. Eli Lilly & Co. 94 USPQ2d 1161, 1176-77 (Fed. Cir. 2010), wherein the court explained:

> Here, the specification at best describes decoy molecule structures and hypothesizes with no accompanying description that they could be used to reduce NF-KB activity. Yet the asserted claims are far broader. We therefore conclude that the jury lacked substantial evidence for its verdict that the asserted claims were supported by adequate written description, and thus hold the asserted claims invalid.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. See *Enzo Biochem*, 323

F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

See also MPEP 2163 for a detailed discussion of guidelines concerning analysis of written description issues.

Here, the specification does not provide a reasonably representative disclosure of useful benzodiazepine "compounds" generally, a potentially huge genus inclusive of many different compounds having widely divergent structures and functions. Specifically, the specification discloses only a limited number of species at e.g. page 4, paragraph 20 and these are not viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus. By contrast, the state of the art is poorly developed with regard to the claimed subject matter, as confirmed by the specification, given that there is no general structure or definition provided. Accordingly, the specification does not appear to adequately describe benzodiazepam compounds.

Also, with regard to claim 27, the specification does not provide a reasonably representative disclosure of useful tocopherol or tocatrienol esters, analogs, and derivatives. Specifically, the specification discloses only a limited number of species at e.g. page 2, paragraph 12 and these are not viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus. By contrast, the state of the art is poorly developed with regard to the claimed subject matter, as confirmed by the specification, given that there is no general structure or definition provided. Accordingly, the specification does not appear to adequately describe tocopherol or tocatrienol esters, analogs, and derivatives.

### *Claim Rejections - 35 USC § 112 - 2nd Paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 20-22 and 25-47** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 recites "one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof, ... and one or more alcohols or glycols, or any combinations thereof". The meaning of "or any combinations thereof" is unclear when the phrase "one or more" is already included and would to include combinations of tocopherols and tocotrienols as well as combinations of alcohols or glycols. Examiner suggests deleting the phrase "or any combination thereof".

***Claim Rejections – 35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

**Claims 20-24 and 27-45** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sonne (U.S. 6,193,985- See IDS dated 9/16/2009).

Sonne teaches tocopherol compositions for the delivery of biologically active agents which are only sparingly soluble in water (col. 1, lines 7-13), such as diazepam (col. 1, lines 7-14). One particular nasal formulation contains 5g of diazepam, 44 g Tenox GT2 (70% tocopherol), 5 g Vitamin E TPGS, 1.45 g Pluronic and 0.1g benzalkonium chloride (example 1 at col. 7, lines 32-45). In preparing the formulation, the ingredients are heated slowly until a homogeneous phase is achieved (Sonne also teaches that co-solvent such as ethanol, benzyl alcohol, sesame oil and propylene glycol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53). When ethanol is used in the formulations, it may be used in an amount of about 11% by weight of the formulation (See example 3 at col.8, lines 28-43). When sesame oil is used, it may be used in an amount of about 44% (example18, col12, lines 37-51) or about 60% (example 16 at col.12, lines 10-17). α-tocopherol may be used in amounts of 20 to 99.9% (col.5, lines 56-61). The active ingredient should be present in an amount of 0.001% to 40% (col.5, lines 55-61). Diazepam may be present at about 5% by weight (example 11 at col. 11, lines 1-13). Preservative as well as odor masking compounds may be included in the (col.7, lines 4-12). The

composition may be in the form of a spray formulation (col. 6, lines 28-35). In general, administration to the nose can be difficult because of the limited volume which is acceptable for the nose, which is about 100μL (col.7, lines 25-30).

The prior art does not appear to provide sufficient specificity, i.e., involves too much "picking and choosing" to give rise to anticipation. See *Corning Glass Works v. Sumitomo Elec.*, 868 F.2d 1251, 1262 (Fed. Circ. 1989). That being said, it must be remembered that "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect…. the combination is obvious". *KSR v. Teleflex*, 127 S.Ct. 1727, 1740 (2007) (quoting *Sakraida v. A.G. Pro*, 425 U.S. 273, 282 (1976)). Consistent with this reasoning, it would have obvious to one of ordinary skill in the art to have selected the various combinations of features claimed from within the prior art disclosure (specifically, diazepam, alcohol or glycol, and α-tocopherol) to arrive at the instantly claimed subject matter. Specifically, it would have been obvious to choose an alcohol or glycol as as the co-solvent, given that both are taught as possible cosolvents and to include α-tocopherol given that it is taught to be included in the compositions in amounts of 20 to 99.9%.

For the purposes of applying prior art and absent a limiting definition by the specification, the term "about" will be interpreted broadly. The scope of term may be considerable where the components of the respective compositions merely perform substantially the same function in substantially the same manner:

> As we have held, because of the way that the patentee has used the word 'about' in the context of the written description and the claims in this case construction of the term 'about 30 um' requires consideration of the purpose or 'criticality' of the limitation to the invention… As our construction makes clear, 'about 30 um' encompasses particle diameters that perform the same function, in the same way, with the same result as the 30 um particles, as long as those diameters are within the range left open by the specific disclosures of the specification.

Cohesive Technologies v. Waters Corp., 88 USPQ2d 1903, 1916 (Fed. Cir. 2008)

Here, with regard to instant claim 36, the range of about 25% to about 40% is interpreted to include 44% co-surfactant as taught by Sonne. Note Sonne also teaches alcohols and glycols are suitable co-surfactants.

Further, given that administration to the nose is taught to be difficult because of the limited volume which is acceptable for the nose, it would have been obvious to one of ordinary skill in the art to administer the nasal spray to both nostrils in order to maximize the acceptable volume. Similarly, it would have been obvious to one of ordinary skill in the art to repeat the administration once a previously administered volume was absorbed.

**Claims 25, 26, 46 and 47** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sonne (U.S. 6,193,985) in view of Meezan (U.S. 2006/0046962).

Sonne is discussed above, but does not teach the addition of a alkyl glycoside in an amount from 0.01% to 1%.

Meezan teaches that alkyl glycosidase is an absorption enhancer for drug administration (¶150). Specifically, Meezan demonstrates that the addition of 0.25% of alkyl glycoside can increase drug absorption from about 3% bioavailabilty to about 90% bioavailability when the drug is administered via a nasal spray. Meezan further teaches that the active ingredient for the nasal spray may be in the form of nanoparticles (¶63).

Meezan does not teach using a benzodiazapine active ingredient.

It would have been obvious to one of ordinary skill in the art to incorporate the alkyl glycosidase of Meezan into the nasal spray of Sonne in order to increase absorption, and thus the bioavailability, of the active ingredient.

It would have also been obvious to include the active ingredient in the form of nanoparticles, given that such a form is taught to be suitable by Meezan. Further, one of ordinary skill in the art would recognize

that smaller active ingredient particles are typically more bioavailable than larger particles of active ingredient due to the smaller particles having increased surface area.

***Nonstatutory Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Claims 20-47** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-19, 22, 23, 26, 27, 30 and 31 of copending Application No. 12/116,842 in view of Sonne (U.S. 6,193,985) and Meezan (U.S. 2006/0046962).

| Notice of References Cited | Application/Control No. 12/413,439 | Applicant(s)/Patent Under Reexamination CARTT ET AL. | |
|---|---|---|---|
| | Examiner ADAM C. MILLIGAN | Art Unit 1612 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-2006/0046962 | 03-2006 | Meezan et al. | 514/012 |
| | B | US- | | | |
| | C | US- | | | |
| | D | US- | | | |
| | E | US- | | | |
| | F | US- | | | |
| | G | US- | | | |
| | H | US- | | | |
| | I | US- | | | |
| | J | US- | | | |
| | K | US- | | | |
| | L | US- | | | |
| | M | US- | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
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| | N | | | | | |
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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
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| | U | |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 12413439 | CARTT ET AL. |
| | **Examiner** | **Art Unit** |
| | ADAM C MILLIGAN | 1612 |

## SEARCHED

| Class | Subclass | Date | Examiner |
|---|---|---|---|
| | | | |

## SEARCH NOTES

| Search Notes | Date | Examiner |
|---|---|---|
| Palm Inventor Search | 3/11/2011 | AM |
| EAST Search - see attached search history | 3/11/2011 | AM |
| NPL Search - caplus (benzodiazepine and alcohol or glycol and tocopherol or tocatrienol) | 3/11/2011 | AM |

## INTERFERENCE SEARCH

| Class | Subclass | Date | Examiner |
|---|---|---|---|
| | | | |

PTO/SB/08 (01-08)
Approved for use through 05/31/2008. OMB 0651-0031
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| Substitute for form 1449/PTO | | | | Complete if Known | |
|---|---|---|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)* | | | | Application Number | 12/413,439 |
| | | | | Filing Date | March 27, 2009 |
| | | | | First Named Inventor | Steve Cartt |
| | | | | Art Unit | 1614 |
| | | | | Examiner Name | Ardin H. Marschel |
| Sheet | 1 | Of | 1 | Attorney Docket Number | 35401-716.201 |

**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] |
|---|---|---|---|---|---|---|
| | 1. | WO-2005-044234 A2 | 05-19-2005 | Elan Pharma | | |

**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[6] |
|---|---|---|---|
| | 2. | WERMELING et al., "Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers," Anesthesia & Analgesia 103(2):344-349 (2006) | |
| | 3. | EP08747813 Supplementary Search Report dated June 2, 2010 | |

| Examiner Signature | /Adam Milligan/ | Date Considered | 03/14/2011 |
|---|---|---|---|

*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.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
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PTO/SB/08 (01-08)
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| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)* | | | | Application Number | 12/413,439 |
| | | | | Filing Date | March 27, 2009 |
| | | | | First Named Inventor | Steve Cartt |
| | | | | Art Unit | 1614 |
| | | | | Examiner Name | Not Yet Assigned |
| Sheet | 1 | Of | 3 | Attorney Docket Number | 35401-716.201 |

## 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 |
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| Examiner Signature | /Adam Milligan/ | Date Considered | 03/14/2011 |
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|---|---|---|---|---|---|
| | | | | Application Number | 12/413,439 |
| | | | | Filing Date | March 27, 2009 |
| | | | | First Named Inventor | Steve Cartt |
| | | | | Art Unit | 1614 |
| | | | | Examiner Name | Not Yet Assigned |
| Sheet | 2 | Of | 3 | Attorney Docket Number | 35401-716.201 |

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|---|---|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Document Number<br>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 |
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| Examiner Signature | /Adam Milligan/ | Date Considered | 03/14/2011 |
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**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[6] |
|---|---|---|---|
| | 47. | PCT/US08/62961 Search Report dated 7/25/08 | |

| Examiner Signature | /Adam Milligan/ | Date Considered | 03/14/2011 |
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| | | | | Art Unit | 1614 |
| | | | | Examiner Name | Ardin H. Marschel |
| Sheet | 1 | Of | 1 | Attorney Docket Number | 35401-716.201 |

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|---|---|---|---|---|---|---|
| | 1. | WO-2007-043057 A2 | 04-19-2007 | Touitou, Elka et al. | | |
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**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[6] |
|---|---|---|---|
| | 5. | PCT/US09/38696 Search Report dated 9/28/09 | |

| Examiner Signature | /Adam Milligan/ | Date Considered | 03/14/2011 |
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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | |
|---|---|
| In re the Patent Application of:<br><br>Applicant: Steve Cartt<br><br>Serial No.: 12/413,439<br><br>Filed: 03/27/2009<br><br>Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS | Confirmation No.: 9049<br><br>Group Art Unit: 1612<br><br>Examiner: Milligan, Adam C.<br><br>Certificate of Electronic Filing<br><br>I hereby certify that the attached Response to Office Action and all marked attachments are being deposited by Electronic Filing on September 19, 2011 by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.<br><br>By: Linda Anders<br>Linda Anders |

Dear Sir/Madam:

## RESPONSE TO OFFICE ACTION DATED MARCH 18, 2011

Applicant hereby submits a timely response to the Office Action mailed March 18, 2011, in the above referenced application. Applicants also submit herewith a three (3) month extension of time and the requisite fee. In the event any additional fees are due, please charge to Deposit Account No. 23-2415, referencing Docket No. 35401-716.201.

**Amendments to the claims** begin on page **2** of this paper.
**Remarks** begin on page 8 of this paper.

## CLAIMS

**Amendments to the Claims**

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicants reserve the right to pursue the subject matter of the withdrawn claim in this or any other appropriate patent application.

1. (Withdrawn) A pharmaceutical composition for nasal administration comprising:

(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); and

(c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w),

in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient.

2. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The pharmaceutical composition 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, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

4. (Withdrawn) The pharmaceutical composition of claim 3, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

5. (Withdrawn) The pharmaceutical composition of claim 1, wherein the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof.

6. (Withdrawn) The pharmaceutical composition of claim 5, wherein the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm.

7. (Withdrawn) The pharmaceutical composition of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: $\alpha$-tocopherol, $\beta$-tocopherol, $\gamma$-tocopherol, $\delta$-tocopherol, $\alpha$-tocotrienol, $\beta$- tocotrienol, $\gamma$- tocotrienol, $\delta$- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

8. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The pharmaceutical composition of claim 1, wherein the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.

10. (Withdrawn) The pharmaceutical composition of claim 1, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 1 mg/mL to about 600 mg/mL.

11. (Withdrawn) The pharmaceutical composition of claim 1, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 10 mg/mL to about 250 mg/mL.

12. (Withdrawn) The pharmaceutical composition of claim 11, wherein the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 50 mg/mL.

13. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The pharmaceutical composition of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 60% to about 75% (w/w).

15. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The pharmaceutical composition 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. (Withdrawn) The composition of one of claims 1 - 16, further comprising at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

18. (Withdrawn) The composition of claim 1, wherein the pharmaceutically-acceptable formulation comprises at least about 0.01% (w/w) of an alkyl glycoside.

19. (Withdrawn) The composition of claim 18, wherein the pharmaceutically-acceptable formulation about 0.01% to 1% (w/w) of an alkyl glycoside.

20. (Currently Amended) A method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising:

~~(a)~~ administering to one or more nasal mucosal membranes of a patient a pharmaceutical ~~composition~~ solution for nasal administration ~~comprising~~ 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), and one or more alcohols or glycols, ~~or any combinations thereof,~~ in an amount from about 10% to about 70% (w/w) and optionally one or more alkyl glycosides.

21. (Original) The method of claim 20, 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).

22. (Original) The method of claim 21, wherein said patient is a human.

23. (Original) The method of claim 20, 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, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

24. (Original) The method of claim 23, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

25. (Canceled)

26. (Canceled)

27. (Original) The method of claim 20, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: $\alpha$-tocopherol, $\beta$-tocopherol, $\gamma$-tocopherol, $\delta$-tocopherol, $\alpha$-tocotrienol, $\beta$- tocotrienol, $\gamma$- tocotrienol, $\delta$- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

28. (Original) The method of claim 20, 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.

29. (Original) The method of claim 20, wherein the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.

30. (Currently Amended) The method of claim 20, wherein the benzodiazepine drug is present in the pharmaceutical ~~composition~~ solution in a concentration from about 1 mg/mL to about 600 mg/mL.

31. (Currently Amended) The method of claim 30, wherein the benzodiazepine drug is present in the pharmaceutical ~~composition~~ solution in a concentration of from about 10 mg/mL to about 250 mg/mL.

32. (Currently Amended) The method of claim 31, wherein the benzodiazepine drug is present in the pharmaceutical ~~composition~~ solution in a concentration of from about 20 mg/mL to about 50 mg/mL.

33. (Currently Amended) The method of claim 20, wherein the pharmaceutical ~~composition~~ 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).

34. (Currently Amended) The method claim 33, wherein the pharmaceutical ~~composition~~ 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).

35. (Currently Amended) The method of claim 20, wherein the pharmaceutical ~~composition~~ solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w).

36. (Currently Amended) The method of claim 35, wherein the pharmaceutical ~~composition~~ solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w).

37. (Canceled)

38. (Currently Amended) The method of claim 20, wherein the pharmaceutical ~~composition~~ solution is ~~in~~ a pharmaceutically-acceptable spray formulation.

39. (Original) The method of claim 38, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.

40. (Currently Amended) The method of claim 39, wherein said pharmaceutical ~~composition~~ solution is ~~in~~ a pharmaceutically-acceptable spray formulation having volume from about 10 $\mu$L to about 200 $\mu$L.

41. (Currently Amended) The method of claim 40, wherein the administration of the pharmaceutical ~~composition~~ solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril.

42. (Currently Amended) The method of claim 40, wherein the administration of the pharmaceutical ~~composition~~ solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.

43. (Currently Amended) The method of claim 42, wherein the administration of the pharmaceutical ~~composition~~ solution comprises spraying a first quantity of the pharmaceutical ~~composition~~ solution into the first nostril, spraying a second quantity of the pharmaceutical ~~composition~~ solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical ~~composition~~ solution into the first nostril.

44. (Currently Amended) The method of claim 43, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical ~~composition~~ solution to the second nostril.

45. (Currently Amended) The method of claim 43, wherein nasal administration of the pharmaceutical ~~composition~~ solution begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical composition.

46. (Curently Amended) The method of claim 20, wherein the ~~pharmaceutically acceptable formulation comprises~~ pharmaceutical solution contains at least about 0.01% (w/w) of an alkyl glycoside.

47. (Currently Amended) The method of ~~claim 21~~ claim 20, wherein the ~~pharmaceutically acceptable formulation~~ pharmaceutical solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.

48. (New) The method of claim 20, wherein the pharmaceutical solution consists of diazepam, vitamin E, ethanol and optionally an alkyl glycoside.

49. (New) The method of claim 48, wherein the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof.

50. (New) The method of claim 49, wherein the alkyl glycoside is dodecyl maltoside.

## REMARKS

Upon entry of the foregoing amendment, claim 20 has been amended to recite 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, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and optionally one or more alkyl glycosides. Claims 30-36, 38 and 40-47, which depend from claim 20 have been amended to conform to the language of claim 20. New claims 48-50 are directed to the elected species of a diazepam, Vitamin E, ethanol and dodecyl maltoside. Support for the claim amendments are found throughout the original specification, including paragraphs [044], [0194]-[0199] and [209]. Claims 25, 26 and 37 are canceled. Claims 1-19 are withdrawn as being drawn to non-elected subject matter. Thus, claims are 20-24, 27-36 and 38-50 are pending and under consideration.

**Response to § 112, First Paragraph, Written Description Rejection**

Claims 20-47 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Office Action, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

According to the Office Action, "benzodiazepine 'compounds'" represent a "potentially huge genus inclusive of many different compounds having widely divergent structures and functions. According to the Office Action, "the specification discloses only a limited number of species at e.g. page 4, paragraph 20," which are not considered to be reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific examples of the claimed genus. According to the Office Action, the state of the art is "poorly developed" with regard to the claimed subject matter, "given that there is no general structure or definition

provided." Thus, the Office Action concludes that the specification "does not appear to adequately describe benzodiazepine compounds."

The Office Action raises similar objections to the use of "tocopherol or tocotrienol esters, analogs and derivatives." Again, the Office Action alleges that "only a limited number of species" of such compounds are disclosed, "given that there is no general structure or definition provided." Thus, according to the Office Action, "the specification does not appear to adequately describe tocopherol or tocatrienol esters, analogs and derivatives."

Applicants traverse the Written Description rejection. The M.P.E.P. clearly states that what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. M.P.E.P. § 2163 (citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94 and *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005)("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.)

First, the Office Action evinces an incorrect interpretation of the claims in that it reads the term "benzodiazepine drug" in claim 20 as "benzodiazepine compounds." Whatever the merits of the Office Action's position with respect to "benzodiazepine compounds", the term used in the claims is "benzodiazepine drug", which is more than adequately described in the specification. Representative benzodiazepine drugs described in *e.g.* paragraph 37, 49, 71, 77-126, 177-193. Not only are the structures of such benzodiazepines generically described in paragraph 126 of the specification, several benzodiazepine drugs are known and described in the specification. For example, in paragraph 78, alprazolam is described as a benzodiazepine drug having sedative, tranquilizing, muscle relaxing and anxiolytic properties. In paragraph 84, diazepam is described as a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. In paragraph 90 flurazepam is described as a benzodiazepine drug having sedative (especially soporific and hypnotic), anxiolytic, anticonvulsant and muscle relaxing properties. In paragraph 96, lorazepam is described as a benzodiazepine drug having sedative, tranquilizing,

anticonvulsant, amnesic and muscle relaxing properties. The activities and structures of medazepam, mexazolam, midazolam and temazepam are also described. Dosages and indications for each of these benzodiazepine drugs are described in paragraphs 77-125.

The Office Action cites *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir. 2004) in support of the Written Description rejection. However, this case can be distinguished from *Rochester* on its facts. In *Rochester*, the patent's claims were directed to a compound having particular (COX-II inhibitory) activity, yet the patent's specification did not describe a single chemical species possessing that particular activity. In contrast, Applicants have provided several examples of particular benzodiazepine drugs, and have in fact recited several such examples in particular dependent claims (see claims 23 and 48). Moreover, as clearly described in paragraph 126, benzodiazepines possess a common structural core. Moreover, the activity of benzodiazepine drugs is both well-known and adequately described in the specification. Given that each of the exemplified benzodiazepine drugs is known to the person skilled in the art, the current case bears no resemblance to that of *Rochester*. Rather, the genus of benzodiazepine drugs is well-known, and Applicants should not have had to describe that which is well-known beyond what is necessary for the person skilled in the art to know what the Applicant's invention is. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

The same reasoning applies to "tocopherol or tocotrienol esters, analogs and derivatives." Again, the Office Action alleges that "only a limited number of species" of such compounds are disclosed, "given that there is no general structure or definition provided." However, Applicants need not describe that which is well-known in the art. Tocopherols are described in general in paragraphs [0130]-[0133], with several well-known species of tocopherols described therein (*e.g.* $\alpha$-tocopherol, $\beta$-tocopherol, $\gamma$-tocopherol and $\delta$-tocopherol). Several species of tocotrienols are also described (*e.g.* $\alpha$-tocotrienol, $\beta$-tocotrienol, $\gamma$-tocotrienol and $\delta$-tocotrienol). Paragraph [0130] states that tocopherols and tocotrienols can be used in the compositions and methods of the invention, and there is nothing in the record that contradicts this plain statement of the Applicants. Again, it is noted that the inventors need not

(and preferably will not) describe that which is well-known in the art. *Hybritech*, 802 F.2d at 1379-80, 231 USPQ at 90. And again, this case is easily distinguished from *Rochester* in that the specification clearly sets forth several extant examples of species within the claimed genus, whereas in *Rochester* there was not even one such extant species.

In considering the claims as a whole, the instant case is distinguishable from *Rochester* in that the specification describes specific examples of solutions falling within the claims. Example 1, for instance, sets forth a solution formulation consisting of diazepam, $\alpha$-tocopherol and ethanol. Example 3 describes a solution formulation consisting of diazepam, Vitamin E USP and dehydrated ethanol USP. The example also states that other ingredients, such as alkyl glycoside, can be added at a suitable step in the process. Evidence that these solutions were actually prepared and characterized can be seen in Example 5, where the stability of solutions according to the invention are characterized. Solutions 00-70 and 02-70 were actually prepared and tested. The existence of such solutions, coupled with the detailed description in the other parts of the specification, is adequate evidence that the Applicants possessed the invention at the time the application was made. At the very least, they suffice to distinguish the instant case from that of *Rochester*, in which there were no species that satisfied the claim language described in the specification, and there was no teaching of how to make species falling within the claimed genus.

At least for the reasons set forth above, Applicants submit that the § 112, first paragraph rejection for lack of written description is untenable and should be withdrawn. Such action is requested for all of the pending claims.

The foregoing arguments are considered relevant to all the pending claims. In addition, Applicants submit that the rejection should not apply to new claims 48-50. The new claims are directed to the pharmaceutical solution consisting of diazepam, vitamin E, ethanol and optionally an alkyl glycoside. Each of the constituents of the claims is well-known, described in the specification, and exemplified as discussed in detail above. There is no reason for the person skilled in the art to question whether Applicants possessed the invention of claims 48-

50. Accordingly, there should be no rejection of claims 48-50 for lack of written description under § 112, first paragraph.

**Response to § 103(a) Obviousness Rejections**

***The pending claims are not obvious over of Sonne within the meaning of 35 U.S.C. § 103(a)***

Claims 20-24 and 27-45 were rejected under 35 U.S.C. § 1039a) as being unpatentable over Sonne (U.S. 6,193,985). Applicants traverse this rejection.

Current claim 20 reads:

> 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, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and optionally one or more alkyl glycosides.

As can be seen in claim 20, the solution recited in claim 20 consists of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols and optionally one or more alkyl glycosides. In other words, the recited solution contains: each of a benzodiazepin drug; one or more tocopherols or tocotrienols; one or more alcohols or glycols; and optionally one or more alkylglycosides; and the solution excludes anything else. In particular, the solution excludes water and oil.

Sonne fails to teach nasal administration of a solution consisting of benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols and optionally one or more alkyl glycosides. While Sonne speaks of dissolving a substantially water-insoluble or sparingly water-soluble biologically active agent in tocopherol or a derivative thereof, Sonne also teaches that addition of co-solvents such as ethanol is less desired, since such solutions "tend to be irritating to certain mucosal tissues." Col. 3, lines 1-4

and 65-67. Thus, the bulk of Sonne's description relates to preparation of emulsions, which necessarily include oil and water. See col. 4, line 1 through col. 7, line 12 and Examples 1-3, 5-10, 15, 17, 19, 21. Indeed, consistent with Sonne's general teaching at column 3, lines 65-67, none of the Examples taught by Sonne suggest nasal administration of a benzodiazepine drug formulation that contains only tocopherol or tocotrienol, a alcohol and optionally an alkylglcoside.

Sonne teaches specific benzodiazepine formulations in Examples 1-3, 7-11, 17-19 and 22-23. Of these, Examples 1-3, 7-11, 17, 19 and 22-23 each describe an oil-in-water emulsion of the benzodiazepine. Such emulsions are specifically excluded from the instant claims, which recite solutions (not emulsions) and exclude any ingredients (such as water and oil) not included within the group of benzodiazepine drugs, tocopherols or tocotrienols, alcohols or glycols, and optionally alkyglycosides. Of the remaining examples, Example 18 is a solution of alprazolam in $\alpha$-tocopherol in sesame oil for oral administration. Thus, each of the benzodiazepine compositions taught by Sonne contains oil in some form or another.

The person of ordinary skill in the art would not have found it obvious to practice the method of the instant claims, which requires 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, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and optionally one or more alkyl glycosides. Sonne counsels against administering alcohol-containing solutions to certain mucosal tissues. Col. 3, lines 65-67. Sonne teaches emulsions as lower viscosity formulations for nasal administration. Col. 3, line 60 through col. 4, line 2. Indeed, Sonne specifically teaches that 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." Col. 4, lines 14-16. In teaching that a high concentration of oil phase is required for nasal administration, Sonne is teaching away from nasal administration of compositions that contain no oil whatsoever. Thus, Sonne teaches away from the claimed methods.

This teaching away is underscored by the fact that none of Sonne's examples is drawn to a nasally-administered solution consisting of sparingly water soluble active, tocopherol or tocotrienol, alcohol or glycol and optionally an alkyl glycoside. Examples 1-3, 7-11, 17, 19 and 22-23 each describe an oil-in-water emulsion of a benzodiazepine for nasal administration. Example 4 concerns a nasal formulation of cinnarizine as an oil-in-water emulsion. Example 5 is an oral formulation of miconazole. Example 6 is a vaginal composition of miconazole. Each of these miconazole formulations is an oil-in-water emulsion. Example 11 is an oral solution of diazepam, $\alpha$-tocopherol and triacetin (or "glycerine triacetate" a tri-esterified form of glycerine). Example 12 is an oil-based formulation of cinnarizine for oral administration consisting of cinnarizine, $\alpha$-tocopherol, ethanol and fractionated coconut oil. Example 13 is cinnarizine in $\alpha$-tocopherol for oral administration. Example 14 is another oral formulation containing miconazole, $\alpha$-tocopherol and ethanol. Examples 16 and 17 are oil-containing formulations of budesonide. Example 16 is an oil-in-water emulsion containing budesonide, while Example 17 consists of budesonide, $\alpha$-tocopherol and sesame oil. Example 18 is an oral solution consisting of alprazolam, $\alpha$-tocopherol and sesame oil. Example 20 is an oral solution of disulfram and $\alpha$-tocopherol.

The person of skill in the art would reasonably infer from the teachings of column 3, lines 65-67 and the various examples that nasal formulations should be oil-in-water formulations, with a high concentration of oil. The person of ordinary skill would not have been led to the instant method of treatment, which requires administration to the nasal mucosa of a pharmaceutical <u>solution</u> for nasal administration <u>consisting of</u> a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and optionally one or more alkyl glycosides.

For at least the foregoing reasons, Applicants submit that claims 20-24 and 27-45 are not rendered obvious by Sonne. Withdrawal of the rejection is therefore respectfully requested.

For at least the reasons given above, Applicants submit that claims 48-50 are not obvious in view of the teaching of Sonne and should not be subjected to the outstanding rejection.

***The pending claims are not obvious over the combination of Sonne and Meezan within the meaning of 35 U.S.C. § 103(a)***

Claims 25, 26, 46 and 47 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sonne in view of Meezan (U.S. 2006/0046962). Applicants traverse this rejection.

As Applicants understand the rejection, Sonne was relied upon for its teaching as discussed in the foregoing discussion and that Meezan was relied upon for its teaching of alkyl glycosides as penetration enhancers. Applicants submit that claims 25, 26, 46 and 47 would not have been obvious to one of ordinary skill in the art for at least the same reasons as set forth in the discussion above. Furthermore, Applicants submit that the Examiner has failed to adequately articulate a reason, design need, market pressure, teaching suggestion or motivation that would have led the person of ordinary skill in the art to combine the references in the manner prescribed in the Office Action. Accordingly, Applicants submit that this rejection is untenable and should be withdrawn.

First, Applicants traverse this rejection because, as explained above, the Sonne reference fails to teach a method of *e.g.* claim 20, and Meezan fails to provide a reason, design need or market pressure, teaching suggestion or motivation such that the person of ordinary skill in the art would have found the method of *e.g.* claim 20 obvious. Since claim 20 is the basis for claims 25, 26, 46 and 47, each of these claims includes the limitations of claim 20. As argued above, Sonne fails to render obvious method comprising administering to one or more nasal mucosal membranes of a patient a pharmaceutical <u>solution</u> for nasal administration <u>consisting of</u> a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and optionally one or more alkyl glycosides. Meezan fails to provide any teaching, suggestion or motivation to modify the

teaching of Sonne to arrive at such a method. Moreover, Meezan fails to provide any reason why the person of ordinary skill in the art would carry out such a method. Meezan also fails to identify a design need or market pressure to provide such a method. Accordingly, the rejection of claims 25, 26, 46 and 47 as being obvious over Sonne and Meezan is untenable essentially for the reasons already articulated above, with the additional reason that Meezan adds nothing to the teaching of Sonne that would render obvious claim 20, from which claims 25, 26, 46 and 47 ultimately depend. For at least this reason alone, Applicants submit that the rejection of claims 25, 26, 46 and 47 is untenable and should be withdrawn.

Moreover, the person of ordinary skill in the art would not have combined the references as suggested in the Office Action. There is no identified reason, design need or market pressure to do so. Neither Sonne nor Meezan teaches or suggests that there was a reason for the person of ordinary skill in the art to prepare a composition consisting of a benzodiazepine drug, one or more tocopherols or tocotrienols, one or more alcohols or glycols, and one or more alkyl glycosides. There is no design need identified in either reference, as Sonne does not suggest that there was a need for a penetration enhancer and Meezan does not suggest that alkyl glycosides assist benzodiazepines in crossing the nasal mucosa. There was no identified market pressure to produce a benzodiazepine solution comprising alkyl glycosides.

Contrary to the position implied in the Office Action, Meezan does not teach that nasal co-administration of alkyl glycoside and <u>any</u> drug increases bioavailability from 3% to 90%. Rather, in the very specific instance of calcitonin (a polypeptide of 32 amino acids having a molecular weight of 3454.93 grams/mole) such dramatic increases in bioavailability were seen. Benzodiazepines are not polypeptides, and their molecular weights differ from that of calcitonin by about an order of magnitude. There is no teaching or suggestion in Meezan that alkyl glycosides would enhance the nasal bioavailability of benzodiazepines, nor does Meezan identify a design need or market pressure to enhance the nasal bioavailability of benzodiazepines by co-administering benzodiazepine and an alkyl glycoside. Sonne is completely silent with respect to the need to provide additional penetration enhancing aside

from what may be provided by vitamin E. Col. 2, 46-49. One of ordinary skill in the art would have inferred no design need or market pressure to combine the penetration enhancers of Meezan with the Sonne's compositions.

In view of the complete failure to identify any reason to combine the references, any design need or market pressure to do so, or any teaching, suggestion or motivation in the prior art to suggest the combination, Applicants submit that the combination of references is improper and the obviousness rejection is therefore untenable. *Unigene Laboratories Inc. v. Apotex Inc.* 2010-1006, slip op. at 14 (Fed. Cir., August 25, 2011)(citing *KSR Int'l Co. v Teleflex Inc.,* 550 U.S. 398, 418 (2007)). Accordingly, the rejection is untenable and should be withdrawn. *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998). Such action is respectfully requested.

**Response to Obviousness-Type Double Patenting Rejection**

Claims 20-47 were ***provisionally*** rejected on the basis of the judge-made rule of obviousness double patenting over claims 17-19, 22, 23, 26, 27, 30 and 31 of copending application number 12/116,842 in view of Sonne and Meezan. Applicants traverse this rejection. There is no reasoned basis given for the rejection, as the Office Action unexpectedly terminates at page 12. Thus the Office Action omits the required reasoned basis for the rejection. In any case, Applicants note that the rejection is *provisional,* and may be withdrawn if such action is warranted by the progress of the claims in the parallel application. Applicants traverse the rejection for lack of reasoned basis, but note that if conditions warrant its being repeated, it may be overcome by submission of a duly filed terminal disclaimer, as the applications in question were and are commonly owned.

## CONCLUSION

Applicant timely submits these remarks in response to the Office Communication dated March 18, 2011. In the event that fees are due in connection with the filing of this response, please charge the necessary fees to Deposit Account No. 23-2415 referencing Docket No. 35401-716.201. Should the examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (858) 350-2332.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
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Date: September 19, 2011

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# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 12413439 |
| **Filing Date:** | 27-Mar-2009 |
| **Title of Invention:** | ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS |
| **First Named Inventor/Applicant Name:** | Steve Cartt |
| **Filer:** | Peter R. Munson./Linda Anders/MG |
| **Attorney Docket Number:** | 35401-716.201 |

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 | 555 | 555 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **555** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 10976845 |
| **Application Number:** | 12413439 |
| **International Application Number:** | |
| **Confirmation Number:** | 9049 |
| **Title of Invention:** | ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS |
| **First Named Inventor/Applicant Name:** | Steve Cartt |
| **Customer Number:** | 21971 |
| **Filer:** | Peter R. Munson./Linda Anders/MG |
| **Filer Authorized By:** | Peter R. Munson. |
| **Attorney Docket Number:** | 35401-716.201 |
| **Receipt Date:** | 19-SEP-2011 |
| **Filing Date:** | 27-MAR-2009 |
| **Time Stamp:** | 13:58:49 |
| **Application Type:** | Utility under 35 USC 111(a) |

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| Submitted with Payment | yes |
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## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 35401-716-201-response.pdf | 899827<br>1c748bffbac7fc6c0356d7a07b841c6cc431450d | yes | 18 |
| | **Multipart Description/PDF files in .zip description** | | | | |
| | **Document Description** | | **Start** | **End** | |
| | Amendment/Req. Reconsideration-After Non-Final Reject | | 1 | 1 | |
| | Amendment Copy Claims/Response to Suggested Claims | | 2 | 7 | |
| | Applicant Arguments/Remarks Made in an Amendment | | 8 | 18 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 30088<br>e30569783951f5cd62ed8b43236cd05f40fa79ed | no | 2 |
| **Warnings:** | | | | | |
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**<u>New Applications Under 35 U.S.C. 111</u>**
**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.**

**<u>National Stage of an International Application under 35 U.S.C. 371</u>**
**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.**

**<u>New International Application Filed with the USPTO as a Receiving Office</u>**
**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.**

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# PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

| Application or Docket Number | Filing Date | |
|---|---|---|
| 12/413,439 | 03/27/2009 | ☐ To be Mailed |

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY ☒ RATE ($) | SMALL ENTITY FEE ($) | OR | OTHER THAN SMALL ENTITY RATE ($) | OTHER THAN SMALL ENTITY FEE ($) |
|---|---|---|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | | | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | | | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | | OR | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | | | 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 $250 ($125 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 | | | TOTAL | |

## APPLICATION AS AMENDED – PART II

AMENDMENT 09/19/2011

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE ($) | SMALL ENTITY ADDITIONAL FEE ($) | OR | OTHER THAN SMALL ENTITY RATE ($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * 47 | Minus | ** 62 | = 0 | X $26 = | 0 | OR | X $ = | |
| Independent (37 CFR 1.16(h)) | * 2 | Minus | ***3 | = 0 | X $110 = | 0 | OR | X $ = | |
| ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | 0 | OR | TOTAL ADD'L FEE | |

AMENDMENT

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) | | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | | OR | X $ = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | | OR | X $ = | |
| ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/DIANE JOHNSON/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

UNITED STATES PATENT AND TRADEMARK OFFICE

**UNITED STATES DEPARTMENT OF COMMERCE**
**United States Patent and Trademark Office**
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Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/413,439 | 03/27/2009 | Steve Cartt | 35401-716.201 | 9049 |

21971 7590 11/21/2011
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 |
|---|---|
| 11/21/2011 | 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. | Applicant(s) | |
|---|---|---|---|
| | 12/413,439 | CARTT ET AL. | |
| | Examiner | Art Unit | |
| | ADAM C. MILLIGAN | 1612 | |

***-- 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 3 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 19 September 2011.

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) 1-24,27-36 and 38-50 is/are pending in the application.

5a) Of the above claim(s) 1-19 is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) 20-24,27-36 and 38-50 is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**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).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

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.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' arguments, filed 9/19/2011, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Claim Rejections - 35 USC § 103*

**Claims 20-24, 27-36, 38-45 and 48** stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sonne (U.S. 6,193,985- See IDS dated 9/16/2009).

Applicants argue that Sonne teaches the addition of co-solvents such as ethanol is less desired since such solutions tend to be irritating to certain mucosal tissues. Applicants also argue that the bulk of Sonne's description, as well as the examples provided, relate to the preparation of emulsions, which necessarily include oil and water. Further, none of the examples taught by Sonne teach nasal administration of a drug formulation that contains only tocopherol or tocotrienol, an alcohol and optionally one or more alkyl glycosides. Specifically, Applicants cite Sonne for allegedly teaching away from the instant invention by stating "due to the small administration volume required, it has generally been found that a high concentration of the oil (or lipid) phase is required".

Examiner disagrees. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843

(Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Here, the broad disclosure of Sonne teaches that the “compositions of the invention may be used directly as solution of bioactive agents in the tocopherol solvent” (col.3, lines 60-61) and "[v]iscosity can be reduced by the addition of co-solvents such as ethanol (col.3, lines 65-66). Sonne teaches that “transmucosal delivery is preferred" (col.3, line 54) and "[n]asal...administrations are particularly preferred" (col.3, lines 58-59). The compositions of the invention may contain from 1-99.99% tocopherol (col.5, lines 55-57). Sonne also teaches that a co-solvent such as ethanol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53). When ethanol is used in the formulations, ethanol may be present in an amount of about 11% by weight of the formulation (See e.g. example 3 at col.8, lines 28-43). Thus, one of ordinary skill in the art would have found it obvious to nasally administer a composition that contains only tocopherol or tocotrienol, an alcohol and optionally one or more alkyl glycosides.

With regard to new claim 48, note that Sonne teaches diazepam as a suitable benzodiazepine drug (col.5, line 34).

**Claims 46, 47, 49 and 50** stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sonne (U.S. 6,193,985) in view of Meezan (U.S. 2006/0046962).

First, Applicants argue that for the reasons presented above, this rejection should be withdawn, as Meezan does not cure the deficiencies of Sonne.

Second, Applicants argue that there is no reason to combine the references given that Sonne is silent with respect to the addition of penetration enhancers aside from vitamin E.

Examiner disagrees. First, for the reasons discussed above with regard to Sonne, this rejection is maintained.

Second, Sonne teaches the possible use of Vitamin E and its derivatives as penetration enhancers. Sonne also teaches that an increased rate of absorption is preferred (col.2, lines 44-48). Thus, it would have been obvious to one of ordinary skill in the art to add an additional penetration enhancer in order to improve the rate of absorption.

With regard to new claims 49 and 50, note that Meezan teaches a preferred penetration enhancing glycoside is dodecyl maltoside. Thus, it would have been obvious to have used known penetration enhancing agents to increase the rate of absorption of the composition disclosed in Sonne.

### ***Nonstatutory Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Claims 20-24, 27-36 and 38-50** stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-19, 22, 23, 26, 27, 30 and 31 of copending Application No. 12/116,842 in view of Sonne (U.S. 6,193,985) and Meezan (U.S. 2006/0046962).

The copending application teaches a nasal spray for administering nanoparticulate benzodiazapine wherein the benzodiazapine may be diazepam.

The copending application does not teach the addition of a tocopherol is an amount of about 30 to 90% or the addition of an alcohol or glycol in an amount of about 10% to about 70%.

It would have been obvious to use a nasal spray formulation of Sonne when practicing the method of administering benzodiazepines recited in the copending 12/116,842 application given that benzodiazepines are known to have low aqueous solubility and Sonne teaches a method for delivering compounds of low aqueous solubility using co-solvents in order to yield the desired bioadhesion, sprayability, and viscosity.

Further, it would have been obvious to one of ordinary skill in the art to include the absorption enhancer taught by Meezan in order to increase the bioavailability of the active ingredient.

This is a provisional obviousness-type double patenting rejection.

Applicants argue that the rejection was cut off early and no complete reasoned basis was provided for the rejection. Nevertheless, Applicants state that since the rejection is provisional, it may be withdrawn depending on the progress of the claims in the parallel application or the filing of a terminal disclaimer.

Since the "parallel" application is still pending, the claims therein still render the instant claims obvious in view of Sonne and Meezan, and no terminal disclaimer has been filed, the instant rejection is maintained.

## *Conclusion*

No claims allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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 MILLIGAN/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 12413439 | CARTT ET AL. |
| | **Examiner** | **Art Unit** |
| | ADAM C MILLIGAN | 1612 |

## SEARCHED

| Class | Subclass | Date | Examiner |
|---|---|---|---|
| | | | |

## SEARCH NOTES

| Search Notes | Date | Examiner |
|---|---|---|
| Palm Inventor Search | 3/11/2011 | AM |
| EAST Search - see attached search history | 3/11/2011 | AM |
| NPL Search - caplus (benzodiazepine and alcohol or glycol and tocopherol or tocatrienol) | 3/11/2011 | AM |
| Updated EAST and STN Search | 11/12/2011 | AM |

## INTERFERENCE SEARCH

| Class | Subclass | Date | Examiner |
|---|---|---|---|
| | | | |

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Inventor: Steve Cartt, et al. | Group Art Unit: 1612 |
| Serial Number: 12/413,439 | Examiner: Adam C. Milligan |
| Filing Date: 03/27/2009 | **CONFIRMATION NO: 9049** |
| Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS | |

Certificate of Electronic Filing

I hereby certify that the attached Request for Correction of Inventorship and all marked attachments are being deposited by Electronic Filing on 3-30, 2012 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 Date: 3-30-2012
Linda Anders

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## REQUEST FOR CORRECTION OF INVENTORSHIP IN A PATENT APPLICATION UNDER 37 CFR §1.48

Sir:

Applicant(s) hereby request(s) that the inventorship of the above-referenced patent application be amended pursuant to 37 C.F.R. §1.48 to name only the actual inventors.

☒ The Office is requested to amend the inventorship to **ADD** the following omitted inventor(s): Edward T. Maggio

This application is a nonprovisional patent application, other than a reissue application, pursuant to 35 U.S.C. § 116.

☒ ***37 C.F.R. 1.48(a). Correction of inventorship for Nonprovisional application after the oath/declaration is filed.*** The inventive entity was set forth in error in an executed oath or declaration under 37 C.F.R. § 1.63 in a nonprovisional application. This error arose without deceptive intent on the part of the person named as an inventor in error or on the part of the person who through error was not named as an inventor.

In support of this Request, Applicant(s) provide(s):

☒ (1) A statement from each person being added as an inventor and/or from each person being deleted as an inventor that the error in inventorship occurred without deceptive intention on his or her part;

☒ (2) An oath or declaration by the actual inventor or inventors as required by 37 C.F.R. § 1.63, or as permitted by §§ 1.42, 1.43 or 1.47;;

☒ (3) The processing fee set forth in 37 C.F.R. § 1.17(i); and

☒ (4) If an assignment has been executed by any of the original named inventors, the written consent of the assignee.

☒ *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.35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: March 30, 2012

By: Peter R. Munson
Reg. No. 43,821
Attorney for Applicant

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Inventor: Steve Cartt, et al. | Group Art Unit: 1612 |
| Serial Number: 12/413,439 | Examiner: Adam C. Milligan |
| Filing Date: 03/27/2009 | **CONFIRMATION NO: 9049** |
| Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS | |

Certificate of Electronic Filing

I hereby certify that the attached Request for Correction of Inventorship and all marked attachments are being deposited by Electronic Filing 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 Date: 3-30-2012
Linda Anders

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

**STATEMENT FROM EACH PERSON BEING ADDED PURSUANT TO 37 CFR §1.48**

I, Edward T. Maggio, declare as follows:

1. Upon review of the specification and claims presently pending in the above-referenced patent application, it is my belief that I am an inventor of the claimed subject matter described in the pending patent application.

2. Upon review of the specification and claims presently pending in the above-referenced patent application, it is my belief that it is necessary to add me as an inventor to the application as a result of the addition of newly claimed subject matter.

3. The error in inventorship occurred without deceptive intent on my part.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: March 16, 2012

By: _____
Edward T. Maggio

PTO/SB/01 (10-08)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

# DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing *OR* ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16(f) required)

| | |
|---|---|
| Attorney Docket Number | 35401-716.201 |
| First Named Inventor | Steve Cartt |
| *COMPLETE IF KNOWN* | |
| Application Number | 12/413,439 |
| Filing Date | 03/27/2009 |
| Art Unit | 1614 |
| Examiner Name | Not yet assigned |

**I hereby declare that:**

(1) Each inventor's residence, mailing address, and citizenship are as stated below next to their name; and

(2) I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS**

*(Title of the Invention)*

the specification of which

☐ is attached hereto

*OR*

☒ was filed on (MM/DD/YYYY) 03/27/2009 as United States Application Number or PCT International

Application Number 12/413,439 and was amended on (MM/DD/YYYY) 09/19/2011 (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

**Authorization to Permit Access To Application by Participating Offices**

☒ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified application is filed to have access to the application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the application-as-filed with respect to: 1) the above-identified application, 2) any foreign application to which the above-identified application claims priority under 35 USC 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified US application, and 3) any U.S. application from which benefit is sought in the above-identified application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.



This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

# DECLARATION — Utility or Design Patent Application

**Claim of Foreign Priority Benefits**

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? Yes | No |
|---|---|---|---|---|---|
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

PTO/SB/01 (10-08)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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# DECLARATION — Utility or Design Patent Application

| | | | |
|---|---|---|---|
| Direct all correspondence to: | ☒ The address associated with Customer Number: | 021971 | OR ☐ Correspondence address below |
| Name | | | |
| Address | | | |
| City | State | ZIP | |
| Country | Telephone | Email @wsgr.com | |

**WARNING:**

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type or personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: *Patent Application Files*. Documents not retained in an application file (such as the PTO-2083) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: *Deposit Accounts and Electronic Funds Transfer Profiles*.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

| | | | |
|---|---|---|---|
| **NAME OF SOLE OR FIRST INVENTOR:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle [if any]) **Steve** | | Family Name or Surname **Cartt** | |
| Inventor's Signature | | | Date |
| Residence: City **Union City** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **3260 Whipple Road** | | | |
| City **Union City** | State **CA** | ZIP **94587** | Country **US** |

☒ Additional inventors or a legal representative are being named on the 2 supplemental sheet(s) PTO/SB/02A or 02LR attached hereto.

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# DECLARATION

**ADDITIONAL INVENTOR(S)**
**Supplemental Sheet**



| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any) | | Family Name or Surname | |
| **David** | | **Medeiros** | |
| Inventor's Signature | | | Date |
| Residence: City **South San Francisco** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **212 Crown Circle** | | | |
| Mailing Address | | | |
| City **South San Francisco** | State **CA** | ZIP **94080** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any)) | | Family Name or Surname | |
| GARRY ~~Gary~~ Thomas | | **Gwozdz** | |
| Inventor's Signature | | | Date |
| Residence: City JIM THORPE ~~Nazareth~~ | State **PA** | Country **US** | Citizenship **US** |
| Mailing Address ~~329 South Main Street~~ 432 PINE ST | | | |
| Mailing Address | | | |
| City JIM THORPE ~~Nazareth~~ | State **PA** | ZIP 18229 ~~18064~~ | Country **US** |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any)) | | Family Name or Surname | |
| **Andrew** | | **Loxley** | |
| Inventor's Signature | | | Date 3/23/12 |
| Residence: City **Philadelphia** | State **PA** | Country **US** | Citizenship **GB** |
| Mailing Address **126 Market Street, #5** | | | |
| City **Philadelphia** | State **PA** | ZIP **19106** | Country **US** |

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

PTO/SB/02A (07-07)
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| DECLARATION | ADDITIONAL INVENTOR(S) Supplemental Sheet Page 2 of 2 |
|---|---|

| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle (if any) | Family Name or Surname | | |
| Mark | Mitchnick | | |
| Inventor's Signature Mitch | | Date 23 March 2012 | |
| Residence: City East Hampton | State NY | Country US | Citizenship US |
| Mailing Address 80 Three Mile Harbor Drive | | | |
| City East Hampton | State NY | Zip 11937 | Country US |
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle (if any)) | Family Name or Surname | | |
| David | Hale | | |
| Inventor's Signature | | Date | |
| Residence: City San Diego | State CA | Country US | Citizenship US |
| Mailing Address 9232 Bernardo Lakes Drive | | | |
| City San Diego | State CA | Zip 92127 | Country US |
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle (if any)) | Family Name or Surname | | |
| Edward T. | Maggio | | |
| Inventor's Signature | | Date | |
| Residence: City San Diego | State CA | Country USA | Citizenship USA |
| Mailing Address 18775 Bernard Trails Drive | | | |
| Mailing Address | | | |
| City San Diego | State CA | ZIP 92128 | Country USA |

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

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# DECLARATION — Supplemental Priority Data Sheet

Foreign applications:

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? Yes | No |
|---|---|---|---|---|---|
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.*

Doc Code: OATH
Document Description: Oath or declaration filed

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# DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing *OR* ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16(f) required)

| | |
|---|---|
| Attorney Docket Number | 35401-716.201 |
| First Named Inventor | Steve Cartt |
| *COMPLETE IF KNOWN* | |
| Application Number | 12/413,439 |
| Filing Date | 03/27/2009 |
| Art Unit | 1614 |
| Examiner Name | Not yet assigned |

**I hereby declare that:**

(1) Each inventor's residence, mailing address, and citizenship are as stated below next to their name; and

(2) I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS**

*(Title of the Invention)*

the specification of which

☐ is attached hereto

*OR*

☒ was filed on (MM/DD/YYYY) 03/27/2009 as United States Application Number or PCT International Application Number 12/413,439 and was amended on (MM/DD/YYYY) 09/19/2011 (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

**Authorization to Permit Access To Application by Participating Offices**

☒ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified application is filed to have access to the application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the application-as-filed with respect to: 1) the above-identified application, 2) any foreign application to which the above-identified application claims priority under 35 USC 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified US application, and 3) any U.S. application from which benefit is sought in the above-identified application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.



This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# DECLARATION — Utility or Design Patent Application

**Claim of Foreign Priority Benefits**

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? Yes | No |
|---|---|---|---|---|---|
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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# DECLARATION — Utility or Design Patent Application

| | | | |
|---|---|---|---|
| Direct all correspondence to: | ☒ The address associated with Customer Number: | 021971 | OR ☐ Correspondence address below |
| Name | | | |
| Address | | | |
| City | State | ZIP | |
| Country | Telephone | Email @wsgr.com | |

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

| | | | |
|---|---|---|---|
| **NAME OF SOLE OR FIRST INVENTOR:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle [if any]) **Steve** | | Family Name or Surname **Cartt** | |
| Inventor's Signature | | | Date |
| Residence: City **Union City** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **3260 Whipple Road** | | | |
| City **Union City** | State **CA** | ZIP **94587** | Country **US** |
| ☒ Additional inventors or a legal representative are being named on the 2 supplemental sheet(s) PTO/SB/02A or 02LR attached hereto. | | | |

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| DECLARATION | ADDITIONAL INVENTOR(S) Supplemental Sheet Page 1 of 2 |
|---|---|

| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any) | | Family Name or Surname | |
| **David** | | **Medeiros** | |
| Inventor's Signature | | | Date |
| Residence: City **South San Francisco** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **212 Crown Circle** | | | |
| Mailing Address | | | |
| City **South San Francisco** | State **CA** | ZIP **94080** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any)) | | Family Name or Surname | |
| **Gary Thomas** | | **Gwozdz** | |
| Inventor's Signature | | | Date |
| Residence: City **Nazareth** | State **PA** | Country **US** | Citizenship **US** |
| Mailing Address **329 South Main Street** | | | |
| Mailing Address | | | |
| City **Nazareth** | State **PA** | ZIP **18064** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any)) | | Family Name or Surname | |
| **Andrew** | | **Loxley** | |
| Inventor's Signature | | | Date |
| Residence: City **Philadelphia** | State **PA** | Country **US** | Citizenship **GB** |
| Mailing Address **126 Market Street, #5** | | | |
| City **Philadelphia** | State **PA** | ZIP **19106** | Country **US** |

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| DECLARATION | ADDITIONAL INVENTOR(S) Supplemental Sheet Page 2 of 2 |
|---|---|

| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any) | | Family Name or Surname | |
| **Mark** | | **Mitchnick** | |
| Inventor's Signature | | | Date |
| Residence: City **East Hampton** | State **NY** | Country **US** | Citizenship **US** |
| Mailing Address **80 Three Mile Harbor Drive** | | | |
| City **East Hampton** | State **NY** | Zip **11937** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any)) | | Family Name or Surname | |
| **David** | | **Hale** | |
| Inventor's Signature David F Hale | | | Date 3/10/12 |
| Residence: City **San Diego** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **9232 Bernardo Lakes Drive** | | | |
| City **San Diego** | State **CA** | Zip **92127** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any)) | | Family Name or Surname | |
| **Edward T.** | | **Maggio** | |
| Inventor's Signature | | | Date |
| Residence: City **San Diego** | State **CA** | Country **USA** | Citizenship **USA** |
| Mailing Address 18775 Bernard Trails Drive | | | |
| Mailing Address | | | |
| City **San Diego** | State **CA** | ZIP **92128** | Country **USA** |

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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# DECLARATION — Supplemental Priority Data Sheet

Foreign applications:

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? Yes | No |
|---|---|---|---|---|---|
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing *OR* ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16(f) required)

| | |
|---|---|
| Attorney Docket Number | 35401-716.201 |
| First Named Inventor | Steve Cartt |
| *COMPLETE IF KNOWN* | |
| Application Number | 12/413,439 |
| Filing Date | 03/27/2009 |
| Art Unit | 1614 |
| Examiner Name | Not yet assigned |

**I hereby declare that:**

(1) Each inventor's residence, mailing address, and citizenship are as stated below next to their name; and

(2) I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS**

*(Title of the Invention)*

the specification of which

☐ is attached hereto

*OR*

☒ was filed on (MM/DD/YYYY) 03/27/2009 as United States Application Number or PCT International

Application Number 12/413,439 and was amended on (MM/DD/YYYY) 09/19/2011 (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

**Authorization to Permit Access To Application by Participating Offices**

☒ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, or other intellectual property office in which a foreign application claming priority to the above-identified application is filed to have access to the application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the application-as-filed with respect to: 1) the above-identified application, 2) any foreign application to which the above-identified application claims priority under 35 USC 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified US application, and 3) any U.S. application from which benefit is sought in the above-identified application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.



This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
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# DECLARATION — Utility or Design Patent Application

**Claim of Foreign Priority Benefits**

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? Yes | No |
|---|---|---|---|---|---|
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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# DECLARATION — Utility or Design Patent Application

| | | | |
|---|---|---|---|
| Direct all correspondence to: | ☒ The address associated with Customer Number: | 021971 | OR ☐ Correspondence address below |
| Name | | | |
| Address | | | |
| City | | State | ZIP |
| Country | Telephone | | Email @wsgr.com |

**WARNING:**

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type or personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: *Patent Application Files*. Documents not retained in an application file (such as the PTO-2083) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: *Deposit Accounts and Electronic Funds Transfer Profiles*.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

| | | | |
|---|---|---|---|
| **NAME OF SOLE OR FIRST INVENTOR:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle [if any]) **Steve** | | Family Name or Surname **Cartt** | |
| Inventor's Signature | | | Date |
| Residence: City **Union City** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **3260 Whipple Road** | | | |
| City **Union City** | State **CA** | ZIP **94587** | Country **US** |

☒ Additional inventors or a legal representative are being named on the 2 supplemental sheet(s) PTO/SB/02A or 02LR attached hereto.

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| DECLARATION | ADDITIONAL INVENTOR(S) Supplemental Sheet Page 1 of 2 |
|---|---|

| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle (if any) | Family Name or Surname | | |
| **David** | **Medeiros** | | |
| Inventor's Signature | | | Date |
| Residence: City **South San Francisco** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **212 Crown Circle** | | | |
| Mailing Address | | | |
| City **South San Francisco** | State **CA** | ZIP **94080** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle (if any)) | Family Name or Surname | | |
| **Gary Thomas** | **Gwozdz** | | |
| Inventor's Signature | | | Date |
| Residence: City **Nazareth** | State **PA** | Country **US** | Citizenship **US** |
| Mailing Address **329 South Main Street** | | | |
| Mailing Address | | | |
| City **Nazareth** | State **PA** | ZIP **18064** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle (if any)) | Family Name or Surname | | |
| **Andrew** | **Loxley** | | |
| Inventor's Signature | | | Date |
| Residence: City **Philadelphia** | State **PA** | Country **US** | Citizenship **GB** |
| Mailing Address **126 Market Street, #5** | | | |
| City **Philadelphia** | State **PA** | ZIP **19106** | Country **US** |

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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| DECLARATION | ADDITIONAL INVENTOR(S) Supplemental Sheet Page 2 of 2 |
|---|---|

| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle (if any) | Family Name or Surname | | |
| **Mark** | **Mitchnick** | | |
| Inventor's Signature | | Date | |
| Residence: City **East Hampton** | State **NY** | Country **US** | Citizenship **US** |
| Mailing Address **80 Three Mile Harbor Drive** | | | |
| City **East Hampton** | State **NY** | Zip **11937** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle (if any)) | Family Name or Surname | | |
| **David** | **Hale** | | |
| Inventor's Signature | | Date | |
| Residence: City **San Diego** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **9232 Bernardo Lakes Drive** | | | |
| City **San Diego** | State **CA** | Zip **92127** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle (if any)) | Family Name or Surname | | |
| **Edward T.** | **Maggio** | | |
| Inventor's Signature *Edward T. Maggio* | | Date **15Mar2012** | |
| Residence: City **San Diego** | State **CA** | Country **USA** | Citizenship **USA** |
| Mailing Address **18775 Bernard Trails Drive** | | | |
| Mailing Address | | | |
| City **San Diego** | State **CA** | ZIP **92128** | Country **USA** |

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# DECLARATION — Supplemental Priority Data Sheet

Foreign applications:

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? Yes | No |
|---|---|---|---|---|---|
| | | | ☐ | ☐ | ☐ |
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| | | | ☐ | ☐ | ☐ |

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# DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing *OR* ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16(f) required)

| | |
|---|---|
| Attorney Docket Number | 35401-716.201 |
| First Named Inventor | Steve Cartt |
| *COMPLETE IF KNOWN* | |
| Application Number | 12/413,439 |
| Filing Date | 03/27/2009 |
| Art Unit | 1614 |
| Examiner Name | Not yet assigned |

**I hereby declare that:**

(1) Each inventor's residence, mailing address, and citizenship are as stated below next to their name; and

(2) I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS**

*(Title of the Invention)*

the specification of which

☐ is attached hereto

*OR*

☒ was filed on (MM/DD/YYYY) 03/27/2009 as United States Application Number or PCT International

Application Number 12/413,439 and was amended on (MM/DD/YYYY) 09/19/2011 (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

**Authorization to Permit Access To Application by Participating Offices**

☒ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified application is filed to have access to the application.

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# DECLARATION — Utility or Design Patent Application

**Claim of Foreign Priority Benefits**

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? Yes | No |
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| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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# DECLARATION — Utility or Design Patent Application

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|---|---|---|---|
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| Name | | | |
| Address | | | |
| City | | State | ZIP |
| Country | Telephone | | Email @wsgr.com |

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

| | | | |
|---|---|---|---|
| **NAME OF SOLE OR FIRST INVENTOR:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle [if any]) **Steve** | | Family Name or Surname **Cartt** | |
| Inventor's Signature | | | Date 3-16-12 |
| Residence: City **Union City** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **3260 Whipple Road** | | | |
| City **Union City** | State **CA** | ZIP **94587** | Country **US** |

☒ Additional inventors or a legal representative are being named on the 2 supplemental sheet(s) PTO/SB/02A or 02LR attached hereto.

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| DECLARATION | ADDITIONAL INVENTOR(S) Supplemental Sheet Page 1 of 2 |
|---|---|

| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any) | | Family Name or Surname | |
| **David** | | **Medeiros** | |
| Inventor's Signature | | | Date 03/21/12 |
| Residence: City **South San Francisco** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **212 Crown Circle** | | | |
| Mailing Address | | | |
| City **South San Francisco** | State **CA** | ZIP **94080** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any)) | | Family Name or Surname | |
| **Gary Thomas** | | **Gwozdz** | |
| Inventor's Signature | | | Date |
| Residence: City **Nazareth** | State **PA** | Country **US** | Citizenship **US** |
| Mailing Address **329 South Main Street** | | | |
| Mailing Address | | | |
| City **Nazareth** | State **PA** | ZIP **18064** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any)) | | Family Name or Surname | |
| **Andrew** | | **Loxley** | |
| Inventor's Signature | | | Date |
| Residence: City **Philadelphia** | State **PA** | Country **US** | Citizenship **GB** |
| Mailing Address **126 Market Street, #5** | | | |
| City **Philadelphia** | State **PA** | ZIP **19106** | Country **US** |

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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| DECLARATION | ADDITIONAL INVENTOR(S) Supplemental Sheet Page 2 of 2 |
|---|---|

| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any) | | Family Name or Surname | |
| **Mark** | | **Mitchnick** | |
| Inventor's Signature | | | Date |
| Residence: City **East Hampton** | State **NY** | Country **US** | Citizenship **US** |
| Mailing Address **80 Three Mile Harbor Drive** | | | |
| City **East Hampton** | State **NY** | Zip **11937** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any)) | | Family Name or Surname | |
| **David** | | **Hale** | |
| Inventor's Signature | | | Date |
| Residence: City **San Diego** | State **CA** | Country **US** | Citizenship **US** |
| Mailing Address **9232 Bernardo Lakes Drive** | | | |
| City **San Diego** | State **CA** | Zip **92127** | Country **US** |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | |
| Given Name (first and middle (if any)) | | Family Name or Surname | |
| **Edward T.** | | **Maggio** | |
| Inventor's Signature | | | Date |
| Residence: City **San Diego** | State **CA** | Country **USA** | Citizenship **USA** |
| Mailing Address 18775 Bernard Trails Drive | | | |
| Mailing Address | | | |
| City **San Diego** | State **CA** | ZIP **92128** | Country **USA** |

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# DECLARATION — Supplemental Priority Data Sheet

Foreign applications:

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? Yes | No |
|---|---|---|---|---|---|
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.*

**Attorney Docket No. 35401-716.201**
**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Inventor: Steve Cartt, et al. | Group Art Unit: 1612 |
| Serial Number: 12/413,439 | Examiner: Adam C. Milligan |
| Filing Date: 03/27/2009 | **CONFIRMATION NO: 9049** |
| Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS | |

Certificate of Electronic Filing

I hereby certify that the attached Request for Correction of Inventorship and all marked attachments are being deposited by Electronic Filing 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 Date: 3-30-2012
Linda Anders

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

**ASSENT OF ASSIGNEE TO AMENDMENT OF INVENTORSHIP PURSUANT TO 37 CFR §1.48**

Hale Biopharma Ventures LLC states that it is:

☒ The assignee of the entire right, title and interest, or

☐ An assignee of less than the entire right, title and interest.

in the patent application identified above by virtue of either:

☐ An assignment from the inventor(s) of the patent application identified above. The assignment was recorded in the U.S. Patent and Trademark Office at Reel___, Frame___, or for which a copy thereof is attached.

—OR—

☒ A chain of title from the inventor(s), of the patent application to the current assignee is as follows:

1. From: Inventors Steve Cartt, Dave Medeiros, Gary Thomas Gwozdz, Andrew Loxley, Mark Mitchnick, David F. Hale TO: HALE BIOPHARMA VENTURES, LLC,
Recorded in the U.S. Patent and Trademark Office at Reel 022897, Frame 0583, ***or for which a copy is attached.***

2. From: Edward T. Maggio TO: HALE BIOPHARMA VENTURES, LLC,
Recorded in the U.S. Patent and Trademark Office at Reel ___, Frame ___, ***or for which a copy is attached.***

☒ Copies of assignments or other documents in the chain of title are attached.

The undersigned is authorized to act on behalf of the Assignee.

The Assignee hereby assents to the Amendment of Inventorship requested in Request for Correction of Inventorship in a Patent Application, in the above-referenced application, filed herewith.

Dated: March _____, 2012

David F. Hale
Chairman and CEO
Hale Biopharma Ventures, LLC

| PATENT ASSIGNMENT | Docket Number 35401-716.201 |
|---|---|

WHEREAS, the undersigned:

1. Edward T. Maggio
   16870 W. Bernardo Drive
   Suite 390
   San Diego, CA 92127

(hereinafter "Inventor(s))," have invented certain new and useful improvements in

**ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS**

☒ for which Application No. 12/413,439 was filed on March 27, 2009 in the United States Patent Office;

WHEREAS, HALE BIOPHARMA VENTURES, LLC, a limited liability company of the State of California, having a place of business at 1042-B N. El Camino Real, Suite 430, Encinitas, CA 92024, (hereinafter "Assignee"), is desirous of acquiring the entire right, title and interest in and to said Application(s) and the inventions disclosed therein, and in and to all embodiments of the inventions, heretofore conceived, made or discovered, whether jointly or severally, by said Inventor(s) (hereinafter collectively referred to as "Inventions"), and in and to any and all patents, inventor's certificates and other forms of protection (hereinafter "Patent(s)") thereon granted in the United States, foreign countries, or under any international convention, agreement, protocol, or treaty.

NOW, THEREFORE, in consideration of good and valuable consideration acknowledged by said Inventor(s) to have been received in full from said Assignee:

1. Said Inventor(s) do hereby sell, assign, transfer and convey unto said Assignee the entire right, title and interest (a) in and to said Inventions and Applications, including the right to claim priority to said Inventions and said Applications; (b) in and to all rights to all United States and corresponding non-United States patent applications and Patent(s), including those filed under the Paris Convention for the Protection of Industrial Property, The Patent Cooperation Treaty or otherwise; (c) in and to any and all applications filed and any and all Patent(s) granted on said Inventions in the United States, in any foreign country, or under any international convention, agreement, protocol, or treaty, including each and every application filed and any and all Patent(s) granted on any application which is a divisional, substitution, continuation, or continuation-in-part of any of said Application(s); and (d) in and to each and every reissue, reexamination, or extensions of any of said Patent(s).

2. Said Inventor(s) hereby covenant and agree to cooperate with said Assignee to enable said Assignee to enjoy to the fullest extent the right, title and interest herein conveyed in the United States, foreign countries, or under any international convention, agreement, protocol, or treaty. Such cooperation by said Inventor(s) shall include prompt production of pertinent facts and documents, giving of testimony, execution of petitions, oaths, specifications, declarations or other papers, and other assistance all to the extent deemed necessary or desirable by said Assignee (a) for perfecting in said Assignee the right, title and interest herein conveyed; (b) for prosecuting any applications covering said Inventions; (c) for filing and prosecuting substitute, divisional, continuing or additional applications covering said Inventions; (d) for filing and prosecuting applications for reissuance of any said Patent(s); (e) for interference or other priority proceedings involving said Inventions; and (f) for legal proceedings involving said Inventions and any applications therefor and any Patent(s) granted thereon, including without limitation reissues and reexaminations, opposition proceedings, cancellation proceedings, priority contests, public use proceedings, infringement actions and court actions; provided, however, that the expense incurred by said Inventor(s) in providing such cooperation shall be paid for by said Assignee.

3. The terms and covenants of this assignment shall inure to the benefit of said Assignee, its successors, assigns and other legal representatives, and shall be binding upon said Inventor(s), their respective heirs, legal representatives and assigns.

4. Said Inventor(s) hereby warrant and represent that they have not entered and will not enter into any assignment, contract, or understanding in conflict herewith.

5. Said Inventor(s) hereby request that any Patent(s) issuing in the United States, foreign countries, or under any international convention, agreement, protocol, or treaty, be issued in the name of the Assignee, or its successors and assigns, for the sole use of said Assignee, its successors, legal representatives and assigns.

6. This instrument will be interpreted and construed in accordance with the laws of the State of California, without regard to conflict of law principles. If any provision of this instrument is found to be illegal or unenforceable, the other provisions shall remain effective and enforceable to the greatest extent permitted by law. This instrument may be executed in counterparts, each of which is deemed an original, but all of which together constitute one and the same agreement.

| PATENT ASSIGNMENT | Docket Number 35401-716.201 |
|---|---|

IN WITNESS WHEREOF, said Inventor(s) have executed and delivered this instrument to said Assignee as of the dates written below:

Date: 16March2012 Edward T. Maggio

**Edward T. Maggio**

RECEIVED AND AGREED TO BY ASSIGNEE:

Date: 3/10/12

By: David F Hale

Name: David F. Hale

Title: Chief Executive Officer

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 12441157 |
| **Application Number:** | 12413439 |
| **International Application Number:** | |
| **Confirmation Number:** | 9049 |
| **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:** | 35401-716.201 |
| **Receipt Date:** | 30-MAR-2012 |
| **Filing Date:** | 27-MAR-2009 |
| **Time Stamp:** | 19:04:37 |
| **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 | | 35401-716-201-reqcorrinventor.pdf | 1730428<br>1d80af4503fec0323cfe35d6aad58976d32b3f7b | yes | 32 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Request under Rule 48 correcting inventorship | 1 | 4 |
| | Oath or Declaration filed | 5 | 10 |
| | Oath or Declaration filed | 11 | 16 |
| | Oath or Declaration filed | 17 | 22 |
| | Oath or Declaration filed | 23 | 28 |
| | Request under Rule 48 correcting inventorship | 29 | 30 |
| | Assignee showing of ownership per 37 CFR 3.73(b). | 31 | 32 |

**Warnings:**

**Information:**

| **Total Files Size (in bytes):** | 1730428 |
|---|---|

**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.**

**<u>New Applications Under 35 U.S.C. 111</u>**
**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.**

**<u>National Stage of an International Application under 35 U.S.C. 371</u>**
**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.**

**<u>New International Application Filed with the USPTO as a Receiving Office</u>**
**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/30 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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# Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

| | |
|---|---|
| Application Number | 12/413,439 |
| Filing Date | 03/27/2009 |
| First Named Inventor | Steve Cartt |
| Art Unit | 1612 |
| Examiner Name | Milligan, Adam C. |
| Attorney Docket Number | 35401-716.201 |

**This is a Request for Continued Examination (RCE) under 37 CFR 1 .114 of the above-identified application.**
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☒ Enclosed

      i. ☒ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☐ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a

   a. ☐ period of ___ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   The Director is hereby authorized to charge the following fees any underpayment of fees or credit any overpayments to

   a. ☒ Deposit Account No. 23-2415 .

      i. ☒ RCE fee required under 37 CFR 1.17(e)

      ii ☒ Extension of time fee (37 CFR 1.136 and 1.17)

      iii ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

***SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED***

| | | | |
|---|---|---|---|
| Signature | Matthew W. Grumbling | Date | 05/21/2012 |
| Name (Print/Type) | Matthew Grumbling | Registration No. | 44,427 |

***CERTIFICATE OF MAILING OR TRANSMISSION***

I hereby certify that this correspondence is being electronically filed via EFS Filing System with the U.S. Patent and Trademark Office on the date shown below.

| | | | |
|---|---|---|---|
| Signature | Linda Anders | | |
| Name (Print/Type) | Linda Anders | Date | 05/21/2012 |

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re the Patent Application of:<br><br>Applicant: Steve Cartt<br><br>Serial No.: 12/413,439<br><br>Filed: 03/27/2009<br><br>Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS | Confirmation No.: 9049<br><br>Group Art Unit: 1612<br><br>Examiner: Milligan, Adam C.<br><br>Customer Number: 21971<br><br>Certificate of Electronic Filing<br><br>I hereby certify that the attached Response to Office Action and all marked attachments are being deposited by Electronic Filing by EFS – Web patent filing system on May 21, 2012.<br><br>By: Linda Anders<br>Linda Anders |

**FILED ELECTRONICALLY ON: MAY 21, 2012**

Dear Madam:

**RESPONSE TO FINAL OFFICE ACTION DATED NOVEMBER 21, 2011**

Applicant hereby submits a timely response to the Office Action mailed November 21, 2011, in the above referenced application. Applicants also submit herewith a three (3) month extension of time, a Request for Continued Examination (RCE) and the requisite fees. In the event any additional fees are due, please charge to Deposit Account No. 23-2415, referencing Docket No. 35401-716.201.

A **Request for Continued Examination** (RCE) is filed concurrently as a separate paper.

**Amendments to the claims** begin on page **2** of this paper.

**Remarks** begin on page **6** of this paper.

## CLAIMS

**Amendments to the Claims**

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicants reserve the right to pursue the subject matter of the withdrawn claim in this or any other appropriate patent application.

1-19. (Canceled).

20. (Currently Amended) A method of treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure 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 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and ~~optionally~~ about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides.

21. (Original) The method of claim 20, 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).

22. (Original) The method of claim 21, wherein said patient is a human.

23. (Original) The method of claim 20, 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, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

24. (Original) The method of claim 23, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

25. (Canceled)

26. (Canceled)

27. (Original) The method of claim 20, 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.

28. (Original) The method of claim 20, 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.

29. (Original) The method of claim 20, wherein the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.

30. (Previously Presented) The method of claim 20, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration from about 1 mg/mL to about 600 mg/mL.

31. (Previously Presented) The method of claim 30, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.

32. (Previously Presented) The method of claim 31, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.

33. (Previously Presented) The method of claim 20, 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).

34. (Previously Presented) The method claim 33, 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).

35. (Previously Presented) The method of claim 20, 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).

36. (Previously Presented) The method of claim 35, 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).

37. (Canceled)

38. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution is a pharmaceutically-acceptable spray formulation.

39. (Canceled).

40. (Currently Amended) The method of ~~claim 39~~ claim 38, wherein said pharmaceutical solution is a pharmaceutically-acceptable spray formulation having volume from about 10 μL to about 200 μL.

41. (Previously Presented) The method of claim 40, 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.

42. (Previously Presented) The method of claim 40, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.

43. (Previously Presented) The method of claim 42, 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.

44. (Previously Presented) The method of claim 43, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical solution to the second nostril.

45. (Previously Presented) The method of claim 43, 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 composition.

46. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution contains at least about 0.01% (w/w) of an alkyl glycoside.

47. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.

48. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution consists of diazepam, vitamin E, ethanol and optionally an alkyl glycoside.

49. (Previously Presented) The method of claim 48, wherein the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof.

50. (Previously Presented) The method of claim 49, wherein the alkyl glycoside is dodecyl maltoside.

51. (New) The method of claim 20, wherein the pharmaceutical solution consists of 1-20 mg diazepam, 45 % (w/w) to 85 % (w/w) vitamin E, 15% (w/w) to 55 % (w/w) of a combination of ethanol and benzyl alcohol, and 0.01 % (w/v) to 1 % (w/v) of alkyl glycoside.

52. (New) The method of claim 51, wherein the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof.

53. (New) The method of claim 52, wherein the alkyl glycoside is dodecyl maltoside.

## REMARKS

Responsive to the Final Rejection mailed November 21, 2011, Applicants having filed herewith a Request for Continued Examination (RCE), requesting reconsideration of the outstanding rejections is requested in view of the foregoing amendment and the following remarks.

### The Amendments to the Claims

Upon entry of the foregoing amendment, claim 20 has been amended to recite a method of treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and 0.01 % (w/v) to 1 % (w/v) of one or more alkyl glycosides. New claims 51-53 are directed to a more specific embodiment of the invention. Support for the claim amendments are found throughout the original specification, including paragraphs [075], [0194]-[0199] and [209]. Claims 1-19, 25, 26, 37 and 39 are canceled, without prejudice. Thus, claims are 20-24, 27-36, 38 and 40-53 are pending and under consideration.

### *Addition of Inventor, Ed Maggio*

A Request to Correct Inventorship under 37 C.F.R. 1.48(a) was previously filed on March 30, 2012. The Request was filed along with: Declarations of each of the Inventors under 37 CFR § 1.63; a statement from the added inventor (Ed Maggio) that the error in inventorship occurred without deceptive intention on his part; an Assignee Assent to Change of Inventorship for each of Hale Biopharma Ventures LLC and Aegis Therapeutics LLC; and a Power of Attorney for Aegis Therapeutics, LLS. The Power of Attorney was accepted by the Office on April 9, 2012. Applicants respectfully request acknowledgement of the change of inventorship.

**Response to § 103(a) Obviousness Rejections**

***The pending claims are not obvious over of Sonne within the meaning of 35 U.S.C. § 103(a)***

Claims 20-24, 27-36, 38-45 and 48 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sonne (U.S. 6,193,985). Claims 46-50 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sonne (U.S. 6,193,985) in view of Meezan (US 2006/0046962). Applicants traverse these rejections.

Current claim 20, from which each of the remaining pending claims depend, reads:

> A method of treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides.

As can be seen in claim 20, the claimed method comprises treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder. The method comprises administering a nasal solution consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols and one or more alkyl glycosides. Thus, the recited solution contains: each of 1-20 mg of a benzodiazepine drug; one or more tocopherols or tocotrienols; one or more alcohols or glycols; and one or more alkylglycosides; and the solution excludes anything else. In particular, the solution excludes water and oil.

Sonne fails to teach or fairly suggest treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder. Indeed, aside from general teaching of nasal administration, Sonne is entirely silent

with respect to the particulars any treatment, let alone treatment of a seizure disorder. More specifically, Sonne teaches nothing about treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides.

As noted in the previous response, Sonne teaches that addition of co-solvents such as ethanol is less desired, since such solutions "tend to be irritating to certain mucosal tissues." Col. 3, lines 1-4 and 65-67. In fact, the bulk of Sonne's description relates to preparation of emulsions, which necessarily include oil and water. See col. 4, line 1 through col. 7, line 12 and Examples 1-3, 5-10, 15, 17, 19, 21. Consistent with Sonne's general teaching at column 3, lines 65-67, none of the Examples taught by Sonne suggest <u>nasal</u> administration of a benzodiazepine drug formulation that contains only tocopherol or tocotrienol, a alcohol and optionally an alkylglcoside. And none of Sonne's examples are directed to treating a patient with a seizure disorder.

Sonne teaches specific benzodiazepine formulations in Examples 1-3, 7-11, 17-19 and 22-23. Of these, Examples 1-3, 7-11, 17, 19 and 22-23 each describe an oil-in-water emulsion of the benzodiazepine. Such emulsions are specifically excluded from the instant claims, which recite <u>solutions</u> (not emulsions) and exclude any ingredients (such as water and oil) not included within the group of benzodiazepine drugs, tocopherols or tocotrienols, alcohols or glycols, and optionally alkyglycosides. Of the remaining examples, Example 18 is a solution of alprazolam in α-tocopherol <u>and sesame oil</u> for <u>oral administration</u>. Thus, each of the benzodiazepine compositions taught by Sonne contains oil, which is excluded from the instant claims, in some form or another (oil solution or emulsion).

The person of ordinary skill in the art would not have found it obvious to practice the claimed method, which requires treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides. In addition to Sonne's counsel against administering alcohol-containing solutions to certain mucosal tissues (col. 3, lines 65-67) and Sonne's teaching of emulsions as lower viscosity formulations for nasal administration (col. 3, line 60 through col. 4, line 2), as well as Sonne's teaching that, 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" (col. 4, lines 14-16), Sonne is entirely silent with respect to treatment of a patient having a seizure disorder. The person of skill in the art would not have found it obvious to treat a patient having a seizure disorder in light of Sonne's silence on the matter; and the person of skill in the art would have found it particularly unobvious to do so with the formulation recited in the instant claim, given Sonne's general teaching away from administering alcohol-containing solutions to certain mucosal membranes.

For at least the reasons given above, Applicants submit that the pending claims are not obvious within the meaning of § 103(a) in view of the teaching of Sonne. Withdrawal of the § 103(a) rejection is respectfully requested.

***The pending claims are not obvious over the combination of Sonne and Meezan within the meaning of 35 U.S.C. § 103(a)***

Claims 46, 47, 49 and 50 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sonne in view of Meezan (U.S. 2006/0046962). Applicants traverse this rejection.

As Applicants understand the rejection, the Office Action relied upon Sonne for its teaching, which is addressed in the foregoing discussion, and upon Meezan for its teaching of

alkyl glycosides as penetration enhancers. Applicants submit that Meezan fails to make up for the deficiencies noted above with respect to Sonne. Thus, claims 46-50, which depend ultimately from claim 20, would not have been rendered obvious to the person of ordinary skill in the art for at least the same reasons articulated above. Moreover, Applicants maintain that the combination of Sonne and Meezan is improper. Accordingly, Applicants submit that this rejection is untenable and should be withdrawn.

As Applicants assert above, Sonne fails to teach a method of treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides. Meezan fails to supply missing teaching of Sonne, such as the dosage of benzodiazepine, as well as an operative method of treating a patient having a seizure disorder with a benzodiazepine. Having failed to teach or suggest each element of the claimed invention, the combination of references fails to render the claims obvious within the meaning of § 103(a). *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998).

In any case, the person of ordinary skill in the art would not have combined the references as suggested in the Office Action. The more recent Office Action did attempt to identify a reason, design need or market pressure combine the references. That reason, however, is specious at best. In particular, the Office Action states, "Sonne also teaches that an increased rate of absorption is preferred (col. 2, lines 44-48)." Office Action page 4. However the pertinent part of Sonne reads as follows:

> 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.

Sonne, col. 2, lines 39-49. In context, the pertinent part of Sonne does not provide a reason, a design need or a market pressure to combine the teaching of Sonne with that of Meezan. Rather, at best, Sonne suggests that any design need or market pressure for enhancing penetration would be provided by vitamin E (a tocopherol).[1] In other words, to the extent that Sonne suggests a need for a penetration enhancer, the person of ordinary skill in the art would interpret Sonne as teaching that the need was fully met by the inclusion of tocopherol in the emulsions disclosed therein. The person of ordinary skill in the art would not have found reason in Sonne to look farther afield, to the publication of Meezan or anywhere else, for penetration enhancers. Far from motivating a search for additional enhancers, Sonne would have suggested to the person of ordinary skill in the art that the need for a penetration enhancer, to the extent that it existed, was met by vitamin E in their emulsions.

In view of the foregoing, Applicants submit that the cited references fail to teach or fairly suggest the subject matter of any of the pending claims within the meaning of § 103(a). Withdrawal of the § 103(a) rejection is respectfully requested.

**Response to Obviousness-Type Double Patenting Rejection**

Claims 20-47 were provisionally rejected on the basis of the judge-made rule of obviousness double patenting over claims 17-19, 22, 23, 26, 27, 30 and 31 of copending application number 12/116,842 (the "copending application") in view of Sonne and Meezan. Applicants traverse this rejection.

[1] Indeed, Applicants cited this particular passage of Sonne in their last response; and the Office Action's reliance upon it for exactly the opposite teaching is particularly puzzling.

The instant claims are drawn to a method of treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides. The claims of the copending application do not render this subject matter obvious. Indeed, the rejection is so lacking merit that it fails to set forth a proper reasoned basis for its conclusion.

The reasoned basis for the rejection fails to establish that the instant claims would have been anticipated or obvious in view of the claims of the copending application. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968, 58 USPQ2d 1869, 1878 (Fed. Cir. 2001). The allegation that "It would have been obvious to use nasal spray formulation of Sonne when practicing the method of administering benzodiazepines recited in the copending 12/116,842 application" is a mere conclusion without factual or legal basis. Factually, the cited claims of the copending application are drawn to methods comprising administration of <u>multimodal particulate</u> compositions, while, in contrast, the instant claims are drawn to methods comprising administering non-aqueous <u>solutions</u>. Neither Sonne nor Meezan teaches or suggests that multimodal particulate compositions are obvious variants of the solutions recited in the instant claims. Moreover, there is not a single species within the scope of the claims of the copending application that would also lie within the scope of the pending claims in the instant application.

Thus, the rejection is entirely without basis in either law or fact. As there is no overlap in claim scope between the claims of the copending application and the instant application, the Double Patenting rejection is without sufficient basis and should be withdrawn. Such action is respectfully requested.

## CONCLUSION

Applicant timely submits these remarks in response to the Office Communication dated November 21, 2011. In the event that fees are due in connection with the filing of this response, please charge the necessary fees to Deposit Account No. 23-2415 referencing Docket No. 35401-716.201. Should the examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (858) 350-2332.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: May 21, 2011

By: Matthew V. Grumbling

Matthew V. Grumbling
Registration No. 44,427

650 Page Mill Road
Palo Alto, CA 94304
(858) 350-2306
Customer No. 021971

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 12413439 |
| **Filing Date:** | 27-Mar-2009 |
| **Title of Invention:** | ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS |
| **First Named Inventor/Applicant Name:** | Steve Cartt |
| **Filer:** | Matthew Virgil Grumbling/Linda Anders |
| **Attorney Docket Number:** | 35401-716.201 |

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 | 635 | 635 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| Request for continued examination | 2801 | 1 | 465 | 465 |
| | | **Total in USD ($)** | | **1100** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 12824382 |
| **Application Number:** | 12413439 |
| **International Application Number:** | |
| **Confirmation Number:** | 9049 |
| **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:** | 35401-716.201 |
| **Receipt Date:** | 21-MAY-2012 |
| **Filing Date:** | 27-MAR-2009 |
| **Time Stamp:** | 14:45:34 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $1100 |
| RAM confirmation Number | 1139 |
| 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 | | 35401-716-201-responsefinal.pdf | 723642<br>c21d094068e34465db417775b094aa7c4cb b50c1 | yes | 14 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Request for Continued Examination (RCE) | 1 | 1 |
| Amendment After Final | 2 | 2 |
| Amendment Copy Claims/Response to Suggested Claims | 3 | 6 |
| Applicant Arguments/Remarks Made in an Amendment | 7 | 14 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 32429<br>3597b14a8cf7942bef3caa178d03118aaef5 ef81 | no | 2 |

**Warnings:**

**Information:**

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| **Total Files Size (in bytes):** | 756071 |

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**<u>New Applications Under 35 U.S.C. 111</u>**
**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.**

**<u>National Stage of an International Application under 35 U.S.C. 371</u>**
**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.**

**<u>New International Application Filed with the USPTO as a Receiving Office</u>**
**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 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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 | Filing Date | |
|---|---|---|
| 12/413,439 | 03/27/2009 | ☐ To be Mailed |

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY ☒ RATE ($) | SMALL ENTITY FEE ($) | OR | OTHER THAN SMALL ENTITY RATE ($) | OTHER THAN SMALL ENTITY FEE ($) |
|---|---|---|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | | | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | | | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | | OR | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | | | 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 $250 ($125 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 | | | TOTAL | |

## APPLICATION AS AMENDED – PART II

AMENDMENT 05/21/2012

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE ($) | SMALL ENTITY ADDITIONAL FEE ($) | OR | OTHER THAN SMALL ENTITY RATE ($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * 30 | Minus | ** 62 | = 0 | X $30 = | 0 | OR | X $ = | |
| Independent (37 CFR 1.16(h)) | * 1 | Minus | ***3 | = 0 | X $125 = | 0 | OR | X $ = | |
| ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | 0 | OR | TOTAL ADD'L FEE | |

AMENDMENT

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) | | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | | OR | X $ = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | | OR | X $ = | |
| ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/PAUL STANBACK/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| In re Application: | | | |
| Inventor: | Steve Cartt, et al. | Confirmation No.: | **9049** |
| Application No.: | 12/413,439 | Examiner: | Not yet assigned |
| Filed: | March 27, 2009 | Group Art Unit: | 1614 |
| Title: | **ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS** | Customer No. **021971** | |
| | | **File No. 35401-716.201** | |

**POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO and 3.73 STATEMENT**

☒ I hereby appoint the practitioners associated with Customer Number: **021971**

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO).

☒ Please address all correspondence for the above-identified application to: **021971**

## STATEMENT UNDER 37 CFR 3.73(b)

**Hale BioPharma Ventures LLC** a _____ limited liability company
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is: the assignee of the entire right, title and interest; in the patent application/patent identified above by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel , Frame , ***or for which a copy thereof is attached.***

***OR***

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: ___ To:
   The document was recorded in the United States Patent and Trademark Office at
   Reel ___, Frame ___, ***or for which a copy thereof is attached.***
2. From: ___To:
   The document was recorded in the United States Patent and Trademark Office at
   Reel ___, Frame ___, ***or for which a copy thereof is attached.***

I am an authorized representative of the:

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
*Statement under 37 CFR 3.73(b) is incorporated herein.*

**SIGNATURE of Assignee of Record**

Hale BioPharma Ventures LLC

Signature _____

Name/Title David F. Hale, Chairman

Date 6/24/09 Telephone No. 858-756-2480

| ASSIGNMENT OF APPLICATION | Docket Number 35401-716.201 |
|---|---|

WHEREAS, the undersigned:

1. CARTT, Steve
   3260 Whipple Road
   Union City, CA 94587
2. MEDEIROS, David
   212 Crown Circle
   South San Francisco, CA 94080
3. GWOZDZ, Gary Thomas
   329 South Main Street
   Nazareth, PA 18064
4. LOXLEY, Andrew
   126 Market Street, #5
   Philadelphia, PA 19106
5. MITCHNICK, Mark
   80 Three Mile Harbor Drive
   East Hampton, NY 11937
6. HALE, David F.
   1042-B N. El Camino Real, Suite 430
   Encinitas, CA 92024

(hereinafter "Inventor(s))," have invented certain new and useful improvements in

**ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS**

☒ for which Application No. 12/413,439 was filed on March 27, 2009 in the United States Patent Office;

WHEREAS, Hale BioPharma Ventures., a corporation of the state of California, having a place of business at 1042-B N. El Camino Real, Suite 430, Encinitas, CA 92024, (hereinafter "Assignee"), is desirous of acquiring the entire right, title and interest in and to said Application(s) and the inventions disclosed therein, and in and to all embodiments of the inventions, heretofore conceived, made or discovered, whether jointly or severally, by said Inventor(s) (hereinafter collectively referred to as "Inventions"), and in and to any and all patents, inventor's certificates and other forms of protection (hereinafter "Patent(s)") thereon granted in the United States, foreign countries, or under any international convention, agreement, protocol, or treaty.

NOW, THEREFORE, in consideration of good and valuable consideration acknowledged by said Inventor(s) to have been received in full from said Assignee:

1. Said Inventor(s) do hereby sell, assign, transfer and convey unto said Assignee the entire right, title and interest (a) in and to said Inventions, including the right to claim priority to said Inventions; (b) in and to all rights to all United States and corresponding non-United States patent applications and Patent(s), including those filed under the Paris Convention for the Protection of Industrial Property, The Patent Cooperation Treaty or otherwise; (c) in and to any and all applications filed and any and all Patent(s) granted on said Inventions in the United States, in any foreign country, or under any international convention, agreement, protocol, or treaty, including each and every application filed and any and all Patent(s) granted on any application which is a divisional, substitution, continuation, or continuation-in-part of any of said Application(s); and (d) in and to each and every reissue, reexamination, or extensions of any of said Patent(s).

2. Said Inventor(s) hereby covenant and agree to cooperate with said Assignee to enable said Assignee to enjoy to the fullest extent the right, title and interest herein conveyed in the United States, foreign countries, or under any international convention, agreement, protocol, or treaty. Such cooperation by said Inventor(s) shall include prompt production of pertinent facts and documents, giving of testimony, execution of petitions, oaths, specifications, declarations or other papers, and other assistance all to the extent deemed necessary or desirable by said Assignee (a) for perfecting in said Assignee the right, title and interest herein conveyed; (b) for prosecuting any applications covering said Inventions; (c) for filing and prosecuting substitute, divisional, continuing or additional applications covering said Inventions; (d) for filing and prosecuting applications for reissuance of any said Patent(s); (e) for interference or other priority proceedings involving said Inventions; and (f) for legal proceedings involving said Inventions and any applications therefor and any Patent(s) granted thereon, including without limitation reissues and reexaminations, opposition proceedings, cancellation proceedings, priority contests, public use proceedings, infringement actions and court actions; provided, however, that the expense incurred by said Inventor(s) in providing such cooperation shall be paid for by said Assignee.

3. The terms and covenants of this assignment shall inure to the benefit of said Assignee, its successors, assigns and other legal representatives, and shall be binding upon said Inventor(s), their respective heirs, legal representatives and assigns.

4. Said Inventor(s) hereby warrant and represent that they have not entered and will not enter into any assignment, contract, or understanding in conflict herewith.

5. Said Inventor(s) hereby request that any Patent(s) issuing in the United States, foreign countries, or under any international convention, agreement, protocol, or treaty, be issued in the name of the Assignee, or its successors and assigns, for the sole use of said Assignee, its successors, legal representatives and assigns.

IN WITNESS WHEREOF, said Inventor(s) have executed and delivered this instrument to said Assignee as of the dates written below:

Date: 6-4-09 _____ Steve Cart

Date: _____ _____ Andrew Loxley

Date: 06/09/09 _____ David Medeiros

Date: _____ _____ Mark Mitchnick

Date: _____ _____ Gary Thomas Gwozdz

Date: _____ _____ David F. Hale

RECEIVED AND AGREED TO BY ASSIGNEE: Hale BioPharma Ventures LLC

Date: _____

By: _____
Name: David F. Hale
Title: Chairman

IN WITNESS WHEREOF, said Inventor(s) have executed and delivered this instrument to said Assignee as of the dates written below:

Date: _____ _____
Steve Cartt

Date: 22 June 2009 _____
Andrew Loxley

Date: _____ _____
David Medeiros

Date: 22 June 2009 _____
Mark Mitchnick

Date: 23 Jun 2009 _____
Gary Thomas Gwozdz

Date: _____ _____
David F. Hale

RECEIVED AND AGREED TO BY ASSIGNEE:

Hale BioPharma Ventures LLC

Date: _____

By: _____
Name: David F. Hale
Title: Chairman

IN WITNESS WHEREOF, said Inventor(s) have executed and delivered this instrument to said Assignee as of the dates written below:

| | | | |
|---|---|---|---|
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| **First Named Inventor/Applicant Name:** | Steve Cartt |
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## NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/31/2012.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/snguyen/

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**U.S. PATENT DOCUMENTS**

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|---|---|---|---|---|---|
| | 1. | US-2008/0279784 A1 | 11/13/2008 | Cartt et al. | |
| | 2. | US-2009/0130216 A1 | 05/21/2009 | Cartt et al. | |
| | 3. | US-2009/0258865 A1 | 10/15/2009 | Cartt et al. | |
| | 4. | US-2009/0304801 A1 | 12/10/2009 | Liversidge et al. | |

**FOREIGN PATENT DOCUMENTS**

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| | 5. | WO-2005/117830 A1 | 12/15/2005 | Camurus, AB | | |
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**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] |
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**(54) Title:** LIQUID DEPOT FORMULATIONS

**(57) Abstract:** The present invention relates to pre-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 preformulations are suitable for generating parenteral, non-parenteral and topical depot compositions for sustained release of active agents. 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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## Lipid Depot 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 at least one bioactive agent which undergo at least one phase transition upon exposure to aqueous fluids, such as body fluids, thereby forming a controlled release matrix which optionally is bioadhesive.

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.

Various method have been used and proposed for the sustained release of biologically active agents. Such methods include slow-release, orally administered compositions, such as coated tablets, formulations designed for gradual absorption,

such as transdermal patches, and slow-release implants such as "sticks" implanted under the skin.

One method by which the gradual release of a bioactive agent has been proposed is a so-called "depot" injection. In this method, a bioactive agent is formulated with carriers providing a gradual release of active agent over a period of a number of hours or days. These are often based upon a degrading matrix which gradually disperses in the body to release the active agent.

The most common of the established methods of depot injection relies upon a polymeric depot system. This is typically a biodegradable polymer such poly (lactic acid) (PLA) and/or poly (lactic-co-glycolic acid) (PLGA) and may be in the form of a solution in an organic solvent, a pre-polymer mixed with an initiator, encapsulated polymer particles or polymer microspheres. The polymer or polymer particles entrap the active agent and are gradually degraded releasing the agent by slow diffusion and/or as the matrix is absorbed. Examples of such systems include those described in US 4938763, US 5480656 and US 6113943 and can result in delivery of active agents over a period of up to several months. These systems do, however, have a number of limitations including the complexity of manufacturing and difficulty in sterilising (especially the microspheres). The local irritation caused by the lactic and/or glycolic acid which is released at the injection site is also a noticeable drawback. There is also often quite a complex procedure to prepare the injection dose from the powder precursor

From a drug delivery point of view, polymer depot compositions also have the disadvantage of accepting only relatively low drug loads and having a "burst/lag" release profile. The nature of the polymeric matrix, especially when applied as a solution or pre-polymer, causes an initial burst of drug release when the composition is first administered. This is followed by a period of low release, while the degradation of the matrix begins, followed finally by an increase in the release rate to the desired sustained profile. This burst/lag release profile can cause the *in vivo* concentration of active agent to burst above the functional window immediately following administration, then drop back through the bottom of the functional window during the lag period before reaching a sustained functional concentration. Evidently, from a functional and toxicological point of view this burst/lag release profile is undesirable and could be dangerous. It may also limit the equilibrium

concentration which can be provided due to the danger of adverse effects at the "peak" point.

Previous depot systems have been sought to address the problem of burst release. In particular, the use of hydrolysed polylactic acid and the inclusion of poly lactic acid-polyethylene glycol block copolymers have been proposed to provide the "low burst" polymeric system described in US 6113943 and US 6630115. These systems provide improved profiles but the burst/lag effect remains and they do not address other issues such as the irritation caused by the use of polymers producing acidic degradation products.

One alternative to the more established, polymer based, depot systems was proposed in US 5807573. This proposes a lipid based system of a diacylglycerol, a phospolipid and optionally water, glycerol, ethylene glycol or propylene glycol to provide an administration system in the reversed micellar "L2" phase or a cubic liquid crystalline phase. Since this depot system is formed from physiologically well tolerated diacyl glycerols and phospholipids, and does not produce the lactic acid or glycolic acid degradation products of the polymeric systems, there is less tendency for this system to produce inflammation at the injection site. The liquid crystalline phases are, however, of high viscosity and the L2 phase may also be too viscous for ease of application. The authors of US 5807573 also do not provide any *in vivo* assessment of the release profile of the formulation and thus it is uncertain whether or not a "burst" profile is provided.

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.

While the effectiveness of known lipid depot formulations is high, there are certain aspects in which the performance of these is less than ideal. In particular, cubic liquid crystalline phases proposed are relatively viscous in nature. This makes application with a standard syringe difficult, and possibly painful to the patient, and makes sterilisation by filtration impossible because the composition cannot be passed through the necessary fine-pored membrane. As a result, the compositions must be prepared under highly sterile conditions, which adds to the complexity of manufacturing. Where L2 phases are used, these are generally of lower viscosity but these may still cause difficulty in application and allow access to only a small region of the phase diagram. Specifically, the solvents used in known lipid formulations have only a limited effect in reducing the viscosity of the mixture. Water, for example, will induce the formation of a highly viscous liquid crystalline phase and solvents such as glycerol and glycols have a high viscosity and do not provide any greatly advantageous decrease in the viscosity of the composition. Glycols are also typically toxic or poorly tolerated *in vivo* and can cause irritation when applied topically.

Furthermore, the known lipid compositions in the low-solvent L2 phase may support only a relatively low level of many bioactive agents because of their limited solubility in the components of the mixture in the absence of water. In the presence of water, however, the formulations adopt a highly viscous cubic liquid crystalline

phase. It would be a clear advantage to provide a depot system that could be injected at low viscosity and allowed release of the required concentration of bioactive with a smaller depot composition volume.

The known lipid depot compositions also have practical access to only certain phase structures and compositions because other mixtures are either too highly viscous for administration (such as those with high phospholipid concentrations) or run the risk of separation into two or more separate phases (such as an L2 phase in equilibrium with a phase rich in phospholipid). In particular, phospholipid concentrations above 50% are not reachable by known methods and from the phase diagram shown in US 5807573 it appears that the desired cubic phase is stable at no higher than 40% phospholipid. As a result, it has not been possible in practice to provide depot compositions of high phospholipid concentration or having a hexagonal liquid crystalline phase structure.

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 depot formulations. In particular, the pre-formulation is easy to manufacture, may be sterile-filtered, it has low viscosity (allowing easy and less painful administration), allows a high level of bioactive agent to be incorporated (thus allowing a smaller amount of composition to be used) and/or forms a desired non-lamellar depot composition *in vivo* having a controllable "burst" or "non-burst" release profile. The compositions are also formed from materials that are non-toxic, biotolerable and biodegradable. Furthermore, the pre-formulation is suitable for the formation of depot compositions following parenteral administration and also following non-parenteral (e.g. topical) administration to body cavities and/or surfaces of the body or elsewhere.

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;

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.

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 administering (preferably parenterally) 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 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. 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 parenteral depot will thus be formed by parenteral (e.g. subcutaneous or intramuscular) administration while 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 at least one bioactive agent dissolved or dispersed in the low viscosity mixture, to an aqueous fluid (particularly *in vivo and/or particularly a body fluid as indicated herein*). Preferably the pre-formulation administered is a pre-formulation of the present invention as described herein. The exposure to a fluid "in vivo" may evidently be internally within the body or a body cavity, or may be at a body surface such as a skin surface, depending upon the nature of the composition.

The liquid crystalline composition formed in this method is preferably 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 (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 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 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.

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 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 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. 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 will typically 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. The composition of the present invention may, however, contain a greater quantity of solvent than would be acceptable in an immediate dosage composition. This is because the process by which the active agents are slowly released (e.g. formation of shells of liquid crystalline phase se described herein) also

serve to retard the passage of solvent from the composition. As a result, the solvent is released over some time (e.g. minutes or hours) rather than instantaneously and so can be better tolerated by the body.

Higher proportions of solvent may also be used for non-parenteral (e.g. topical) applications, especially to 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 (non-parenteral) aerosol spray compositions (e.g. for topical or systemic 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.

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 is preferably (especially for injectable depots) 2 to 30% and more preferably 5 to 20% by weight.

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

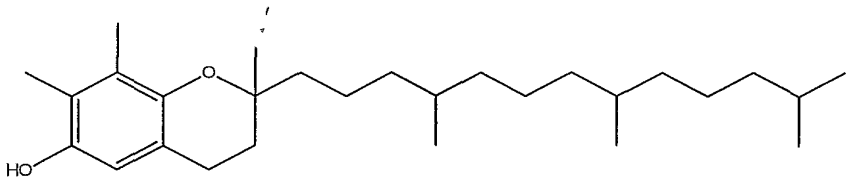
as acetate or succinate esters. Preferred polar groups are glycerol and diglycerol, especially glycerol.

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 are to 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.

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, especially for parenteral depots, since less immune system activity is recruited to the administration site. 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).

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 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.

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 10%, 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.

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. Where the depot composition is to be formed non-parenterally a greater range of solvents may evidently be used than where the depot is to be parenteral.

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 *in vivo* formation of the depot composition, 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.

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.

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 (including local concentrations for topical compositions). Under some circumstances one or more of components a, b and/or c may also be an active agent, although it is preferred that the active agent should not be one of these components. Most preferred active agents are pharmaceutical agents including drugs, vaccines, and diagnostic agents.

Drug agents that may be delivered by the present invention include drugs which act on cells and receptors, peripheral nerves, adrenergic receptors, 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.

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 including cholesterol lowering and blood-pressure lowing agents, analgesics, antipsychotics and antidepressants including seritonin uptake inhibitors, prostaglandins and derivatives, vaccines, and bone modulators. Diagnostic agents include radionuclide labelled compounds and contrast agents including X-ray, ultrasound and MRI contrast enhancing agents. Nutrients include vitamins, coenzymes, dietary supplements etc.

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. 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 depot composition formed from the pre-formulation of the present invention, the agents are provided at a sustained level for a length of time which may stretch to days, weeks or even several months in spite of having rapid 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.

Peptide and protein based active agents 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 situations where patient compliance is difficult, unreliable or where a level dosage is highly important, such as mood-altering actives, those actives with a narrow therapeutic window, and those administered to children or to people who's lifestyle is incompatible with a reliable dosing regime. Also for "lifestyle" actives where the inconvenience of repeated dosing might outweigh the benefit of the active. Particular classes of actives for which this aspect offers a particular advantage include contraceptives, hormones including contraceptive hormones, and particularly hormones used in children such as growth hormone, anti-addictive agents, supplements such as vitamin or mineral supplements, anti-depressants and anticonvulsants

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, 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).

A particular advantage of the present invention when used in combination with protein / peptide active agents is that aggregation of the active agent is suppressed. In one preferred embodiment, the present invention thus provides a depot precursor and particularly a depot composition as described herein comprising at least one peptide (e.g. antibody) or protein active agent wherein no more than 5% of the active agent is in aggregated form. Preferably no more than 3% is aggregated and most preferably no more than 2% (especially less than 2%) is in aggregated form. This stabilisation of non-aggregated protein is highly advantageous from the point of view of high effectiveness, low side effects and predictable absorption profile. Furthermore, it is increasingly expected that protein / peptide therapeutics will have low levels of protein aggregation in order to secure regulatory approval.

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 daily dose multiplied by the number of days the formulation is to provide release. 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.

In one embodiment, the pre-formulations of the present invention will generally be administered parenterally. This administration will generally not be an intra-vascular method but will preferably be subcutaneous intracavitary or intramuscular. Typically the administration will be by injection, which term is used herein to indicate any method in which the formulation is passed through the skin, such as by needle, catheter or needle-less injector.

In parenteral (especially sub cutaneous) depot precursors, preferred active agents are those suitable for systemic administration including antibacterials (including amicacin, monocycline anddoxycycline), local and systemic anagesics (including bupivacain, tramadol, fentanyl, morphine, hydromorphone, methadone, oxycodone, codeine, asperine, acetaminophen), NSAIDS (such as ibuprofene, naproxene, keteprofene, indomethansine, sulindac, tolmethin, salysylic acids such as salisylamide, diflunisal), Cox1 or Cox2 inhibitors (such as celecoxib, rofecoxib, valdecoxib) anticancer agents (including octreotide, lanreotide, buserelin, luprorelin, goserelin, triptorelin, avorelin, deslorein, abarelix, degarelix, fulvestrant, interferon alpha, interferon beta, darbepoetin alpha, epoetin alpha, beta, delta, and paclitaxel), antipsychotics (like bromperidol, risperidone, olanzapine, iloperidone, paliperadone, pipotiazine and zuclopenthixol), antivirals, anticonvulsants (for instance tiagabine topiramate or gabapentin) or nicotine, hormones (such as testosterone, and testosterone undecanoate, medroxyprogesterone, estradiol) growth hormones (like human growth hormone), and growth factors (like granulocyte macrophage colony-stimulating factor)

In an alternative embodiment, the formulations of the present invention may form non-parenteral depots where the active agent is slowly released at a body surface. It is especially important in this embodiment that the pre-formulations of the invention and/or the liquid crystalline depot compositions formed therefrom should preferably be bioadhesive. 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 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 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.

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" are 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 or to 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) 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.

Non-parenteral depots may also be used for application to surfaces, particularly of implants and materials which will be in contact with the body or a body part or fluid. Devices such as implants, catheters etc. may thus be treated e.g. by dipping or spraying with the preformulations of the invention, which will form a robust layer to reduce the introduction of infection. Anti-infective actives are particularly suited to this aspect.

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). 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 antiinfectives, especially benzydamine, tramadol and 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 comprises intra oral, buccal, nasal, ophthalmic, dermal, 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, 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).

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

For long acting injectable depot products of hydrophilic active agents;

i. octreotide (or other somatostatin analogues such as lanreotide for treatment of carcoid and VIP producing tumours and acromegali). Subcutaneous depots formable, especially with GDO and PC having a sustained release duration of more than one month and showing less than 20% octreotide degraded in one month in water-swollen depot at 37°C. Surprisingly good stability was observed and found to be better than octreotide formulated in microspheres. Depot showed less than 5% degradation in product preformulation over eight weeks at 4°C.

ii. human growth hormone. For treatment of growth disorders and growth hormone deficiencies. Subcutaneous depot formable, especially with GDO and PC having a sustained release duration of more than two weeks

iii. interferon alpha, for treatment of cancer and viral infections. Subcutaneous depots formable, especially with GDO and PC, having a sustained release duration of more than one month

iv. leuprolide. Depots formable having continuous delivery (preferably continuous delivery inside therapeutic window) for minimum of one month.

For long acting injectable depots of lipophilic/amphiphilic actives;

i. risperidone

ii. olanzapine

iii. testosterone undecanoate

Depots i to iii formable having continuous delivery (preferably continuous delivery inside therapeutic window) for minimum of two weeks.

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
ii. diazepam (anti anxiety) provides non-parenteral, nasal 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.

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 (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 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.

The pre-formulations of the present invention provide non-lamellar liquid crystalline depot compositions upon exposure to aqueous fluids, especially *in* vivo and 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, 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 $L_2$ 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, especially with substantial sized

administrations of internal depots. 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 $L_{\alpha}$, $I_2$, $L_2$, 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 greater than 10 wt% 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.

Upon administration, the pre-formulations of the present invention undergo a phase structure transition from a low viscosity mixture to a high viscosity (generally 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 days, weeks or months, 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).

It is an unexpected finding of the present inventors that the pre-formulations result in a depot composition that have very little "burst" effect in the active agent release

profile. This is unexpected because it might be expected that the low viscosity mixture (especially if this is a solution) of the pre-composition would rapidly lose active agent upon exposure to water. In fact, pre-formulations of the invention have shown considerably less of an initial "burst" than previously known polymer-base depot compositions. This is illustrated in the Examples below and Figures attached hereto. In one embodiment, the invention thus provides injectable preformulations and resulting depot compositions wherein the highest plasma concentration of active after administration is no more than 5 times the average concentration between 24 hours and 5 days of administration. This ratio is preferably no more than 4 times and most preferably no more than 3 times the average concentration.

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.

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 shows the plasma concentration (in rats) of salmon calcitonin (sCT) after subcutaneous injection of various PC/GDO/EtOH depot precursors containing 500 μg sCT / g of formulation;

Figure 4 shows the initial *in vivo* release (up to 48 hours) to plasma (in rats) of sCT from two different depot formulations following subcutaneous injection;

Figure 5 shows the plasma concentration (in rats) of octreotide (OCT) following subcutaneous injection of a depot formulation comprising PC/GDO/EtOH (36/54/10 wt%) containing 5 mg OCT / g formulation, corresponding to 0.5% drug load.

Figure 6 shows the plasma concentration (in rats) of octreotide (OCT) following subcutaneous injection of a depot formulation comprising PC/GDO/EtOH (47.5/47.5/5.0 wt%) containing 30 mg OCT / g formulation, corresponding to 3% drug load.

Figure 7 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 | $H_{II}/L_\alpha$ |

$L_2$ = reversed micellar phase

$I_2$ = reversed cubic liquid crystalline phase

$H_{II}$ = reversed hexagonal liquid crystalline phase

$L_\alpha$ = 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 | $H_{II}/L_\alpha$ |

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**

***In vivo* release study from depot formulations subcutaneously administered**

Formulations E to I in Example 4 were used in an *in vivo* drug release study in rat. The formulations were administrated subcutaneously between the scapulae by using a syringe (21G, 0.6mm x 30mm) and the dose of sCT was 500 μg/ kg body weight. The release profile was monitored for a period of 13 days. The sCT concentration in the rat plasma samples was analysed with sandwich-type immunoassay using a commercial kit from DSLabs.

Figure 3 shows the results (n=4). A pure triglyceride vehicle based on sesame oil was selected as a lipid reference system.

**Example 7**

***In vivo* release study in the initial phase**

Formulations F and G as in Example 6 were used in an *in vivo* study in rat designed to investigate the initial "burst effect". From Figure 4 (n=8) it appears that none of the investigated formulations has a severe burst effect.

**Example 8:** 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 9:** Preparation of depot composition containing human growth hormone (HGH).

Human growth hormone (hGH) plays a critical role in stimulating body growth and development, and is involved in the production of muscle protein and in the breakdown of fats. A deficiency of the hormone adversely affects numerous body processes such as lipid profile, insulin status, physical performance, bone-mineral density and quality of life. A targeted dose every 2 weeks is estimated at 0.10 to 0.24 mg/kg of body weight.
1ml of a 2 weeks depot formulation precursor was formed by sequentially mixing 10mg hGH and 360mg PC in 0.1ml NMP. 540mg GDO was added to the mixture to obtain a low viscosity depot formulation precursor. Injecting the formulation precursor into excess water (syringe 23G; 0.6mm x 30mm) resulted in a monolithic liquid crystalline phase ($I_2$ structure).

**Example 10:** Preparation of depot composition containing a sparingly soluble active substance.

Risperidone is an antipsychotic medication agent belonging to the chemical class of benzisoxazole derivatives. It is a very strong dopamine blocker (antagonist); ie, it inhibits functioning of dopamine receptors, it is practically insoluble in water, and it has log(P)= 3.49.

1g of a depot formulation containing 50mg of risperidone was prepared by dissolving the active substance in 0.7g of a mixture 95%wt in EtOH (99.5%) and 5%wt in acetic acid. 0.34g PC and 0.51g GDO were subsequently dissolved in this solution followed by solvent reduction to remaining 0.15g solvent (0.55g was evaporated under vacuum). The composition of the final homogenous and clear depot formulation with 50mg risperidone was PC/GDO/solvent/risperidone (32/49/14/5). Injecting the formulation precursor into excess water (syringe 23G; 0.6mm x 30mm) resulted in a monolithic liquid crystalline phase ($I_2$ structure). I.e. the amount of active substance (5%) did not change monolith formation and phase behavior after exposure to an aqueous environment.

**Example 11:** Alternate preparation of depot composition containing risperidone.

A risperidone depot precursor formulation could also be prepared by using a solvent mixture composed of 90%wt EtOH (99.5%) and 10%wt in acetic acid.

50mg of risperidone was dissolved in 0.7g of the solvent mixture, after which 0.36g PC and 0.54g GDO were subsequently dissolved in this solution. 0.60g of the solvent mixture was evaporated under vacuum to a homogenous and clear depot formulation precursor with 50mg risperidone (PC/GDO/solvent/risperidone (34/51/10/5)). Injecting the formulation precursor into excess water (syringe 23G; 0.6mm x 30mm) resulted in a monolithic liquid crystalline phase ($I_2$ structure). I.e. the amount of active substance (5%) did not change monolith formation and phase behavior after exposure to an aqueous environment.

**Example 12:** Temperature stability of depot composition containing a sparingly soluble active substance.

The risperdone depot precursor formulations in examples 10 and 11 were tested for stability against crystallization during storage. Each formulation was stable at 25°C for at least two weeks and at +8°C for at least one week.

**Example 13:** 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 14:** 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 15:** 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 16:** Preparation of depot precursor being a dispersion or solution of the peptide salmon calcitonin.

By adding 500µg sCT/g formulation to a solution of PC/GDO/EtOH (36/54/10), obtained as in Example 1, a dispersion of sCT was formed.

In an alternative method, 500µg sCT was dissolved in excess of EtOH followed by addition of PC and GDO. The solvent concentration was then reduced (EtOH evaporation) to form a homogenous (active drug in solution) formulation. This latter technique can be used to obtain higher drug loads. Precursor compositions corresponding to at least 1500µg dissolved sCT per gram of the final depot precursor composition could be obtained by this method.

**Example 17:** In vivo release study from depot formulation subcutaneously administered.

The two sCT compositions described in Example 16 were administered in an *in vivo* rat model by subcutaneous injection (between the scapulae). The first depot precursor having dispersed sCT was found to give somewhat unstable initial plasma concentrations, while the second depot precursor, having sCT dissolved therein, gave much more stable initial plasma levels (see Table 5).

Table 5

| Formulations | Coefficient of variation (%CV) |
|---|---|
| Dispersed: 500μg sCT/g PC/GDO/EtOH (36/54/10) | 32-127 |
| Dissolved: 500μg sCT/g PC/GDO/EtOH (36/54/10) | 20-37 |

**Example 18:** Preparation of depot composition containing the peptide octreotide.

Octreotide is an acetate salt of a synthetic octa-peptide and is similar to the hormone somatostatin. Octreotide decreases production of substances such as growth hormone, insulin and glucagons. It is used in treatment of acromegaly, and to reduce flushing and watery diarrhoea caused by metastatic cancerous tumors (carcinoid syndrome) or tumors called vasoactive intestinal peptide tumors (VIPomas).

24mg or 60mg octreotide was dissolved in 0.1g EtOH. 0.36g PC and 0.54g GDO were subsequently dissolved in this solution and a depot formulation precursor was obtained. Injecting the formulation precursor into excess aqueous phase (syringe 23G; 0.6mm x 30mm) resulted in a monolithic liquid crystalline phase ($I_2$ structure). I.e. octreotide (2.4% or 6.0%) did not change monolith formation and phase behaviour after exposure to an aqueous environment.

The octreotide depot precursor formulations in this Example were tested for stability against crystallization during storage. Each formulation was stable at 4-8°C for at least two weeks.

**Example 19:** In vivo release study from depot formulation containing octreotide subcutaneously administered.

In an in vivo rat model the drug release of octreotide was followed during 28 days. The formulations were administered subcutaneously between the scapulae by using a syringe (23G, 0.6mm x 25mm). The octreotide concentration in the rat plasma was followed for a period of 28 days (see Figure 5). The dose was 5 mg/kg and volume 1 ml/kg corresponding to a drug load of 0.5% octreotide in the depot formulation precursor (PC/GDO/EtOH (36/54/10)).
From Figure 5 (n=3) it appears that the investigated formulation gives a release profile essentially without a burst effect.

Figure 5 shows Octreotide plasma levels in the rat model following administration of octreotide formulation precursor (0.5% in octreotide).

**Example 20:** Degradation of depot formulation in the rat.

Various volumes (1, 2, 6 ml/kg) of the depot precursor (36%wt PC, 54%wt GDO, and 10%wt EtOH) were injected in the rat and were removed again after a period of 14 days. It was found that substantial amounts of the formulations were still present subcutaneously in the rat after this time, see Table 6.

Table 6. Mean diameter of depot monolith.

| Dose (ml/kg) | Mean diameter day 3 (mm) | Mean diameter day 14 (mm) |
|---|---|---|
| 1 (n=3) | 15.8 | 12.5 |
| 2 (n=3) | 18.5 | 15.3 |
| 6 (n=3) | 23.3 | 19.3 |

**Example 21:** In vitro study of formation of depot monolith after injection of depot formulation precursor between the bone and periostium.

A precursor (36%wt PC, 54%wt GDO, and 10%wt EtOH prepared as described in Example 1) was injected by syringe between the bone and periostium. The composition was observed to spread to fill voids and after uptake of aqueous fluids formed a monolith that was bioadhesive to both the bone and periostium.

**Example 22:** 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 23:** Robustness of a topical film.

After applying the depot precursor formulation, as described in Example 22, (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 24:** 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 25:** 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 26:** 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 27:** 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 28:** 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 29:** 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 30:** 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 31** - Bioadhesive depot for nails

The mixture in Example 29 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 32:** Loading capacity of the bioactive agent benzydamine in the formulation precursors.

Formulations with compositions as specified in Table 7 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 7.

Table 7

| 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 33:** 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 8.

Table 8

| 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 34:** Composition containing octreotide

60mg octreotide was dissolved in 0.1g EtOH. 0.25g PC and 0.59g α-tocopherol were subsequently dissolved in this solution and a depot formulation precursor was obtained. Injecting the formulation precursor into excess aqueous solution (phosphate buffered saline - PBS) resulted in a monolithic liquid crystalline phase ($I_2$ structure) i.e. octreotide (6.0%) did not change monolith formation and phase behaviour after exposure to an aqueous environment.

The octreotide depot precursor formulation in this Example was tested for stability against crystallization during storage. The formulation was stable at 4-8°C for at least two weeks.

**Example 35:** 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 9) 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 9

| 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 36: **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 37: **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 38: **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 39: **Interferon Alpha-2a**

Interferons (IFNs) are used as a treatment for many types of systemic cancer, often in combination with chemotherapy or radiation. Recent data suggest that IFN Alpha is a multifunctional immunomodulatory cytokine with profound effects on the cytokine cascade including several anti-inflammatory properties. These newly identified immunoregulatory and anti-inflammatory functions may also be of importance in treatment of diseases such as chronic viral hepatitis and help to explain some of the IFN mechanisms.

A non-aqueous precursor formulation was formed by dissolving PC (360 mg) and GDO (540 mg) in EtOH (100 mg). Interferon Alpha-2a (4 mg) was dissolved in water (76 mg) and this solution was thereafter added to the non-aqueous precursor formulation to form a depot formulation precursor of low viscosity.

Injecting the depot precursor into excess water (syringe 23 G; 0.6mm x 30 mm) resulted in a monolithic liquid crystalline phase ($I_2$ structure).

Example 40 **Leuprorelin (Leuprolide)**

Leuprorelin acetate (or leuprolide acetate) is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) that, when given continuously (e.g. as a depot formulation), inhibits pituitary gonadotropin secretion and suppresses testicular and ovarion steroidogenesis. Leuprorelin is used for the treatment of advanced prostate cancer.

A depot formulation precursor was formed by sequentially dissolving 22.5 mg leuprorelin acetate and 360 mg PC in 100 mg of NMP. 540 mg of GDO was added to the mixture yielding a molecular solution depot formulation precursor of low viscosity. Injecting the formulation precursor into excess water (syringe 23 G; 0.6mm x 30 mm) resulted in a monolithic liquid crystalline phase ($I_2$ structure).

Example 41: **Alendronate**

Bisphosphonates are structural analogues of pyrophosphates and have pharmacologic activity specific for bone due to the strong affinity of bisphosphonates for hydroxyapatite, a major inorganic component of bone. The compounds are used to treat postmenopausal osteoporosis, hypercalcemia of malignancy and metastatic bone disease (MBD).

A non-aqueous precursor formulation was formed by dissolving PC (360 mg) and GDO (540 mg) in EtOH (100 mg). Alendronate (12 mg) was dissolved in water (80 mg) and this solution was thereafter added to the non-aqueous precursor formulation to form a depot formulation precursor of low viscosity. Injecting the depot precursor into excess water (syringe 23 G; 0.6mm x 30 mm) resulted in a monolithic liquid crystalline phase ($I_2$ structure).

Example 42: **Olanzapine**

Olanzapine is a low molecular weight drug used for the treatment of patients with schizophrenia.

A depot formulation precursor was formed by sequentially mixing 50 mg olanzapine, 360 mg PC and 100 mg of EtOH. 540 mg of GDO was added to the mixture resulting in the final depot formulation precursor.

Injecting the formulation precursor into excess water (syringe 23 G; 0.6mm x 30 mm) resulted in a monolithic liquid crystalline phase ($I_2$ structure).

Example 43: **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 44: **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 45: **Occtreotide Formulation compositions**

Formulations were prepared as in Example 1 by mixing the peptide active octreotide with a mixture of GDO (at one of several purity levels) or tocopherol, PC, ethanol and optionally dioleoyl PG in the following proportions (by weight)

| Formulation | OCT | EtOH | PC | GDO1 | GDO2 | GDO3 | TP | DOPG |
|---|---|---|---|---|---|---|---|---|
| E | 2 | 10 | 35.2 | - | - | 52.8 | - | - |
| F | 2 | 10 | 35.2 | 52.8 | - | - | - | - |
| G | 2 | 10 | 35.2 | - | 52.8 | - | - | - |
| H | 2 | 10 | 26.4 | - | - | - | 61.6 | - |
| I | 1 | 10 | 35.6 | 53.4 | - | - | - | - |
| J | 2 | 5 | 37.2 | - | - | 55.8 | - | - |
| K | 3 | 5 | 36.8 | - | - | 55.2 | - | - |
| L | 6 | 5 | 35.6 | - | - | 53.5 | - | - |
| M | 3 | 5 | 35.8 | - | - | 55.2 | - | 1 |
| N | 3 | 5 | 33.8 | - | - | 55.2 | - | 3 |
| O | 3 | 5 | 30.8 | - | - | 55.2 | - | 6 |
| P | 3 | 5 | 46 | - | - | 46 | - | - |
| Q | 3 | 10 | 43.5 | - | - | 43.5 | - | - |
| R | 6 | 10 | 42 | - | - | 42 | - | - |
| S | 3 | 7 | 45 | - | - | 45 | - | - |
| T | 6 | 7 | 43.5 | - | - | 43.5 | - | - |

where OCT is octreotide, EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, TP is α-tocopherol, DOPG is dioleoyl phosphatidylglycerol

**GDO quality (according to AC)**

| | Monoglycerides | Diglycerides | Triglycerides |
|---|---|---|---|
| GDO1 | 10.9% | 87.5% | 1.4% |
| GDO2 | 4.2% | 92.1% | 3.5% |
| GDO3 | 0.5% | 95.3% | 4.0% |

Formulation P (for composition see above) was administered by s.c.injection in the rat at a level of 1 ml formulation per kg body weight, corresponding to 30 mg/kg of octreotide.

Octreotide plasma levels after administration were monitored for 5 days to examine any burst profile. It was observed that the highest plasma concentration was less than three fold greater than the average plasa concentration over the first 5 days.

The results of the study are shown in Figure 6

*Example 46:* ***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 47: **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 studdied. 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 7 demonstrates the sustained and essentially uniform release of chlorhexidine from the formulation over a period of 24 hours.

Claims:

1) A pre-formulation comprising a low viscosity, non-liquid crystalline, 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 and wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid.

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 claim 1 or claim 2 wherein component a) consists essentially of at least one tocopherol.

5) A pre-formulation as claimed in claim 1 or claim 2 wherein component a) consists essentially of a mixture of GDO and tocopherol.

6) A pre-formulation as claimed in any of claims 1 to 5 wherein component b) is selected from phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines, phosphatidylinositols and mixtures thereof.

7) A preformulation as claimed in any of claims 1 to 6 having a viscosity of 0.1 to 5000 mPas.

8) A preformulation as claimed in any of claims 1 to 7 having a molecular solution, $L_2$ and/or $L_3$ phase structure.

9) A preformulation as claimed in any of claims 1 to 8 having a ratio of a) to b) of between 95:5 and 5:95 by weight.

10) A preformulation as claimed in any of claims 1 to 9 having 0.5 to 50% component c) by weight of components a) + b) + c).

11) A preformulation as claimed in any of claims 1 to 10 wherein component c) is selected from alcohols, ketones, esters , ethers, amides, sulphoxides and mixtures thereof.

12) A preformulation as claimed in any of claims 1 to 11 additionally comprising up to 10% by weight of a)+b) of a charged amphiphile.

13) A preformulation as claimed in any of claims 1 to 12 wherein said active agent is selected from drugs, antigens, nutrients, cosmetics, fragrances, flavourings, diagnostic agents, vitamins, dietary supplements and mixtures thereof.

14) A preformulation as claimed in calim 13 wherein said drus is selected from hydrophilic small molecule drugs, lipophilic small molecule drugs, amphiphilic small molecule drugs, peptides, proteins, oligonucleotids and mixtures thereof.

15) A preformulation as claimed in claim 13 wherein said drug is selected from somatostatin related peptides, interferons, glucagon-like peptides 1 and 2, GnRH agonists, GnRH antagonists, bisphosponates, chlorhexidine and mixtures thereof.

16) A preformulation as claimed in any of claims 1 to 15 which is administrable by injection.

17) A preformulation as claimed in any of claims 1 to 15 which is administrable by spraying, dipping, rinsing, application from a pad or ball roller, painting, dropping, aerosol spraying or pump spraying.

18) An injectable preformulation as claimed in any of claims 1 to 16 which forms a depot providing continuous release of active agent for at least two weeks, wherein said active agent comprises at least one selected from

i. octreotide
ii. human growth hormone
iii. interferon alpha
iv. leuprolide

19) An injectable preformulation as claimed in any of claims 1 to 16 which forms a depot providing continuous release of active agent for at least two weeks, wherein said active agent comprises at least one selected from

i. risperidone
ii. olanzapine
iii. testosterone undecanoate

20) A topical formulation as claimed in any of claims 1 to 15 for intraoral administration which forms a bioadhesive, controlled release product, wherein said active agent comprises at least one selected from

i. benzydamine
ii. tramadol

21) A topical preformulation as claimed in any of claims 1 to 15 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.

22) A non-parenteral formulation as claimed in any of claims 1 to 15 for intranasal spray administration which forms a bioadhesive, controlled release product, wherein said active agent comprises at least one selected from

i. fentanyl
ii. diazepam

23) A topical formulation as claimed in any of claims 1 to 15 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.

24) A non-parenteral formulation as claimed in any of claims 1 to 15 for dermatological administration which forms a bioadhesive, controlled release product, wherein the active agent is selected from;

i. acyclovir

ii. testosterone undecanoate.

25) A topical formulation as claimed in any of claims 1 to 15 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.

26) 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.

27) A method as claimed in claim 26 wherein said preformulation is a preformulation as claimed in any of claims 1 to 25.

28) The method as claimed in claim 26 or claim 27 wherein said pre-formulation is administered by a method selected from subcutaneous injection, intramuscular injection, intra-cavity injection through tissue, intra-cavity injection into an open cavity without tissue penetration, spraying, rolling, wiping, dabbing, painting, rinsing, or dropping.

29) A method for the preparation of a liquid crystalline composition comprising exposing 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 dissolved or dispersed in the low viscosity mixture, to an aqueous fluid *in vivo*.

30) A method as claimed in claim 29 wherein said preformulation is a preformulation as claimed in any of claims 1 to 25.

31) A process for the formation of a pre-formulation suitable for the administration of a bioactive agent to a (preferably mammalian) subject, said process comprising forming 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 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.

32) A process as claimed in claim 31 wherein said preformulation is a preformulation as claimed in any of claims 1 to 25.

33) 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 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.

34) The use as claimed in claim 33 wherein said preformulation is a preformulation as claimed in any of claims 1 to 25.

35) 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 25.

36) The method of claim 35 for the treatment of a condition selected from bacterial infection, fungal infection, skin soreness, eye conditions, genital soreness, infections and conditions for the finger and/or toe nails, travel sickness, addiction including nicotine addiction, periodontal infection, conjunctivitis, glaucoma and hormone deficiency or imbalance.

37) The method of claim 35 for prophylaxis against at least one condition selected from infection during surgery, infection during implantation, sunburn, infection at the site of burns, cuts or abrasions, oral infections, genital infections and infections resulting from activities resulting in exposure to infective agents.

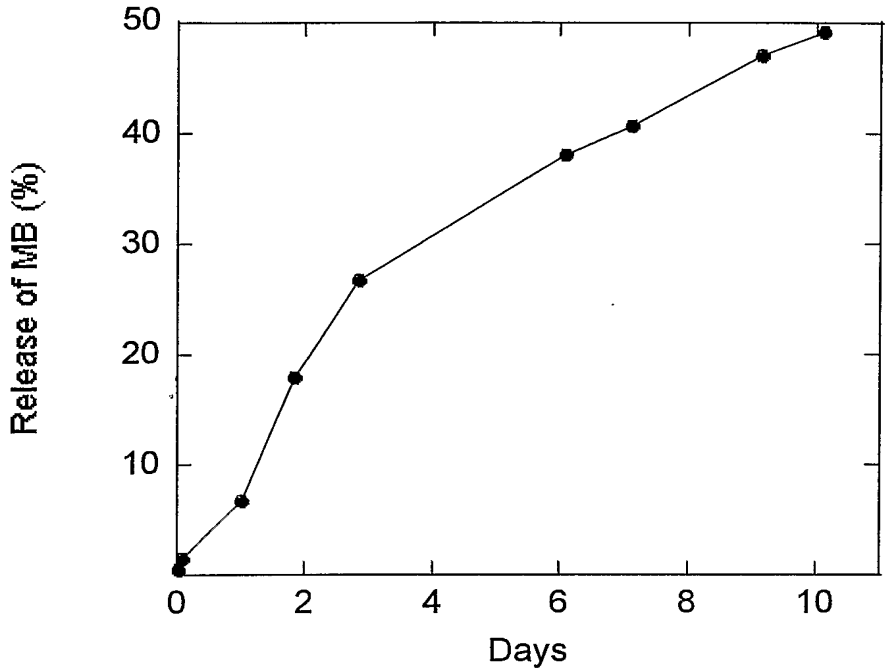



Figure 1. Cumulative release of MB from a depot forming a reversed hexagonal $H_{II}$ phase.

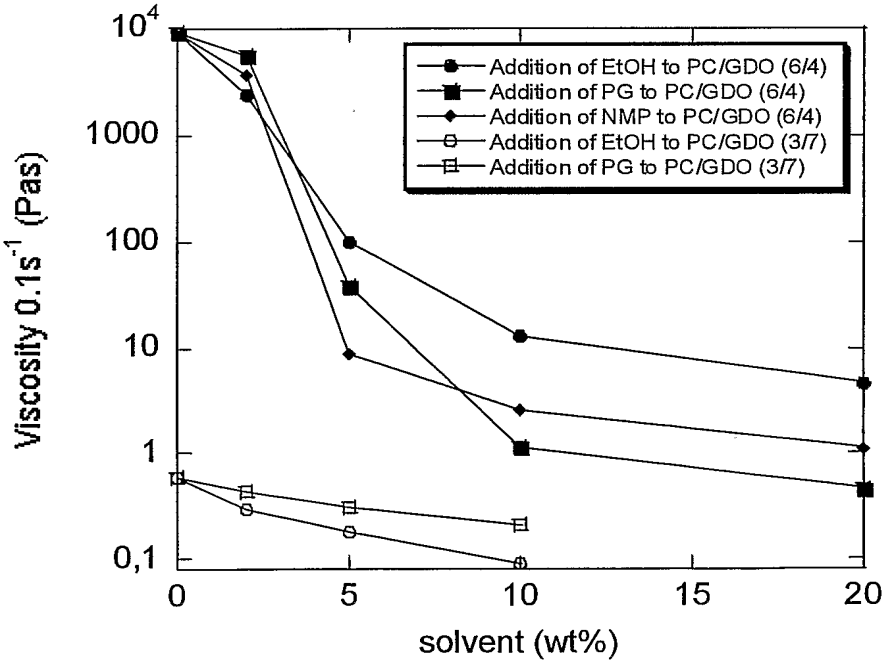



*Figure 2. Decrease in viscosity of the depot precursor on addition of solvents. PC/GDO (6/4) is a precursor to a reversed hexagonal $H_{II}$ phase and PC/GDO (3/7) is a precursor to a reversed cubic $I_2$ phase.*

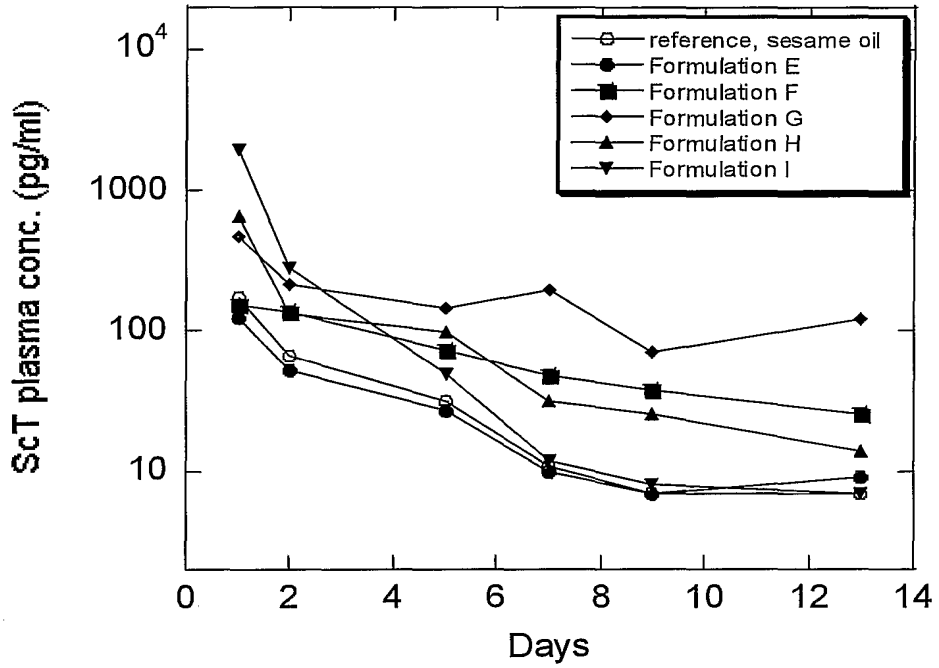



*Figure 3. Plasma concentrations in the rat model after subcutaneous administration of formulations E to I. A depot based on sesame oil was used as reference.*

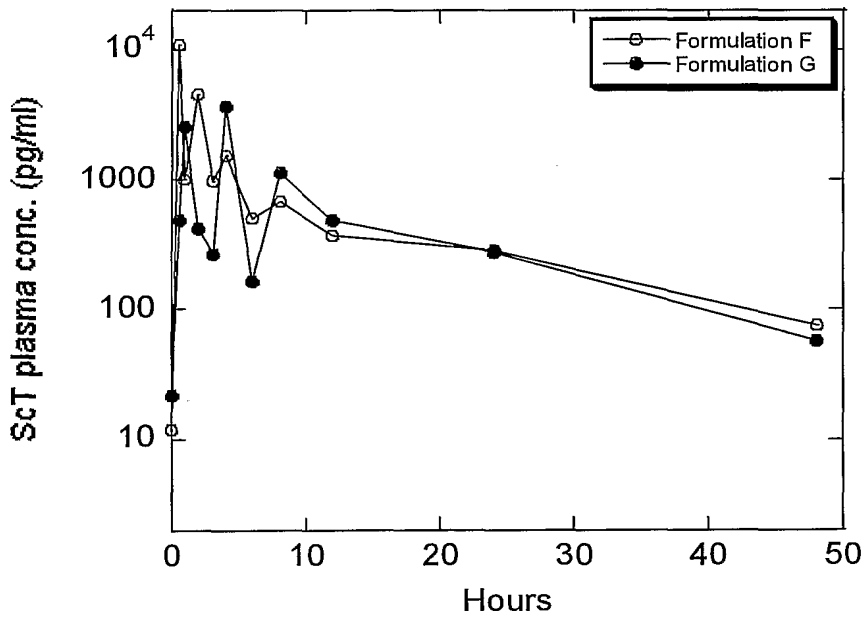



Figure 4. Plasma concentrations in the rat model after subcutaneous administration of formulations F and G.

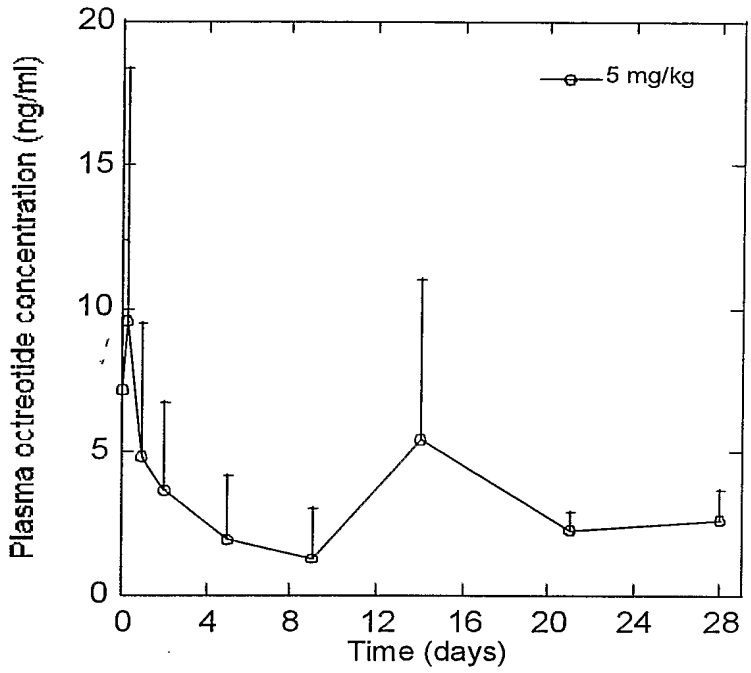



Figure 5: Octreotide plasma levels in the rat model following administration of octreotide formulation precursor (0.5% by weight octreotide).

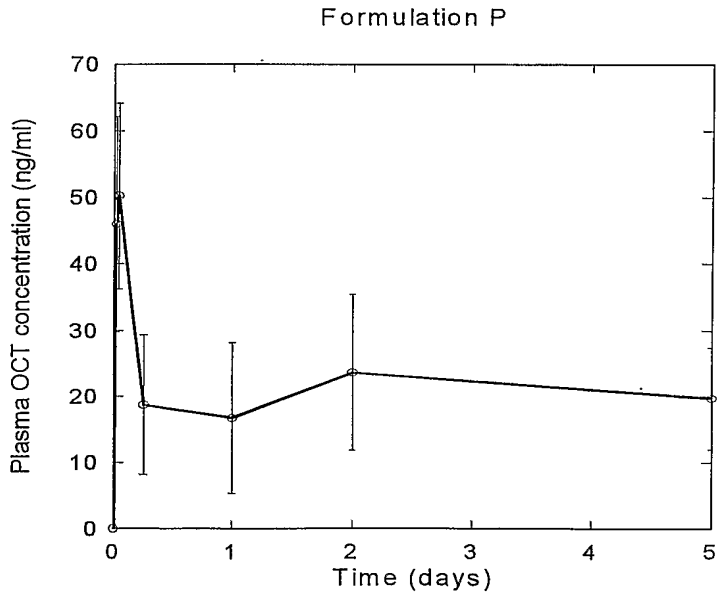



Figure 6: Octreotide plasma levels in the rat model following administration of octreotide formulation P, see Example 45.

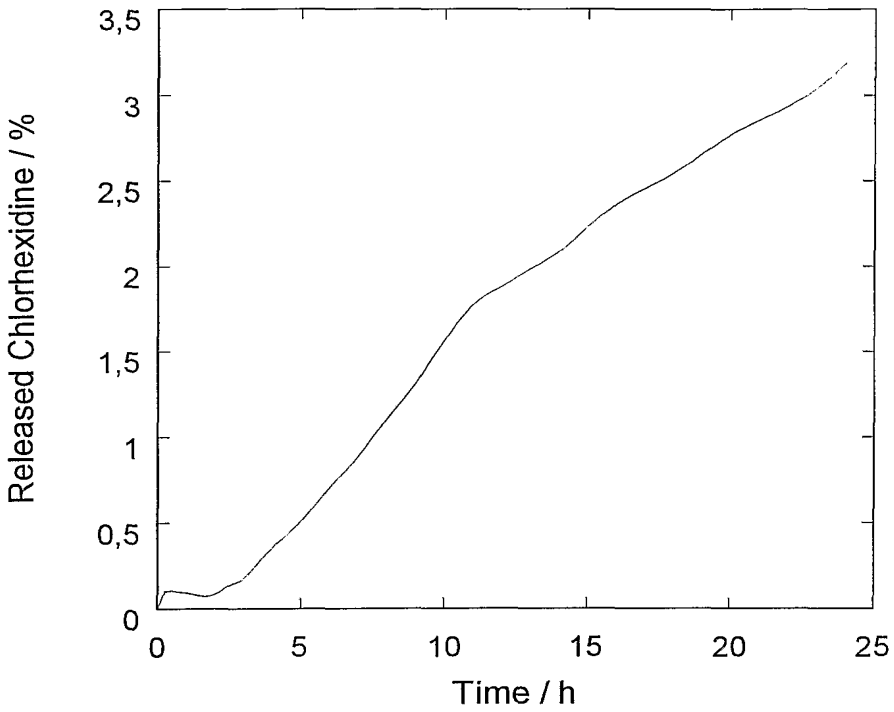



Figure 7: Release of Chlorhexidine from formulation A, see Example 47.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/002217

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 7 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)
IPC 7 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. |
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 |
|---|---|
| 7 October 2005 | 19/10/2005 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Giménez Miralles, J |

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Form PCT/ISA/210 (second sheet) (January 2004)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/002217

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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1

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/002217

**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.: 26-28, 35-37
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-28 and 35-37 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

International Application No
PCT/GB2005/002217

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PCT

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*A61K 9/06* (2006.01)

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| PCT/GB2005/002217 | 6 June 2005 (06.06.2005) | GB |


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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search 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: 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.

WO 2006/075123 A1

# 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.

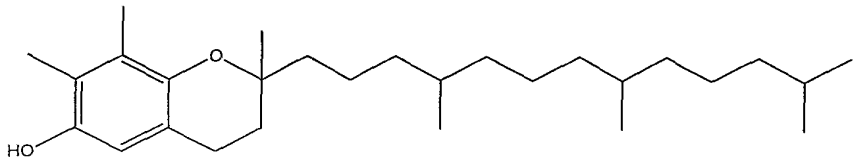
In one preferred aspect, component a is a diacyl lipid in that it has two non-polar "tail" groups. This is generally preferable to the use of mono-acyl ("lyso") lipids because these are typically less well tolerated *in vivo*. The two non-polar groups may have the same or a differing number of carbon 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 $L_\alpha$, $I_2$, $L_2$, 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 | $H_{II}/L_\alpha$ |

$L_2$ = reversed micellar phase

$I_2$ = reversed cubic liquid crystalline phase

$H_{II}$ = reversed hexagonal liquid crystalline phase

$L_\alpha$ = 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 $0.1 s^{-1}$ 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 | $H_{II}/L_\alpha$ |

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.

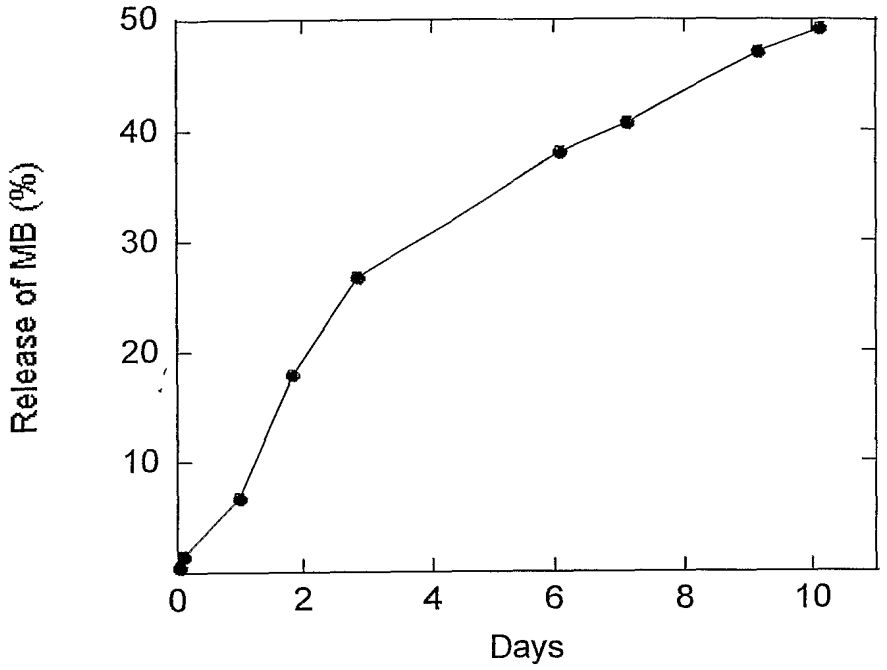



Figure 1. of MB from a depot forming a reversed hexagonal $H_{II}$ phase.

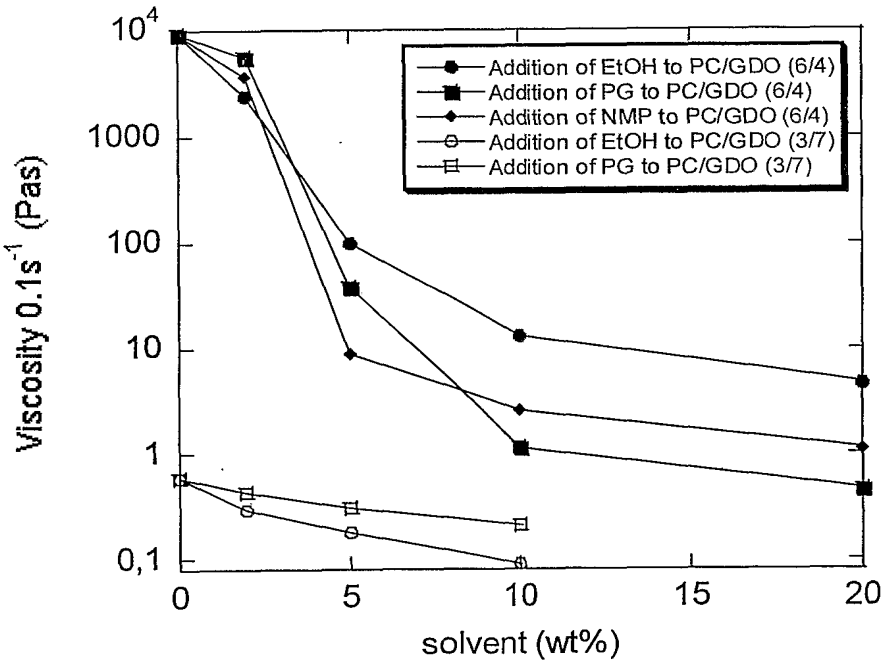



*Figure 2.*

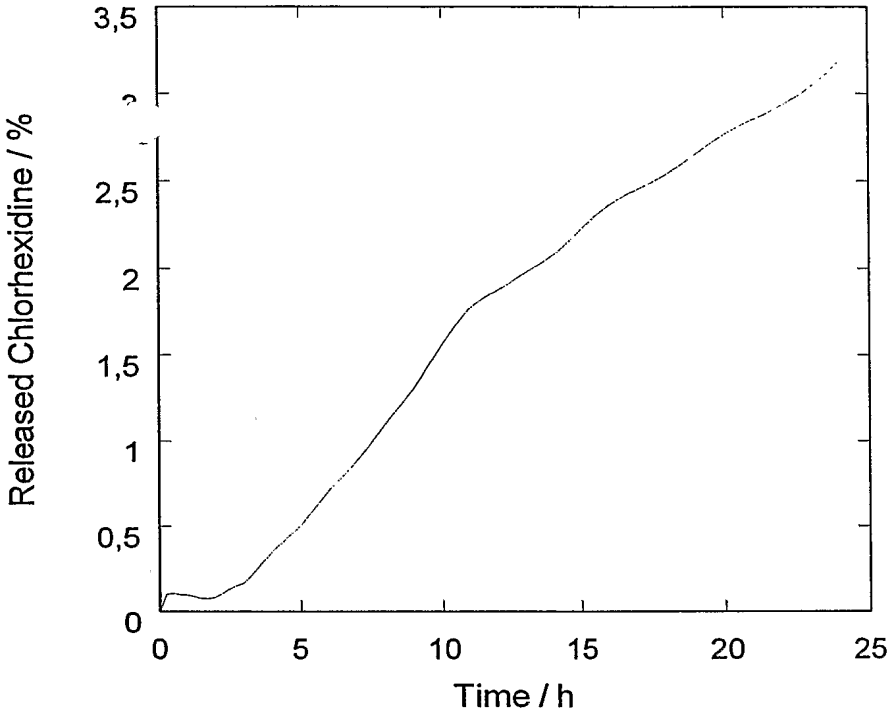



Figure 3

# 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. |
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-/--

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

[X] See patent family annex.

* Special categories of cited documents :

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"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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| 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<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Giménez Miralles, J |

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Inter ıal application No
PCT/GB2005/004746

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# 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

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Information on patent family members

Inter nal application No
PCT/GB2005/004746

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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**Published:**
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*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.*

WO 2007/043057 A2

(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.

# 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.

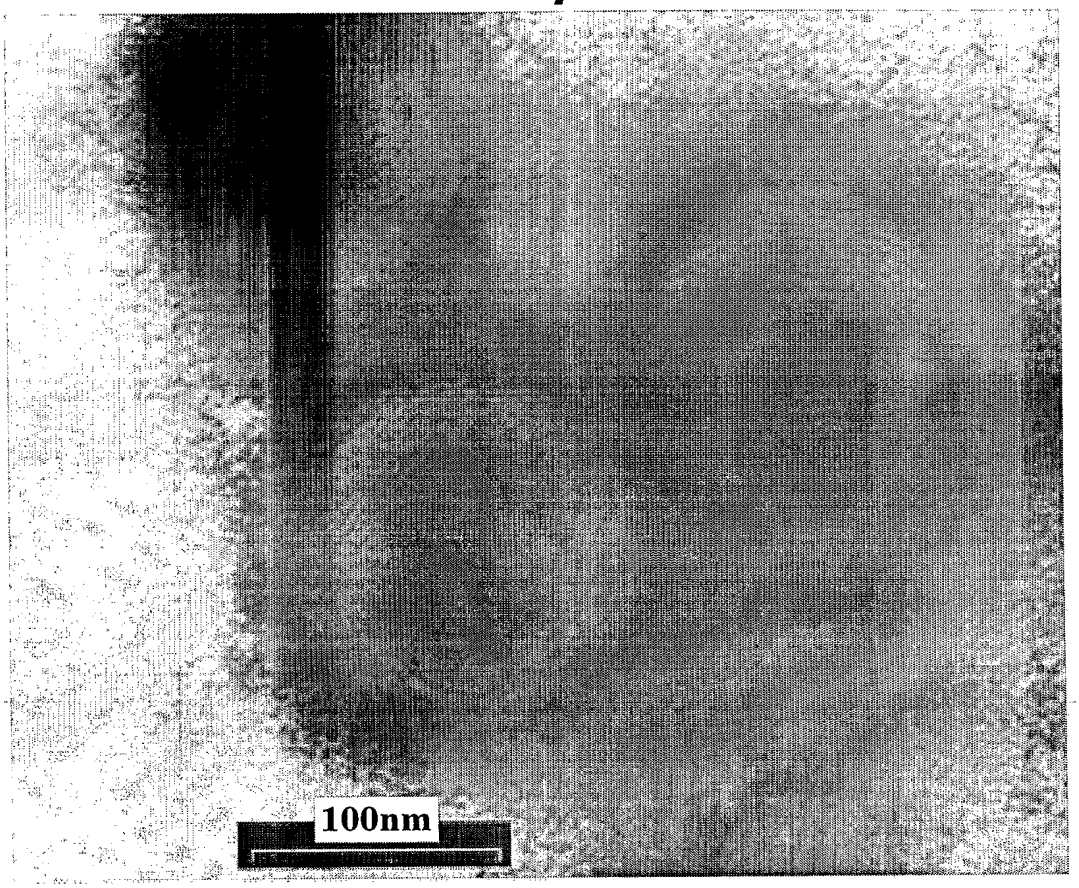
100nm

Fig. 1

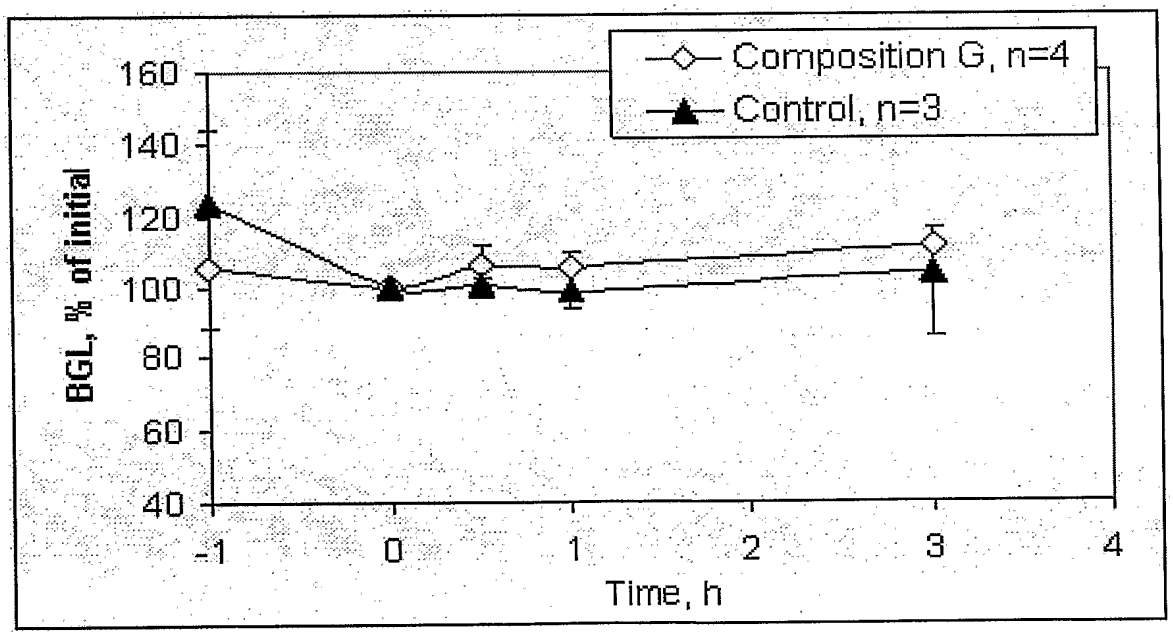
Composition G, n=4
Control, n=3
BGL, % of initial
160
140
120
100
80
60
40
-1
0
1
2
3
4
Time, h

Fig. 2

2/7

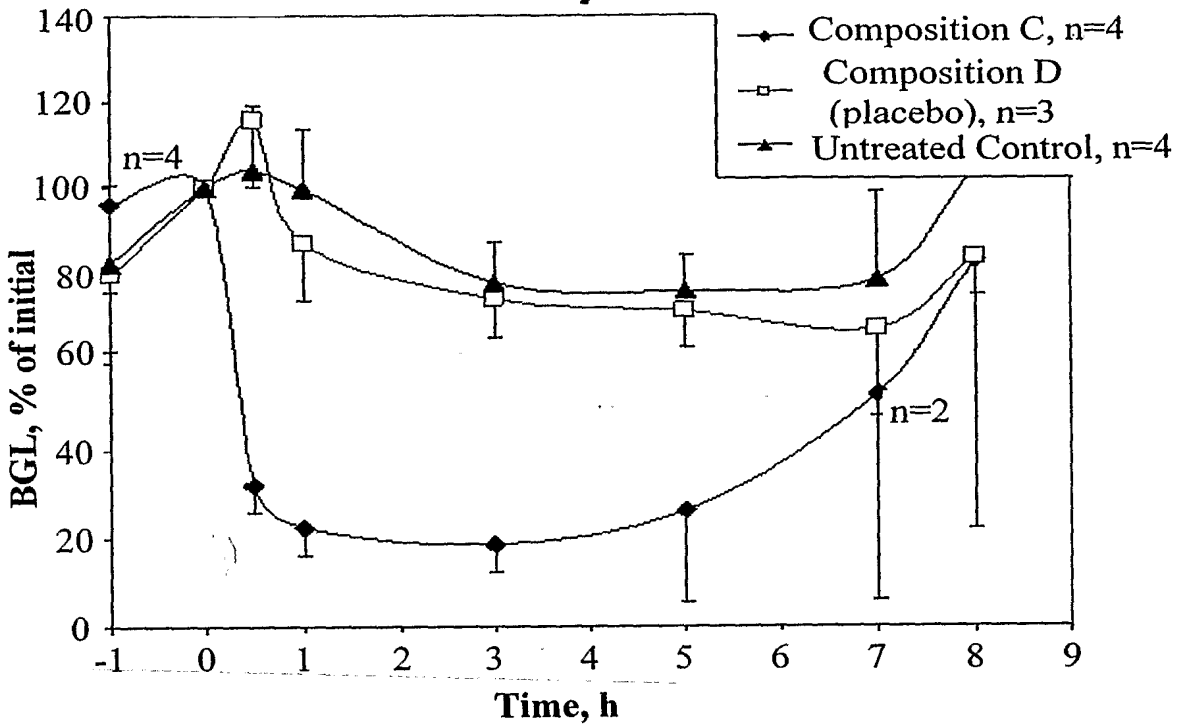
Composition C, n=4
Composition D (placebo), n=3
Untreated Control, n=4
n=4
n=2
BGL, % of initial
Time, h
140
120
100
80
60
40
20
0
-1
0
1
2
3
4
5
6
7
8
9

Fig. 3

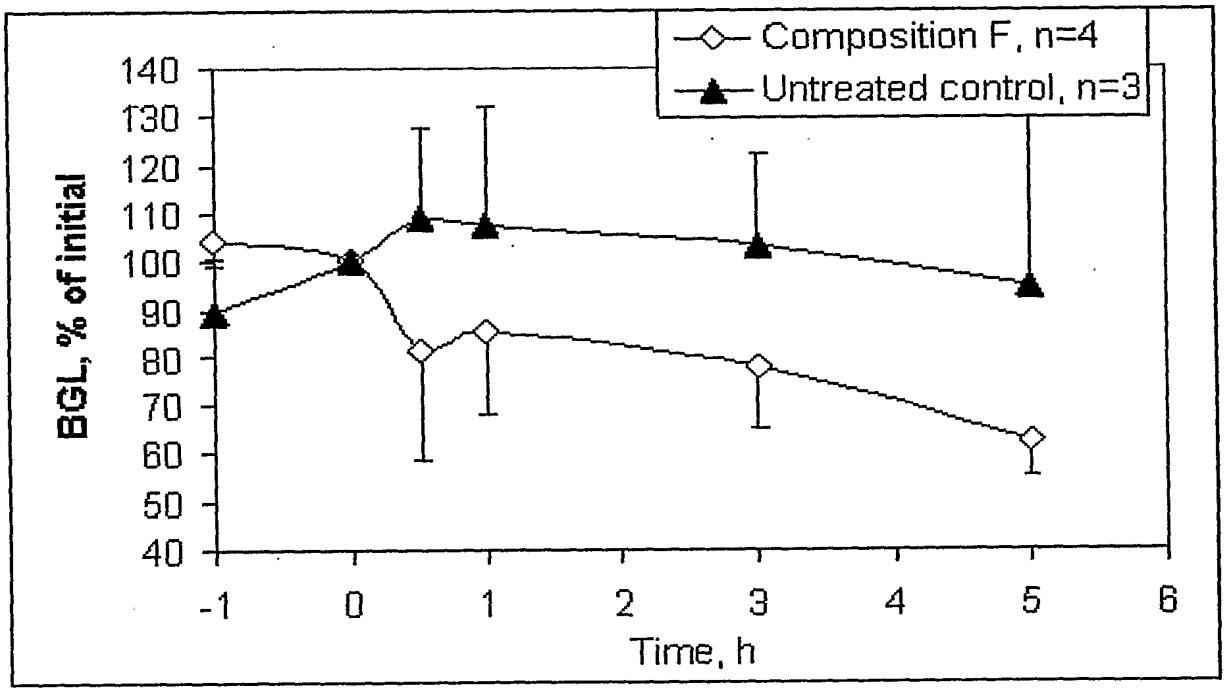
Composition F, n=4
Untreated control, n=3
BGL, % of initial
Time, h
140
130
120
110
100
90
80
70
60
50
40
-1
0
1
2
3
4
5
6

Fig. 4

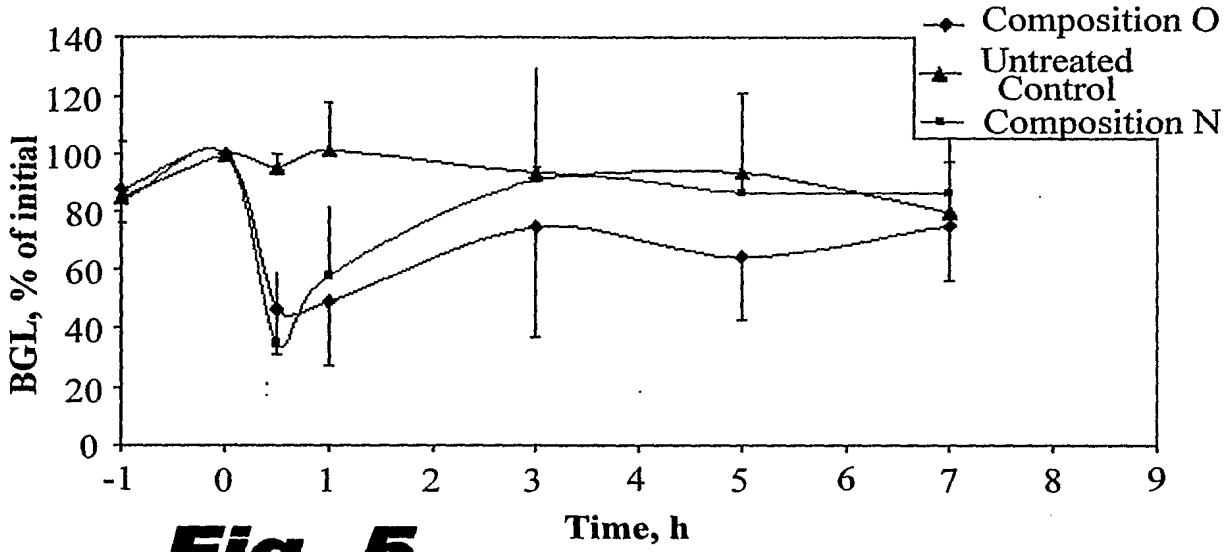
Composition O
Untreated Control
Composition N
BGL, % of initial
140
120
100
80
60
40
20
0
-1
0
1
2
3
4
5
6
7
8
9
Time, h

Fig. 5

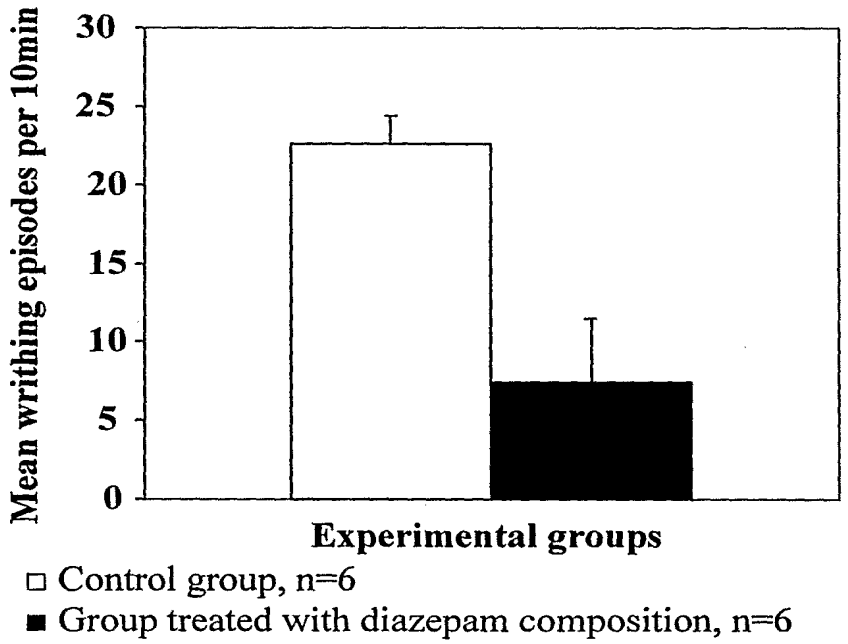
Mean writhing episodes per 10min
30
25
20
15
10
5
0
Experimental groups
Control group, n=6
Group treated with diazepam composition, n=6

Fig. 6

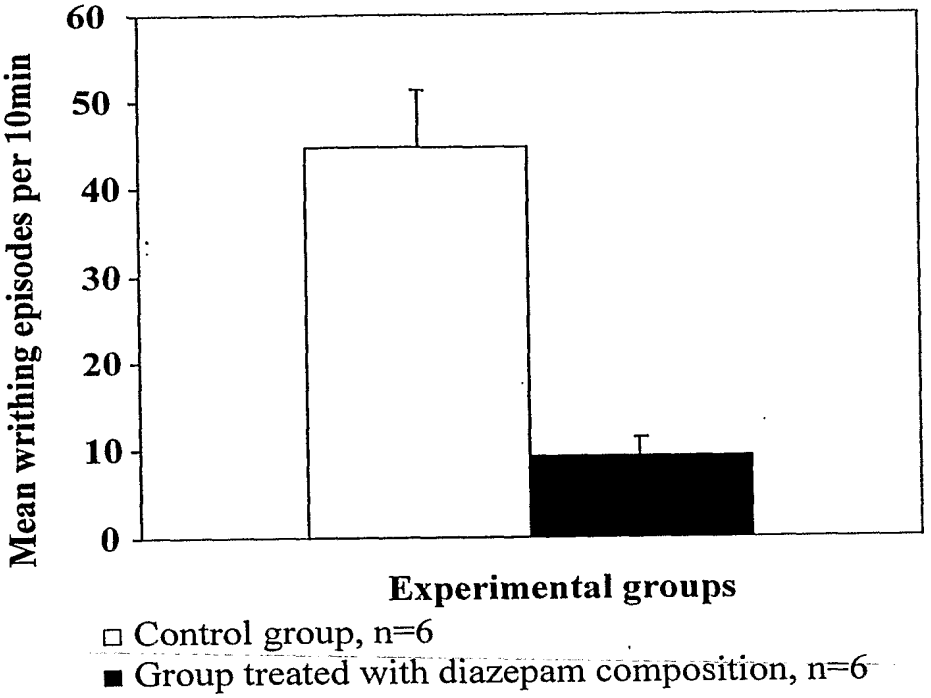
60
50
40
30
20
10
0
Mean writhing episodes per 10min
Experimental groups
Control group, n=6
Group treated with diazepam composition, n=6

**Fig. 7**

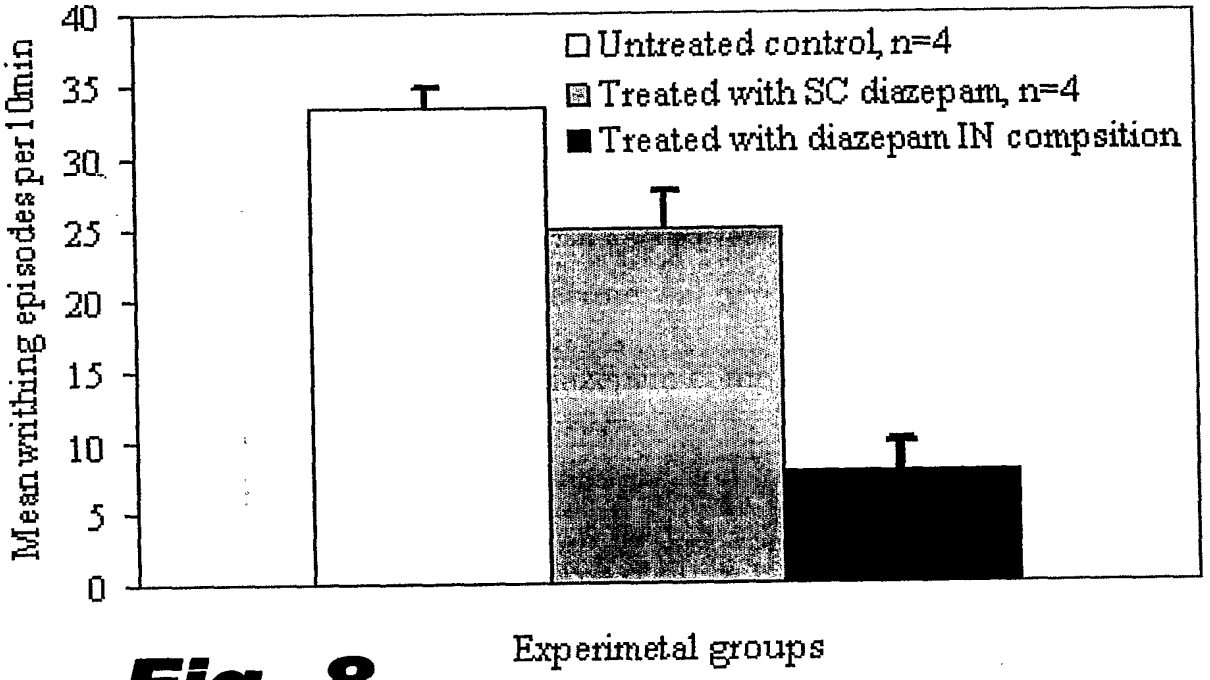
40
35
30
25
20
15
10
5
0
Mean writhing episodes per 10min
Untreated control, n=4
Treated with SC diazepam, n=4
Treated with diazepam IN compsition
Experimetal groups

**Fig. 8**

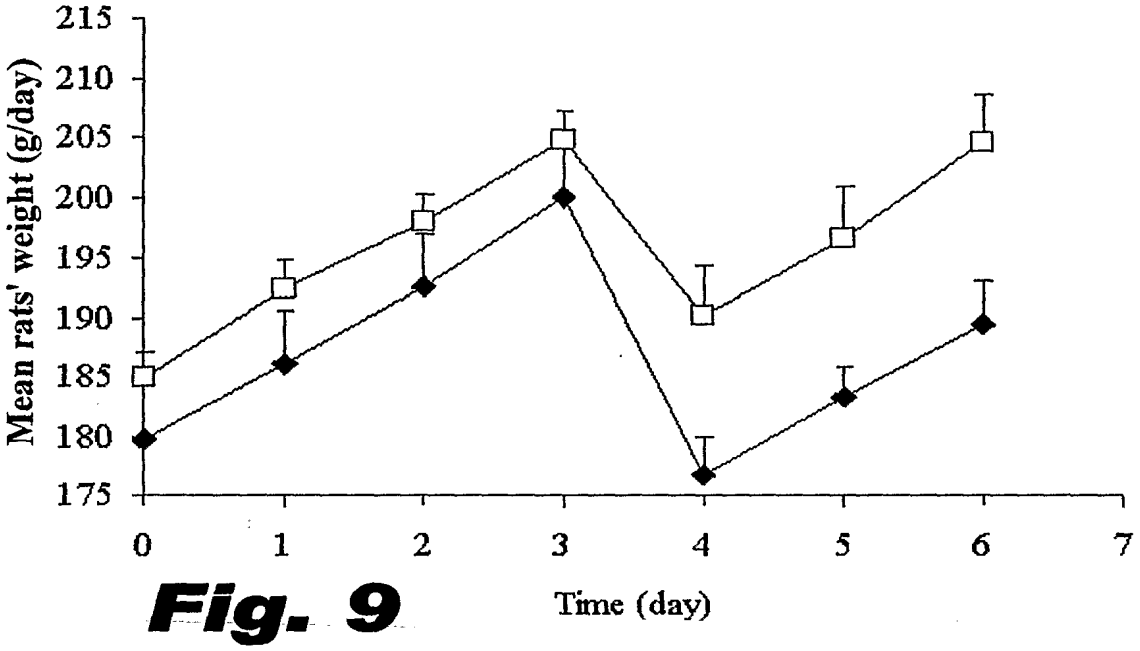
Mean rats' weight (g/day)
215
210
205
200
195
190
185
180
175
0
1
2
3
4
5
6
7
Time (day)

Fig. 9

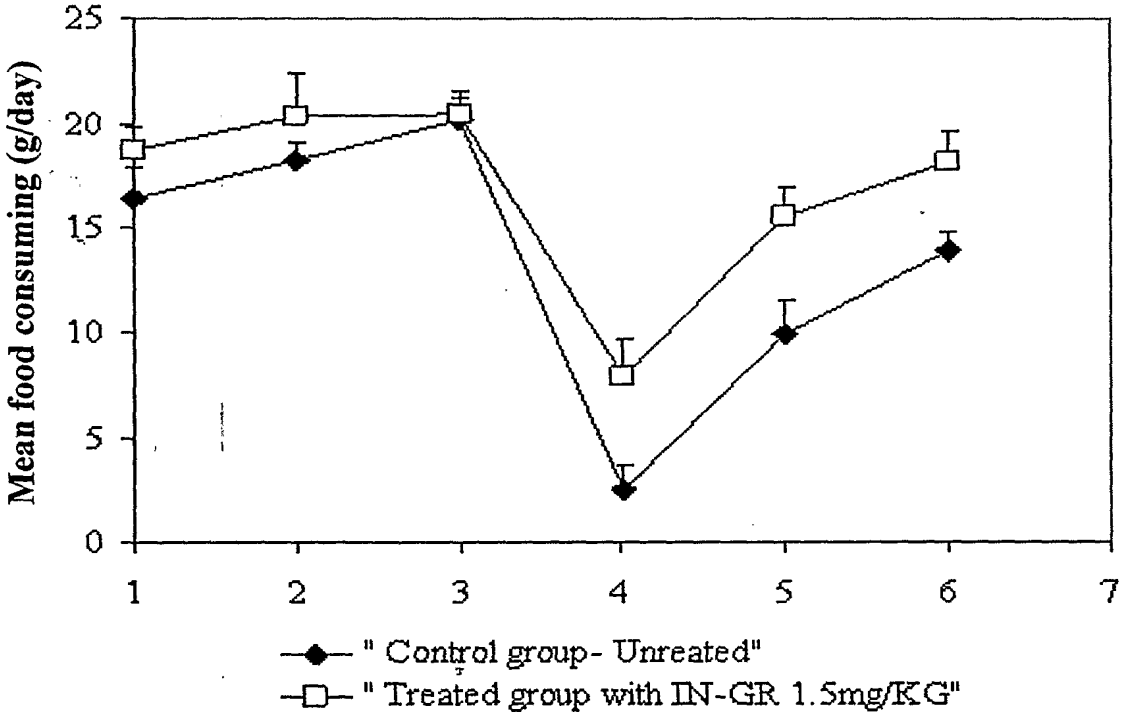
Mean food consuming (g/day)
25
20
15
10
5
0
1
2
3
4
5
6
7
" Control group- Unreated"
" Treated group with IN-GR 1.5mg/KG"

Fig. 10

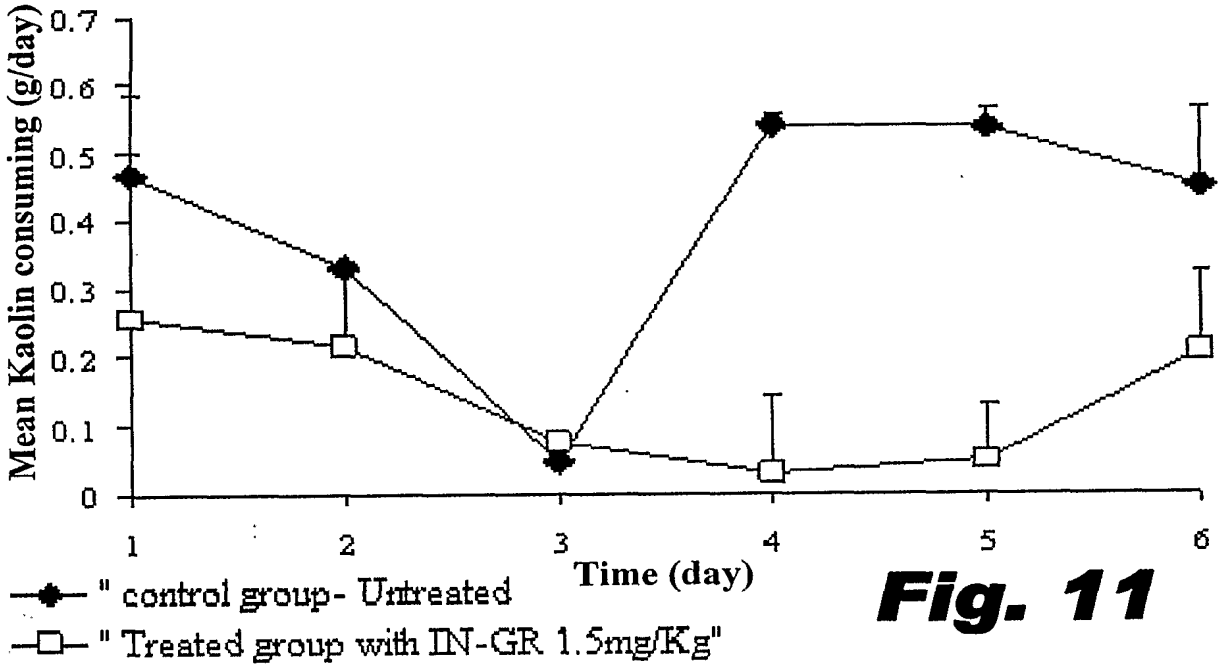
Mean Kaolin consuming (g/day)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
5
6
Time (day)
" control group- Untreated
" Treated group with IN-GR 1.5mg/Kg"

Fig. 11

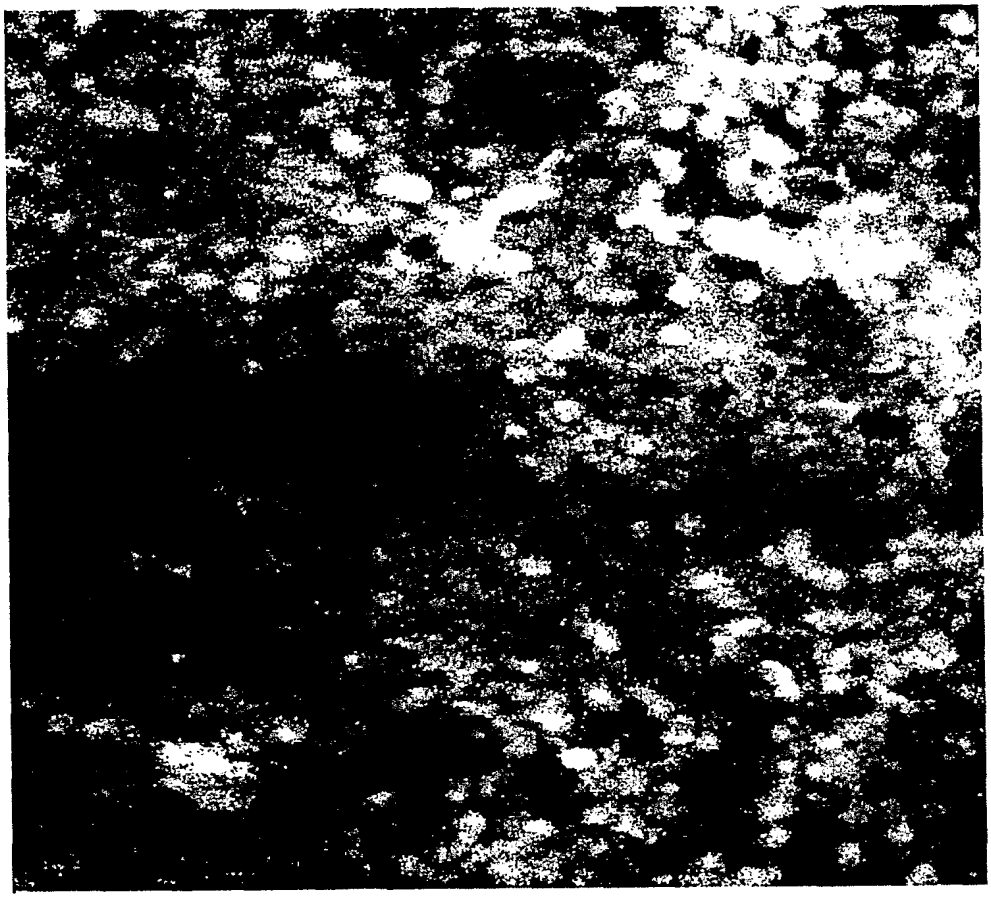

Fig. 12

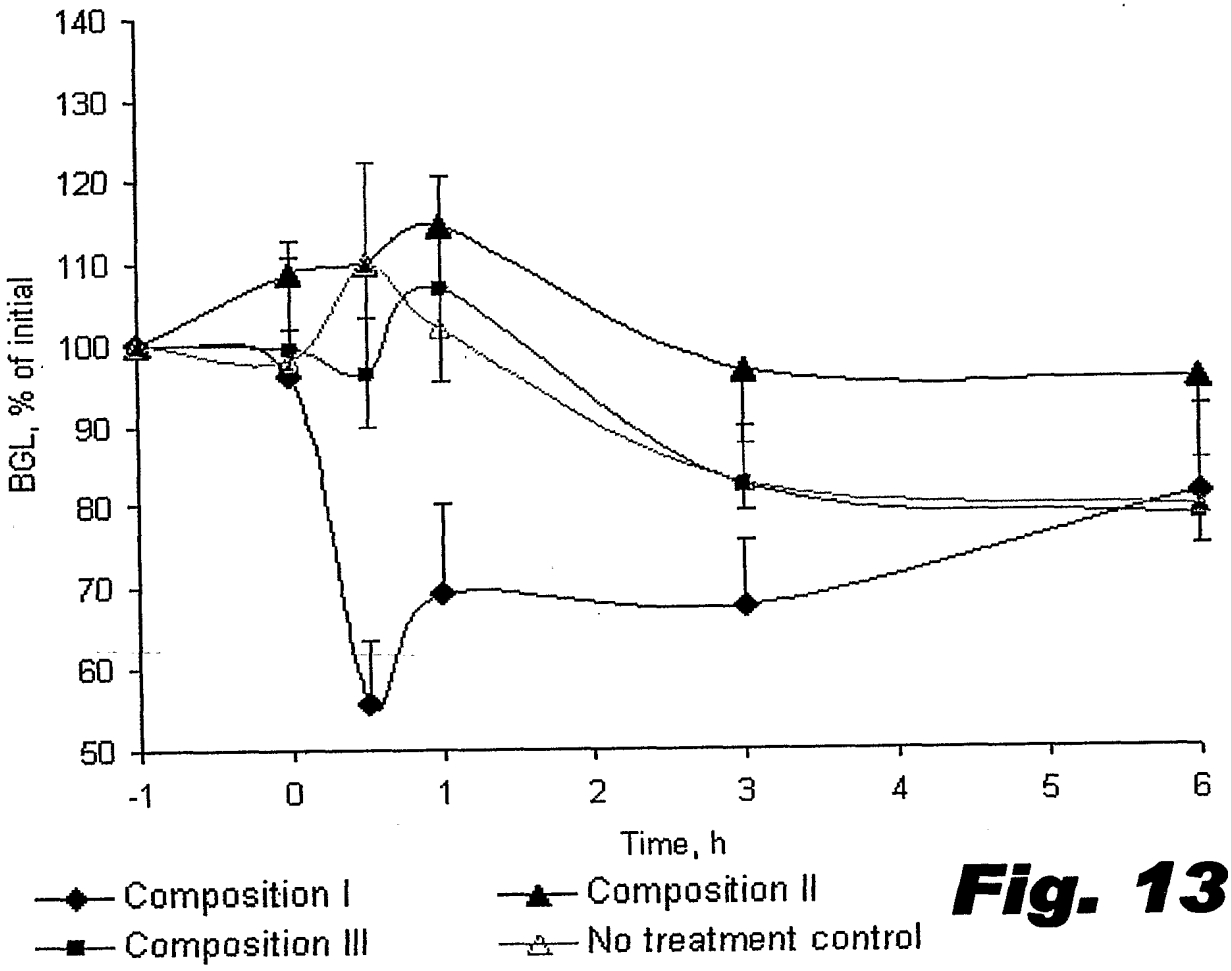
140
130
120
110
100
90
80
70
60
50
BGL, % of initial
-1
0
1
2
3
4
5
6
Time, h
Composition I
Composition II
Composition III
No treatment control

Fig. 13

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
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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 Raucherentwöhonung 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-