United States of America

To Promote the Progress of Science and Useful Arts

The Director

of the United States Patent and Trademark Office has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this United States

Patent

grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America, and if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States of America, products made by that process, for the term set forth in 35 U.S.C. 154(a)(2) or (c)(1), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b). See the Maintenance Fee Notice on the inside of the cover.

Director of the United States Patent and Trademark Office

described herein is stable in that after an extended period of time the miniemulsion still has a mean particle size of 1 μm or less. In one embodiment, the miniemulsion described herein is stable from at least one month up to about three years without refrigeration. Preferably, the miniemulsion is stable without refrigeration for at least about one year. More preferably, the miniemulsion is stable without refrigeration for at least about two years. In one embodiment, after about three years at least 70% of the particles are 1 μm or less. In another embodiment, after about three years the mean particle size has increased by less than 0.05 μm.

In one aspect, a miniemulsion provided by a method described above may be formulated to include a bioactive agent or multiple bioactive agents in combination. A wide variety of bioactive agents can be used with the methods described herein. A liquid or solid bioactive agent can be incorporated into the miniemulsion described herein. The bioactive agents can include salts of the active ingredient. As such, the bioactive agents can be acidic, basic, or amphoteric salts. They can be non-ionic molecules, polar molecules, prodrugs, solvates, polymorphs or molecular complexes capable of hydrogen bonding. The bioactive agent can be included in the compositions in the form of, for example, an uncharged molecule, a molecular complex, a salt, an ether, an ester, an amide, polymer drug conjugate, or other form to provide the effective biological or physiological activity.

Examples of bioactive agents that may be incorporated into systems herein include, but are not limited to, peptides, proteins such as hormones, enzymes, antibodies, antibody fragments and the like, nucleic acids such as aptamers, siRNA, DNA, RNA, antisense nucleic acid or the like, antisense nucleic acid analogs or the like, low-molecular weight compounds, or high-molecular weight compounds. Bioactive agents contemplated for use in the disclosed miniemulsion include anabolic agents, antacids, anti-asthmatic agents, anti-cholesterolemic and anti-lipid agents, anti-coagulants, anti-convulsants, anti-diarrheals, anti-emetics, anti-infective agents including antibacterial and antimicrobial agents, anti-inflammatory agents, anti-manic agents, antimetabolite agents, anti-nauseants, anti-neoplastic agents, anti-obesity agents, anti-pyretic and analgesic agents, anti-spasmodic agents, anti-thrombotic agents, antitussive agents, anti-uricemic agents, anti-vascular growth agents, anti-vascular endothelial growth agents, anti-anginal agents, antihistamines, appetite suppressants, biologicals, cerebral dilators, coronary dilators, bronchiodilators, cytotoxic agents, decongestants, diuretics, diagnostic agents, erythropoietic agents, expectorants, gastrointestinal sedatives, hyperglycemic agents, hypnotics, hypoglycemic agents, immunomodulating agents, ion exchange resins, laxatives, mineral supplements, mucolytic agents, neuromuscular drugs, peripheral vasodilators, psychotropics, sedatives, stimulants, thyroid and anti-thyroid agents, tissue growth agents, vascular growth agents, vascular endothelial growth agents, uterine relaxants, vitamins, or antigenic materials.

Other bioactive agents include androgen inhibitors, polysaccharides, growth factors, hormones, anti-angiogenesis factors, dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate, chlophedianol hydrochloride, chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, phenyltoloxamine citrate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, ephedrine, codeine phosphate, codeine sulfate morphine, mineral supplements, cholestryramine, N-acetylprocainamide, acetaminophen, aspirin, ibuprofen, phenyl propanolamine hydrochloride, caffeine, guaifenesin, aluminum hydroxide, magnesium hydroxide, peptides, polypeptides, proteins, amino acids, hormones, interferons, cytokines, and vaccines.

Representative drugs that can be used as bioactive agents in the miniemulsion include, but are not limited to, peptide drugs, protein drugs, desensitizing materials, antigens, anti-infective agents such as antibiotics, antimicrobial agents, antiviral, antibacterial, antiparasitic, antifungal substances and combination thereof, antiallergenics, androgenic steroids, decongestants, hypnotics, steroidal anti-inflammatory agents, anticholinergics, sympathomimetics, sedatives, miotics, psychic energizers, tranquilizers, vaccines, estrogens, progestational agents, humoral agents, prostaglandins, analgesics, antispasmodics, antimalarials, antihistamines, cardioactive agents, nonsteroidal anti-inflammatory agents, antiparkinsonian agents, antihypertensive agents, beta-adrenergic blocking agents, alpha-adrenergic antagonists, nutritional agents, opium alkaloids and the benzophenanthridine alkaloids. The agent can further be a substance capable of acting as a stimulant, sedative, hypnotic, analgesic, anticonvulsant, and the like.

Other bioactive agents include but are not limited to the bioactive agent comprises an antibiotic. The antibiotic can be, for example, one or more of Amikacin. Gentamicin, Kanamycin, Neomycin, Netilmicin, Streptomycin, Tobramycin, Paromomycin, Ansamycins, Geldanamycin, Herbimycin, Carbacephem, Loracarbef, Carbapenems, Ertapenem, Doripenem, Imipenem/Cilastatin, Meropenem, Cephalosporins (First generation), Cefadroxil, Cefazolin, Cefalotin or Cefalothin, Cefalexin, Cephalosporins (Second generation), Cefaclor, Cefamandole, Cefoxitin, Cefprozil, Cefuroxime, Cephalosporins (Third generation), Cefixime, Cefdinir, Cefditoren, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftriaxone, Cephalosporins (Fourth generation), Cefepime, Cephalosporins (Fifth generation), Ceftobiprole, Glycopeptides, Teicoplanin, Vancomycin, Macrolides, Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Roxithromycin, Troleandomycin, Telithromycin, Spectinomycin, Monobactams, Aztreonam, Penicillins, Amoxicillin, Ampicillin, Aziocillin, Carbenicillin, Cloxacillin, Dicloxacillin, Flucloxacillin, Mezlocillin, Meticillin, Nafcillin, Oxacillin, Penicillin, Piperacillin, Ticarcillin, Polypeptides, Bacitracin, Colistin, Polymyxin B, Quinolones, Ciprofloxacin, Enoxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Ofloxacin, Trovafloxacin, Sulfonamides, Mafenide, Prontosil (archaic), Sulfacetamide, Sulfamethizole, Sulfanilimide (archaic), Sulfasalazine, Sulfisoxazole, Trimethoprim, Trimethoprim-Sulfamethoxazole (Co-trimoxazole) (TMP-SMX), Tetracyclines, including Demeclocycline, Doxycycline, Minocycline, Oxytetracycline, Tetracycline, and others; Arsphenamine, Chloramphenicol, Clindamycin, Lincomycin, Ethambutol. Fosfomycin, Fusidic acid, Furazolidone, Isoniazid, Linezolid, Metronidazole, Mupirocin, Nitrofurantoin, Platensimycin, Pyrazinamide, Quinupristin/Dalfopristin, Rifampicin (Rifampin in U.S.), Tinidazole, or a combination thereof.

The bioactive agent can also be an immunomodulator, including, for example, cytokines, interleukins, interferon, colony stimulating factor, tumour necrosis factor, and the like; allergens such as cat dander, birch pollen, house dust mite, grass pollen, and the like; antigens of bacterial organisms such as *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pyrogenes, Corynebacterium diphteriae, Listeria monocytogenes, Bacillus anthracis, Clostridium tetani, Clostridium botulinum, Clostridium perfringens, Neisseria meningitides, Neis-*

seria gonorrhoeae, Streptococcus mutans, Pseudomonas aeruginosa, Salmonella typhi, Haemophilus parainfluenzae, Bordetella pertussis, Francisella tularensis, Yersinia pestis, Vibrio cholerae, Legionella pneumophila, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Leptspirosis interrogans, Borrelia burgddorferi, Campylobacter jejuni, and the like; antigens of such viruses as smallpox, influenza A and B, respiratory synctial, parainfluenza, measles, HIV, SARS, varicella-zoster, herpes simplex 1 and 2, cytomeglavirus, Epstein-Barr, rotavirus, rhinovirus, adenovirus, papillomavirus, poliovirus, mumps, rabies, rubella, coxsackieviruses, equine encephalitis, Japanese encephalitis, yellow fever, Rift Valley fever, lymphocytic choriomeningitis, hepatitis B, and the like; antigens of such fungal, protozoan, and parasitic organisms such as *Cryptococcuc neoformans, Histoplasma capsulatum, Candida albicans, Candida tropicalis, Nocardia asteroids, Rickettsia rickets, Rickettsia typhi, Mycoplasma pneumoniae, Chlamyda psittaci, Chlamydia trachomatis, Plasmodium falciparum, Trypanasoma brucei, Entamoeba histolytica, Toxoplasma gondii, Trichomonas vaginalis, Schistosoma mansoni*, and the like. These antigens may be in the form of whole killed organisms, peptides, proteins, glycoproteins, carbohydrates, or combinations thereof.

In a further specific aspect, analgesics such as acetaminophen, acetylsalicylic acid, and the like: anesthetics such as lidocaine, lignocaine, xylocaine, and the like; anorexics such as dexadrine, phendimetrazine tartrate, and the like; antiarthritics such as methylprednisolone, ibuprofen, and the like; antiasthmatics such as terbutaline sulfate, theophylline, ephedrine, and the like; antibiotics such as sulfisoxazole, penicillin G, ampicillin, cephalosporins, amikacin, gentamicin, tetracyclines, chloramphenicol, erythromycin, clindamycin, isoniazid, rifampin, and the like; antifungals such as amphotericin B, nystatin, ketoconazole, and the like; antimicrobials such as cetrimide, and the like; antivirals such as acyclovir, amantadine, and the like; anticancer agents such as cyclophosphamide, methotrexate, etretinate, and the like; anticoagulants such as heparin, warfarin, and the like; anticonvulsants such as phenytoin sodium, diazepam, and the like; antidepressants such as isocarboxazid, amoxapine, and the like; antihistamines such as diphenhydramine HCl, chlorpheniramine maleate, and the like; hormones such as insulin, progestins, estrogens, corticoids, glucocorticoids, androgens, and the like; tranquilizers such as thorazine, diazepam, chlorpromazine HCl, reserpine, chlordiazepoxide HCl, and the like; antispasmodics such as belladonna alkaloids, dicyclomine hydrochloride, papaverine, and the like; vitamins and minerals such as essential amino acids, calcium, iron, potassium, zinc, vitamin B 12, vitamin C, vitamin D and the like; cardiovascular agents such as prazosin HCl, nitroglycerin, propranolol HCl, hydralazine HCl, pancrelipase, succinic acid dehydrogenase, and the like; peptides and proteins such as LHRH, somatostatin, calcitonin, growth hormone, glucagon-like peptides, growth releasing factor, angiotensin, FSH, EGF, bone morphogenic protein (BMP), erythopoeitin (EPO), interferon, interleukin, collagen, fibrinogen, insulin, Factor VIII, Factor IX, Enbrel®, Rituxam®, Herceptin, alpha-glucosidase, Cerazyme/Ceredose®, vasopressin. ACTH, human serum albumin, gamma globulin, structural proteins, blood product proteins, complex proteins, enzymes, antibodies, monoclonal antibodies, antibody fragments, and the like; prostaglandins such as prostaglandin E1, prostaglandin 12, prostaglandin E2, and the like; nucleic acids; carbohydrates; fats; narcotics such as morphine, codeine, and the like; psychotherapeutics; nonsteroidal anti-inflammatory agents such as ibuprofen, diclofenac and the like; antihypertensive agents such as phentolamine HCl, and the like; anti-malarials, L-dopa, diuretics such as furosemide, spironolactone, and the like; antiulcer drugs such as ranitidine HCl, cimetidine HCl, and the like.

In certain aspects, the bioactive agent can be present as a component in a pharmaceutical composition. Pharmaceutical compositions can be conveniently prepared in a desired dosage form, including, for example, a unit dosage form or controlled release dosage form, and prepared by any of the methods well known in the art of pharmacy. In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the bioactive agent into association with a liquid carrier or a finely divided solid carrier, or both. The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen. Other pharmaceutically acceptable carriers or components that can be mixed with the bioactive agent can include, for example, a fatty acid, a sugar, a salt, a water-soluble polymer such as polyethylene glycol, a protein, polysacharride, or carboxmethyl cellulose, a surfactant, a plasticizer, a high- or low-molecular weight porosigen such as polymer or a salt or sugar, or a hydrophobic low-molecular weight compound such as cholesterol or a wax.

The method of incorporating the bioactive agent into the miniemulsion will be dependent on the properties of the bioactive agent. For example, a lipophillic agent will generally be dissolved in the lipid and be dispersed with the lipid in the lipid droplet, while a hydrophilic agent will generally be dissolved in the aqueous phase. However, hydrophilic and lipophilic agents may also be chemically or physically bound to polymers, lipids and/or surfactants. Methods of incorporating the bioactive agent into the miniemulsion would be well known to persons skilled in the art (see, for example, Hendrickson, R. Ed. Remington: The Science and Practice of Pharmacy, 21st ed.; Lippincott Williams & Wilkins: Baltimore Md., 2005).

In one embodiment, the second phase comprises lipid and a bioactive agent. It will be apparent that the presently disclosed methods provide, in one aspect, a high concentration of bioactive active agent, relative to the size of the emulsified particle. As described supra, the miniemulsion described here can contain up to 40% w/w oil. This high oil content allows a high concentration of bioactive agent to be incorporated into the miniemulsion. For example, the miniemulsion can comprise 0.1% w/w, 0.5% w/w, 2% w/w, 3% w/w, 5% w/w, 10% w/w, 15% w/w, 30% w/w or 40% w/w bioactive agent, including any range between the disclosed percentages. In one embodiment, the miniemulsion comprises at least about 0.2% w/w, or for example, from about 0.2% w/w to about 8% w/w, or from about 10% w/w to about 15% w/w bioactive agent.

In a particular aspect, the preferred bioactive agent is a "hydrophobic compound" or "lipophilic compound". The term "hydrophobic compound" refers to a compound with limited water solubility. The term "lipophilic compound" refers to a compound that is characterized by its favourable interaction with lipids. Examples of such compounds include organic molecules which lack groups that may support a formal charge (e.g., carboxylic acid and amino groups) or which lack polar groups such as hydroxyl groups. Such compounds may be amino acid-based (e.g., amino acids, peptides, polypeptide and proteins), wherein the

amino acids are exclusively or predominantly hydrophobic (e.g., leucine, valine, etc.). Examples of hydrophobic bioactive agents useful for various medical applications include propanidid; propofol, alphadione, lidocaine, lignocaine, echinomycin, miconazole nitrate, taxanes (also known as taxines or taxoids) such as paclitaxel and docetaxel; podophyllotoxins, camptothecins such as camptothecin, 9-aminocamptothecin, 9-nitrocamptothecin, camptothecin-11 ("Irinotecan"), topotecan, vinca alkaloids and their analogs (vincristine, vinorelbine, vindesine, vintripol, vinxaltine, ancitabine), lipophilic anthracyclines, decarbazine, lonidamine, piroxantrone, anthrapyrazoles, etoposide, bleomycin, 6-aminochrysene, navelbine, tributyrin, teniposide, platinum-based agents, praziquantel, cyclosporin A, 18-hydroxydeoxycorticosterone, rapamycin, prednisolone, vitamin A, vitamin E, purpurin, tin etiopurpurin, porphyrins, paraaminobenzoic acid, diazepam, delta 9-tetrahydrocannabinol, BBB-MDP, verapamil and nifedipine. In one embodiment, the bioactive agent is lidocaine or lignocaine.

In another embodiment, the first phase comprises a bioactive agent. In this case the preferred bioactive agent is a "hydrophilic compound" or "lipophobic compound". The term "hydrophilic compound" refers to a compound that is soluble in water. Examples of hydrophilic bioactive agents useful for various medical applications would be well known to those skilled in the art, for example, lignocaine HCl.

Accordingly, in one aspect, the method and miniemulsion described above may form a delivery system for a bioactive agent. Due to the size of the emulsified particles being fpm or smaller, the delivery system described herein can be administered by topical, enteral or parenteral routes. For example, the delivery system can be administered orally, nasally, intravenously, intramuscularly, subcutaneously, sublingually, intrathecally, intraperitoneally, intratumorally, topically, transdermally or intradermally. The route of administration can depend on a variety of factors, such as the environment and therapeutic goals. Further non-limiting pharmaceutically suitable materials that may be incorporated in pharmaceutical preparations/compositions disclosed herein include absorption enhancers, pH-adjusting agents and buffers, osmolarity adjusters, preservatives, stabilizers, antioxidants, surfactants, thickening agents, co-solvents, emollients, dispersing agents, flavouring agents, colouring agents and wetting agents and ligands/pilote/targeting molecules. The delivery system may be in the form of a liquid, a powder, an aerosol, a capsule, a tablet, a suppository, a cream, a gel and an ointment. Exemplary types of liquid include a lotion and a spray. In particular embodiments, the delivery system is formulated for administration as a spray or as an aerosol. Methods for preparing appropriate formulations are well known in the art (see, for example, Hendrickson, R. Ed. Remington: The Science and Practice of Pharmacy, 21st ed.; Lippincott Williams & Wilkins: Baltimore Md., 2005).

In one particular example, the miniemulsion may be formulated into a composition capable of reducing pain sensation or nociception, whether the pain incurred is a result of disease, inflammation, trauma or psychosomatic reaction. The composition will therefore be administered as an effective amount to a subject in need of pain relief. The phrase "in need of pain relief" as applied to a subject herein embraces a subject suffering mild to intense pain at the time of administration of the composition, as well as a subject that can reasonably be expected to have an imminent onset of mild to intense pain, eg., within about 1 to about 2 hours and especially within about 30 minutes, if no pain relief is administered.

The term "effective amount" refers to that amount which is sufficient to induce or maintain pain relief when administered to a subject; i.e., a pain relieving amount. What constitutes an effective pain-relieving amount, or dose, of the composition depends, among other factors, on the body weight of the subject and the intensity of the pain being treated.

An "effective pain relieving concentration" or "effective pain relieving plasma concentration" as used herein is intended to mean a plasma level in a subject which when tested in a standardised test involving the subject scoring the severity of pain, achieves a mean score indicating pain relief. In one such test as described herein below, patients score pain on a scale of from 10 (no reduction in severity of pain) to 0 (complete relief of pain) and a mean score equal to or greater than a given value is deemed to constitute effective pain-relief. A mean score of 5.0 or less and, more preferably, 2.0 or less in such a test, as exemplified herein, is deemed to constitute effective pain relief. The skilled artisan will appreciate, however, that other approaches can be used to assess the severity of pain and relief from such pain.

Thus, one aspect of the miniemulsion method described herein involves a therapeutic method for pain relief in which a miniemulsion comprising lidocaine is administered to a subject, in a formulation which provides detectable pain relief. By "detectable pain relief", it is meant that the formulation produces effective pain relief which is measurable by a standard method such as that described above. For example, a formulation, which achieves a mean score of 5.0 or less and, more preferably, 2.0 or less on a scale of from 0 to 10 in a testing system as described above, is deemed to provide detectable pain relief. The disclosure is not limited to use of any particular type of formulation, so long as it exhibits the pharmacokinetic profile defined herein. In one embodiment, the miniemulsion is formulated into an aerosol spray comprising lidocaine or lignocaine for use in pain relief.

The miniemulsion or delivery system described herein can be administered to any desired subject. The subject can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. The subject of the herein disclosed methods can be, for example, a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered.

The disclosure will now be further described by way of reference only to the following non-limiting examples. It should be understood, however, that the examples following are illustrative only, and should not be taken in any way as a restriction on the generality of the disclosure described above.

EXAMPLES

Example 1 Miniemulsion Preparation

Miniemulsions of 100 g were prepared with various concentrations of surfactant using the following process:

Lecithin	1.00-3.00% w/w
Tween 80 (Polysorbate 80)	1.50-4.50% w/w
Soybean oil	14.50% w/w
Water for Injection (WFI)	up to weight

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(54) **METHODS FOR FORMING MINIEMULSIONS AND USE THEREOF FOR DELIVERING BIOACTIVE AGENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to methods of forming miniemulsions and use of the miniemulsions as a delivery system for bioactive agents. In particular, the present invention relates to methods for forming a miniemulsion comprising providing a first phase comprising a hydrophilic surfactant, lipophillic surfactant and water and a second phase comprising a lipid, wherein said miniemulsion comprises emulsified particles having a mean diameter of 1 μm or less.

8 Claims, 13 Drawing Sheets