METHODS AND COMPOSITIONS FOR TREATING PAIN OF THE MUCOUS MEMBRANE

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ABSTRACT
Compositions useful for long-lasting pain relief from mucosal damage, such as mucosal inflammation, abrasions, ulcerations, lesions, trauma and incisions, without significant systemic absorption. The compositions of the invention are particularly suitable for application to the mucous membrane of the nasal cavity and buccal cavity. To relieve pain, the compositions of the invention are topically applied directly to the affected area.
METHODS AND COMPOSITIONS FOR TREATING PAIN OF THE MUCOUS MEMBRANE

[0001] This application claims the benefit of U.S. Provisional patent application serial No. 60/222,164, filed Jun. 26, 2000, hereby incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] The invention relates to methods and compositions for treating the pain associated with mucosal damage, such as inflammation, abrasions, ulcers, lesions, incisions, and trauma.

BACKGROUND OF THE INVENTION

[0003] The term mucous membrane refers to the moist linings of the buccal cavity, nasal cavity, gastrointestinal tract, respiratory tract, conjunctiva, vagina, colon, urinary bladder, and urethra (Forstner et al., 1973 J. Cell. Sci. 12:565; Peppas et al., 1985 J Control Release 2:257; Lehri et al., 1992 J. Control. Release 18:249; Sprito, 1970 Ann. Rev. Biochem. 39:599; Lebat-Robert et al., 1979 Path. Biol. 24:241). The normally smooth, moist, and pink buccal mucosa is very sensitive and inflammation or ulceration (oral mucositis) causes severe pain. Dental surgery, such as root canal and tooth extraction can also severely damage the buccal mucosa causing severe pain. Moreover, oral mucositis and dental surgery can induce secondary conditions, such as weight loss and dehydration from reluctance to eat or drink, infection (bacterial, fungal, and viral), fever, nausea, and diarrhea.

[0004] Oral mucositis has a variety of causes, for example, bacterial infections, such as streptococci; viral infections, such as herpes simplex virus; fungal infections; side effects of systemic diseases; vitamin deficiency; iron deficiency; check biting; mouth breathing; jagged teeth; orthodontic appliances; ill-fitting dentures; excessive use of alcohol or tobacco; thermally-hot foods; spicy foods; and as a side effect of medication. Severely-painful oral mucositis is a symptom endured by almost all chemotherapy patients. Mucositis symptoms peak 7 to 10 days following chemotherapy, and gradually recede over the following two weeks. For a discussion of the causes and symptoms of mucositis, see The Merck Manual, Fifteenth Edition, Merck Sharp & Dohme Research Laboratories, Rahway, N.J., (1987) pp. 2322-2320.

[0005] Topical application of local anesthetics can provide some relief of oral-mucositis and dental-surgery pain but absorption through the mucous membranes occurs rapidly, and pharmaceuticals applied to the mucous membrane for their local effect can sometimes cause systemic toxicity (Goodman and Gilman’s The Pharmacological Basis of Therapeutics 9th ed. J. G. Harman and L. E. Limbird Eds., McGraw-Hill New York 1996 p. 8) especially with the higher doses required for adequate pain relief. Systemic absorption is even more likely when the mucous membrane is ulcerated or inflamed. Thus, with traditional anesthetic compositions for mucositis, e.g., 2 percent lidocaine oral rinse or 5% lidocaine ointment, systemic toxicity limits the dosage and so adequate pain relief is difficult to achieve. Other less toxic pain relieving compositions, such as rinses comprising hydrogen peroxide and sodium bicarbonate are less effective at reducing pain. An additional problem with oral rinses is, that following application, the action of swallowing and saliva reduces the concentration of active agent on the affected area, thus oral rinses comprising local anesthetics have a low duration of activity.

[0006] In summation, a long-lasting, non-toxic anesthetic composition effective for amelioration of the severe pain induced by mucosal damage, such as mucositis and dental surgery, is needed.

SUMMARY OF THE INVENTION

[0007] In one aspect, the invention provides compositions and methods that provide long-lasting local anesthesia and effective pain relief. The compositions of the invention can be topically applied to the affected area, for example, via a dose-metered applicator adapted for spraying or adapted for use with a cannula. When topically applied, the compositions of the invention provide a powerful local-anesthetizing effect, in spite of low anesthetic concentration. Hence, the compositions of the invention provide significant pain relief with low systemic absorption and, therefore, low systemic toxicity. The compositions of the invention, in addition to the ability to remain on the affected area for extended periods, hydrate and soothe.

[0008] In one embodiment, the compositions of the invention can be topically applied directly to the affected area to alleviate pain in a subject on any area of a subject’s body.

[0009] In another embodiment, the compositions of the invention are useful for topical application to a subject’s mucous membrane, to induce a long-lasting local-anesthetic effect, thereby relieving pain from mucositis, such as mucosal inflammation, abrasions, ulcers, lesions, and lesions, without significant systemic absorption.

[0010] In yet another embodiment, the compositions of the invention are useful for topical application to the site of dental surgery, such as root-canal or tooth-extraction surgery, to induce a long-lasting local-anesthetic effect, thereby relieving the surgical pain, without significant systemic absorption.

[0011] In one more embodiment, the invention relates to compositions comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof. In a preferred embodiment, the compositions contain water and are sterile. In a more preferred embodiment, the compositions of the invention, further comprise a chelating agent and a preservative.

[0012] In another embodiment, the invention relates to a container adapted for topical application and containing a pharmaceutically-acceptable composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof. Preferably, the container is adapted for dose-metered application, such as a dose-metered pump for use with a spray applicator or cannula.

[0013] In still another embodiment, the invention relates to a method of inducing local anesthesia in a subject’s mucosal membrane by topically applying a pharmaceutically-acceptable composition comprising a local anesthetic or a pharmaceutically-acceptable salt thereof and an opioid or a pharmaceutically-acceptable salt thereof to the subject’s mucosal membrane. Preferably, the composition is applied
to an area within the subject’s buccal or nasal cavity. Preferably, the composition further comprises a mucoadhesive.

[0014] In yet another embodiment, the invention relates to a method of inducing local anesthesia in a subject by topically applying a composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof to a subject. Preferably, the composition is applied to a mucosal surface of the subject, for example, an area within the subject’s buccal or nasal cavity.

[0015] These and other features, aspects, and advantages of the invention will become better understood with reference to the following detailed description, examples, and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The phrase “pharmaceutically-acceptable salt(s),” as used herein includes but is not limited to salts of acidic or basic groups that may be present in compounds used in the present compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically-acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, sulfuric, citric, maleic, acetic, oxalic, hydrochloric, hydrobromic, hydroiodic, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, olate, tannate, pantothenate, bitartrate, ascorbate, succinate, malate,gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylenegbis(2-hydroxy-3-naphthoate)) salts.

[0017] Compounds included in the present compositions that include an amino moiety may form pharmaceutically-acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds, included in the present compositions, that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. For a review on pharmaceutically-acceptable salts see Berge et al., 1977 J Pharm. Sci., 66:1, incorporated herein by reference.

[0018] As used herein the term “opioid” means all agonists and antagonists of opioid receptors, such as mu (μ), kappa (κ), and delta (δ) opioid receptors and subtypes thereof. For a discussion of opioid receptors and subtypes see Goodman and Gilman’s The Pharmacological Basis of Therapeutics 9th ed. J. G. Harman and L. E. Limbird Eds., McGraw-Hill New York:1996 pp. 521-555, incorporated herein by reference. The opioid can be any opioid receptor agonist or antagonist known or to be developed. Preferred opioids interact with the μ-opioid receptor, the δ-opioid receptor, or both. Preferably, the opioid is an opioid-receptor agonist.

[0019] Examples of suitable opioids for use with the invention include, but are not limited to, alfentanil, allylpronide, alphaprodine, amileridine, benzylmorphine, benziramide, nor-binaltorphimine, bremazocine, buprenorphine, butorphanol, clonitazene, codeine, CTOP, DAMGO, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphone enol acetate, dihydromorphone, dimenoxidol, dimethylpentanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprenorphine, DPDPPE, eptazocine, etioheptazine, etylketocyclazocine, ethynethyliothiambucine, etontizene, etorphine, fentanyl, hydrocodeine, hydromorphone, hydroxypropyphendine, isomethe- done, ketobemidone, levorphanol, lofentanil, loperamide, meperidine, meptazinol, metazocaine, methadone, metopon, morphone, nalmefene, naltrexone, nalorphine, naltrexone, norlevorphan, norbuprenaline, normorphine, norpipanone, opium, oxycodone, oxycodeine, papaveretum, papaverine, pentazocine, phendoxone, phenazocine, phenoperidine, pimidolone, piramidone, proheptazine, promedol, propiram, propyroxphene, remifentanil, spiradol, sufentanil, tilidine, u50,488, and U69,593, amiphenazole, cyclazocine, levalorphan, nalbuphene, nalorphine, naloxone, and naltrexone or pharmaceutically-acceptable salts thereof, or mixtures thereof.


[0021] As used herein, the term “local anesthetic” means any drug that provides local numbness or analgesia or any drug that provides a regional blockage of nociceptive pathways (afferent and/or efferent) and that is not an agonist or an antagonist of an opioid receptors. The local anesthetic can be any local anesthetic known or to be developed. Examples of local anesthetics suitable for use with the invention include: ambeucaine, amolalane, amylycaine, benzoin, benzocaine, betoxycaine, biphenamine, bupivacaine,
butacaine, butamben, butanilicaine, butethamine, butoxycaine, carteicaine, chloroprocaine, cocaine, cyclomethylene, dibucaine, dimethisquoin, dimethocaine, diperoxod, dyclonine, ecgonidine, eucrocin, fenacolome, formocaina, hexylcaine, hydroxytertacaine, isobutylp-aminozoante, leucinocaine, levoradrol, lidocaine, mepivacaine, meprycaine, metabutoxyacine, methyl chloride, myrtecaine, naepeca, octacaine, orthocaine, oxethazaine, parenthoxycaine, phenacaine, phenol, piperoxar, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanocaine, propacaine, propoxycaine, propoxycaine, pseudococaine, pyrrocaine, ropivacaine, salicyl alcohol, tetracaine, tolycaine, tramcaine, zolamine, or pharmaceutically-acceptable salts thereof, or mixtures thereof.

[0022] The amide and ester type local anesthetics are preferred. Amide type local anesthetics are characterized by an amide functionality, while ester type local anesthetics contain an ester functionality. Preferred amide type local anesthetics include lidocaine, bupivacaine, prilocaine, mepivacaine, etidocaine, ropivacaine, dibucaine, and pharmaceutically-acceptable salts thereof and mixtures thereof. Preferred ester type local anesthetics include tetracaine, procaine, benzocaine, chloroprocaine, and pharmaceutically-acceptable salts thereof and mixtures thereof. The most preferred local anesthetic is lidocaine. The meaning of “local anesthetic” also encompasses drugs not traditionally associated with local anesthetic properties but which have a local-anesthetic effect, for example, non-narcotic analgesics, such as, acetylsalicylic acid, ketoprofen, piroxicam, diclofenac, indomethacin, ketorolac, Vioxx®, and Celebrex®. Furthermore, in order to improve the effectiveness and duration of the present topically-effective therapy, local anesthetics with different pharmacodynamics and pharmacokinetics may be combined in a composition of the invention. A preferred combination of local anesthetics is lidocaine and prilocaine and another preferred combination is lidocaine and tetracaine.

[0023] As used herein, the term “local delivery” of a therapeutic, means topical application of the therapeutic to a subject, wherein a therapeutically-effective amount of the therapeutic is absorbed in the immediate application area, preferably, without significant absorption into the blood stream.

[0024] As used herein, a “therapeutically-effective amount” of the compositions of the invention means the amount required to induce a local-anesthetic effect or numbness sufficient to ameliorate pain induced by laceration, inflammation, or lesions of the buccal or nasal membrane or other mucous membranes or the pain associated with mucosal trauma, such as dental surgery. Preferably, the active agents of the composition are not absorbed systemically.

[0025] As used herein, the term “subject” means any animal, preferably a mammal, more preferably a human.

[0026] As used herein, the term “mucosal adhesive” means a natural or synthetic substance, e.g., gels, pastes, macromolecules, polymers, and oligomers, or mixtures thereof, that can adhere to a subject’s mucous membrane for a period of time sufficient to locally deliver a therapeutically-effective amount of a composition of the invention to a subject. Adhesion of mucosal adhesives to the mucous membrane occurs primarily via secondary chemical bonds, such as hydrogen bonding and Van der Waal forces (Taber et al., 1977 J Colloid Interface Sci. 58:2 and Good 1977 J Colloid Interface Sci. 59:398). Mucosal adhesives often are formed in viscous aqueous solutions. The composition itself does not need to be mucosal adhesive, as long as it can form a mucosal adhesive gel upon the contact with the mucous membrane. For example, gellan gum itself is a very weak mucosal adhesive. On contact with the buccal membrane, gellan gum can interact with the ions in the mucous membrane and form an adhesive gel layer. According to the invention, mucosal adhesives possess binding properties that may be distinguished from non-mucosal adhesives by comparing the degree of adhesion to a mucosal surface. For example, comparison of a potential mucosal adhesive with a control emulsion of comparable viscosity prepared without mucosal adhesive properties, e.g., a starch solution. At similar viscosities, the emulsion prepared with the mucosal adhesive will bind to the mucosal surface more strongly than will the control emulsion, preferably at least 25% greater mucosal binding than the control emulsion, more preferably at least 50% greater, still more preferably at least 100% greater mucosal binding. Either mechanical binding to mucous membrane per se or the degree of biological effect of a drug delivered may be used as a measurement parameter for mucosal adhesive. This test may be used to distinguish preferred mucosal adhesives. Substances can be screened for their ability to be used as mucosal adhesives for local delivery of compositions of the invention according to the methodology described in Smart et al., 1982 J Pharm. Pharmacol. 34:70P and Smart et al., 1984 J Pharm. Pharmacol. 36:295, which methodology comprises estimating values of adhesive strength between the substance and the mucous membrane. Preferably, the mucosal adhesive is water soluble, such that at least 1% by weight of the mucosal adhesive is soluble in water at 25°C. In a preferred embodiment, the mucosal adhesive will exhibit non-Newtonian fluid properties, i.e., the viscosity decreases with increasing shear forces. Accordingly, the viscosity of the composition can be modulated by altering the shear forces present when the composition is applied to a surface. A composition with non-Newtonian fluid properties, becomes less viscous when shaken or atomized, then, upon standing, returns to its original viscosity.

[0027] Examples of mucosal adhesives for use in the present invention include, but are not limited to, pectin, alginate acid, chitosan, hyaluronic acid, polysorbates, such as polysorbate-20, -21, -40, -60, -61, -80, -81, -85, polyethylene glycol), such as PEG-7, -14, -16, -18, -55, -90, -100, -135, -180, -4, -240, -6, -8, -9, -10, -12, -20, or -32, oligosaccharides and polysaccharides, such as gellan, carrageenan, xanthan gum, gum Arabic, and dextran; cellulose esters and cellulose ethers; modified cellulose polymers, such as carboxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl ethylcellulose; polyester polymers and oligomers, such as poloxymethylene; condensation products of poly(ethylene oxide) with various reactive hydrogen containing compounds having long hydrophobic chains (e.g., aliphatic chains of about 12 to 20 carbon atoms), for example, condensation products of poly(ethylene oxide) with fatty acids, fatty alcohols, fatty amides, polyhydric alcohols; polyester compounds, such as poly(methyl vinyl ether), polyoxypropylene of less than 10 repeating units; polyester compounds, such as block copolymers of ethylene oxide and propylene oxide; mixtures of block copolymers of
ethylene oxide and propylene oxide with other excipients, for example, pluronic lethicin organogel (see 1997 International Journal of Pharmaceutical Compounding 1:71); poly(vinyl alcohol); polyacrylamide; hydrolyzed polyacryla-
The pH of the composition is preferably within the range of from about 2 to about 9, more preferably, about 3 to about 7, even more preferably about 4 to about 5. Under acidic conditions, protonation permits H-bonding between the polymer and the mucin network, resulting in enhanced retention of the polymer in contact with a mucosal surface. The pH can be adjusted by adding an aqueous acid or base, dropwise to the composition until the desired pH is obtained. Any physiologically acceptable pH adjusting acids, bases or buffers are acceptable, e.g., acids, such as acetic, boric, citric, lactic, phosphoric, hydrochloric; bases, such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, THAM (tris(hydroxymethyl)aminomethane); and buffers such as citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures thereof, preferably, 0.1 normal hydrochloric acid for a pH of less than 7 and 0.1 normal aqueous sodium hydroxide for a pH of greater than 7.

The composition of the invention can also comprise NMDA receptor antagonists including, but not limited to, dextromethorphan, dextrophan, ketamine, pyroloquinolin quinone, cis-4-(phosphononylmethyl)-2-piperidinedicarboxylic acid, MK801, memantine, D-methadone, or pharmaceutically-acceptable salts thereof.

The compositions of the invention can also include other excipients and pharmaceuticals. Examples of excipients that can be included in the topical compositions of the invention include, but are not limited to, antibacterials, analgesics, anti-inflammatory agents, anti-tussive agents, expectorants, glucocorticoids, vitamins, antioxidants, flavoring agents, sweetening agents, iso-osmotic agents, moisturizers, emollients, buffering agents, solubilizing agents, penetration agents, protectants, surfactants, and propellants, and other conventional systemic or topical pain relief therapies, analgesics, and pharmaceuticals.

Examples of suitable antibiotics include, but are not limited to, aminopenicillins; such as ampicillin, amoxicillin, amoxicillin-benzylpenicillin, ampicillin-sulbactam, and amoxicillin-clavulanate; cephalosporins; such as cephalothin, cefazolin, cefuroxime, ceftriaxone, cefotaxime, and cefepime; cephemycins; such as cefuroxime and cefotaxime; monobactams, such as aztreonam, carbenem, and imipenem; oxacephems, such as flumeoxef, and moxalactam; penicillins, such as amoxicillin, ampicillin, and ampicillin-sulbactam; cephalosporins, such as cefuroxime, and cefotaxime; and cephalosporins, such as cefadroxil, cefadroxil, and cefuroxime. Examples of suitable anti-inflammatory agents include, but are not limited to, acetylsalicylic acid, ibuprofen, ketoprofen, ketorolac, and flurbiprofen. Examples of suitable antifungal agents include, but are not limited to, amphotericin B, ketoconazole, clotrimazole, and bifonazole.
guacil, bromfenac, bufexamac, cimetacin, clopirac, diclofenac sodium, etodolac, felbinac, fenclazole, fen-tiazac; glaucetinac, ibufenac, indomethacin, isoflozal isoxyac, lonazolac, metaznic acid, molezolac, oxametacine, pirazolac, progluacetan, sulinda, taramide, tolmetin, tropesin, and zomepirac; arybutiric acid derivatives, such as bumadizon, butifufen, fenbufen, xenubucin; arylecarboxylic acids, such as clobidac, ketorolac, toridinone; arylpropionic acid derivatives, such as alminofenop, benoxaprofen, bupolic acid, carprofen, fenoprofen, fluoxaprofen, flurbiprofen, ibuprofen, ibuproxam, indoprofen, ketoprofen, loxoprofen, naproxen, oxaprin, piketoprofen, pirprofen, pranoprofen, protzinic acid, suprofen, tiaprofenic acid, ximoprofen, and zaltoprofen; pyrazolones, such as difenamizole and epizoprole; pyrazolones and, such as azapone, benzyperyron, feprazone, mebufatuzone, morazine, oxphenbutazone, phenylbutazone, pipebuzone, prophyzenzone, ramifeneza, sibuxibzone, and thizolinobutuzone; salicylic acid derivatives, such as acetaminsalol, aspirin, benorylate, bromosaligenin, calcium acetyl salicylate, difufinal, etersalate, fendosal, gentic acid, glyc salicylate, imidazole salicylate, linsine acetyl salicylate, mesalamine, morpholine salicylate, 1-naphthyl salicylate, obsalazine, parsalmin, phenyl acetyl salicylate, phenyl salicylate, salazalamine, salicylamide a-acetic acid, salicylsulfonic acid, salsalate, sulfasalazone; thiazincarboxamides, such as amipoxicam, droxicam, isoxicam, lornoxicam, piroxicam, and tenoxicam; and others, such as e-acetamidoacapric acid, s-adenosyethylthione, 3-amino 4-hydroxybutyric acid, amoxetine, bendazac, benzylamine, c-nisabrol, bucololme, difenpiramide, ditazol, emorozone, fepradnol, guaizulena, nubometone, nimesulide, oxaceprol, paralyline, periosusal, proquaquone, supersoxide dismutase, tenidap, and zilekton.

Examples of suitable antitussive agents include, but are not limited to, alcloclamide, amicibo, benproperine, benzonatate, bibenzonum bromide, bromiform, butamitate, butethamate, caramphethanethiolurate, carbetapente, chlorphenel, clbutanol, cloperastine, codeine, codeine methyl bromide, codeine 2-oxide, codeine phosphate, codeine sulfate, clyrexanone, dimethoxanate, dpropipizine, drotenbol, epravizone, ethyl dibunate, ethylmorphine, fominoben, guiapate, hydrocodone, isoonimine, levropoxynyn, morfocyte, narcine, mormethadone, noscapine, oxeladin, oxolamine, phocoline, picipine, pipazethate, piperedone, prnoexdiazon hydrochloride, racemethaphen, sodium dibunate, tipepine, and zipropro.

Examples of suitable expectorants include, but are not limited to, abroxol, ammonium bicarbonat, ammonium carbonate, bromhexine, calcium iodide, carbocysteine, guaical, guaicil benzoate, guaicacarbonate, guaicacol phosphate, gualfencines, gualthylene, hydroric acid, iodinated glycerc, potassium guaicacolsulfate, potassium iodide, sodium citrate, sodium iodide, storax, terbene, terpin, and trifluorol.

Examples of suitable glucocorticoids include, but are not limited to, 21-acetoxypregnolone, aclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroopenidinosone, clobetasol, clotebasone, clotocrolone, clotepinol, cortocortone, cortisone, cortizol, dexamethasone, desonide, desoximetasone, dexamethasone, diflo- raseone, dulfutocortone, difluprednate, enoxolone, flutazacort, flurorconone, flumethasone, fluposolide, flucinolone

[0043] Suitable vitamins include, but are not limited to citrapostrin, calcirol, ergosterol, 1α-hydroxylcalcirol, vitamin D3, vitamin D2, ascorbic acid, calcium ascorbate, nicotinamide ascorbate, sodium ascorbate, α-carote, β-carotene, δ-carotene, vitamin A, esteramide, folic acid, hydrocobicolin, sodium folate, vitamin B12, menadiol, menadione, menoxazone, phyloquinone, vitamin K3, unsol, α-tocopherol, γ-tocopherol, δ-tocopherol, vitamin E, vitamin E acetate, and vitamin E.

Examples of suitable anti-oxidants include, but are not limited to, aseamic acid, sodium ascorb ate, sodium bisulfite, sodium thio sulfate, δ-hydroxy quinoline, and N-aceyl cysteine.

Examples of suitable flavoring agents include, but are not limited to, oil of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalyptus, marjoram, cinnamon, lemon, and orange, and methyl salicylate.

Examples of suitable sweetening agents include, but not limited to, sucrose, lactose, maltose, sorbitol, xylitol, sodium cyclamate, perillartine, AMP (asparyl phenyl alanine, methyl ester), and saccharine.

The compositions of the present invention optionally can include an iso-osmotic agent which functions to prevent irritation of the mucosa by the composition. Examples of pharmaceutically-acceptable iso-osmotic agents which can be used include sodium chloride, dextrose, and calcium chloride.

Preferably, the amount of local anesthetic in the composition is within the range of from about 0.005 percent to about 2 percent of the total weight of the composition, more preferably, of from about 0.01 percent to about 0.5 percent of the total weight of the composition.

For treatment of oral mucositis, a preferred concentration of local anesthetic is from about 0.02 percent to about 0.1 percent of the total weight of the composition, more preferably, from about 0.04 percent to about 0.08 percent. For treatment of more painful conditions, such as dental surgery (e.g., tooth extraction or root canal), a preferred concentration of local anesthetic is from about 0.1 percent to about 0.4 percent of the total weight of the composition, more preferably, from about 0.2 percent to about 0.3 percent.

Preferably, the amount of opioid in the composition is within the range of from about 0.005 percent to about 3 percent of the total weight of the composition, more preferably, of from about 0.01 percent to about 2 percent, still more preferably, of from about 0.05 percent to about 1 percent of the total weight of the composition. For treatment of oral mucositis, a preferred concentration of opioid is from
about 0.1 percent to about 0.3 percent of the total weight of the composition. For treatment of more painful conditions, such as dental surgery, a preferred concentration of opioid is from about 0.5 percent to 20 about 0.5 percent of the total weight of the composition, more preferably, about 0.4 percent to about 0.5 percent.

[0051] Preferably, the amount of mucosaladhesive in the composition is within the range of from about 0.1 percent to about 40 percent of the total weight of the composition, more preferably, of from about 10 percent to about 30 percent, and optimally, of from about 15 percent to about 25 percent of the total weight of the composition.

[0052] Preferably, the amount of water in the composition is within the range of from about 95 percent to about 10 percent of the total weight of the composition, more preferably, of from about 90 percent to about 50 percent, and optimally, of from about 85 percent to about 75 percent of the total weight of the composition.

[0053] When a chelating agent is used, preferably, it is present in an amount within the range of from about 0.005 percent to about 1 percent of the total weight of the composition, more preferably, of from about 0.01 percent to about 0.5 percent, still more preferably, of from about 0.05 percent to about 0.2 percent of the composition.

[0054] When a preservative is used, preferably, it is present in an amount within the range of from about 0.0001 percent to about 0.2 percent of the total weight of the composition, more preferably, of from about 0.0005 percent to about 0.1 percent, and optimally, of from about 0.001 percent to about 0.05 percent of the total weight of the composition.

[0055] To relieve pain from mucositis, the compositions or the invention are topically applied directly to the affected area. The compositions of the invention can be applied to the affected area of the mucous membrane in any conventional manner well known in the art, for example, as a mist via an aerosol applicator, by cannula, via a patch, by a dropper, or by an applicator stick, preferably as a mist, more preferably as a metered-dose mist. A mist can be sprayed onto the area to be treated via an aerosol container, pressurized or non-pressurized, preferably a non-pressurized pump. For more specific applications, a cannula can be used. The cannula can be attached to a pressurized or non-pressurized pump, preferably a non-pressurized pump.

[0056] A suitable non-pressurized pump for application of compositions of the invention can comprise a container, a valve, an actuator, and optionally a dip tube. The non-pressurized pump's container can be metal, such as a tin plated steel or aluminum, glass, or plastic. The valve's primary purpose is to regulate the flow of product from the container. It provides a means of discharging the desired amount. Suitable spray valves are described in Remington's Pharmaceutical Sciences 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, Pa., 1990 pp. 1703-1704, incorporated herein by reference. The actuator provides a means for releasing the contents from a pressurized container. Suitable actuators are described in Remington's Pharmaceutical Sciences 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, Pa., 1990 pp. 1704-1705, incorporated herein by reference.

[0057] Preferably, the metered pump is a VP 7 Screw-On Pump (90 ml, 18/415) commercially available from Valois of America, Inc. (Greenwich, Conn.). The VP 7 screw-on pump is manufactured from polyethylene and polypropylene. It is designed in a way such that the hydraulically opening clapper eliminates the use of any elastomeric gaskets in contact with the product. The pump has an annular dosing chamber, which fills only at the full return of the actuator to ensure full dosing and precision.

[0058] The preferred actuator is the 132C-BL GP4 BL long throat actuator commercially available from Valois Pharmaceuticals, Inc. Preferably, the actuator is manufactured from polyethylene and polypropylene and, preferably, contains a captive insert to provide a well-atomized spray pattern. The captive insert also reduces the dead volume in the actuator.

[0059] When a cannula is used, for application to a specific area rather than as a spray, the preferred actuator is a stainless-steel cannula of about 73 mm in length, for example, the 215 stainless-steel cannula commercially available from Valois Pharmaceuticals, Inc. Polyethylene or polypropylene cannulas can also be used.

[0060] The compositions of the invention can also be delivered to the buccal or nasal cavity via a patch that is applied adjacent to the area of skin to be treated. As used herein a “patch” comprises at least a composition of the invention and a covering layer, such that, the patch can be placed over the area to be treated. Preferably, the patch is designed to maximize local delivery and to minimize absorption into the circulatory system, reduce lag time, promote uniform absorption, and reduce mechanical rub-off. Suitable patches are described in Transdermal and Topical Drug Delivery Systems, Interpharm Press, Inc. p. 249-297, incorporated herein by reference. Suitable patches for buccal delivery of compositions of the invention is disclosed in U.S. Pat. Nos. 5,713,582 and 4,900,552, both of which are incorporated herein by reference.

[0061] The amount of the composition of the invention applied to the buccal or nasal passages will vary depending on the particular mucosaladhesive, local anesthetic, and opioid used; the nature and severity of the mucosal lesion or inflammation being treated, and the subject. The composition should be applied to the affected area as recommended by a physician, preferably, as needed by the patient to relieve pain. For example, a dose of about 0.05 mg to about 4 mg morphine sulfate and 0.02 mg to about 3 mg of lidocaine hydrochloride in about 0.5% to about 3% of composition can be delivered to the affected area. When applying as a spray, a dose of about 2 mg morphine sulfate and about 1 mg lidocaine hydrochloride in about 1.5 g of composition can be delivered to the affected area. For more precise applications by cannula, a dose of about 2 mg morphine sulfate and about 1 mg lidocaine hydrochloride in about 0.4 g of composition can be delivered to the affected area.

[0062] In a preferred embodiment of administration, the dose is delivered with a spray actuator in about 8 to about 20 separate spray shots, more preferably about 16 spray shots, wherein each spray shot weighs about 50 mg to about 150 mg, more preferably about 100 mg. In another preferred embodiment of administration, the dose is delivered via cannula in about 4 spray shots, wherein each spray shot weighs about 100 mg.

[0063] Although the present invention has been described in considerable detail with reference to certain preferred
EXAMPLES

[0064] The following examples are provided for illustrative purposes only and are not to be construed as limiting the invention’s scope in any manner.

EXAMPLE 1

[0065] A composition of the present invention is described in Table 2 below.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight</th>
<th>Weight percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate pentahydate</td>
<td>122.6 mg</td>
<td>0.2</td>
</tr>
<tr>
<td>Lidocaine hydrochloride monohydrate</td>
<td>65.4 mg</td>
<td>0.06</td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>20 g</td>
<td>19.3</td>
</tr>
<tr>
<td>Edetate disodium dihydrate</td>
<td>100 mg</td>
<td>0.1</td>
</tr>
<tr>
<td>Benzalkonium chloride (50% aqueous solution)</td>
<td>30 mg</td>
<td>0.03</td>
</tr>
<tr>
<td>Sterile water</td>
<td>80 g</td>
<td>77.4</td>
</tr>
<tr>
<td>0.05 N aqueous hydrochloric acid</td>
<td>3 g</td>
<td>2.9</td>
</tr>
</tbody>
</table>

[0066] Morphine sulfate pentahydate (122.6 mg), lidocaine (65.4 mg) hydrochloride monohydrate, and edetate disodium dihydrate (100 mg) were dissolved in 80 g of sterile water. The resulting solution was cooled to 10°C in an ice bath and poloxamer 407 (20g) was slowly added with mixing until the Poloxamer 407 completely dissolved. The solution was maintained at about 10°C until the foam collapsed. About 4 g of the solution was added to a 5 ml vial and a Valois VP4/90 18/415 pump was screwed onto the vial and refrigerated at 4°C for 30 minutes. The vial was removed from the refrigerator and the metered pump was primed using the Valois 165 actuator. The Valois 165 actuator was removed and the filled vial was stored at 4°C until the foam collapsed. The vial was removed from the refrigerator and kept at room temperature (25°C) until the contents gelled.

[0067] The viscosity of the above-prepared oral spray was measured using a Brookfield RVT viscometer. At 30°C the viscosity was 82,666 cps (averaged over three determinations) and at 40°C the viscosity was 95,666 cps (averaged over three determinations).

[0068] The composition can be applied as follows. Attach the long throat actuator to the metering pump and store the unit at 4°C. For at least 30 minutes. To prime the pump (7-8 sprays), with actuator in the up position, press the actuator firmly and quickly to spray into a waste container, hold the actuator for about one second when it is in the pressed position following each spray. With actuator in the up position, press the actuator firmly and quickly to spray onto the surface of the subject to be treated. Hold the actuator for two to three seconds when it is in the pressed position following each spray. Apply a total of 16 spray shots of for a total application of about 2 mg morphine sulfate and about 1 mg lidocaine hydrochloride in about 1.5 g of composition. Once the spray makes contact with the mucous membrane at body temperature, the liquid will form a viscous mucosal adhesive gel. If it takes more than 90 seconds to apply 16 spray shots, store the unit at 4°C for 10 minutes to cool the content before further usage.

EXAMPLE 2

[0069] A second composition of the present invention is described in Table 2 below.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight</th>
<th>Weight percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate pentahydate</td>
<td>490.5 mg</td>
<td>0.48%</td>
</tr>
<tr>
<td>Lidocaine hydrochloride monohydrate</td>
<td>261.5 mg</td>
<td>0.25%</td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>20 g</td>
<td>19.4%</td>
</tr>
<tr>
<td>Edetate disodium dihydrate</td>
<td>100 mg</td>
<td>0.93%</td>
</tr>
<tr>
<td>Benzalkonium chloride (50% aqueous solution)</td>
<td>30 mg</td>
<td>0.029%</td>
</tr>
<tr>
<td>Sterile water</td>
<td>80 g</td>
<td>77.6%</td>
</tr>
<tr>
<td>0.05 N aqueous hydrochloric acid</td>
<td>2.5 g</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

[0070] Morphine sulfate pentahydate (490.48 mg), lidocaine (261.6 mg) hydrochloride monohydrate, and edetate disodium dihydrate (100 mg) were dissolved in 80 g of sterile water. The resulting solution was cooled to 10°C in an ice bath and poloxamer 407 (20g) was slowly added with mixing until the Poloxamer 407 completely dissolved. The solution was maintained at about 10°C until the foam collapsed. About 4 g of the solution was added to a 5 ml vial and a Valois VP4/90 18/415 pump was screwed onto the vial and refrigerated at 4°C for 30 minutes. The vial was removed from the refrigerator and the metered pump was primed using the Valois 165 actuator. The Valois 165 actuator was removed and the filled vial was stored at 4°C until the foam collapsed. The vial was removed from the refrigerator and kept at room temperature (25°C) until the contents gelled.

[0071] The viscosity of the above-prepared oral spray was measured using a Brookfield RVT viscometer. At 30°C the viscosity was 81,000 cps (averaged over three determinations) and at 40°C the viscosity was 94,333 cps (averaged over three determinations).

[0072] The composition can be applied using a long-throat actuator as described above (for spray application) or by cannula (for application to a specific area). A total of 4 spray shots is recommended. For application to a specific area by cannula rather than as a spray, the preferred actuator is a stainless-steel cannula of about 73 mm in length, for example, the 215 stainless-steel cannula commercially available from Valois Pharmaceuticals, Inc.

[0073] The foregoing has outlined rather broadly the more pertinent and important features of the present invention. While it is apparent that the invention disclosed herein is well calculated to fulfill the objects stated above, it will be appreciated that numerous modifications and embodiments may be devised by those skilled in the art. Therefore, it is intended that the appended claims cover all such modifications.

What is claimed is:

1. A composition comprising a mucosal adhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof.
2. The composition of claim 1, wherein an amount of the local anesthetic is within a range of from about 0.01 percent to about 0.5 percent of a total weight of the composition.

3. The composition of claim 1, wherein an amount of the opioid is within a range of from about 0.05 percent to about 1 percent of a total weight of the composition.

4. The composition of claim 1, wherein an amount of the mucoadhesive is within a range of from about 0.1 percent to about 40 percent of a total weight of the composition.

5. The composition of claim 1, wherein an amount of the mucoadhesive is within a range of from about 15 percent to about 25 percent of a total weight of the composition.

6. The composition of claim 1, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide.

7. The composition of claim 1, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide of a formula I:

   \[
   HO-\left(CH_2CH_2O_{x}\right)y\left(CH_3\right)zH
   \]

   wherein \(x\) is an integer having an average value ranging from about 2 to about 128; \(y\) is an integer having an average value ranging from about 14 to about 80; and \(z\) is an integer having an average value ranging from about 2 to about 128.

8. The composition of claim 1, wherein the mucoadhesive is poloxamer 407.

9. The composition of claim 1, wherein the local anesthetic is selected from the group consisting of lidocaine, tetracaine, bupivacaine, prilocaine, mepivacaine, procaine, chloroprocaine, ropivacaine, dibucaine, etidocaine, benzocaine, a pharmaceutically-acceptable salt thereof, and a mixture thereof.

10. The composition of claim 1, wherein the local anesthetic is lidocaine or a pharmaceutically-acceptable salt thereof.

11. The composition of claim 1, wherein the opioid is morphine or loperamide or a pharmaceutically-acceptable salt thereof.

12. The composition of claim 1, wherein the opioid is morphine or a pharmaceutically-acceptable salt thereof.

13. A container adapted for topical application containing a composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof.

14. The container of claim 13, packaged in association with instructions, the instructions comprising: topicaly applying the composition onto a mucous membrane of a subject.

15. The container of claim 13, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide.

16. The container of claim 13, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide of a formula I:

   \[
   HO-\left(CH_2CH_2O_{x}\right)y\left(CH_3\right)zH
   \]

   wherein \(x\) is an integer having an average value ranging from about 2 to about 128; \(y\) is an integer having an average value ranging from about 14 to about 80; and \(z\) is an integer having an average value ranging from about 2 to about 128.

17. The container of claim 13, wherein the mucoadhesive is poloxamer 407.

18. The container of claim 13, wherein the local anesthetic is selected from the group consisting of lidocaine, tetracaine, bupivacaine, prilocaine, mepivacaine, procaine, chloroprocaine, ropivacaine, dibucaine, etidocaine, benzocaine, a pharmaceutically-acceptable salt thereof, and a mixture thereof.

19. The container of claim 13, wherein the local anesthetic is lidocaine or a pharmaceutically-acceptable salt thereof.

20. The container of claim 13, wherein the opioid is morphine or loperamide or a pharmaceutically-acceptable salt thereof.

21. The container of claim 13, wherein the opioid is morphine or a pharmaceutically-acceptable salt thereof.

22. A method of inducing local anesthesia in a subject comprising topicaly applying a composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof to a subject.

23. The method of claim 22, wherein the composition is applied to the buccal mucous membrane.

24. The method of claim 22, wherein an amount of the local anesthetic is within a range of from about 0.01 percent to about 0.5 percent of a total weight of the composition.

25. The method of claim 22, wherein an amount of the opioid is within a range of from about 0.05 percent to about 1 percent of a total weight of the composition.

26. The method of claim 22, wherein an amount of the mucoadhesive is within a range of from about 0.1 percent to about 40 percent of a total weight of the composition.

27. The method of claim 22, wherein an amount of the mucoadhesive is within a range of from about 15 percent to about 25 percent of a total weight of the composition.

28. The method of claim 22, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide.

29. The method of claim 22, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide of a formula I:

   \[
   HO-\left(CH_2CH_2O_{x}\right)y\left(CH_3\right)zH
   \]

   wherein \(x\) is an integer having an average value ranging from about 2 to about 128; \(y\) is an integer having an average value ranging from about 14 to about 80; and \(z\) is an integer having an average value ranging from about 2 to about 128.
31. The method of claim 22, wherein the local anesthetic is selected from the group consisting of lidocaine, tetracaine, bupivacaine, prilocaine, mepivacaine, procaine, chloroprocaine, ropivacaine, dibucaine, etidocaine, benzocaine, a pharmaceutically-acceptable salt thereof, and a mixture thereof.

32. The method of claim 22, wherein the local anesthetic is lidocaine or a pharmaceutically-acceptable salt thereof.

33. The method of claim 22, wherein the opioid is morphine or loperamide or a pharmaceutically-acceptable salt thereof.

34. The method of claim 22, wherein the opioid is morphine or a pharmaceutically-acceptable salt thereof.