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(54) Title: TOPICAL PREPARATION FOR BYPASSING GI TRACT, DELIVERY OF THERAPEUTICS, AND TRANS-EPITHELIAL DRUG DELIVERY SYSTEM

(57) Abstract: A topical composition for therapeutic delivery including a driver for delivering a therapeutic to the bloodstream and having the ability to bypass the GI tract, avoid side effects of oral administration, and avoid a first pass effect, and an effective amount of the therapeutic. A method of delivering a therapeutic by applying a topical composition including a driver and a therapeutic to a subject's skin, and delivering the therapeutic to the bloodstream and bypassing the GI tract. A method of delivering a therapeutic by applying a topical composition including a driver and a therapeutic to a subject's skin, and delivering the therapeutic to the bloodstream and avoiding side effects of oral administration. A method of delivering a therapeutic by applying a topical composition including a driver and a therapeutic to a subject's skin, and delivering the therapeutic to the bloodstream and avoiding a first pass effect.

TOPICAL PREPARATION FOR BYPASSING GI TRACT, DELIVERY OF THERAPEUTICS, AND TRANS-EPITHELIAL DRUG DELIVERY SYSTEM

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

[0001] The present invention relates to methods and topical compositions for drug delivery. More specifically, the present invention relates to topical compositions that bypass GI tract absorption, deliver therapeutics, and avoid first pass effect.

2. BACKGROUND ART

[0002] Local anesthetics are used in many medical procedures in order to prevent or relieve pain, itching, and burning for a temporary period of time through the blocking of nerve signals and are advantageous when rapid relief is needed. Examples of procedures that local anesthetics are used in include dental procedures such as teeth cleaning and filling cavities, and minor surgeries. Local anesthetics are of two different types, aminoamides and aminoesters. The aminoamides include articaine, bupivacaine, cinchocaine, etidocaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, ropivacaine, and trimecaine. The aminoesters include benzocaine, chloroprocaine, cyclomethycaine, dimethocaine, piperocaine, propoxycaine, procaine, proparacaine, and tetracaine. Local anesthetics can be used topically or injected.

[0003] U.S. Patent Nos. 5,650,157, 5,709,855, and 6,201,022 to Bockow

disclose topical analgesic creams that have superior transdermal absorption and absorption speed. Some otherwise desirable oil compositions derived from natural sources are characterized by an unpleasant odor. Fractions or combinations of such oils may also be so characterized. Stable, deodorized oils may be prepared by adding an amount of a deodorizing agent effective to substantially reduce the odor of the derived oil composition, fraction or combination thereof to that oil composition, fraction or combination. The pharmaceutical topical compositions of these patents contain these stable, deodorized oil compositions and exhibit enhanced penetration properties and achieve enhanced patient response. A composition for preventing or treating inflammation and/or pain by topical administration are disclosed. The composition contains an omega fatty acid in combination with spirulina. Preferably, the omega fatty acid is a mixture of omega-3 fatty acids and omega-6 fatty acids. Omega-3 fatty acids include eicosapentaenoic acid and docosahexanoic acid, and omega-6 fatty acids include gamma-linolenic acid and dihomo-gamma-linolenic acid. The composition may further include pharmaceutically acceptable carriers or diluents, vitamins A and E, and a cyclooxygenase inhibitor such as methyl salicylate. The pharmaceutical compositions can be used to manage pain and/or to treat the underlying ailments. Methods of making such topical pharmaceutical compositions are also discussed.

[0004] There are currently many medications that produce unwanted side effects when passing through the gastrointestinal (GI) tract or digestive system after oral administration. Many of these medications are very common, such as NSAIDs, aspirin, antibiotics, vitamins, nitrates, calcium channel blockers, and birth control

pills. For example, some side effects include irritation of the esophagus (including strictures, scleroderma, achalasia, stroke, and ulcers), esophageal reflux, irritation of the stomach, constipations, and diarrhea. These side effects can in turn lead to ulcers, bleeding, or other painful and/or dangerous conditions. Additionally, muscle relaxers can provide too much relaxation after being absorbed in the gut, causing unwanted side effects.

[0005] There are also many drugs that undergo a significant first pass effect after oral administration. In other words, the drugs are metabolized at a point after administration, lowering their bioavailability and the concentration of the active agent available to the body. Most commonly, the first pass effect is experienced at the liver, but it can also happen at the gastrointestinal (GI) tract, blood, vascular endothelium, lungs, and other sites. Several drugs that undergo a first pass effect with oral administration include alprenolol, amitriptyline, dihydroergotamine, 5-fluorouracil, hydralazine, isoprenaline (isoproterenol), lignocaine (lidocaine), lorcainide, pethidine (meperidine), mercaptopurine, metoprolol, morphine, neostigmine, nifedipine, pentazocine and propranolol. In order to provide the optimal bioavailability, larger oral doses must be given to a patient. This can result in negative side effects. Otherwise, intravenous administration must be used to avoid this.

[0006] There have been several attempts at delivery of drugs topically. Cha, et al. (2001) describes a binary vehicle system of isopropyl-myristate and ethoxydiglycol for delivering DA-5018, a synthesized capsaicin analog that acts as an analgesic. Ellis, et al. (2012) describes the use of boronic acids for enhancing

cytosolic delivery of a protein toxin.

[0007] U.S. Patent No. 5,837,289 to Grasela discloses a transdermal administration composition that includes at least two penetration enhancers of ethoxydiglycol and isopropyl miristate. U.S. Patent No. 6,562,606 to Elias, et al. discloses a method for disrupting epithelial barrier function in a host in need of the topical administration of a physiologically active substance which comprises applying to the epithelium of the host, barrier-disrupting amount of at least one agent selected from the group consisting of an inhibitor of ceramide synthesis, inhibitor of acylceramide synthesis, inhibitor of glucosylceramide synthesis, and inhibitor of sphingomyelin synthesis, an inhibitor of fatty acid synthesis, an inhibitor of cholesterol synthesis, a degradation enzyme of ceramides, acylceramide, glucosylceramides, sphingomyelin, an inhibitor of phospholipid, glycosphingolipid, including glucosylceramide, acylceramide or sphingomyelin degradation, and both inhibitors and stimulators of metabolic enzymes of free fatty acids, ceramide, and cholesterol, as well as a topical composition useful therefor. U.S. Patent No. 6,582,724 to Hsu, et al. discloses a permeation enhancer composition for increasing the permeability of skin or mucosal tissue to topically or transdermally administered pharmacologically or cosmeceutically active agents. The composition is comprised of a hydroxide-releasing agent and a lipophilic co-enhancer such as a fatty alcohol, a fatty ether, or a fatty acid ester, including fatty acid esters of polyols such as propylene glycol and glycerol. Methods of administering active agents topically with enhanced permeation are also disclosed. U.S. Patent No. 6,689,399 to Dickson discloses an anti-inflammatory composition for treatment of joint and muscle pain

through transdermnal delivery of a capsacinoid in conjunction with glucosamine.

[0008] U.S. Patent Application Publication No. 2007/0243132 to Russell-Jones, et al. discloses a topical delivery system of microemulsions which assists penetration of a desired pharmaceutically active agent, such as peptides, polypeptides and proteins, water soluble vitamins, NSAIDs, genetic molecules and chemical compounds into the skin, which does not necessitate the use of chemical enhancers, nor electrical or ultrasonic energy to facilitate penetration into and though the skin. U.S. Patent Application Publication No. 2011/0008413 to Qui, et al. discloses compositions and transdermal drug delivery systems of synthetic local anesthetic and/or synthetic glucocorticoids and/or non-steroidal anti-inflammatory agents for the treatment and/or relief of symptoms associated with carpal tunnel syndrome or tendonitis. U.S. Patent Application Publication No. 2007/0269379 to Jain, et al. discloses a high throughput screening and isolation system that identifies rare enhancer mixtures from a candidate pool of penetration enhancer combinations, an active component, such as a drug, is then combined with the combination in a formulation which is tested for the ability of the drug to penetrate into or through skin, and specific unique and rare mixtures of chemical penetration enhancers that enhance skin permeability to hydrophilic macromolecules by more than 50-fold without inducing skin irritation, such as combinations of sodium laurel ether sulfate and 1-phenyl piperazine, and combinations of N-lauryl sarcosine and Span 20/sorbitan monolaurate.

[0009] There remain drawbacks to the currently used methods of topical delivery. There remains a need for a safe and effective topical drug delivery system

that can deliver drugs, bypass the GI tract, overcome first pass metabolism experienced with oral administration, and eliminate dangerous side effects.

SUMMARY OF THE INVENTION

[00010] The present invention provides for a topical composition for therapeutic delivery including a driver for delivering a therapeutic to the bloodstream and having the ability to bypass the GI tract, avoid side effects of oral administration, and avoid a first pass effect, and an effective amount of said therapeutic.

[00011] The present invention also provides for a method of delivering a therapeutic by applying a topical composition including a driver and a therapeutic to a subject's skin, and delivering the therapeutic to the bloodstream and bypassing the GI tract.

[00012] The present invention provides for a method of delivering a therapeutic by applying a topical composition including a driver and a therapeutic to a subject's skin, and delivering the therapeutic to the bloodstream and avoiding side effects of oral administration.

[00013] The present invention further provides for a method of delivering a therapeutic by applying a topical composition including a driver and a therapeutic to a subject's skin, and delivering the therapeutic to the bloodstream and avoiding a first pass effect.

DETAILED DESCRIPTION OF THE INVENTION

[00014] The present invention provides generally for a topical composition for

delivery of therapeutics that bypasses the GI tract and avoids first pass metabolism (i.e. avoids the therapeutic being absorbed by the digestive system and entering the hepatic portal system where it is metabolized by the liver, reducing bioavailability), and that reduces or eliminates side effects of oral administration. The topical composition can avoid many problems experienced with oral administration of drugs due to the nature of the drugs or conditions of the patient when the drugs are desired to be taken.

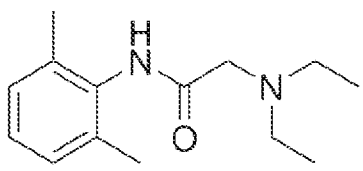
[00015] The topical composition can include any drivers that are capable of delivering the therapeutics to the bloodstream through topical administration. Preferably, the drivers can deliver the therapeutics to the bloodstream while bypassing the GI tract. Also preferably, the drivers allow for avoiding first pass metabolism. The drivers are able to provide deep penetration of the therapeutics into the skin and subsequently into the bloodstream. The drivers are able to provide a better uptake of therapeutics into the skin and the bloodstream than currently available drivers. Because of this, not only are therapeutics able to be delivered that previously have not been able to be delivered topically, but lower doses of the therapeutics can be used to provide a therapeutic effect than have been previously used, further reducing negative side effects. The drivers are also able to deliver therapeutics in a range of molecular sizes, even over 500 kDa.

[00016] The topical composition preferably includes a driver including an amino benzoate local anesthetic, methylsulfonylmethane (MSM), and ethoxydiglycol. These three components work together synergistically to deliver a therapeutic where the composition is applied. In other words, the effect of the three components

together is more than additive. Therefore, lower amounts of each of these components can be used than would normally be used alone to deliver a therapeutic. Due to the synergy of the amino benzoate local anesthetic, MSM, and ethoxydiglycol, patients benefit from increased speed to anesthesia, and a reduction of amino benzoate local anesthetic concentration because of improved penetration. Furthermore, the three components unexpectedly result in deep penetration of the active ingredients (i.e. the amino benzoate along with the therapeutic), resulting in effective analgesia. The amino benzoate local anesthetic blocks nerve signals where applied.

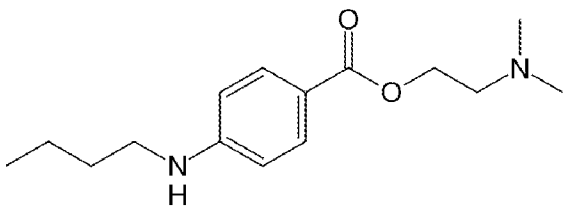
[00017] Many different amino benzoate local anesthetics can be used, such as, but not limited to, lidocaine, benzocaine (5-10%), prilocaine (1%), and tetracaine (2%). Alternatively, any other suitable local anesthetic can be used (not necessarily an amino benzoate), such as, but not limited to, amylocaine, articaine, benzonatate, bupivacaine, butacaine, chloroprocaine, cinchocaine, dimethocaine, eucaine, etidocaine, hexylcaine, levobupivacaine, mepivacaine, meprylcaine, metabutoxycaine, orthocaine, oxetacaine, oxybuprocaine, phenacaine, piperocaine, pramocaine, procaine, proparacaine, propoxycaine, quinisocaine, ropivacaine, or trimecaine

[00018] The amino benzoate local anesthetic is preferably lidocaine (or lidocaine HCl), also known as 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide shown in Formula (I).

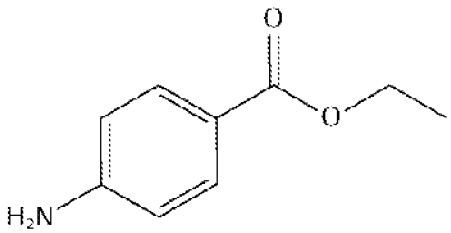
[00019] 

(I)

[00020] Lidocaine can be administered in amounts of 0.5 to 4.5 mg/kg/dose. The lidocaine can be in the form of viscous lidocaine 2% generally used to treat sore throat, teething, mouth or esophageal sores, or swelling inside the mouth. Viscous lidocaine can also be used to prevent gagging during dental procedures. Lidocaine spray 4% can be used under "crash" circumstances, where speed is of the essence. Lidocaine spray is generally used when a breathing tube is inserted down the larynx during intubation to numb the gag reflex. Combined with the other components of the topical composition for fast anesthesia, time to perform intubation can be decreased where even a few seconds reduced can save a life. Lidocaine spray can also be used during childbirth. Lidocaine spray is also available in 10%, and the maximum dose per day is 30 mg within 30 minutes. Other amino benzoate local anesthetics with similar dosing to lidocaine include tetracaine (2-(dimethylamino)ethyl 4-(butylamino)benzoate), shown in Formula (II), and benzocaine (ethyl 4-aminobenzoate), shown in Formula (III).

[00021] 

(II)

[00022] 

(III)

[00023] MSM (formula $(CH_3)_2SO_2$) is an organosulfur compound, and also known as $DMSO_2$, methyl sulfone, and dimethyl sulfone. MSM is currently available

as a dietary supplement for osteoarthritis. MSM can be administered in up to 6 g/day.

[00024] Ethoxydiglycol (also known as diethylene glycol monethyl ether, formula $CH_3CH_2OCH_2CH_2OCH_2CH_2OH$) is a cosmetic grade solvent and carrier that is used to provide an even distribution of the ingredients throughout a product. The CAS registry number is 111-90-0.

[00025] The composition can further include various carriers and excipients such as, but not limited to, water, polyacrylamide (a flocculant), C13-14 isoparaffin (an emollient), laureth-7 (surfactant and emulsifier), propylene glycol (penetration enhancer), triethanolamine (pH balancer), emu oil (antifungal agent), tea tree oil (antifungal agent), arnica Montana extract (anti-inflammatory), ethylhexylglycerin (deodorizing agent), phenoxyethanol (bactericide), isopropyl palmitate (emollient, moisturizer, thickening agent, anti-static), stearic acid (surfactant and softening agent), glucosamine sulfate (anti-arthritic), and chondroitin sulfate (anti-arthritic). An example formulation is provided in Table 1, along with possible ranges for the components. Any other suitable excipients in these categories can also be used.

Table 1

Ingredient	Amount	Range
Deionized water	QS	1-50%
Polyacrylamide, C13-14 isoparaffin, laureth-7	6.50%	1-20%
Lidocaine HCl	4.00%	1-20%
Methylsulfonylmethane (MSM)	3.00%	1-10%

Ethoxydiglycol	1.00%	0.10-5%
Propylene Glycol	1.00%	0.10-5%
Triethanolamine	0.90%	0.10-5%
Emu Oil	0.25%	0.10-5%
Tea Tree Oil	0.20%	0.10-5%
Arnica Montana Extract	0.50%	0.10-5%
Ethylhexylglycerin	0.40%	0.10-5%
Phenoxyethanol	0.40%	0.10-5%
Isopropyl Palmitate	0.20%	0.10-5%
Stearic Acid	0.15%	0.05-5%
Glucosamine Sulfate	0.10%	0.05-5%
Chondroitin Sulfate	0.10%	0.05-5%

[00026] The composition can also include agents that assist in maintaining the molecular structure integrity of the therapeutic or help deliver the therapeutic through the skin, such as, but not limited to, solvents that break down lipophilic therapeutics or adjust ionic charge for easier delivery into skin, detergents (such as, but not limited to, anionic detergents (alkylbenzenesulfonates), cationic detergents, non-ionic detergents (ethoxylates, PEGylates), or zwitterionic detergents (3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate)), cyclodextrins (that readily complex with lipophilic therapeutics like steroids, including α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin), other complexing agents (i.e. chelating agents with

two or more separate coordinate bonds between a multiple bonded ligand and a central atom (metal), such as, but not limited to, glutamic acid, histidine, malate, phytochelatin, hemoglobin, chlorophyll, ethylenediaminetetraacetic acid (EDTA), amino acid chelates, and dimercaprol), and other amphipathic chemicals.

[00027] The topical composition can further include at least one therapeutic. Preferably, a symphony of therapeutics is delivered that harmonize within the body. This harmonization can occur because they address different symptoms of an ailment or disease at the same time and through administration in the same topical composition. The harmonization can also occur because different ingredients and/or therapeutics within the topical composition metabolize each other to an active compound.

[00028] The therapeutic can be one that has the side effect of GI tract irritation when administered orally, such as, but not limited to, benzonatate, brimonidine, carboplatin, chloride ion, colestipol, colistin, dextrose, dicloxacillin, doxazosin, estramustine phosphate sodium, glipizide, imatinib mesylate, insulin recombinant human, lenalidomide, meloxicam, metformin, moricizine, myambutol, naltrexone, nifedipine, nystatin, oxacillin, penicillin g, phenoxybenzamine, procainamide hydrochloride, telithromycin, or tramadol.

[00029] The therapeutic can be at least one analgesic for relieving pain. The analgesic can be a non-steroidal anti-inflammatory drug (NSAID) such as, but not limited to, acetaminophen, salicylates (aspirin, diflunisal, salsalate), acetic acid derivatives (indomethacin, ketorolac, sulindac etodolac, diclofenac, nabumetone), propionic acid derivatives (ibuprofen, naproxen, flurbiprofen, ketoprofen, oxaprozin,

fenoprofen, loxoprofen), fenamic acid derivatives (meclofenamic acid, mefenamic acid, flufenamic acid, tolfenamic acid), oxicam (enolic acid) derivatives (piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam), arylalkanoic acid derivatives (tolmetin); or selective COX-2 inhibitors (celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib, firocoxib), opiates or morphinomimetics (morphine, codeine, oxycodone, hydrocodone, dihydromorphine, pethidine, buprenorphine, or tramadol), flupirtine, or steroids. Combinations of any of the analgesics described herein can also be used.

[00030] The therapeutic can be one that has a first pass effect when administered orally, such as, but not limited to, alprenolol, amitriptyline, buprenorphine, cimetidine, diazepam, demerol, dihydroergotamine, 5-fluorouracil, hydralazine, imipramine, isoprenaline (isoproterenol), lorcainide, pethidine (meperidine), mercaptopurine, metoprolol, midazolam, morphine, neostigmine, nifedipine, pentazocine, propranolol, lidocaine, or verapamil. Combinations of any of the therapeutics described herein can also be used.

[00031] The therapeutic can also be generally from the classes antihistamines, anti-infective agents, antineoplastic agents, autonomic drugs, blood derivatives, blood formation, coagulation, and thrombosis agents, cardiovascular drugs, cellular therapy, central nervous system agents, contraceptives, dental agents, diagnostic agents, disinfectants, electrolytic, caloric, and water balance, enzymes, respiratory tract agents, eye, ear, nose, and throat preparations, gold compounds, heavy metal antagonists, hormones and synthetic substitutes, oxytocics, radioactive agents, serums, toxoids, and vaccines, skin and mucous membrane agents, smooth muscle

relaxants, and vitamins.

[00032] The topical composition can also be used with therapeutics that are commonly or otherwise formulated as prodrugs. The prodrugs are normally activated during first pass metabolism. Examples include, but are not limited to, antibiotics such as chloramphenicol, and anticancer drugs such as taxols and cisplatin. Examples of prodrugs include, but are not limited to, using boronate derivatives, using ester forms of the therapeutic that are subsequently hydrolyzed, using forms of the therapeutic that must be phosphorylated. The prodrug can be bioactivated inside cells (intracellularly) or outside cells (extracellularly). The therapeutic can be administered in the present invention without the prodrug portion because the active therapeutic can be delivered with high efficiency to the blood without modification in any way, or a different type of prodrug can be used that captures its pathway that otherwise would be downstream of the hepatic portal.

[00033] The topical composition can be in any number of forms. Preferably, the topical composition is a cream or gel that can be applied to an affected area of the skin of a subject (human or animal). The topical composition can be in the form of a patch that releases the composition into the skin. The topical composition can also be a spray (aerosol or non-aerosol). Different release profiles can be achieved with different forms, such as rapid release, extended release, or sustained release. The topical composition can be applied multiple times a day, once per day, or as often as needed. Also, the treatment of the patient can be multi-site, by administering the present invention at the temples, injections in the back of the neck, or any other desired site or combinations of sites. Delivery of the topical composition can be by

transdermal (across the skin) or subdermal (underneath the skin) methods. For subdermal methods, it should be understood that application is by injection or implantation in the methods described below. The topical composition can be delivered directly into the blood stream as well, such as by injection.

[00034] The present invention provides generally for a method of delivering a therapeutic, by applying the topical composition to a subject's skin, and delivering the therapeutic to the bloodstream while bypassing the GI tract. A synergistically effective amount of the topical composition and the therapeutic can be used, and lower than normal doses can be used for the therapeutic due to the synergy. The present invention has the advantage of being able to deliver a therapeutic to any area of the body desired and bypassing the GI tract because the topical composition can be applied to a particular area of the body. This is particularly advantageous in delivering therapeutics to subjects with digestive problems, whether caused by disorders or illnesses such as the flu. Furthermore, with more vascular exposure to the therapeutic, a greater delivery of the therapeutic can be achieved proximal to the site of function of the therapeutic.

[00035] The present invention provides generally for a method of delivering a therapeutic, by applying the topical composition including the therapeutic to a subject's skin, and delivering the therapeutic to the blood stream and avoiding side effects of oral administration. A synergistically effective amount of the topical composition and the therapeutic can be used, and lower than normal doses can be used for the therapeutic due to the synergy. The present invention has the advantage of being able to deliver a therapeutic to any area of the body desired

without the unwanted side effects experienced with oral administration because the topical composition can be applied to a particular area of the body. With more vascular exposure to the therapeutic, a greater delivery of the therapeutic can be achieved proximal to the site of function.

[00036] For example, the topical composition can include an analgesic and a muscle relaxer in order to avoid side effects commonly experienced with taking these two therapeutics separately. A combined anti-spasmodic effect and anti-pain effect are experienced, providing a symphony of functional results: i.e. a relief from pain as well as a relief from spasms.

[00037] The present invention provides generally for a method of delivering a therapeutic, by applying the topical composition to a subject's skin, and delivering the therapeutic to the blood stream while avoiding first pass metabolism. A synergistically effective amount of the topical composition and the therapeutic can be used, and lower than normal doses can be used for the therapeutic due to the synergy.

[00038] The present invention has the advantage of being able to deliver a therapeutic to any area of the body desired and avoiding first pass metabolism because the topical composition can be applied to a particular area of the body and does not require oral administration. The therapeutics do not have to pass into blood vessels via the stomach lining or intestinal lining. This avoids effects due to acid in the stomach and avoids subsequent enzymatic metabolism that dramatically lowers effectiveness. Doses can be lower to achieve a greater bioavailability than with oral doses, thereby reducing unwanted side effects because the therapeutics

are delivered with high efficiency to the blood. Furthermore, with more vascular exposure to the therapeutic, a greater delivery of the therapeutic can be achieved proximal to the site of function.

[00039] The composition of the present invention can provide different biodistribution than other delivery vehicles. Different formulations and doses can be used depending on a subject's fat content, as some therapeutic can be lost to the fat layer (the rate and extent of the diffusion of the therapeutic and amino benzoate local anesthetic can vary).

[00040] The compound of the present invention is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, patient age, sex, body weight and other factors known to medical practitioners. The pharmaceutically "effective amount" for purposes herein is thus determined by such considerations as are known in the art. The amount must be effective to achieve improvement including but not limited to improved survival rate or more rapid recovery, or improvement or elimination of symptoms and other indicators as are selected as appropriate measures by those skilled in the art.

[00041] In the method of the present invention, the compound of the present invention can be administered in various ways. It should be noted that it can be administered as the compound and can be administered alone or as an active ingredient in combination with pharmaceutically acceptable carriers, diluents, adjuvants and vehicles. The patient being treated is a warm-blooded animal and, in particular, mammals including man. The pharmaceutically acceptable carriers,

diluents, adjuvants and vehicles as well as implant carriers generally refer to inert, non-toxic solid or liquid fillers, diluents or encapsulating material not reacting with the active ingredients of the invention.

[00042] The doses can be single doses or multiple doses over a period of several days. The treatment generally has a length proportional to the length of the disease process and drug effectiveness and the patient species being treated.

[00043] Throughout this application, various publications, including United States patents, are referenced by author and year and patents by number. Full citations for the publications are listed below. The disclosures of these publications and patents in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

[00044] The invention has been described in an illustrative manner, and it is to be understood that the terminology, which has been used is intended to be in the nature of words of description rather than of limitation.

[00045] Obviously, many modifications and variations of the present invention are possible in light of the above teachings. It is, therefore, to be understood that within the scope of the appended claims, the invention can be practiced otherwise than as specifically described.

CLAIMS

What is claimed is:

1. A topical composition for therapeutic delivery comprising driver means for delivering a therapeutic to the bloodstream and having the ability to bypass the GI tract, avoid side effects of oral administration, and avoid a first pass effect, and an effective amount of said therapeutic.

2. The topical composition of claim 1, wherein said driver means is further defined as amino benzoate local anesthetic, methylsulfonylmethane (MSM), ethoxydiglycol,

3. The topical composition of claim 1, wherein said therapeutic is further defined as a symphony of therapeutics.

4. The topical composition of claim 1, wherein said therapeutic is further defined as a therapeutic that has the side effect of GI tract irritation when administered orally chosen from the group consisting of benzonatate, brimonidine, carboplatin, chloride ion, colestipol, colistin, dextrose, dicloxacillin, doxazosin, estramustine phosphate sodium, glipizide, imatinib mesylate, insulin recombinant human, lenalidomide, meloxicam, metformin, moricizine, myambutol, naltrexone, nifedipine, nystatin, oxacillin, penicillin g, phenoxybenzamine, procainamide hydrochloride, telithromycin, tramadol, and combinations thereof.

5. The topical composition of claim 1, wherein said therapeutic is further defined as an analgesic for relieving pain chosen from the group consisting of a non-steroidal anti-inflammatory drug (NSAID), selective COX-2 inhibitors, opiates, morphinomimetics, flupirtine, steroids, and combinations thereof.

6. The topical composition of claim 1, wherein said therapeutic is further defined as an analgesic and a muscle relaxer.

7. The topical composition of claim 1, wherein said therapeutic is further defined as a therapeutic that has a first pass effect when administered orally chosen from the group consisting of alprenolol, amitriptyline, buprenorphine, cimetidine, diazepam, demerol, dihydroergotamine, 5-fluorouracil, hydralazine, imipramine, isoprenaline, lorcainide, pethidine, mercaptopurine, metoprolol, midazolam, morphine, neostigmine, nifedipine, pentazocine, propranolol, lidocaine, or verapamil, and combinations thereof.

8. The topical composition of claim 1, wherein said therapeutic is chosen from the group consisting of antihistamines, anti-infective agents, antineoplastic agents, autonomic drugs, blood derivatives, blood formation, coagulation, and thrombosis agents, cardiovascular drugs, cellular therapy, central nervous system agents, contraceptives, dental agents, diagnostic agents, disinfectants, electrolytic, caloric, and water balance, enzymes, respiratory tract agents, eye, ear, nose, and throat

preparations, gold compounds, heavy metal antagonists, hormones and synthetic substitutes, oxytocics, radioactive agents, serums, toxoids, and vaccines, skin and mucous membrane agents, smooth muscle relaxants, vitamins, and combinations thereof.

9. The topical composition of claim 1, wherein said therapeutic is otherwise formulated as a prodrug.

10. The topical composition of claim 2, wherein said amino benzoate local anesthetic is administered in the amount of 0.5-4.5 mg/kg/dose, and said MSM is administered in the amount of up to 6 g/day.

11. The topical composition of claim 2, wherein said amino benzoate local anesthetic is chosen from the group consisting of lidocaine, benzocaine 5-10%, prilocaine 1%, tetracaine 2%, and combinations thereof.

12. The topical composition of claim 2, wherein said composition further includes at least one excipient chosen from the group consisting of water, polyacrylamide, C13-14 isoparaffin, laureth-7, propylene glycol, triethanolamine, emu oil, tea tree oil, arnica Montana extract, ethylhexylglycerin, phenoxyethanol, isopropyl palmitate, stearic acid, glucosamine sulfate, chondroitin sulfate, and combinations thereof.

13. The topical composition of claim 2, wherein said composition includes 1-50%

deionized water, 1-20% polyacrylamide, 1-20% C13-14 isoparaffin, 1-20% laureth-7, 1-20% lidocaine HCl, 1-10% MSM, 0.10-5% ethoxydiglycol, 0.10-5% propylene glycol, 0.10-5% triethanolamine, 0.10-5% emu oil, 0.10-5% tea tree oil, 0.10-5% Arnica Montana extract, 0.10-5% ethylhexylglycerin, 0.10-5% phenoxyethanol, 0.10-5% isopropyl palmitate, 0.05-5% stearic acid, 0.05-5% glucosamine sulfate, and 0.05-5% chondroitin sulfate.

14. The topical composition of claim 1, further including at least one agent means for assisting in maintaining the molecular structure integrity of said therapeutic and helping deliver said therapeutic through the skin.

15. The topical composition of claim 1, wherein said composition is in an administration form chosen from the group consisting of a cream, a gel, a patch, or a spray.

16. A method of delivering a therapeutic, including the steps of:

applying a topical composition including a driver and a therapeutic to a subject's skin; and

delivering the therapeutic to the bloodstream and bypassing the GI tract.

17. The method of claim 16, wherein the driver and therapeutic are synergistic.

18. The method of claim 16, wherein the driver includes amino benzoate local

anesthetic, methylsulfonylmethane (MSM), ethoxydiglycol.

19. The method of claim 16, wherein the therapeutic is further defined as a symphony of therapeutics.

20. The method of claim 16, wherein the therapeutic is further defined as a therapeutic that has the side effect of GI tract irritation when administered orally chosen from the group consisting of benzonatate, brimonidine, carboplatin, chloride ion, colestipol, colistin, dextrose, dicloxacillin, doxazosin, estramustine phosphate sodium, glipizide, imatinib mesylate, insulin recombinant human, lenalidomide, meloxicam, metformin, moricizine, myambutol, naltrexone, nifedipine, nystatin, oxacillin, penicillin g, phenoxybenzamine, procainamide hydrochloride, telithromycin, tramadol, and combinations thereof.

21. The method of claim 16, wherein the subject has digestive problems.

22. The method of claim 16, wherein said delivering step further includes the step of delivering the therapeutic proximal to the site of function of the therapeutic.

23. A method of delivering a therapeutic, including the steps of:

applying a topical composition including a driver and a therapeutic to a subject's skin; and

delivering the therapeutic to the bloodstream and avoiding side effects of oral

administration.

24. The method of claim 23, wherein the driver and therapeutic are synergistic.

25. The method of claim 23, wherein the driver includes amino benzoate local anesthetic, methylsulfonylmethane (MSM), ethoxydiglycol

26. The method of claim 23, wherein the therapeutic is further defined as a symphony of therapeutics.

27. The method of claim 23, wherein the therapeutic is further defined as an analgesic and a muscle relaxer.

28. The method of claim 23, wherein said delivering step further includes the step of delivering the therapeutic proximal to the site of function of the therapeutic.

29. A method of delivering a therapeutic, including the steps of:

applying a topical composition including a driver and a therapeutic to a subject's skin; and

delivering the therapeutic to the bloodstream and avoiding a first pass effect.

30. The method of claim 29, wherein the driver and therapeutic are synergistic.

31. The method of claim 29, wherein the driver includes amino benzoate local anesthetic, methylsulfonylmethane (MSM), ethoxydiglycol.

32. The method of claim 29, wherein the therapeutic is further defined as a symphony of therapeutics.

33. The method of claim 29, wherein the therapeutic is further defined as a therapeutic that has a first pass effect when administered orally chosen from the group consisting of alprenolol, amitriptyline, buprenorphine, cimetidine, diazepam, demerol, dihydroergotamine, 5-fluorouracil, hydralazine, imipramine, isoprenaline, lorcainide, pethidine, mercaptopurine, metoprolol, midazolam, morphine, neostigmine, nifedipine, pentazocine, propranolol, lidocaine, or verapamil, and combinations thereof.

34. The method of claim 29, wherein said delivering step further includes the step of delivering the therapeutic proximal to the site of function of the therapeutic.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/035285

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M 37/00 (2014.01)
USPC - 424/449
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(8) - A61K 9/06, 9/10, 31/08, 31/10, 31/74, 31/196, 45/06, 47/06; A61M 37/00; A61P 23/00, 29/00; A61Q 19/00 (2014.01)
USPC - 424/449, 484; 514/1, 567, 944, 946, 947

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 9/0014, 31/08, 31/10, 31/167, 31/196, 31/245, 31/573, 45/06 (2014.06)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,837,289 A (GRASELA et al) 17 November 1998 (17.11.1998) entire document	1-9, 11, 14-34
Y	US 6,190,894 B1 (THORNFELDT et al) 20 February 2001 (20.02.2001) entire document	1-9, 11, 14-34
Y	US 2009/0247635 A1 (EHRENPREIS) 01 October 2009 (01.10.2009) entire document	2, 18, 25, 31
Y	US 2007/0243132 A1 (RUSSELL-JONES et al) 18 October 2007 (18.10.2007) entire document	9
A	US 7,033,998 B2 (FISHMAN) 25 April 2006 (25.04.2006) entire document	1-34
A	US 6,689,399 B1 (DICKSON) 10 February 2004 (10.02.2004) entire document	1-34
A	US 6,399,093 B1 (PETRUS) 04 June 2002 (04.06.2002) entire document	1-34

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"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
14 August 2014	03 SEP 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774