Title: TRANSDERMAL DRUG DELIVERY SYSTEMS, DEVICES, AND METHODS EMPLOYING OPIOID AGONIST AND/OR OPIOID ANTAGONIST

Abstract: Systems, devices, and methods for transdermal delivery of one or more therapeutic active agents to a biological interface. An iontophoretic drug delivery system is provided for transdermal delivery of one or more therapeutic active agents to a biological interface of a subject. The iontophoretic drug delivery system includes at least one active agent reservoir. The at least one active agent reservoir may include a pharmaceutical composition including at least one opioid agonist and/or opioid antagonist.
CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 60/722,136 filed September 30, 2005, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND

Field

This disclosure generally relates to the field of iontophoresis and, more particularly, to transdermal drug delivery systems, devices, and methods employing opioid agonist and/or opioid antagonist.

Description of the Related Art

Iontophoresis employs an electromotive force and/or current to transfer an active agent (e.g., a charged substance, an ionized compound, an ionic a drug, a therapeutic, a bioactive-agent, and the like), to a biological interface (e.g., skin, mucus membrane, and the like), by applying an electrical potential to an electrode proximate an iontophoretic chamber containing a similarly charged active agent and/or its vehicle.

Iontophoresis devices typically include an active electrode assembly and a counter electrode assembly, each coupled to opposite poles or terminals of a power source, for example a chemical battery or an external power source. Each electrode assembly typically includes a respective electrode element to apply an electromotive force and/or current. Such electrode elements often comprise a sacrificial element or compound, for example silver or silver chloride. The active agent may be either cationic or anionic, and the power source may be configured to apply the appropriate
voltage polarity based on the polarity of the active agent. Iontophoresis may be advantageously used to enhance or control the delivery rate of the active agent. The active agent may be stored in a reservoir such as a cavity. See e.g., U.S. Patent No. 5,395,310. Alternatively, the active agent may be stored in a reservoir such as a porous structure or a gel. An ion exchange membrane may be positioned to serve as a polarity selective barrier between the active agent reservoir and the biological interface. The membrane, typically only permeable with respect to one particular type of ion (e.g., a charged active agent), prevents the back flux of the oppositely charged ions from the skin or mucous membrane.

Commercial acceptance of iontophoresis devices is dependent on a variety of factors, such as cost to manufacture, shelf life, stability during storage, efficiency and/or timeliness of active agent delivery, biological capability, and/or disposal issues. Furthermore, an iontophoresis device that is able to deliver an active agent and is effective at inducing analgesia or anesthesia in a subject is likewise desirable.

The present disclosure is directed to overcome one or more of the shortcomings set forth above, and provide further related advantages.

BRIEF SUMMARY

In one aspect, the present disclosure is directed to a self-contained iontophoretic drug delivery system. The system includes at least one active agent reservoir, an active electrode assembly including at least one active electrode element, a power source, and a biocompatible backing. In some embodiments, the system is configured for providing transdermal delivery of one or more therapeutic active agents to a biological interface of a subject and inducing analgesia or anesthesia in the subject for a limited period of time.

The at least one active agent reservoir includes a pharmaceutical composition for inducing analgesia or anesthesia in the subject. The pharmaceutical composition for inducing analgesia or
anesthesia in the subject may include at least one analgesic or anesthetic active agent in combination with at least one opioid antagonist.

The at least one active electrode element is operable to provide an electromotive force for driving the pharmaceutical composition (comprising the at least one analgesic or anesthetic active agent in combination with the at least one opioid antagonist) for inducing analgesia or anesthesia in the subject from the at least one active agent reservoir, to the biological interface of the subject.

The power source is electrically coupleable to the active electrode assembly, and is operable for supplying an electromotive force to the active electrode assembly. The biocompatible backing is configured to encase the at least one active agent reservoir and the active electrode assembly.

In another aspect, the present disclosure is directed to a method for systemic treatment of at least one condition associated with pain, neuropathic pain, acute pain, chronic pain, or cancer pain. The method includes contacting a location on a biological interface with an iontophoretic drug delivery device that includes an active electrode assembly having at least one active agent reservoir. The at least one active agent reservoir includes a pharmaceutical composition including at least a therapeutically effective amount of at least one opioid agonist and at least one opioid antagonist.

The method further includes applying a sufficient amount of current to the active electrode assembly for transdermal administering a therapeutically effective amount of the pharmaceutical composition comprising the therapeutically effective amount of the at least one opioid agonist and the at least one opioid antagonist.

In another aspect, the present disclosure is directed to a method of treating opiate dependency and/or eliciting a substantially opiate free state in a subject in need thereof. The method includes contacting a location on a biological interface of the subject with an iontophoretic drug delivery operable for iontophoretically delivering a pharmaceutical
composition comprising a therapeutically effective amount of at least one opioid antagonist. The method further includes transdermal delivering a therapeutically effective amount of the pharmaceutical composition comprising the therapeutically effective amount of the least one opioid antagonist.

In another aspect, the present disclosure is directed to a method of inducing anesthesia, analgesia, or anti-hyperalgesia in a subject. The method includes positioning an active electrode and a counter electrode of an iontophoretic delivery device on a biological interface of the subject. In some embodiments, the iontophoretic drug delivery device is operable for iontophoretically delivering a pharmaceutical composition comprising an effective amount of at least one opioid agonist and at least one opioid antagonist. The method further includes iontophoretically delivering an anesthesia inducing, an analgesia inducing, or an anti-hyperalgesia inducing synergistic amount of a pharmaceutical composition comprising at least one opioid agonist and at least one opioid antagonist.

In yet another aspect, the present disclosure is directed to a method of treating opiate agonist-induced narcotic/respiratory depression in a subject in need thereof. The method includes contacting a location on a biological interface of the subject with an iontophoretic drug delivery device operable for iontophoretically delivering a pharmaceutical composition comprising a therapeutically effective amount of at least one opioid antagonist. The method further includes transdermal delivering a therapeutically effective amount of the pharmaceutical composition comprising the therapeutically effective amount of the least one opioid antagonist.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

In the drawings, identical reference numbers identify similar elements or acts. The sizes and relative positions of elements in the drawings are not necessarily drawn to scale. For example, the shapes of various elements and angles are not drawn to scale, and some of these
elements are arbitrarily enlarged and positioned to improve drawing legibility. Further, the particular shapes of the elements as drawn, are not intended to convey any information regarding the actual shape of the particular elements, and have been solely selected for ease of recognition in the drawings.

Figure 1A is a top, front view of a transdermal drug delivery system according to one illustrated embodiment.

Figure 1B is a top, plan view of a transdermal drug delivery system according to one illustrated embodiment.

Figure 2A is a schematic diagram of the iontophoresis device of Figures 1A and 1B comprising an active and counter electrode assemblies according to one illustrated embodiment.

Figure 2B is a schematic diagram of the iontophoresis device of Figure 2A positioned on a biological interface, with an optional outer release liner removed to expose the active agent, according to another illustrated embodiment.

Figure 2C is a schematic diagram of the iontophoresis device comprising an active and counter electrode assemblies and a plurality of microneedles according to one illustrated embodiment.

Figure 3A is a bottom, front view of a plurality of microneedles in the form of an array according to one illustrated embodiment.

Figure 3B is a bottom, front view of a plurality of microneedles in the form of one or more arrays according to another illustrated embodiment.

Figure 4 is a flow diagram of a method for systemic treatment of at least one condition associated with pain, neuropathic pain, acute pain, chronic pain, or cancer pain according to one illustrated embodiment.

Figure 5 is a flow diagram of a method of inducing anesthesia, analgesia, or anti-hyperalgesia in a subject according to one illustrated embodiment.
Figure 6 is a flow diagram of a method of treating opiate dependency and/or eliciting a substantially opiate free state in a subject in need thereof according to one illustrated embodiment.

Figure 7 is a flow diagram of a method of treating opiate agonist-induced narcotic/respiratory depression in a subject in need thereof according to one illustrated embodiment.

Figure 8 is a Time (min) vs. Drug Transported (µg) plot for hydromorphone delivery across human skin according to one illustrated embodiment.

Figure 9 is a mass spectrum plot for hydromorphone in serum according to one illustrated embodiment.

Figure 10 is a Time (min) vs. Hydromorphone (ng/ml) plot showing hydromorphone levels in test animals following iontophoretic delivery according to one illustrated embodiment.

DETAILED DESCRIPTION

In the following description, certain specific details are included to provide a thorough understanding of various disclosed embodiments. One skilled in the relevant art, however, will recognize that embodiments may be practiced without one or more of these specific details, or with other methods, components, materials, etc. In other instances, well-known structures associated with iontophoresis devices including but not limited to voltage and/or current regulators have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments.

Unless the context requires otherwise, throughout the specification and claims which follow, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is as "including, but not limited to."

Reference throughout this specification to "one embodiment," or "an embodiment," or "in another embodiment" means that a particular
referent feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearance of the phrases "in one embodiment," or "in an embodiment," or "in another embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

It should be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to an iontophoresis device including "an electrode element" includes a single electrode element, or two or more electrode elements. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

As used herein the term "membrane" means a boundary, a layer, barrier, or material, which may, or may not be permeable. The term "membrane" may further refer to an interface. Unless specified otherwise, membranes may take the form a solid, liquid, or gel, and may or may not have a distinct lattice, non cross-linked structure, or cross-linked structure.

As used herein the term "ion selective membrane" means a membrane that is substantially selective to ions, passing certain ions while blocking passage of other ions. An ion selective membrane, for example, may take the form of a charge selective membrane, or may take the form of a semi-permeable membrane.

As used herein the term "charge selective membrane" means a membrane that substantially passes and/or substantially blocks ions based primarily on the polarity or charge carried by the ion. Charge selective membranes are typically referred to as ion exchange membranes, and these terms are used interchangeably herein and in the claims. Charge selective or ion exchange membranes may take the form of a cation exchange membrane, an anion exchange membrane, and/or a bipolar membrane. A cation exchange membrane substantially permits the
passage of cations and substantially blocks anions. Examples of commercially available cation exchange membranes include those available under the designators NEOSEPTA, CM-1, CM-2, CMX, CMS, and CMB from Tokuyama Co., Ltd. Conversely, an anion exchange membrane substantially permits the passage of anions and substantially blocks cations. Examples of commercially available anion exchange membranes include those available under the designators NEOSEPTA, AM-1, AM-3, AMX, AHA, ACH, and ACS also from Tokuyama Co., Ltd.

As used herein and in the claims, the term "bipolar membrane" means a membrane that is selective to two different charges or polarities. Unless specified otherwise, a bipolar membrane may take the form of a unitary membrane structure, a multiple membrane structure, or a laminate. The unitary membrane structure may include a first portion including cation exchange materials or groups and a second portion opposed to the first portion, including anion exchange materials or groups. The multiple membrane structure (e.g., two film structure) may include a cation exchange membrane laminated or otherwise coupled to an anion exchange membrane. The cation and anion exchange membranes initially start as distinct structures, and may or may not retain their distinctiveness in the structure of the resulting bipolar membrane.

As used herein and in the claims, the term "semi-permeable membrane" means a membrane that is substantially selective based on a size or molecular weight of the ion. Thus, a semi-permeable membrane substantially passes ions of a first molecular weight or size, while substantially blocking passage of ions of a second molecular weight or size, greater than the first molecular weight or size. In some embodiments, a semi-permeable membrane may permit the passage of some molecules at a first rate, and some other molecules at a second rate different from the first. In yet further embodiments, the "semi-permeable membrane" may take the form of a selectively permeable membrane allowing only certain selective molecules to pass through it.
As used herein and in the claims, the term "porous membrane" means a membrane that is not substantially selective with respect to ions at issue. For example, a porous membrane is one that is not substantially selective based on polarity, and not substantially selective based on the molecular weight or size of a subject element or compound.

As used herein and in the claims, the term "gel matrix" means a type of reservoir, which takes the form of a three dimensional network, a colloidal suspension of a liquid in a solid, a semi-solid, a cross-linked gel, a non cross-linked gel, a jelly-like state, and the like. In some embodiments, the gel matrix may result from a three dimensional network of entangled macromolecules (e.g., cylindrical micelles). In some embodiments, a gel matrix may include hydrogels, organogels, and the like. Hydrogels refer to three-dimensional network of, for example, cross-linked hydrophilic polymers in the form of a gel and substantially composed of water. Hydrogels may have a net positive or negative charge, or may be neutral.

As used herein and in the claims, the term "reservoir" means any form of mechanism to retain an element, compound, pharmaceutical composition, active agent, and the like, in a liquid state, solid state, gaseous state, mixed state and/or transitional state. For example, unless specified otherwise, a reservoir may include one or more cavities formed by a structure, and may include one or more ion exchange membranes, semi-permeable membranes, porous membranes and/or gels if such are capable of at least temporarily retaining an element or compound. Typically, a reservoir serves to retain a biologically active agent prior to the discharge of such agent by electromotive force and/or current into the biological interface. A reservoir may also retain an electrolyte solution.

As used herein and in the claims, the term "active agent" refers to a compound, molecule, or treatment that elicits a biological response from any host, animal, vertebrate, or invertebrate, including for example fish, mammals, amphibians, reptiles, birds, and humans. Examples of active agents include therapeutic agents, pharmaceutical agents, pharmaceuticals (e.g., a drug, a therapeutic compound,
pharmaceutical salts, and the like) non-pharmaceuticals (e.g., cosmetic substance, and the like), a vaccine, an immunological agent, a local or general anesthetic or painkiller, an antigen or a protein or peptide such as insulin, a chemotherapy agent, an anti-tumor agent.

In some embodiments, the term "active agent" further refers to the active agent, as well as its pharmacologically active salts, pharmaceutically acceptable salts, prodrugs, metabolites, analogs, and the like. In some further embodiment, the active agent includes at least one ionic, cationic, ionizeable, and/or neutral therapeutic drug and/or pharmaceutical acceptable salts thereof. In yet other embodiments, the active agent may include one or more "cationic active agents" that are positively charged, and/or are capable of forming positive charges in aqueous media. For example, many biologically active agents have functional groups that are readily convertible to a positive ion or can dissociate into a positively charged ion and a counter ion in an aqueous medium. Other active agents may be polarized or polarizable, that is exhibiting a polarity at one portion relative to another portion. For instance, an active agent having an amino group can typically take the form an ammonium salt in solid state and dissociates into a free ammonium ion (NH4+) in an aqueous medium of appropriate pH.

The term "active agent" may also refer to electrically neutral agents, molecules, or compounds capable of being delivered via electro-osmotic flow. The electrically neutral agents are typically carried by the flow of, for example, a solvent during electrophoresis. Selection of the suitable active agents is therefore within the knowledge of one skilled in the relevant art.

In some embodiments, one or more active agents may be selected from analgesics, anesthetics, anesthetics vaccines, antibiotics, adjuvants, immunological adjuvants, immunogens, tolerogens, allergens, toll-like receptor agonists, toll-like receptor antagonists, immuno-adjuvants, immuno-modulators, immuno-response agents, immuno-stimulators,
specific immuno-stimulators, non-specific immuno-stimulators, and immuno-suppressants, or combinations thereof.

Non-limiting examples of such active agents include lidocaine, articaine, and others of the -caine class; morphine, hydromorphone, fentanyl, oxycodone, hydrocodone, buprenorphine, methadone, and similar opioid agonists; sumatriptan succinate, zolmitriptan, naratriptan HCl, rizatriptan benzoate, almotriptan malate, frovatriptan succinate and other 5-hydroxytryptamine receptor subtype agonists; resiquimod, imiquimod, and similar TLR 7 and 8 agonists and antagonists; domperidone, granisetron hydrochloride, ondansetron and such anti-emetic drugs; Zolpidem tartrate and similar sleep inducing agents; L-dopa and other anti-Parkinson's medications; aripiprazole, olanzapine, quetiapine, risperidone, clozapine, and ziprasidone, as well as other neuroleptica; diabetes drugs such as exenatide; as well as peptides and proteins for treatment of obesity and other maladies.

Further non-limiting examples of anesthetic active agents or pain killers include ambucaaine, amthocaine, isobutyl p-aminobenzoate, amolanone, amoxecaine, amylocaine, aprotocaine, azacaine, bencaaine, benoxinate, benzocaine, N,N-dimethylalanylbenzocaine, N,N-dimethylglycylbenzocaine, glycylbenzocaine, beta-adrenoceptor antagonists betoxycaine, bumeacaine, bupivicaine, levobupivicaine, butacaine, butamben, butanilicaine, butethamine, butoxycaine, metabutoxycaine, carbizocaine, carticaine, centbucridine, cepacaine, cetacaine, chloroprocaine, cocaethylene, cocaine, pseudococaine, cyclomethycaine, dibucaine, dimethisoquin, dimethocaine, diperodon, dyclonine, ecogneine, ecogonidine, ethyl aminobenzoate, etidocaine, euprocin, fenalcomine, fomocaine, heptacaine, hexacaine, hexocaine, hexylcaine, ketocaine, leucinocaine, levoxadrol, lignocaine, lotucaine, marcaine, mepivacaine, metacaine, methyl chloride, myrtecaine, naepaine, octacaine, orthocaine, oxethazaine, parenthoxycaine, pentacaine, phencaine, phenol, piperocaine, pirdocaine, polidocanol, polycaine, prilocaine, pramoxine, procaine (Novocaine®), hydroxyprocaine, propanocaine, proparacaine, propipocaine,
propoxycaine, pyrrocaine, quatacaine, rhinocaine, risocaine, rodocaine, ropivacaine, salicyl alcohol, tetracaine, hydroxyltetraacaine, tolcyca,
trapencaine, tricaine, trimecaine tropacocaine, zolamine, a pharmaceutically
acceptable salt thereof, and mixtures thereof.

As used herein and in the claims, the term "subject" generally
refers to any host, animal, vertebrate, or invertebrate, and includes fish,
mammals, amphibians, reptiles, birds, and particularly humans.

As used herein and in the claims, the term "agonist" refers to a
compound that can combine with a receptor (e.g., an opioid receptor, Toll-
like receptor, and the like) to produce a cellular response. An agonist may
be a ligand that directly binds to the receptor. Alternatively, an agonist may
combine with a receptor indirectly by forming a complex with another
molecule that directly binds the receptor, or otherwise resulting in the
modification of a compound so that it directly binds to the receptor.

As used herein and in the claims, the term "antagonist" refers
to a compound that can combine with a receptor (e.g., an opioid receptor, a
Toll-like receptor, and the like) to inhibit a cellular response. An antagonist
may be a ligand that directly binds to the receptor. Alternatively, an
antagonist may combine with a receptor indirectly by forming a complex with
another molecule that directly binds to the receptor, or otherwise results in
the modification of a compound so that it directly binds to the receptor.

As used herein and in the claims, the term "effective amount"
or "therapeutically effective amount" includes an amount effective at
dosages and for periods of time necessary, to achieve the desired result.
The effective amount of a composition containing a pharmaceutical agent
may vary according to factors such as the disease state, age, gender, and
weight of the subject.

As used herein and in the claims, the term "analgesic" refers to
an agent that lessens, alleviates, reduces, relieves, or extinguishes a neural
sensation in an area of a subject's body. In some embodiments, the neural
sensation relates to pain, in other aspects the neural sensation relates to
discomfort, itching, burning, irritation, tingling, "crawling," tension,
temperature fluctuations (such as fever), inflammation, aching, or other neural sensations.

As used herein and in the claims, the term "anesthetic" refers to an agent that produces a reversible loss of sensation in an area of a subject's body. In some embodiments, the anesthetic is considered to be a "local anesthetic" in that it produces a loss of sensation only in one particular area of a subject's body.

As one skilled in the relevant art would recognize, some agents may act as both an analgesic and an anesthetic, depending on the circumstances and other variables including but not limited to dosage, method of delivery, medical condition or treatment, and an individual subject's genetic makeup. Additionally, agents that are typically used for other purposes may possess local anesthetic or membrane stabilizing properties under certain circumstances or under particular conditions.

As used herein and in the claims, the term "immunogen" refers to any agent that elicits an immune response. Examples of an immunogen include, but are not limited to natural or synthetic (including modified) peptides, proteins, lipids, oligonucleotides (RNA, DNA, etc.), chemicals, or other agents.

As used herein and in the claims, the term "allergen" refers to any agent that elicits an allergic response. Some examples of allergens include but are not limited to chemicals and plants, drugs (such as antibiotics, serums), foods (such as milk, wheat, eggs, etc), bacteria, viruses, other parasites, inhalants (dust, pollen, perfume, smoke), and/or physical agents (heat, light, friction, radiation). As used herein, an allergen may be an immunogen.

As used herein and in the claims, the term "adjuvant" and any derivations thereof, refers to an agent that modifies the effect of another agent while having few, if any, direct effect when given by itself. For example, an adjuvant may increase the potency or efficacy of a pharmaceutical, or an adjuvant may alter or affect an immune response.
As used herein and in the claims, the term "opioid" generally refers to any agent that binds to and/or interacts with opioid receptors. Among the opioid classes examples include endogenous opioid peptides, opium alkaloids (e.g., morphine, codeine, and the like), semi-synthetic opioids (e.g., heroin, oxycodone and the like), synthetic opioids (e.g., buprenorphinemeperidine, fentanyl, morphinan, benzomorphan derivatives, and the like), as well as opioids that have structures unrelated to the opium alkaloids (e.g., pethidine, methadone, and the like).

As used herein and in the claims, the terms "vehicle," "carrier," "pharmaceutically vehicle," "pharmaceutically carrier," "pharmaceutically acceptable vehicle," or "pharmaceutically acceptable carrier" may be used interchangeably, and refer to pharmaceutically acceptable solid or liquid, diluting or encapsulating, filling or carrying agents, which are usually employed in pharmaceutical industry for making pharmaceutical compositions. Examples of vehicles include any liquid, gel, salve, cream, solvent, diluent, fluid ointment base, vesicle, liposomes, nisomes, ethasomes, transfersomes, virosornes, non ionic surfactant vesicles, phospholipid surfactant vesicles, micelle, and the like, that is suitable for use in contacting a subject.

In some embodiments, the pharmaceutical vehicle may refer to a composition that includes and/or delivers a pharmacologically active agent, but is generally considered to be otherwise pharmacologically inactive. In some other embodiments, the pharmaceutical vehicle may have some therapeutic effect when applied to a site such as a mucous membrane or skin, by providing, for example, protection to the site of application from conditions such as injury, further injury, or exposure to elements. Accordingly, in some embodiments, the pharmaceutical vehicle may be used for protection without a pharmacological agent in the formulation.

The headings provided herein are for convenience only and do not interpret the scope or meaning of the embodiments.

Figures 1A and 1B show an exemplary iontophoretic drug delivery system 6 for delivering of one or more active agents to a subject.
The system 6 includes an iontophoresis device 8 including active and counter electrode assemblies 12, 14, respectively, and a power source 16. The active and counter electrode assemblies 12, 14, are electrically coupleable to the power source 16 to supply an active agent contained in the active electrode assembly 12, via iontophoresis, to a biological interface 18 (e.g., a portion of skin or mucous membrane). The iontophoresis device 8 may optionally include a biocompatible backing 19. In some embodiments, the biocompatible backing 19 encases the iontophoresis devices 8. In some other embodiments, the biocompatible backing 19 physically couples the iontophoresis device 8 to the biological interface 18 of the subject. In some embodiments, the system 6 is configured for providing transdermal delivery of one or more therapeutic active agents to a biological interface of a subject and inducing analgesia or anesthesia in the subject for a limited period of time.

As shown in Figures 2A and 2B, the active electrode assembly 12 may further comprise, from an interior 20 to an exterior 22 of the active electrode assembly 12: an active electrode element 24, an electrolyte reservoir 26 storing an electrolyte 28, an inner ion selective membrane 30, one or more inner active agent reservoirs 34, storing one or more active agents 36, an optional outermost ion selective membrane 38 that optionally caches additional active agents 40, and an optional further active agent 42 carried by an outer surface 44 of the outermost ion selective membrane 38. The active electrode assembly 12 may further comprise an optional outer release liner 46.

In some embodiments, the one or more active agent reservoirs 34 are loadable with a vehicle and/or pharmaceutical composition for transporting, delivering, encapsulating, and/or carrying the one or more active agents 36, 40, 42. In some embodiments, at least one active agent reservoir 34 includes a pharmaceutical composition for inducing analgesia or anesthesia in the subject. The pharmaceutical composition for inducing analgesia or anesthesia in the subject may include at least one analgesic or anesthetic active agent in combination with at least one opioid antagonist.
In some embodiments the pharmaceutical composition includes at least a therapeutically effective one or more active agents 36, 40, 42 selected from one or more opioid agonist. In some embodiments, the pharmaceutical composition includes at least a therapeutically effective one or more active agents 36, 40, 42 selected from one or more opioid antagonist. In yet some further embodiments, the pharmaceutical composition includes a therapeutically effective amount of at least one opioid agonist and at least one opioid antagonist.

The at least one opioid agonist may be selected from endogenous opioid peptides, opium alkaloids, semi-synthetic opioids, and fully synthetic opioids, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof. In some embodiments, the at least one opioid agonist is selected from (5α,7α,8β-(-)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro(4, 5)dec-8-yl]-benzene-acetamide (U69,593)), [D-Ala²,N-Me-Phe⁴,Gly⁵-ol]enkephalin (DAMGO), delta-([D-Pen²,D-Pen⁵]-enkephalin (DPDPE)), buprenorphine, codeine, dextromoramide, dihydrocodeine, fentanyl, heroin, hydrocodone, hydromorphone, meperidine, methadone, morphine, nicomorphine, opium, oxycodone, oxymorphone, pentazocine, pethidine, propoxyphene, and tilidine, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

The at least one opioid antagonist may be selected from [(-)-(1R,5R,9R)-5,9-diethyl-2-(3-furyl-methyl)-2 1-hydroxy-6,7-benzomorphan] (MR2266), [allyl]2-tyr-alpha-amino-isobutyric acid (Aib)-Aib-Phe-Leu-OH (ICI-174864), 4-(3-hydroxyphenyl)-34-dimethyl-alpha-phenyl-1-piperidinepropanol (LY117413), 6β-Naltrexol, 7-Benzylidenenaltrexone (BNTX), b-funaltrexamine (b-FNA), cyclozocine, cyclorphan, dezocine, diprenorphine, levorphanol, meptazinol, methiodide, methylnaltrexone, nalide, nalmefene, nalmexone, nalorphine, nalorphine dinicotinate, naloxonazine, naloxone, naltrexone, naltriben (NTB), naltrindole (NTI), naltrindole isothiocyanate (NTII), N-cyclopropylmethyl-4,14-dimethoxy-morphinan-6-one (cyprodime), nor-binaltorphimine (nor-BNI), oxllorphan,
nalbuphine, and trans-3,4-dimethyl-4-phenylpiperides, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

In some embodiments, the at least one opioid antagonist is selected from hydromorphone, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof; and the at least one opioid antagonist is selected from naloxone, naltrexone, nalmefene, naloxonazine, NTI, nor-BNI, LY25506, LY9935, LY255582, and LY117413, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

In some embodiments, the at least one opioid antagonist is selected from hydromorphone, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof; and the at least one opioid antagonist is selected from naloxone, naltrexone, 6β-naltrexol, nalmefene, and naloxonazine, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof. In some embodiments, the at least one opioid antagonist is selected from palladone, Palladone® SR, Dilaudid® and hydromorphone hydrochloride; and the at least one opioid antagonist is selected from Narcan®, Trexan®, Revex®, Nubian®, nalaxone hydrochloride, naltrexone hydrochloride, nalmefene hydrochloride, and nulbuphine hydrochloride. In some embodiments, the at least one opioid agonist and at least one opioid antagonist are present in synergistic anti-hyperalgesic effective amounts.

The pharmaceutical composition may further comprises at least one active agent selected from vaccines, antibiotics, adjuvants, immunological adjuvants, immunogens, tolerogens, allergens, toll-like receptor agonists, and toll-like receptor antagonists, immuno-adjuvants, immuno-modulators, immuno-response agents, immuno-stimulators, specific immuno-stimulators, non-specific immuno-stimulators, and immuno-suppressants, or combinations thereof.

In some embodiments, the pharmaceutical composition may include a therapeutically effective amount of at least one opioid agonist, at least one opioid antagonist, and at least one active agent selected from an
antihistamine drug, a vasoconstrictor drug (e.g., epinephrine, adrenaline, norepinephrine, and the like), a steroid, and the like.

The pharmaceutical composition may be useful for systemic treatment of at least one condition associated with pain, neuropathic pain, acute pain, chronic pain, or cancer pain. In some embodiments, the at least one condition associated with pain, neuropathic pain, acute pain, chronic pain, or cancer pain includes cancer; chemotherapy; alcoholism; amputation; a back, leg, or hip problem; diabetes; a facial nerve problem; an HIV infection or AIDS; multiple sclerosis; spinal surgery; opiate induced narcotic/respiratory depression; or detoxification of opiate-dependency.

The onset of acute pain brought on by, for example, injury to a tissue typically results from the stimulation of special nerve endings called nociceptors. The nociceptors respond to a variety of stimuli including burns, cuts, infection, chemical changes, pressure, and many other sensations that are interpreted as pain by a biological subject. By eliminating the cause of such nociceptive pain and allowing the healing process to commence, the tenderness and pain associated with the injury or other stimulus typically dissipates. Although neuropathic pain is certainly real, the cause may be difficult to determine.

Neuropathic pain is often described as shooting, stabbing, burning or searing. As used herein and in the appended claims, such pain is termed "neuropathic pain." Conditions with which neuropathic pain may be commonly associated include, but are not limited to, shingles (herpes zoster virus infection; post-herpetic pain); cancer; chemotherapy; alcoholism; amputation (e.g., phantom limb syndrome); back, leg, and hip problems (sciatica); diabetes; facial nerve problems (trigeminal neuralgia); HIV infection or AIDS; multiple sclerosis; and spinal surgery. Chronic pain may also occur without any known injury or disease. For example, subjects may experience pain with no obvious injury or other stimulus. In some other cases, subjects may experience chronic pain that persist for prolonged periods including months, years, or even decades. Such pain predominantly results from damage within the peripheral or central nervous system.
Although the cause of neuropathic pain may be unknown, or uncontrollable, in one disclosed embodiment a treatment may include chronic ongoing administration of drugs or other active agents that ameliorate the pain, such as analgesic active agents, anesthetic active agents and/or painkillers. Such drugs or other active agents may be administered passively by application of one or more devices 8 to a biological interface 18 (e.g., skin or mucous membrane) at or near areas where a subject is experiencing neuropathic pain. Once the device 8 is in contact with the biological interface 18, the one or more agents are deliverable from the device 8 onto or into the biological interface 18 to exert its effect in alleviating the pain. Alternatively, one or more agents may advantageously be actively administered by a device 8 through a biological interface 18 and tissue into the systemic circulation. Accordingly, the agent may exert its therapeutic effect locally and more broadly. In one embodiment, for example, one or more active agents are administered through area portion of a biological interface from which they may enter the blood stream and be carried systemically into a capillary bed or other vasculature of an area experiencing pain (e.g., neuropathic pain and the like). In certain embodiments, the device for active administration of an anesthetic or painkiller is an iontophoretic device, as described in detail herein.

As used herein and in the appended claims, "systemic circulation" typically refers to movement of blood through the portion of a cardiovascular system and/or circulatory system that carries oxygenated blood from the heart to the body and oxygen-depleted blood from the body back to the heart. Within this portion of the cardiovascular system, blood may flow through vessels that include, but are not necessarily limited to, arteries, arterioles, capillaries, venules, and veins. Systemic circulation, as used herein and in the claims, may also refer to movement of fluids through a lymphatic system, which collects lymph from tissues and returns it to the cardiovascular circulatory system. Lymph typically originates from blood plasma that leaks from the cardiovascular system into spaces within tissue.
"Systemic delivery", as used herein and in the claims, refers to movement of compounds, such as active agents, from one location to another via systemic circulation.

Referring to Figures 2A and 2B, the active electrode assembly 12 of the iontophoretic delivery device 8 may further comprise an optional inner sealing liner (not shown) between two layers of the active electrode assembly 12, for example, between the inner ion selective membrane 30 and the inner active agent reservoir 34. The inner sealing liner, if present, would be removed prior to application of the iontophoretic device to the biological surface 18. Each of the above elements or structures will be discussed in detail below.

In some embodiments, the system 6 takes the form of a self-contained iontophoretic drug delivery system. The system 6 includes at least one active agent reservoir 34, an active electrode assembly 12 including at least one active electrode element 24, and a power source 16. The at least one active agent reservoir 34 includes a pharmaceutical composition for inducing analgesia or anesthesia in the subject. The pharmaceutical composition for inducing analgesia or anesthesia in the subject may include at least one analgesic or anesthetic active agent in combination with at least one opioid antagonist.

The active electrode element 24 is electrically coupled to a first pole 16a of the power source 16 and positioned in the active electrode assembly 12 to apply an electromotive force to transport the active agent 36, 40, 42 via various other components of the active electrode assembly 12. Under ordinary use conditions, the magnitude of the applied electromotive force is generally that required to deliver the one or more active agents according to a therapeutic effective dosage protocol. In some embodiments, the magnitude is selected such that it meets or exceeds the ordinary use operating electrochemical potential of the iontophoresis delivery device 8. The at least one active electrode element 24 is operable to provide an electromotive force for driving the pharmaceutical composition (comprising the at least one analgesic or anesthetic active agent in
combination with the at least one opioid antagonist) for inducing analgesia or anesthesia in the subject from the at least one active agent reservoir 34, to the biological interface 18 of the subject.

The active electrode element 24 may take a variety of forms. In one embodiment, the active electrode element 24 may advantageously take the form of a carbon-based active electrode element. Such may, for example, comprise multiple layers, for example a polymer matrix comprising carbon and a conductive sheet comprising carbon fiber or carbon fiber paper, such as that described in commonly assigned pending Japanese patent application 2004/317317, filed October 29, 2004. The carbon-based electrodes are inert electrodes in that they do not themselves undergo or participate in electrochemical reactions. Thus, an inert electrode distributes current through the oxidation or reduction of a chemical species capable of accepting or donating an electron at the potential applied to the system, (e.g., generating ions by either reduction or oxidation of water). Additional examples of inert electrodes include stainless steel, gold, platinum, capacitive carbon, or graphite.

Alternatively, an active electrode of sacrificial conductive material, such as a chemical compound or amalgam, may also be used. A sacrificial electrode does not cause electrolysis of water, but would itself be oxidized or reduced. Typically, for an anode a metal/metal salt may be employed. In such case, the metal would oxidize to metal ions, which would then be precipitated as an insoluble salt. An example of such anode includes an Ag/AgCl electrode. The reverse reaction takes place at the cathode in which the metal ion is reduced and the corresponding anion is released from the surface of the electrode.

The electrolyte reservoir 26 may take a variety of forms including any structure capable of retaining electrolyte 28, and in some embodiments may even be the electrolyte 28 itself, for example, where the electrolyte 28 is in a gel, semi-solid or solid form. For example, the electrolyte reservoir 26 may take the form of a pouch or other receptacle, a
membrane with pores, cavities, or interstices, particularly where the electrolyte 28 is a liquid.

In one embodiment, the electrolyte 28 comprises ionic or ionizable components in an aqueous medium, which can act to conduct current towards or away from the active electrode element. Suitable electrolytes include, for example, aqueous solutions of salts. Preferably, the electrolyte 28 includes salts of physiological ions, such as, sodium, potassium, chloride, and phosphate. In some embodiments, the one or more electrolyte reservoirs 24 including an electrolyte 28 comprising at least one biologically compatible anti-oxidant selected from ascorbate, fumarate, lactate, and malate, or salts thereof.

Once an electrical potential is applied, when an inert electrode element is in use, water is electrolyzed at both the active and counter electrode assemblies. In certain embodiments, such as when the active electrode assembly is an anode, water is oxidized. As a result, oxygen is removed from water while protons (H+) are produced. In one embodiment, the electrolyte 28 may further comprise an anti-oxidant. In some embodiments, the anti-oxidant is selected from anti-oxidants that have a lower potential than that of, for example, water. In such embodiments, the selected anti-oxidant is consumed rather than having the hydrolysis of water occur. In some further embodiments, an oxidized form of the anti-oxidant is used at the cathode and a reduced form of the anti-oxidant is used at the anode. Examples of biologically compatible anti-oxidants include, but are not limited to, ascorbic acid (vitamin C), tocopherol (vitamin E), or sodium citrate.

As noted above, the electrolyte 28 may take the form of an aqueous solution housed within a reservoir 26, or in the form of a dispersion in a hydrogel or hydrophilic polymer capable of retaining substantial amount of water. For instance, a suitable electrolyte may take the form of a solution of 0.5 M disodium fumarate: 0.5 M polyacrylic acid: 0.15 M anti-oxidant.

The inner ion selective membrane 30 is generally positioned to separate the electrolyte 28 and the inner active agent reservoir 34, if such a
membrane is included within the device. The inner ion selective membrane 30 may take the form of a charge selective membrane. For example, when the active agent 36, 40, 42 comprises a cationic active agent, the inner ion selective membrane 30 may take the form of an anion exchange membrane, selective to substantially pass anions and substantially block cations. The inner ion selective membrane 30 may advantageously prevent transfer of undesirable elements or compounds between the electrolyte 28 and the inner active agent reservoir 34. For example, the inner ion selective membrane 30 may prevent or inhibit the transfer of sodium (Na+) ions from the electrolyte 28, thereby increasing the transfer rate and/or biological compatibility of the iontophoresis device 8.

The inner active agent reservoir 34 is generally positioned between the inner ion selective membrane 30 and the outermost ion selective membrane 38. The inner active agent reservoir 34 may take a variety of forms including any structure capable of temporarily retaining active agent 36. For example, the inner active agent reservoir 34 may take the form of a pouch or other receptacle, a membrane with pores, cavities, or interstices, particularly where the active agent 36 is a liquid. The inner active agent reservoir 34 further may comprise a gel matrix.

Optionally, an outermost ion selective membrane 38 is positioned generally opposed across the active electrode assembly 12 from the active electrode element 24. The outermost membrane 38 may, as in the embodiment illustrated in Figures 2A and 2B, take the form of an ion exchange membrane having pores 48 (only one called out in Figures 2A and 2B for sake of clarity of illustration) of the ion selective membrane 38 including ion exchange material or groups 50 (only three called out in Figures 2A and 2B for sake of clarity of illustration). Under the influence of an electromotive force or current, the ion exchange material or groups 50 selectively substantially passes ions of the same polarity as active agent 36, 40, while substantially blocking ions of the opposite polarity. Thus, the outermost ion exchange membrane 38 is charge selective. Where the active agent 36, 40, 42 is a cation (e.g., lidocaine), the outermost ion
selective membrane 38 may take the form of a cation exchange membrane, thus allowing the passage of the cationic active agent while blocking the back flux of the anions present in the biological interface, such as skin.

The outermost ion selective membrane 38 may optionally cache active agent 40. Without being limited by theory, the ion exchange groups or material 50 temporarily retains ions of the same polarity as the polarity of the active agent in the absence of electromotive force or current and substantially releases those ions when replaced with substitutive ions of like polarity or charge under the influence of an electromotive force or current.

Alternatively, the outermost ion selective membrane 38 may take the form of semi-permeable or microporous membrane which is selective by size. In some embodiments, such a semi-permeable membrane may advantageously cache active agent 40, for example by employing the removably releasable outer release liner to retain the active agent 40 until the outer release liner is removed prior to use.

The outermost ion selective membrane 38 may be optionally preloaded with the additional active agent 40, such as ionized or ionizable drugs or therapeutic agents and/or polarized or polarizable drugs or therapeutic agents. Where the outermost ion selective membrane 38 is an ion exchange membrane, a substantial amount of active agent 40 may bond to ion exchange groups 50 in the pores, cavities or interstices 48 of the outermost ion selective membrane 38.

The active agent 42 that fails to bond to the ion exchange groups of material 50 may adhere to the outer surface 44 of the outermost ion selective membrane 38 as the further active agent 42. Alternatively, or additionally, the further active agent 42 may be positively deposited on and/or adhered to at least a portion of the outer surface 44 of the outermost ion selective membrane 38, for example, by spraying, flooding, coating, electrostatically, vapor deposition, and/or otherwise. In some embodiments, the further active agent 42 may sufficiently cover the outer surface 44 and/or be of sufficient thickness to form a distinct layer 52. In other embodiments,
the further active agent 42 may not be sufficient in volume, thickness, or coverage as to constitute a layer in a conventional sense of such term.

The active agent 42 may be deposited in a variety of highly concentrated forms such as, for example, solid form, nearly saturated solution form, or gel form. If in solid form, a source of hydration may be provided, either integrated into the active electrode assembly 12, or applied from the exterior thereof just prior to use.

In some embodiments, the active agent 36, additional active agent 40, and/or further active agent 42 may be identical or similar compositions or elements. In other embodiments, the active agent 36, additional active agent 40, and/or further active agent 42 may be different compositions or elements from one another. Thus, a first type of active agent may be stored in the inner active agent reservoir 34, while a second type of active agent may be cached in the outermost ion selective membrane 38. In such an embodiment, either the first type or the second type of active agent may be deposited on the outer surface 44 of the outermost ion selective membrane 38 as the further active agent 42. Alternatively, a mix of the first and the second types of active agent may be deposited on the outer surface 44 of the outermost ion selective membrane 38 as the further active agent 42. As a further alternative, a third type of active agent composition or element may be deposited on the outer surface 44 of the outermost ion selective membrane 38 as the further active agent 42. In another embodiment, a first type of active agent may be stored in the inner active agent reservoir 34 as the active agent 36 and cached in the outermost ion selective membrane 38 as the additional active agent 40, while a second type of active agent may be deposited on the outer surface 44 of the outermost ion selective membrane 38 as the further active agent 42. Typically, in embodiments where one or more different active agents are employed, the active agents 36, 40, 42 will all be of common polarity to prevent the active agents 36, 40, 42 from competing with one another. Other combinations are possible.
The outer release liner may generally be positioned overlying or covering further active agent 42 carried by the outer surface 44 of the outermost ion selective membrane 38. The outer release liner may protect the further active agent 42 and/or outermost ion selective membrane 38 during storage, prior to application of an electromotive force or current. The outer release liner may be a selectively releasable liner made of waterproof material, such as release liners commonly associated with pressure sensitive adhesives.

An interface-coupling medium (not shown) may be employed between the electrode assembly and the biological interface 18. The interface-coupling medium may take, for example, the form of an adhesive and/or gel. The gel may take, for the form of a hydrating gel. Selection of suitable bioadhesive gels is within the knowledge of one skilled in the relevant art.

In the embodiment illustrated in Figures 2A and 2B, the counter electrode assembly 14 comprises, from an interior 64 to an exterior 66 of the counter electrode assembly 14: a counter electrode element 68, an electrolyte reservoir 70 storing an electrolyte 72, an inner ion selective membrane 74, an optional buffer reservoir 76 storing buffer material 78, an optional outermost ion selective membrane 80, and an optional outer release liner (not shown).

The counter electrode element 68 is electrically coupled to a second pole 16b of the power source 16, the second pole 16b having an opposite polarity to the first pole 16a. In one embodiment, the counter electrode element 68 is an inert electrode. For example, the counter electrode element 68 may take the form of the carbon-based electrode element discussed above.

The electrolyte reservoir 70 may take a variety of forms including any structure capable of retaining electrolyte 72, and in some embodiments may even be the electrolyte 72 itself, for example, where the electrolyte 72 is in a gel, semi-solid or solid form. For example, the electrolyte reservoir 70 may take the form of a pouch or other receptacle, or
a membrane with pores, cavities, or interstices, particularly where the electrolyte 72 is a liquid.

The electrolyte 72 is generally positioned between the counter electrode element 68 and the outermost ion selective membrane 80, proximate the counter electrode element 68. As described above, the electrolyte 72 may provide ions or donate charges to prevent or inhibit the formation of gas bubbles (e.g., hydrogen or oxygen, depending on the polarity of the electrode) on the counter electrode element 68 and may prevent or inhibit the formation of acids or bases or neutralize the same, which may enhance efficiency and/or reduce the potential for irritation of the biological interface 18.

The inner ion selective membrane 74 is positioned between and/or to separate, the electrolyte 72 from the buffer material 78. The inner ion selective membrane 74 may take the form of a charge selective membrane, such as the illustrated ion exchange membrane that substantially allows passage of ions of a first polarity or charge while substantially blocking passage of ions or charge of a second, opposite polarity. The inner ion selective membrane 74 will typically pass ions of opposite polarity or charge to those passed by the outermost ion selective membrane 80 while substantially blocking ions of like polarity or charge. Alternatively, the inner ion selective membrane 74 may take the form of a semi-permeable or microporous membrane that is selective based on size.

The inner ion selective membrane 74 may prevent transfer of undesirable elements or compounds into the buffer material 78. For example, the inner ion selective membrane 74 may prevent or inhibit the transfer of hydroxy (OH-) or chloride (Cl-) ions from the electrolyte 72 into the buffer material 78.

The optional buffer reservoir 76 is generally disposed between the electrolyte reservoir and the outermost ion selective membrane 80. The buffer reservoir 76 may take a variety of forms capable of temporarily retaining the buffer material 78. For example, the buffer reservoir 76 may take the form of a cavity, a porous membrane, or a gel. The buffer material
78 may supply ions for transfer through the outermost ion selective membrane 42 to the biological interface 18. Consequently, the buffer material 78 may comprise, for example, a salt (e.g., NaCl).

The outermost ion selective membrane 80 of the counter electrode assembly 14 may take a variety of forms. For example, the outermost ion selective membrane 80 may take the form of a charge selective ion exchange membrane. Typically, the outermost ion selective membrane 80 of the counter electrode assembly 14 is selective to ions with a charge or polarity opposite to that of the outermost ion selective membrane 38 of the active electrode assembly 12. The outermost ion selective membrane 80 is therefore an anion exchange membrane, which substantially passes anions and blocks cations, thereby prevents the back flux of the cations from the biological interface. Examples of suitable ion exchange membranes include the previously discussed membranes.

Alternatively, the outermost ion selective membrane 80 may take the form of a semi-permeable membrane that substantially passes and/or blocks ions based on size or molecular weight of the ion.

The outer release liner (not shown) may generally be positioned overlying or covering an outer surface 84 of the outermost ion selective membrane 80. The outer release liner may protect the outermost ion selective membrane 80 during storage, prior to application of an electromotive force or current. The outer release liner may be a selectively releasable liner made of waterproof material, such as release liners commonly associated with pressure sensitive adhesives. In some embodiments, the outer release liner may be coextensive with the outer release liner (not shown) of the active electrode assembly 12.

The iontophoresis device 8 may further comprise an inert molding material 86 adjacent exposed sides of the various other structures forming the active and counter electrode assemblies 12, 14. The molding material 86 may advantageously provide environmental protection to the various structures of the active and counter electrode assemblies 12, 14.
Enveloping the active and counter electrode assemblies 12, 14 is a housing material 90.

As best seen in Figure 2B, the active and counter electrode assemblies 12, 14 are positioned on the biological interface 18. Positioning on the biological interface may close the circuit, allowing electromotive force to be applied and/or current to flow from one pole 16a of the power source 16 to the other pole 16b, via the active electrode assembly, biological interface 18 and counter electrode assembly 14.

In use, the outermost active electrode ion selective membrane 38 may be placed directly in contact with the biological interface 18. Alternatively, an interface-coupling medium (not shown) may be employed between the outermost active electrode ion selective membrane 22 and the biological interface 18. The interface-coupling medium may take, for example, the form of an adhesive and/or gel. The gel may take, for example, the form of a hydrating gel or a hydrogel. If used, the interface-coupling medium should be permeable by the active agent 36, 40, 42.

In some embodiments, the power source 16 is selected to provide sufficient voltage, current, and/or duration to ensure delivery of the one or more active agents 36, 40, 42 from the reservoir 34 and across a biological interface (e.g., a membrane) to impart the desired physiological effect. The power source 16 may take the form of one or more chemical battery cells, super- or ultra-capacitors, fuel cells, secondary cells, thin film secondary cells, button cells, lithium ion cells, zinc air cells, nickel metal hydride cells, and the like. The power source 16 may, for example, provide a voltage of 12.8 V DC, with tolerance of 0.8 V DC, and a current of 0.3 mA. The power source 16 may be selectively, electrically coupled to the active and counter electrode assemblies 12, 14 via a control circuit, for example, via carbon fiber ribbons. The iontophoresis device 8 may include discrete and/or integrated circuit elements to control the voltage, current, and/or power delivered to the electrode assemblies 12, 14. For example, the iontophoresis device 8 may include a diode to provide a constant current to the electrode elements 24, 68.
As suggested above, the one or more active agents 36, 40, 42 may take the form of one or more ionic, cationic, ionizeable, and/or neutral drugs or other therapeutic agents. Consequently, the poles or terminals of the power source 16 and the selectivity of the outermost ion selective membranes 38, 80 and inner ion selective membranes 30, 74 are selected accordingly.

During iontophoresis, the electromotive force across the electrode assemblies, as described, leads to a migration of charged active agent molecules, as well as ions and other charged components, through the biological interface into the biological tissue. This migration may lead to an accumulation of active agents, ions, and/or other charged components within the biological tissue beyond the interface. During iontophoresis, in addition to the migration of charged molecules in response to repulsive forces, there is also an electroosmotic flow of solvent (e.g., water) through the electrodes and the biological interface into the tissue. In certain embodiments, the electroosmotic solvent flow enhances migration of both charged and uncharged molecules. Enhanced migration via electroosmotic solvent flow may occur particularly with increasing size of the molecule.

In certain embodiments, the active agent may be a higher molecular weight molecule. In certain aspects, the molecule may be a polar polyelectrolyte. In certain other aspects, the molecule may be lipophilic. In certain embodiments, such molecules may be charged, may have a low net charge, or may be uncharged under the conditions within the active electrode. In certain aspects, such active agents may migrate poorly under the iontophoretic repulsive forces, in contrast to the migration of small more highly charged active agents under the influence of these forces. These higher molecular weight active agents may thus be carried through the biological interface into the underlying tissues primarily via electroosmotic solvent flow. In certain embodiments, the high molecular weight polyelectrolytic active agents may be proteins, polypeptides, or nucleic acids. In other embodiments, the active agent may be mixed with another
agent to form a complex capable of being transported across the biological interface via one of the motive methods described above.

In some embodiments, the transdermal drug delivery system 6 includes an iontophoretic drug delivery device 8 for providing transdermal delivery of one or more therapeutic active agents 36, 40, 42 to a biological interface 18. The delivery device 8 includes active electrode assembly 12 including at least one active agent reservoir and at least one active electrode element operable to provide an electromotive force to drive an active agent from the at least one active agent reservoir. The delivery device 8 may include a counter electrode assembly 14 including at least one counter electrode element 68, and a power source 16 electrically coupled to the at least one active and the at least one counter electrode elements 20, 68. In some embodiments, the iontophoretic drug delivery 8 may further include one or more active agents 36, 40, 42 loaded in the at least one active agent reservoir 34.

As shown in Figure 2C, the delivery device 8 may further include a substrate 10 including a plurality of microneedles 17 in fluidic communication with the active electrode assembly 12, and positioned between the active electrode assembly 12 and the biological interface 18. The substrate 10 may be positioned between the active electrode assembly 12 and the biological interface 18. In some embodiments, the at least one active electrode element 20 is operable to provide an electromotive force to drive an active agent 36, 40, 42 from the at least one active agent reservoir 34, through the plurality of microneedles 17, and to the biological interface 18.

As shown in Figures 3A and 3B, the substrate 10 includes a first side 102 and a second side 104 opposing the first side 102. The first side 102 of the substrate 10 includes a plurality of microneedles 17 projecting outwardly from the first side 102. The microneedles 17 may be individually provided or formed as part of one or more arrays. In some embodiments, the microneedles 17 are integrally formed from the substrate 10. The microneedles 17 may take a solid and permeable form, a solid and
semi-permeable form, and/or a solid and non-permeable form. In some other embodiments, solid, non-permeable, microneedles may further comprise grooves along their outer surfaces for aiding the transdermal delivery of one or more active agents. In some other embodiments, the microneedles 17 may take the form of hollow microneedles. In some embodiments, the hollow microneedles may be filled with ion exchange material, ion selective materials, permeable materials, semi-permeable materials, solid materials, and the like.

The microneedles 17 are used, for example, to deliver a variety of pharmaceutical compositions, molecules, compounds, active agents, and the like to a living body via a biological interface, such as skin or mucous membrane. In certain embodiments, pharmaceutical compositions, molecules, compounds, active agents, and the like may be delivered into or through the biological interface. For example, in delivering pharmaceutical compositions, molecules, compounds, active agents, and the like via the skin, the length of the microneedle 17, either individually or in arrays 100a, 100b, and/or the depth of insertion may be used to control whether administration of a pharmaceutical compositions, molecules, compounds, active agents, and the like is only into the epidermis, through the epidermis to the dermis, or subcutaneous. In certain embodiments, the microneedle 17 may be useful for delivering high-molecular weight active agents, such as those comprising proteins, peptides and/or nucleic acids, and corresponding compositions thereof. In certain embodiments, for example, wherein the fluid is an ionic solution, the microneedles 17 can provide electrical continuity between the power source 16 and the tips of the microneedles 17. In some embodiments, the microneedles 17, either individually or in arrays 100a, 100b, may be used to dispense, deliver, and/or sample fluids through hollow apertures, through the solid permeable or semi permeable materials, or via external grooves. The microneedles 17 may further be used to dispense, deliver, and/or sample pharmaceutical compositions, molecules, compounds, active agents, and the like by iontophoretic methods, as disclosed herein.
Accordingly, in certain embodiments, for example, a plurality of microneedles 17 in an array 100a, 100b may advantageously be formed on an outermost biological interface-contacting surface of a transdermal drug delivery system 6. In some embodiments, the pharmaceutical compositions, molecules, compounds, active agents, and the like delivered or sampled by such a system 6 may comprise, for example, high-molecular weight active agents, such as proteins, peptides, and/or nucleic acids.

In some embodiments, a plurality of microneedles 17 may take the form of a microneedle array 100a, 100b. The microneedle array 100a, 100b may be arranged in a variety of configurations and patterns including, for example, a rectangle, a square, a circle (as shown in Figure 3A), a triangle, a polygon, a regular or irregular shapes, and the like. The microneedles 17 and the microneedle arrays 100a, 100b may be manufactured from a variety of materials, including ceramics, elastomers, epoxy photoresist, glass, glass polymers, glass/polymer materials, metals (e.g., chromium, cobalt, gold, molybdenum, nickel, stainless steel, titanium, tungsten steel, and the like), molded plastics, polymers, biodegradable polymers, non-biodegradable polymers, organic polymers, inorganic polymers, silicon, silicon dioxide, polysilicon, silicon rubbers, silicon-based organic polymers, superconducting materials (e.g., superconductor wafers, and the like), and the like, as well as combinations, composites, and/or alloys thereof. Techniques for fabricating the microneedles 17 are well known in the art and include, for example, electro-deposition, electro-deposition onto laser-drilled polymer molds, laser cutting and electro-polishing, laser micromachining, surface micro-machining, soft lithography, x-ray lithography, LIGA techniques (e.g., X-ray lithography, electroplating, and molding), injection molding, conventional silicon-based fabrication methods (e.g., inductively coupled plasma etching, wet etching, isotropic and anisotropic etching, isotropic silicon etching, anisotropic silicon etching, anisotropic GaAs etching, deep reactive ion etching, silicon isotropic etching, silicon bulk micromachining, and the like), complementary-symmetry/metal-oxide semiconductor (CMOS) technology, deep x-ray
exposure techniques, and the like. See for example, U.S. Patent Nos. 6,256,533; 6,312,612; 6,334,856; 6,379,324; 6,451,240; 6,471,903; 6,503,231; 6,51,1,463; 6,533,949; 6,565,532; 6,603,987; 6,611,707; 6,663,820; 6,767,341; 6,790,372; 6,815,360; 6,881,203; 6,908,453; and 6,939,311. Some or all of the teachings therein may be applied to microneedle devices, their manufacture, and their use in iontophoretic applications. In some techniques, the physical characteristics of the microneedles 17 depend on, for example, the anodization conditions (e.g., current density, etching time, HF concentration, temperature, bias settings, and the like) as well as substrate properties (e.g., doping density, doping orientation, and the like).

The microneedles 17 may be sized and shaped to penetrate the outer layers of skin to increase its permeability and transdermal transport of pharmaceutical compositions, molecules, compounds, active agents, and the like. In some embodiments, the microneedles 17 are sized and shaped with an appropriate geometry and sufficient strength to insert into a biological interface (e.g., the skin or mucous membrane on a subject, and the like), and thereby increase a trans-interface (e.g., transdermal) transport of pharmaceutical compositions, molecules, compounds, active agents, and the like.

Figure 4 shows an exemplary method 400 for systemic treatment of at least one condition associated with pain, neuropathic pain, acute pain, chronic pain, or cancer pain.

At 402, the method includes contacting a location on a biological interface 18 with an iontophoretic drug delivery device 8 that includes an active electrode assembly 12 having at least one active agent reservoir 34. The at least one active agent reservoir 34 includes a pharmaceutical composition including at least a therapeutically effective amount of at least one opioid agonist and at least one opioid antagonist.

In some embodiments, the at least one opioid agonist is selected from endogenous opioid peptides, opium alkaloids, semi-synthetic
opioids, and fully synthetic opioids, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

In some embodiments, the at least one opioid agonist is selected from \((5\alpha,7\alpha,8\beta-(\cdot))\text{-}N\text{-}methyl\text{-}N\text{-}[7\text{-}(1\text{-}pyrrolidinyl)\text{-}1\text{-}oxaspiro}(4,5)\text{dec}8\text{-}\text{yl}]\text{-}benzene\text{-}acetamide (1169,593)), [D\text{-}Ala2,N\text{-}Me\text{-}Phe4,Gly5\text{-}oljenencephalin (DAMGO), delta-\((D\text{-}Pen2,D\text{-}Pen5\text{-}enkephalin (DPDPE), buprenorphine, codeine, dextromoramide, dihydrocodeine, fentanyl, heroin, hydrocodone, hydromorphone, meperidine, methadone, morphine, nicomorphine, opium, oxycodone, oxymorphone, pentazocine, pethidine, propoxyphene, and tilidine, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

In some embodiments, the at least one opioid antagonist is selected from \([-\text{-}(1\text{-}R,5\text{-}R,9\text{-}R})\text{-}5,9\text{-}\text{diethyl}2\text{-}(3\text{-}furyl\text{-}methyl)\text{-}2\text{\textquotesingle}-\text{hydroxy}\text{-}6,7\text{-benzomorphan} (MR2266), [allyl]2\text{-}\text{tyr}\text{-alpha}\text{-}amino\text{-}isobutyric acid (Aib)\text{-}Aib\text{-}Phe\text{-}Leu\text{-}OH (ICI\text{-}174864), 4\text{-}(3\text{-}hydroxyphenyl)\text{-}3\text{-}4\text{-}dimethyl\text{-}alpha\text{-}phenyl\text{-}1\text{-}piperidinopropanol (LY117413), 6\beta\text{-}Naltrexol, 7\text{-}Benzylidenenaltrexone (BNTX), b\text{-}funaltrexamine (b\text{-}FNA), cyclazocine, cyclorphan, dezocine, diprenorphine, levorphanol, meptazinol, methiodide, methylnaltrexone, nalide, nalmefene, nalmexone, nalorphine, nalorphine dinicotinate, naloxonazine, naloxone, naltrexone, naltriben (NTB), naltrindole (NTI), naltrindole isothiocyanate (NTII), N\text{-}cyclopropyl\text{-}methyl\text{-}4,14\text{-}dimethoxy\text{-}morphinan\text{-}6\text{-}one (cyprodime), nor\text{-}binaltorphimine (nor\text{-}BNI), oxllorphan, nalbuphine, and trans\text{-}3,4\text{-}dimethyl\text{-}4\text{-}phenylpiperides, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

In some embodiments, the at least one opioid antagonist is selected from hydromorphone, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof; and the at least one opioid antagonist is selected from naloxone, naltrexone, nalmefene, naloxonazine, NTI, nor\text{-}BNI, LY25506, LY9935, LY255582, and LY117413, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.
In some embodiments, the at least one opioid antagonist is selected from hydromorphone, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof; and the at least one opioid antagonist is selected from naloxone, naltrexone, 6β-naltrexol, nalmefene, and naloxonazine, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof. In some embodiments, the at least one opioid antagonist is selected from palladone, Palladone® SR, Dilaudid® and hydromorphone hydrochloride; and the at least one opioid antagonist is selected from Narcan®, Trexan®, Revex®, Nubian®, nalaxone hydrochloride, naltrexone hydrochloride, nalmefene hydrochloride, and nulbuphine hydrochloride.

In yet some further embodiments, the least one opioid agonist and at least one opioid antagonist are present in synergistic anti-hyperalgesic effective amounts.

In some embodiments, the at least one condition associated with pain, neuropathic pain, acute pain, chronic pain, or cancer pain includes: cancer; chemotherapy; alcoholism; amputation (e.g., phantom limb syndrome); a back, leg, or hip problem (sciatica); diabetes; a facial nerve problem (trigeminal neuralgia); an HIV infection or AIDS; multiple sclerosis; spinal surgery; opiate induced narcotic/respiratory depression; or detoxification of opiate-dependency.

In some embodiments, the pharmaceutical composition further comprises at least one active agent selected from vaccines, antibiotics, adjuvants, immunological adjuvants, immunogens, tolerogens, allergens, toll-like receptor agonists, and toll-like receptor antagonists, immuno-adjuvants, immuno-modulators, immuno-response agents, immuno-stimulators, specific immuno-stimulators, non-specific immuno-stimulators, and immuno-suppressants, or combinations thereof.

At 404, the method further includes applying a sufficient amount of current to the active electrode assembly 12 for transdermal^ administering a therapeutically effective amount of the pharmaceutical composition comprising the therapeutically effective amount of the at least
one opioid agonist and the at least one opioid antagonist. In some embodiments, applying a sufficient amount of current to the active electrode assembly 12 comprises providing a sufficient voltage and current for a time interval, to the to the active electrode assembly 12, for delivering a therapeutically effective amount of the pharmaceutical composition comprising the therapeutically effective amount of the at least one opioid agonist and the at least one opioid antagonist, from the at least one active agent reservoir 34 to the location on the biological interface 18. In some embodiments, applying a sufficient amount of current comprises providing a sufficient voltage and current for a time interval to the active electrode assembly 12 to substantially achieve sustained-delivery or controlled-delivery of the pharmaceutical composition comprising the therapeutically effective amount of the at least one opioid agonist and the at least one opioid antagonist, over an extended period of time, so as to produce anesthethestic, analgesic, or anti-hyperalgesic therapy in a subject.

Figure 5 shows an exemplary method 500 of inducing anesthesia, analgesia, or anti-hyperalgesia in a subject.

At 502, the method includes positioning an active electrode and a counter electrode of an iontophoretic delivery device on a biological interface of the subject. In some embodiments, the iontophoretic drug delivery device 8 is operable for iontophoretically delivering a pharmaceutical composition comprising an effective amount of at least one opioid agonist and at least one opioid antagonist.

At 504, the method further includes iontophoretically delivering an anesthesia inducing, an analgesia inducing, or an anti-hyperalgesia inducing synergistic amount of a pharmaceutical composition comprising at least one opioid agonist and at least one opioid antagonist.

Figure 6 shows an exemplary method 600 of treating opiate dependency and/or eliciting a substantially opiate free state in a subject in need thereof.

At 602, the method includes contacting a location on a biological interface 18 of the subject with an iontophoretic drug delivery 8
operable for iontophoretically delivering a pharmaceutical composition comprising a therapeutically effective amount of at least one opioid antagonist.

At, 604, the method further includes transdermal\(^{\text{a}}\) delivering a therapeutically effective amount of the pharmaceutical composition comprising the therapeutically effective amount of the least one opioid antagonist.

At, 606, the method further includes providing sufficient voltage and current to deliver the therapeutically effective amount of the pharmaceutical composition comprising the therapeutically effective amount of the least one opioid antagonist to the location on the biological interface 18 of the subject, so as to eliciting the substantially opiate free state.

Figure 7 shows an exemplary method 600 of method of treating opiate agonist-induced narcotic/respiratory depression in a subject in need thereof.

At 702, the method includes contacting a location on a biological interface 18 of the subject with an iontophoretic drug delivery device 8 operable for iontophoretically delivering a pharmaceutical composition comprising a therapeutically effective amount of at least one opioid antagonist.

At 704, the method further includes transdermal\(^{\text{a}}\) delivering a therapeutically effective amount of the pharmaceutical composition comprising the therapeutically effective amount of the least one opioid antagonist.

Figure 8 shows a Time (min) vs. Drug Transported (\(\mu\)g) plot for hydromorphone delivery across human skin according to one illustrated embodiment. A Franz cell setup using dermatomed human skin as the barrier to the center chamber was used to demonstrate transport across human skin in a benchtop setting. Hydromorphone was diluted in water at 1 mg/ml and placed in contact with the anodal side of an iontophoresis delivery device 8. A 0.33 mA/cm\(^2\) current density was applied to the cell and time points taken as demonstrated in the Time (min) vs. Drug Transported.
(µg) plot. Samples were analyzed for the presence of hydromorphone and plotted as a function of time.

As shown in Figure 9, mass spectrum analysis was performed on guinea pig serum samples following iontophoretic delivery of hydromorphone according to one illustrated embodiment. 250 µl of plasma were combined with 1.25 ml of borate buffer (11 g sodium borate and 6.5 g boric acid per liter of water) at pH=8.9. 5 ng of internal standard (hydromorphone-d₆) were added and mixed. SPE tubes (Varian Inc. Harbor City, CA) were prepared by washing with 2 ml of methanol followed by 2 ml of deionized water. The samples were applied and pulled through under vacuum. SPE tubes were then washed with 2 ml of deionized water, 2 ml of 10 mM ammonium acetate pH = 4, and 2 ml of methanol. The SPE tubes were then dried under high vacuum for 5 minutes. Material was eluted with 2 ml of 80:20:2 methylene chloride:isopropyl alcohol:ammonium hydroxide. The eluant was evaporated at 40 °C under a stream of air. The residue was then reconstituted in 75 µl of HPLC mobile phase and injected onto an HPLC column. HPLC-MS is an Agilent Technologies (Palo Alto, CA.) 1100 series including binary pump, degassing module, autosampler, column compartment, and mass spectrometer. The column was a Zorbax SB-C18 150 mm x 2.1 mm x 5 µ (Agilent Technologies, Palo Alto, CA.). The column was maintained at 30 °C. The mobile phase consisted of 91:9 10 mM ammonium acetate pH = 4:acetonitrile. The flow rate was 0.25 ml/min. The mass spectrometer was operated in the ESI⁺ mode using selected ion monitoring (SIM) for maximum sensitivity. Ions monitored were m/z 286 for hydromorphone and m/z 292 for hydromorphone-de. The lower limit of quantization of this assay is 0.2 ng/ml and the lower limit of detection is 0.1 ng/ml based upon a 0.25 ml sample size.

Figure 10 shows a Time (min) vs. Hydromorphone (ng/ml) plot of a Guinea pig in vivo experiment according to one illustrated embodiment. For the electrode, a carbon on polyethylene film base was used. The backing material of the patch was from 3M (polyolefin closed cell foam medical backing, product # 9773). The reservoir material was polyester
fabric (Textile Development Associates, #PETNF322.3030), 17 mm diameter, and 2 mm nominal thickness. The disks were specially treated by saturating with a 2% wt/v solution of hydroxypropyl cellulose (Klucel, MF Pharm, Hercules Corp.) and dried in a convection oven. The delivery solution was prepared by dissolving 2.1 mg of hydromorphone HCl (Sigma Chemical Co., Lot # 024K1167) into 10 ml of buffer solution containing 0.155 M Na Ascorbate, pH 4.55) to give a final concentration of 2.1 mg/mL. (Sodium Ascorbate USP, Spectrum Chemical Co., Product # S1349, Lot # UH0989 and Ascorbic Acid USP, Spectrum Chemical Co., Product #AS105, Lot # UI0026). The counter electrode solution was 0.5 M Disodium Fumarate (Fluka, Product # 47970, Lot # 44341 1/1). All buffer and drug solution were made on the same day of the experiment. The patch was made by placing the screen-printed electrode (TTI) onto a backing of the backing material. Over this, two layers of the backing material with 17 mm holes punched to cover the carbon electrode were placed. Into the holes, the HPC-treated reservoir disks were placed. An aliquot (325 μL) of either the drug or the counter solution was placed on the appropriate reservoir and allowed to hydrate the coated polyester fabric. (In the case of the control patches, the ascorbate buffer solution alone was used in the delivery side.) After hydration (~2 min), the release paper of the foam backing material was removed and the reservoir disk was covered by a protective hydrophilic membrane. Another release paper liner (3M) was then placed over the reservoirs until use.

The patches were powered by 8-channel potentiostat/galvanostat (Solartron Analytical Model 1480) running Cell Test software (Solartron Analytical) for instrument control and data acquisition. The drug delivery electrode was connected to the anode (+) and the counter electrode was connected to the cathode (-). Current was delivered under a controlled current protocol at 1 mA (patch area 2.27 cm², current density 0.44 mA/cm²) for 45 min duration. The instrument captured the total voltage drop across the patch reflecting the sum of the voltages (resistance to current passage) across each electrode, the skin at both interfaces and the
underlying tissue. Samples were collected at the indicated time points and analyzed as shown in Figure 10.

The above description of illustrated embodiments, including what is described in the Abstract, is not intended to be exhaustive or to limit the claims to the precise forms disclosed. Although specific embodiments and examples are described herein for illustrative purposes, various equivalent modifications can be made without departing from the spirit and scope of the disclosure, as will be recognized by those skilled in the relevant art. The teachings provided herein can be applied to other agent delivery systems and devices, not necessarily the exemplary iontophoresis active agent system and devices generally described above. For instance, some embodiments may include additional structure. For example, some embodiments may include a control circuit or subsystem to control a voltage, current, or power applied to the active and counter electrode elements 20, 68. Also for example, some embodiments may include an interface layer interposed between the outermost active electrode ion selective membrane 22 and the biological interface 18. Some embodiments may comprise additional ion selective membranes, ion exchange membranes, semi-permeable membranes and/or porous membranes, as well as additional reservoirs for electrolytes and/or buffers.

Various electrically conductive hydrogels have been known and used in the medical field to provide an electrical interface to the skin of a subject or within a device to couple electrical stimulus into the subject. Hydrogels hydrate the skin, thus protecting against burning due to electrical stimulation through the hydrogel, while swelling the skin and allowing more efficient transfer of an active component. Examples of such hydrogels are disclosed in U.S. Patents 6,803,420; 6,576,712; 6,908,681; 6,596,401; 6,329,488; 6,197,324; 5,290,585; 6,797,276; 5,800,685; 5,660,178; 5,573,668; 5,536,768; 5,489,624; 5,362,420; 5,338,490; and 5,240995, herein incorporated in their entirety by reference. Further examples of such hydrogels are disclosed in U.S. Patent applications 2004/166147; 2004/105834; and 2004/247655, herein incorporated in their entirety by
reference. Product brand names of various hydrogels and hydrogel sheets include CorplexTM by Corium, TegagelTM by 3M, PuraMatrixTM by BD; VigilonTM by Bard; ClearSiteTM by Conmed Corporation; FlexiGelTM by Smith & Nephew; Derma-GelTM by Medline; Nu-GelTM by Johnson & Johnson; and CuragelTM by Kendall, or acrylhydrogel films available from Sun Contact Lens Co., Ltd.

In certain embodiments, compounds or compositions can be delivered by an iontophoresis device comprising an active electrode assembly and a counter electrode assembly, electrically coupled to a power source to deliver an active agent to, into, or through a biological interface. The active electrode assembly includes the following: a first electrode member connected to a positive electrode of the power source; an active agent reservoir having a drug solution that is in contact with the first electrode member and to which is applied a voltage via the first electrode member; a biological interface contact member, which may be a microneedle array and is placed against the forward surface of the active agent reservoir; and a first cover or container that accommodates these members. The counter electrode assembly includes the following: a second electrode member connected to a negative electrode of the voltage source; a second electrolyte holding part that holds an electrolyte that is in contact with the second electrode member and to which voltage is applied via the second electrode member; and a second cover or container that accommodates these members.

In certain other embodiments, compounds or compositions can be delivered by an iontophoresis device comprising an active electrode assembly and a counter electrode assembly, electrically coupled to a power source to deliver an active agent to, into, or through a biological interface. The active electrode assembly includes the following: a first electrode member connected to a positive electrode of the voltage source; a first electrolyte reservoir having an electrolyte that is in contact with the first electrode member and to which is applied a voltage via the first electrode member; a first anion-exchange membrane that is placed on the forward
surface of the first electrolyte holding part; an active agent reservoir that is placed against the forward surface of the first anion-exchange membrane; a biological interface contacting member, which may be a microneedle array and is placed against the forward surface of the active agent reservoir; and a first cover or container that accommodates these members. The counter electrode assembly includes the following: a second electrode member connected to a negative electrode of the voltage source; a second electrolyte holding part having an electrolyte that is in contact with the second electrode member and to which is applied a voltage via the second electrode member; a cation-exchange membrane that is placed on the forward surface of the second electrolyte reservoir; a third electrolyte reservoir that is placed against the forward surface of the cation-exchange membrane and holds an electrolyte to which a voltage is applied from the second electrode member via the second electrolyte holding part and the cation-exchange membrane; a second anion-exchange membrane placed against the forward surface of the third electrolyte reservoir; and a second cover or container that accommodates these members.

The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety, including but not limited to:


Japanese patent application Serial No. 11-041416, filed February 19, 1999,
having Japanese Publication No. 2000-237327;
Japanese patent application Serial No. 11-042752, filed February 22, 1999,
having Japanese Publication No. 2000-237328;
Japanese patent application Serial No. 11-042753, filed February 22, 1999,
having Japanese Publication No. 2000-237329;
Japanese patent application Serial No. 11-099008, filed April 6, 1999,
having Japanese Publication No. 2000-288098;
Japanese patent application Serial No. 11-099009, filed April 6, 1999,
having Japanese Publication No. 2000-288097;
U.S. patent application Serial No. 10/488970, filed March 9, 2004;
Japanese patent application 2004/317317, filed October 29, 2004;
U.S. provisional patent application Serial No. 60/627,952, filed November 16,
2004;
Japanese patent application Serial No. 2004-347814, filed November 30, 2004;
Japanese patent application Serial No. 2004-357313, filed December 9, 2004;
Japanese patent application Serial No. 2005-027748, filed February 3, 2005;
U.S. Provisional Patent Application No. 60/722,136 filed September 30, 2005;
U.S. Provisional Patent Application No. 60/754,688 filed December 29, 2005;
U.S. Provisional Patent Application No. 60/755,199 filed December 30, 2005;
and
As one skill in the relevant art would readily appreciate, the present disclosure comprises methods of treating a subject by any of the compositions and/or methods described herein.

Aspects of the various embodiments can be modified, if necessary, to employ systems, circuits and concepts of the various patents, applications and publications to provide yet further embodiments, including those patents and applications identified herein. While some embodiments may include all of the membranes, reservoirs and other structures discussed above, other embodiments may omit some of the membranes, reservoirs, or other structures. Still other embodiments may employ additional ones of the membranes, reservoirs, and structures generally described above. Even further embodiments may omit some of the membranes, reservoirs and structures described above while employing additional ones of the membranes, reservoirs and structures generally described above.

These and other changes can be made in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to be limiting to the specific embodiments disclosed in the specification and the claims, but should be construed to include all systems, devices and/or methods that operate in accordance with the claims. Accordingly, the invention is not limited by the disclosure, but instead its scope is to be determined entirely by the following claims.
CLAIMS

What is claimed is:

1. A method for systemic treatment of at least one condition associated with pain, neuropathic pain, acute pain, chronic pain, or cancer pain, comprising:

   contacting a location on a biological interface with an iontophoretic drug delivery device, the iontophoretic drug delivery device comprising an active electrode assembly having at least one active agent reservoir, the at least one active agent reservoir including a pharmaceutical composition comprising at least a therapeutically effective amount of at least one opioid agonist and at least one opioid antagonist; and

   applying a sufficient amount of current to the active electrode assembly for transdermal^ administering a therapeutically effective amount of the pharmaceutical composition comprising the therapeutically effective amount of the at least one opioid agonist and the at least one opioid antagonist.

2. The method of claim 1 wherein applying a sufficient amount of current to the active electrode assembly comprises:

   providing sufficient voltage, current, or current for a predetermined time interval to the active electrode assembly for delivering a therapeutically effective amount of the pharmaceutical composition comprising the therapeutically effective amount of the at least one opioid agonist and the at least one opioid antagonist, from the at least one active agent reservoir to the location on the biological interface.

3. The method of claim 1 wherein applying a sufficient amount of current comprises:

   providing a sufficient voltage and current for a time interval to the active electrode assembly to substantially achieve sustained-delivery or
controlled-delivery of the pharmaceutical composition comprising the therapeutically effective amount of the at least one opioid agonist and the at least one opioid antagonist, over an extended period of time, so as to produce anesthetesthetic, analgesic, or anti-hyperalgesic therapy in a subject.

4. The method of claim 1 wherein the at least one opioid agonist is selected from endogenous opioid peptides, opium alkaloids, semi-synthetic opioids, and fully synthetic opioids, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

5. The method of claim 1 wherein the at least one opioid agonist is selected from (5α,7α,8β(-)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro(4,5)dec-8-yl]-benzene-acetamide (U69,593), [D-Ala²,N-Me-Phe⁴,Gly⁸]enkephalin (DAMGO), delta-[(D-Pen²,D-Pen⁵]-enkephalin (DPDPE)), buprenorphine, codeine, dextromoramide, dihydrocodeine, fentanyl, heroin, hydrocodone, hydromorphone, meperidine, methadone, morphine, nicomorphine, opium, oxycodone, oxymorphone, pentazocine, pethidine, propoxyphene, and tilidine, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

6. The method of claim 1 wherein the at least one opioid antagonist is selected from [(-)-(1 R,5R,9R)-5,9-diethyl-2-(3-furyl-methyl)-2'-hydroxy-6,7-benzomorphan] (MR2266), [allyl]2-tyr-alpha-amino-isobutyric acid (Aib)-Aib-Phe-Leu-OH (ICM 74864), 4-(3-hydroxyphenyl)-34-dimethyl-alpha-phenyl-1-piperidinepropanol (LY1 17413), 6β-Naltrexol, 7-Benzylidenenaltrexone (BNTX), b-funaltrexamine (b-FNA), cyclazocine, cyclorphan, dezocine, diprenorphine, levorphanol, meptazinol, methiodide, methylnaloxone, nalide, nalmefene, nalnemexone, nalorphine, nalorphine dinicotinate, naloxonazine, naloxone, naltrexone, naltriben (NTB), naltrindole (NTI), naltrindole isothiocyanate (NTII), N-cyclopropylmethyl-4,14-dimethoxy-morphinan-6-one (cyprodime), nor-binaltorphimine (nor-BNI), oxllorphan, nalbuphine, and trans-3,4-dimethyl-4-phenylpiperides, or
analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

7. The method of claim 1 wherein the at least one opioid antagonist is selected from hydromorphone, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof; and the at least one opioid antagonist is selected from naltrexone, nalmefene, naloxonazine, NTI, nor-BNI, LY25506, LY9935, LY255582, and LY117413, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

8. The method of claim 1 wherein the at least one opioid antagonist is selected from hydromorphone, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof; and the at least one opioid antagonist is selected from naloxone, naltrexone, 6β-naltrexol, nalmefene, and naloxonazine, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

9. The method of claim 1 wherein the at least one opioid antagonist is selected from PALLADONE, PALLADONE® SR, DILAUDID® and hydromorphone hydrochloride; and the at least one opioid antagonist is selected from NARCAN®, TREXAN®, REVEX®, NUBIAN®, naloxone hydrochloride, naltrexone hydrochloride, nalmefene hydrochloride, and nulbuphine hydrochloride.

10. The method of claim 1 wherein the at least one condition associated with pain, neuropathic pain, acute pain, chronic pain, or cancer pain includes: cancer; chemotherapy; alcoholism; amputation; a back, leg, or hip problem; diabetes; a facial nerve problem; an HIV infection or AIDS; multiple sclerosis; spinal surgery; opiate induced narcotic/respiratory depression; or detoxification of opiate-dependency.
11. The method of claim 1 wherein the pharmaceutical composition further comprises at least one active agent selected from vaccines, antibiotics, adjuvants, immunological adjuvants, immunogens, tolerogens, allergens, toll-like receptor agonists, and toll-like receptor antagonists, immuno-adjuvants, immuno-modulators, immuno-response agents, immuno-stimulators, specific immuno-stimulators, non-specific immuno-stimulators, and immuno-suppressants, or combinations thereof.

12. The method of claim 1 wherein the least one opioid agonist and at least one opioid antagonist are present in synergistic anti-hyperalgesic effective amounts.

13. A self-contained iontophoretic drug delivery system for providing transdermal delivery of one or more therapeutic active agents to a biological interface of a subject and inducing analgesia or anesthesia in the subject for a limited period of time, comprising:

at least one active agent reservoir, the at least one active agent reservoir including a pharmaceutical composition for inducing analgesia or anesthesia in the subject, the pharmaceutical composition for inducing analgesia or anesthesia in the subject comprising at least one analgesic or anesthetic active agent in combination with at least one opioid antagonist;

an active electrode assembly including at least one active electrode element, the at least one active electrode element operable to provide an electromotive force for driving the pharmaceutical composition for inducing analgesia or anesthesia in the subject comprising the at least one analgesic or anesthetic active agent in combination with the at least one opioid antagonist, from the at least one active agent reservoir, to the biological interface of the subject;

a power source electrically coupled to the active electrode assembly, the power source operable to supply an electromotive force to the active electrode assembly; and
a biocompatible backing configured to encase the at least one active agent reservoir and the active electrode assembly.

14. The system of claim 13 wherein the at least one opioid agonist is selected from endogenous opioid peptides, opium alkaloids, semisynthetic opioids, and fully synthetic opioids, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

15. The system of claim 13 wherein the at least one opioid antagonist is selected from naloxone, naltrexone, 6β-naltrexol, nalmefene, and naloxonazine, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

16. The system of claim 13 wherein the at least one opioid antagonist is selected from hydromorphone, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof; and the at least one opioid antagonist is selected from naloxone, naltrexone, 6β-naltrexol, nalmefene, and naloxonazine, or analogs or derivatives, or pharmaceutically acceptable salts or solvates thereof.

17. The system of claim 13 wherein the power source includes at least one of a chemical battery cell, super- or ultra-capacitor, a fuel cell, a secondary cell, a thin film cell, a button cell, a lithium ion cell, zinc air cell, and a nickel metal hydride cell.

18. The system of claim 13, further comprising: a circuit operable to manage a duty cycle associated with delivering a therapeutically effective amount of the pharmaceutical composition for inducing analgesia or anesthesia in the subject comprising the at least one analgesic or anesthetic active agent in combination with the at least one opioid antagonist over a predetermined period.
19. The system of claim 13 wherein the system is operable to transdermal delivery the least one opioid agonist and at least one opioid antagonist in synergistic anti-hyperalgesic effective amounts.

20. The system of claim 13, further comprising:
   an outer adhesive surface for physically coupling the self-contained iontophoretic drug delivery system to the biological interface of the subject.

21. The system of claim 13, further comprising:
   a controller electrically coupled to the power source;
   a counter electrode assembly including at least one counter electrode element electrically coupled to the power source; and
   one or more electrolyte reservoirs, the one or more electrolyte reservoirs including an electrolyte comprising at least one biologically compatible anti-oxidant selected from ascorbate, fumarate, lactate, and malate, or salts thereof.
FIG. 4

CONTACTING A LOCATION ON A BIOLOGICAL INTERFACE WITH AN IONTOPHORETIC DRUG DELIVERY DEVICE

APPLYING A SUFFICIENT AMOUNT OF CURRENT

FIG. 5

POSITIONING AN ACTIVE ELECTRODE AND A COUNTER ELECTRODE OF AN IONTOPHORETIC DELIVERY DEVICE ON A BIOLOGICAL INTERFACE OF THE SUBJECT

DELIVERING A PHARMACEUTICAL COMPOSITION
FIG. 6

- Contacting a location on a biological interface of the subject
- Transdermally delivering a therapeutically effective amount of a pharmaceutical composition
- Providing sufficient voltage and current

FIG. 7

- Contacting a location on a biological interface of the subject
- Transdermally delivering a therapeutically effective amount of a pharmaceutical composition
FIG. 10
### A. CLASSIFICATION OF SUBJECT MATTER

**INV.** A61N1/30

**ADD.** A61N1/34

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)

A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and where practical, search terms used)

EPO-Internal, wpi Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document with indication where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 4 626 539 A (AUNGST BRUCE [US] ET AL) 2 December 1986 (1986-12-02) the whole document</td>
<td>13-21</td>
</tr>
</tbody>
</table>

* Special categories of cited documents

A* document defining the general state of the art which is not considered to be of particular relevance

E* earlier document but published on or after the international filing date

L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O* document referring to an oral disclosure, use, exhibition or other means

P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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S* document member of the same patent family

Date of the actual completion of the international search: 8 February 2007

Date of mailing of the international search report: 20/02/2007

Name and mailing address of the ISA:

European Patent Office, P B 5818 Patentlaan 2
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Tel (+31-70) 340-2048, Tx 31 651 eps nl,
Fax (+31-70) 340-3016

Authorized officer:

SOPELANA MARTINEZ, J
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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**INTERNATIONAL SEARCH REPORT**

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

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

1. **X** Claims Nos 1-12 because they relate to subject matter not required to be searched by this Authority namely Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy.

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

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

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

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

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

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

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

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

Remark on Protest

- **☐** The additional search fees were accompanied by the applicant’s protest.
- **☐** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
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