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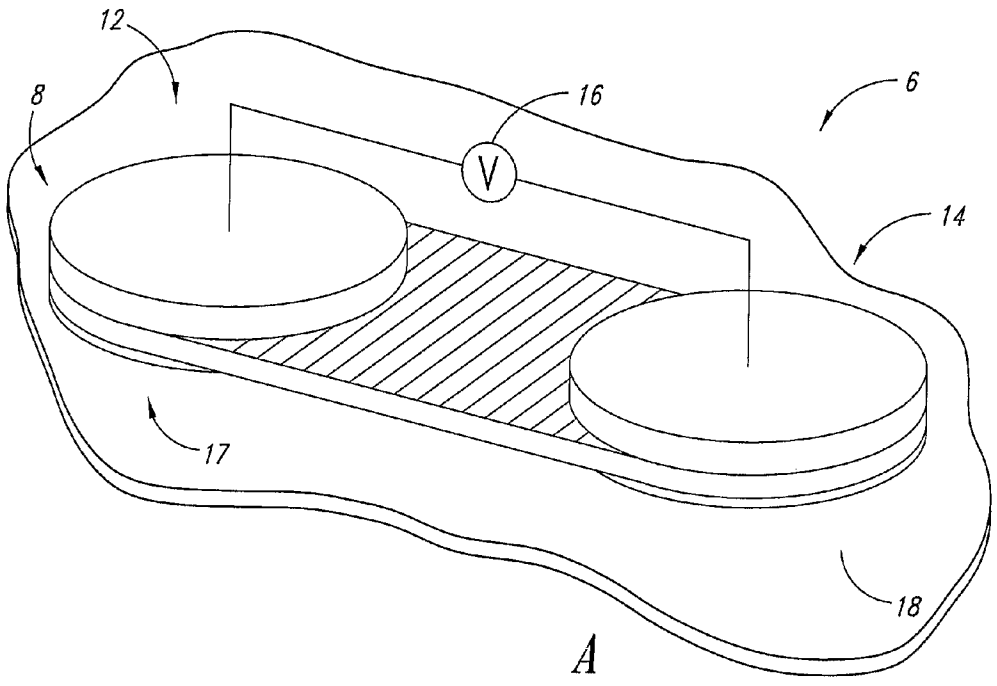
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(54) **Title:** IONTOPHORESIS METHOD AND APPARATUS FOR SYSTEMIC DELIVERY OF ACTIVE AGENTS



(57) **Abstract:** A method and an iontophoretic device are provided for delivery of one or more active agents via a circulatory system of a subject to a site of pain in the subject. In certain aspects, systemic delivery of active agents may alleviate pain at a site in a subject. Active agents may be selected from -caine-type anesthetics or painkillers. The device for delivery of an active agent may include a control unit.

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IONTOPHORESIS METHOD AND APPARATUS FOR SYSTEMIC DELIVERY OF ACTIVE AGENTS

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; and U.S. Provisional Patent Application No. 60/839,747, filed August 24, 2006, where these two provisional applications are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

Field of the Invention

This disclosure generally relates to the field of iontophoresis, and more particularly to the systemic delivery of active agents via a biological interface under the influence of electromotive force and/or current to a site of pain in a subject.

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 drug, a therapeutic, a bioactive agent, and the like), to a biological interface (e.g., skin, mucous membrane, and the like), by using a small 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 or stability during storage, efficiency and/or timeliness of active agent delivery, biological capability and/or disposal issues. An iontophoresis device that addresses one or more of these factors is desirable. Furthermore, a device that is able to deliver an active agent to and/or to provide advantageous effects at sites in a subject other than the localized site of application is desirable.

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

BRIEF SUMMARY OF THE INVENTION

A method is provided for systemic delivery of one or more active agents to a site of pain in a subject by use of an iontophoretic delivery device. In certain embodiments, the method may comprise identifying a site of pain in a subject; obtaining an iontophoretic delivery device comprising one or more active agents; activating the delivery device to transdermally transport the one or more active agents through a biological interface of the subject into a circulatory system of the subject; and allowing the circulatory system of the subject to deliver the one or more active agents to the site of pain in the

subject. In certain aspects, an active agent may be selected from the –caine class of compounds. In further aspects, a method for systemic delivery may include selecting a location on a biological interface of a subject through which one or more active agents may be transported to a circulatory system that supplies a site of pain in a subject. In certain such aspects, the method for systemic delivery may include contacting the selected location on the biological interface of the subject with the delivery device.

A method is provided for alleviating pain at a site of pain in a subject by use of an iontophoretic device for systemic delivery of one or more active agents to the site of pain in the subject. In such aspects, one or more active agents are delivered for a period of time sufficient to alleviate pain.

An iontophoretic device is provided for use in a method for systemic delivery of one or more active agents to a site of pain in a subject. In certain such aspects, the device is provided for use in a method for alleviating pain at the site of pain in the subject. In certain embodiments, a method in which an iontophoretic device is used may comprise identifying a site of pain in a subject; obtaining an iontophoretic device comprising one or more active agents; contacting a location on a biological interface of the subject with the device; activating the device to transdermally transport the one or more active agents through a biological interface of the subject into a circulatory system of the subject; and allowing the circulatory system of the subject to deliver the one or more active agents to the site of pain in the subject. In certain aspects, an active agent may be selected from the –caine class of compounds.

In certain aspects, a site of pain in a subject may be a site of neuropathic pain. In certain other embodiments, a site of pain may be a site of nociceptive pain.

In certain embodiments, an iontophoretic device for systemic delivery of one or more active agents to a site of pain in a subject is a device that comprises at least an active electrode assembly and a counter electrode assembly. In certain such embodiments, the active electrode assembly comprises at least an active electrode element operable to supply an electrical

potential of a first polarity and an inner active agent reservoir, and the counter electrode assembly comprises at least a counter electrode element operable to apply an electrical potential of a second polarity. In at least one embodiment, delivery of one or more active agents to a site of pain in a subject includes supplying an electrical potential of a first polarity to an active electrode element and supplying an electrical potential of a second polarity to a counter electrode element.

In certain embodiments, a delivery device for practice of methods described herein may include a control unit. In certain such embodiments, activating a delivery device may include operating the control unit. In at least one embodiment, a control unit may include at least one switch. In certain such embodiments, a method of delivery of an active agent to a site in a subject may include activating the switch. In at least one other embodiment, a control unit may be programmable. In certain such embodiments, a method for delivery of an active agent to a site in a subject may include programming the control unit.

In certain embodiments, a delivery device for practice of methods described herein may comprise a power source. In certain aspects, activating an iontophoretic delivery device may include electrically coupling a power source to close a circuit that includes a subject.

In certain embodiments, a method for systemic delivery of an active agent as described herein may include affixing a delivery device to a biological interface, or a portion of a biological interface, using an adhesive. In certain embodiments, a delivery device for practice of methods described herein may be in the form of a patch.

In certain embodiments, a biological interface may be a skin, a portion of skin, a mucous membrane, or a portion of mucous membrane.

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 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 line removed to expose the active agent, according to another 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 "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 appearances 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 electron 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 and in the claims, the term "membrane" means a boundary, a layer, a 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 of 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 and in the claims, 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 and in the claims, 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 ion exchange materials or groups and a second portion, opposed to the first portion, including anion ion 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 than 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 networks 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 or mechanism to retain an element, compound, pharmaceutical composition, diagnostic 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.

Pain in a subject is usually a natural result of injury to a tissue of the subject. Such pain is typically acute and is caused by stimulation of special

nerve endings called nociceptors. As used herein and in the appended claims, such pain is termed "nociceptive pain." Nociceptors respond to a variety of stimuli, including burns, cuts, infection, chemical changes, pressure, and many other sensations, each of which is interpreted by the subject as pain. For such nociceptive pain, once the cause is eliminated and the healing process is underway, the tenderness and pain associated with the injury or other stimulus will typically begin to disappear.

Alternatively, subjects may experience pain with no obvious injury or other stimulus or pain that is chronic, in that it may persist for months, years, or even decades. Such pain predominantly results from damage within the peripheral or central nervous system. 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 know injury or disease.

As used herein and in the appended claims, "systemic circulation" typically refers to movement of blood through the portion of a cardiovascular 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. The cardiovascular system is also referred to as the circulatory system. 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.

As used herein and in the claims, "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.*, a cosmetic substance, and the like), diagnostic agents, a vaccine, an immunological agent, a local or general anesthetic or painkiller, an antigen or a protein or a peptide, such as insulin, a chemotherapy agent, or an anti-tumor agent.

In some embodiments, the term "active agent" refers to the active agent itself, as well as its pharmacologically active salts, pharmaceutically or diagnostically acceptable salts, pro-drugs, metabolites, analogs, and the like. In some further embodiments, the active agent includes at least one ionic, cationic, ionizable, and/or neutral therapeutic drug and/or pharmaceutically 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. For instance, an active agent having an amino group can typically take the form of an ammonium salt in solid state and dissociate into a free ammonium ion (NH_4^+) in an aqueous medium of appropriate pH. Other active agents may have functional groups that are readily convertible to a negative ion or can dissociate into a negatively charged ion and a counter ion in an aqueous medium. Yet other active agents may be polarized or polarizable, that is, exhibiting a polarity at one portion relative to another portion.

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, 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.

Further non-limiting examples of 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-hydroxytryptamine1 receptor subtype agonists; resiquimod, imiquimod, and similar TLR 7 and TLR 8 agonist and antagonists; domperidone, granisetron hydrochloride, ondansetron, and other 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.

Additional non-limiting examples of anesthetic active agents or pain killers include ambucaine, amethocaine, isobutyl p-aminobenzoate, amolanone, amoxecaine, amylocaine, aptocaine, azacaine, bencaine, benoxinate, benzocaine, N,N-dimethylalanylbenzocaine, N,N-dimethylglycylbenzocaine, glycylbenzocaine, beta-adrenoceptor antagonists betoxycaine, bumecaine, bupivicaine, levobupivicaine, butacaine, butamben, butanilicaine, butethamine, butoxycaine, metabutoxycaine, carbizocaine,

carticaine, centbucridine, cepacaine, cetacaine, chloroprocaine, cocaethylene, cocaine, pseudococaine, cyclomethycaine, dibucaine, dimethisoquin, dimethocaine, diperodon, dyclonine, ecognine, 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, phenacine, phenol, piperocaine, piridocaine, polidocanol, polycaine, prilocaine, pramoxine, procaine (Novocaine®), hydroxyprocaine, propanocaine, proparacaine, propipocaine, propoxycaine, pyrrocaine, quatacaine, rhinocaine, risocaine, rodocaine, ropivacaine, salicyl alcohol, tetracaine, hydroxytetracaine, tolycaine, trapencaine, tricaine, trimecaine tropacocaine, zolamine, a pharmaceutically acceptable salt thereof, and mixtures thereof.

As used herein and in the claims, "antigen" or "antigenic" or "antigenicity" refers to a protein, polypeptide or carbohydrate, and the like, that is recognized by the body as foreign and that stimulates the immune system to produce an antibody; as used herein and in the claims, "antigenic determinant", also commonly referred to as "epitope," refers to a specific area or structure (that is, an "antigenic site") on the surface of an antigen that can cause an immune response, thus stimulating production of an antibody that can recognize and bind to the antigenic site or to structurally related antigenic sites. As used herein and in the claims, an "antigenic portion" of an antigen is a portion that is capable of reacting with serum obtained from an individual infected with an organism from which the antigen is derived or with the antigen itself.

As used herein and in the claims, a polypeptide comprising an antigenic determinant that is "similar to" an antigenic determinant located on an *M. tuberculosis* antigen refers to a polypeptide that elicits an immune response comparable to that elicited by the *M. tuberculosis* antigen.

As used herein and in the claims, the term "immunogen" or "immunogenicity" 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, carbohydrates, lipids, oligonucleotides (RNA, DNA, etc.), chemicals, or other agents.

As used herein and in the claims, the term "polypeptide" encompasses amino acid chains of any length, including full-length proteins, wherein the amino acid residues are linked by covalent peptide bonds.

As used herein and in the claims, a "variant" is a polypeptide that differs from a native antigen only in conservative substitutions and/or modifications, such that antigenic properties of the native antigen are retained. Such variants may generally be identified by modifying a polypeptide sequence and evaluating the antigenic properties of the modified polypeptide. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties. In general, the following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. Variants may also, or alternatively, be modified by, for example, the deletion or addition of amino acids that have minimal influence on the antigenic properties or structural characteristics of the polypeptide.

As used herein and in the claims, a "fusion protein" or "fusion polypeptide" comprises two or more protein/polypeptide sequences joined via a peptide linkage into a single amino acid chain. The sequences may be joined directly, without intervening amino acids, or by way of a linker amino acid sequence.

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 effects 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 "agonist" refers to a compound that can combine with a receptor (*e.g.*, a 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.*, 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 "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 "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 terms "vehicle," "carrier," "pharmaceutical vehicle," "pharmaceutical carrier," "pharmaceutically acceptable vehicle," "pharmaceutically acceptable carrier," "diagnostic vehicle," "diagnostic carrier," "diagnostically acceptable vehicle," or "diagnostically acceptable carrier" may be used interchangeably, depending on whether the use is pharmaceutical or diagnostic, and refer to pharmaceutically or diagnostically acceptable solid or liquid, diluting or encapsulating, filling or carrying agents, which are usually employed in pharmaceutical or diagnostic industry for making pharmaceutical or diagnostic compositions. Examples of vehicles include any liquid, gel, salve, cream, solvent, diluent, fluid ointment base, vesicle, liposomes, niosomes, ethasomes, transfersomes, virosomes, cyclic oligosaccharides, non ionic surfactant vesicles, phospholipid surfactant vesicles, micelle, and the like, that is suitable for use in contacting a subject.

In some embodiments, a 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 pharmacologically active agent in the formulation.

As used herein and in the claims, the term "cyclodextrin" refers to any of a family of cyclic oligosaccharides. Cyclodextrins, also sometimes called cycloamyloses, are composed of, but are not necessarily limited to, five or more D-glucopyranoside units, connected by α-(1,4) glycosidic linkages, as in amylase. Cyclodextrins having as many as 32 1,4-glucopyranoside units have been well characterized. Typically, cyclodextrins contain, but are not necessarily limited to, six to eight glucopyranoside units in a ring, commonly termed α-cyclodextrin (six units), β-cyclodextrin (seven units), and γ-cyclodextrin (eight units). These may be naturally occurring or produced synthetically.

As used herein and in the claims, "in conjunction with" and any derivations thereof refers to administration of an active agent, vehicle, carrier, and the like, simultaneously with, prior to, or subsequent to administration of a further active agent, vehicle, carrier, and the like.

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 appended claims, a "controller" may be identified as a "control unit."

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 transdermal 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 coupled 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). In some embodiments, the iontophoresis device 8 may optionally include an outer adhesive surface 19 for physically coupling the iontophoresis device 8 to the biological interface 18 of the subject.

As shown in Figures 2A and 2B, the active electrode assembly 12 comprises, 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, an inner active agent reservoir 34 storing active agent 36, an optional outermost ion selective membrane 38 that optionally caches additional active agent 40, an optional further active agent 42 carried by an outer surface 44 of the outermost ion selective membrane 38, and an optional outer release liner 46.

The active electrode assembly 12 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 interface 18. Each of the above elements or structures will be discussed in detail below.

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 or diagnostic effective dosage protocol. In some embodiments, the magnitude is selected such that it meets or may exceed the ordinary use operating electrochemical potential of the iontophoresis delivery device 8.

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 an 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.

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 be in 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. Alternative or additional components may include ascorbate, lactate, and the like.

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. Alternatively, where the active agent 36, 40, 42 is an anion, the outermost ion selective membrane 38 may take the form of an anion exchange membrane, thus allowing the passage of anionic active agent.

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 a semi-permeable or microporous membrane that 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 46 to retain the active agent 40 until the outer release liner 46 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 or diagnostic agents and/or polarized or polarizable drugs or therapeutic or diagnostic 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 so as 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 embodiments, 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 46 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 46 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 46 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, for example, take the form of an adhesive and/or gel. The gel may, for example, take 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 82.

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 hydroxyl (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, for example, comprise 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 are discussed above.

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 82 may generally be positioned overlying or covering an outer surface 84 of the outermost ion selective membrane 80. The outer release liner 82 is shown in place in Figure 2A and removed in Figure 2B. The outer release liner 82 may protect the outermost ion selective membrane 80 during storage, prior to application of an electromotive force or current. The outer release liner 82 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 82 may be coextensive with the outer release liner 46 of the active electrode assembly 12.

The iontophoresis device 8 may further comprise an inert molding material 186 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, for example, take the form of an adhesive and/or gel. The gel may, for example, take 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 cationic or an anionic drugs or other therapeutic or diagnostic 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 delivery system 6 includes an iontophoretic delivery device 8 for providing transdermal delivery of one or more therapeutic or diagnostic 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 24, 68. In some embodiments, the iontophoretic delivery device 8 may further include one or more active agents 36, 40, 42 loaded in the at least one active agent reservoir 34.

Iontophoretic devices and methods are provided for systemic delivery of one or more active agents to a site in a subject. In certain aspects, a site to which an active agent is delivered may be one at which pain has been identified or diagnosed. In certain such aspects, the method may include first identifying a site of pain. In certain embodiments, delivery of one or more active agents to such a site may be for alleviation of pain at that site.

As disclosed elsewhere herein, pain may be neuropathic or nociceptive. Neuropathic pain may be chronic, demanding chronic treatment. As the cause of neuropathic pain may be unknown or may not be possible to control, in one embodiment treatment may include chronic ongoing administration of drugs that ameliorate the pain, such as anesthetic active agents or painkillers identified herein. Such agents may be administered passively by application of one or more devices to a biological interface (e.g., skin or mucous membrane) at or near areas where a subject is experiencing neuropathic pain. Once the device is in contact with the interface, an agent may then diffuse from the device onto or into the interface to exert its effect in alleviating the pain. Alternatively, an agent may advantageously be actively administered by a device through a biological interface and tissue into the systemic circulation, whereby the agent may exert its therapeutic effect locally and more broadly. In one embodiment, for example, an active agent may be administered through area portion of a biological interface from which it may enter the blood stream and be carried systemically into a capillary bed or other vasculature in an area experiencing neuropathic pain. In certain embodiments,

the device for active administration of an anesthetic or painkiller is an iontophoretic device, as described in greater detail herein.

In certain embodiments, a delivery device for use according to any of the methods for systemic delivery of active agents, as disclosed herein, may be selected from any of the iontophoretic devices described and disclosed elsewhere herein. In certain aspects, a delivery device may be selected for use. In certain such aspects, the selected delivery device may be removed from packaging and prepared for use. In further such aspects, the delivery device may be prepared for use by removal of a release liner.

In certain embodiments, a method as disclosed herein may comprise physically coupling an iontophoretic delivery device to a biological interface of a subject with an iontophoretic delivery device and activating the device to transport an active agent through the biological interface and into or through a tissue into a circulatory system of a subject. In certain aspects, a device may be activated prior to contacting a biological interface. In certain embodiments, an active agent may be selected from the –caine class of anesthetic compounds or painkillers.

In certain aspects, an active agent may be delivered for a specific duration of time. In certain such embodiments, the duration of delivery may be selected to be sufficient to alleviate pain. In certain aspects, duration of delivery may be established empirically. For example, duration may be determined on the basis of alleviation of pain as identified by the subject. In other aspects, duration of delivery may be established on the basis of a delivered dose, as determined, for example, by the rate of delivery of an active agent by an iontophoretic device. Duration of delivery by a device may depend on a number of factors, including, for example, concentration of active agent within an active electrode structure, magnitude of an electrical potential applied, and flux of an active agent through a biological interface and a tissue. Method protocols for duration of delivery and effective dosages of an active agent may readily be established, for example, on the basis of results of clinical studies.

In certain aspects, duration of delivery may be manually controlled by a subject. For example, a subject may initiate delivery of an active agent by manually activating a switch. The subject may then end delivery by manually deactivating the switch. In certain such embodiments, the subject may end delivery after a pre-determined duration of time. In other such embodiments, the subject may end delivery upon noting a physiological effect, for example, a decrease in pain to a level acceptable to the subject. In yet other such embodiments, deactivation of the device to end delivery may depend on measurement and monitoring of levels of active agent or some other related compound within the blood stream of the subject. Such monitoring may be performed automatically with appropriate monitoring instruments or by testing blood samples taken periodically and analyzed for such active agents or related compounds.

In certain embodiments, duration of delivery may be controlled automatically. For example, an iontophoretic delivery device having a programmable control unit may be programmed prior to contacting a biological interface with the device. At some time after contacting the biological interface, the device may activate automatically to initiate delivery of an active agent and, after a pre-determined duration of time, as programmed, de-activate to end delivery of the active agent. Alternatively, the device may be manually activated to initiate delivery and automatically deactivated to cease delivery. In certain aspects, programmed duration of delivery may be determined by previously established conditions for delivery of a particular active agent. For example, dosage levels may be determined to provide a desired physiological effect in a subject. In certain embodiments, a delivery device may be produced having a fixed program that cannot be altered when the device is used. In certain such embodiments, activation of the program and the device may occur automatically as a result of contact of the device with a biological interface. Alternatively, the fixed program may be initiated and the device activated manually.

In certain embodiments, a method and device as disclosed herein may operate in a pulsed manner wherein intervals between delivery pulses may be programmed to vary widely, depending on a specific use of the device and/or requirements for treatment. In such embodiments, for example, programmed pulsed delivery of active agent may provide an ongoing circulating level of active agent. A circulating level may be selected, for example, to treat chronic conditions without displaying toxicity, under conditions in which toxicity at certain levels may be a possible adverse side effect.

In certain aspects, one or more active agents may be administered iontophoretically to a subject for systemic delivery to a site of neuropathic pain in the subject. In certain such aspects, there may be alleviation of the neuropathic pain. Methods and devices disclosed herein may be advantageously applied to treatment of such conditions, particularly wherein such conditions are chronic and may thus benefit from ongoing, long-term administration and delivery. In certain embodiments, for example, active agents, such as –caine-type anesthetics and painkillers, may be iontophoretically administered and systemically delivered at therapeutic levels adequate to maintain relief from chronic pain. In certain other embodiments, active agents may be administered in a pulsed manner to maintain relief. In certain embodiments, neuropathic pain may be associated with, for example, conditions such as cancer; chemotherapy; alcoholism; amputation (e.g., phantom limb syndrome); back, leg, or hip problems (sciatica); diabetes; facial nerve problems (trigeminal neuralgia); HIV infection or AIDS; multiple sclerosis; or spinal surgery. In certain other embodiments, neuropathic pain may be associated with shingles (herpes zoster virus infection; post-herpetic pain).

In certain aspects, methods and devices disclosed herein may be applied to alleviation of nociceptive pain. While nociceptive pain is typically an acute condition wherein pain occurs until the cause has been successfully treated and healing has occurred, pain relief may nevertheless be necessary for a period of days, or even weeks. Under such conditions, use of methods and devices disclosed herein may be advantageous. In certain embodiments,

nociceptive pain to be alleviated may, for example, be associated with and/or result from burns, damaged tissue, infection, chemical changes, or pressure at the site of the pain.

In certain embodiments of the methods disclosed herein, an active agent may be delivered preferentially to a particular site or region. For example, nerve damage may result in pain that may be localized even though the location of damage may be unknown. In certain such embodiments, an active agent such as a –caine-type anesthetic or painkiller may be directed preferentially to the site of pain by contacting a biological interface through which the active agent may be administered to enter blood vessels that supply the site at which pain is experienced by the subject. In certain such embodiments, for example, a –caine-type anesthetic or painkiller may be iontophoretically administered to enter arterioles supplying a capillary bed in the region wherein a subject experiences chronic pain. In some such aspects, levels of active agent may be delivered at elevated therapeutic levels within the circulation supplying blood, and thus active agent, to a particular region requiring pain relief. In such aspects, the elevated levels of active agent may become diluted as the active agent moves through the circulatory system away from the region of pain, thus limiting or eliminating any possible systemic toxic effects of such elevated therapeutic levels of active agent.

Any iontophoretic device disclosed herein may be used in the practice of the methods for systemic delivery of active agents, in particular –caine-type anesthetics or painkillers, disclosed herein. In at least one embodiment, a device may include at least an active electrode assembly having an active electrode element to supply an electrical potential of a first polarity and at least a counter electrode assembly having a counter electrode element to supply an electrical potential of a second polarity. In at least one embodiment, an active electrode assembly may include an inner active agent reservoir storing a first active agent. In at least one such embodiment, the stored first active agent may be of the –caine type of anesthetics or painkillers. In at least one embodiment, an active electrode assembly may further include a

second active agent, wherein the second active agent may or may not be of the –caine type of anesthetics or painkillers. In at least one such embodiment, the second active agent may be stored with the first active agent. Alternatively, the second active agent may be stored separately from the first active agent. One or more possible locations for storage of a first and a second active agent within the active electrode assembly are disclosed herein.

In certain embodiments, a single active agent may be systemically delivered according to methods and for uses disclosed herein. In certain other embodiments, more than one active agent may be systemically delivered according to methods and for uses disclosed herein. In certain embodiments, active agents systemically delivered according to methods and for uses disclosed herein are selected from the –caine type of anesthetics or painkillers. In certain other embodiments, active agents systemically delivered according to methods and for uses disclosed herein may include active agents other than those selected from the –caine type of anesthetics or painkillers.

As is known in the art, lidocaine is routinely combined with a vasoconstrictor, such as epinephrine, and the like, for superficial iontophoretic administration of lidocaine as a local anesthetic. In contrast, absence of a vasoconstrictor, or even inclusion of a vasodilator, in compositions, devices and methods for system delivery of active agents may be particularly advantageous. Vasodilators that may be used in devices and methods as disclosed herein are well known in the art.

In certain embodiments, a method of systemic delivery of an active agent to a site in a subject may include supplying an electrical potential of a first polarity to an active electrode element of a delivery device and supplying an electrical potential of a second polarity to a counter electrode element of a device. In certain aspects, an electrical potential supplied to an active electrode element and to a counter electrode element may be supplied continuously and at a fixed level. In certain other aspects, an electrical potential may be supplied continuously and at a variable level. In yet other aspects, an electrical potential may be supplied in a non-continuous pulsed

manner with levels of all pulses identical. In yet further aspects, an electrical potential may be supplied in a non-continuous pulsed manner with levels of pulses differing from one another.

In certain embodiments, a delivery device for practice of methods described herein may include a control unit. In certain such embodiments, activating a delivery device may include operating the control unit. In certain aspects, a control unit may include at least one switch. In certain such aspects, a method of delivery of an active agent to a site in a subject may comprise activating the switch. In certain other aspects, a control unit may be programmable. In certain such aspects, a method for systemic delivery of an active agent as described herein may comprise programming the control unit. In some aspects, a programmable control unit may be programmed before bringing a delivery device into contact with a biological interface. In other aspects, a programmable control unit may be programmed after bringing a device into contact with the biological interface. In some embodiments, a control unit may be an integral part of a device. In other embodiments, a control unit may be external to and electrically connected to a device.

In certain embodiments, a delivery device for practice of methods described herein may comprise a power source. In certain such aspects, activating a delivery device may include electrically coupling the power source to close a circuit that includes a subject.

In certain embodiments, an iontophoretic device for practice of methods described herein may be in the form of a patch. In certain aspects, a method for systemic delivery of an active agent as described herein may comprise affixing a delivery device to a biological interface, or a portion of a biological interface, using an adhesive, a gel matrix, or other material suitable for affixing a device to a biological interface and electrically conductive as necessary for operation of the device.

In certain aspects, an iontophoretic delivery device, and methods of use thereof, according to the present disclosure, may deliver active agents for systemic circulation at particular serum therapeutic levels. In certain

embodiments, for example, lidocaine may be delivered to yield a plasma concentration of 100-500 ng/ml. In certain other embodiments, lidocaine may be delivered to yield a plasma concentration of 500-1000 ng/ml. In yet other embodiments, lidocaine may be delivered to yield a plasma concentration of 1000-1500 ng/ml.

In some embodiments, an iontophoretic device for use in systemic delivery of active agents as disclosed herein may have a surface that is oversized compared to the surface of iontophoretic devices known in the art. In such embodiments, a surface of increased size may be particularly advantageous for delivery of levels of active agent adequate to yield useful therapeutic levels within the circulation of the subject.

In certain embodiments, an iontophoretic delivery device, as described herein, is provided for use in a method for alleviating pain at a site of pain in a subject by systemic delivery of one or more active agents to the site of pain in the subject, as described herein.

In certain embodiments, an iontophoretic delivery device, as described herein, is provided for systemic delivery of xylocaine (Lidocaine®) to a site of pain in a subject.

In at least one embodiment of an iontophoretic device for use in a method for systemic delivery, according to the present disclosure, an active electrode assembly comprises a Lidocaine® bulk drug solution, and a counter electrode assembly comprises a saline counter solution. In further embodiments, the device may comprise a controller and a power source.

In certain embodiments, a biological interface may be a skin, a portion of skin, a mucous membrane, or a portion of mucous membrane.

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

or instead of the migration of charged active agents in response to repulsive forces, active agents may also be transported by electroosmotic flow of solvent (e.g., water) through the electrodes and the biological interface into the tissue. In certain embodiments, 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 active agent molecule.

In certain embodiments, an active agent may be a higher molecular weight molecule. In certain aspects, a molecule may be a polar polyelectrolyte. In certain other aspects, a molecule may be lipophilic. In certain embodiments, molecules may be charged, may have a low net charge, or may be uncharged under the conditions within the active electrode. In certain aspects, 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. In such aspects, higher molecular active agents may thus be carried through the biological interface into the underlying tissues primarily via electroosmotic solvent flow. In certain embodiments, high molecular weight polyelectrolytic active agents may be proteins, polypeptides or nucleic acids.

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 invention, 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 omit one or more reservoirs, membranes or other structure. In other instances, 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 24, 68. Also for example, some embodiments may include an interface layer interposed between the outermost active electrode ion selective membrane 38 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 Corplex™ by Corium, Tegagel™ by 3M, PuraMatrix™ by BD; Vigilon™ by Bard; ClearSite™ by Conmed Corporation; FlexiGel™ by Smith & Nephew; Derma-Gel™ by Medline; Nu-Gel™ by Johnson & Johnson; and Curagel™ by Kendall, or acrylhydrogel films available from Sun Contact Lens Co., Ltd. In certain embodiments, preparations of these various hydrogels may be made to incorporate proteins or polypeptides, or fusion proteins or fusion polypeptides, for use with the devices and methods disclosed herein. In certain embodiments, such hydrogel preparations may serve as reservoirs for the various active agents. Such hydrogel preparations may constitute, for example, inner active agent reservoir 34 or layer 52 of the active electrode assembly in Figures 2A and 2B.

Various embodiments discussed herein may advantageously employ microstructures, for example, microneedles. Microneedles and microneedle arrays, their manufacture, and use have been described. Microneedles, either individually or in arrays, may be hollow; solid and permeable; solid and semi-permeable; or solid and non-permeable. Solid, non-permeable microneedles may further comprise grooves along their outer surfaces. Microneedles and microneedle arrays may be manufactured from a variety of materials, including silicon; silicon dioxide; molded plastic materials, including biodegradable or non-biodegradable polymers; ceramics; and metals. Microneedles, either individually or in arrays, may be used to dispense or sample fluids. Microneedle devices may be used, for example, to deliver any of a variety of compounds and/or compositions to the living body via a biological interface, such as skin or mucous membrane. In certain embodiments, the active agent compounds and compositions may be delivered into or through the biological interface. For example, in delivering compounds or compositions via the skin, the length of the microneedle(s), either individually or in arrays, and/or the depth of insertion may be used to control whether administration of a compound or composition is only into the epidermis, through the epidermis to the dermis, or subcutaneous. In certain embodiments, microneedle devices may be useful for delivery of 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, microneedle(s) or microneedle array(s) can provide electrical continuity between a power source and the tip of the microneedle(s). Microneedle(s) or microneedle array(s) may be used advantageously to deliver or sample compounds or compositions by iontophoretic methods, as disclosed herein. In certain embodiments, for example, a plurality of microneedles in an array may advantageously be formed on an outermost biological interface-contacting surface of an iontophoresis device.

Certain details of microneedle devices, their use and manufacture, are disclosed in 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; 6,511,463; 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; 6,939,311; all of which are incorporated herein by reference in their entirety. Some or all of the teaching therein may be applied to microneedle devices, their manufacture, and their use in iontophoretic applications.

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 solution of an active agent, such as a drug or therapeutic or diagnostic agent, 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 reservoir 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 reservoir; 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 reservoir 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 reservoir 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. H03-86002, filed March 27, 1991, having Japanese Publication No. H04-297277, issued on March 3, 2000 as Japanese Patent No. 3040517; Japanese patent application Serial No. 11-033076, filed February 10, 1999, having Japanese Publication No. 2000-229128; Japanese patent application Serial No. 11-033765, filed February 12, 1999, having Japanese Publication No. 2000-229129; Japanese patent application Serial No. 11-041415, filed February 19, 1999, having Japanese Publication No. 2000-237326; 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; PCT patent application WO 2002JP4696, filed May 15, 2002, having PCT Publication No. WO03037425; 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; and Japanese patent application Serial No. 2005-081220, filed March 22, 2005.

As one skilled 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

We/I claim:

1. A method for alleviating pain at a site of pain in a subject by systemic delivery of one of more active agents to the site of pain in the subject, comprising:

identifying the site of pain in the subject;

obtaining an iontophoretic delivery device comprising one or more active agents;

positioning the delivery device at a location on a biological interface of the subject;

activating the delivery device to transdermally transport the one or more active agents through the biological interface of the subject into a circulatory system of the subject; and

delivering the one or more active agents to the site of pain in the subject by means of the circulatory system of the subject;

wherein the one or more active agents are of the –caine class of compounds.

2. The method of claim 1, further comprising: identifying a location on the biological interface of the subject through which one or more active agents may be transported to a circulatory system that supplies the site of pain in the subject.

3. The method of claim 2, further comprising: positioning the iontophoretic delivery device at the location on the biological interface through which the one or more active agents may be transported.

4. The method of claim 1 wherein the pain is a neuropathic pain.

5. The method of claim 4 wherein the pain is associated with a cancer; chemotherapy; alcoholism; an 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; or spinal surgery.

6. The method of claim 1 wherein the pain is associated with shingles (herpes zoster virus infection; post-herpetic pain).

7. The method of claim 1 wherein the pain is a nociceptive pain.

8. The method of claim 7 wherein the nociceptive pain is associated with a burn, a damaged tissue, an infection, a chemical change, or a pressure at the site of pain.

9. The method of claim 1 wherein the active agent is selected from ambucaine, amethocaine, amoxecaine, amylocaine, aptocaine, articaine, azacaine, bencaine, benzocaine, N,N-dimethylalanylbenzocaine, N,N-dimethylglycylbenzocaine, glycylbenzocaine, betoxycaine, bumecaine, bupivicaine, levobupivicaine, butacaine, butanilicaine, butoxycaine, metabutoxycaine, carbizocaine, carbocaine, carticaine, cepacaine, cetacaine, chloroprocaine, cocaine, pseudococaine, cyclomethycaine, dibucaine, dimethocaine, etidocaine, fomocaine, heptacaine, hexacaine, hexocaine, hexylcaine, ketocaine, leucinocaine, lotucaine, marcaine, mepivacaine, metacaine, myrtecaine, naepaine, octacaine, orthocaine, oxetacaine, oxethacaine, oxethazaine, oxycaine, parenthoxycaine, pentacaine, piperocaine, piridocaine, polycaine, pramocaine, prilocaine, procaine, hydroxyprocaine, propanocaine, proparacaine, propipocaine, propoxycaine, pyrrocaine, quatacaine, rhinocaine, risocaine, rodocaine, ropivacaine, tetracaine, hydroxytetracaine, tolycaine, trapencaine, tricaine, trimecaine; or tropacocaine.

10. The method of claim 1 wherein the active agent is isicaine, lidocaine, lignocaine, or xylocaine.

11. The method of claim 10 wherein the active agent is lidocaine.

12. The method of claim 11 wherein the lidocaine is delivered to yield a plasma concentration of 100-500 ng/ml.

13. The method of claim 11 wherein the lidocaine is delivered to yield a plasma concentration of 500-1000 ng/ml.

14. The method of claim 11 wherein the lidocaine is delivered to yield a plasma concentration of 1000-1500 ng/ml.

15. An iontophoretic delivery device operated according to any of claims 1-14

16. The device of claim 15, comprising:

an active electrode assembly, the active electrode assembly comprising at least an active electrode element operable to supply an electrical potential of a first polarity and an inner active agent reservoir; and

a counter electrode assembly, the counter electrode assembly comprising at least a counter electrode element operable to apply an electrical potential of a second polarity,

wherein activating the delivery device includes supplying the electrical potential of the first polarity to the active electrode element and supplying the electrical potential of the second polarity to the counter electrode element.

17. The device of claim 16 wherein the device further comprises a control unit and activating the delivery device includes operating the control unit.

18. The device of claim 17 wherein the control unit includes at least one switch and activating the delivery device includes activating a switch.

19. The device of claim 17 wherein the control unit is programmable.

20. The device of claim 16 wherein the device further comprises a power source and wherein activating the device to transport active agent includes electrically coupling the power source to close a circuit.

21. The device of claim 1 wherein the device is in the form of a patch.

22. The device of claim 1 wherein the biological interface is a portion of a skin or a portion of a mucous membrane.

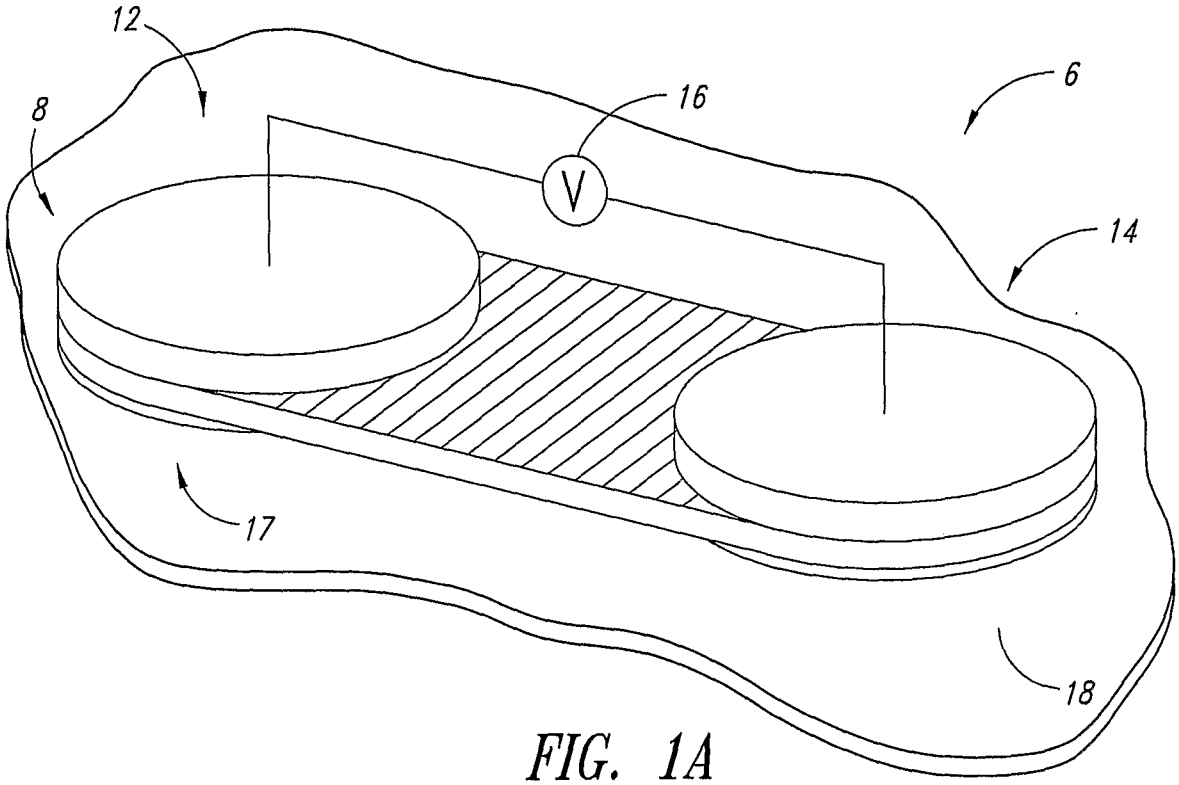


FIG. 1A

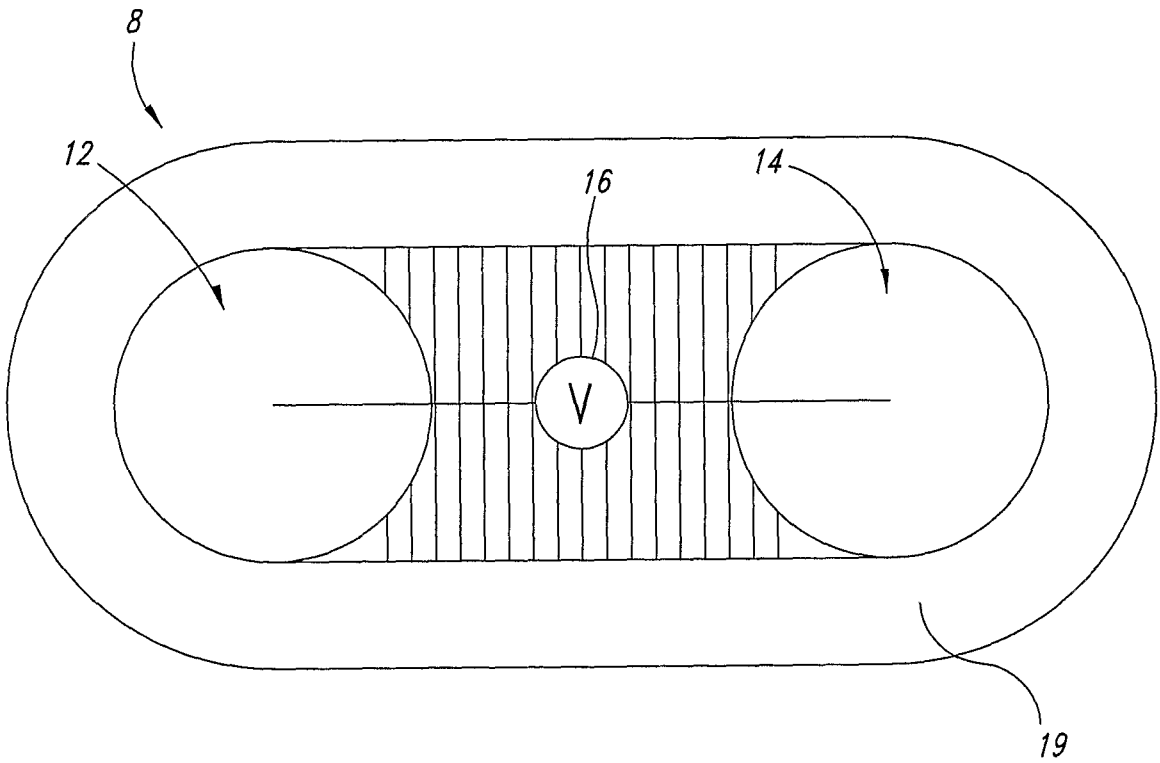


FIG. 1B

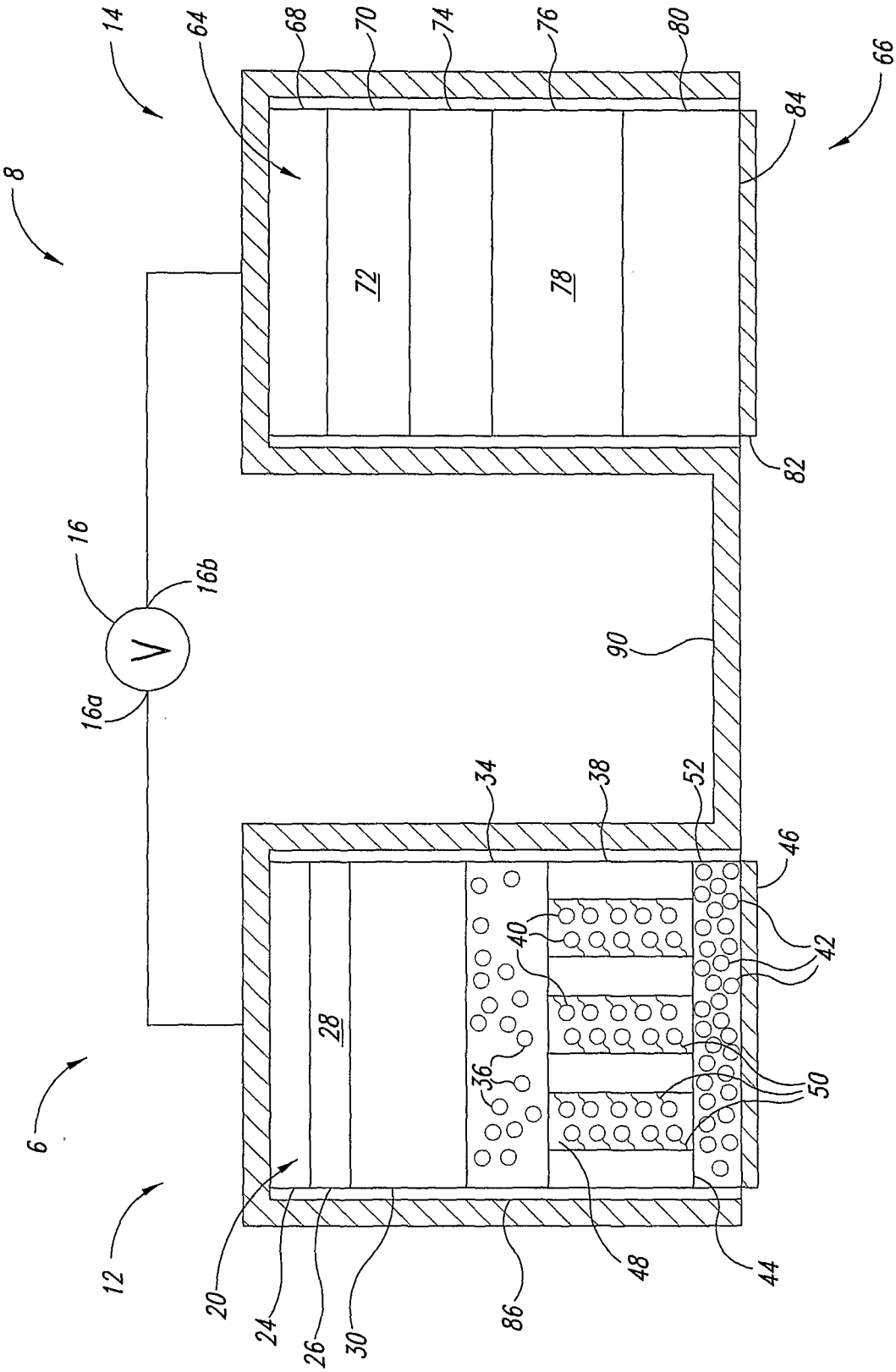

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FIG. 2A

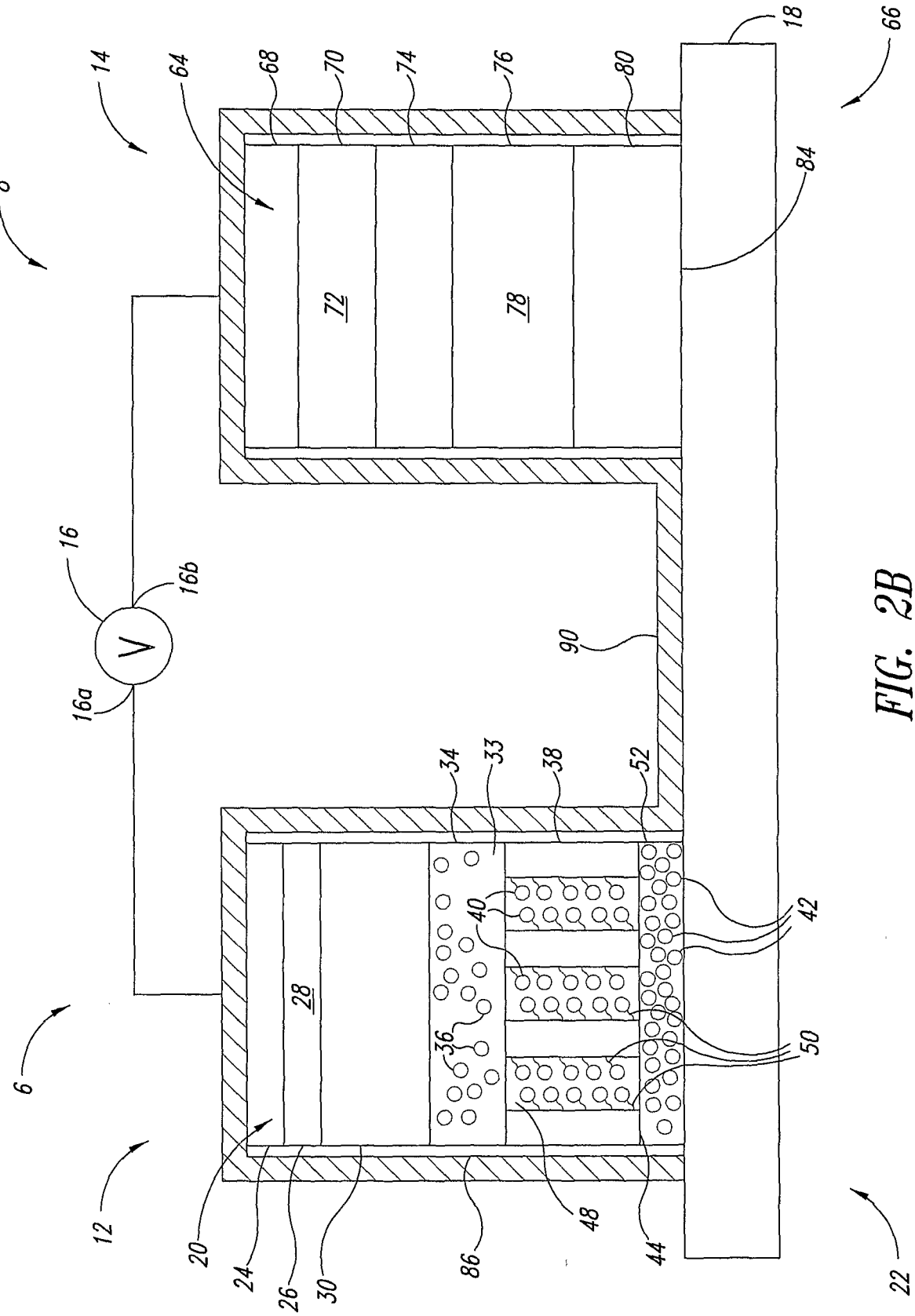

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FIG. 2B