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(71) Applicant *(for all designated States except US)*: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).

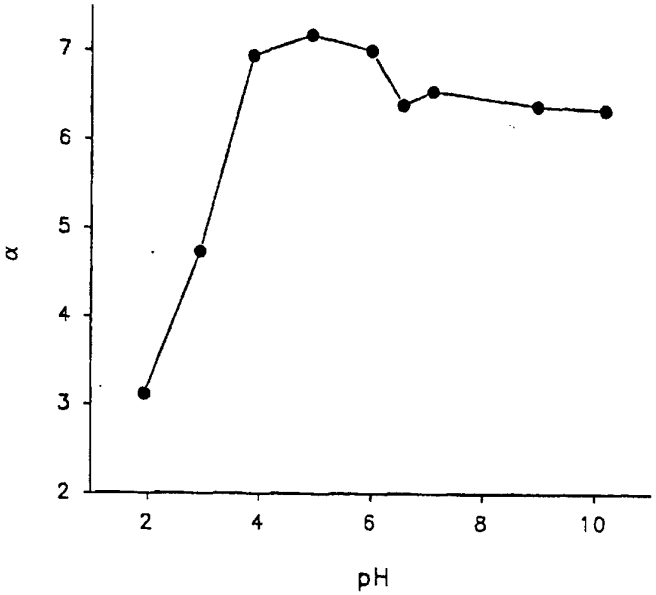
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CORMIER, Michael, J., N. [FR/US]; 278 Andsbury Avenue, Mountain View, CA 94043 (US). LEDGER, Philip, W. [GB/GB]; 57 The Causeway, Carlton, Bedford MK43 7LU (GB). JOHNSON, Juanita [US/US]; 45 B Joy Avenue, Brisbane, CA 94005 (US). PHIPPS, Joseph, B. [US/US]; 5309 Ximines Lane, Plymouth, MN 55442 (US). CHAO, Stella [US/US]; 156 Glasgow, San Carlos, CA 94070 (US).

(74) Agents: MILLER, D., Bryon et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).

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(54) Title: REDUCTION OF SKIN IRRITATION AND RESISTANCE DURING ELECTROTRANSPORT



(57) Abstract

An electrotransport delivery device (10) utilizing reservoir (16, 18) buffering at select pH ranges in order to reduce skin irritation and skin resistance is provided. Cathodic reservoirs are buffered to a pH of less than about 4, preferably to a pH in the range of about 2 to 4, while anodic reservoirs are buffered to a pH above about 4, preferably to a pH in the range of about 4 to 10. Another electrotransport delivery device (10) utilizes a potassium sensor to monitor potassium efflux from the skin. Potassium efflux above a certain predetermined level has been found to be a precursor to skin irritation/erythema. Operation of the device is modified (e.g., terminated) when the predetermined potassium efflux level is sensed.

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REDUCTION OF SKIN IRRITATION AND RESISTANCE DURING ELECTROTRANSPORT

TECHNICAL FIELD

This invention relates to electrotransport agent delivery devices, compositions, and methods. More particularly, this invention relates to methods of reducing skin irritation and electrical skin resistance during transdermal electrotransport agent delivery.

BACKGROUND ART

The term "electrotransport" as used herein refers generally to the delivery of an agent (eg, a drug) through a membrane, such as skin, mucous membrane, or nails, which delivery is induced by application of an electrical potential. For example, a beneficial therapeutic agent may be introduced into the systemic circulation of a human body by electrotransport delivery through the skin. A widely used electrotransport process, iontophoresis, involves the electrically induced transport of charged ions. Another type of electrotransport, electroosmosis, involves the flow of a liquid, which liquid contains the agent to be delivered, under the influence of an electric field. Still another type of electrotransport process, electroporation, involves the formation of transiently-existing pores in a biological membrane by the application of an electric field, through which pores an agent can be delivered either passively (ie, without electrical assistance) or actively (ie, under the influence of an electric potential). However, in any given electrotransport process, more than one of these processes may be occurring simultaneously to a certain extent.

Accordingly, "electrotransport", as used herein, should be given its broadest possible interpretation so that it includes the electrically induced or enhanced transport of at least one agent, which may be charged, uncharged, or a mixture thereof, regardless of the specific mechanism or mechanisms by which the agent actually is transported.

Electrotransport devices generally use at least two electrodes which are in electrical contact with some portion of the skin, nails, mucous membrane, or other surface of the body. One electrode, commonly referred to as the "donor" or "active" electrode, is the electrode from which the agent is delivered into the body. The other electrode, typically termed the "counter" or "return" electrode, serves to close the electrical circuit through the body. For example, if the agent to be delivered is positively charged, ie a cation, then the anode will be the active or donor electrode, while the cathode serves to complete the circuit. Alternatively, if an agent is negatively charged, ie an anion, the cathode will be the donor electrode. Additionally, both the anode and cathode may be considered donor electrodes if both anionic and cationic agent ions are to be delivered.

Furthermore, electrotransport delivery systems generally require at least one reservoir or source of the agent to be delivered to the body. Examples of such donor reservoirs include a pouch or cavity, a porous sponge or pad, and a hydrophilic polymer or a gel matrix. Such donor reservoirs are electrically connected to, and positioned between, the anode or cathode and the body surface, to provide a fixed or renewable source of one or more agents or drugs. Electrotransport devices also have an electrical power source such as one or more batteries. Typically, one pole of the power source is connected to the donor electrode, while the opposite pole is connected to the counter electrode. In addition, some electrotransport devices have an electrical controller which controls the current applied through the electrodes, thereby regulating the rate of agent delivery. Furthermore, passive flux control membranes, adhesives for maintaining device contact with a body surface, insulating members, and impermeable backing members are some other potential components of electrotransport devices.

Although the advantages of electrotransport delivery are numerous (eg, enhanced transmembrane flux of beneficial agents compared to

passive, ie, non-electrically assisted flux; precise control of agent delivery, including patterned delivery, etc.), there are disadvantages under certain application conditions. One potential problem with electrotransport transdermal delivery is skin irritation. For instance, applying electric current through skin under certain conditions has been known to cause skin irritation. See for example, "Skin Biological Issues in Electrically Enhanced Transdermal Delivery", P. Ledger, Advanced Drug Delivery Reviews, Vol. 9 (1992), pp 289-307.

In addition to the level of applied electric current, other factors can cause, or at least contribute to, skin irritation during transdermal electrotransport agent delivery. For example, most electrotransport drug delivery devices use an aqueous solution or suspension of the agent to be delivered, since water is a biocompatible solvent and since many drug salts are water soluble. Under certain conditions, especially in electrotransport devices having electrodes formed of an electrochemically inert (ie, catalytic) material, such as platinum or stainless steel, water hydrolysis tends to occur at the interface between the electrode and the drug solution (donor reservoir) or electrolyte salt solution (counter reservoir). The products of water hydrolysis (ie, hydronium ions are produced by water hydrolysis at the anode and hydroxyl ions are produced by water hydrolysis at the cathode) compete with the drug ions of like charge for delivery into the skin, thereby altering skin pH. Since (i) highly basic or acidic solutions in contact with the skin surface and (ii) highly basic or acidic conditions within the skin itself are known to damage tissue, the pH-altering effects of electrotransport devices, independent of current density effects, can also cause skin irritation.

In order to prevent water hydrolysis, prior art devices used electrodes composed of electrochemically reactive materials (eg, silver anodes and silver chloride cathodes) which materials were oxidized or reduced in lieu of water hydrolysis. See for example Phipps et al US Patents 4,744,787 and

4,747,819; Petelenz et al US Patent 4,752,285 and Untereker et al US Patent 5,135,477.

In addition to electrochemically reactive electrode materials, the prior art has also utilized conventional buffering agents to control the pH of the donor and counter reservoirs. See for example Jacobsen et al US Patent 4,416,274 (sodium phosphate buffers) and Hillman et al US Patent 5,088,978 (citric acid/citrate salt buffers). Although conventional buffers are effective to maintain donor reservoir pH, they introduce undesirable extraneous ions which tend to compete with the drug ions for delivery. For example, when an anodic donor reservoir for delivering a cationic drug D^+ is buffered with a citrate salt (eg, sodium citrate), the citrate buffer absorbs hydronium ions produced by water hydrolysis at the anode but leaves extraneous sodium ions which compete with the drug ions, D^+, for delivery. Whenever a significant amount of competing ions are present, the rate of drug delivery cannot be accurately predicted simply by measuring or controlling the amount of electric current applied by the device.

In response to these problems, the prior art used buffering agents which were substantially immobile. See Sanderson et al, US Patent 4,722,726 and Johnson et al, US Patent 4,973,303.

Most prior art devices used buffering agents to maintain the donor (drug) and counter (electrolyte) reservoirs at pH levels at or near skin pH. For instance, Hillman et al, US Patent 5,088,978, discloses an anodic electrode buffered at pH 4-5 to resist pH changes associated with proton generation from water hydrolysis. This patent further discloses buffering an "indifferent", cathodic electrode at pH 4-7.

The effects of anodic and cathodic pH on selected buffers in iontophoresis are discussed in "Some Hazards of the Sweat Test" by Schwarz, V. et al, Arch. Dis. Childh. (1968) 43, 695-701. Carbon and

copper electrodes were used in the reported experimentation. This reference indicates that blistering of the skin in contact with either the cathode or anode is dependent upon both the pH and the buffer composition of the anodic and cathodic reservoirs.

However, according to "Structure-Transport Relationships in Transdermal Iontophoresis" by Yoshida et al, Ad. Drug Del. Rev. (1992), 9, 239-264, the preferred pH range for avoiding skin irritation for the donor reservoir, independent of the buffer used, is 3 to 8. Outside this pH range, according to this reference, irritation and/or damage of the stratum corneum can occur.

Thus, literature and patent references have presented overlapping pH ranges for minimizing skin irritation. Certain references have focussed primarily on providing neutral solutions or solutions having pH near that of human skin at both the anodic and cathodic reservoirs. Other references are predominantly concerned with counteracting the acidic and caustic irritation problems associated with water hydrolysis at the anode and cathode, respectively. Furthermore, the references have focussed primarily on donor (drug) reservoir pH control since the solubility of the drug in the liquid solvent is in many cases highly dependent on solution pH. Thus, minimizing skin irritation by control of counter reservoir pH has received only cursory attention in the prior art. Furthermore, previous disclosures relating to minimizing skin irritation from electrotransport devices have concentrated on the active or donor reservoir. However, electrotransport devices apply as much current through the counter electrode as through the donor electrode, and hence, skin irritation due solely to application of electric current also occurs beneath the counter reservoir or counter electrode. In a typical electrotransport device, the area of device/skin contact beneath the counter reservoir is nearly equivalent to the area beneath the donor reservoir. Hence, skin erythema, irritation, and/or damage in the counter reservoir

contact area may be similar in magnitude to that in the donor reservoir contact area.

DISCLOSURE OF THE INVENTION

Hence, it is an object of this invention to provide means by which tissue irritation, erythema and/or damage may be reduced or eliminated during and after electrotransport of an agent through a body surface (eg, skin).

It is a further object of the present invention to optimize the pH of a reservoir in an electrotransport device, particularly counter electrode reservoir pH, for purposes of reducing skin irritation during and after transdermal electrotransport drug delivery.

It is still another object of the present invention to reduce the electrical power requirements for an electrotransport device for delivering an agent through a body surface.

Another object of this invention is to provide means by which the electrical resistance to electrotransport agent delivery may be reduced during electrotransport of the agent through a body surface.

A further object of this invention is to improve patient compliance with electrotransport drug administration schedules.

Satisfaction of these objects and other advantages of this invention will become apparent from the electrotransport devices and methods of the present invention. The electrotransport devices contain cathodic and anodic electrodes and cathodic and anodic reservoirs. In one embodiment, the cathodic reservoir pH is maintained below about 4, preferably from about 2

to 4. In another embodiment, the anodic reservoir pH is maintained above about 4, preferably from about 4 to 10.

In a further preferred embodiment, the pH of one or both of the reservoirs is maintained using a suitable buffer. Most preferably, the cathodic reservoir is buffered using a cationic buffer and/or the anodic reservoir is buffered using an anionic buffer. Most preferably, the cathodic and/or anodic electrodes are composed of electrochemically reactive materials, ie, an electrochemically oxidizable anode and an electrochemically reducible cathode, in order to reduce water hydrolysis and the attendant production of hydronium and hydroxyl ions in the anodic and cathodic reservoirs, respectively.

In another embodiment of the present invention, a method of reducing skin resistance and/or erythema during transdermal electrotransport delivery of an agent is presented. One method involves placing the anodic and cathodic reservoirs of an electrotransport delivery device in ion-transmitting relation with a body surface, applying an electrical potential across the reservoirs, and maintaining the cathodic reservoir pH below about 4, preferably from about pH 2 to 4, during electrotransport delivery in order to reduce skin resistance and/or irritation, erythema or damage at the skin site adjacent to the cathodic reservoir. Another method involves placing the anodic and cathodic reservoirs in ion-transmitting relation with a body surface, applying an electrical potential across the reservoirs, and maintaining the anodic reservoir pH above about 4, preferably from about pH 4 to 10, during electrotransport delivery in order to reduce skin resistance and/or irritation, erythema or damage at the skin site adjacent the anodic reservoir.

In accordance with another embodiment of the present invention, a method of avoiding, or at least reducing, skin irritation, erythema and/or damage due to electrotransport agent delivery through the skin is provided.

The method involves monitoring for potassium efflux from the skin site through which electric current is applied by the electrotransport delivery device during operation of the device. Once potassium efflux reaches a predetermined value, the operation of the delivery device is altered in a manner designed to avoid, or at least reduce, further skin irritation, erythema and/or damage. Preferably, a potassium sensor is placed in the cathodic electrode assembly in order to monitor potassium efflux from the patient's skin. Once the potassium sensor senses a certain level of potassium efflux, the operation of the device is altered, eg, by reducing the level of current applied by the device or by alerting the patient, eg, through an audible and/or visible alarm. The device may then be removed from the original skin site and placed on an alternate skin site and electrotransport agent delivery thereafter resumed.

BRIEF DESCRIPTION OF THE DRAWINGS

This invention will be described in further detail with reference to the accompanying drawings wherein:

Fig. 1 is a sectional view of one embodiment of an electrotransport device useful in accordance with the present invention.

Figs. 2 and 3 are graphs of skin irritation (α) and skin resistance (R), respectively, as a function of cathodic reservoir pH.

Figs. 4 and 5 are graphs of skin irritation (α) and skin resistance (R), respectively, as a function of anodic reservoir pH.

Figs. 6 and 7 are graphs of skin irritation (α) and skin resistance (R), respectively, as a function of cathodic reservoir pH.

Figs. 8 and 9 are graphs of skin irritation (α) and skin resistance (R), respectively, as a function of anodic reservoir pH.

Fig. 10 is a graph of skin irritation (α) as a function of cathodic reservoir pH.

Figs. 11 and 12 are graphs of skin irritation (α) and skin resistance (R), respectively, as a function of cathodic reservoir pH.

Figs. 13 and 14 are graphs of skin irritation (α) and skin resistance (R), respectively, as a function of hours after electrotransport device removal from the skin surface.

Figs. 15 and 16 are graphs of skin irritation (α) and skin resistance (R), respectively, as a function of hours after application of the electrotransport device to the skin surface.

Figs. 17 and 18 are graphs of skin irritation (α) as a function of wearing time for the skin sites in contact with an anodic reservoir and a cathodic reservoir, respectively.

MODES FOR CARRYING OUT THE INVENTION

The present invention may be utilized in a wide variety of electrotransport devices. In general, electrotransport devices have a source of electrical power (eg, one or more batteries) which is, or may be, electrically connected to a donor electrode including a reservoir capable of holding a liquid solution or suspension of the agent to be delivered and a counter electrode including a liquid solution or suspension of an electrolyte salt. One example of an electrotransport device 10 is illustrated in Figure 1. Device 10 has two electrodes, comprised of electrically conductive materials, referred to herein as a donor electrode 12 and a counter electrode 14. The

donor and counter electrodes 12 and 14 are positioned adjacent to, and in electrical contact with, the donor reservoir 16 and the counter reservoir 18, respectively. The donor reservoir 16 contains the agent to be delivered, while the counter reservoir 18 may contain a biocompatible electrolytic salt or another agent to be delivered. An electrical insulator 20 is positioned between (i) the donor electrode 12 and donor reservoir 16 and (ii) the counter electrode 14 and counter reservoir 18. Insulator 20, which may be an air gap or may be composed of a material which neither conducts electrons or ions, prevents device 10 from short-circuiting through a path which does not include the body surface 40 to which device 10 is applied. The device 10 optionally includes a backing layer 22 composed of a liquid impermeable non-conducting material. Device 10 has an electronic circuit, illustrated schematically in Fig. 1 as layer 24, having a DC power source (eg, one or more batteries) therein. Typically, the electronic circuit layer 24 is relatively thin and preferably comprised of electronically conductive pathways printed, painted or otherwise deposited on a thin, flexible substrate such as, for example, a film or polymeric sheet, eg, the electronic circuit layer 24 is a printed flexible circuit. In addition to the power source, the electronic circuit layer 24 may also include one or more electronic components which control the level, waveform shape, polarity, timing, etc. of the electric current applied by device 10. For example, circuit layer 24 may contain one or more of the following electronic components: control circuitry such as a current controller (eg, a resistor or a transistor-based current control circuit), an on/off switch, and/or a microprocessor adapted to control the current output of the power source over time. The outputs of circuit layer 24 are electrically connected to the electrodes 12 and 14 such that each electrode is in electrical contact with an opposite pole of the power source within circuit layer 24. The device adheres to the body surface in this embodiment by means of a peripheral adhesive layer 28. Optionally, the device may contain an in-line adhesive layer, ie, an adhesive layer positioned between the reservoirs 16 and/or 18 and the skin. An in-line adhesive must be composed of an ion-transmitting material, ie, donor agent ions must be capable of penetrating the adhesive

layer to reach the body surface. Optional flux control membranes 30 and 32 are positioned between donor reservoir 16 and body surface 40 and between counter reservoir 18 and body surface 40, respectively, in order to limit or control the amount of passive (ie, not electrically assisted) flux of agent to body surface 40.

The device 10 of Figure 1 is merely one example of an electrotransport device useful in accordance with present invention. The present invention is useful in a wide variety of electrotransport devices, including those devices which are not unitary, ie those which have a power source component and two electrode components, wherein the components are connected only by wiring. An example of a non-unitary or "satellite" device appears in Petelenz et al, US Patent 4,752,285 (see Figure 6), which is incorporated herein by reference. In addition, the device 10 may contain other features, such as a removable release liner (not shown) on the adhesive layer 28 and/or the body surface-contacting face of the device. Furthermore, certain components in device 10 are unnecessary or optional for practicing the instant invention. For example, if electrodes 12 and 14 are chosen such that a galvanic couple exists, an independent power source in circuit layer 24 may be an optional component. Thus, device 10 of Figure 1 is presented solely for illustration of one embodiment of the present invention.

If the agent to be delivered is anionic, ie, negatively charged, the cathodic electrode is the donor electrode and the cathodic reservoir is the donor reservoir, containing the agent, and the anodic reservoir is the counter reservoir, containing a biocompatible electrolytic salt. Alternatively, if the agent to be delivered is cationic, ie positively charged, the anodic electrode is the "donor" electrode and the anodic reservoir is the donor reservoir containing the agent to be delivered and the cathodic reservoir is the counter reservoir.

In accordance with one embodiment of the present invention, the pH of the cathodic reservoir, regardless of whether the cathodic reservoir is the donor (ie, agent-containing) or counter (ie, electrolyte-containing) reservoir, is maintained during electrotransport agent delivery at a pH below about 4. By maintaining the cathodic reservoir pH below about pH 4 during electrotransport agent delivery (i) the electrical resistance of the skin site adjacent the cathodic reservoir is reduced and (ii) skin irritation, erythema and/or damage is also reduced. This reduced skin resistance translates into reduced voltage and power requirements needed to drive a particular level of electric current through the body surface. Thus, maintaining the cathodic reservoir pH below about 4 reduces the cost and/or size of the power source. Further, reduced skin irritation, erythema and/or damage results in better acceptance of the treatment regimen by the patient. Accordingly, patient compliance with prescribed treatment using the electrotransport device is improved.

Preferably, the cathodic reservoir pH is maintained in a range from about 1.4 to about 4, most preferably about 2 to 4. Whereas the prior art taught avoiding low pH in reservoirs in contact with the skin due to a belief that the contact would cause acid burns, it has now surprisingly been discovered that, at least over wearing times of up to about 2 days, low pH (eg, pH 2 to 4) cathodic reservoirs minimize skin irritation. Even so however, at very low reservoir pH, eg, at about a pH of 1 and particularly as the wearing time becomes longer (eg, 1 day or longer), the skin may experience acidic burns. At these high hydronium ion concentrations, the beneficial effect (ie, lower electrical skin resistance) of maintaining the cathodic reservoir at a low pH is outweighed by the damage caused by acid burning. Since irritation, erythema, and/or skin damage may increase at very low reservoir pH, maintaining the cathodic reservoir below a pH of about 1.4 is less preferred particularly for longer wearing periods.

The pH of the cathodic reservoir may be maintained below about pH 4 by any number of means. In applications where the electrotransport device is operated at low current densities (eg less than about 200 $\mu A/cm^2$) using electrochemically reducible cathode materials such as silver chloride (both of which minimize the formation of hydroxyl ions at the cathode) and/or for short periods of time (eg, <1 hour), it may be sufficient to simply add an acid (eg, citric acid) to the cathodic reservoir to maintain the desired pH. However, while acids are effective in achieving a low cathodic reservoir pH, they introduce undesirable competing ions in those instances where the cathodic electrode is the donor electrode. Thus, adding citric acid to a cathodic donor reservoir containing salicylate anions undesirably adds citrate ions which compete with the salicylate ions for delivery into the body. The competing citrate ions also introduce uncertainty in the salicylate delivery rate since it is difficult to predict what percentage of the total applied current is carried by the competing citrate ions.

In applications where the electrotransport agent delivery (i) must be precisely controlled, (ii) is conducted for longer periods of time (eg, >12 hours), (iii) is conducted using cathodic reservoirs having a small volume (pH is a measure of concentration and hence is highly dependant on the volume of the reservoir, with small volume reservoirs being more susceptible to pH changes during operation of the electrotransport device), (iv) is conducted using high current densities, and/or (v) is conducted using a cathode composed of an electrochemically catalytic material (eg, platinum or stainless steel), then the cathodic reservoir is preferably buffered at a pH below about 4. A variety of buffers may be useful in maintaining cathodic reservoir pH below about 4. Table 1 lists preferred amino acids and the approximate pH range for cationic behavior. Preferably, these amino acids or combinations thereof are chosen as cationic buffers for the cathodic reservoir.

Preferably, the cathodic reservoir contains at least one cationic buffer. A buffer cation within the cathodic reservoir will tend not to be

electrotransported through the skin since anions, and not cations, are predominantly delivered from the cathodic reservoir by electrotransport. A poorly transported buffer is preferred in order to avoid depletion of the buffer from the reservoir as well as any irritation associated with buffer ion being transported into the skin. Amino acids are preferred cationic buffers. Preferably, the counter ion, ie anion, to the buffer cation is chloride. In many cases, the counter anions to the buffer ions are transported into the skin from the cathodic reservoir. Chloride is a preferred counter anion because the skin has a high concentration of chloride ions in its natural state. Hence, use of chloride buffering salts in the cathodic reservoir minimizes irritation potential.

The concentration of buffer required in the reservoir will depend on the properties of the specific buffer selected. Generally, the buffer concentration will range from about 0.01 M to about 1.0 M. Preferably, the buffer concentration will be about 0.01 M to about 0.50 M. More preferably, the buffer concentration will be about 0.01 M to about 0.20 M.

TABLE 1

Cationic Amino Acid Buffers
for Cathodic Reservoir

AMINO ACID	pH RANGE FOR CATIONIC BEHAVIOR	PREFERRED pH RANGE FOR CATIONIC BEHAVIOR
histidine	1-5	2-4
lysine	1-4	1.5-3.5
arginine	1-4	1.5-3.5
aspartic acid	1-3	2-3
glutamic acid	1-3.2	2-3.2
cysteine	1-4	2-3
tyrosine	1-4	2-3
other amino acids	1-4	2-3.5

Alternatively, the cathodic reservoir may be buffered using an anionic or negatively charged buffer, which is electrotransported through the skin, or alternatively, mixtures of a cationic buffer from Table 1 and an anionic buffer from Table 2 may also be used. However, the cationic buffers of Table 1 are preferred, particularly when the cathodic electrode is the donor electrode, since buffer cations will not be electrotransported through the skin. Thus, irritation from the presence of a buffer ion in the skin is minimized, as discussed above. The preferred anionic buffers include those named in Tabel 2.

TABLE 2

Anionic Acid Buffers for
Cathodic Reservoir

BUFFER	pH RANGE FOR ANIONIC BEHAVIOR	PREFERRED pH RANGE FOR ANIONIC BEHAVIOR
aspartic acid	3-5	3-4
glutamic acid	3.2-5	3.2-4
citric acid	1-5	2-4
succinic acid	2-5	3-4
phosphoric acid	1-5	2-4
acetic acid	3.5-5	3.5-4
EDTA	1-5	2-4
lactic acid	2.7-4.5	2.7-4
benzoic acid	3-5	3-4
tartaric acid	1.8-4.5	2.3-4
maleic acid	1-5	2-4
fumaric acid	1.8-5	2.3-4
sulfuric acid	1-3.2	1.5-3
formic acid	1.8-5	2.3-4
malic acid	2.1-5	2.6-4
malonic acid	1.7-5	2.1-4
glutaric acid	3-5	3-4
adipic acid	3-5	3-4

Other ionic compounds, such as sodium chloride, with little or no buffering capacity may optionally be incorporated into the cathodic reservoir. Such additives may be advantageous in decreasing the potential buffer depletion from the reservoir. A disadvantage of adding sodium chloride to the reservoir, at least in the case where the cathodic reservoir is the agent-containing "donor" reservoir, is that more potentially competing ions, ie ions that compete for electrotransport with the agent to be delivered, are introduced.

As an alternative to the addition of either an acid or a buffering agent to the cathodic reservoir in order to maintain the pH below about 4, and preferably within the range of about 2 to 4, the pH of the cathodic reservoir may also be appropriately maintained by operating a suitable secondary electrode of the type, and in a manner, described in Phipps et al US Patent 5,125,894, the disclosure of which is incorporated herein by reference. See in particular column 20, lines 53 to 68; column 28, lines 20 to 68; and column 29, lines 1 to 61 of the Phipps et al US Patent 5,125,894 wherein a secondary electrode composed of a material which can be reversibly oxidized and reduced (eg, iridium oxide) to produce either hydronium ions (in the case of oxidation) or hydroxyl ions (in the case of reduction) in order to control pH in the reservoir. Control of pH can be accomplished, via feedback by providing a pH sensor in the reservoir in communication with the control circuitry for the secondary electrode.

With any of the embodiments described hereinabove wherein the pH of the cathodic reservoir is appropriately maintained, a potassium sensor may optionally be incorporated into the cathodic reservoir to monitor for potassium ion efflux from the skin into the cathodic reservoir. Excessive potassium ion efflux from the skin has been found to occur concurrently with skin irritation and/or erythema accompanying transdermal electrotransport agent delivery. Since potassium is a cation, the electrotransport-driven efflux from the skin tends to deliver potassium ions into the cathodic reservoir. The potassium efflux can therefore be monitored directly by measuring the amount of potassium in the cathodic reservoir. We have observed that potassium effluxes of less than about 5 $\mu g/cm^2 \cdot h$ correlate with very little skin irritation or redness whereas potassium effluxes of greater than about 10 $\mu g/cm^2 \cdot h$ correspond to moderate levels of skin irritation and redness. When the potassium concentration of the cathodic reservoir exceeds a predetermined value, eg, a concentration which corresponds to a level of potassium efflux which is a predecessor of skin irritation, erythema and/or damage, the controller component of the electrotransport system can be

made to respond so that the electrotransport agent delivery is either modified or terminated. The response by the controller can take several forms, including (i) signalling the patient to turn off the electrotransport device, remove the device and/or move the site of application of the electrotransport device, (ii) automatic termination, interruption or reduction of the level of electric current applied by the device, and/or (iii) operation of a secondary electrode of the type described in Phipps et al US Patent 5,125,894 to alter the pH of the cathodic and/or anodic reservoirs.

In accordance with another embodiment of the present invention, the pH of the anodic reservoir is maintained during electrotransport agent delivery above about 4, and preferably at a pH from about 4 to about 10. By maintaining the anodic reservoir pH above about pH 4 during electrotransport agent delivery, (i) the electrical resistance of the skin site adjacent the anodic reservoir is reduced, and (ii) skin irritation, erythema and/or damage to the skin site adjacent to the anodic reservoir is also reduced. This reduced skin resistance translates into reduced voltage and power requirements needed to drive a particular level of electric current through the body surface. Thus, maintaining the anodic reservoir pH above about 4 reduces the cost and/or size of the power source.

The pH of the anodic reservoir may be maintained above pH 4 by any number of means. In applications where the electrotransport device is operated at low current densities (eg, less than 200 $\mu A/cm^2$) using electrochemically oxidizable anode materials such as silver (both of which minimize the formation of hydronium ions at the anode) and/or for short periods of time (eg, less than 1 hour), it may be sufficient to simply add a weak acid (eg, a carboxylic acid) or a base to the anodic reservoir to maintain the desired pH. However, while weak acids or bases are effective in achieving an appropriate anodic reservoir pH, they introduce undesirable competing ions in those instances where the anodic electrode is the donor electrode. Thus, adding a carboxylic acid, or sodium hydroxide, to an anodic

donor reservoir containing lidocaine cations undesirably adds hydronium ions, or sodium ions, respectively, which ions compete with the lidocaine/sodium ions for delivery into the body. The competing hydronium ions also introduce uncertainty in the lidocaine delivery rate since it is difficult to predict what percentage of the total applied current is carried by the competing hydronium ions.

In applications where the electrotransport agent delivery (i) must be precisely controlled, (ii) is conducted for longer periods of the time (eg, >12 hours), (iii) is conducted using an anodic reservoir having a small volume (pH is measure of concentration and hence is highly dependent on the volume of the reservoir, with small volume reservoirs being more susceptible to pH changes during operation of the electrotransport device), (iv) is conducted using high current densities, and/or (v) is conducted using an anode composed of an electrochemically catalytic material (eg, platinum or stainless steel), the anodic reservoir is preferably buffered at a pH above about 4. More preferably, the buffer has a relatively low anodic electrotransport rate through the skin. Preferred buffers include amino acids exhibiting anionic behavior at a pH greater than 4, as listed in Table 3. Of the amino acids, cysteine, histidine, and tyrosine are most preferred.

TABLE 3

Anionic Amino Acid Buffers for
Anodic Reservoir

AMINO ACID	pH RANGE FOR ANIONIC BEHAVIOR	PREFERRED pH RANGE FOR ANIONIC BEHAVIOR
histidine	7.5-10.5	7.5-10
cysteine	7-12	7.5-11.5
tyrosine	7.8-11.4	8.3-10.9
lysine	9.7-11.8	9.7-11.3
arginine	10.8-13	10.8-12
aspartic acid	3-5.2 8.5-11.1	4-4.6 9.1 -10.5
glutamic acid	3.2-5.5 8.4-11	4-5 8.9-10.4
other amino acids	8-12	9-11

Other anodic reservoir buffers include certain zwitterions, examples of which are listed in Table 4. Preferred zwitterions are N-2-Hydroxyethylpiperazine-N'-2-ethane sulfonic acid (HEPES) and 2-(N-Morpholino)-propane sulfonic acid (MOPS).

TABLE 4

Zwitterion Buffers for
Anodic Reservoir

ZWITTERION (Abbreviation)	ZWITTERION (Full Chemical Name)	pH RANGE FOR ANIONIC BEHAVIOR	PREFERRED pH RANGE FOR ANIONIC BEHAVIOR
MES	2-(N-morpholino)-ethane sulfonic acid	4.8-7.4	5.4-6.8
PIPES	1,4-piperazine-bis-(ethanesulfonic acid)	5-7.6	5.6-7
ADA	N-2-acetamido iminodiacetic acid	5.3-7.9	5.9-7.3
ACES	N-2(2-acetamido)-2-aminoethane sulfonic acid	5.6-8.2	6.2-7.6
BES	N,N-bis(2-hydroxyethyl)-2-aminoethane sulfonic acid	5.9-8.4	6.4-7.8
MOPS	2-(N-morpholino)-propane sulfonic acid	5.9-8.5	6.5-7.9
TES	N-tris(hydroxymethyl) methyl-2-aminoethane sulfonic acid	6.2-8.8	6.8-8.2
HEPES	N-2-hydroxyethylpiperazine-N'-2-ethane sulfonic acid	6.2-8.8	6.8-8.2
EPPS	4-(2-hydroxyethyl)-1-piperazine propane sulfonic acid	6.7-9.3	7.3-8.7
TAPS	N-tris(hydroxymethyl) methyl-2-aminopropane sulfonic acid	7.1-9.7	7.7-9.1
CHES	2-cyclohexylamino-1-ethane sulfonic acid	8.2-10.8	8.8-10.2
CAPS	3-cyclohexylamino-1-propanesulfonic acid	9.1-11.7	9.7-11.1

In addition, acids having a pKa between 2 and 10 are suitable anionic buffers for the anodic reservoir. Examples of such acids can be found in

Table 5. The preferred anionic acid buffers include citric acid, succinic acid, phosphoric acid, maleic acid, and malonic acid.

TABLE 5

Anionic Acid Buffers for
Anodic Reservoir

BUFFER	ANIONIC pH RANGE	PREFERRED ANIONIC pH RANGE
citric acid	3-8	4-7
succinic acid	3-7.5	4-6.5
phosphoric acid	3-9	4-8
maleic acid	3-7.5	4-7
malonic acid	3-7.5	4-7
acetic acid	3-6	4-5.5
boric acid	8-10.5	8.5-9.9
EDTA	3-12	4-11
lactic acid	3-5	4-5
benzoic acid	3.5-5.5	4-5.5
tartaric acid	3-5.6	4-5.1
fumaric acid	3-6	4-5.1
formic acid	3.5-5	4-4.5
malic acid	3-6.3	4-5.8
carbonic acid	5.2-7.8	5.6-7.1
glutamic acid	3-7	4-6.5
adipic acid	3-7	4-6.5

Alternatively, the anodic reservoir may be buffered using a buffer which has a relatively high anodic electrotransport rate, ie, a cationic or positively charged buffer which buffers the anodic reservoir at a pH greater than about 4, preferably at a pH of about 4 to 10. Suitable cationic buffers include bases having at least one pKa between 2 and 10, certain other bases, and amino acids displaying cationic behavior at the reservoir pH.

Examples of cationic buffers suitable for the anodic reservoir are listed in Table 6. In addition, mixtures of an acid from Table 5 and a base from Table 6 may also be used to buffer the anodic reservoir. However, the buffers of Table 5 are preferred over the buffers of Table 6, particularly when the anodic electrode is the donor electrode since the Table 5 buffers do not compete with the agent for delivery into the body. The preferred bases for use in the anodic reservoir include tromethamine, triethanolamine and imidazole.

TABLE 6

Cationic Bases and Amino Acids for the Anodic Reservoir

BASE BUFFER	pH RANGE FOR CATIONIC BEHAVIOR	PREFERRED pH RANGE FOR CATIONIC BEHAVIOR
tromethamine	6.8-9.3	7.3-8.8
triethanolamine	6.5-9	7-8.5
imidazole	5.8-8.2	6.3-7.7
ammonia	8-10.5	8.5-10
ethanolamine	8.2-10.8	8.8-10.2
diethanolamine	7.6-10.2	8.2-9.6
histidine	3-7.5	4-7.5
lysine	7.7-9.7	8.2-9.7
arginine	7.8-10.8	8.3-10.8

The concentration of buffer required in the anodic reservoir, as in the cathodic reservoir, will depend on the properties of the specific buffer selected. Generally, the buffer concentration in the anodic reservoir will range from about 0.01 M to about 1.0 M. Preferably, the buffer concentration will be about 0.01 M to about 0.50 M. More preferably, the buffer concentration will be about 0.01 M to about 0.20 M.

As an alternative to the addition of either a weak acid, a base, or a buffering agent to the anodic reservoir in order to maintain the pH above about 4, and preferably in the range of about 4 to 10, the pH of the anodic reservoir may also be appropriately maintained by operating a suitable secondary electrode of the type, and in a manner, described in Phipps et al US Patent 5,125,894, discussed earlier herein.

With any of the embodiments described hereinabove wherein the pH of the anodic reservoir is appropriately maintained, a potassium sensor may optionally be incorporated into the cathodic reservoir to monitor for potassium ion efflux from the skin into the cathodic reservoir. When the potassium concentration of the reservoir exceeds a value which corresponds to a predetermined potassium efflux, the controller component of the electrotransport system can be made to respond as described hereinearlier.

In those cases where competition from buffer ions/counterions must be minimized or eliminated, the buffer added to the anodic or cathodic reservoir is preferably polymeric. Examples of polymeric buffers include, without limitation, those listed in Table 7. Table 7 also lists pH ranges for anionic and cationic behavior for the listed buffers. The polymeric buffers used in the cathodic reservoir are preferably those displaying polymer cationic behavior at a pH of less than about 4. The preferred polymeric buffers for the anodic reservoir are those in which the polymer is anionic at a pH greater than about 4.

TABLE 7

POLYMERIC BUFFER	ANIONIC pH RANGE	CATIONIC pH RANGE
polyacrylic acid	3-8	
polymethacrylic acid	3-8	
poly(styrene maleic anhydride)	3-8	
methacrylate/divinyl benzene copolymers[1]	3-8	
poly(2-acrylamido-2-methylpropane sulfonate)	1-5	
copolymers of acrylic acid and long chain acrylate esters[2]	3-8	
poly(methylvinyl ether-maleic acid)[3]	2-8	
vinylpyrrolidone/ quaternized dimethylamino-ethylmethacrylate copolymers[4]		7-10
vinylcaprolactam/ vinylpyrrolidone/ dimethylamino ethylmethacrylate terpolymers[5]		7-10
polyvinylpyridine		6-9
methacrylate/divinyl benzene copolymers		6-9

The pH of a given reservoir affects primarily the skin directly adjacent (eg, in contact with) that reservoir. Thus, the cathodic reservoir pH affects the irritation and electrical resistance of the skin site adjacent to the cathodic

[1] Amberlite IRP-64, an insoluble, weakly acidic, cation exchange resin sold by Rohm and Haas Co., Philadelphia, PA.

[2] Pemulen polymeric emulsifiers, sold by B. F. Goodrich Co., Specialty Polymers & Chemicals Division, Brecksville, OH.

[3] Gantrez S95 and S97, made and sold by ISP Technologies, Inc. of Wayne, NJ.

[4] Gafquat 755 and 755N, made and sold by ISP Technologies, Inc. of Wayne, NJ.

[5] Gaffix VC-713, made and sold by ISP Technologies, Inc. of Wayne, NJ.

reservoir, while the anodic reservoir pH affects the irritation and electrical resistance of the skin site adjacent to the anodic reservoir. Accordingly, this invention contemplates those devices in which (i) the cathodic reservoir pH is maintained below 4, (ii) the anodic reservoir pH is maintained above 4 and (iii) both reservoir pH's are appropriately maintained. However, in the preferred practice of the invention, both the anodic reservoir is maintained at a pH above about 4, and the cathodic reservoir is maintained at a pH below about 4. More preferably, both the anodic and cathodic reservoirs are buffered at the appropriate pH.

As mentioned herein earlier, the pH of the donor (drug-containing) reservoir is in many cases not subject to adjustment in accordance with the ranges specified herein since the solubility of the drug in the liquid solvent may be insufficient at those pH ranges. Thus, the present invention has particular utility when used to adjust the pH of the counter reservoir from which no drug is being delivered. Thus, in cases where a cationic drug is being delivered from an anodic reservoir, the present invention is particularly useful in maintaining the pH of the counter cathodic reservoir below about 4, preferably from about pH 2 to 4. Conversely, when delivering an anionic drug from the cathodic reservoir, the present invention is particularly useful in adjusting the pH of the counter anodic counter reservoir to a pH above about 4, preferably from about pH 4 to 10. Even in those cases where the pH of the donor reservoir cannot be adjusted in accordance with the ranges disclosed herein, the electrical resistance and irritation of the skin which is adjacent the counter reservoir can still be substantially reduced. Thus, at the very least, the present invention provides a method for (i) reducing the electrical resistance of at least one of the two skin sites through which electric current is applied during electrotransport agent delivery; and (ii) reducing or eliminating at least about one half of the skin irritation potential (ie, the skin site beneath the counter electrode reservoir) due to electrotransport agent delivery. Of course, it is most preferred that the pH of both the donor and counter electrode reservoirs be appropriately maintained

in order to reduce the electrical resistance and the irritation potential for both the skin site adjacent the counter electrode reservoir and the skin site adjacent the donor electrode reservoir.

In the situation where the agent is delivered primarily by electromigration, then the pH of the donor electrode reservoir can be appropriately maintained as described herein as long as at that pH, at least about 50% of the agent to be delivered is charged. Those skilled in the art will clearly appreciate that for agents being delivered primarily by electromigration, the pH of the donor reservoir can be set to minimize electrical resistance and irritation potential as taught herein only if the agent being delivered has one or more appropriate pK's, ie, a pK which allows the donor reservoir pH to be set as taught herein (ie, anodic donor reservoir pH above 4 and/or cathodic donor reservoir pH below 4) and which pH allows the agent to exist in a state wherein at least 50% of the agent has a charge of the appropriate sign (+/-). For example, morphine, a narcotic analgesic, has a pK of 8.3 at 25°C. Thus, in a solution of morphine with a pH of 8.3, 50% of the morphine is positively charged and 50% is uncharged. Accordingly, the appropriate pH range for the anodic morphine-containing donor electrode in an electrotransport device for delivering morphine primarily by electromigration is pH 4 to 8.3.

The donor reservoir and counter reservoir can be formed of any material adapted to absorb and hold a sufficient quantity of liquid therein in order to permit transport of agent therethrough by electrotransport. For example, gauzes, pads or sponges composed of cotton or other absorbent fabric, both natural and synthetic, may be used. Preferably, the matrices of the reservoirs are composed, at least in part, of hydrophilic polymer material. Hydrophilic polymers are typically preferred because water is the preferred ion transport medium, and hydrophilic polymers have a relatively high equilibrium water content. More preferably, the matrices of the reservoirs are solid polymer matrices composed, at least in part, of an insoluble

hydrophilic polymer. Insoluble hydrophilic polymer matrices are preferred for structural reasons over soluble hydrophilic polymers, ie reservoir shape may be more easily retained upon hydration of a hydrophilic polymer matrix composed of a water insoluble polymer compared to a matrix composed of a water soluble polymer or gel.

The matrices can be crosslinked with the agent in place, such as with a silastic matrix, or the polymers can be prefabricated and sorbed with the components from solutions as is the case with cellulose, woven fiber pads and sponges. The reservoirs can alternately be a gel matrix structure, formed similarly to the polymeric matrix structure, wherein the gel is formed of a hydrophilic polymer which is swellable or soluble in water. Such polymers can be blended with the components in any ratio, but preferably represent from a few percent up to about 50 percent by weight of the reservoir. The polymers can be linear or cross-linked. Suitable hydrophilic polymers include copolyesters such as HYTREL (DuPont De Nemours & Co., Wilmington,DE), polyvinylpyrrolidones, polyvinyl alcohol, polyethylene oxides such as POLYOX (Union Carbide Corp.), CARBOPOL (BF Goodrich of Akron, OH), blends of polyoxyethylene or polyethylene glycols with polyacrylic acid such as POLYOX blended with CARBOPOL, polyacrylamide, KLUCEL, cross-linked dextran such as SEPHADEX (Pharmacia Fine Chemicals, AB, Uppsala, Sweden), WATER LOCK (Grain Processing Corp., Muscatine, Iowa) which is a starch-graft-poly(sodium acrylate-co-acrylamide) polymer, cellulose derivatives such as hydroxyethyl cellulose, hydroxypropylmethylcellulose, low-substituted hydroxypropylcellulose, and cross-linked Na-carboxymethylcellulose such as Ac-Di-Sol (FMC Corp., Philadelphia, PA), hydrogels such as polyhydroxylethyl methacrylate (National Patent Development Corp.), natural gums, chitosan, pectin, starch, guar gum, locust bean gum, and the like, along with blends thereof. This list is merely exemplary of the materials suited for use in this invention. Other suitable hydrophilic polymers can be found in J. R. Scott & W. J. Roff,

Handbook of Common Polymers (CRC Press, 1971), which is hereby incorporated by reference.

Optionally, the matrices of the reservoirs may contain a hydrophobic polymer for enhanced structural rigidity or improved bonding characteristics. Preferably the hydrophobic polymer is heat fusible, in order to improve the lamination of the reservoirs to adjacent components, such as an insulating material or a rate-controlling membrane. Suitable hydrophobic polymers for use in the reservoir matrices include, but are not limited to, polyisobutylenes, polyethylene, polypropylene, polyisoprenes and polyalkenes, rubbers, copolymers such as KRATON®, polyvinylacetate, ethylene vinyl acetate copolymers, polyamides such as nylons, polyurethanes, polyvinylchloride, acrylic or methacrylic resins such as polymers of esters of acrylic or methacrylic acid with alcohols such as n-butanol, 1-methyl pentanol, 2-methyl pentanol, 3-methyl pentanol, 2-ethyl butanol, isooctanol, n-decanol, alone or copolymerized with ethylenically unsaturated monomers such as acrylic acid, methacrylic acid, acrylamide, methacrylamide, N-alkoxymethyl acrylamides, N-alkoxymethyl methacrylamides, N-tert-butylacrylamide, itaconic acid, N-branched alkyl maleamic acids wherein the alkyl group has 10-24 carbon atoms, glycol diacrylates, and blends thereof. Most of the above-mentioned hydrophobic polymers are heat fusible.

The reservoir matrices may be a polymeric matrix structure formed by blending the desired agent, drug, electrolyte, or other component(s), with an inert polymer by processes such as melt blending, solvent casting, or extrusion. The donor reservoir contains an agent to be delivered, while the counter reservoir may contain an electrolyte, eg a water soluble biocompatible salt, such as sodium chloride. In addition to the delivery agent and electrolyte, the reservoirs may also contain other conventional materials such as water, permeation enhancers, dyes, pigments, inert fillers, and the like.

The electrodes of the present invention are composed of an electrically conductive material such as a metal. For example, the electrodes may be formed from metal foil, metal screen, metal deposited or painted on a suitable backing, calendaring, film evaporation, or by embedding a metal powder in a binder matrix. Examples of suitable metals include silver, zinc, silver chloride, aluminum, platinum, stainless steel, gold, and titanium. For example, the anodic electrode may be composed of silver, while the cathodic electrode may be composed of silver chloride.

Further, if the electrodes are selected from dissimilar materials, a galvanic couple may be formed. A galvanic couple may provide all or at least part of the electrical potential required to operate the device. Exemplary of such a galvanic couple are a pair of electrodes formed from silver and zinc chloride.

Alternatively, the electrodes may be formed of a polymer matrix containing a conductive filler such as a metal powder, powdered graphite, carbon fibers, or other electrically conductive filler material. The polymer-based electrodes may be produced by mixing the conductive filler in a polymer matrix, preferably hydrophobic in order to minimize interaction with any water present in the reservoirs.

Preferably, the electrodes of the present invention are comprised of electrochemically reactive materials, ie, the anode is composed of an electrochemically oxidizable material (eg, silver) and/or the cathode is composed of an electrochemically reducible material (eg, silver chloride). Electrochemically reactive electrode materials are preferred because their use minimizes water hydrolysis, which results in the production of hydroxyl (OH^-) and hydronium (H^+) ions, which can alter reservoir pH and also introduces competing ions in the donor reservoir. Hydroxyl or hydronium ions may be transported into the skin causing a high or low, respectively, pH in the skin, thereby causing erythema, irritation, and/or damage. The

preferred electrochemically reactive electrodes are the aforementioned silver and silver chloride electrodes.

This invention has utility in connection with the delivery of agents within the broad class deliverable through body surfaces, including skin, mucosa, and nails. The expressions "drug" and "agent" are used interchangeably herein and are intended to have their broadest interpretation as any substance which is delivered to a living organism to produce a desired, usually beneficial, effect. In general, this includes therapeutic agents in all of the major therapeutic areas including, but not limited to, anti-infectives such as antibiotics and antiviral agents, analgesics including fentanyl, sufentanil, buprenorphine and analgesic combinations, anesthetics, anorexics, antiarthritics, antiasthmatic agents such as terbutaline, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine preparations, antimotion sickness preparations such as scopolamine and ondansetron, antinauseants, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, including gastrointestinal and urinary, anticholinergics, antiulceratives such as ranitidine, sympathomimetrics, xanthine derivatives, cardiovascular preparations including calcium channel blockers such as nifedipene, beta-blockers, beta-agonists such as dobutamine and ritodrine, antiarrythmics, antihypertensives such as atenolol, ACE inhibitors such as enalapril, benzodiazepine antagonists such as flumazenil, diuretics, vasodilators, including general, coronary, peripheral and cerebral, central nervous system stimulants, cough and cold preparations, decongestants, diagnostics, hormones such as parathyroid hormone, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetrics, prostaglandins, proteins, peptides, psychostimulants, sedatives and tranquilizers.

The invention is also useful in the controlled delivery of peptides, polypeptides, proteins and other macromolecules. These macromolecular

substances typically have a molecular weight of at least about 300 daltons, and more typically a molecular weight in the range of about 300 to 40,000 daltons. Specific examples of peptides, and proteins and macromolecules in this size range include, without limitation, LHRH, LHRH analogs such as buserelin, gonadorelin, napharelin and leuprolide, GHRH, GHRF, insulin, insulotropin, heparin, calcitonin, octreotide, endorphin, TRH, NT-36 (chemical name: N=[[(s)-4-oxo-2-azetidinyl]carbonyl]-L-histidyl-L-prolinamide), liprecin, pituitary hormones (eg, HGH, HMG, HCG, desmopressin acetate, etc.), follicle luteoids, αANF, growth factors such as growth factor releasing factor (GFRF), βMSH, somatostatin, atrial natriuretic peptide, bradykinin, somatotropin, platelet-derived growth factor, asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic gonadotropin, corticotropin (ACTH), epidermal growth factor, erythropoietin, epoprostenol (platelet aggregation inhibitor), follicle stimulating hormone, glucagon, hirulog, hyaluronidase, interferon, insulin-like growth factors, interleukin-1, interleukin-2, menotropins (urofollitropin (FSH) and LH), oxytocin, streptokinase, tissue plasminogen activator, urokinase, vasopressin, desmopressin, ACTH analogs, ANP, ANP clearance inhibitors, angiotensin II antagonists, antidiuretic hormone agonists, antidiuretic hormone antagonists, bradykinin antagonists, CD4, ceredase, CSF's, enkephalins, FAB fragments, IgE peptide suppressors, IGF-1, neuropeptide Y, neurotrophic factors, oligodeoxynucleotides and their analogues such as antisense RNA, antisense DNA and anti-gene nucleic acids, opiate peptides, colony stimulating factors, parathyroid hormone and agonists, parathyroid hormone antagonists, prostaglandin antagonists, pentigetide, protein C, protein S, ramoplanin, renin inhibitors, thymosin alpha-1, thrombolytics, TNF, vaccines, vasopressin antagonist analogs, alpha-1 anti-trypsin (recombinant), and TGF-beta.

Having thus generally described the invention, the following examples will illustrate how the invention may be utilized to accomplish effective transdermal electrotransport agent delivery with reduced skin resistance and reduced skin irritation, erythema and/or damage.

EXAMPLE I

In this set of experiments, sodium phosphate buffer (ie, negatively charged phosphate buffer) was added to the cathodic reservoir and various positively charged buffers having chloride counter ions were added to the anodic reservoir. The pH at the cathodic reservoir was varied from 1.35 to 8.17. The purpose of these experiments was to study the effect of reservoir pH on skin irritation/erythema and skin resistance during the application of an electric current, ie, current carried by the movement of ions, through the skin. Since many drugs have at least some potential to irritate the skin upon contact therewith, the only ionic species added to the anodic and cathodic reservoirs were the buffering agents themselves. Hence, no drug was placed in the reservoirs in these Examples. Delivery of drug from the reservoirs is not necessary to study the effects of reservoir pH on the skin since any mobile ionic species can be used to study the effects of electric current through skin.

The electrotransport device had a silver foil anode and a silver chloride cathode. The reservoir gel (ie, both the anodic and cathodic gels) sizes were each approximately 200 µL and had a skin contacting surface area of about 1.25 cm^2. For pH 1.35, 1.78, and 1.86, the reservoir gels contained about 0.15 M phosphoric acid, 3% by weight hydroxyethyl cellulose, NaOH q.s. to the desired pH, and q.s. water. The 0.15 M phosphoric acid was replaced with 0.15 M monobasic sodium phosphate for the other pH values examined.

Experiments were performed in vivo on hairless guinea pigs. Both the anodic reservoir and the cathodic reservoir were applied to the backs of the guinea pigs using an adhesive overlay. The two reservoirs were generally spaced about 5 to 7.5 cm apart. The electrodes were connected to a DC power source which supplied a constant current of 0.125 mA (ie, current density of 0.1 mA/cm^2). Current was applied for 30 minutes, after which time

the electrodes were disconnected from the power source and the gels were removed from the guinea pigs. The skin resistance measurements were made by recording the applied voltage after 5 minutes of applying 0.125 mA of current. Skin resistance (R) values (KOhms·cm^2) were calculated by multiplying the measured voltage (V) across the electrodes by the surface area (A) of the contact (ie, 1.25 cm^2) and dividing that product by the applied current (I) (ie, 0.1 mA) in accordance with the following equation: $R = VA/I$. Skin irritation measurements were taken about 5 minutes after removal of the electrodes from the skin. Each data point represents an average of the measurements taken from four skin samples, each sample from a different guinea pig.

Quantitative skin irritation (α) measurements were obtained from color measurements generated by a Minolta Chroma Meter Model No. CR 200 (sold by Minolta Camera Corp., Ltd., Osaka, Japan) for this and all subsequent Examples. The Minolta Chroma Meter is a portable tristimulus color analyzer which converts all colors within the range of human perception into a numerical code using the L*a*b* color notation system. L* (luminance) expresses brightness on the black-white axis; a*, hue on the red-green axis; and b*, chroma on the yellow-blue axis so that a specific numerical code enables an exact color description of an object. The numerical values for α are generated by the Minolta Chroma Meter and have no particular units. The Minolta Chroma Meter utilizes a numerical range of -60 (green) to +60 (red) for a* hue. Typically, human skin ranges from 0 to 10 on the a* hue scale. An α value of 1 to 2 represents a slight redness or erythema; an α value of 3.5 to 4.5 represents a moderate redness or erythema; and an α value of above 7 represents severe redness or erythema. The measurement of skin irritation for these tests is given as α, which is defined herein as the difference of the mean a^* reading for the electrotransport-treated samples minus the mean a^* reading for the untreated samples, ie $\alpha = a^*_{treated} - a^*_{untreated}$. Minolta measurements were made by taking the mean a* value of three readings at adjacent untreated sites and subtracting that value from the mean of three readings taken at the treated

site. Since changes in redness intensity were made from the a* reading, only a* values were employed for the purposes of skin site checks following electrode removal.

A skin irritation value (α) and skin resistance (R), were tabulated for each pH value studied. Skin irritation and skin resistance as a function of pH are listed for the cathodic reservoir in Table 8 and for the anodic reservoir in Table 9. Figures 2 and 4 illustrate a plot of skin irritation versus pH for the cathodic and anodic reservoirs, respectively. Figures 3 and 5 illustrate a plot of skin resistance versus pH for the cathodic and anodic reservoirs, respectively.

TABLE 8

CATHODIC RESERVOIR pH	SKIN RESISTANCE (R) ($KOhms \cdot cm^2$)	SKIN IRRITATION (α)
1.35	19.3	3.1
1.78	19.5	3.7
1.86	25.9	4.6
4.92	41.4	6.3
5.47	46.1	5.7
6.45	44.0	6.9
7.42	43.8	5.6
8.00	42.4	6.4
8.17	51.1	5.5

TABLE 9

BUFFER	ANODIC RESERVOIR pH	SKIN RESISTANCE (KOhms·cm^2)	SKIN IRRITATION (α)
0.15 M calcium chloride dihydrate	4.88	48.3	5.1
0.15 M triethanolamine hydrochloride	5.28	33.9	1.7
0.15 M magnesium chloride heptahydrate	5.3	41.7	2.6
0.15 M diethanolamine hydrochloride	5.5	29.8	1.7
0.15 M ammonium chloride	5.58	26.4	2.0
0.15 M ethanolamine hydrochloride	5.6	22.4	2.2
0.15 M potassium chloride	5.65	22.7	1.6
0.15 M sodium chloride	6.14	25.6	2.1

The compounds used to adjust the pH of the anodic reservoirs (ie, the Table 9 compounds) were cations which tend to be delivered into the skin by electromigration. At least one of these cations (magnesium; see third line of Table 8) is known to be skin irritating. Thus, the skin irritation (α) value for magnesium chloride heptahydrate may be higher (ie, higher than triethanolamine HCl at a similar pH) due to the irritating effect of magnesium ions.

As Table 8 and Figures 2-3 illustrate, cathodic reservoir pH values of less than about pH 4, and particularly at pH's of about 2, resulted in lower skin resistance and less skin irritation compared to cathodic reservoir pH's ranging from about 5 to 8. Similarly, Table 9 and Figures 4-5 indicate that high pH, ie, greater than about pH 4 to about 5, at the anodic reservoir results in low skin resistance and low skin irritation.

EXAMPLE II

These experiments involved the use of histidine, lysine, and arginine, all positively charged buffers in the form of chloride salts, in the cathodic reservoir and citric acid, monobasic sodium phosphate, and boric acid, all negatively charged buffers in the form of sodium salts in the anodic reservoir. All reservoir compositions contained about 3% by weight hydroxypropyl cellulose (HPC) and q.s. water. Either HCl or NaOH were added q.s. to achieve the desired pH. The other conditions were the same as described in Example I.

Skin resistance (R) and skin irritation (α) as a function of pH are listed (i) in Table 10 for the cathodic reservoirs buffered with L-lysine or L-histidine; (ii) in Table 11 for the anodic reservoir buffered with citric acid, boric acid, or monobasic sodium phosphate, (iii) in Table 12 for the cathodic reservoirs buffered with L-histidine, L-lysine, or L-arginine, and (iv) in Table 13 for the cathodic reservoirs buffered with phosphoric acid and monobasic sodium phosphate.

Irritation and resistance values from Table 10 are plotted versus pH in Figures 6 and 7, respectively. Irritation and resistance values from Table 11 are plotted versus pH in Figures 8 and 9, respectively. Irritation values from Tables 12 (open dot) and 13 (solid dot) are plotted versus pH in Figure 10.

TABLE 10

CATHODIC RESERVOIR COMPOSITION (all include 0.1 M NaCl, 3% HPC, HCl q.s. to desired pH, and water q.s.)	CATHODIC RESERVOIR pH	SKIN RESISTANCE (R) (KOhms·cm^2)	SKIN IRRITATION (α)
0.05 M L-histidine base	1.93	18.9	3.1
0.05 M L-histidine base	2.92	32.4	4.7
0.05 M L-histidine base	3.88	35.2	6.9
0.05 M L-histidine base	4.93	37.6	7.2
0.05 M L-histidine base	6.00	45.4	7.0
0.05 M L-lysine base	6.55	32.1	6.4
0.05 M L-histidine base	7.09	38.9	6.6
0.05 M L-lysine base	8.98	30.1	6.4
0.05 M L-lysine base	10.19	34.0	6.3

TABLE 11

ANODIC RESERVOIR COMPOSITION (all include 0.1 M NaCl, 3% HPC, NaOH q.s. to desired pH, and water q.s.)	ANODIC RESERVOIR pH	SKIN RESISTANCE (R) (KOhms·cm^2)	SKIN IRRITATION (α)
0.05 M citric acid	2.11	51.6	4.7
0.05 M citric acid	2.72	50.9	5.3
0.05 M citric acid	3.62	45.6	4.0
0.05 M citric acid	4.52	33.2	2.7
0.05 M citric acid	5.31	29.6	2.7
0.05 M citric acid	6.55	27.4	3.3
0.05 M sodium phosphate monobasic	7.47	23.4	2.6
0.05 M boric acid	8.80	22.5	2.5
0.05 M boric acid	9.93	23.5	2.5

TABLE 12

CATHODIC RESERVOIR COMPOSITION (all include 0.1 M NaCl, 3% HPC, HCl q.s. to desired pH, and water q.s.)	CATHODIC RESERVOIR pH	SKIN IRRITATION (α)
0.05 M L-histidine base	1.93	3.1
0.05 M L-histidine base	2.92	4.7
0.05 M L-histidine base	3.88	6.9
0.05 M L-histidine base	4.93	7.1
0.05 M L-histidine base	6.00	7.0
0.05 M L-lysine base	6.55	6.4
0.05 M L-histidine base	7.09	6.6
0.05 M L-lysine base	8.98	6.4
0.05 M L-arginine base	10.19	6.4

TABLE 13

CATHODIC RESERVOIR COMPOSITION (all include 0.1 M NaCl, 3% HPC, NaOH q.s. to desired pH, and water q.s.)	CATHODIC RESERVOIR pH	SKIN IRRITATION (α)
0.15 M phosphoric acid	1.35	3.1
0.15 M phosphoric acid	1.78	3.7
0.15 M phosphoric acid	1.86	4.6
0.15 M monobasic sodium phosphate	4.92	6.3
0.15 M monobasic sodium phosphate	5.47	5.7
0.15 M monobasic sodium phosphate	6.45	6.9
0.15 M monobasic sodium phosphate	7.42	5.6
0.15 M monobasic sodium phosphate	8.00	6.4
0.15 M monobasic sodium phosphate	8.17	5.5

Because the buffer ions in this Example had a charge which was opposite the charge on the electrode (ie, positively charged buffer ions in the cathodic reservoir and negatively charged buffer ions in the anodic

reservoir), a negligible amount of buffer ions were transported into the skin by electromi-gration. The skin irritation and skin resistance results were similar to those obtained in Example I, ie, cathodic reservoir pH's of less than about 4 and/or anodic reservoir pH's of greater than about 4 result in reduced skin resistance and reduced skin irritation compared to cathodic reservoir pH's greater than about 4 and/or anodic reservoir pH's less than about 4. Furthermore, buffering of the reservoirs alone is sufficient to reduce skin irritation and skin resistance, and the charge of the buffer ion (which charge effects whether or not the buffer ion is delivered at a significant rate into the skin) does not appear to significantly affect the results, at least during short periods (ie, up to 30 minutes) of electrotransport administration.

EXAMPLE III

Cathodic reservoir compositions containing sodium phosphate buffers (negatively charged buffer ions) were evaluated in this set of experi-ments. All compositions contained 0.05 M phosphoric acid, 0.1 M sodium chloride, 6% polyvinyl alcohol, 4% hydroxypropyl methylcellulose, and q.s. water. Sodium hydroxide was added q.s. to achieve the desired pH.

In this set of experiments, the electrotransport was conducted on the inner arm of human volunteers. The skin contact area of the electrode reservoir gels (ie, both the anodic gel and the cathodic gel) were each approximately 5.1 cm^2, and the reservoir gel volume was about 800 µL. The anodic electrode was silver foil and the cathodic electrode was silver chloride (ie, silver foil treated with HCl to form a surface layer of AgCl). The electrodes were connected to a DC power source which delivered a constant current of 0.51 mA, resulting in a current density of about 0.1 mA/cm^2. Electrode gels were placed on the skin and connected to the DC power source. The power source delivered current through the gels for about 4 hours, after which time the electrodes were disconnected and the gels removed. After removal from the arms of the patients, the potassium

content of the cathode gels was measured and potassium efflux ($\mu g/cm^2 \cdot h$) was calculated by dividing the measured potassium content by the product of gel skin contact area (ie, 5.1 cm^2) and time of application (ie, 4 h).

Skin resistance was measured (as in Example I) at 1 hour after gel application and skin irritation measurements were taken about 24 hours after the gels were removed.

Table 14 gives averaged results for six subjects. Figures 11 and 12 illustrate plots of the skin irritation and skin resistance values, respectively, as a function of cathodic reservoir pH. Table 14 also lists the average potassium efflux values at each pH. The potassium efflux was about 2 $\mu g/cm^2 \cdot h$ at pH values below about 4, when there was substantially no skin irritation or redness (ie, α of 0.2 or 0.6). Conversely, the potassium efflux was greater than 10 $\mu g/cm^2 \cdot h$ at pH values of 6.7 and 8.9 when there was visible skin irritation and redness (ie, α of 2.6). While the mechanism responsible for the enhanced efflux of potassium accompanying skin irritation is unclear, the correlation between greater skin irritation/redness and higher potassium efflux is clearly demonstrated in Table 14. One possible explanation is that the applied electric current causes the skin cells to rupture or otherwise release their cytoplasmic potassium content. The cytoplasmic potassium concentration (ie, the potassium concentration within the skin cells) is about forty times greater than that of the interstitial fluid outside the skin cells. This at least suggests that skin irritation which occurred when electric current was applied at pH values greater than 4, caused expulsion of potassium from the interior of cells into the interstitial fluid, where it effluxed from the skin into the cathode hydrogel due to the applied electric field.

TABLE 14

CATHODIC RESERVOIR pH	SKIN RESISTANCE (R) ($KOhm \cdot cm^2$)	SKIN IRRITATION (α)	POTASSIUM EFFLUX ($\mu g/cm^2 \cdot h$)
3.5	9.1	0.2	2.1
4.2	10.6	0.6	2.0
6.7	26.9	2.6	13.4
8.9	26.0	2.6	18.6

In this example, negatively charged phosphate buffer ions were present in the cathodic reservoir and hence, were transported into the skin. As Figures 11 and 12 illustrate, the skin irritation and resistance results followed the same trend as in Examples I and II. At a cathodic reservoir pH of 3.5 to 4.2, the skin beneath the reservoir had resistances less than about 11 $KOhm \cdot cm^2$ and irritation values of less than about 0.6. However, at the higher cathodic reservoir pH levels of 6.7 and 8.9, the skin resistances exceeded 25 $KOhms \cdot cm^2$ and irritation values exceeded 2.5. Thus, cathodic reservoir pH below about 4 produced lower skin irritation and skin resistance than pH above about 4.

EXAMPLE IV

Cathodic reservoir formulations containing histidine chloride buffer (ie, positively charged histidine buffer ions) and sodium citrate buffer (ie, negatively charged citrate buffer ions) at pH 3 and 4 were studied. All compositions contained 0.1 M buffer (histidine or citrate), 6% polyvinyl alcohol (PVA), 4% hydroxypropylmethylcellulose (HPMC), either HCl (for histidine) or NaOH (for citric acid) q.s. to the desired pH, and q.s. water.

As in Example III, the electrotransport was conducted on the inner arm of human volunteers. The electrode materials, the gel volume and skin

contact area, the current, the current density and the wearing time were the same as in Example III.

Skin resistance (R) was measured (as in Example I) at 0.5, 1, 2, 3 and 4 hours of wearing. Skin irritation (α) was measured (as in Example I) at 1, 4 and 24 hours after the end of wearing. Both R and α values are given in Table 15 as a function of buffer, pH, and number of hours after removal. Each data point for pH 4 represents an average of readings for seven human subjects, while for pH 3, each data point represents an average of eight human subjects.

Table 15 presents skin irritation (α) as a function of hours after device removal for both citrate and histidine buffers at pH 3 and 4. Similarly, Table 16 presents skin resistance (R) as a function of hours after device removal for both citrate and histidine buffers at pH 3 and 4.

Figures 13 and 14 show plots of skin irritation (α) and skin resistance (R), respectively, versus hours after device removal for citric acid and histidine buffers at pH 4. Figures 15 and 16 show plots of skin irritation (α) and skin resistance (R), respectively, versus hours after device removal for citric acid and histidine buffers at pH 3.

TABLE 15

HOURS AFTER DEVICE REMOVAL	IRRITATION (α) AT pH 3 FOR HISTIDINE	IRRITATION (α) AT pH 3 FOR CITRATE	IRRITATION (α) AT pH 4 FOR HISTIDINE	IRRITATION (α) AT pH 4 FOR CITRATE
1	0.4	0.7	0.6	0.9
4	0.3	1.4	0.7	1.5
24	-0.2	0.3	-0.4	0.7

TABLE 16

HOURS AFTER DEVICE REMOVAL	RESISTANCE AT pH 3 FOR HISTIDINE ($KOHM \cdot CM^2$)	RESISTANCE AT PH 3 FOR CITRATE ($KOHM \cdot CM^2$)	RESISTANCE AT PH 4 FOR HISTIDINE ($KOHM \cdot CM^2$)	RESISTANCE AT PH 4 FOR CITRATE ($KOHM \cdot CM^2$)
0.5	5.3	3.7	10.1	6.1
1	2.6	2.0	5.6	3.4
2	1.7	1.3	4.3	3.7
3	1.6	1.4	4.0	2.4
4	2.0	1.2	3.1	2.0

In one set of tests, the cathodic reservoir contained positively charged histidine buffer, while in the other set, the cathodic reservoir contained negatively charged citrate buffer. Hence, the citrate buffer ions were transported into the skin by electromigration while the histidine buffer ions were not. Although skin resistance values for the two buffers were not significantly different (see Figs. 14 and 16), buffering the cathodic reservoir with histidine resulted in lower skin irritation compared to buffering with citric acid (see Figs. 13 and 15). Therefore, preventing or at least minimizing buffer transport into the skin (ie, through use of a cationic buffer in the cathodic reservoir and/or an anionic buffer in the anodic reservoir) is preferred for minimizing skin irritation.

EXAMPLE V

Six electrolyte compositions were studied to determine the effect of cathodic reservoir pH on skin irritation. These compositions consisted of three ionic species (lactate, sulfate, and tartrate) in which two different pH's were evaluated for each ionic species. All reservoir electrolyte compositions were about 0.1 molar (M).

Current was applied at 100 μA/cm^2 for five hour periods. Skin resistance values were determined from Ohm's Law, by measuring the applied voltage after 5 hours and the current applied. After application of current was discontinued, the skin beneath the cathodic reservoir was visually evaluated for redness.

Irritation measurements are expressed on a relative scale in Table 17, as a function of pH and electrolyte composition. These ratings were determined by visually comparing, for erythema (redness), each treated skin site to every other treated skin site in the study. A rating of -1 for worse, 0 for substantially the same, and +1 for better was assigned to each comparison. The sums of these numbers represents a relative ranking of the sites for erythema, which sums are reported in Table 17. The visual determinations were made at one and 24 hours after current application was initiated. Three samples were evaluated for each electrolyte, ie n=3, and an averaged value is reported in Table 17. The reservoir composition which has the highest ranking produced the least irritation, and vice versa. The minimum possible value is zero, which would indicate that the three sites contacting that electrolyte were rated worse than all other sites. The maximum possible value is 34, which would indicate that the three sites in contact with that electrolyte were rated better than all other sites.

TABLE 17

ELECTROLYTE	IONIC SPECIES	pH	AVERAGE IRRITATION RANKING AFTER 1 HOUR	AVERAGE IRRITATION RANKING AFTER 24 HOURS	RESISTANCE ($KOhm \cdot cm^2$) AFTER 5 HOURS
sodium lactate	lactate	5.5	8.3	2.0	18.3
lactic acid	lactate	2.2	12.0	11.0	10.1
sodium sulfate	sulfate	6.0	12.6	12.0	15.5
sodium hydrogen sulfate	sulfate	1.5	24.0	24.6	12.4
sodium tartrate	tartrate	7.4	21.3	15.6	16.0
sodium hydrogen tartrate	tartrate	2.0	24.3	24.6	10.4

Table 17 shows that, for each ionic species studied, a lower pH produced lower comparative irritation rankings. Further, for each ionic species, a lower pH produced a lower skin resistance.

EXAMPLE VI

Cathodic reservoir formulations containing histidine chloride buffer adjusted to the desired pH with hydrochloric acid were placed on chest and arm sites of five different groups of human subjects. All sites were exposed to a DC current density of about 0.1 mA/cm^2 for 4 to 6 hours. After completion of each experiment, the potassium content of the cathode hydrogels was determined and potassium efflux values calculated.

Table 18 summarizes the potassium efflux values calculated for the five groups of subjects. This data confirms the strong correlation between pH and potassium efflux discussed in Example III. As in Example III,

cathodic pH values greater than 4 correlated with a four to five-fold enhancement in potassium efflux.

TABLE 18

CATHODE GEL pH	NUMBER OF SUBJECTS	NUMBER OF SITES TESTED	SITE LOCATION	POTASSIUM EFFLUX ($\mu g/cm^2 \cdot h$)
2.5	3	3	Arm	2.3
3	6	6	Chest	3.0
3	5	20	Arm	3.0
7	6	6	Chest	12.2
7	6	6	Chest	13.1

EXAMPLE VII

An electrotransport device for delivering lidocaine HCl and having a configuration as illustrated in Figure 1, but without the membranes 30 and 32, is constructed. The anode 12 is comprised of silver and the cathode 14 is comprised of silver chloride. Both the anodic reservoir 16 and the cathodic reservoir 18 are comprised of a polyvinyl alcohol based hydrogel. Each of the reservoirs 16 and 18 has a volume of 1 cm^3 and a skin contact area of 10 cm^2. The reservoir 16 gel is imbibed with an aqueous solution of lidocaine HCl and the reservoir 18 gel is imbibed with an aqueous saline solution. A miniature potassium sensing probe sold by Microelectrodes, Inc. of Londenerry, NH, Model No. MI-402 is inserted into the cathodic reservoir 18 and connected to the power source in circuit layer 24. The potassium sensing probe, and the control circuit therefor, are set to measure the potassium concentration in the cathodic reservoir every 0.1 h. The sensed concentration is compared to the previously sensed concentration by an electronic comparator. When the change in the potassium concentration exceeds 5 $\mu g/cm^3$ over the 0.1 h interval (ie, a rate of change of concentration of 50 $\mu g/cm^3 \cdot h$), which change in concentration corresponds to

a potassium efflux of about 5 μg/cm^2· h, an LED which is visible from the exterior of the device is activated, thereby signalling the patient to move the device to another skin site.

EXAMPLE VIII

These experiments used anodic reservoirs containing 0.6 M aqueous sodium chloride solutions and cathodic reservoirs containing 0.4 M aqueous sodium chloride solutions (ie, sodium chloride as a model drug salt). The cathodic reservoirs were buffered to pH 3 or 4 using histidine, a positively charged buffer in the form of the chloride salt, and the anodic reservoirs were buffered to pH 5, 6 and 7 using citric acid, a negatively charged buffer in the form of its sodium salt. All reservoir compositions contained about 3% by weight hydroxyethylcellulose (HEC) and q.s. water. Either HCl or NaOH were added q.s. to achieve the desired pH.

In this set of experiments, the electrotransport was conducted on the inner arm of human volunteers. A custom electrotransport device was designed with an on-board power source, a current controlling electrical circuit and a waterproof backing material to permit patient bathing. The device had a foam housing which was adhered to the patients' skin throughout the experiment. The housing had cut-outs which held the anodic and cathodic reservoir gels. The skin contact area of the electrode reservoir gels (ie, both the anodic gel and the cathodic gel) were each approximately 2 cm^2, and the reservoir gel volume was about 250 μL. The anodic electrode was silver foil and the cathodic electrode was silver chloride (ie, silver foil treated with HCl to form a surface layer of AgCl). The electrodes were connected to the DC power source which delivered a constant current of 0.1 mA, resulting in an applied constant current density of about 50 μA/cm^2. A fresh set of anode and cathode gels were worn for about 24 hours, after which time the electrodes were disconnected and the gels removed from the adhered (ie, to the skin) foam housing. Skin irritation and

resistance measurements were taken and then a fresh set of anode and cathode gels were inserted into the housing. This schedule of wearing/measurement and gel replacement was repeated 3 times for a total wearing time of about 72 hours.

Figures 17 and 18 illustrate plots of the skin irritation as a function of time for both the skin sites in contact with the anodic reservoir and the cathodic reservoir, respectively.

Having thus generally described the invention and described in detail certain preferred embodiments thereof, it will be readily apparent that various modifications to the invention may be made by workers skilled in the art without departing from the scope of this invention, which is limited only by the following claims.

CLAIMS

1. An electrotransport device (10) for delivering an agent through a body surface, comprising a cathodic reservoir (16 or 18) and an anodic reservoir (16 or 18), each of said reservoirs (16, 18) being adapted to be placed in ion-transmitting relation with a body surface, one of said reservoirs (16, 18) containing the agent to be delivered, and a source of electrical power (24) which can apply a voltage across the anodic and cathodic reservoirs (16, 18) in order to deliver a predetermined level of electric current therethrough and through said body surface; wherein during electrotransport agent delivery,

(a) said anodic reservoir is maintained at a pH above about 4; and/or

(b) said cathodic reservoir is maintained at a pH below about 4.

2. The device of claim 1, wherein the anodic reservoir pH is maintained within the range of about 4 to 10.

3. The device of claim 1 or 2, wherein said anodic reservoir is buffered.

4. The device of claim 3, wherein said buffer is an anionic buffer.

5. The device of claim 4, wherein said anionic buffer is selected from the group consisting of histidine, lysine, arginine, aspartic acid, glutamic acid, cysteine, tyrosine and combinations thereof.

6. The device of claim 3, wherein said anodic reservoir is buffered with:

(a) a buffer selected from the group consisting of aspartic acid, glutamic acid, citric acid, succinic acid, phosphoric acid, acetic acid,

EDTA, lactic acid, boric acid, carbonic acid, monobasic sodium phosphate, benzoic acid, tartaric acid, maleic acid, fumaric acid, sulfuric acid, formic acid, malic acid, malonic acid, glutaric acid, and adipic acid;

(b) a buffer selected from the group consisting of tromethamine, triethanolamine, imidazole, ammonia, ethanolamine, diethanolamine, histidine, lysine, and arginine;

(c) a buffer selected from the group consisting of calcium chloride dihydrate, triethanolamine hydrochloride, magnesium chloride heptahydrate, diethanolamine hydrochloride, ammonium chloride, ethanolamine hydrochloride, potassium chloride, and sodium chloride;

(d) a zwitterionic buffer selected from the group consisting of 2-(N-morpholino)-ethane sulfonic acid, 1,4-piperazine-bis-(ethanesulfonic acid), N-2-acetamido iminodiacetic acid, N-2(2-acetamido)-2-aminoethane sulfonic acid, N,N-bis(2-hydroxyethyl)-2-aminoethane sulfonic acid, 2-(N-morpholino)-propane sulfonic acid, N-tris hydroxymethyl) methyl-2-aminoethane sulfonic acid, N-2-hydroxyethyl piperazine-N'-2-ethane sulfonic acid, 4-(2-hydroxyethyl)-1-piperazine propane sulfonic acid, N-tris(hydroxymethyl) methyl-2-aminopropane sulfonic acid, 2-cyclohexylamino-1-ethane sulfonic acid, 3-cyclohexylamino-1-propanesulfonic acid and mixtures thereof; or

(e) a polymeric buffer selected from the group consisting of polyacrylic acid, polymethacrylic acid, poly(styrene maleic anhydride), methacrylic/divinyl benzene copolymers, poly(2-acrylamido-2-methylpropane sulfonate), copolymers of acrylic acid and long chain acrylate esters, and poly(methylvinyl ether-maleic acid).

7. The device of claim 1, wherein the cathodic reservoir pH is maintained in the range of about 2 to 4.

8. The device of claim 1 or 7, wherein the cathodic reservoir is buffered.

9. The device of claim 7, wherein said cathodic reservoir is buffered with a cationic buffer.

10. The device claim 9, wherein said cationic buffer is selected from the group consisting of histidine, lysine, arginine, aspartic acid, glutamic acid, cysteine, tyrosine, and combinations thereof.

11. The device of claim 9, wherein said cathodic reservoir is buffered with:

(a) a buffer selected from the group consisting of aspartic acid, glutamic acid, citric acid, succinic acid, phosphoric acid, acetic acid, EDTA, lactic acid, succinic acid, phosphoric acid, acetic acid, EDTA, lactic acid, benzoic acid, tartaric acid, maleic acid, fumaric acid, sulfuric acid, formic acid, malic acid, malonic acid, glutaric acid, and adipic acid; or

(b) a polymeric buffer selected from the group consisting of vinylpyrrolidone/quaternized dimethylaminoethylmethacrylate copolymers, vinylcaprolactam/vinylpyrrolidone/dimethylamino ethylmethacrylate terpolymers, polyvinylpyrrolidone, and methacrylate/divinyl benzene copolymers.

12. The device of claim 1, including a secondary electrode in communication with:

(a) the anodic reservoir, said secondary electrode being comprised of a material which can be reversibly oxidized and reduced and means for operating the secondary electrode to maintain the anodic reservoir pH above about 4; or

(b) the cathodic reservoir, said secondary electrode being comprised of a material which can be reversibly oxidized and reduced and means for operating the secondary electrode to maintain the cathodic reservoir pH below about 4.

13. The device of claim 1, including a potassium sensor for sensing the potassium content in the cathodic reservoir.

14. The device of claim 13, including a means for altering the operation of the device when the potassium sensor senses a predetermined level of potassium efflux from the body surface into the cathodic reservoir.

15. The device of claim 1, wherein:

(a) the cathodic reservoir contains the agent to be delivered and the anodic reservoir is maintained at a pH above about 4; or

(b) the anodic reservoir contains the agent to be delivered and the cathodic reservoir is maintained at a pH below about 4.

16. The device of claim 1, said device having an effect selected from the group consisting of lowering electrical resistance of the body surface during the electrotransport agent delivery, lessening irritation to the body surface caused by the electrotransport agent delivery, lessening erythema to the body surface caused by the electrotransport agent delivery, lessening damage to the body surface caused by the electrotransport agent delivery, and combinations thereof.

17. A method of delivering an agent by electrotransport through a body surface, said method including placing an anodic reservoir (16 or 18) and a cathodic reservoir (16 or 18) of an electrotransport agent delivery device (10) in ion-transmitting relation with said body surface, at least one of the reservoirs (16, 18) containing the agent to be delivered, applying an electrical potential across the anodic and cathodic reservoirs (16, 18) in order to deliver the agent through the body surface by electrotransport; and during said electrotransport agent delivery

(a) maintaining the anodic reservoir at a pH above about 4; and/or

(b) maintaining the cathodic reservoir at a pH below about 4.

18. The method of claim 17, wherein the anodic reservoir pH is maintained within the range of about 4 to 10.

19. The method of claim 17 or 18, further comprising buffering said anodic reservoir.

20. The method of claim 19, wherein said anodic reservoir is buffered with an anionic buffer.

21. The method of claim 20, wherein said anionic buffer is selected from the group consisting of histidine, lysine, arginine, aspartic acid, glutamic acid, cysteine, tyrosine, and combinations thereof.

22. The method of claim 19, wherein said anodic reservoir is buffered with:

(a) a buffer selected from the group consisting of aspartic acid, glutamic acid, citric acid, succinic acid, phosphoric acid, acetic acid, EDTA, lactic acid, boric acid, carbonic acid, monobasic sodium phophate, benzoic acid, tartaric acid, maleic acid, fumaric acid, sulfuric acid, formic acid, malic acid, malonic acid, glutaric acid, and adipic acid;

(b) a buffer selected from the group consisting of tromethamine, triethanolamine, imidazole, ammonia, ethanolamine, diethanolamine, histidine, lysine, and arginine;

(c) a buffer selected from the group consisting of calcium chloride dihydrate, triethanolamine hydrochloride, magnesium chloride heptahydrate, diethanolamine hydrochloride, ammonium chloride, ethanolamine hydrochloride, potassium chloride, and sodium chloride; or

(d) a zwitterionic buffer selected from the group consisting of 2-(N-morpholino)-ethane sulfonic acid, 1,4-piperazine-bis-(ethanesulfonic

acid), N-2-acetamido iminodiacetic acid, N-2(2-acetamido)-2-aminoethane sulfonic acid, N,N-bis(2-hydroxyethyl)-2-aminoethane sulfonic acid, 2-(N-morpholino)-propane sulfonic acid, N-tris hydroxymethyl) methyl-2-aminoethane sulfonic acid, N-2-hydroxyethyl piperazine-N'-2-ethane sulfonic acid, 4-(2-hydroxyethyl)-1-piperazine propane sulfonic acid, N-tris(hydroxymethyl) methyl-2-aminopropane sulfonic acid, 2-cyclohexylamino-1-ethane sulfonic acid, 3-cyclohexylamino-1-propanesulfonic acid and mixtures thereof.

(e) a polymeric buffer selected from the group consisting of polyacrylic acid, polymethacrylic acid, poly(styrene maleic anhydride), methacrylic/divinyl benzene copolymers, poly(2-acrylamido-2-methylpropane sulfonate), copolymers of acrylic acid and long chain acrylate esters, and poly(methylvinyl ether-maleic acid);

23. The method of claim 17, wherein the cathodic reservoir pH is maintained in the range of about 2 to 4.

24. The method of claim 17 or 23, further comprising buffering said cathodic reservoir.

25. The method of claim 24, wherein said cathodic reservoir is buffered with a cationic buffer.

26. The method of claim 25, wherein said cationic buffer is selected from the group consisting of histidine, lysine, arginine, aspartic acid, glutamic acid, cysteine, tyrosine, and combinations thereof.

27. The method of claim 17 or 24, wherein said cathodic reservoir is buffered with:

(a) a polymeric buffer selected from the group consisting of vinylpyrrolidone/quaternized dimethylamino-ethylmethacrylate copolymers, vinylcaprolactam/vinylpyrrolidone/dimethylamino ethylmethacrylate

terpolymers, polyvinylpyrrolidone, and methacrylate/divinyl benzene copolymers; or

(b) a buffer selected from the group consisting of aspartic acid, glutamic acid, citric acid, succinic acid, phosphoric acid, acetic acid, EDTA, lactic acid, benzoic acid, tartaric acid, maleic acid, fumaric acid, sulfuric acid, formic acid, malic acid, malonic acid, glutaric acid, and adipic acid.

28. The method of claim 17, including operating a secondary electrode, which secondary electrode is in communication with the anodic reservoir or the cathodic reservoir, by reversibly oxidizing and/or reducing the secondary electrode in a manner effective to maintain the pH of said reservoir in communication with the secondary electrode.

29. The method of claim 17, including sensing potassium content of the cathodic reservoir.

30. The method of claim 29, including altering the electrotransport agent delivery upon sensing a predetermined level of potassium content in the cathodic reservoir.

31. The method of claim 17, wherein:

(a) said cathodic reservoir contains the agent to be delivered and said method further comprises delivering the agent from the anodic reservoir through the body surface by electrotransport; or

(b) said anodic reservoir contains the agent to be delivered and said method further comprises delivering the agent from the cathodic reservoir through the body surface by electrotransport.

32. The method of claim 17, said method having an effect selected from the group consisting of lowering electrical resistance of the body surface during the electrotransport agent delivery, lessening irritation to the

body surface caused by the electrotransport agent delivery, lessening erythema to the body surface caused by the electrotransport agent delivery, lessening damage to the body surface caused by the electrotransport agent delivery, and combinations thereof.

33. In an electrotransport delivery device (10) having an anodic electrode assembly (12, 16 or 14, 18), a cathodic electrode assembly (12, 16 or 14, 18), a source of electrical power (24) electrically connected to the electrode assemblies and an agent reservoir (16, 18) in at least one of the electrode assemblies, the improvement comprising a potassium sensor in said cathodic electrode assembly, and means for altering operation of the device when the potassium sensor senses a parameter selected from the group consisting of (i) a predetermined potassium content in the cathodic electrode assembly and (ii) a predetermined rate of change of potassium content in the cathodic electrode assembly.

34. The device of claim 33, wherein said means for altering the operation of the delivery device comprises a means for reducing a level of electric current applied by the device.

35. The device of claim 34, wherein the means for reducing reduces the applied electric current to substantially zero.

36. The device of claim 33, including means for emitting a signal when the potassium content in the cathodic electrode assembly reaches said predetermined value.

37. The device of claim 33, including means for emitting a signal when the rate of change of potassium content reaches said predetermined value.

38. The device of claim 33, wherein the potassium sensor comprises a potassium sensing electrode.

39. In a method of operating an electrotransport delivery device which delivers an agent by electrotransport through a skin site, the device having an anodic electrode assembly, a cathodic electrode assembly, a source of electrical power electrically connected to the electrode assemblies and an agent reservoir in at least one of the electrode assemblies, the improvement comprising;

monitoring potassium efflux from the skin site during electrotransport agent delivery; and

altering operation of the delivery device when the potassium efflux reaches a predetermined value.

40. The method of claim 39, wherein said altering of the operation of the delivery device comprises reducing a level of electric current applied by the device.

41. The method of claim 39, wherein the applied electric current is reduced to substantially zero.

42. The method of claim 39, wherein said altering of the operation of the delivery device comprises emitting a signal.

43. The method of claim 39, wherein said altering of the operation of the delivery device includes removing said delivery device from the skin site and reapplying the device to another skin site.

44. The method of claim 39, wherein said altering of the operation of the delivery device includes removing said delivery device from the skin site and thereafter delivering the agent by electrotransport through another skin site.

45. The method of claim 39, including monitoring the potassium content in the cathodic electrode assembly.

46. The method of claim 45, wherein the potassium content is monitored by a sensor.

FIG. 1

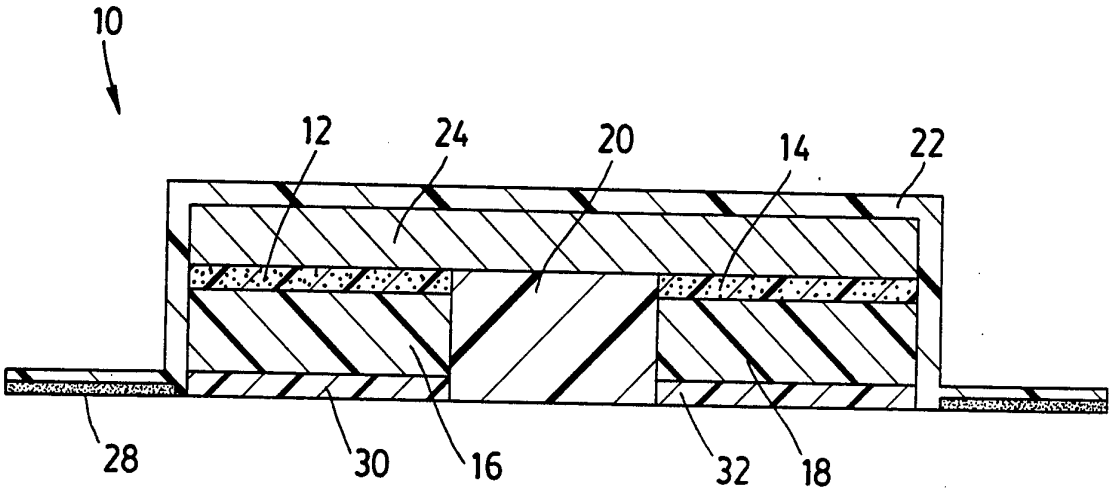


FIG. 2

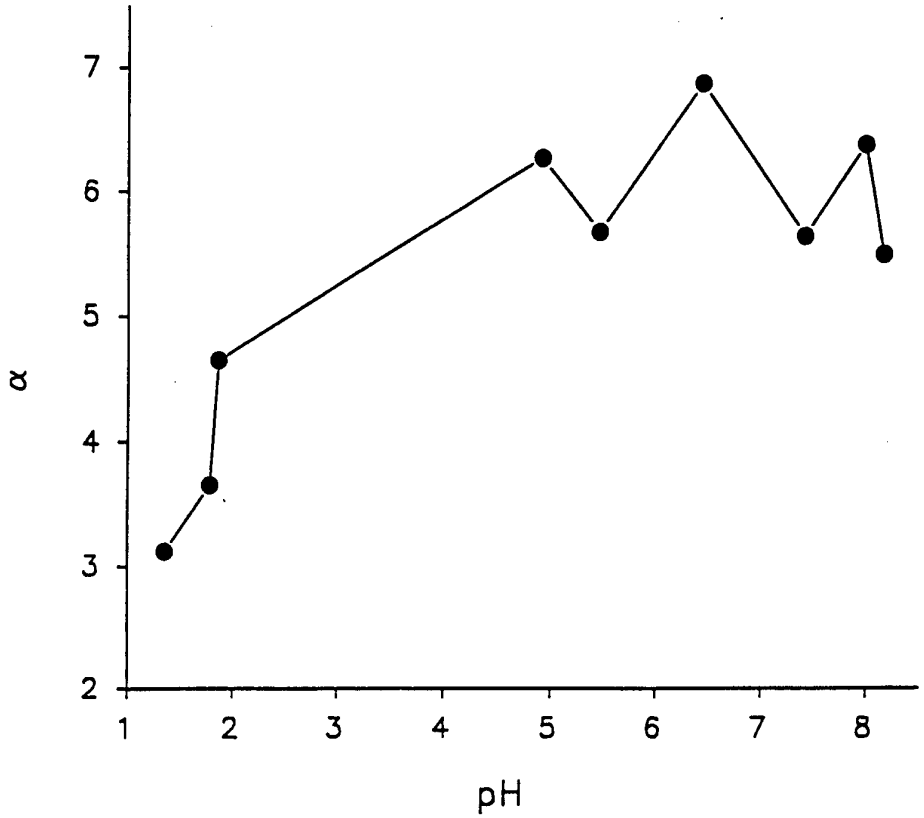


FIG. 3

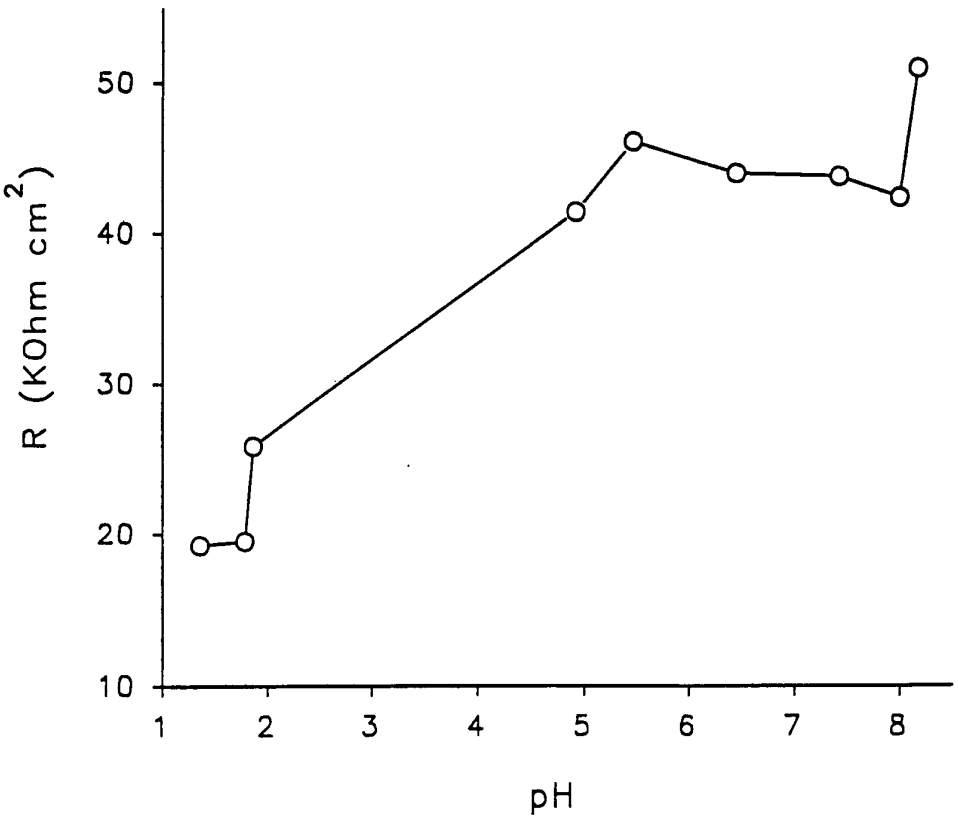


FIG. 4

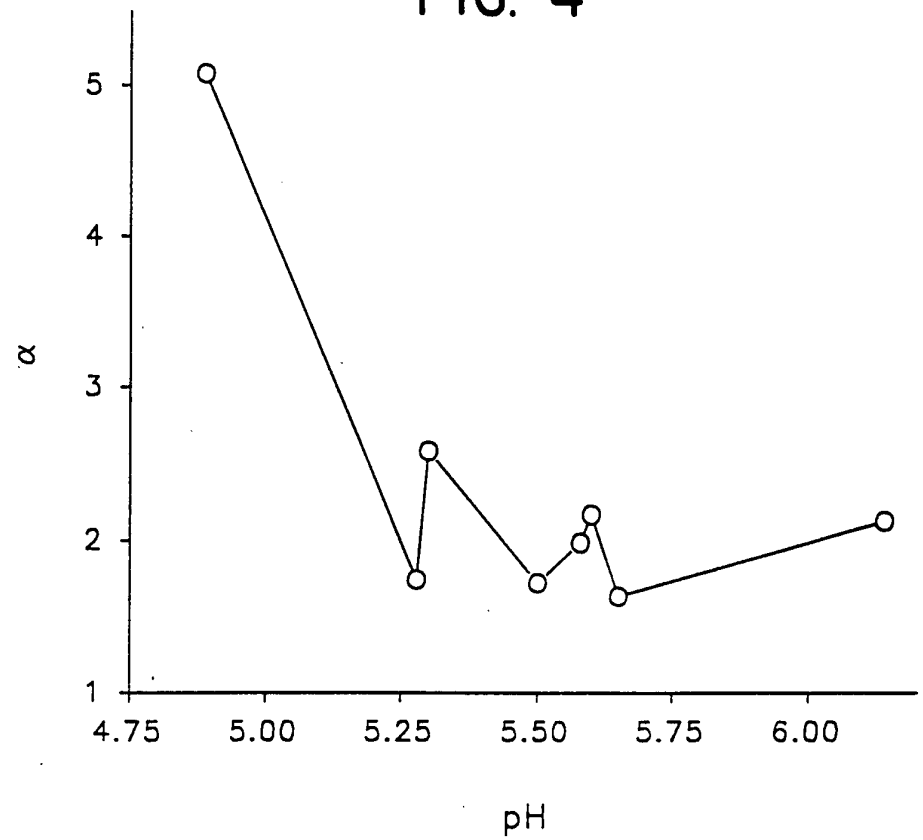

α
5
4
3
2
1
4.75
5.00
5.25
5.50
5.75
6.00
pH

FIG. 5

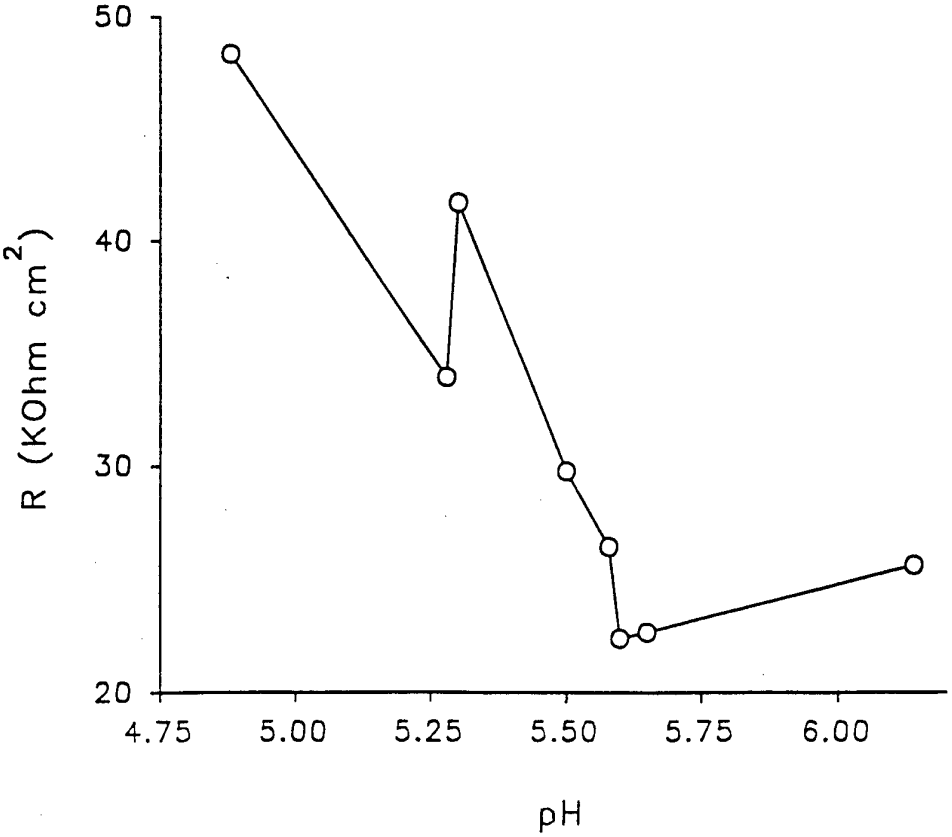

R (KOhm cm²)
50
40
30
20
4.75
5.00
5.25
5.50
5.75
6.00
pH

FIG. 6

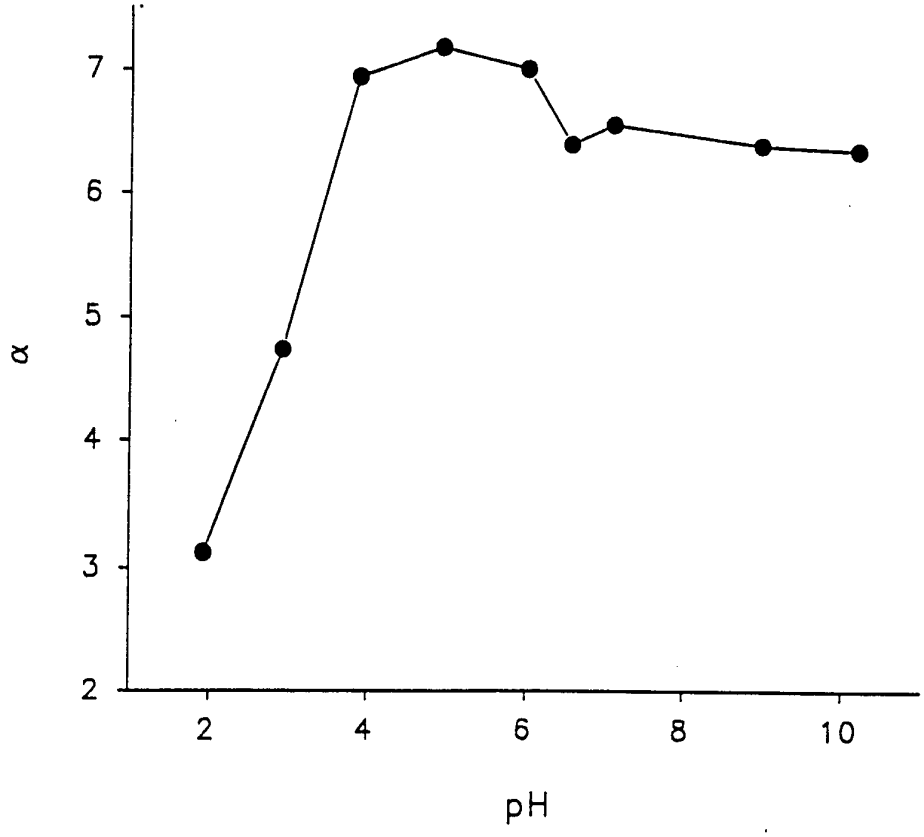


FIG. 7

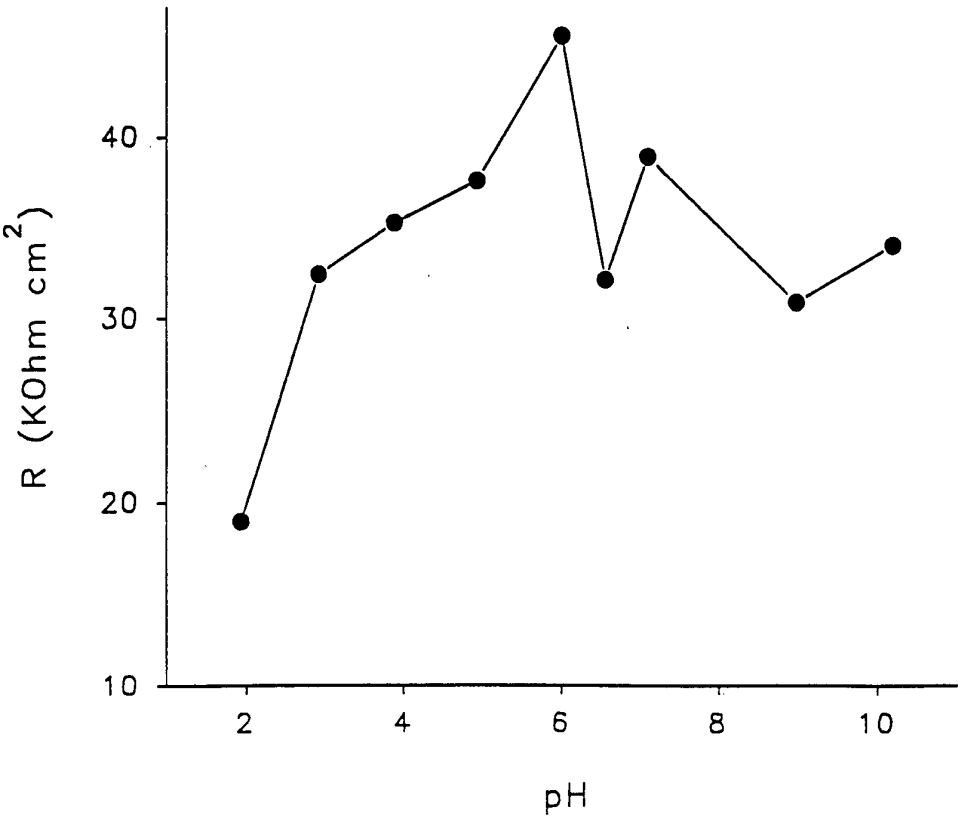


FIG. 8

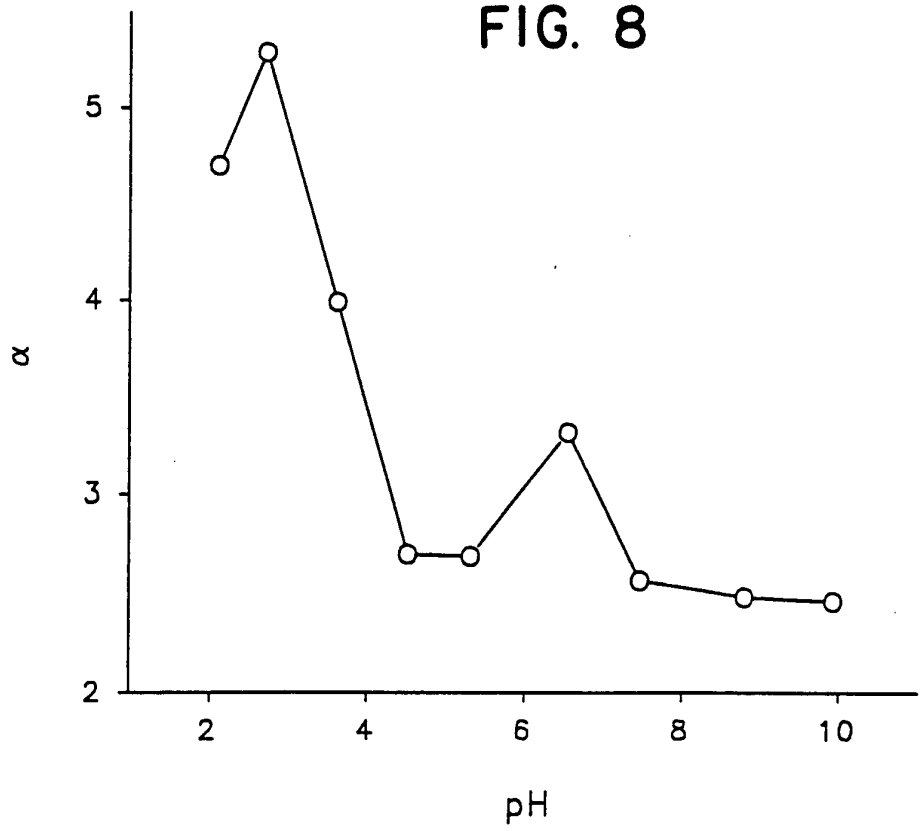


FIG. 9

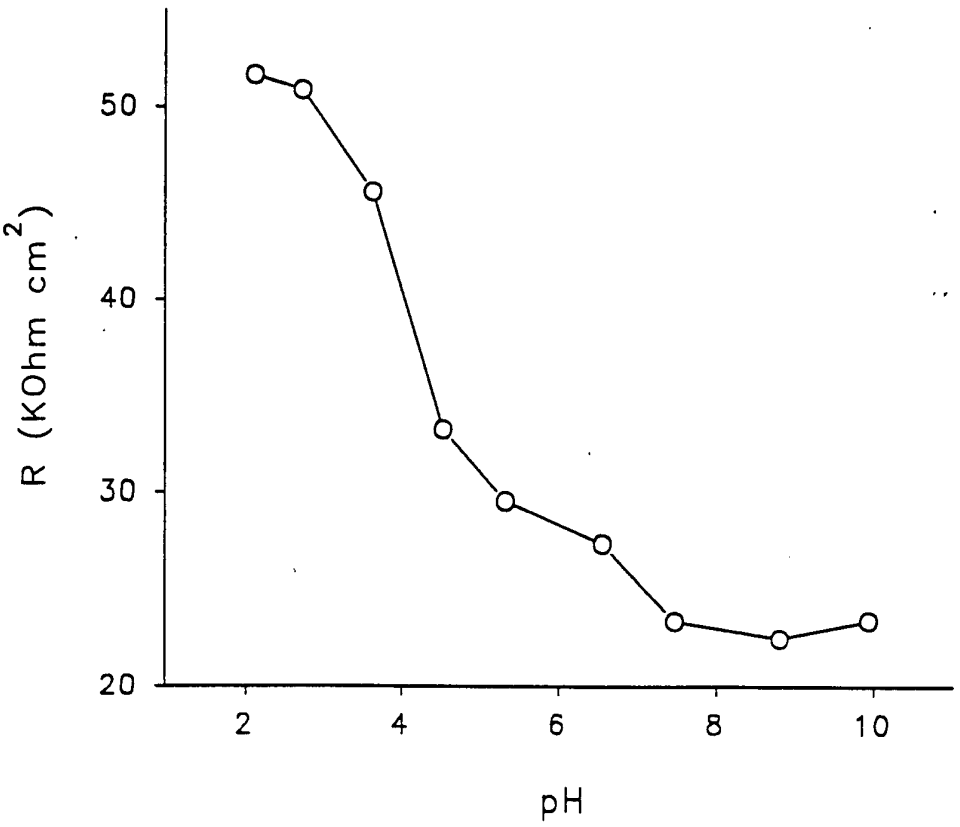


FIG. 10

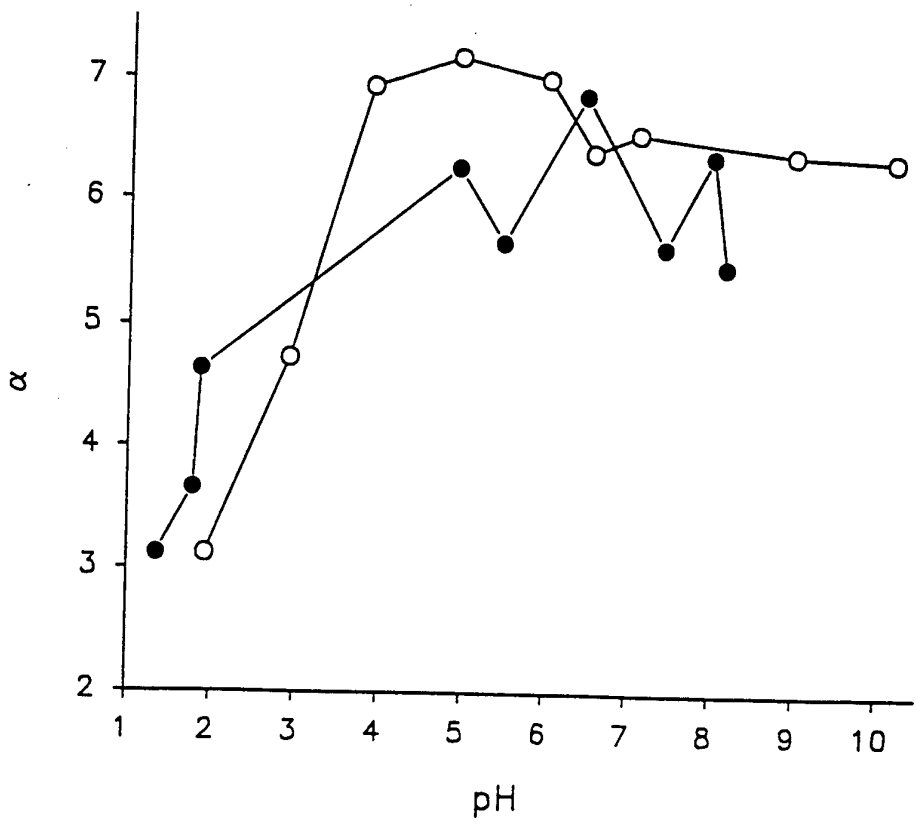


FIG. 11

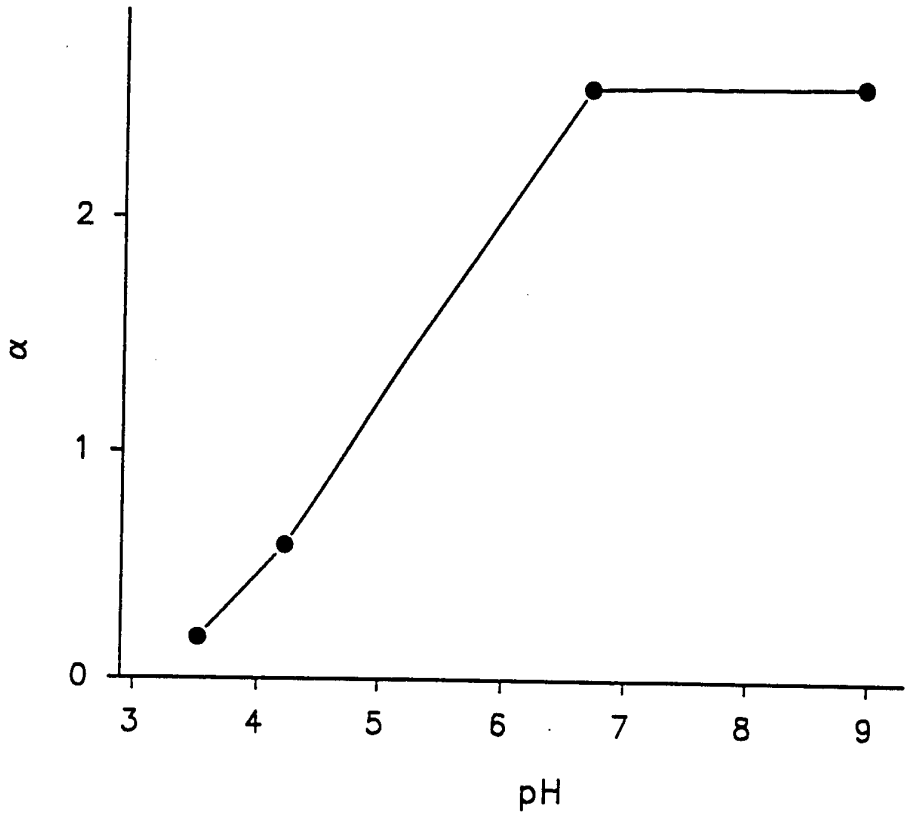


FIG. 12

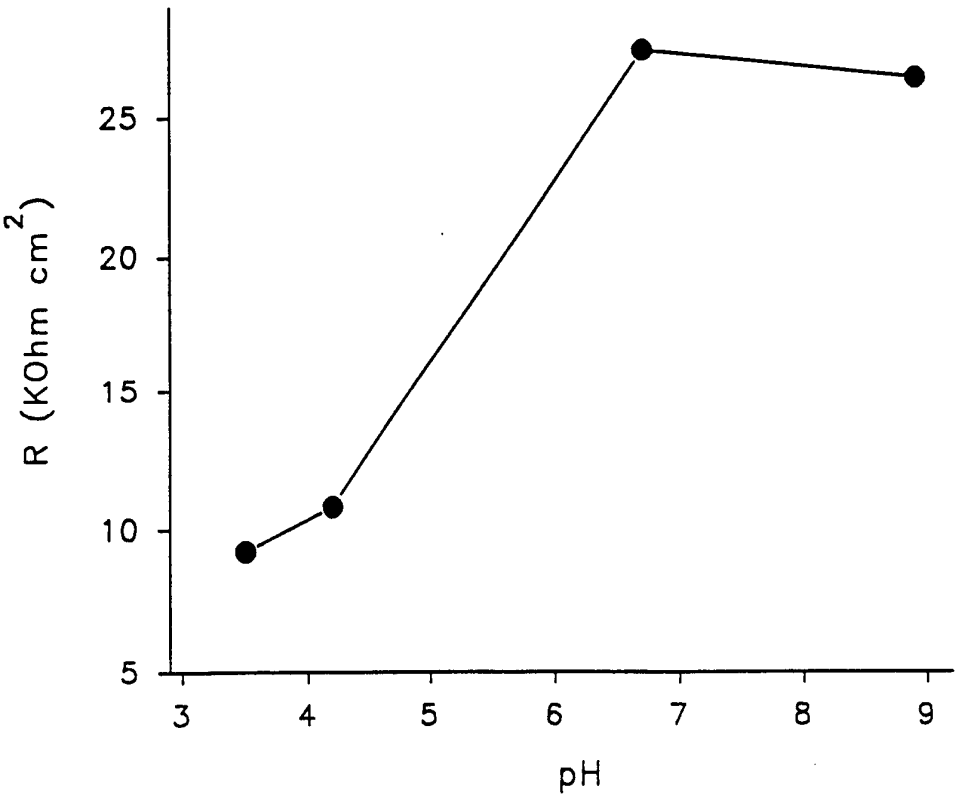


FIG. 13

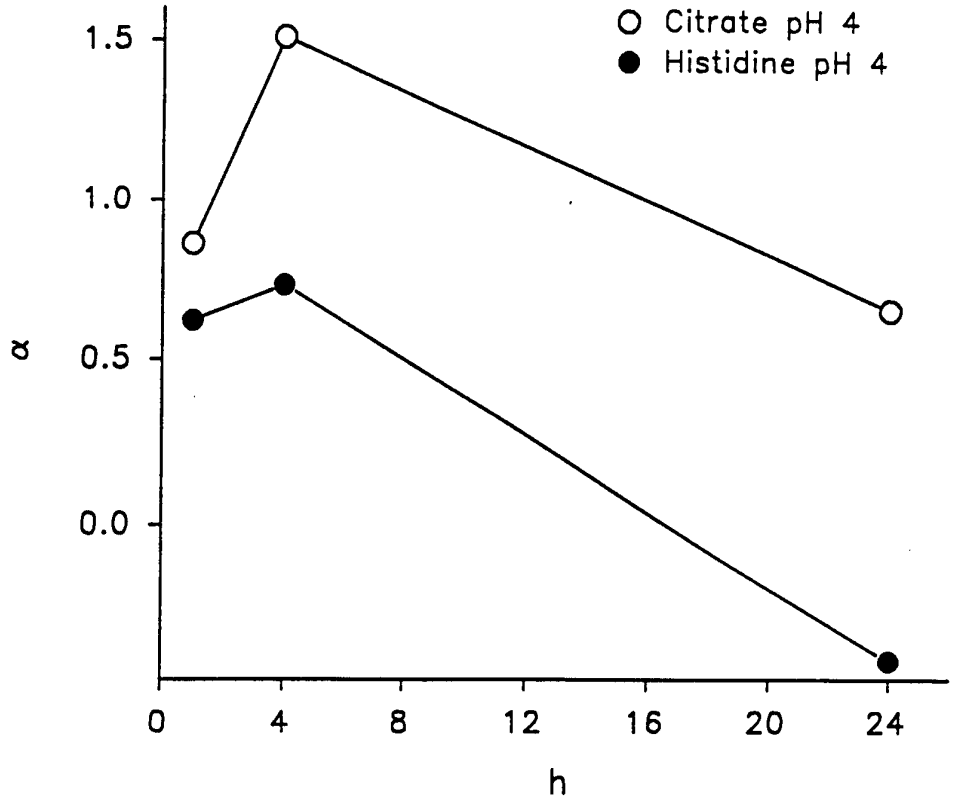

Citrate pH 4
Histidine pH 4
1.5
1.0
0.5
0.0
α
0
4
8
12
16
20
24
h

FIG. 14

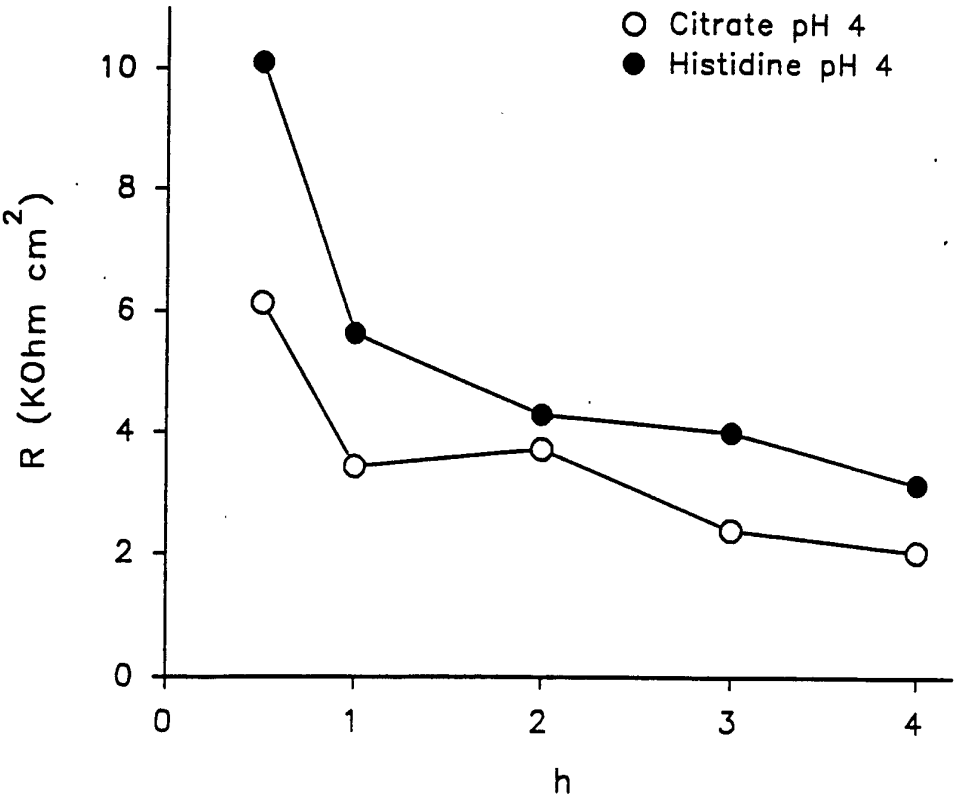

Citrate pH 4
Histidine pH 4
10
8
6
4
2
0
R (KOhm cm^2)
0
1
2
3
4
h

FIG. 15

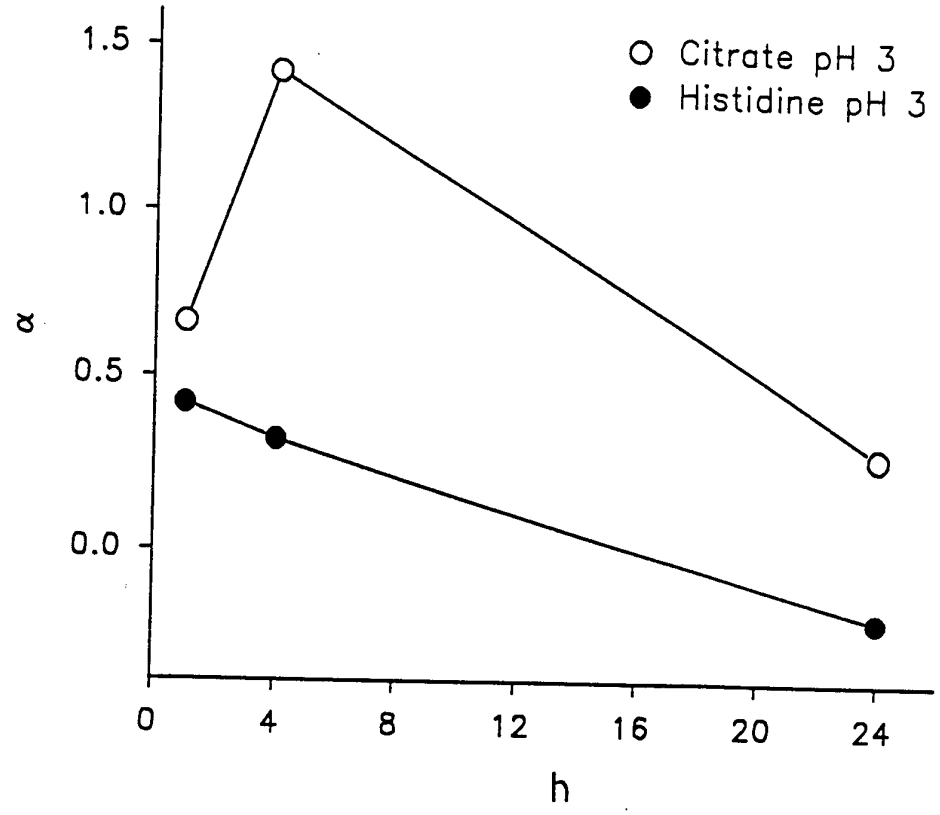

1.5
1.0
0.5
0.0
α
0
4
8
12
16
20
24
h
Citrate pH 3
Histidine pH 3

FIG. 16

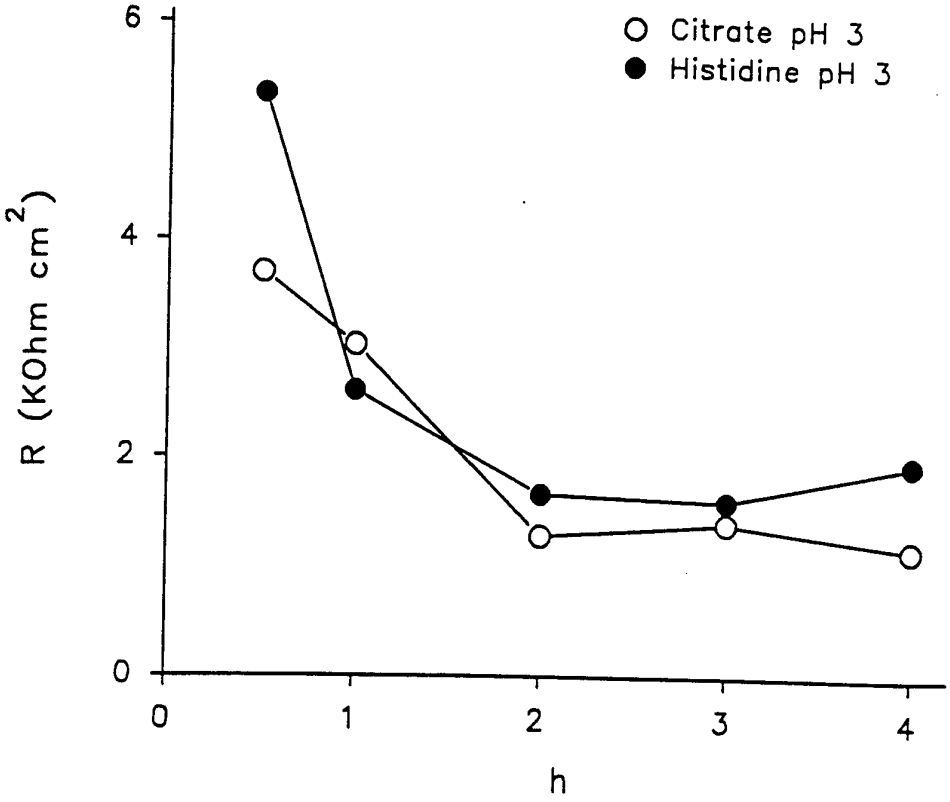

6
4
2
0
R (KOhm cm^2)
0
1
2
3
4
h
Citrate pH 3
Histidine pH 3

FIG. 17

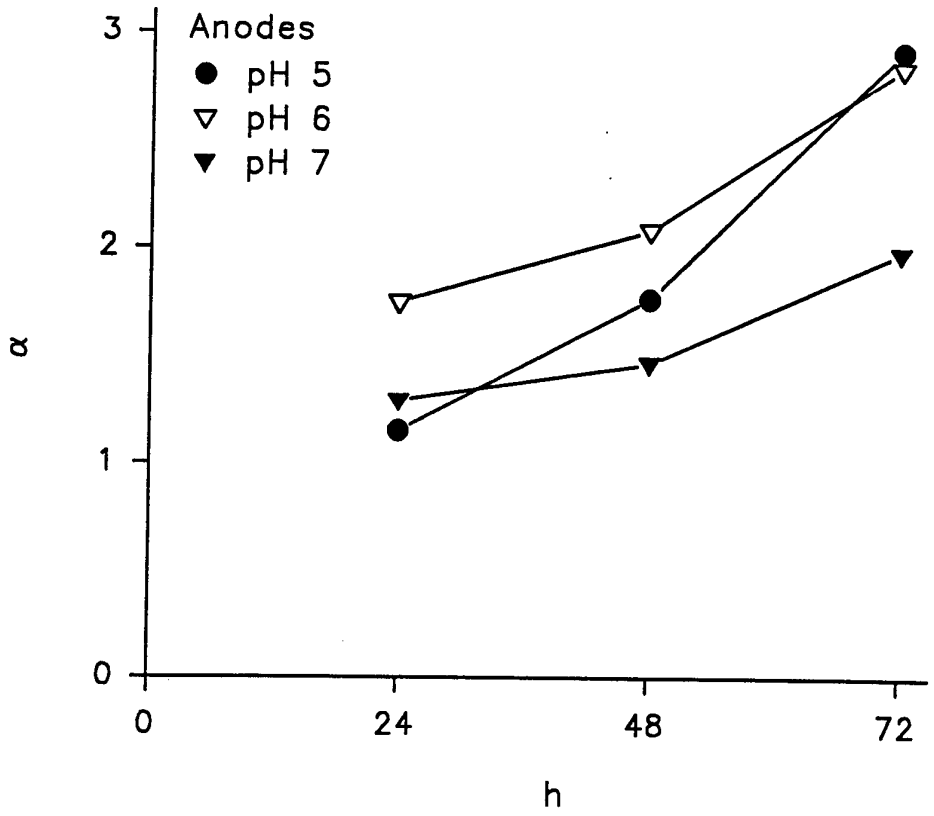
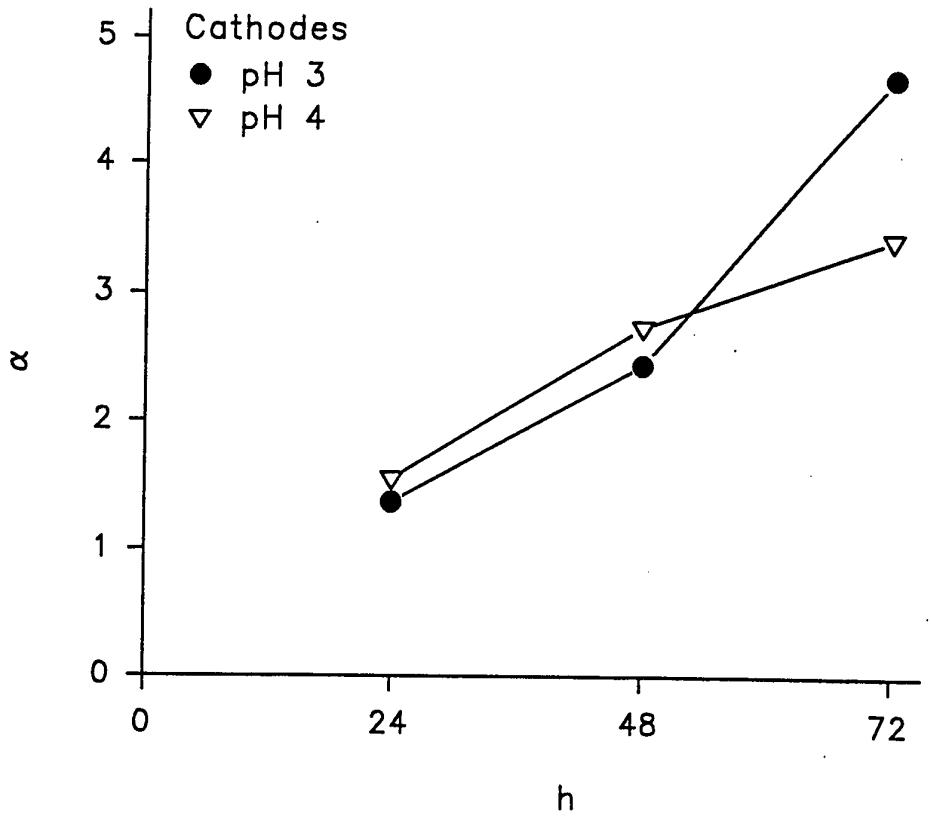


FIG. 18



INTERNATIONAL SEARCH REPORT

International Application No PCT/US 94/10054

A. CLASSIFICATION OF SUBJECT MATTER

A 61 N 1/30

According to International Patent Classification (IPC) or to both national classification and IPC 6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 N

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A, 91/11 215 (GENSIA) 08 August 1991 (08.08.91), page 5, lines 24-37; page 9, lines 1-31; claims 1,3,4,9-11.	1
A	--	6-8, 15,17, 21,22
A	WO, A, 93/03 790 (RUTGERS) 04 March 1993 (04.03.93), fig. 1; page 54, lines 25-35; page 58, lines 35-41; page 59, lines 35-41.	1,4,6, 11
X	-- US, A, 5 088 978	1

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1994	03. 02. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	ZAWODSKY et al.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	(HILLMAN) 18 February 1992 (18.02.92), column 3, lines 33-54; column 5, lines 36-68; column 5, lines 37-68 (cited in the application).	
A	--	6,11
A	US, A, 5 125 894 (PHIPPS) 30 June 1992 (30.06.92), abstract; fig. 2,3; column 2, line 53 - column 4, line 6; column 5, lines 5-39; column 9, lines 1-12; column 13, lines 11-47; column 22, lines 13-31; column 27, lines 1-35; column 28, lines 20-66; column 32, lines 39-44; column 33, lines 53-60.	1,6, 10-13, 22,28, 30,33, 39
	--	
A	EP, A, 0 278 473 (DRUG DELIVERY SYSTEMS) 17 August 1988 (17.08.88), page 4, lines 38-43; page 7, table 1; page 8, lines 34-44; page 13, lines 11-29; fig. 1.	1,5,6, 10,11, 21

ANHANG — ANNEX — ANNEXE

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

to the International Search Report to the International Patent Application No.

au rapport de recherche international relatif á la demande de brevet international n°

PCT/US 9410054 SAE 97557

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les reseignements fournis sont donnés á titre indicatif et n'engagent pas la responsibilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9111215	08-08-91	AU A1 73193/91	21-08-91
		AU B2 645541	20-01-94
		CA AA 2074091	27-07-91
		EP A1 512065	11-11-92
		EP A4 512065	30-12-92
		FI A 923375	24-07-92
		FI AO 923375	24-07-92
		JP T2 5503454	10-06-93
		NO A 922919	23-07-92
		NO AO 922919	23-07-92
		NZ A 236777	27-09-93
		US A 5088978	18-02-92
WO A1 9303790	04-03-93	AU A1 25632/92	16-03-93
		EP A1 604504	06-07-94
US A 5088978	18-02-92	AU A1 73193/91	21-08-91
		AU B2 645541	20-01-94
		CA AA 2074091	27-07-91
		EP A1 512065	11-11-92
		EP A4 512065	30-12-92
		FI A 923375	24-07-92
		FI AO 923375	24-07-92
		JP T2 5503454	10-06-93
		NO A 922919	23-07-92
		NO AO 922919	23-07-92
		NZ A 236777	27-09-93
		WO A1 9111215	08-08-91
US A 5125894	30-06-92	keine - none - rien	
EP A1 278473	17-08-88	AT E 79036	15-08-92
		AU A1 10986/88	11-08-88
		AU B2 609769	09-05-91
		CA A1 1319608	29-06-93
		DE CO 3873366	10-09-92
		DE T2 3873366	10-12-92
		EP B1 278473	05-08-92
		ES T3 2033349	16-03-93
		JP A2 63200774	19-08-88
		US A 4940456	10-07-90