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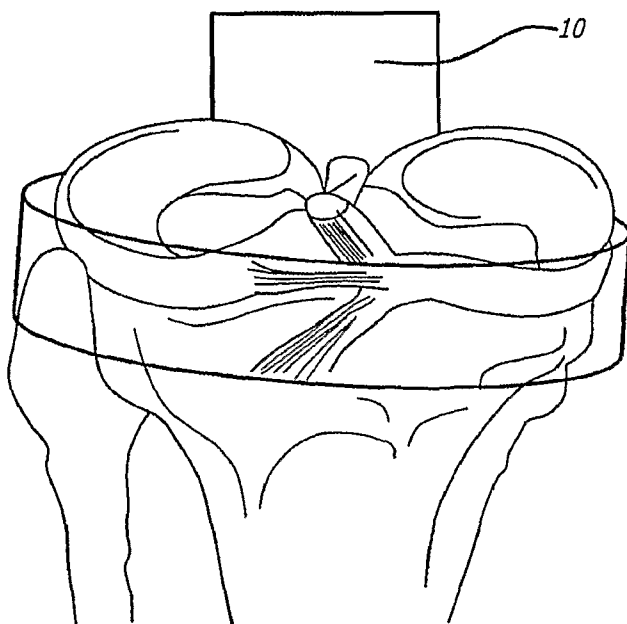
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(54) Title: STIMULATING GALVANIC OR SLOW AC CURRENT FOR THERAPEUTIC PHYSIOLOGICAL EFFECTS



(57) Abstract: Systems, devices and methods for the therapeutic use of currents are disclosed. Direct electrical current is conducted through the skin of a body being treated, the electrical current is periodically reversed and the current is conducted through the skin in the opposite direction, to effectively deliver very low frequency AC current, substantially in the critical range of approximately 0.0027 Hz to 20 Hz.

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STIMULATING GALVANIC OR SLOW AC CURRENT FOR THERAPEUTIC PHYSIOLOGICAL EFFECTS

[0001] The present disclosure relates generally to improvements in electrotherapeutic systems and, more particularly, to stimulating galvanic or slow AC current for therapeutic physiological effects.

Cross-References to Related Applications

[0002] This application is claiming the benefit of U.S. Provisional Application No. 60/772,762 filed February 13, 2006 and U.S. Patent Application Serial No. 11/651,931 filed on January 10, 2007. The following documents are incorporated herein by reference: United States Publication No. US 2005/0192528 A1, Publication Date September 1, 2005 entitled METHODS, APPARATUS AND CHARGED CHEMICALS FOR CONTROL OF IONS, MOLECULES OR ELECTRONS; United States Patent Publication No. US 2006/0025714 A1, Publication Date February 2, 2006 entitled METHODS, APPARATUS AND CHARGED CHEMICALS FOR CONTROL OF IONS, MOLECULES OR ELECTRONS; United States Letters Patent No. 5,224,927 issued July 6, 1993 entitled IONTOPHORETIC TREATMENT SYSTEM and United States Letters Patent No. 4,340,047 issued July 20, 1982 entitled IONTOPHORETIC TREATMENT APPARATUS. These four documents are enclosed with the present application as appendices.

Background

[0003] Medical galvanism or slow AC current has different application and effects compared to iontophoretic devices which are intended to infuse ionic medication or drugs and is wholly dependent on the polarity at that moment. The galvanic current causes vasomotor stimulation of the skin and increased local blood circulation and nutrition of the parts between the electrodes irrespective of polarity. The generally accepted explanation of the therapeutic effect is that the improvement of blood circulation speeds up resorption of inflammatory products, reflex stimulation or relief of pressure and relieves pain. In addition, local and general function may be appreciably stimulated. The galvanic current has proven clinically useful in a number of acute and chronic inflammatory conditions, such as: (1) selected cases of arthritis

and rheumatic conditions, neuritis and neuralgia, mostly in the chronic stage; (2) selected cases of traumatism, contusions, sprains, myositis, both in the acute and in the chronic stage.

[0004] Accordingly, there has been a long existing need for improved electrotherapeutic stimulating systems.

Summary

[0005] Basically, the present disclosure is directed to a new and improved system for the therapeutic use of currents which includes conducting direct electrical current through the skin of a body being treated, and periodically reversing the electrical current and conducting the current through the skin in the opposite direction, to effectively deliver very low frequency AC current, substantially in the critical range of approximately 0.0027 Hz to 20 Hz. It has been discovered that, within this substantially critical frequency window between approximately six minutes per full cycle and approximately ten cycles per second, a dramatic cancellation of skin damaging ions takes place. At frequencies higher than approximately 20 Hz, the effect is to diminish its DC-like blood stimulation. At frequencies lower than approximately 0.0027 Hz, the risk of skin injury increases substantially. It is well known that the positive electrode unfortunately produces skin damaging hydrochloric acid. Likewise, the negative electrode unfortunately also produces skin damaging sodium hydroxide. However, within the aforementioned frequency range of the present disclosure, either polarity stimulates blood circulation, but also cancels the undesired skin damaging ions with the reverse portion of the electrical cycle. The reason for neutralization of the harsh injury producing chemicals, i.e., hydrochloric acid and sodium hydroxide, is that both of these chemicals require a finite period of time on the skin to cause damage. Hence, these damaging chemicals are made to cancel each other before damage takes place, by critical frequency selection, in accordance with the present disclosure, of the AC driving signal. Therefore, optimization of a long sought electrotherapeutic device with reduced side effects has been achieved. Another use of the safe AC currents cited above and/or a DC signal with charged membranes preventing injury is its application to wound healing. The conductive electrodes for these devices may take either of two forms, i.e., one may be

non-metallic carbon-filled silicone or, preferably of powdered carbon particles. A second form may be a metallic electrode preferably of aluminum, copper, zinc and/or magnesium as examples of metallic electrodes but not necessarily limited to these metals. These metals are preferably in powdered form and contained within a porous membrane with a small opening to attach a conductive lead to a battery source. Still other applications of the innovative use in electrotherapy of charged membranes and/or powdered metal electrodes is its use for drug delivery and diagnostic purposes. For instance, a membrane enclosed stainless steel powdered negative electrode may be used in the pickup probe for glucose detection. Charged membranes would surround the probe as an intervenor between skin and the electrode.

[0006] These and other objects and advantages of the present disclosure will become apparent from the following more detailed description, when taken in conjunction with the accompanying drawings of an illustrative embodiment.

Brief Description of the Drawings

[0007] Figure 1 is an internal perspective view of an osteoarthritic knee with the system of the present disclosure installed for treatment;

[0008] Figure 2 is an external perspective of a treatment pad/ electrode held against the skin of the subject by a support sock;

[0009] Figure 3 is a perspective view of the electronic components installed on the treatment subject; and

[0010] Figures 4-1 through 4-9 are an electrical schematic of circuitry suitable for practice of the present disclosure.

Detailed Description

[0011] Investigations have shown that a galvanic treatment of sufficient intensity exerts vasomotor stimulation lasting for several hours. Since the effect at each pole is about the same, no special attention has to be paid to the direction of current flow or polarity. This therefore, equates to a very slow AC signal which while behaving like DC, does not have its problems. The value of an AC signal over DC is apparent when

one considers that a DC signal will develop skin injury producing chemicals. The positive pole sends hydrochloric acid to the skin causing irritation and the negative pole sends sodium hydroxide to the skin causing burns and possible permanent scarring. With the use of a slow AC signal at a frequency slow enough to mimic the DC therapeutic effect, the unwanted acid and alkaline chemicals are neutralized. Another innovation which makes a DC signal usable without the aforementioned skin injury problems is the use of charged membranes, such as those described in the aforescribed applications, to prevent the hydrochloric acid ions and the sodium hydroxide ions from reaching the skin. The charged membranes are placed between the electrode and the skin and also act as a water reservoir for electrical conductivity between these two points. Another preventative of skin injury in a DC device would be to use aluminum powder on the positive electrode and stainless steel on the negative electrode. A typical use for the system using either a slow AC or DC signal would be for relief of pain of an osteoarthritic knee joint. Literature indicates a patient with this problem lacks a normal blood flow in this area leading to loss of cartilage with resulting pain. Application of this device with either current and with the aforementioned protective charged membranes will restore blood flow, reduce pain and not incur skin injury. Other applications would be treatments of carpal tunnel syndrome, wound healing, decubitus ulcers, tremors, diabetic feet and any other problems that would benefit from increased blood circulation. The conductive electrodes for these devices may take either of two forms, i.e., one may be non-metallic carbon-filled silicone or, preferably of powdered carbon particles. A second form may be a metallic electrode preferably of aluminum, copper, zinc and/or magnesium as examples of metallic electrodes but not necessarily limited to these metals. These metals are preferably in powdered form and in a mixture with a saline gel.

[0012] The present disclosure includes shock and pain prevention which may be further enhanced by slow ramp up and/or down of the applied electrical current (e.g., see U.S. Patent No. 4,340,047), and/or a new and improved system for the therapeutic use of currents which includes conducting direct electrical current through the skin of a subject being treated, and periodically reversing the electrical current and conducting the current through the skin in the opposite direction, to effectively deliver

very low frequency AC current, substantially in the critical range of approximately 0.0027 Hz to 20 Hz. It has been discovered that, within this substantially critical frequency window between approximately six minutes per full cycle and approximately ten cycles per second, a dramatic cancellation of skin damaging ions takes place. At frequencies higher than approximately 20 Hz, the effect is to diminish its DC-like blood stimulation. At frequencies lower than approximately 0.0027 Hz, the risk of skin injury increases substantially. It is well known that the positive electrode unfortunately produces skin damaging hydrochloric acid. Likewise, the negative electrode unfortunately also produces skin damaging sodium hydroxide. However, within the aforementioned frequency range of the present disclosure, either polarity stimulates blood circulation, but also cancels the undesired skin damaging ions with the reverse portion of the electrical cycle. The reason for neutralization of the harsh injury producing chemicals, i.e., hydrochloric acid and sodium hydroxide, is that both of these chemicals require a finite period of time on the skin to cause damage. Hence, these damaging chemicals are made to cancel each other before damage takes place, by critical frequency selection, in accordance with the invention, of the AC driving signal. Therefore, optimization of a long sought electrotherapeutic device with reduced side effects has been achieved. Another use of the safe AC currents cited above and/or a DC signal with charged membranes preventing injury is its application to wound healing. The conductive electrodes for these devices may take either of two forms, i.e., one may be non-metallic carbon-filled silicone or, preferably of powdered carbon particles. A second form may be a metallic electrode preferably of aluminum, copper, zinc and/or magnesium as examples of metallic electrodes but not necessarily limited to these metals. These metals are preferably in powdered form and contained within a porous membrane with a small opening to attach a conductive lead to a battery source. The powdered electrodes are desirably mixed with a saline gel. Still other applications of the innovative use in electrotherapy of charged membranes and/or powdered metal electrodes is its use for drug delivery and diagnostic purposes. For instance, a membrane enclosed stainless steel powdered negative electrode may be used in the pickup probe for glucose detection. Charged membranes would surround the probe as an intervenor between skin and the electrode.

[0013] The AC frequency may even be used for enhanced iontophoretic (drug delivery) purposes with the use of charged membranes or metal powder electrodes is included to prevent injury.

[0014] The DC unit of the present disclosure may also be used for drug delivery with novel protection against skin injury by the metal powders or charged membranes described above.

[0015] Fig. 1 shows wetted felt pads 10 between electrodes and skin to treat cartilage area.

[0016] Fig. 2 shows the treatment pad/electrode held against skin by a support sock (second pad/electrode on back of knee not shown).

[0017] Fig. 3 shows electronic components 11 and 12 mounted outside the support sock but covered by pockets (not shown). Component 11 is a flat pack 9 volt battery or the like. Component 12 is a flexible circuit board for generating an AC signal.

[0018] Figures 4-1 through 4-9 are an electric schematic for operating the system electronics.

[0019] Briefly, a new and improved system for the therapeutic use of currents which includes conducting direct electrical current through the skin of a body being treated, and periodically reversing the electrical current and conducting the current through the skin in the opposite direction, to effectively deliver very low frequency AC current, substantially in the critical range of approximately 0.0027 Hz to 20 Hz. It has been discovered that, within this substantially critical frequency window between approximately six minutes per full cycle and approximately ten cycles per second, a dramatic cancellation of skin damaging ions takes place. At frequencies higher than approximately 20 Hz, the effect is to diminish its DC-like blood stimulation. At frequencies lower than approximately 0.0027 Hz, the risk of skin injury increases substantially. It is well known that the positive electrode unfortunately produces skin damaging hydrochloric acid. Likewise, the negative electrode unfortunately also produces skin damaging sodium hydroxide. However, within the aforementioned frequency range of the present invention, either polarity stimulates blood circulation,

but also cancels the undesired skin damaging ions with the reverse portion of the electrical cycle. The reason for neutralization of the harsh injury producing chemicals, i.e., hydrochloric acid and sodium hydroxide, is that both of these chemicals require a finite period of time on the skin to cause damage. Hence, these damaging chemicals are made to cancel each other before damage takes place, by critical frequency selection, in accordance with the invention, of the AC driving signal. Therefore, optimization of a long sought electrotherapeutic device with reduced side effects has been achieved. Another use of the safe AC currents cited above and/or a DC signal with charged membranes preventing injury is its application to wound healing. The conductive electrodes for these devices may take either of two forms, i.e., one may be non-metallic carbon-filled silicone or, preferably of powdered carbon particles. A second form may be a metallic electrode preferably of aluminum, copper, zinc and/or magnesium as examples of metallic electrodes but not necessarily limited to these metals. These metals are preferably in powdered form and contained within a porous membrane with a small opening to attach a conductive lead to a battery source. Still other applications of the innovative use in electrotherapy of charged membranes and/or powdered metal electrodes is its use for drug delivery and diagnostic purposes. For instance, a membrane enclosed stainless steel powdered negative electrode may be used in the pickup probe for glucose detection. Charged membranes would surround the probe as an intervenor between skin and the electrode.

[0020] Thus, improvements in therapeutic systems and, more particularly, to stimulating galvanic or slow AC current for therapeutic physiological effects is described in conjunction with one or more specific embodiments. It will be apparent from the foregoing that, while particular forms of the invention have been illustrated and described, various alternatives, modifications and variations can be made without departing from the spirit and scope of the invention. Accordingly, the invention is intended to embrace all such alternatives, modifications and variations and it is not intended that the invention be limited, except as by the appended claims.



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Tapper(10) **Pub. No.: US 2005/0192528 A1**(43) **Pub. Date: Sep. 1, 2005**(54) **METHODS, APPARATUS AND CHARGED
CHEMICALS FOR CONTROL OF IONS,
MOLECULES OR ELECTRONS**on Feb. 9, 2004. Provisional application No. 60/593,
030, filed on Jul. 29, 2004.(76) **Inventor: Robert Tapper, Los Angeles, CA (US)****Publication Classification**Correspondence Address:
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424/65**(21) **Appl. No.: 11/029,904**(22) **Filed: Jan. 4, 2005****Related U.S. Application Data**(60) **Provisional application No. 60/535,470, filed on Jan.
8, 2004. Provisional application No. 60/543,446, filed**(57) **ABSTRACT**

A system including methods, apparatus, components and charged chemicals for control of ions, molecules or electrons whereby charged membranes, testing devices, electrode patch structures and the like utilize features of the invention for control of flow in a wide variety of new and improved medical, testing, cosmetic, personal care, flow delivery applications and the like.

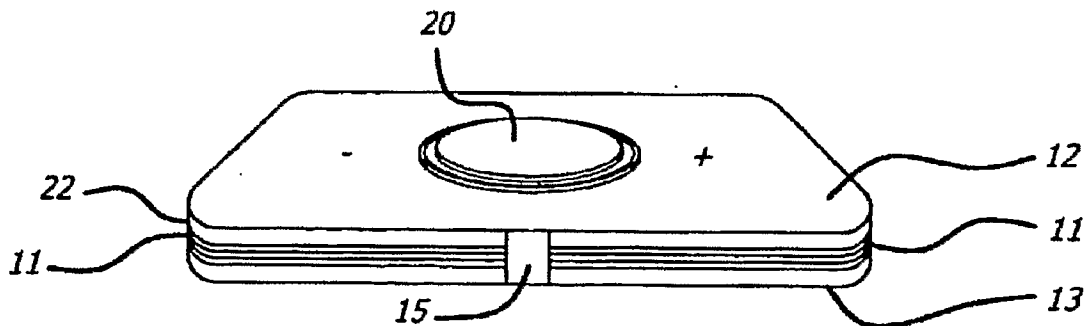


FIG. 1

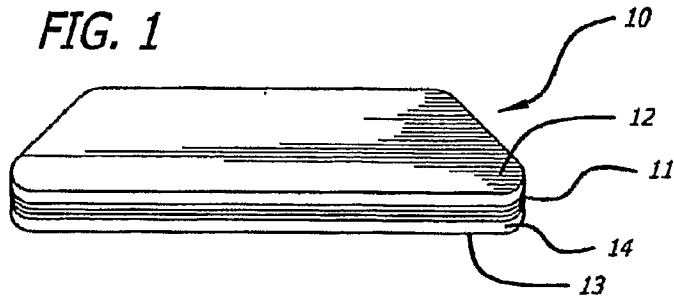


FIG. 2

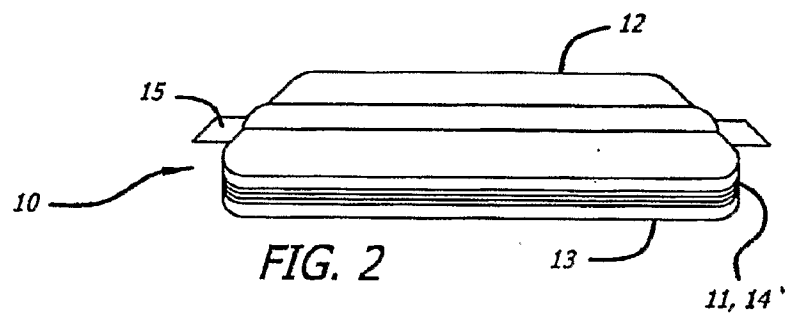


FIG. 3

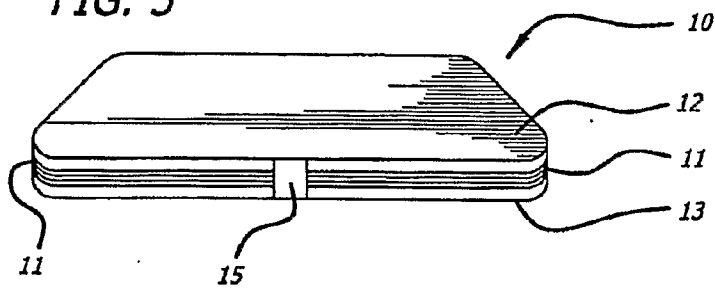


FIG. 4

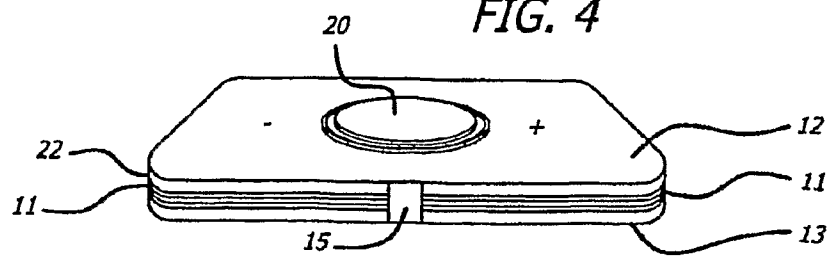


FIG. 5

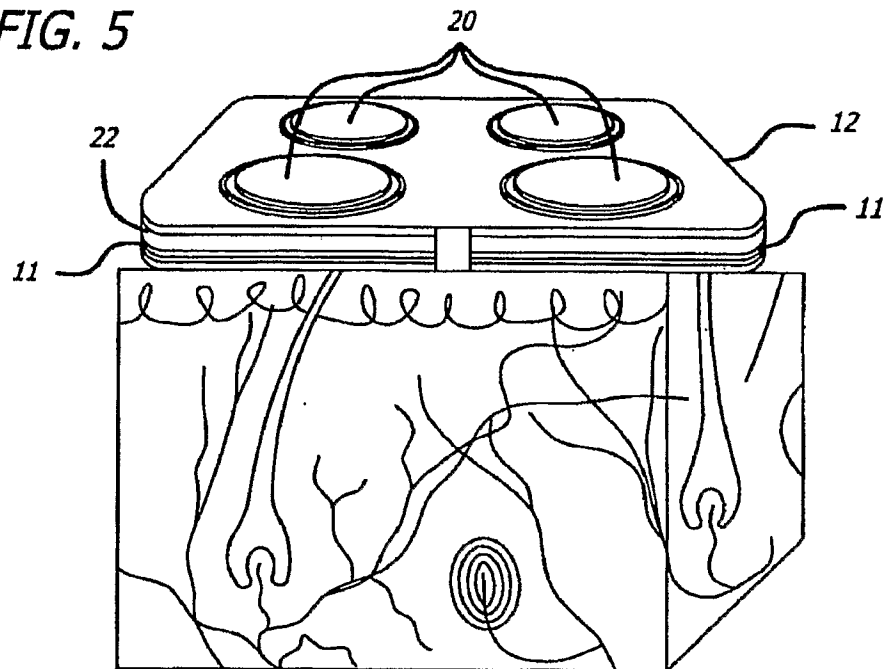


FIG. 5a

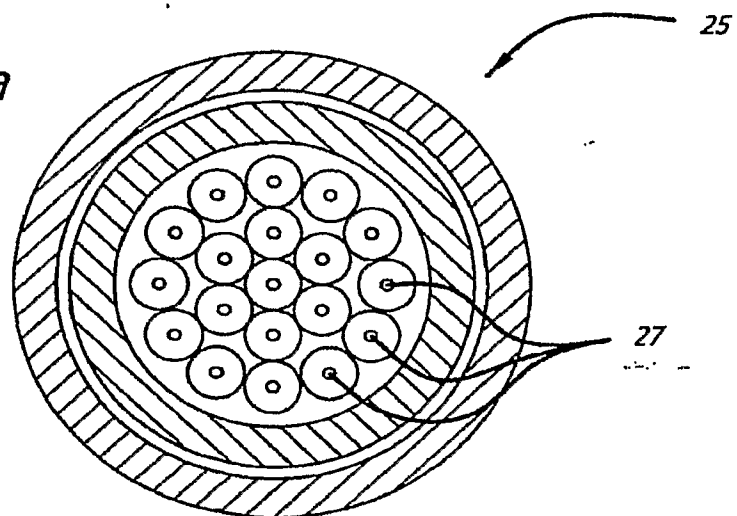


FIG. 6a

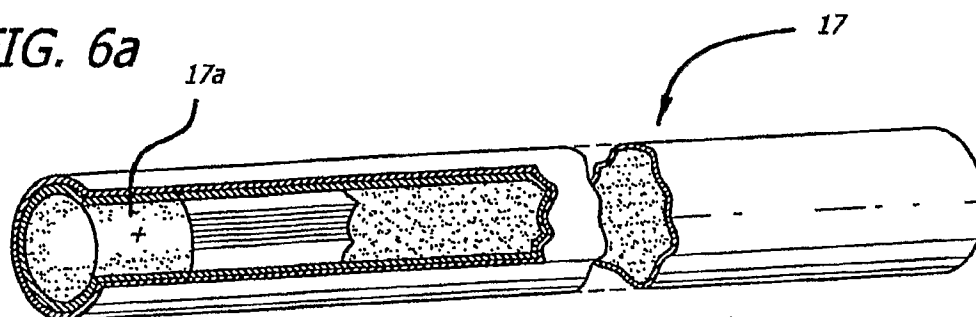


FIG. 6b

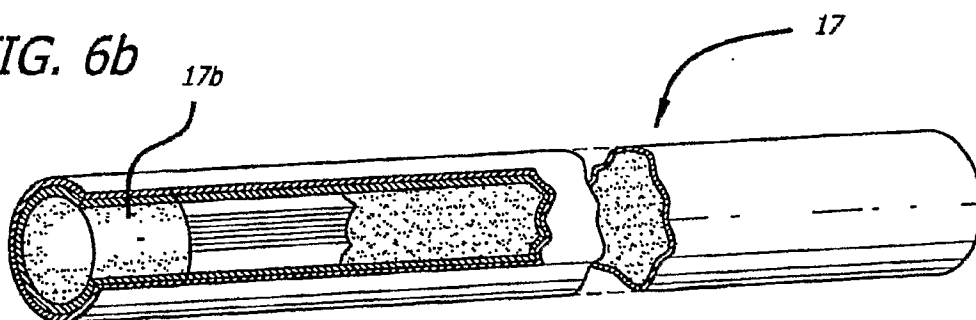
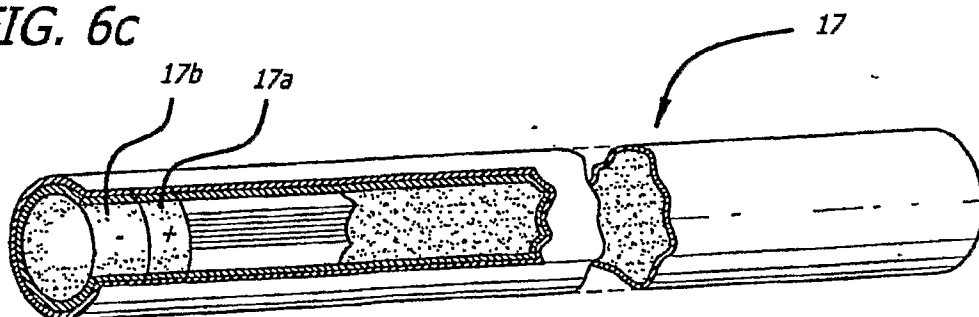
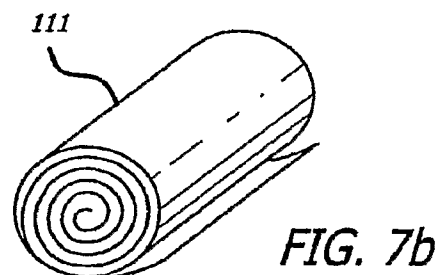
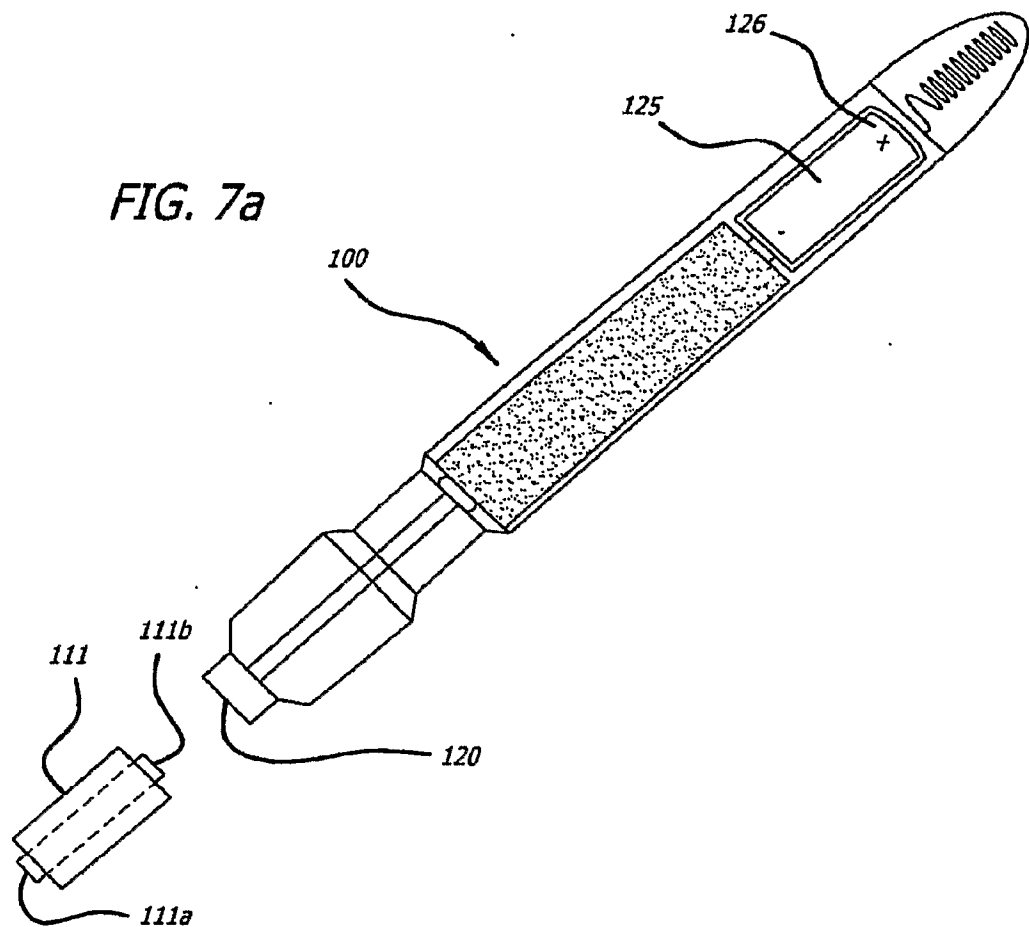


FIG. 6c





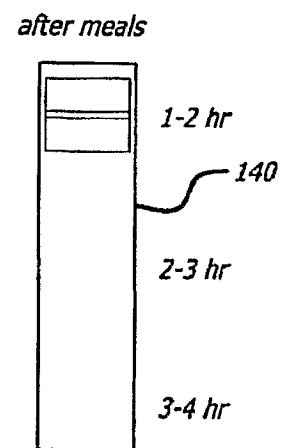
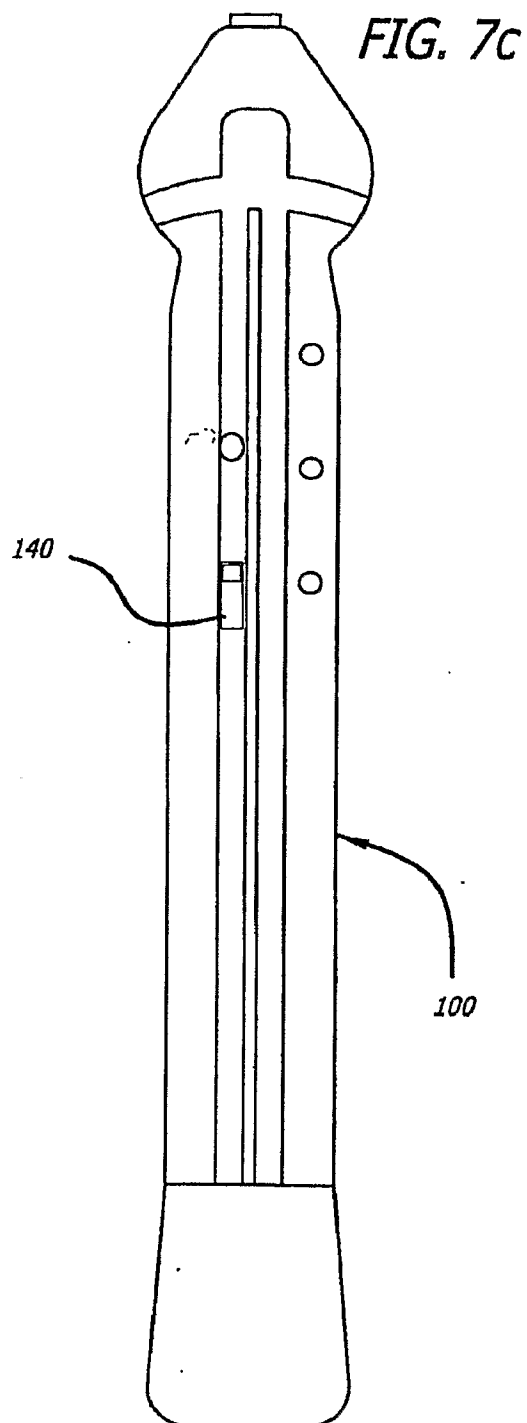


FIG. 7d

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METHODS, APPARATUS AND CHARGED CHEMICALS FOR CONTROL OF IONS, MOLECULES OR ELECTRONS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is claiming the benefit of a co-pending provisional application Ser. No. 60/535,470 filed on Jan. 8, 2004, co-pending Ser. No. 60/543,446 filed on Feb. 9, 2004 and co-pending Ser. No. 60/593,030 filed on Jul. 29, 2004. The material of the related provisional applications are incorporated by reference herein.

FIELD OF THE INVENTION

[0002] This invention relates generally to methods and apparatus pertaining to charged particles flow and, more particularly, to improvements in methods, apparatus, systems and materials for control of flow and level of ions, molecules, or electrons using charged chemicals and any/all applications thereof.

BACKGROUND OF THE INVENTION

[0003] Typical drug delivery systems range from small particulate carriers through passive patches to sophisticated iontophoretic propulsion delivery systems. Ideally, they attempt to deliver beneath the skin beneficial chemicals or drugs in the largest controlled amounts, in the shortest time, up to the largest molecular size and without chemically caused skin injury or microneedle puncture. No commercially available product can do all of this today. Accordingly, those of ordinary skill in the art have long recognized the need for improvements in these areas, and the present invention fulfills all of these needs.

INVENTION SUMMARY

[0004] Basically, the present invention satisfies the aforementioned needs with improvements in methods, apparatus, components and chemistry including the use of charged chemicals of either polarity or both as chemically integral surfaces on support membranes or equivalent support materials such as felt or like materials made of natural or synthetic fibers or impregnated filter paper or other materials in a drug delivery or diagnostic withdrawal system. The charged chemicals may also be used without a support structure. They allow multiple hybridizations that could include a neutral charge among other effects. Examples of these membranes manufactured by Pall Corporation of 25 Harbor Park Drive, Port Washington, N.Y. 11050 are Mustang S, Mustang Q, Mustang C and Biodyne A, Biodyne B and Biodyne C. The Mustang series are of special interest with Mustang S giving a strong negative polarity with its surface modified by sulfonic acid. Mustang Q gives a strong positive polarity with its surface modified by quaternary amine. It should be understood that the chemicals cited are for example only and are not the only chemicals that can polarize support structures or control ion or molecule flow without a support structure. For instance, Mustang C is polarized with carboxylic acid. Other examples of functional groups that can bear a charge would be the hydroxyl, phosphate moieties. A unique feature of the invention is the use of charged or polarized chemicals on support members or not, to control a flux, current, or signal of polarized

molecules, ions or electrons and even polar neutral compounds as in an electroosmotic withdrawal system and a drug delivery system.

[0005] The invention is contemplated, in its various forms and applications as including the following and other features:

[0006] 1) The use of charged chemicals of either negative or positive polarity on support members that could include a) membranes, b) felt pads made of natural or synthetic fibers, c) impregnated filter paper, d) liquid form, e) any material that allows charged chemicals to control ions, molecules or electrons;

[0007] 2) The use of charged chemicals of either negative or positive polarity formulated with an increased concentration of the charged chemicals causing either negative or positive polarity to increase their effectiveness;

[0008] 3) For use in a DC iontophoretic drug delivery system, the presence of charged chemicals in solution as an integral part of a felt pad(s) or a membrane(s) to prevent: a) injurious chemicals emanating from the electrode from reaching the skin, b) sodium hydroxide developed at the negative terminal is prevented from reaching the skin with either a negatively charged or positively charged intervenor between the skin and the electrode in an electrically conductive circuit, c) hydrochloric acid generated at the positive electrode can be prevented from reaching the skin with either positively charged or negatively charged chemicals on an appropriate support intervenor spaced between the electrode and the skin in an electrically conductive system;

[0009] 4) The chemically charged intervenor(s) acting as a reservoir or storage area for the drug to be delivered;

[0010] 5) In iontophoresis or reverse iontophoresis or drug delivery or similar chemical or drug transport system, the use of currents above the traditional 0.5 ma per cm². The aforementioned charged chemicals either on support structure or without support structure, enable these high currents to be achieved. Large molecular delivery also benefits from high electrical current along with Tapper U.S. Pat. Nos. 6,238,381 and 6,425,891;

[0011] 6) In a powered patch, electrical currents can be further increased by a new physical configuration of the active, drug delivery applicator. High density current can be tolerated when multiple small circles of current emitting membranes are clustered instead of one large flat delivery surface;

[0012] 7) The use of the aforementioned charged chemicals of both negative and positive polarity together or separately to meet all objectives of these inventions;

[0013] 8) The use of charged chemicals on an intervenor or in combination with both polarities in an AC iontophoretic device;

[0014] 9) The use of histamines in the positive applicator to lessen the pain from this applicator and allow an increase in current;

[0015] 10) The use of charged membrane(s) in an otherwise unpowered patch (passive patch) to propel the drug(s) into the skin at greatly increased levels compared to other unpowered patches;

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[0016] 11) The use of charged membrane(s) in an unpowered patch as a storage area or reservoir for drugs.

[0017] 12) The use of charged membrane(s) of either polarity or in combination to increase infusion in an otherwise unpowered patch;

[0018] 13) The use of charged membranes between skin and output electrode as the conductive element when wetted with distilled water without the need of a saline solution;

[0019] 14) The use in iontophoresis or reverse iontophoresis of charged membranes between the skin and output electrode as the conductive element when wetted with distilled water as a means of avoiding clutter from conductive chemicals that may be added to enhance transport;

[0020] 15) The use of charged membrane(s) in a powered patch of either polarity or in combination as an intervenor to prevent skin injury;

[0021] 16) The use of charged membrane(s) in a powered patch of either polarity or in combination to act as a drug storage area or reservoir;

[0022] 17) The use of charged membrane(s) in a powered patch of either polarity or in combination as a reservoir and intervenor to increase currents above 0.5 ma per cm² without skin injury;

[0023] 18) In drug delivery, a small amount of glucose (0.2 mol/l) in solution with insulin can be amplified 9 times in an unpowered environment using charged membranes;

[0024] 19) Feature 18 wherein the above solution is in a powered environment will increase the signal many-fold;

[0025] 20) Feature 19 in a powered environment with the use of polarized membranes to act both to prevent skin injury and further enhance amplification;

[0026] 21) In drug delivery, any chemical or drug in a powered environment and stored in oppositely charged membrane(s) will cause amplification;

[0027] 22) Another example of drug or chemical amplification is using the phenomena of oppositely charged drugs to create recycling and thus amplification would be with glucosamine and chondroitin. Glucosamine is positive and chondroitin is negative and the two in solution with the appropriately charged membranes and in an appropriately polarized field, would benefit from amplification;

[0028] 23) The use of charged chemicals on filters in cigarettes positioned between the tobacco and the end held in the mouth to prevent the migration of deleterious tobacco chemicals from entering the mouth upon inhaling;

[0029] 24) The use of charged chemicals of either polarity or in combination on impregnated filter paper or membranes as an intervenor between tobacco and mouth to prevent polarized harmful chemicals from reaching the mouth.

[0030] 25) The use of a tobacco extract or flavor in combination with Items 23 and 24;

[0031] 26) A charged membrane of the same polarity of the tobacco extract or flavor to propel the extract or flavor into the mouth;

[0032] 27) The use of charged chemicals as an inherent part of a bandage or the like, to have an antibacterial effect when placed over a wound;

[0033] 28) The use of a chemically charged bandage or the like that comes precoated with an antiseptic or the antiseptic is added later. The charged chemicals will drive the antiseptic into the wound continuously when wetted or in gel form for communication between all elements;

[0034] 29) The use of a chemically charged bandage or the like to enhance and speed wound healing when wetted;

[0035] 30) The use of a charged chemical of negative polarity in a toothpaste containing fluoride to infuse the fluoride below the tooth's surface and gum to prevent cavities and disease;

[0036] 31) The use of a charged chemical of negative polarity as an integral part or coating of toothbrush bristles to cause the fluoride of a toothpaste to be driven or infused into the teeth or gums;

[0037] 32) The use of charged chemicals of either polarity as an additive to a germ-killing mouthwash to infuse the antiseptic into the teeth and gums;

[0038] 33) The use of a charged chemical of negative polarity to be used as an intervenor between a battery-powered iontophoretic toothbrush and the bristles to prevent injurious sodium hydroxide from the negative terminal of the battery from reaching the teeth, gums or mucous membrane;

[0039] 34) A stent coated with either positive or negative chemicals or both to cause elution and prevent restenosis.

[0040] 35) A stent with a coating of charged chemicals of either charge or both that will elute like-charged chemicals coated on top of the charged coating to prevent restenosis;

[0041] 36) A stent with a coating of charged chemicals either positively or negatively charged or both integrated with like-charged chemicals that will be propelled or eluted from the surface to prevent restenosis;

[0042] 37) A stent coated with quaternary amine, sulfonic acid or carboxyl acid or the equivalent to cause elution either with another chemical that will be driven beyond the surface or the charged coating alone to elute when surrounding tissue and body fluids come in contact;

[0043] 38) For cosmetic application, the use of charged chemicals in liquid form as a spray to be applied over a moisturizer base or any other skin conditioner. This will drive a like-charged cosmetic ingredient or skin improvement product deeper into the skin than topical application;

[0044] 39) The use of salicylic acid and/or its derivative in combination with a charged chemical to limit its travel beneath the skin and thus prevent irritation;

[0045] 40) The use of positively charged salicylic acid in combination with negatively charged sulfonic acid or carboxyl acid or the like to bind to each other and thus limit migration of the salicylic acid beneath the epidermis;

[0046] 41) The use of salicylic acid as a skin spray as part of a two component system wherein a negatively charged spray follows;

[0047] 42) Salicylic acid's pH buffered from three to four to a nonirritating pH of approximately five and infused into the skin by a like-charged chemical;

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[0048] 43) The use of negatively charged sodium salicylate with negatively charged chemicals to infuse the sodium salicylate into the skin for beneficial effects. The sodium salicylate and the negatively charged chemicals may be in formulation or they may be in the form of a two component system whereby the sodium salicylate is applied first as perhaps a spray and followed by a spray of negatively charged chemicals;

[0049] 44) For cosmetic and personal care application, the use of charged chemicals in formulation with like-charged skin improvement material. The repelled skin improvement materials will be infused deeper into the skin;

[0050] 45) The use of the negative and positive charges in formulation to result in a neutral charge and then mixed with the salicylic acid to limit its penetration to the epidermis;

[0051] 46) The neutral formulation of Item 45 to be used as a spray following the application of salicylic acid to limit its penetration;

[0052] 47) The use of positively charged chemicals such as quaternary amine in solution with salicylic acid to limit the depth of its penetration to the epidermis;

[0053] 48) The use of charged or neutral control chemicals in the form of a spray to be applied over the initial application of salicylic acid to limit its depth of penetration to the epidermis;

[0054] 49) In a permanent hair remover (Tapper U.S. Pat. Nos. 6,094,594 and 6,206,869) wherein a depilatory is driven into the follicle by an iontophoretic device, the use of a charged intervenor between battery and skin for the purposes of: a) to use high currents to expedite treatment, b) to use chemically charged intervenor to prevent skin injury, c) to use the chemically charged intervenor as the storage or reservoir vehicle for the depilatory;

[0055] 50) A non-invasive diagnostic withdrawal device using a charged or polarized membrane(s), one end of which is positioned to touch the skin and the other end touching the electrode;

[0056] 51) An alternate construction of Item 50 is the use of two membranes, one charged or conductive and the other nonconductive in direct contact with each other and spaced between the skin and the electrode;

[0057] 52) The use of a charged membrane and an uncharged membrane in a withdrawal system whereby the uncharged membrane is placed in contact with the skin and the charged membrane in contact with the electrode to complete the circuit.

[0058] 53) The use of a wool felt nib such as from a marker pen as the intervenor between the skin and electrode to prevent the passage of sodium hydroxide from the negative electrode from passing to the skin. The wool nib may or may not be coated with charged chemicals;

[0059] 54) The charged or polarized intervenor of Item 50 that is approximately a half-inch in length and placed between skin and electrode;

[0060] 55) The membrane of Items 50-54 between the skin and the electrode to protect against skin injury;

[0061] 56) Increasing the height of this membrane of Items 50, 41 and 55 allows the use of currents above 0.5 ma per cm²;

[0062] 57) This charged membrane intervenor of Items 50, 54, 55 and 56 allows the use of high currents above the traditional 0.5 ma/cm²;

[0063] 58) Increasing the level of charge of the aforementioned membrane(s) by higher concentrations of the polarized material improves the benefits cited above;

[0064] 59) A positively charged wetted (gel) membrane prevents skin injury by stopping the sodium hydroxide ions emitted from the negative electrode in an electrically conductive circuit;

[0065] 60) The charged membrane interposed between skin and negative terminal also stores the solution (or gel) necessary to effect communication or current flow between skin and electrode;

[0066] 61) The target withdrawn glucose analyte passes through the membrane to the end that touches the negative electrode and becomes the critical pick-up point for the glucose monitor to read. This pick-up point for the withdrawn glucose analyte is unique in that it is against the electrode and not at membrane entry point in contact with the skin;

[0067] 62) The charged membrane is constructed in a rolled form so that one side of the membrane touches the skin and the other side touches the electrode. In other words, when viewed from the skin, the withdrawn analyte sees only straight line, unbroken surfaces while migrating to the electrode;

[0068] 63) The membrane form of Item 62 that causes the withdrawn glucose analyte to flow in a straight line while migrating to the electrode;

[0069] 64) The structure of Items 62 and 63 that causes the withdrawn glucose signal deposition on the end of the membrane in direct contact with the electrode;

[0070] 65) The use of a high pH from the electrode that attracts the glucose to this point of signal deposition;

[0071] 66) The structure of Features 62, 63, 64 and 65 wherein the membrane end in contact with the electrode is the pick-up point for the withdrawn glucose which is then placed in contact with the monitor's strip for analysis or direct reading;

[0072] 67) The positive return electrode may also use charged membranes to prevent skin damage and allows toleration of higher currents;

[0073] 68) The positive return electrode of the system described above may also be used to monitor drug pharmacokinetics;

[0074] 69) A solution formulated with glucose in a solvent of distilled deionized water;

[0075] 70) The solution of Item 69 wherein the glucose must totally saturate the distilled deionized water to prevent absorption of the withdrawn glucose;

[0076] 71) The solution of Items 69 and 70 must have a surplus of glucose (distilled deionized water solvent totally saturated) with a monitor reading between 1 and 400 mg/dl or more;

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[0077] 72) Adding a small quantity of insulin to the glucose solutions of Items 69, 70 and 71, perhaps 0.3% or less, greatly increases the analyte signal or causes amplification;

[0078] 73) The solution of Items 69, 70, 71 and 72 that may include stabilizers or preservatives;

[0079] 74) Chemical amplification of the minute subpicomole withdrawn analyte takes place in the environment disclosed. When at least two differently charged substances occupy the same area, they become reagents to a signal passing through. The reagents cause recycling of the signal resulting in amplification. The charged positive membrane in the negative field acts as a reagent to the withdrawn glucose analyte and amplifies it;

[0080] 75) Another form of this would be the use of a positive and negative membrane adjacent to each other to cause recycling and therefore amplification of analyte;

[0081] 76) Amplification would take place if all the polarities cited above were reversed;

[0082] 77) Charged membranes made with higher concentration of charged chemicals will show increased amplification;

[0083] 78) More presence of charged membrane will increase the reaction and therefore increase amplification;

[0084] 79) This invention lends itself for the new technology of 'labs-on-a-chip';

[0085] 80) The electrode is a screen made of stainless steel to evenly disperse sodium hydroxide and pH;

[0086] 81) The power supply consists of a 6 volt battery with circuitry to increase the DC output voltage to 70 volts. Note: voltage may be higher or lower. A safety circuit or fail-safe circuit is included;

[0087] 82) The circuit includes a dosimetry circuit (Tapper patents) that precisely controls the analyte withdrawal quantity based on time and current;

[0088] 83) This non-invasive diagnostic device includes a calibration switch;

[0089] 84) A multi-position switch that selects the withdrawal time/current to match the highs, lows, and in-between time glucose levels of the patient caused by meals, physical exercise, or insulin dose;

[0090] 85) A multiple position switch that selectively adjusts time and current to conform with well established periods of glucose change related to meal intake (also physical exercise and insulin dose);

[0091] 86) The switch of Items 84 and 85 for following selections: Position 1 (1-2 hours after meals), Position 2 (2-3 hours after meals), and Position 3 (3-4 hours after meals);

[0092] 87) Different time/current rates are assigned to each of the three switch positions;

[0093] 88) A submultiple or multiple of the meter reading to extend range;

[0094] 89) After gross selection is made with switch according to Items 83, 84, 85, 86, 87 and 88, a precise reading is obtained when the withdrawn glucose specimen is

processed at the strip and results in a meter reading based on the glucose concentration or density in the withdrawn interstitial fluid; and

[0095] 90) An LED to indicate the precise end to the withdrawal process.

[0096] These and other objects and advantages of the invention will become apparent from the following more detailed description, when taken in conjunction with the accompanying drawings of illustrative embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0097] FIG. 1 is a perspective view of one embodiment of a passive patch construction in accordance with the present invention;

[0098] FIG. 2 is a perspective view of another passive patch constructed in accordance with the invention;

[0099] FIG. 3 is a perspective view of still another passive patch constructed in accordance with the present invention;

[0100] FIG. 4 is a perspective view of a powered patch construction in accordance with the present invention;

[0101] FIG. 5 is a perspective view of another powered patch in accordance with the present invention, shown in place upon the skin;

[0102] FIG. 5a is a perspective view

[0103] FIG. 5b is a sectional view of a drug delivery device utilizing the present invention and illustrating multiple clustered electrical current emitting membranes;

[0104] FIGS. 6a, 6b and 6c are fragmentary perspective views of filter devices embodying features of the invention;

[0105] FIG. 7 is an exploded perspective view of a diagnostic probe constructed in accordance with the present invention;

[0106] FIG. 7b is a perspective view of a rolled charged membrane embodying the present invention;

[0107] FIG. 7c is an enlarged longitudinal view of a probe including a switch and LED; and

[0108] FIG. 7d is an enlarged view of the electrical switch for the probe shown in FIG. 7c.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0109] Referring now to the drawings, wherein like reference numerals refer to like or corresponding elements throughout the various figures of the drawings, there is shown in FIG. 1 an improved passive patch 10 embodying features of the present invention. The use of this technology in its simplest form without the use of battery power would be with the commercially available passive patch 10 that is unpowered. The use of one or more polarized membranes 11 beneath a backing 12 acts to propel a drug into the skin if the polarity of the drug (or other chemical) and the membranes 11 were the same. In this instance, a liner 13 would be removed and the charged membranes 11 in communication with a drug-in-adhesive system 14 would propel the drug into the skin (not shown). Another configuration would be for the charged chemicals to be an inherent part of the drug-in-adhesion.

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[0110] As shown in FIG. 2, the charged membranes 11 also act as a reservoir for the drug 14 with adhesion of the patch 10 made by separate tape 15 or any of a variety of taping means. For the first time, an infusion system without battery, would force much greater quantities of drug (or other chemicals) into the skin. They allow multiple hybridizations that could include a neutral charge among other effects. Examples of these membranes manufactured by Pall Corporation of 25 Harbor Park Drive, Port Washington, N.Y. 11050 are Mustang S, Mustang Q, Mustang C and Biodyne A, Biodyne B and Biodyne C. The Mustang series are of special interest with Mustang S giving a strong negative polarity with its surface modified by sulfonic acid. Mustang Q gives a strong positive polarity with its surface modified by quaternary amine. It should be understood that the chemicals cited are for example only and are not the only chemicals that can polarize support structures or control ion or molecule flow without a support structure. For instance, Mustang C is polarized with carboxylic acid. Other examples of functional groups that can bear a charge would be the hydroxyl, phosphate moieties. A unique feature of the invention is the use of charged or polarized chemicals on support members or not, to control a flux, current, or signal of polarized molecules, ions or electrons and even polar neutral compounds as in an electroosmotic withdrawal system and a drug delivery system.

[0111] Referring to FIG. 3 of the drawings, a variation of the patch 10 would be for the inside of the backing 12 to be divided in half by an electrical insulator 15, such as a plastic divider, so that two different medicaments could be placed in each half—one of negative polarity and one of positive polarity with like-polarized membranes in each half to drive the drugs into the skin.

[0112] Another variation would be for the patch 10 to have a polarized membranes 11 under the backing 12 with a like-polarized drug saturating it and an opposite charged membrane 11 configured in a circle in close proximity around the inner drug bearing membrane but electrically insulated from it. Over 620 millivolts exist between polarized membranes 11 of one polarity and the skin. This value can be increased by adding more membranes 11 to the stack. It can also be increased by using charged chemicals in greater concentration. Still greater efficiency can be obtained by using charged membranes (or fells, filters, etc.) of both polarities with a membrane battery separator (not shown) in between.

[0113] Another very important application of these polarized membranes would be for wound dressing to promote wound healing or infection control. Published papers show that tissue growth is promoted when minor currents traverse the wound. Another paper attributes this growth to the anti-bacterial effect of low currents across a wound. In accordance with the invention, bacterial and fungal infection can be controlled with the electro-chemical effect of charged membranes, bandages or dressing over infected body areas.

[0114] A major problem with catheters is their propensity to cause infection at the body insertion opening. Coating or bonding charged chemicals of both polarities separated from each other onto the catheter tubing will give wide spectrum protection against bacterial infection. Medical use of this technology would be for stent coating. The charged coating (either charge or both) would have an eluting effect to

prevent restenosis. Another medical use of this technology could include microscopic drug delivery for both external and internal application.

[0115] The charged membranes can also infuse an anti-septic for enhanced control. It may also be applied with a spray of the charged chemicals, sulfonic acid or quaternary amine or both or the equivalent. An example of such an application would be to apply a treatment cream or medicament over an area and then spray the polarized chemical over it. If the beneficial formulation applied to the skin is of the same polarity as the charged material on top, the treatment formulas (skin conditioners, etc.) or medicament will be driven into the skin. A variation of this would be to mix the treatment formula of known polarity with a charged chemical of the same polarity and then apply topically to the skin. The like-charged treatment formula will be driven into the skin.

[0116] Another example of the practice of this invention is to mix a positively charged chemical with a common "over the counter" antiperspirant. The charged chemical will drive the aluminum chloride or the like deep down the eccrine sweat duct for far more effectiveness than topical application. Another form of this would be a two-component system whereby aluminum chlorhydrate antiperspirant is topically sprayed under the arm and is followed with a spray of a positively charged chemical to infuse the aluminum chlorhydrate deep within the eccrine sweat duct.

[0117] Conversely with the above applications wherein there is an effort to drive or infuse the active drug or cosmetic deeper into the skin, there are certain applications where it is desirable to limit the travel of the active components to the epidermis (outer skin). Salicylic acid is an example of this. Salicylic acid and/or its derivative is the treatment of choice for acne, psoriasis, or photoaging. Because of its low pH (3-4), positively charged salicylic acid is capable of penetrating deeply through the epidermis, dermis and receptor fluid causing irritation. To overcome this problem, the use of the negatively charged chemicals of sulfonic acid or carboxyl acid or the like as a control for the permeation of the salicylic acid is suggested. When formulated with the salicylic acid, the negatively charged ions will combine with the positively charged salicylic acid and, when properly balanced, will limit the depth of penetration of the salicylic acid to the epidermis, thus eliminating irritation. Two other combinations using charged chemicals to limit the flow of the active salicylic acid to the epidermis would be the use of the negative and positive charges in formulation to result in a neutral charge. Still another impediment to the salicylic acid flow below the epidermis, would be the use of positively charged chemicals such as quaternary amine in solution with salicylic acid. These charged or neutral control chemicals can be in the form of spray to be applied over the initial application of salicylic acid.

[0118] Referring now more particularly to FIGS. 6a, 6b and 6c of the drawings, another major beneficial application of the present invention would be for the use of the positive membrane Mustang Q or a filter paper impregnated with Mustang Q or the like, to repel the positively charged nicotine chemical that is inhaled during smoking to prevent addiction. These membranes or filter paper or the like would take the form of layered filters 17a, 17b, 17c at any location

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between the lips and the tobacco and will effectively repel nicotine and other harmful chemicals from leaving the cigarette.

[0119] Carbon monoxide is another danger to the smoker. Carbon monoxide is formed by the combustion of carbon with a limited supply of air. As best shown in FIG. 6c, a positive membrane or impregnated filter paper 17a in direct contact with a negative membrane or filter paper 17b constitutes a battery and as a result liberates oxygen at the positive membrane and hydrogen at the negative membrane. These added gases would act to neutralize the carbon monoxide. The membranes could be 'wetted' with a pre-coated hydrogel or 'self-wetting' since the direct contact between the negative and positive membranes create a 'moist' condition. This would be an obvious boon to smokers worldwide since the medical community relates cancer, heart problems, pulmonary problems, etc. to the inhalation of tobacco smoke.

[0120] Also contemplated within the purview of the invention is a cigarette filter, as shown in FIG. 6, having a charged chemical(s) which attracts or repels unwanted polarized ions or molecules from a tobacco smoke stream so that they do not enter the mouth. The charged or polarized chemicals (FIGS. 6a, 6b, 6c) are covalently bonded to a non-volatile inorganic substrate which is incorporated in the filter. The filter can remove nicotine, carbon monoxide, cadmium, lead, mercury, nickel, cyanide among other dangerous elements from tobacco smoke. These charged or polarized chemicals can be covalently bonded to silica gel (APS silica gel) or the like. The charged chemical(s) can be contained in a space in the filter or incorporated in one or more filter elements such as tipping paper, shaped paper insert, mouthpiece plug, solid filter element, or free-flow filter element. The charged chemicals can be part of or coated on paper such as tipping or filter paper or incorporated in non-paper filter elements formed from fibrous materials such as cellulose acetate or polypropylene fibers. The use of the charged chemicals on any of the aforementioned exemplary support structures addresses the safety aspect of the invention.

[0121] Other aspects of cigarette acceptability involve the tobacco flavor that a smoker seeks for gratification. With the source for this tobacco taste diminished or stopped by the charged membrane(s), it can be restored with the use of tobacco extracts or flavors in the space between the end of the cigarette that goes into the mouth and the membrane or filter in contact with the tobacco. Another variation of this is to coat a charged membrane with the same polarity tobacco extract to propel the extract or flavor into the mouth. The smoker will now experience a cigarette that is safe, imparts flavor, and exudes smoke that is psychologically satisfying.

[0122] Another application of the invention having major universal value would be in the field of dentistry. It has long been known that fluoride has beneficial effects for the care and well being of teeth. In this regard, the government has allowed fluoride to be added to the water system. An extension of this is a means of infusing fluoride below the surface of the teeth instead of topical application with a common dentifrice. This has been recognized by the FDA as the ultimate means of preventing cavities and they approved a methodology that uses an iontophoretic toothbrush to infuse a fluoride toothpaste beneath the surface of the tooth. Attempts were made to commercially introduce such a

device but it failed at the marketplace. Among the problems is the short-term treatment of a brushing that would have questionable value. If the electrical current were raised, there could be a danger of injury to the very sensitive surrounding mucous membranes and the gum.

[0123] With the use of charged chemicals as a stand alone component away from membranes or felt pads, a new application of the present invention presents itself. The negatively charged chemicals (typically sulphonic acid or carboxyl acid and the like) when placed in a mouthwash or dentifrice with the presence of fluoride will act to infuse fluoride beneath the surface of the tooth. In addition, this process could continue over time for the ultimate cavity protection because residual activity may linger for hours. Some high potency fluoride toothpastes are recommended to be used without rinsing. Under these conditions, it is apparent that negatively charged chemicals will repel the negatively charged fluoride over time for the ultimate protection against tooth decay and the prevention of gum disease.

[0124] A major advance in noninvasive drug delivery is to introduce a battery 20 (see FIGS. 4 and 5) or any electrical power source to greatly increase fluxes of both ionic and polar neutral compounds. This process known as iontophoresis, works through one or a combination of the following mechanisms: electrophoresis, electroosmosis, and electroporation. While this process was known for over 100 years, its use was extremely limited because of the burns and irritation it could cause, slow treatment since an increase in electrical current would cause unacceptable pain, and an inability to deliver large molecular drugs at therapeutic levels because of low current requirements as well as other needs. All of these handicaps that limit acceptability of a powered superior drug or chemical delivery system are now overcome by means of the present invention directed to the use of charged or polarized membranes.

[0125] The following examples of systems using charged membranes with electrically powered systems or battery, presumes the reader is aware that the drug or chemical to be delivered is in solution that could take the form of a liquid, gel or paste or equivalent that links the active elements together. In this instance, the membranes serve the purpose of a reservoir for this solution. The second purpose of the membranes 11 is to protect the skin from injury. Stacked or coiled charged membranes 11 or the equivalent will stop the migration of harmful ions from the battery 20 or electrical power source connected electrodes 22. For instance, multiple Mustang S membranes placed between the negative electrode and the skin will prevent sodium hydroxide from reaching the skin, yet it will allow the flow of electrical current between these two points. Multiple Mustang Q membranes placed between the positive electrode and the skin will prevent hydrochloric acid from reaching the skin. Very importantly, this allows enormous electrical current levels to be used with no skin injury and lessened pain. This means that noninvasive iontophoretic devices can deliver therapeutic levels of drug in the fastest possible time.

[0126] Combinations of these membranes 11 may be used under the same electrode 22. For instance, one use of the polarized membrane 11 would be to use the negative membrane against the negative electrode to repel the injury causing sodium hydroxide from reaching the skin. The positive charged membranes could also be used with the

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negative electrode because the unlike negative ions would bind to the positive membrane and therefore stop the injury causing ions from reaching the skin. Conversely, we may use the negatively charged membrane against the positive electrode to stop the injury causing hydrochloric acid from reaching the skin. The communicating link between electrical power source, through solution wetted membrane to skin, includes the drug or chemical of choice. The solution may even be non-conductive. Conductivity between the power source and the skin is made because the wetted membrane is conductive by virtue of its charged chemicals that electrically link the electrode to the skin. The charged membranes may be renewed and life-extended by simply reversing the polarity of the battery 20 or power source.

[0127] The device may be used with an AC signal (as in U.S. Pat. No. 5,224,927). Mixed polarity membranes may be used under each electrode in this instance. Mixed polarity membranes may also be used in a DC system under the same electrode. This has a stabilizing effect and enhances regulation.

[0128] A major challenge of this non-invasive technology is the infusion of large molecular drugs such as insulin. Also, the diabetic may need a 'bolus' shot (an exceptionally high infusion). Infusion of large molecular drugs requires high electrical currents to drive them into the skin. Another example of the need for high currents to drive extremely high molecular drugs into the skin is the transport of glucosamine and chondroitin. These two chemicals can lessen pain and affect cartilage repair for knee osteoarthritis. Presently, these two chemicals require very large oral administration dosage to be effective. Losses created by first pass metabolism before they reach the area of effectiveness, make it necessary for large oral dosages. Direct application of these drugs to the knee area is superior. The problem arises because negatively charged chondroitin has a molecular weight of 60,000 daltons—over 10 times more than insulin! The aforementioned means of large electrical currents to give high current density are very effective to deliver these large molecules. Skin preps to aid permeability should be used with these drugs for non-invasive delivery. These preps include sodium salicylate and/or depilatories.

[0129] In still another effort to increase electrical current, in accordance with the invention, by reconfiguring the traditional flat surface of the active drug-carrying applicator we were able to increase current. Referring to FIG. 5b, a drug-carrying applicator 25 is shown to be multiple small, membrane containing openings 27. As before, the membrane acts as a drug reservoir and as an injury-preventing intervenor between the skin and the source of power. By breaking up a large flat delivery surface, in accordance with the invention, the electrical current could be increased appreciably.

[0130] It has been found that another contributor to pain during the iontophoretic process comes from the positive applicator of the device. The cause for the pain and therefore a limiting current factor at the positive output, is believed to be the fact that this polarity causes vasoconstriction. Vasoconstriction effects the nerve endings which we perceive as pain. By adding a very small percentage of a histamine to the positive applicator, the pain can be offset because the histamine is a vasodilator. In accordance with the invention, this facilitates increasing the electrical current. For example,

if the vasodilators of acetylcholine (ACh) or methacholine (MCh) are added to the solution on the positive applicator, it will be infused along with any other elements within the solution thereby lessening the pain sensation and allowing for an increase of current.

[0131] In addition to the large electrical current capability of this invention, amplification also contributes to an enormous signal to significantly increase drug delivery. Subsequently described in this application is a competitive environment of two different charge levels in solution that acts to recycle and thus amplify. Drug delivery of insulin can also be greatly enhanced with the use of a small quantity of glucose (perhaps 0.2 mol/l) in solution with insulin. The insulin infusion could be increased about 9 times with this glucose additive. Conversely, a small quantity of insulin added to the glucose withdrawal solution will increase the withdrawn analyte sample in a reverse iontophoresis modality. Still another method of increasing flux or signal amplification in drug delivery is with the use of charged chemicals as an integral part of a support structure or in a solution that communicates between skin and electrode. When two differently charged substances are in solution, they become reagents, thereby causing recycling resulting in amplification of the delivered drug. The use of negatively or positively charged insulin (charge depends on pH) in an environment of a positively charged membrane and using a negative power source to drive this solution into the skin, also increases amplification.

[0132] The aforescribed systems describe various applications of charged molecules in either chemical form or as an integral part of a membrane, felt or equivalent support material. These applications include use of the polarized characteristic as a stand-alone infusion or delivery system, use of the polarized property to control bacterial or fungal infection and to promote healing, use of the charged property as a filter to stop movement of injury causing chemicals coming from tobacco and the like, use of the polarized characteristic to stop injurious chemicals coming from a battery or power supply in addition to various other applications. The use of charged chemicals or membranes or the like modified with these chemicals or the equivalent carrier of these chemicals is so unique and widely diverse that the present invention is directed to and includes the universality of use other than those limited prior uses by the aforementioned Pall Corporation for use in lab assays and industrial or clean air filters, but not for medical devices or personal care products and uses to enhance delivery of a beneficial flux, signal, or current.

Non-Invasive Diagnostic Device

[0133] A major aspect this invention is the ultimate application of the use of chemically charged membranes or charged chemicals in liquid form making possible the first non-invasive rapid diagnostic test for glucose or other analytes. The finished device has a number of other innovations for its successful operability.

[0134] To better understand the details of these features and their contribution to the complete working unit, an overview of the elements and workings of the device is presented. While the device can be worn as a watch on the wrist or placed in other areas, it is perhaps easier to follow in the form of a probe because the active elements are stacked sequentially in the probe and can be more readily understood in that form.

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[0135] As shown in FIG. 7 the working probe is held as a pen 100 and placed on top of a vein on the wrist and makes an adequate glucose withdrawal within 95 seconds. The element touching the skin is a rolled, chemically charged membrane 111 that is wetted with a unique solution, gel or equivalent. The other end 111b of the membrane is in direct electrical contact with the negative terminal 120 of a power supply (battery) 125. There is now continuous electrical communication between the membrane end 111a that touches the skin and the negative terminal 120 because of the conductive, charged membrane 111. The circuit is complete when the patient is connected to the positive terminal 126 of the power source. The return electrode may also be placed on the forearm above of the wrist where a sample is taken. Another arrangement may be the grounding of the metal tube that is held by the hand applying the device to the wrist vein. The return electrode may also benefit from the use of charged membranes to prevent the hydrochloric acid generated at the positive electrode from reaching the skin. There are additional benefits with the use of the charged membranes. The charged membranes 111 are wetted with distilled deionized water and are conductive to the skin because the charged or ionic membranes are in direct contact with the skin. This eliminates the traditional saline wetted return electrode. It has been determined that the saline actually interfered with the withdrawn glucose sample giving distorted information. While the system described is intended to withdraw neutral or zwitterionic species by convective flow with the negative polarity to measure such clinically important substances as glucose, cholesterol, lactate etc., it has other uses without departing from the spirit and scope of the invention.

[0136] The invention may also be used to monitor drug pharmacokinetics by non-invasive electromigration withdrawal with the use of an opposite polarity electrode.

[0137] Each element of the diagnostic probe will now be explained to further disclose the unique features of the invention and how each element contributes to a working device.

[0138] **CHEMICALLY CHARGED MEMBRANE(S) or FELT PADS**—This is the building block of the device 100. Its multi-functions include: the need to stop the sodium hydroxide (lye) coming from the negative battery terminal. If not stopped, the sodium hydroxide would cause skin injury resulting in permanent scarring. This is prevented when a positively charged membrane is the intervenor between the negative terminal and the skin. The negative sodium hydroxide ions are attracted to the positively charged membrane and stopped from migrating to the skin. Meanwhile, the membrane(s) 111 allow the transport in the opposite direction of the withdrawn interstitial fluid containing glucose to travel to the negative electrode 120. This is aided by the fact that the surface of the negative electrode has a very high pH (because of the sodium hydroxide emitted there) that attracts glucose. It is essential that the inherent, extreme pH perform its function of glucose attraction. The charged membrane intervenor allows this to happen but prevents the skin-damaging sodium hydroxide from reaching the skin. The opposite end 111a of this membrane that touches the skin is maintained at a near neutral pH for safety. The glucose analyte to be measured accumulates at the end 111a of the membrane 111 touching the negative electrode 120. Accordingly, the probe 100 is designed with

the inside end of the membrane removable from the rest of the probe. After making the withdrawal from the skin, the patient separates this piece from the probe and affixes it to the strip on a glucose monitor (not shown). The deposition of the withdrawn glucose as stated above is uniquely on the inside end 111b of the membrane 111. This point is approximately a half-inch away from the pickup end 111a of the membrane 111 that touches the skin. It is this inside part of the membrane that is placed on the strip of a commercially available monitor that will respond with a glucose reading. This part 111 is then discarded and replaced with a new unit.

[0139] Other key elements in this application of charged membranes is how they are presented to the withdrawn analyte. It is important that the membranes offer a continuous, unbroken path for the glucose to travel to the electrode. Any impediment to this flow results in inaccurate readings. For instance, early investigation made use of membranes positioned flat on the skin pickup area. Since it was essential to increase thickness of the charged membrane between the skin and the high voltage electrode to prevent skin injury and pain, experiments were conducted with layered membranes. Up to 75 and more layers may be necessary to prevent injury and allow enormous current density to speed treatment. Unfortunately, the layered membranes gave false readings because each layer presented an interface to the signal that distorted the readings. A roll of the charged membrane is now used that when positioned on its side, allows the signal to traverse a single surface on its way to the electrode. Increasing the height of the charged membrane increases protection and allows greater current. A half-inch membrane spacing between the skin and electrode may be used, but a greater spacing using a membrane of greater height may provide enhanced results. For instance, literature sets iontophoretic currents at 0.5 ma per cm² for safety and comfort. With the arrangement just described, as much as 31 times more current density could be drawn. The membranes used for this research and development are, again, a product of Pall Corporation with a fixed and limited concentration of charged chemicals as an integral part of the membranes. They were intended for purposes other than those described here in connection with the present invention. Membranes may be improved and its effects more pronounced by using membranes made with charged chemicals of a much higher concentration.

[0140] An alternate configuration to the above design is based on the following performance needs: It has been determined that reducing the conductance of the solution is paramount to performance. One design feature toward this end is the use of neutral glucose as a solution. Another would be for the conductive charged membrane that connects the skin to the wire screen electrode to be made less conductive. To accomplish this a second, nonconductive membrane is introduced that is connected with the conductive charged membrane whose other end touches the electrode. The nonconductive membrane is a thin (typically, about 0.005 inch) membrane that is placed on the end of the charged membrane and comes in direct contact with the skin. In this manner the electrical conductivity of the path between the skin and the electrode is reduced compared to the previous disclosure of a conductive membrane only. With this arrangement, the glucose formulation is also reduced to the vicinity of 250 mg/dl thus further reducing clutter. These steps improve accuracy.

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[0141] **SOLUTION**—The all-important linkage between the active elements to make them function, is the solution. Conductivity between the electrode and the skin, even with a nonconductive solution, is made by virtue of the wetted charged or ionic membrane(s) that is in contact with the electrode and the skin. The formulation for glucose withdrawal should not add clutter that would compete with and impede this extremely small signal. To meet these requirements, glucose (solute) is provided in a distilled deionized water solvent to fulfill these needs and add other essential characteristics. For a formulation to work optimally, it is critical that the solution be saturated with glucose. If not totally saturated, then the water solvent would absorb the glucose signal and none would be available for analysis. Formulations used in the practice of the present invention provide for a glucose reading of 1 mg/dl or higher. This assures a saturated solution. Present formulations use a solute of glucose of 360 or higher mg/dl glucose in a solvent of distilled deionized water. Since analysis is made using the Medisense Precision QID instrument, this high level glucose solution does not affect the reading because the QID strip is unresponsive to this solution. Yet the withdrawn interstitial glucose fluid is processed as a blood sample and would be as reflected with a meter reading. Still another formulation for the solution would include a small quantity of insulin, perhaps 0.3% or less, in solution with the glucose. This combination has been found to greatly increase the signal passing through the membrane 111 on the way to the electrode 120, thus increasing amplification as subsequently described.

[0142] **GLUCOSE AMPLIFICATION**—In the subject invention, extremely low levels of glucose are electroosmotically withdrawn from the unbroken skin. It is very important that this small analyte (subpicomole level) be amplified to effect a reading in the shortest possible time. A novel means of doing this is still another use of the aforementioned chemically charged membranes 111 as a new form of reagent that results in chemical amplification of the glucose analyte with increased sensitivity and responsiveness. The reagent(s) is the charged chemical that is an integral part of a membrane. With the withdrawn glucose in solution passing through this membrane 111 drawn by the high pH negative terminal 120, the glucose reacts with self-replication. Factors that contribute to this amplification are the charged positive polarity of the membrane 111 in the negatively charged field. Another form of this amplification would be two or more adjacent membranes, one charged positively and another charged negatively. Glucose (or any other analyte) passing through these oppositely charged membranes would react by recycling and result in an amplified signal. Another form of this would be a membrane of one charge in an electric field of opposite charge. Another form would be two drugs or chemicals of different charges as previously mentioned. The competitive environment of the two different levels of charge in solution acts to recycle the glucose analyte. This ping-pong effect causing amplification allows analysis and quantification in the shortest possible time so that the reading is in real-time with the rapidly changing glucose in the body system. Increased amplification can be obtained using membranes made with a higher concentration of charged chemicals that will show increased reaction. This invention for chemical analysis lends itself to chip technology and in effect becomes 'lab-on-a-chip'.

[0143] **THREE POSITION CALIBRATION SWITCH**—To cover the wide range of glucose readings necessary for health assessment, it is desirable to have a calibration switch 140 on the probe 100, as best shown in FIG. 7c). The switch is in conformity with the expected glucose changes as a result of food intake. Referring to FIG. 7d, this switch 140 allows an adjustment of the withdrawal time/current for the following criteria: Position 1, (1-2 hours after meals), Position 2 (2-3 hours after meals and Position 3 (3-4 hours after meals). This process of switch position selection at the time of use is so that the end result readings of the detection meter compare with the blood standard within allowable tolerances. By assigning different withdrawal time/current to expected different glucose levels, we are able to cover the widest possible range of readings. In experiments with the Precision QID strips, position 1 represented 1-2 hours after meals and was set at a dosimetry of time and current that related to the high glucose levels of the day. Position 2 related to approximately the midpoint between meals and was set at a dosimetry of time and current to represent this mid level. Position 3 represented the longest period away from the last meal and was set with a low dosimetry of time and current. Extended ranges may be reached when sub-multiple or multiples of the reading are employed to extend range. This factory adjustment can be used to extend the range beyond the present pursuit. Newer generation strips may require different electrical currents and time in each of these three switch positions to function properly. After the gross selections are made with the calibration switch, precise readings are obtained when the withdrawn glucose specimen is processed at the strip and results in a meter reading.

[0144] **ACTIVE ELECTRODE**—The electrode 120 is made of stainless steel, which is resistive to sodium hydroxide. Importantly, the electrode is typically a stainless steel screen. This was selected because the sodium hydroxide that is generated at this electrode would normally travel to the perimeter of a solid surface stainless steel electrode. This would create 'hot spots' and possibly cause distorted readings of the glucose containing membrane 111 in contact with the electrode 120. The use of the screen electrode causes many 'perimeters' and therefore contributes to uniform distribution of sodium hydroxide across its surface for more consistent readings. The power supply within the probe consists of a 6 volt battery with circuitry to increase the voltage to 70 volts. This powers the dosimetry circuitry with switch controls for the time and current of the output feeding the active electrode. The dosimetry circuit integrates time and current and terminates this supply at precisely the same value for every patient. Since every patient's resistance is a variable, this circuit will adjust itself time-wise to compensate for different individual's resistance while holding current constant, so that everyone is treated equally. Tapper U.S. Pat. Nos. 6,485,437 and 6,059,736 describe this in electrical circuitry detail.

[0145] While the above diabetes diagnostic device is described in detail as a probe 100, the technology could all be included in other forms. For instance, the commercial strip used in various monitors could have an additional piece attached to it that could include the membranes and be connected internally to the commercial monitor for power, dosimetry timer, etc. This extended strip piece could be applied to the skin for withdrawal and the withdrawal tip folded back over the enzyme sensitive target for reading. Another structure would be in the form of a watch with a

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rotary dial to select seven positions for up to seven readings a day. Each position would have its own membrane (which should be changed after each reading). The key membrane in play would be connected between the skin and the electrode as described for the probe 100 configuration.

[0146] It will be apparent from the foregoing description, that the new and improved system, method, apparatus and chemistry of the present invention satisfies the following features and other needs and objectives of the invention:

[0147] 1) The use of charged chemicals of either negative or positive polarity on support members that could include a) membranes, b) felt pads made of natural or synthetic fibers, c) impregnated filter paper, d) liquid form, e) any material that allows charged chemicals to control ions, molecules or electrons;

[0148] 2) The use of charged chemicals of either negative or positive polarity formulated with an increased concentration of the charged chemicals causing either negative or positive polarity to increase their effectiveness;

[0149] 3) For use in a DC iontophoretic drug delivery system, the presence of charged chemicals in solution as an integral part of a felt pad(s) or a membrane(s) to prevent: a) injurious chemicals emanating from the electrode from reaching the skin, b) sodium hydroxide developed at the negative terminal is prevented from reaching the skin with either a negatively charged or positively charged intervenor between the skin and the electrode in an electrically conductive circuit, c) hydrochloric acid generated at the positive electrode can be prevented from reaching the skin with either positively charged or negatively charged chemicals on an appropriate support intervenor spaced between the electrode and the skin in an electrically conductive system;

[0150] 4) The chemically charged intervenor(s) acting as a reservoir or storage area for the drug to be delivered;

[0151] 5) In iontophoresis or reverse iontophoresis or drug delivery or similar chemical or drug transport system, the use of currents above the traditional 0.5 ma per cm². The aforementioned charged chemicals either on support structure or without support structure, enable these high currents to be achieved. Large molecular delivery also benefits from high electrical current along with Tapper U.S. Pat. Nos. 6,238,381 and 6,425,891;

[0152] 6) In a powered patch, electrical currents can be further increased by a new physical configuration of the active, drug delivery applicator. High density current can be tolerated when multiple small circles of current emitting membranes are clustered instead of one large flat delivery surface;

[0153] 7) The use of the aforementioned charged chemicals of both negative and positive polarity together or separately to meet all objectives of these inventions;

[0154] 8) The use of charged chemicals on an intervenor or in combination with both polarities in an AC iontophoretic device;

[0155] 9) The use of histamines in the positive applicator to lessen the pain from this applicator and allow an increase in current;

[0156] 10) The use of charged membrane(s) in an otherwise unpowered patch (passive patch) to propel the drug(s) into the skin at greatly increased levels compared to other unpowered patches;

[0157] 11) The use of charged membrane(s) in an unpowered patch as a storage area or reservoir for drugs.

[0158] 12) The use of charged membrane(s) of either polarity or in combination to increase infusion in an otherwise unpowered patch;

[0159] 13) The use of charged membranes between skin and output electrode as the conductive element when wetted with distilled water without the need of a saline solution;

[0160] 14) The use in iontophoresis or reverse iontophoresis of charged membranes between the skin and output electrode as the conductive element when wetted with distilled water as a means of avoiding clutter from conductive chemicals that may be added to enhance transport;

[0161] 15) The use of charged membrane(s) in a powered patch of either polarity or in combination as an intervenor to prevent skin injury;

[0162] 16) The use of charged membrane(s) in a powered patch of either polarity or in combination to act as a drug storage area or reservoir;

[0163] 17) The use of charged membrane(s) in a powered patch of either polarity or in combination as a reservoir and intervenor to increase currents above 0.5 ma per cm² without skin injury;

[0164] 18) In drug delivery, a small amount of glucose (0.2 mol/l) in solution with insulin can be amplified 9 times in an unpowered environment using charged membranes;

[0165] 19) Feature 18 wherein the above solution is in a powered environment will increase the signal many-fold;

[0166] 20) Feature 19 in a powered environment with the use of polarized membranes to act both to prevent skin injury and further enhance amplification;

[0167] 21) In drug delivery, any chemical or drug in a powered environment and stored in oppositely charged membrane(s) will cause amplification;

[0168] 22) Another example of drug or chemical amplification is using the phenomena of oppositely charged drugs to create recycling and thus amplification would be with glucosamine and chondroitin. Glucosamine is positive and chondroitin is negative and the two in solution with the appropriately charged membranes and in an appropriately polarized field, would benefit from amplification;

[0169] 23) The use of charged chemicals on filters in cigarettes positioned between the tobacco and the end held in the mouth to prevent the migration of deleterious tobacco chemicals from entering the mouth upon inhaling;

[0170] 24) The use of charged chemicals of either polarity or in combination on impregnated filter paper or membranes as an intervenor between tobacco and mouth to prevent polarized harmful chemicals from reaching the mouth.

[0171] 25) The use of a tobacco extract or flavor in combination with Items 23 and 24;

[0172] 26) A charged membrane of the same polarity of the tobacco extract or flavor to propel the extract or flavor into the mouth;

[0173] 27) The use of charged chemicals as an inherent part of a bandage or the like, to have an antibacterial effect when placed over a wound;

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[0174] 28) The use of a chemically charged bandage or the like that comes precoated with an antiseptic or the antiseptic is added later. The charged chemicals will drive the antiseptic into the wound continuously when wetted or in gel form for communication between all elements;

[0175] 29) The use of a chemically charged bandage or the like to enhance and speed wound healing when wetted;

[0176] 30) The use of a charged chemical of negative polarity in a toothpaste containing fluoride to infuse the fluoride below the tooth's surface and gum to prevent cavities and disease;

[0177] 31) The use of a charged chemical of negative polarity as an integral part or coating of toothbrush bristles to cause the fluoride of a toothpaste to be driven or infused into the teeth or gums;

[0178] 32) The use of charged chemicals of either polarity as an additive to a germ-killing mouthwash to infuse the antiseptic into the teeth and gums;

[0179] 33) The use of a charged chemical of negative polarity to be used as an intervenor between a battery-powered iontophoretic toothbrush and the bristles to prevent injurious sodium hydroxide from the negative terminal of the battery from reaching the teeth, gums or mucous membrane;

[0180] 34) A stent coated with either positive or negative chemicals or both to cause elution and prevent restenosis.

[0181] 35) A stent with a coating of charged chemicals of either charge or both that will elute like-charged chemicals coated on top of the charged coating to prevent restenosis;

[0182] 36) A stent with a coating of charged chemicals either positively or negatively charged or both integrated with like-charged chemicals that will be propelled or eluted from the surface to prevent restenosis;

[0183] 37) A stent coated with quaternary amine, sulfonic acid or carboxyl acid or the equivalent to cause elution either with another chemical that will be driven beyond the surface or the charged coating alone to elute when surrounding tissue and body fluids come in contact;

[0184] 38) For cosmetic application, the use of charged chemicals in liquid form as a spray to be applied over a moisturizer base or any other skin conditioner. This will drive a like-charged cosmetic ingredient or skin improvement product deeper into the skin than topical application;

[0185] 39) The use of salicylic acid and/or its derivative in combination with a charged chemical to limit its travel beneath the skin and thus prevent irritation;

[0186] 40) The use of positively charged salicylic acid in combination with negatively charged sulfonic acid or carboxyl acid or the like to bind to each other and thus limit migration of the salicylic acid beneath the epidermis;

[0187] 41) The use of salicylic acid as a skin spray as part of a two component system wherein a negatively charged spray follows;

[0188] 42) Salicylic acid's pH buffered from three to four to a nonirritating pH of approximately five and infused into the skin by a like-charged chemical;

[0189] 43) The use of negatively charged sodium salicylate with negatively charged chemicals to infuse the sodium salicylate into the skin for beneficial effects. The sodium salicylate and the negatively charged chemicals may be in formulation or they may be in the form of a two component system whereby the sodium salicylate is applied first as perhaps a spray and followed by a spray of negatively charged chemicals;

[0190] 44) For cosmetic and personal care application, the use of charged chemicals in formulation with like-charged skin improvement material. The repelled skin improvement materials will be infused deeper into the skin;

[0191] 45) The use of the negative and positive charges in formulation to result in a neutral charge and then mixed with the salicylic acid to limit its penetration to the epidermis;

[0192] 46) The neutral formulation of Item 45 to be used as a spray following the application of salicylic acid to limit its penetration;

[0193] 47) The use of positively charged chemicals such as quaternary amine in solution with salicylic acid to limit the depth of its penetration to the epidermis;

[0194] 48) The use of charged or neutral control chemicals in the form of a spray to be applied over the initial application of salicylic acid to limit its depth of penetration to the epidermis;

[0195] 49) In a permanent hair remover (Tapper U.S. Pat. Nos. 6,094,594 and 6,206,869) wherein a depilatory is driven into the follicle by an iontophoretic device, the use of a charged intervenor between battery and skin for the purposes of: a) to use high currents to expedite treatment, b) to use chemically charged intervenor to prevent skin injury, c) to use the chemically charged intervenor as the storage or reservoir vehicle for the depilatory;

[0196] 50) A non-invasive diagnostic withdrawal device using a charged or polarized membrane(s), one end of which is positioned to touch the skin and the other end touching the electrode;

[0197] 51) An alternate construction of Item 50 is the use of two membranes, one charged or conductive and the other nonconductive in direct contact with each other and spaced between the skin and the electrode;

[0198] 52) The use of a charged membrane and an uncharged membrane in a withdrawal system whereby the uncharged membrane is placed in contact with the skin and the charged membrane in contact with the electrode to complete the circuit.

[0199] 53) The use of a wool felt nib such as from a marker pen as the intervenor between the skin and electrode to prevent the passage of sodium hydroxide from the negative electrode from passing to the skin. The wool nib may or may not be coated with charged chemicals;

[0200] 54) The charged or polarized intervenor of Item 50 that is approximately a half-inch in length and placed between skin and electrode;

[0201] 55) The membrane of Items 50-54 between the skin and the electrode to protect against skin injury;

[0202] 56) Increasing the height of this membrane of Items 50, 41 and 55 allows the use of currents above 0.5 ma per cm²;

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[0203] 57) This charged membrane intervenor of Items 50, 54, 55 and 56 allows the use of high currents above the traditional 0.5 ma/cm²;

[0204] 58) Increasing the level of charge of the aforementioned membrane(s) by higher concentrations of the polarized material improves the benefits cited above;

[0205] 59) A positively charged wetted (gel) membrane prevents skin injury by stopping the sodium hydroxide ions emitted from the negative electrode in an electrically conductive circuit;

[0206] 60) The charged membrane interposed between skin and negative terminal also stores the solution (or gel) necessary to effect communication or current flow between skin and electrode;

[0207] 61) The target withdrawn glucose analyte passes through the membrane to the end that touches the negative electrode and becomes the critical pick-up point for the glucose monitor to read. This pick-up point for the withdrawn glucose analyte is unique in that it is against the electrode and not at membrane entry point in contact with the skin;

[0208] 62) The charged membrane is constructed in a rolled form so that one side of the membrane touches the skin and the other side touches the electrode. In other words, when viewed from the skin, the withdrawn analyte sees only straight line, unbroken surfaces while migrating to the electrode;

[0209] 63) The membrane form of Item 62 that causes the withdrawn glucose analyte to flow in a straight line while migrating to the electrode;

[0210] 64) The structure of Items 62 and 63 that causes the withdrawn glucose signal deposition on the end of the membrane in direct contact with the electrode;

[0211] 65) The use of a high pH from the electrode that attracts the glucose to this point of signal deposition;

[0212] 66) The structure of Features 62, 63, 64 and 65 wherein the membrane end in contact with the electrode is the pick-up point for the withdrawn glucose which is then placed in contact with the monitor's strip for analysis or direct reading;

[0213] 67) The positive return electrode may also use charged membranes to prevent skin damage and allows toleration of higher currents;

[0214] 68) The positive return electrode of the system described above may also be used to monitor drug pharmacokinetics;

[0215] 69) A solution formulated with glucose in a solvent of distilled deionized water;

[0216] 70) The solution of Item 69 wherein the glucose must totally saturate the distilled deionized water to prevent absorption of the withdrawn glucose;

[0217] 71) The solution of Items 69 and 70 must have a surplus of glucose (distilled deionized water solvent totally saturated) with a monitor reading between 1 and 400 mg/dl or more;

[0218] 72) Adding a small quantity of insulin to the glucose solutions of Items 69, 70 and 71, perhaps 0.3% or less, greatly increases the analyte signal or causes amplification;

[0219] 73) The solution of Items 69, 70, 71 and 72 that may include stabilizers or preservatives;

[0220] 74) Chemical amplification of the minute subpicomole withdrawn analyte takes place in the environment disclosed. When at least two differently charged substances occupy the same area, they become reagents to a signal passing through. The reagents cause recycling of the signal resulting in amplification. The charged positive membrane in the negative field acts as a reagent to the withdrawn glucose analyte and amplifies it;

[0221] 75) Another form of this would be the use of a positive and negative membrane adjacent to each other to cause recycling and therefore amplification of analyte;

[0222] 76) Amplification would take place if all the polarities cited above were reversed;

[0223] 77) Charged membranes made with higher concentration of charged chemicals will show increased amplification;

[0224] 78) More presence of charged membrane will increase the reaction and therefore increase amplification;

[0225] 79) This invention lends itself for the new technology of 'labs-on-a-chip';

[0226] 80) The electrode is a screen made of stainless steel to evenly disperse sodium hydroxide and pH;

[0227] 81) The power supply consists of a 6 volt battery with circuitry to increase the DC output voltage to 70 volts. Note: voltage may be higher or lower. A safety circuit or fail-safe circuit is included;

[0228] 82) The circuit includes a dosimetry circuit (Tapper patents) that precisely controls the analyte withdrawal quantity based on time and current;

[0229] 83) This non-invasive diagnostic device includes a calibration switch;

[0230] 84) A multi-position switch that selects the withdrawal time/current to match the highs, lows, and in-between time glucose levels of the patient caused by meals, physical exercise, or insulin dose;

[0231] 85) A multiple position switch that selectively adjusts time and current to conform with well established periods of glucose change related to meal intake (also physical exercise and insulin dose);

[0232] 86) The switch of Items 84 and 85 for following selections: Position 1 (1-2 hours after meals), Position 2 (2-3 hours after meals), and Position 3 (3-4 hours after meals);

[0233] 87) Different time/current rates are assigned to each of the three switch positions;

[0234] 88) A submultiple or multiple of the meter reading to extend range;

[0235] 89) After gross selection is made with switch according to Items 83, 84, 85, 86, 87 and 88a precise reading is obtained when the withdrawn glucose specimen is pro-

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cessed at the strip and results in a meter reading based on the glucose concentration or density in the withdrawn interstitial fluid; and

[0236] 90) An LED to indicate the precise end to the withdrawal process.

[0237] It will be apparent from the foregoing that, while particular forms of the invention have been illustrated and described, various alternatives, modifications and variations can be made without departing from the spirit and scope of the invention. Accordingly, the invention is intended to embrace all such alternatives, modifications and variations and it is not intended that the invention be limited, except as by the following claims.

I claim:

1. A flow control system, comprising:
a support member; and
charged chemicals of either negative and/or positive polarity on said support member; whereby said charged chemicals control the flow of ions, molecules or electrons.
2. A flow control system as recited in claim 1, wherein said support member includes membranes.
3. A flow control system as recited in claim 1, wherein said support member includes felt pads made of natural or synthetic fibers.
4. A flow control system as recited in claim 1, wherein said support member includes impregnated filter paper.
5. A flow control system as recited in claim 1, wherein said support member includes a liquid or gel form.
6. A flow control system as recited in claim 1, wherein said support member includes any materials that control the flow of ions, molecules or electrons.
7. A system as set forth in claim 1, wherein said charged chemicals of either negative and/or positive polarity are formulated with an increased concentration of the charged chemicals causing either negative or positive polarity to increase their effectiveness.
8. In an iontophoretic drug delivery system, the combination comprising: an electrode; charged chemicals in solution as an integral part of a support member such as felt pad(s) or a membrane(s) for prevention of a) injurious chemicals emanating from said electrode from reaching the skin, b) sodium hydroxide developed at the negative terminal from reaching the skin with either a negatively charged or positively charged intervenor between the skin and said electrode in an electrically conductive circuit, c) hydrochloric acid generated at the positive electrode terminal from reaching the skin, with either positively charged or negatively charged chemicals on an appropriate support intervenor spaced between the electrode and the skin in an electrically conductive system.
9. A fluid delivery patch for application to a biological subject, comprising:
a chemical to be delivered to the subject;
at least one charged membrane incorporating or adjacent said chemical for electrically driving said chemical into the subject;
and support means for supporting said membrane and said chemical in a proximity to the subject suitable for proper chemical delivery to the subject.

10. A fluid delivery patch as recited in any of claims 1-9 and further including:

additional electrical supply means to further enhance said charged membrane.

11. A system as recited in claim 8 wherein said chemically charged intervenor(s) act as a reservoir or storage area for the drug to be delivered.

12. In a system as recited in any of claims 1-11, the use of electrical currents greater than the traditional 0.5 ma per cm.

13. Apparatus adapted for placement within a biological subject, comprising:

a stent; and

a coating of electrically charged chemicals deposited on said stent.

14. Apparatus as recited in claim 13, wherein said chemicals may be either positive or negative or both to cause elution and prevent restenosis.

15. In an AC iontophoretic device, the use of charged chemicals on an intervenor or in combination with both positive and negative polarities.

16. In an iontophoresis or reverse iontophoresis system, the combination comprising:

electrically charged membranes between the skin, and an output electrode as the conductive element when wetted with distilled water, whereby clutter from conductive chemicals that may be added to enhance transport is avoided.

17. In a drug delivery system, the use of a small amount of glucose in solution with insulin for substantial amplification in a powered environment using charged membranes.

18. In an improved cigarette filter: the use of charged chemicals on the filters positioned between the tobacco and the end held in the mouth of a smoker, to prevent the migration of deleterious tobacco chemicals from entering the mouth upon inhaling.

19. An improved cigarette filter as recited in claim 18, including the use of charged chemicals of either polarity or in combination on impregnated filter paper or membranes, as an intervenor between tobacco and mouth to prevent polarized harmful chemicals from reaching the mouth.

20. In a medical application, the use of a chemically charged bandage or the like to enhance and speed wound healing.

21. For dental applications, the use of a charged chemical of negative polarity to infuse the fluoride in a toothpaste below the tooth's surface and gum to prevent cavities and disease.

22. For use in cosmetic and personal care applications, the method comprising:

use of charged chemicals in liquid form as a spray to be applied over a moisturizer base or any other skin conditioner.

23. A new and improved method, comprising:

using positively charged salicylic acid in combination with negatively charged sulfonic acid or carboxyl acid

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- or the like to bind to each other and thus limit migration of the salicylic acid beneath the epidermis;
24. A new and improved method, comprising:
use of salicylic acid as a skin spray as part of a two component system wherein a negatively charged spray follows.
25. A method for cosmetic and personal care applications, comprising:
the use of charged chemicals in formulation with like-charged skin improvement material, whereby the repelled skin improvement materials will be infused deeper into the skin.
26. A non-invasive diagnostic withdrawal device using a charged or polarized membrane(s), one end of which is positioned to touch the skin and the other end touching an electrode, whereby withdrawal is enhanced and skin injury is mitigated.
27. A withdrawal device as recited in claim 26, wherein the height of said membrane is increased to facilitate the use of currents above 0.5 ma per cm².
28. A withdrawal device as recited in claim 26, and further including:
a positively charged wetted membrane to prevent skin injury by stopping the sodium hydroxide ions emitted from the negative electrode in an electrically conductive circuit.
29. A device as set forth in claim 26, wherein target withdrawn glucose analyte passes through said membrane to the end that touches a negative electrode which becomes the critical pick-up point for a glucose monitor to read.
30. A device as set forth in claim 26, wherein said charged membrane is constructed in a rolled form so that one end of the rolled membrane touches the skin and the other end touches said electrode, whereby the withdrawn analyte sees only straight line, unbroken surfaces while migrating to said electrode.
31. A device as recited in any of claims 26-30, including provision of a high pH from the electrode that attracts the glucose to the point of signal deposition.
32. A device as recited in claim 31, wherein the membrane end in contact with said electrode is the pick-up point for the withdrawn glucose which is then placed in contact with a monitor's strip for analysis or direct reading.
33. A device as recited in claim 26, wherein said electrode includes a screen made of stainless steel to evenly disperse sodium hydroxide and pH.
34. A device as recited in claim 26, wherein a dosimetry circuit is provided that precisely controls the analyte withdrawal quantity based on time and current.
35. A device as recited in claim 26, and further including:
a calibration switch in the form of a multi-position switch that selects the withdrawal time/current to match the highs, lows, and in-between time glucose levels of a patient caused by meals, physical exercise, or insulin dose.
36. A multi-position switch as recited in claim 35, having the following selections: Position 1 (1-2 hours after meals), Position 2 (2-3 hours after meals), and Position 3 (3-4 hours after meals).
37. In an apparatus as recited in either of claims 35 or 36, the improvement comprising:
readout means for obtaining a precise reading when the withdrawn glucose specimen is processed at a strip and provides a readout based on the glucose concentration or density in the withdrawn interstitial fluid.
38. A new and improved method, comprising:
mixing a positively charged chemical with an antiperspirant and
applying the mixture to a biological subject,
whereby said charged chemical will drive said antiperspirant deep down the eccrine sweat duct for greater effectiveness than topical application.
39. A method as recited in claim 38, wherein said antiperspirant is aluminum chloride and the like.
40. A new and improved method, comprising:
applying to a subject a first spray containing a suitable antiperspirant;
following said first spray with a second spray of a positively charged chemical to infuse said antiperspirant deeply into said subject.
41. A method as recited in claim 40, wherein said antiperspirant is aluminum chloride and the like.
42. A new and improved method, comprising:
applying to a subject a first spray containing a suitable substance for infusion into the subject;
following said first spray with a second spray of a charged chemical to infuse said substance deeply into the subject.
43. A device as recited in claim 26 and further including:
the use of two membranes, one charged or conductive and the other nonconductive in direct contact with each other and spaced between the skin and the electrode.
44. A device as recited in claim 43, wherein said nonconductive membrane is placed in contact with the skin and said charged membrane in contact with the electrode to complete the circuit.
45. A device as recited in claim 26, and further including:
a wool felt nib as an intervenor between the skin and said electrode to prevent the passage of sodium hydroxide from the negative electrode to the skin.
46. A device as recited in claim 45 wherein said nib may be coated with charged chemicals.
47. Each and every novel feature and/or combination of features herein disclosed.

* * * * *



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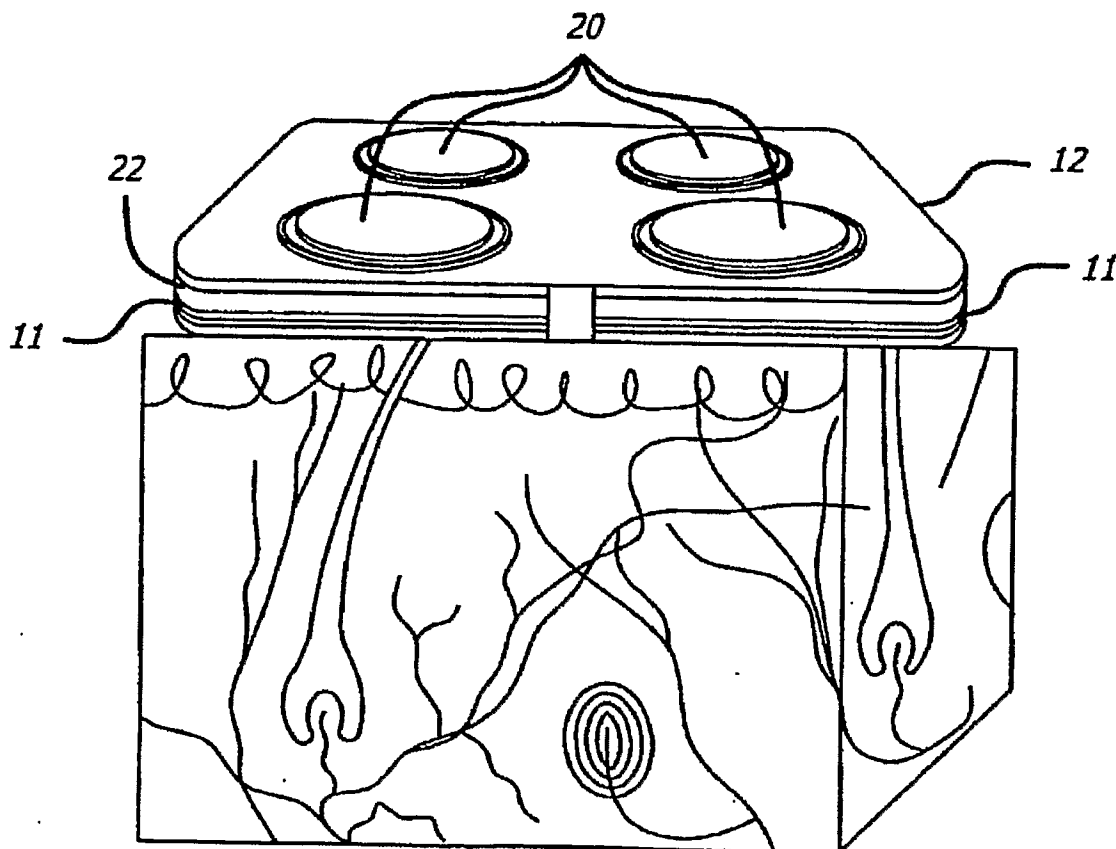
(19) **United States**(12) **Patent Application Publication**
Tapper(10) **Pub. No.: US 2006/0025714 A1**(43) **Pub. Date: Feb. 2, 2006**(54) **METHODS, APPARATUS AND CHARGED
CHEMICALS FOR CONTROL OF IONS,
MOLECULES OR ELECTRONS**(60) Provisional application No. 60/535,470, filed on Jan.
8, 2004. Provisional application No. 60/543,446, filed
on Feb. 9, 2004. Provisional application No. 60/593,
030, filed on Jul. 29, 2004.(76) **Inventor: Robert Tapper, Los Angeles, CA (US)**Correspondence Address:
**FULWIDER PATTON
6060 CENTER DRIVE
10TH FLOOR
LOS ANGELES, CA 90045 (US)****Publication Classification**(51) **Int. Cl.**
A61N 1/30 (2006.01)
(52) **U.S. Cl.** 604/20(57) **ABSTRACT**A system including methods, apparatus, components and
charged chemicals for control of ions, molecules or electrons
whereby charged membranes, testing devices, electrode
patch structures and the like utilize features of the invention
for control of flow in a wide variety of new and improved
medical, testing, cosmetic, personal care, flow delivery
applications and the like, and further including shock pre-
vention and dosimetry control.(21) **Appl. No.: 11/194,142**(22) **Filed: Jul. 29, 2005****Related U.S. Application Data**(63) Continuation-in-part of application No. 11/029,904,
filed on Jan. 4, 2005.

FIG. 1

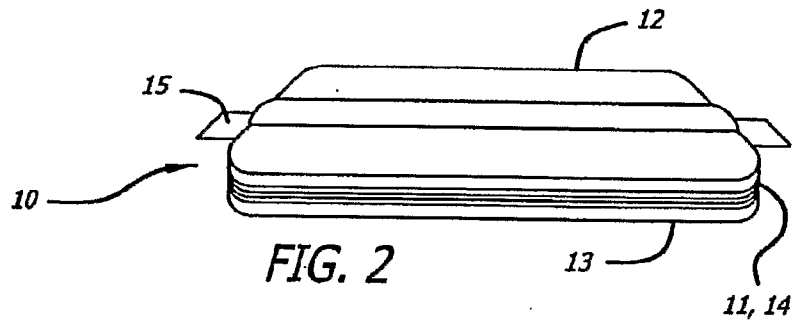
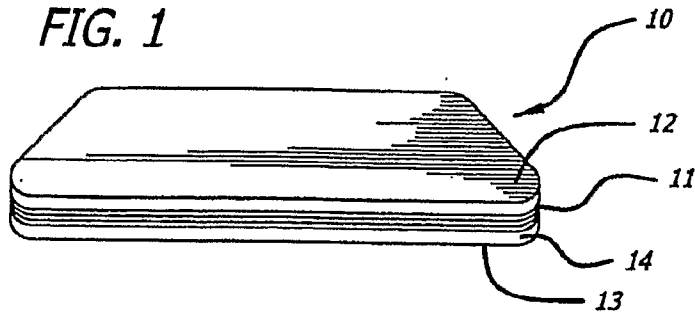


FIG. 2

FIG. 3

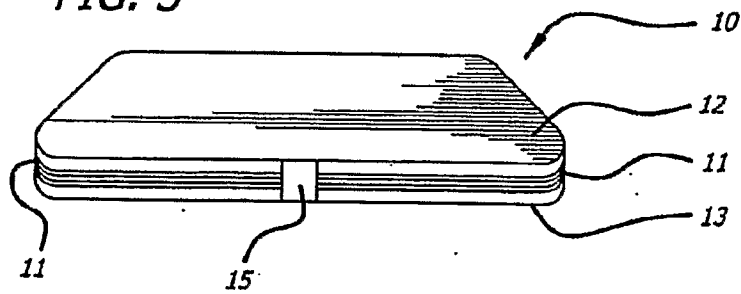


FIG. 4

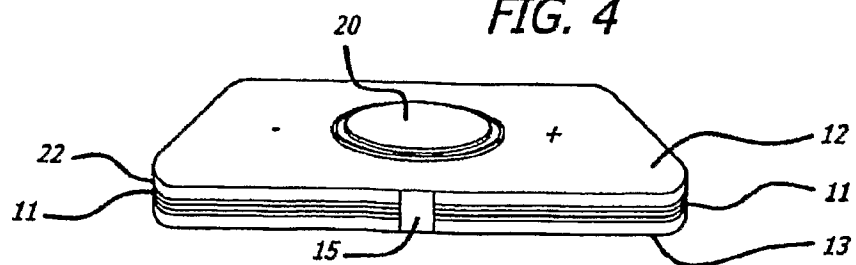


FIG. 5

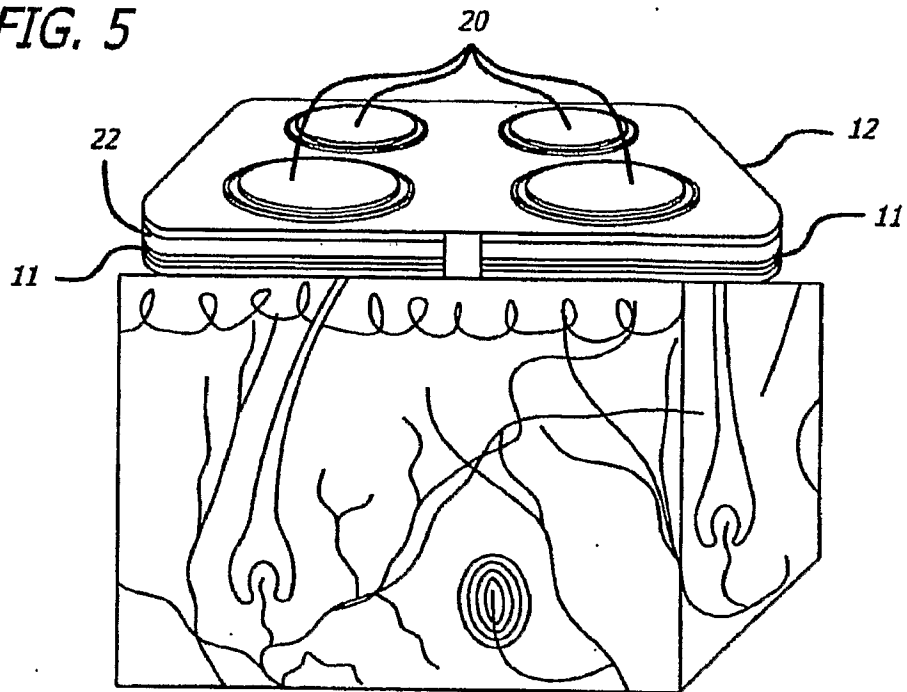


FIG. 5a

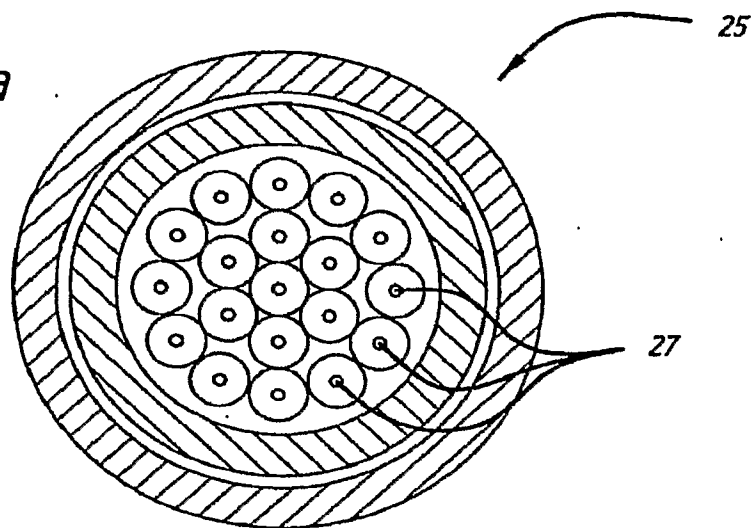


FIG. 6a

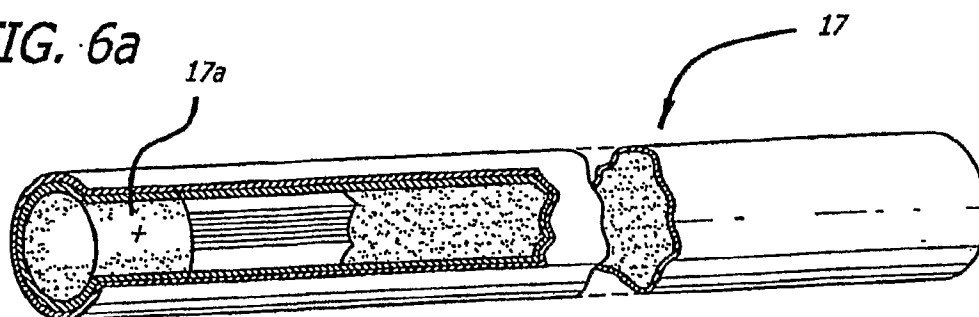


FIG. 6b

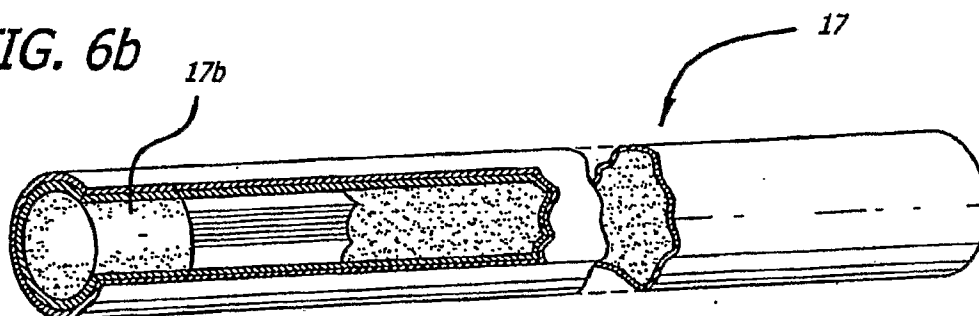
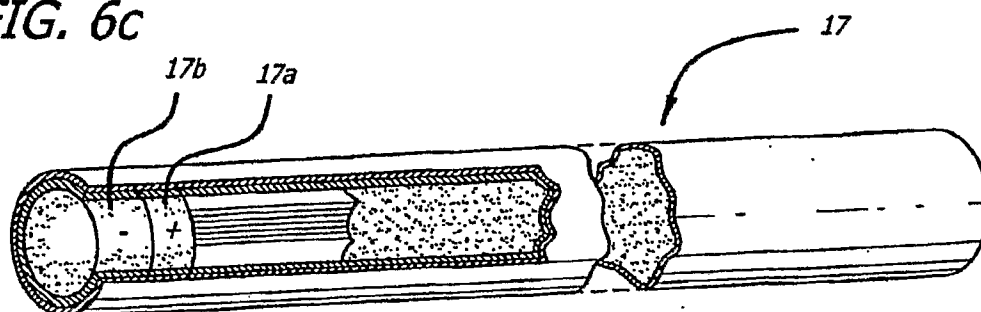
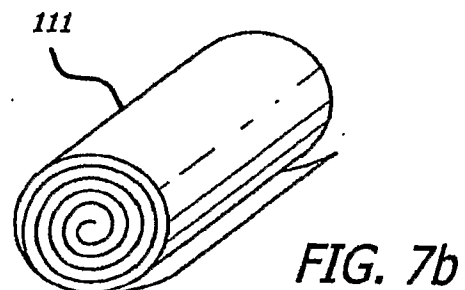
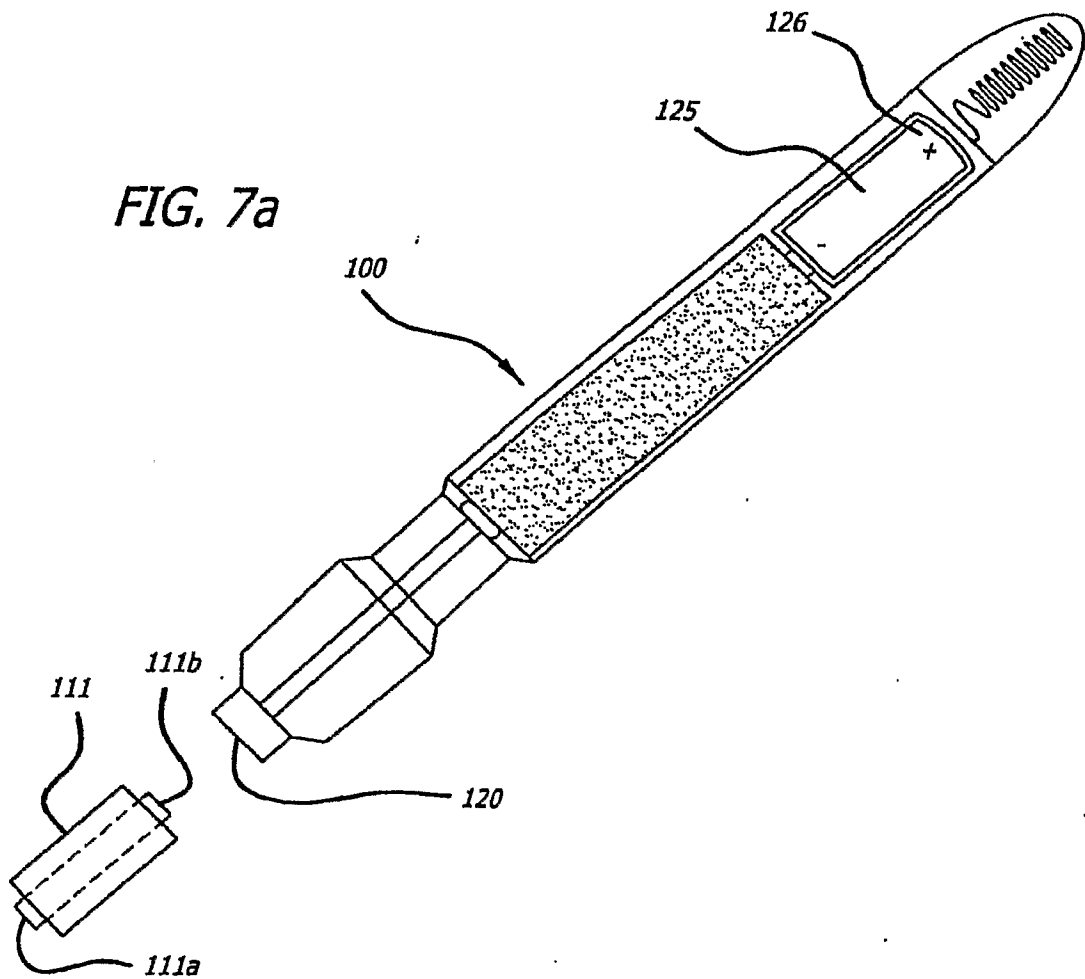


FIG. 6c





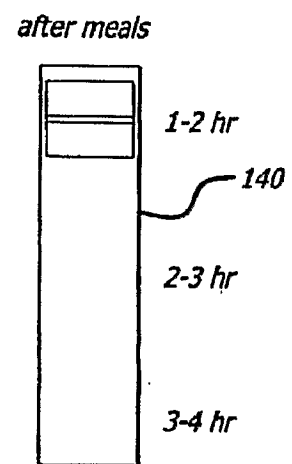
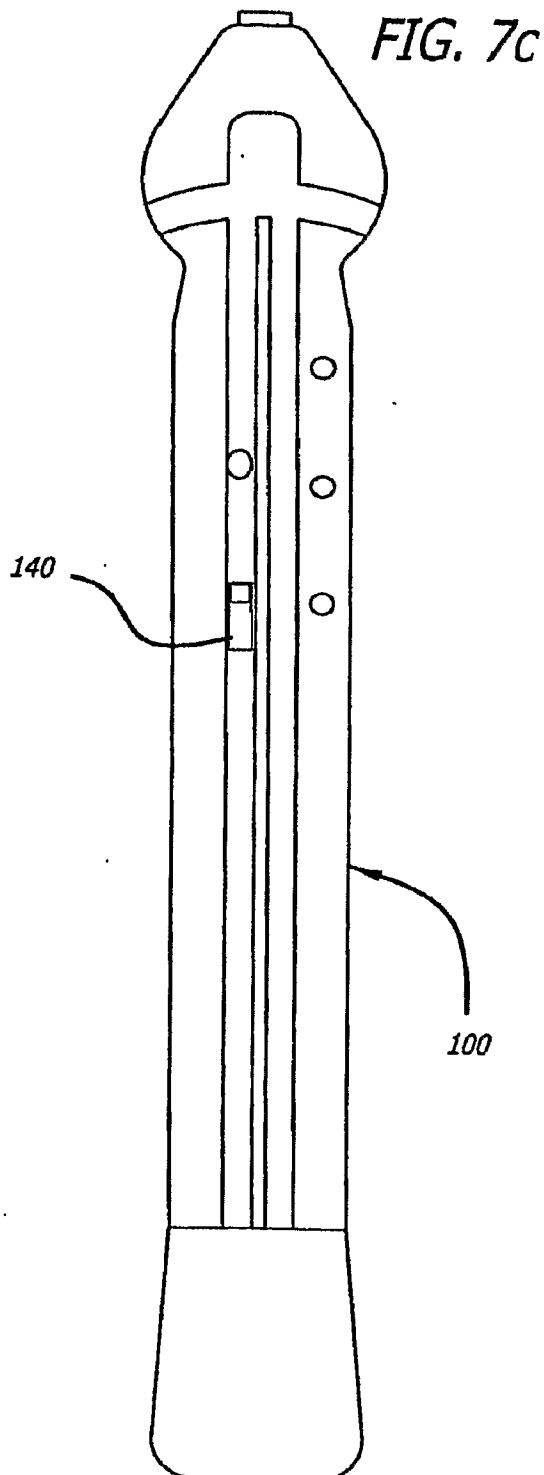


FIG. 7d

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METHODS, APPARATUS AND CHARGED CHEMICALS FOR CONTROL OF IONS, MOLECULES OR ELECTRONS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation-in-part of co-pending application U.S. Ser. No. 11/029,904 filed Jan. 4, 2005 which claims the benefit of U.S. provisional patent application Ser. No. 60/535,470 filed on Jan. 8, 2004, Ser. No. 60/543,446 filed on Feb. 9, 2004 and Ser. No. 60/593,030 filed on Jul. 29, 2004, the disclosures of which are incorporated by reference.

FIELD OF THE INVENTION

[0002] This invention relates generally to methods and apparatus pertaining to charged particles flow and, more particularly, to improvements in methods, apparatus, systems and materials for control of flow and level of ions, molecules, or electrons using charged chemicals and any/all applications thereof.

BACKGROUND OF THE INVENTION

[0003] Topical drug delivery systems range from small particulate carriers through passive patches to sophisticated iontophoretic propulsion delivery systems. Ideally, they attempt to deliver beneath the skin beneficial chemicals or drugs in the largest controlled amounts, in the shortest time, up to the largest molecular size and without chemically caused skin injury or microneedle puncture. No commercially available product can do all of this today. Accordingly, those of ordinary skill in the art have long recognized the need for improvements in these areas, and the present invention fulfills all of these needs.

INVENTION SUMMARY

[0004] Basically, the present invention satisfies the aforementioned needs with improvements in methods, apparatus, components and chemistry including the use of charged chemicals of either polarity or both as chemically integral surfaces on support membranes or equivalent support materials such as felt or like materials made of natural or synthetic fibers or impregnated filter paper or other materials in a drug delivery or diagnostic withdrawal system. The charged chemicals may also be used without a support structure. They allow multiple hybridizations that could include a neutral charge among other effects. Examples of these membranes manufactured by Pall Corporation of 25 Harbor Park Drive, Port Washington, N.Y. 11050 are Mustang S, Mustang Q, Mustang C and Biodyne A, Biodyne B and Biodyne C. The Mustang series are of special interest with Mustang S giving a strong negative polarity with its surface modified by sulfonic acid. Mustang Q gives a strong positive polarity with its surface modified by quaternary amine. It should be understood that the chemicals cited are for example only and are not the only chemicals that can polarize support structures or control ion or molecule flow without a support structure. For instance, Mustang C is polarized with carboxylic acid. Other examples of functional groups that can bear a charge would be the hydroxyl, phosphate moieties. A unique feature of the invention is the use of charged or polarized chemicals on support members or not, to control a flux, current, or signal of polarized

molecules, ions or electrons and even polar neutral compounds as in an electroosmotic withdrawal system and a drug delivery system.

[0005] The invention is contemplated, in its various forms and applications as including the following and other features:

[0006] 1) The use of charged chemicals of either negative or positive polarity on support members that could include a) membranes, b) felt pads made of natural or synthetic fibers, c) impregnated filter paper, d) liquid form, e) any material that allows charged chemicals to control ions, molecules or electrons;

[0007] 2) The use of charged chemicals of either negative or positive polarity formulated with an increased concentration of the charged chemicals causing either negative or positive polarity to increase their effectiveness;

[0008] 3) For use in a DC iontophoretic drug delivery system, the presence of charged chemicals in solution as an integral part of a felt pad(s) or a membrane(s) to prevent: a) injurious chemicals emanating from the electrode from reaching the skin, b) sodium hydroxide developed at the negative terminal is prevented from reaching the skin with either a negatively charged or positively charged intervenor between the skin and the electrode in an electrically conductive circuit, c) hydrochloric acid generated at the positive electrode can be prevented from reaching the skin with either positively charged or negatively charged chemicals on an appropriate support intervenor spaced between the electrode and the skin in an electrically conductive system;

[0009] 4) The chemically charged intervenor(s) acting as a reservoir or storage area for the drug to be delivered;

[0010] 5) In iontophoresis or reverse iontophoresis or drug delivery or similar chemical or drug transport system, the use of currents above the traditional 0.5 ma per cm². The aforementioned charged chemicals either on support structure or without support structure, enable these high currents to be achieved. Large molecular delivery also benefits from high electrical current along with Tapper U.S. Pat. Nos. 6,238,381 and 6,425,891;

[0011] 6) In a powered patch, electrical currents can be further increased by a new physical configuration of the active, drug delivery applicator. High density current can be tolerated when multiple small circles of current emitting membranes are clustered instead of one large flat delivery surface;

[0012] 7) The use of the aforementioned charged chemicals of both negative and positive polarity together or separately to meet all objectives of these inventions;

[0013] 8) The use of charged chemicals on an intervenor or in combination with both polarities in an AC iontophoretic device;

[0014] 9) The use of histamines in the positive applicator to lessen the pain from this applicator and allow an increase in current;

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- [0015] 10) The use of charged membrane(s) in an otherwise unpowered patch (passive patch) to propel the drug(s) into the skin at greatly increased levels compared to other unpowered patches;
- [0016] 11) The use of charged membrane(s) in an unpowered patch as a storage area or reservoir for drugs.
- [0017] 12) The use of charged membrane(s) of either polarity or in combination to increase infusion in an otherwise unpowered patch;
- [0018] 13) The use of charged membranes between skin and output electrode as the conductive element when wetted with distilled water without the need of a saline solution;
- [0019] 14) The use in iontophoresis or reverse iontophoresis of charged membranes between the skin and output electrode as the conductive element when wetted with distilled water as a means of avoiding clutter from conductive chemicals that may be added to enhance transport;
- [0020] 15) The use of charged membrane(s) in a powered patch of either polarity or in combination as an intervenor to prevent skin injury;
- [0021] 16) The use of charged membrane(s) in a powered patch of either polarity or in combination to act as a drug storage area or reservoir;
- [0022] 17) The use of charged membrane(s) in a powered patch of either polarity or in combination as a reservoir and intervenor to increase currents above 0.5 ma per cm² without skin injury;
- [0023] 18) In drug delivery, a small amount of glucose (0.2 mol/l) in solution with insulin can be amplified 9 times in an unpowered environment using charged membranes;
- [0024] 19) Feature 18 wherein the above solution is in a powered environment and will increase the signal many-fold;
- [0025] 20) Feature 19 in a powered environment with the use of polarized membranes to act both to prevent skin injury and further enhance amplification;
- [0026] 21) In drug delivery, any chemical or drug in a powered environment and stored in oppositely charged membrane(s) will cause amplification;
- [0027] 22) Another example of drug or chemical amplification is using the phenomena of oppositely charged drugs to create recycling and thus amplification would be with glucosamine and chondroitin. Glucosamine is positive and chondroitin is negative and the two in solution with the appropriately charged membranes and in an appropriately polarized field, would benefit from amplification;
- [0028] 23) The use of charged chemicals on filters in cigarettes positioned between the tobacco and the end held in the mouth to prevent the migration of deleterious tobacco chemicals from entering the mouth upon inhaling;
- [0029] 24) The use of charged chemicals of either polarity or in combination on impregnated filter paper or membranes as an intervenor between tobacco and mouth to prevent polarized harmful chemicals from reaching the mouth.
- [0030] 25) The use of a tobacco extract or flavor in combination with Items 23 and 24;
- [0031] 26) A charged membrane of the same polarity of the tobacco extract or flavor to propel the extract or flavor into the mouth;
- [0032] 27) The use of charged chemicals as an inherent part of a bandage or the like, to have an antibacterial effect when placed over a wound;
- [0033] 28) The use of a chemically charged bandage or the like that comes precoated with an antiseptic or the antiseptic is added later. The charged chemicals will drive the antiseptic into the wound continuously when wetted or in gel form for communication between all elements;
- [0034] 29) The use of a chemically charged bandage or the like to enhance and speed wound healing when wetted;
- [0035] 30) The use of a charged chemical of negative polarity in a toothpaste containing fluoride to infuse the fluoride below the tooth's surface and gum to prevent cavities and disease;
- [0036] 31) The use of a charged chemical of negative polarity as an integral part or coating of toothbrush bristles to cause the fluoride of a toothpaste to be driven or infused into the teeth or gums;
- [0037] 32) The use of charged chemicals of either polarity as an additive to a germ-killing mouthwash to infuse the antiseptic into the teeth and gums;
- [0038] 33) The use of a charged chemical of negative polarity to be used as an intervenor between a battery-powered iontophoretic toothbrush and the bristles to prevent injurious sodium hydroxide from the negative terminal of the battery from reaching the teeth, gums or mucous membrane;
- [0039] 34) A stent coated with either positive or negative chemicals or both to cause elution and prevent restenosis.
- [0040] 35) A stent with a coating of charged chemicals of either charge or both that will elute like-charged chemicals coated on top of the charged coating to prevent restenosis;
- [0041] 36) A stent with a coating of charged chemicals either positively or negatively charged or both integrated with like-charged chemicals that will be propelled or eluted from the surface to prevent restenosis;
- [0042] 37) A stent coated with quaternary amine, sulfonic acid or carboxyl acid or the equivalent to cause elution either with another chemical that will be driven beyond the surface or the charged coating alone to elute when surrounding tissue and body fluids come in contact;

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- [0043] 38) For cosmetic application, the use of charged chemicals in liquid form as a spray to be applied over a moisturizer base or any other skin conditioner. This will drive a like-charged cosmetic ingredient or skin improvement product deeper into the skin than topical application;
- [0044] 39) The use of salicylic acid and/or its derivative in combination with a charged chemical to limit its travel beneath the skin and thus prevent irritation;
- [0045] 40) The use of positively charged salicylic acid in combination with negatively charged sulfonic acid or carboxyl acid or the like to bind to each other and thus limit migration of the salicylic acid beneath the epidermis;
- [0046] 41) The use of salicylic acid as a skin spray as part of a two component system wherein a negatively charged spray follows;
- [0047] 42) Salicylic acid's pH buffered from three to four to a nonirritating pH of approximately five and infused into the skin by a like-charged chemical;
- [0048] 43) The use of negatively charged sodium salicylate with negatively charged chemicals to infuse the sodium salicylate into the skin for beneficial effects. The sodium salicylate and the negatively charged chemicals may be in formulation or they may be in the form of a two component system whereby the sodium salicylate is applied first as perhaps a spray and followed by a spray of negatively charged chemicals;
- [0049] 44) For cosmetic and personal care application, the use of charged chemicals in formulation with like-charged skin improvement material. The repelled skin improvement materials will be infused deeper into the skin;
- [0050] 45) The use of the negative and positive charges in formulation to result in a neutral charge and then mixed with the salicylic acid to limit its penetration to the epidermis;
- [0051] 46) The neutral formulation of Item 45 to be used as a spray following the application of salicylic acid to limit its penetration;
- [0052] 47) The use of positively charged chemicals such as quaternary amine in solution with salicylic acid to limit the depth of its penetration to the epidermis;
- [0053] 48) The use of charged or neutral control chemicals in the form of a spray to be applied over the initial application of salicylic acid to limit its depth of penetration to the epidermis;
- [0054] 49) In a permanent hair remover (Tapper U.S. Pat. Nos. 6,094,594 and 6,206,869) wherein a depilatory is driven into the follicle by an iontophoretic device, the use of a charged intervenor between battery and skin for the purposes of: a) to use high currents to expedite treatment, b) to use chemically charged intervenor to prevent skin injury, c) to use the chemically charged intervenor as the storage or reservoir vehicle for the depilatory;
- [0055] 50) A non-invasive diagnostic withdrawal device using a charged or polarized membrane(s), one end of which is positioned to touch the skin and the other end touching the electrode;
- [0056] 51) An alternate construction of Item 50 is the use of two membranes, one charged or conductive and the other nonconductive in direct contact with each other and spaced between the skin and the electrode;
- [0057] 52) The use of a charged membrane and an uncharged membrane in a withdrawal system whereby the uncharged membrane is placed in contact with the skin and the charged membrane in contact with the electrode to complete the circuit.
- [0058] 53) The use of a wool felt nib such as from a marker pen as the intervenor between the skin and electrode to prevent the passage of sodium hydroxide from the negative electrode from passing to the skin. The wool nib may or may not be coated with charged chemicals;
- [0059] 54) The charged or polarized intervenor of Item 50 that is approximately a half-inch in length and placed between skin and electrode;
- [0060] 55) The membrane of Items 50-54 between the skin and the electrode to protect against skin injury;
- [0061] 56) Increasing the height of this membrane of Items 50, 41 and 55 allows the use of currents above 0.5 ma per cm²;
- [0062] 57) This charged membrane intervenor of Items 50, 54, 55 and 56 allows the use of high currents above the traditional 0.5 ma/cm²;
- [0063] 58) Increasing the level of charge of the aforementioned membrane(s) by higher concentrations of the polarized material improves the benefits cited above;
- [0064] 59) A positively charged wetted (gel) membrane prevents skin injury by stopping the sodium hydroxide ions emitted from the negative electrode in an electrically conductive circuit;
- [0065] 60) The charged membrane interposed between skin and negative terminal also stores the solution (or gel) necessary to effect communication or current flow between skin and electrode;
- [0066] 61) The target withdrawn glucose analyte passes through the membrane to the end that touches the negative electrode and becomes the critical pick-up point for the glucose monitor to read. This pick-up point for the withdrawn glucose analyte is unique in that it is against the electrode and not at membrane entry point in contact with the skin;
- [0067] 62) The charged membrane is constructed in a rolled form so that one side of the membrane touches the skin and the other side touches the electrode. In other words, when viewed from the skin, the withdrawn analyte sees only straight line, unbroken surfaces while migrating to the electrode;
- [0068] 63) The membrane form of Item 62 that causes the withdrawn glucose analyte to flow in a straight line while migrating to the electrode;
- [0069] 64) The structure of Items 62 and 63 that causes the withdrawn glucose signal deposition on the end of the membrane in direct contact with the electrode;

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- [0070] 65) The use of a high pH from the electrode that attracts the glucose to this point of signal deposition;
- [0071] 66) The structure of Features 62, 63, 64 and 65 wherein the membrane end in contact with the electrode is the pick-up point for the withdrawn glucose which is then placed in contact with the monitor's strip for analysis or direct reading;
- [0072] 67) The positive return electrode may also use charged membranes to prevent skin damage and allows toleration of higher currents;
- [0073] 68) The positive return electrode of the system described above may also be used to monitor drug pharmacokinetics;
- [0074] 69) A solution formulated with glucose in a solvent of distilled deionized water;
- [0075] 70) The solution of Item 69 wherein the glucose must totally saturate the distilled deionized water to prevent absorption of the withdrawn glucose;
- [0076] 71) The solution of Items 69 and 70 must have a surplus of glucose (distilled deionized water solvent totally saturated) with a monitor reading between 1 and 400 mg/dl or more;
- [0077] 72) Adding a small quantity of insulin to the glucose solutions of Items 69, 70 and 71, perhaps 0.3% or less, greatly increases the analyte signal or causes amplification;
- [0078] 73) The solution of Items 69, 70, 71 and 72 that may include stabilizers or preservatives;
- [0079] 74) Chemical amplification of the minute sub-picomole withdrawn analyte takes place in the environment disclosed. When at least two differently charged substances occupy the same area, they become reagents to a signal passing through. The reagents cause recycling of the signal resulting in amplification. The charged positive membrane in the negative field acts as a reagent to the withdrawn glucose analyte and amplifies it;
- [0080] 75) Another form of this would be the use of a positive and negative membrane adjacent to each other to cause recycling and therefore amplification of analyte;
- [0081] 76) Amplification would take place if all the polarities cited above were reversed;
- [0082] 77) Charged membranes made with higher concentration of charged chemicals will show increased amplification;
- [0083] 78) More presence of charged membrane will increase the reaction and therefore increase amplification;
- [0084] 79) This invention lends itself for the new technology of 'labs-on-a-chip';
- [0085] 80) The electrode is a screen made of stainless steel to evenly disperse sodium hydroxide and pH;
- [0086] 81) The power supply consists of a 6 volt battery with circuitry to increase the DC output voltage to 70 volts. Note: voltage may be higher or lower. A safety circuit or fail-safe circuit is included;
- [0087] 82) The circuit includes a dosimetry circuit (Tapper patents) that precisely controls the analyte withdrawal quantity based on time and current;
- [0088] 83) This non-invasive diagnostic device includes a calibration switch;
- [0089] 84) A multi-position switch that selects the withdrawal time/current to match the highs, lows, and in-between time glucose levels of the patient caused by meals, physical exercise, or insulin dose;
- [0090] 85) A multiple position switch that selectively adjusts time and current to conform with well established periods of glucose change related to meal intake (also physical exercise and insulin dose);
- [0091] 86) The switch of Items 84 and 85 for following selections: Position 1 (1-2 hours after meals), Position 2 (2-3 hours after meals), and Position 3 (3-4 hours after meals);
- [0092] 87) Different time/current rates are assigned to each of the three switch positions;
- [0093] 88) A submultiple or multiple of the meter reading to extend range;
- [0094] 89) After gross selection is made with switch according to Items 83, 84, 85, 86, 87 and 88, a precise reading is obtained when the withdrawn glucose specimen is processed at the strip and results in a meter reading based on the glucose concentration or density in the withdrawn interstitial fluid; and
- [0095] 90) An LED to indicate the precise end to the withdrawal process.
- [0096] This invention also makes use of anionic and cationic penetration enhancers/inhibitors. The polarized penetration enhancers (examples set forth herein as typical but not exclusive penetration enhancers/inhibitors) improve drug delivery and analyte withdrawal. Conversely, it may be desirable to limit the penetration of a drug if uncontrolled depth would lead to unwanted side effects. Depth control may be achieved with the use of charged chemicals to repel or absorb the active drug and thus prevent it from further penetration. These charged chemicals may be iontophoretically infused either as a pretreatment or the charged chemicals may be formulated in solution with the active drug to limit the active drug's penetration. With drugs having possible toxic side effects (such as botulinum and the like), it is also very important that dosimetry control be used, e.g., see U.S. Pat. No. 4,822,334, as well as electrical current ramp up, such as that disclosed in U.S. Pat. No. 4,340,047. Both of the patents have as inventor, Robert Tapper, the same inventor as in the present application and may be readily combined with the delivery systems disclosed in the current application.

EXAMPLE 1

[0097] It is well established that the mechanism for iontophoretic sweat control using tap water is that a parakeratotic plug develops within the eccrine sweat duct by virtue of a series of treatments. The limiting factor to the six week sweat control are skin barriers that impede the plug and limit

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its travel within the duct. If a penetration enhancer were added to the solution, the plug will travel deeper down the sweat duct approaching the secretory coils. This results in much longer sweat inhibition since the plug now has a longer path to disgorge, thus ending a period of sweat control. Penetration enhancers capable of this activity are positively charged and therefore cationic. Cationic ions are driven by the positive polarity electrode. Anionic penetrants can also be used in an AC device.

EXAMPLE 2

[0098] In an electroosmosis device the positive polarity functions to drive interstitial water toward the negative polarity. The movement of water invariably includes essential elements that could be picked up at the negative pole and used for analysis (such as glucose analysis). The water movement is enhanced with a cationic penetration enhancer that will deliver larger quantities of the analyte.

EXAMPLE 3

[0099] The use of penetration enhancers with botulinum and/or collagen to improve delivery of these and other very large molecular drugs. Conversely, it may be desirable to limit the depth of infusion of botulinum and the like to avoid side effects, and this is accomplished with the use of polarized chemicals to better control the depth of infusion. Large molecular drugs may also be diluted to a lesser concentration for easier passage through the skin.

[0100] The following refers to various features and uses of iontophoretic devices and the chemicals or drugs they will deliver and the therapy they will perform.

[0101] 91) The use of penetration enhancers to increase the depth of penetration or conversely, penetration inhibitors to limit the depth of penetration of an active drug.

[0102] 92) The use of charged chemicals such as negative sulfonic acid or positive quaternary amine either in solution with botulinum or as a pre-treatment to botulinum infusion to limit the depth of penetration of potent botulinum when indicated.

[0103] 93) The use of cationic penetration enhancers with collagen or other fillers saturating a charged membrane intervenor between electrode and skin. When the filler is negatively charged, it may need an anionic penetration enhancer to enhance depth of penetration.

[0104] 94) The use of penetration enhancers with collagen or other drugs saturating a charged membrane intervenor between a non-metallic electrode such as conductive silicone and the skin.

[0105] 95) The claim of No. 1 to be used to enhance or limit penetration of a drug saturating a reservoir composed of charged membranes.

[0106] 96) The use of reverse iontophoresis or electroosmosis with a penetration enhancer at the positive pole to increase water flow to the negative for analyte pickup.

[0107] 97) The use of a cationic penetration enhancer with other active elements such as aluminum chlorhydrate or other aluminum derivatives, atropine, or the equivalent drug or chemical for sweat inhibition.

[0108] 98) The use of a cationic penetration enhancer saturating charged membranes which are intended to limit skin damage from high currents.

[0109] 99) The use of an anionic penetration enhancer saturating charged membranes which are intended to limit skin damage from high currents.

[0110] 100) The use of a penetration enhancer such as cetyltrimethylammonium bromide (CTAB) as an additive to an antiperspirant. CTAB is also the choice penetrant in an electroosmotic device to be driven by the positive pole.

[0111] 101) The use of a cationic or anionic penetration enhancer or limiter saturating a wool nib felt such as those used in pen markers. The wool felt nib intervenor also acts as a reservoir for an active drug to be driven into the skin from an iontophoretic device.

[0112] 102) The simultaneous infusion of botulinum and collagen or other fillers with penetration enhancers, each drug in a separate positive output using a common negative return.

[0113] 103) The infusion of botulinum with charged chemicals in solution or as a pre-treatment and simultaneously, but with another applicator, the infusion of collagen with a penetration enhancer but with the collagen in a negatively charged liposome and driven by the negative polarity. The botulinum would be driven into the skin by the positive polarity.

[0114] 104) Cationic or anionic penetration enhancers or limiters may also be used in passive or unpowered drug delivery patches. Drug propulsion into the skin would come from the charged membranes which also may be used to store the drug.

[0115] Typical but not Exclusive Penetration Enhancers/Inhibitors

CATIONICS	ANIONICS
Cetylpyridinium chloride	Sodium cetyl stearate
Cetyltrimethylammonium bromide	Sodium diethylsulfosuccinate
Benzalkonium chloride	Sodium dioctylsulfosuccinate
Benzethonium chloride	Sodium lauryl sulfate
Lauryl dimethylamino acid betaine	
Stearyl trimethylammonium chloride	

[0116] These and other objects and advantages of the invention will become apparent from the following more detailed description, when taken in conjunction with the accompanying drawings of illustrative embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0117] FIG. 1 is a perspective view of one embodiment of a passive patch construction in accordance with the present invention;

[0118] FIG. 2 is a perspective view of another passive patch constructed in accordance with the invention;

[0119] FIG. 3 is a perspective view of still another passive patch constructed in accordance with the present invention;

[0120] FIG. 4 is a perspective view of a powered patch construction in accordance with the present invention;

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[0121] FIG. 5 is a perspective view of another powered patch in accordance with the present invention, shown in place upon the skin;

[0122] FIG. 5a is a sectional view of a drug delivery device utilizing the present invention and illustrating multiple clustered electrical current emitting membranes;

[0123] FIGS. 6a, 6b and 6c are fragmentary perspective views of filter devices embodying features of the invention;

[0124] FIG. 7 is an exploded perspective view of a diagnostic probe constructed in accordance with the present invention;

[0125] FIG. 7b is a perspective view of a rolled charged membrane embodying the present invention;

[0126] FIG. 7c is an enlarged longitudinal view of a probe including a switch and LED; and

[0127] FIG. 7d is an enlarged view of the electrical switch for the probe shown in FIG. 7c.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0128] Referring now to the drawings, wherein like reference numerals refer to like or corresponding elements throughout the various figures of the drawings, there is shown in FIG. 1 an improved passive patch 10 embodying features of the present invention. The use of this technology in its simplest form without the use of battery-power would be with the commercially available passive patch 10 that is unpowered. The use of one or more polarized membranes 11 beneath a backing 12 acts to propel a drug into the skin if the polarity of the drug (or other chemical) and the membranes 11 were the same. In this instance, a liner 13 would be removed and the charged membranes 11 in communication with a drug-in-adhesive system 14 would propel the drug into the skin (not shown). Another configuration would be for the charged chemicals to be an inherent part of the drug-in-adhesion.

[0129] As shown in FIG. 2, the charged membranes 11 also act as a reservoir for the drug 14 with adhesion of the patch 10 made by separate tape 15 or any of a variety of taping means. For the first time, an infusion system without battery, would force much greater quantities of drug (or other chemicals) into the skin. They allow multiple hybridizations that could include a neutral charge among other effects. Examples of these membranes manufactured by Pall Corporation of 25 Harbor Park Drive, Port Washington, N.Y. 11050 are Mustang S, Mustang Q, Mustang C and Biodyne A, Biodyne B and Biodyne C. The Mustang series are of special interest with Mustang S giving a strong negative polarity with its surface modified by sulfonic acid. Mustang Q gives a strong positive polarity with its surface modified by quaternary amine. It should be understood that the chemicals cited are for example only and are not the only chemicals that can polarize support structures or control ion or molecule flow without a support structure. For instance, Mustang C is polarized with carboxylic acid. Other examples of functional groups that can bear a charge would be the hydroxyl, phosphate moieties. A unique feature of the invention is the use of charged or polarized chemicals on support members or not, to control a flux, current, or signal of polarized molecules, ions or electrons and even polar

neutral compounds as in an electroosmotic withdrawal system and a drug delivery system.

[0130] Referring to FIG. 3 of the drawings, a variation of the patch 10 would be for the inside of the backing 12 to be divided in half by an electrical insulator 15, such as a plastic divider, so that two different medicaments could be placed in each half—one of negative polarity and one of positive polarity with like-polarized membranes in each half to drive the drugs into the skin.

[0131] Another variation would be for the patch 10 to have a polarized membranes 11 under the backing 12 with a like-polarized drug saturating it and an opposite charged membrane 11 configured in a circle in close proximity around the inner drug bearing membrane but electrically insulated from it. Over 620 millivolts exist between polarized membranes 11 of one polarity and the skin. This value can be increased by adding more membranes 11 to the stack. It can also be increased by using charged chemicals in greater concentration. Still greater efficiency can be obtained by using charged membranes (or felts, filters, etc.) of both polarities with a membrane battery separator (not shown) in between.

[0132] Another very important application of these polarized membranes would be for wound dressing to promote wound healing or infection control. Published papers show that tissue growth is promoted when minor currents traverse the wound. Another paper attributes this growth to the anti-bacterial effect of low currents across a wound. In accordance with the invention, bacterial and fungal infection can be controlled with the electro-chemical effect of charged membranes, bandages or dressing over infected body areas.

[0133] A major problem with catheters is their propensity to cause infection at the body insertion opening. Coating or bonding charged chemicals of both polarities separated from each other onto the catheter tubing will give wide spectrum protection against bacterial infection. Medical use of this technology would be for stent coating. The charged coating (either charge or both) would have an eluting effect to prevent restenosis. Another medical use of this technology could include microscopic drug delivery for both external and internal application.

[0134] The charged membranes can also infuse an anti-septic for enhanced control. It may also be applied with a spray of the charged chemicals, sulfonic acid or quaternary amine or both or the equivalent. An example of such an application would be to apply a treatment cream or medicament over an area and then spray the polarized chemical over it. If the beneficial formulation applied to the skin is of the same polarity as the charged material on top, the treatment formulas (skin conditioners, etc.) or medicament will be driven into the skin. A variation of this would be to mix the treatment formula of known polarity with a charged chemical of the same polarity and then apply topically to the skin. The like-charged treatment formula will be driven into the skin.

[0135] Another example of the practice of this invention is to mix a positively charged chemical with a common "over the counter" antiperspirant. The charged chemical will drive the aluminum chloride or the like deep down the eccrine sweat duct for far more effectiveness than topical application. Another form of this would be a two-component system

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whereby aluminum chlorhydrate antiperspirant is topically sprayed under the arm and is followed with a spray of a positively charged chemical to infuse the aluminum chlorhydrate deep within the eccrine sweat duct.

[0136] Conversely with the above applications wherein there is an effort to drive or infuse the active drug or cosmetic deeper into the skin, there are certain applications where it is desirable to limit the travel of the active components to the epidermis (outer skin). Salicylic acid is an example of this. Salicylic acid and/or its derivative is the treatment of choice for acne, psoriasis, or photoaging. Because of its low pH (3-4), positively charged salicylic acid is capable of penetrating deeply through the epidermis, dermis and receptor fluid causing irritation. To overcome this problem, the use of the negatively charged chemicals of sulfonic acid or carboxyl acid or the like as a control for the permeation of the salicylic acid is suggested. When formulated with the salicylic acid, the negatively charged ions will combine with the positively charged salicylic acid and, when properly balanced, will limit the depth of penetration of the salicylic acid to the epidermis, thus eliminating irritation. Two other combinations using charged chemicals to limit the flow of the active salicylic acid to the epidermis would be the use of the negative and positive charges in formulation to result in a neutral charge. Still another impediment to the salicylic acid flow below the epidermis, would be the use of positively charged chemicals such as quaternary amine in solution with salicylic acid. These charged or neutral control chemicals can be in the form of spray to be applied over the initial application of salicylic acid.

[0137] Referring now more particularly to FIGS. 6a, 6b and 6c of the drawings, another major beneficial application of the present invention would be for the use of the positive membrane Mustang Q or a filter paper impregnated with Mustang Q or the like, to repel the positively charged nicotine chemical that is inhaled during smoking to prevent addiction. These membranes or filter paper or the like would take the form of layered filters 17a, 17b, 17c at any location between the lips and the tobacco and will effectively repel nicotine and other harmful chemicals from leaving the cigarette.

[0138] Carbon monoxide is another danger to the smoker. Carbon monoxide is formed by the combustion of carbon with a limited supply of air. As best shown in FIG. 6c, a positive membrane or impregnated filter paper 17a in direct contact with a negative membrane or filter paper 17b constitutes a battery and as a result liberates oxygen at the positive membrane and hydrogen at the negative membrane. These added gases would act to neutralize the carbon monoxide. The membranes could be 'wetted' with a pre-coated hydrogel or 'self-wetting' since the direct contact between the negative and positive membranes create a 'moist' condition. This would be an obvious boon to smokers worldwide since the medical community relates cancer, heart problems, pulmonary problems, etc. to the inhalation of tobacco smoke.

[0139] Also contemplated within the purview of the invention is a cigarette filter, as shown in FIG. 6, having a charged chemical(s) which attracts or repels unwanted polarized ions or molecules from a tobacco smoke stream so that they do not enter the mouth. The charged or polarized chemicals (FIGS. 6a, 6b, 6c) are covalently bonded to a non-volatile

inorganic substrate which is incorporated in the filter. The filter can remove nicotine, carbon monoxide, cadmium, lead, mercury, nickel, cyanide among other dangerous elements from tobacco smoke. These charged or polarized chemicals can be covalently bonded to silica gel (APS silica gel) or the like. The charged chemical(s) can be contained in a space in the filter or incorporated in one or more filter elements such as tipping paper, shaped paper insert, mouthpiece plug, solid filter element, or free-flow filter element. The charged chemicals can be part of or coated on paper such as tipping or filter paper or incorporated in non-paper filter elements formed from fibrous materials such as cellulose acetate or polypropylene fibers. The use of the charged chemicals on any of the aforementioned exemplary support structures addresses the safety aspect of the invention.

[0140] Other aspects of cigarette acceptability involve the tobacco flavor that a smoker seeks for gratification. With the source for this tobacco taste diminished or stopped by the charged membrane(s), it can be restored with the use of tobacco extracts or flavors in the space between the end of the cigarette that goes into the mouth and the membrane or filter in contact with the tobacco. Another variation of this is to coat a charged membrane with the same polarity tobacco extract to propel the extract or flavor into the mouth. The smoker will now experience a cigarette that is safe, imparts flavor, and exudes smoke that is psychologically satisfying.

[0141] Another application of the invention having major universal value would be in the field of dentistry. It has long been known that fluoride has beneficial effects for the care and well being of teeth. In this regard, the government has allowed fluoride to be added to the water system. An extension of this is a means of infusing fluoride below the surface of the teeth instead of topical application with a common dentifrice. This has been recognized by the FDA as the ultimate means of preventing cavities and they approved a methodology that uses an iontophoretic toothbrush to infuse a fluoride toothpaste beneath the surface of the tooth. Attempts were made to commercially introduce such a device but it failed at the marketplace. Among the problems is the short-term treatment of a brushing that would have questionable value. If the electrical current were raised, there could be a danger of injury to the very sensitive surrounding mucous membranes and the gum.

[0142] With the use of charged chemicals as a stand alone component away from membranes or felt pads, a new application of the present invention presents itself. The negatively charged chemicals (typically sulphonic acid or carboxyl acid and the like) when placed in a mouthwash or dentifrice with the presence of fluoride will act to infuse fluoride beneath the surface of the tooth. In addition, this process could continue over time for the ultimate cavity protection because residual activity may linger for hours. Some high potency fluoride toothpastes are recommended to be used without rinsing. Under these conditions, it is apparent that negatively charged chemicals will repel the negatively charged fluoride over time for the ultimate protection against tooth decay and the prevention of gum disease.

[0143] A major advance in noninvasive drug delivery is to introduce a battery 20 (see FIGS. 4 and 5) or any electrical power source to greatly increase fluxes of both ionic and polar neutral compounds. This process known as iontophoresis, works through one or a combination of the fol-

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lowing mechanisms: electrophoresis, electroosmosis, and electroporation. While this process was known for over 100 years, its use was extremely limited because of the burns and irritation it could cause, slow treatment since an increase in electrical current would cause unacceptable pain, and an inability to deliver large molecular drugs at therapeutic levels because of low current requirements as well as other needs. All of these handicaps that limit acceptability of a powered superior drug or chemical delivery system are now overcome by means of the present invention directed to the use of charged or polarized membranes.

[0144] The following examples of systems using charged membranes with electrically powered systems or battery, presumes the reader is aware that the drug or chemical to be delivered is in solution that could take the form of a liquid, gel or paste or equivalent that links the active elements together. In this instance, the membranes serve the purpose of a reservoir for this solution. The second purpose of the membranes 11 is to protect the skin from injury. Stacked or coiled charged membranes 11 or the equivalent will stop the migration of harmful ions from the battery 20 or electrical power source connected electrodes 22. For instance, multiple Mustang S membranes placed between the negative electrode and the skin will prevent sodium hydroxide from reaching the skin, yet it will allow the flow of electrical current between these two points. Multiple Mustang Q membranes placed between the positive electrode and the skin will prevent hydrochloric acid from reaching the skin. Very importantly, this allows enormous electrical current levels to be used with no skin injury and lessened pain. This means that noninvasive iontophoretic devices can deliver therapeutic levels of drug in the fastest possible time.

[0145] Combinations of these membranes 11 may be used under the same electrode 22. For instance, one use of the polarized membrane 11 would be to use the negative membrane against the negative electrode to repel the injury causing sodium hydroxide from reaching the skin. The positive charged membranes could also be used with the negative electrode because the unlike negative ions would bind to the positive membrane and therefore stop the injury causing ions from reaching the skin. Conversely, we may use the negatively charged membrane against the positive electrode to stop the injury causing hydrochloric acid from reaching the skin. The communicating link between electrical power source, through solution wetted membrane to skin, includes the drug or chemical of choice. The solution may even be non-conductive. Conductivity between the power source and the skin is made because the wetted membrane is conductive by virtue of its charged chemicals that electrically link the electrode to the skin. The charged membranes may be renewed and life-extended by simply reversing the polarity of the battery 20 or power source.

[0146] The device may be used with an AC signal (as in U.S. Pat. No. 5,224,927). Mixed polarity membranes may be used under each electrode in this instance. Mixed polarity membranes may also be used in a DC system under the same electrode. This has a stabilizing effect and enhances regulation.

[0147] A major challenge of this non-invasive technology is the infusion of large molecular drugs such as insulin. Also, the diabetic may need a 'bolus' shot (an exceptionally high infusion). Infusion of large molecular drugs requires high

electrical currents to drive them into the skin. Another example of the need for high currents to drive extremely high molecular drugs into the skin is the transport of glucosamine and chondroitin. These two chemicals can lessen pain and affect cartilage repair for knee osteoarthritis. Presently, these two chemicals require very large oral administration dosage to be effective. Losses created by first pass metabolism before they reach the area of effectiveness, make it necessary for large oral dosages. Direct application of these drugs to the knee area is superior. The problem arises because negatively charged chondroitin has a molecular weight of 60,000 daltons—over 10 times more than insulin! The aforementioned means of large electrical currents to give high current density are very effective to deliver these large molecules. Skin preps to aid permeability should be used with these drugs for non-invasive delivery. These preps include sodium salicylate and/or depilatories.

[0148] In still another effort to increase electrical current, in accordance with the invention, by reconfiguring the traditional flat surface of the active drug-carrying applicator we were able to increase current. Referring to FIG. 5b, a drug-carrying applicator 25 is shown to be multiple small, membrane containing openings 27. As before, the membrane acts as a drug reservoir and as an injury-preventing intervenor between the skin and the source of power. By breaking up a large flat delivery surface, in accordance with the invention, the electrical current could be increased appreciably.

[0149] It has been found that another contributor to pain during the iontophoretic process comes from the positive applicator of the device. The cause for the pain and therefore a limiting current factor at the positive output, is believed to be the fact that this polarity causes vasoconstriction. Vasoconstriction effects the nerve endings which we perceive as pain. By adding a very small percentage of a histamine to the positive applicator, the pain can be offset because the histamine is a vasodilator. In accordance with the invention, this facilitates increasing the electrical current. For example, if the vasodilators of acetylcholine (ACh) or methacholine (MCh) are added to the solution on the positive applicator, it will be infused along with any other elements within the solution thereby lessening the pain sensation and allowing for an increase of current.

[0150] In addition to the large electrical current capability of this invention, amplification also contributes to an enormous signal to significantly increase drug delivery. Subsequently described in this application is a competitive environment of two different charge levels in solution that acts to recycle and thus amplify. Drug delivery of insulin can also be greatly enhanced with the use of a small quantity of glucose (perhaps 0.2 mol/l) in solution with insulin. The insulin infusion could be increased about 9 times with this glucose additive. Conversely, a small quantity of insulin added to the glucose withdrawal solution will increase the withdrawn analyte sample in a reverse iontophoresis modality. Still another method of increasing flux or signal amplification in drug delivery is with the use of charged chemicals as an integral part of a support structure or in a solution that communicates between skin and electrode. When two differently charged substances are in solution, they become reagents, thereby causing recycling resulting in amplification of the delivered drug. The use of negatively or positively charged insulin (charge depends on pH) in an envi-

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ronment of a positively charged membrane and using a negative power source to drive this solution into the skin, also increases amplification.

[0151] The aforescribed systems describe various applications of charged molecules in either chemical form or as an integral part of a membrane, felt or equivalent support material. These applications include use of the polarized characteristic as a stand-alone infusion or delivery system, use of the polarized property to control bacterial or fungal infection and to promote healing, use of the charged property as a filter to stop movement of injury causing chemicals coming from tobacco and the like, use of the polarized characteristic to stop injurious chemicals coming from a battery or power supply in addition to various other applications. The use of charged chemicals or membranes or the like modified with these chemicals or the equivalent carrier of these chemicals is so unique and widely diverse that the present invention is directed to and includes the universality of use other than those limited prior uses by the aforementioned Pall Corporation for use in lab assays and industrial or clean air filters, but not for medical devices or personal care products and uses to enhance delivery of a beneficial flux, signal, or current.

Non-Invasive Diagnostic Device

[0152] A major aspect this invention is the ultimate application of the use of chemically charged membranes or charged chemicals in liquid form making possible the first non-invasive rapid diagnostic test for glucose or other analytes. The finished device has a number of other innovations for its successful operability.

[0153] To better understand the details of these features and their contribution to the complete working unit, an overview of the elements and workings of the device is presented. While the device can be worn as a watch on the wrist or placed in other areas, it is perhaps easier to follow in the form of a probe because the active elements are stacked sequentially in the probe and can be more readily understood in that form.

[0154] As shown in FIG. 7 the working probe is held as a pen 100 and placed on top of a vein on the wrist and makes an adequate glucose withdrawal within 95 seconds. The element touching the skin is a rolled, chemically charged membrane 111 that is wetted with a unique solution, gel or equivalent. The other end 111b of the membrane is in direct electrical contact with the negative terminal 120 of a power supply (battery) 125. There is now continuous electrical communication between the membrane end 111a that touches the skin and the negative terminal 120 because of the conductive, charged membrane 111. The circuit is complete when the patient is connected to the positive terminal 126 of the power source. The return electrode may also be placed on the forearm above of the wrist where a sample is taken. Another arrangement may be the grounding of the metal tube that is held by the hand applying the device to the wrist vein. The return electrode may also benefit from the use of charged membranes to prevent the hydrochloric acid generated at the positive electrode from reaching the skin. There are additional benefits with the use of the charged membranes. The charged membranes 111 are wetted with distilled deionized water and are conductive to the skin because the charged or ionic membranes are in direct contact

with the skin. This eliminates the traditional saline wetted return electrode. It has been determined that the saline actually interfered with the withdrawn glucose sample giving distorted information. While the system described is intended to withdraw neutral or zwitterionic species by convective flow with the negative polarity to measure such clinically important substances as glucose, cholesterol, lactate etc., it has other uses without departing from the spirit and scope of the invention.

[0155] The invention may also be used to monitor drug pharmacokinetics by non-invasive electromigration withdrawal with the use of an opposite polarity electrode.

[0156] Each element of the diagnostic probe will now be explained to further disclose the unique features of the invention and how each element contributes to a working device.

[0157] **CHEMICALLY CHARGED MEMBRANE(S) or FELT PADS**—This is the building block of the device 100. Its multi-functions include: the need to stop the sodium hydroxide (lye) coming from the negative battery terminal. If not stopped, the sodium hydroxide would cause skin injury resulting in permanent scarring. This is prevented when a positively charged membrane is the intervenor between the negative terminal and the skin. The negative sodium hydroxide ions are attracted to the positively charged membrane and stopped from migrating to the skin. Meanwhile, the membrane(s) 111 allow the transport in the opposite direction of the withdrawn interstitial fluid containing glucose to travel to the negative electrode 120. This is aided by the fact that the surface of the negative electrode has a very high pH (because of the sodium hydroxide emitted there) that attracts glucose. It is essential that the inherent, extreme pH perform its function of glucose attraction. The charged membrane intervenor allows this to happen but prevents the skin-damaging sodium hydroxide from reaching the skin. The opposite end 111a of this membrane that touches the skin is maintained at a near neutral pH for safety. The glucose analyte to be measured accumulates at the end 111a of the membrane 111 touching the negative electrode 120. Accordingly, the probe 100 is designed with the inside end of the membrane removable from the rest of the probe. After making the withdrawal from the skin, the patient separates this piece from the probe and affixes it to the strip on a glucose monitor (not shown). The deposition of the withdrawn glucose as stated above is uniquely on the inside end 111b of the membrane 111. This point is approximately a half-inch away from the pickup end 111a of the membrane 111 that touches the skin. It is this inside part of the membrane that is placed on the strip of a commercially available monitor that will respond with a glucose reading. This part 111 is then discarded and replaced with a new unit.

[0158] Other key elements in this application of charged membranes is how they are presented to the withdrawn analyte. It is important that the membranes offer a continuous, unbroken path for the glucose to travel to the electrode. Any impediment to this flow results in inaccurate readings. For instance, early investigation made use of membranes positioned flat on the skin pickup area. Since it was essential to increase thickness of the charged membrane between the skin and the high voltage electrode to prevent skin injury and pain, experiments were conducted with layered membranes. Up to 75 and more layers may be necessary to prevent injury

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and allow enormous current density to speed treatment. Unfortunately, the layered membranes gave false readings because each layer presented an interface to the signal that distorted the readings. A roll of the charged membrane is now used that when positioned on its side, allows the signal to traverse a single surface on its way to the electrode. Increasing the height of the charged membrane increases protection and allows greater current. A half-inch membrane spacing between the skin and electrode may be used, but a greater spacing using a membrane of greater height may provide enhanced results. For instance, literature sets iontophoretic currents at 0.5 ma per cm² for safety and comfort. With the arrangement just described, as much as 31 times more current density could be drawn. The membranes used for this research and development are, again, a product of Pall Corporation with a fixed and limited concentration of charged chemicals as an integral part of the membranes. They were intended for purposes other than those described here in connection with the present invention. Membranes may be improved and its effects more pronounced by using membranes made with charged chemicals of a much higher concentration.

[0159] An alternate configuration to the above design is based on the following performance needs: It has been determined that reducing the conductance of the solution is paramount to performance. One design feature toward this end is the use of neutral glucose as a solution. Another would be for the conductive charged membrane that connects the skin to the wire screen electrode to be made less conductive. To accomplish this a second, nonconductive membrane is introduced that is connected with the conductive charged membrane whose other end touches the electrode. The nonconductive membrane is a thin (typically, about 0.005 inch) membrane that is placed on the end of the charged membrane and comes in direct contact with the skin. In this manner the electrical conductivity of the path between the skin and the electrode is reduced compared to the previous disclosure of a conductive membrane only. With this arrangement, the glucose formulation is also reduced to the vicinity of 250 mg/dl thus further reducing clutter. These steps improve accuracy.

[0160] SOLUTION—The all-important linkage between the active elements to make them function, is the solution. Conductivity between the electrode and the skin, even with a nonconductive solution, is made by virtue of the wetted charged or ionic membrane(s) that is in contact with the electrode and the skin. The formulation for glucose withdrawal should not add clutter that would compete with and impede this extremely small signal. To meet these requirements, glucose (solute) is provided in a distilled deionized water solvent to fulfill these needs and add other essential characteristics. For a formulation to work optimally, it is critical that the solution be saturated with glucose. If not totally saturated, then the water solvent would absorb the glucose signal and none would be available for analysis. Formulations used in the practice of the present invention provide for a glucose reading of 1 mg/dl or higher. This assures a saturated solution. Present formulations use a solute of glucose of 360 or higher mg/dl glucose in a solvent of distilled deionized water. Since analysis is made using the Medisense Precision QID instrument, this high level glucose solution does not affect the reading because the QID strip is unresponsive to this solution. Yet the withdrawn interstitial glucose fluid is processed as a blood sample and would be

as reflected with a meter reading. Still another formulation for the solution would include a small quantity of insulin, perhaps 0.3% or less, in solution with the glucose. This combination has been found to greatly increase the signal passing through the membrane 111 on the way to the electrode 120, thus increasing amplification as subsequently described.

[0161] GLUCOSE AMPLIFICATION—In the subject invention, extremely low levels of glucose are electroosmotically withdrawn from the unbroken skin. It is very important that this small analyte (subpicomole level) be amplified to effect a reading in the shortest possible time. A novel means of doing this is still another use of the aforementioned chemically charged membranes 111 as a new form of reagent that results in chemical amplification of the glucose analyte with increased sensitivity and responsiveness. The reagent(s) is the charged chemical that is an integral part of a membrane. With the withdrawn glucose in solution passing through this membrane 111 drawn by the high pH negative terminal 120, the glucose reacts with self-replication. Factors that contribute to this amplification are the charged positive polarity of the membrane 111 in the negatively charged field. Another form of this amplification would be two or more adjacent membranes, one charged positively and another charged negatively. Glucose (or any other analyte) passing through these oppositely charged membranes would react by recycling and result in an amplified signal. Another form of this would be a membrane of one charge in an electric field of opposite charge. Another form would be two drugs or chemicals of different charges as previously mentioned. The competitive environment of the two different levels of charge in solution acts to recycle the glucose analyte. This ping-pong effect causing amplification allows analysis and quantification in the shortest possible time so that the reading is in real-time with the rapidly changing glucose in the body system. Increased amplification can be obtained using membranes made with a higher concentration of charged chemicals that will show increased reaction. This invention for chemical analysis lends itself to chip technology and in effect becomes 'labs-on-a-chip'.

[0162] THREE POSITION CALIBRATION SWITCH—To cover the wide range of glucose readings necessary for health assessment, it is desirable to have a calibration switch 140 on the probe 100, as best shown in FIG. 7c). The switch is in conformity with the expected glucose changes as a result of food intake. Referring to FIG. 7d, this switch 140 allows an adjustment of the withdrawal time/current for the following criteria: Position 1, (1-2 hours after meals), Position 2 (2-3 hours after meals and Position 3 (3-4 hours after meals). This process of switch position selection at the time of use is so that the end result readings of the detection meter compare with the blood standard within allowable tolerances. By assigning different withdrawal time/current to expected different glucose levels, we are able to cover the widest possible range of readings. In experiments with the Precision QID strips, position 1 represented 1-2 hours after meals and was set at a dosimetry of time and current that related to the high glucose levels of the day. Position 2 related to approximately the midpoint between meals and was set at a dosimetry of time and current to represent this mid level. Position 3 represented the longest period away from the last meal and was set with a low dosimetry of time and current. Extended ranges may be reached when sub-

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multiple or multiples of the reading are employed to extend range. This factory adjustment can be used to extend the range beyond the present pursuit. Newer generation strips may require different electrical currents and time in each of these three switch positions to function properly. After the gross selections are made with the calibration switch, precise readings are obtained when the withdrawn glucose specimen is processed at the strip and results in a meter reading.

[0163] **ACTIVE ELECTRODE**—The electrode 120 is made of stainless steel, which is resistive to sodium hydroxide. Importantly, the electrode is typically a stainless steel screen. This was selected because the sodium hydroxide that is generated at this electrode would normally travel to the perimeter of a solid surface stainless steel electrode. This would create 'hot spots' and possibly cause distorted readings of the glucose containing membrane 111 in contact with the electrode 120. The use of the screen electrode causes many 'perimeters' and therefore contributes to uniform distribution of sodium hydroxide across its surface for more consistent readings. The power supply within the probe consists of a 6 volt battery with circuitry to increase the voltage to 70 volts. This powers the dosimetry circuitry with switch controls for the time and current of the output feeding the active electrode. The dosimetry circuit integrates time and current and terminates this supply at precisely the same value for every patient. Since every patient's resistance is a variable, this circuit will adjust itself time-wise to compensate for different individual's resistance while holding current constant, so that everyone is treated equally. Tapper U.S. Pat. Nos. 6,485,437 and 6,059,736 describe this in electrical circuitry detail.

[0164] While the above diabetes diagnostic device is described in detail as a probe 100, the technology could all be included in other forms. For instance, the commercial strip used in various monitors could have an additional piece attached to it that could include the membranes and be connected internally to the commercial monitor for power, dosimetry timer, etc. This extended strip piece could be applied to the skin for withdrawal and the withdrawal tip folded back over the enzyme sensitive target for reading. Another structure would be in the form of a watch with a rotary dial to select seven positions for up to seven readings a day. Each position would have its own membrane (which should be changed after each reading). The key membrane in play would be connected between the skin and the electrode as described for the probe 100 configuration.

[0165] It will be apparent from the foregoing description, that the new and improved system, method, apparatus and chemistry of the present invention satisfies the following features and other needs and objectives of the invention:

[0166] 1) The use of charged chemicals of either negative or positive polarity on support members that could include a) membranes, b) felt pads made of natural or synthetic fibers, c) impregnated filter paper, d) liquid form, e) any material that allows charged chemicals to control ions, molecules or electrons;

[0167] 2) The use of charged chemicals of either negative or positive polarity formulated with an increased concentration of the charged chemicals causing either negative or positive polarity to increase their effectiveness;

[0168] 3) For use in a DC iontophoretic drug delivery system, the presence of charged chemicals in solution

as an integral part of a felt pad(s) or a membrane(s) to prevent: a) injurious chemicals emanating from the electrode from reaching the skin, b) sodium hydroxide developed at the negative terminal is prevented from reaching the skin with either a negatively charged or positively charged intervenor between the skin and the electrode in an electrically conductive circuit, c) hydrochloric acid generated at the positive electrode can be prevented from reaching the skin with either positively charged or negatively charged chemicals on an appropriate support intervenor spaced between the electrode and the skin in an electrically conductive system;

[0169] 4) The chemically charged intervenor(s) acting as a reservoir or storage area for the drug to be delivered;

[0170] 5) In iontophoresis or reverse iontophoresis or drug delivery or similar chemical or drug transport system, the use of currents above the traditional 0.5 ma per cm². The aforementioned charged chemicals either on support structure or without support structure, enable these high currents to be achieved. Large molecular delivery also benefits from high electrical current along with Tapper U.S. Pat. Nos. 6,238,381 and 6,425,891;

[0171] 6) In a powered patch, electrical currents can be further increased by a new physical configuration of the active, drug delivery applicator. High density current can be tolerated when multiple small circles of current emitting membranes are clustered instead of one large flat delivery surface;

[0172] 7) The use of the aforementioned charged chemicals of both negative and positive polarity together or separately to meet all objectives of these inventions;

[0173] 8) The use of charged chemicals on an intervenor or in combination with both polarities in an AC iontophoretic device;

[0174] 9) The use of histamines in the positive applicator to lessen the pain from this applicator and allow an increase in current;

[0175] 10) The use of charged membrane(s) in an otherwise unpowered patch (passive patch) to propel the drug(s) into the skin at greatly increased levels compared to other unpowered patches;

[0176] 11) The use of charged membrane(s) in an unpowered patch as a storage area or reservoir for drugs.

[0177] 12) The use of charged membrane(s) of either polarity or in combination to increase infusion in an otherwise unpowered patch;

[0178] 13) The use of charged membranes between skin and output electrode as the conductive element when wetted with distilled water without the need of a saline solution;

[0179] 14) The use in iontophoresis or reverse iontophoresis of charged membranes between the skin and output electrode as the conductive element when wet-

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ted with distilled water as a means of avoiding clutter from conductive chemicals that may be added to enhance transport;

[0180] 15) The use of charged membrane(s) in a powered patch of either polarity or in combination as an intervenor to prevent skin injury;

[0181] 16) The use of charged membrane(s) in a powered patch of either polarity or in combination to act as a drug storage area or reservoir;

[0182] 17) The use of charged membrane(s) in a powered patch of either polarity or in combination as a reservoir and intervenor to increase currents above 0.5 ma per cm² without skin injury;

[0183] 18) In drug delivery, a small amount of glucose (0.2 mol/l) in solution with insulin can be amplified 9 times in an unpowered environment using charged membranes;

[0184] 19) Feature 18 wherein the above solution is in a powered environment will increase the signal many-fold;

[0185] 20) Feature 19 in a powered environment with the use of polarized membranes to act both to prevent skin injury and further enhance amplification;

[0186] 21) In drug delivery, any chemical or drug in a powered environment and stored in oppositely charged membrane(s) will cause amplification;

[0187] 22) Another example of drug or chemical amplification is using the phenomena of oppositely charged drugs to create recycling and thus amplification would be with glucosamine and chondroitin. Glucosamine is positive and chondroitin is negative and the two in solution with the appropriately charged membranes and in an appropriately polarized field, would benefit from amplification;

[0188] 23 The use of charged chemicals on filters in cigarettes positioned between the tobacco and the end held in the mouth to prevent the migration of deleterious tobacco chemicals from entering the mouth upon inhaling;

[0189] 24) The use of charged chemicals of either polarity or in combination on impregnated filter paper or membranes as an intervenor between tobacco and mouth to prevent polarized harmful chemicals from reaching the mouth.

[0190] 25) The use of a tobacco extract or flavor in combination with Items 23 and 24;

[0191] 26) A charged membrane of the same polarity of the tobacco extract or flavor to propel the extract or flavor into the mouth;

[0192] 27) The use of charged chemicals as an inherent part of a bandage or the like, to have an antibacterial effect when placed over a wound;

[0193] 28) The use of a chemically charged bandage or the like that comes precoated with an antiseptic or the antiseptic is added later. The charged chemicals will

drive the antiseptic into the wound continuously when wetted or in gel form for communication between all elements;

[0194] 29) The use of a chemically charged bandage or the like to enhance and speed wound healing when wetted;

[0195] 30) The use of a charged chemical of negative polarity in a toothpaste containing fluoride to infuse the fluoride below the tooth's surface and gum to prevent cavities and disease;

[0196] 31) The use of a charged chemical of negative polarity as an integral part or coating of toothbrush bristles to cause the fluoride of a toothpaste to be driven or infused into the teeth or gums;

[0197] 32) The use of charged chemicals of either polarity as an additive to a germ-killing mouthwash to infuse the antiseptic into the teeth and gums;

[0198] 33) The use of a charged chemical of negative polarity to be used as an intervenor between a battery-powered iontophoretic toothbrush and the bristles to prevent injurious sodium hydroxide from the negative terminal of the battery from reaching the teeth, gums or mucous membrane;

[0199] 34) A stent coated with either positive or negative chemicals or both to cause elution and prevent restenosis.

[0200] 35) A stent with a coating of charged chemicals of either charge or both that will elute like-charged chemicals coated on top of the charged coating to prevent restenosis;

[0201] 36) A stent with a coating of charged chemicals either positively or negatively charged or both integrated with like-charged chemicals that will be propelled or eluted from the surface to prevent restenosis;

[0202] 37) A stent coated with quaternary amine, sulfonic acid or carboxyl acid or the equivalent to cause elution either with another chemical that will be driven beyond the surface or the charged coating alone to elute when surrounding tissue and body fluids come in contact;

[0203] 38) For cosmetic application, the use of charged chemicals in liquid form as a spray to be applied over a moisturizer base or any other skin conditioner. This will drive a like-charged cosmetic ingredient or skin improvement product deeper into the skin than topical application;

[0204] 39) The use of salicylic acid and/or its derivative in combination with a charged chemical to limit its travel beneath the skin and thus prevent irritation;

[0205] 40) The use of positively charged salicylic acid in combination with negatively charged sulfonic acid or carboxyl acid or the like to bind to each other and thus limit migration of the salicylic acid beneath the epidermis;

[0206] 41) The use of salicylic acid as a skin spray as part of a two component system wherein a negatively charged spray follows;

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- [0207] 42) Salicylic acid's pH buffered from three to four to a nonirritating pH of approximately five and infused into the skin by a like-charged chemical;
- [0208] 43) The use of negatively charged sodium salicylate with negatively charged chemicals to infuse the sodium salicylate into the skin for beneficial effects. The sodium salicylate and the negatively charged chemicals may be in formulation or they may be in the form of a two component system whereby the sodium salicylate is applied first as perhaps a spray and followed by a spray of negatively charged chemicals;
- [0209] 44) For cosmetic and personal care application, the use of charged chemicals in formulation with like-charged skin improvement material. The repelled skin improvement materials will be infused deeper into the skin;
- [0210] 45) The use of the negative and positive charges in formulation to result in a neutral charge and then mixed with the salicylic acid to limit its penetration to the epidermis;
- [0211] 46) The neutral formulation of Item 45 to be used as a spray following the application of salicylic acid to limit its penetration;
- [0212] 47) The use of positively charged chemicals such as quaternary amine in solution with salicylic acid to limit the depth of its penetration to the epidermis;
- [0213] 48) The use of charged or neutral control chemicals in the form of a spray to be applied over the initial application of salicylic acid to limit its depth of penetration to the epidermis;
- [0214] 49) In a permanent hair remover (Tapper U.S. Pat. Nos. 6,094,594 and 6,206,869) wherein a depilatory is driven into the follicle by an iontophoretic device, the use of a charged intervenor between battery and skin for the purposes of: a) to use high currents to expedite treatment, b) to use chemically charged intervenor to prevent skin injury, c) to use the chemically charged intervenor as the storage or reservoir vehicle for the depilatory;
- [0215] 50) A non-invasive diagnostic withdrawal device using a charged or polarized membrane(s), one end of which is positioned to touch the skin and the other end touching the electrode;
- [0216] 51) An alternate construction of Item 50 is the use of two membranes, one charged or conductive and the other nonconductive in direct contact with each other and spaced between the skin and the electrode;
- [0217] 52) The use of a charged membrane and an uncharged membrane in a withdrawal system whereby the uncharged membrane is placed in contact with the skin and the charged membrane in contact with the electrode to complete the circuit.
- [0218] 53) The use of a wool felt nib such as from a marker pen as the intervenor between the skin and electrode to prevent the passage of sodium hydroxide from the negative electrode from passing to the skin. The wool nib may or may not be coated with charged chemicals;
- [0219] 54) The charged or polarized intervenor of Item 50 that is approximately a half-inch in length and placed between skin and electrode;
- [0220] 55) The membrane of Items 50-54 between the skin and the electrode to protect against skin injury;
- [0221] 56) Increasing the height of this membrane of Items 50, 41 and 55 allows the use of currents above 0.5 ma per cm²;
- [0222] 57) This charged membrane intervenor of Items 50, 54, 55 and 56 allows the use of high currents above the traditional 0.5 ma/cm²;
- [0223] 58) Increasing the level of charge of the aforementioned membrane(s) by higher concentrations of the polarized material improves the benefits cited above;
- [0224] 59) A positively charged wetted (gel) membrane prevents skin injury by stopping the sodium hydroxide ions emitted from the negative electrode in an electrically conductive circuit;
- [0225] 60) The charged membrane interposed between skin and negative terminal also stores the solution (or gel) necessary to effect communication or current flow between skin and electrode;
- [0226] 61) The target withdrawn glucose analyte passes through the membrane to the end that touches the negative electrode and becomes the critical pick-up point for the glucose monitor to read. This pick-up point for the withdrawn glucose analyte is unique in that it is against the electrode and not at membrane entry point in contact with the skin;
- [0227] 62) The charged membrane is constructed in a rolled form so that one side of the membrane touches the skin and the other side touches the electrode. In other words, when viewed from the skin, the withdrawn analyte sees only straight line, unbroken surfaces while migrating to the electrode;
- [0228] 63) The membrane form of Item 62 that causes the withdrawn glucose analyte to flow in a straight line while migrating to the electrode;
- [0229] 64) The structure of Items 62 and 63 that causes the withdrawn glucose signal deposition on the end of the membrane in direct contact with the electrode;
- [0230] 65) The use of a high pH from the electrode that attracts the glucose to this point of signal deposition;
- [0231] 66) The structure of Features 62, 63, 64 and 65 wherein the membrane end in contact with the electrode is the pick-up point for the withdrawn glucose which is then placed in contact with the monitor's strip for analysis or direct reading;
- [0232] 67) The positive return electrode may also use charged membranes to prevent skin damage and allows toleration of higher currents;
- [0233] 68) The positive return electrode of the system described above may also be used to monitor drug pharmacokinetics;
- [0234] 69) A solution formulated with glucose in a solvent of distilled deionized water;

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- [0235] 70) The solution of Item 69 wherein the glucose must totally saturate the distilled deionized water to prevent absorption of the withdrawn glucose;
- [0236] 71) The solution of Items 69 and 70 must have a surplus of glucose (distilled deionized water solvent totally saturated) with a monitor reading between 1 and 400 mg/dl or more;
- [0237] 72) Adding a small quantity of insulin to the glucose solutions of Items 69, 70 and 71, perhaps 0.3% or less, greatly increases the analyte signal or causes amplification;
- [0238] 73) The solution of Items 69, 70, 71 and 72 that may include stabilizers or preservatives;
- [0239] 74) Chemical amplification of the minute sub-picomole withdrawn analyte takes place in the environment disclosed. When at least two differently charged substances occupy the same area, they become reagents to a signal passing through. The reagents cause recycling of the signal resulting in amplification. The charged positive membrane in the negative field acts as a reagent to the withdrawn glucose analyte and amplifies it;
- [0240] 75) Another form of this would be the use of a positive and negative membrane adjacent to each other to cause recycling and therefore amplification of analyte;
- [0241] 76) Amplification would take place if all the polarities cited above were reversed;
- [0242] 77) Charged membranes made with higher concentration of charged chemicals will show increased amplification;
- [0243] 78) More presence of charged membrane will increase the reaction and therefore increase amplification;
- [0244] 79) This invention lends itself for the new technology of 'labs-on-a-chip';
- [0245] 80) The electrode is a screen made of stainless steel to evenly disperse sodium hydroxide and pH;
- [0246] 81) The power supply consists of a 6 volt battery with circuitry to increase the DC output voltage to 70 volts. Note: voltage may be higher or lower. A safety circuit or fail-safe circuit is included;
- [0247] 82) The circuit includes a dosimetry circuit (Tapper patents) that precisely controls the analyte withdrawal quantity based on time and current;
- [0248] 83) This non-invasive diagnostic device includes a calibration switch;
- [0249] 84) A multi-position switch that selects the withdrawal time/current to match the highs, lows, and in-between time glucose levels of the patient caused by meals, physical exercise, or insulin dose;
- [0250] 85) A multiple position switch that selectively adjusts time and current to conform with well established periods of glucose change related to meal intake (also physical exercise and insulin dose);
- [0251] 86) The switch of Items 84 and 85 for following selections: Position 1 (1-2 hours after meals), Position 2 (2-3 hours after meals), and Position 3 (3-4 hours after meals);
- [0252] 87) Different time/current rates are assigned to each of the three switch positions;
- [0253] 88) A submultiple or multiple of the meter reading to extend range;
- [0254] 89) After gross selection is made with switch according to Items 83, 84, 85, 86, 87 and 88a precise reading is obtained when the withdrawn glucose specimen is processed at the strip and results in a meter reading based on the glucose concentration or density in the withdrawn interstitial fluid; and
- [0255] 90) An LED to indicate the precise end to the withdrawal process.
- [0256] Penetration Enhancers/Inhibitors in Iontophoresis
- [0257] This invention also makes use of anionic and cationic penetration enhancers/inhibitors. The polarized penetration enhancers (examples set forth herein as typical but not exclusive penetration enhancers/inhibitors) improve drug delivery and analyte withdrawal. Conversely, it may be desirable to limit the penetration of a drug if uncontrolled depth would lead to unwanted side effects. Depth control may be achieved with the use of charged chemicals to repel or absorb the active drug and thus prevent it from further penetration. These charged chemicals may be iontophoretically infused either as a pretreatment or the charged chemicals may be formulated in solution with the active drug to limit the active drug's penetration. With drugs having possible toxic side effects (such as botulinum and the like), it is also very important that dosimetry control be used, e.g., see U.S. Pat. No. 4,822,334, as well as electrical current ramp up, such as that disclosed in U.S. Pat. No. 4,340,047. Both of these patents have as inventor, Robert Tapper, the same inventor as in the present application and may be readily combined with the delivery systems disclosed in the current application.
- [0258] For shock prevention, the electrical circuit must automatically provide for a slow rise or ramp up of current. This could take up to 4 or 5 seconds and be independent of the operator's (or patient's) control.
- [0259] If the patient is under treatment and suddenly loses contact with the circuit, the circuit must in microseconds, shut down so that the patient is not shocked. This happens because the patient removes their contact in milliseconds and the circuit reacts (shuts down) in microseconds.
- [0260] The same automatic delay as a ramp down must take place at the end of treatment to avoid shock. This delay takes place no matter how fast the inexperienced patient turns the control off.

EXAMPLE 1

[0261] It is well established that the mechanism for iontophoretic sweat control using tap water is that a parakeratotic plug develops within the eccrine sweat duct by virtue of a series of treatments. The limiting factor to the six week sweat control are skin barriers that impede the plug and limit its travel within the duct. If a penetration enhancer were

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added to the solution, the plug will travel deeper down the sweat duct approaching the secretory coils. This results in much longer sweat inhibition since the plug now has a longer path to disgorge, thus ending a period of sweat control. Penetration enhancers capable of this activity are positively charged and therefore cationic. Cationic ions are driven by the positive polarity electrode. Anionic penetrants can also be used in an AC device.

EXAMPLE 2

[0262] In an electroosmosis device the positive polarity functions to drive interstitial water toward the negative polarity. The movement of water invariably includes essential elements that could be picked up at the negative pole and used for analysis (such as glucose analysis). The water movement is enhanced with a cationic penetration enhancer that will deliver larger quantities of the analyte.

EXAMPLE 3

[0263] The use of penetration enhancers with botulinum and/or collagen to improve delivery of these and other very large molecular drugs. Conversely, it may be desirable to limit the depth of infusion of botulinum and the like to avoid side effects, and this is accomplished with the use of polarized chemicals to better control the depth of infusion (also see paragraphs [00044] and [000133]). Large molecular drugs may also be diluted to a lesser concentration for easier passage through the skin.

[0264] The following refers to various features and uses of iontophoretic devices and the chemicals or drugs they will deliver and the therapy they will perform.

[0265] 91) The use of penetration enhancers to increase the depth of penetration or conversely, penetration inhibitors to limit the depth of penetration of an active drug.

[0266] 92) The use of charged chemicals such as negative sulfonic acid or positive quantinary amine either in solution with botulinum or as a pre-treatment to botulinum infusion to limit the depth of penetration of potent botulinum when indicated.

[0267] 93) The use of cationic penetration enhancers with collagen or other fillers saturating a charged membrane intervenor between electrode and skin. When the filler is negatively charged, it may need an anionic penetration enhancer to enhance depth of penetration.

[0268] 94) The use of penetration enhancers with collagen or other drugs saturating a charged membrane intervenor between a non-metallic electrode such as conductive silicone and the skin.

[0269] 95) The claim of No. 1 to be used to enhance or limit penetration of a drug saturating a reservoir composed of charged membranes.

[0270] 96) The use of reverse iontophoresis or electroosmosis with a penetration enhancer at the positive pole to increase water flow to the negative for analyte pickup.

[0271] 97) The use of a cationic penetration enhancer with other active elements such as aluminum chlorhydrate or other aluminum derivatives, atropine, or the equivalent drug or chemical for sweat inhibition.

[0272] 98) The use of a cationic penetration enhancer saturating charged membranes which are intended to limit skin damage from high currents.

[0273] 99) The use of an anionic penetration enhancer saturating charged membranes which are intended to limit skin damage from high currents.

[0274] 100) The use of a penetration enhancer such as cetyltrimethylammonium bromide (CTAB) as an additive to an antiperspirant. CTAB is also the choice penetrant in an electroosmotic device to be driven by the positive pole.

[0275] 101) The use of a cationic or anionic penetration enhancer or limiter saturating a wool nib felt such as those used in pen markers. The wool felt nib intervenor also acts as a reservoir for an active drug to be driven into the skin from an iontophoretic device.

[0276] 102) The simultaneous infusion of botulinum and collagen or other fillers with penetration enhancers, each drug in a separate positive output using a common negative return.

[0277] 103) The infusion of botulinum with charged chemicals in solution or as a pre-treatment and simultaneously, but with another applicator, the infusion of collagen with a penetration enhancer but with the collagen in a negatively charged liposome and driven by the negative polarity. The botulinum would be driven into the skin by the positive polarity.

[0278] 104) Cationic or anionic penetration enhancers or limiters may also be used in passive or unpowered drug delivery patches. Drug propulsion into the skin would come from the charged membranes which also may be used to store the drug.

[0279] Typical but not Exclusive Penetration Enhancers/Inhibitors

CATIONICS	ANIONICS
Cetylpyridinium chloride	Sodium cetyl stearate
Cetyltrimethylammonium bromide	Sodium diethylsulfosuccinate
Benzalkonium chloride	Sodium dioctylsulfosuccinate
Benzethonium chloride	Sodium lauryl sulfate
Lauryl dimethylamino acid betaine	
Stearyl trimethylammonium chloride	

[0280] It will be apparent from the foregoing that, while particular forms of the invention have been illustrated and described, various alternatives, modifications and variations can be made without departing from the spirit and scope of the invention. Accordingly, the invention is intended to embrace all such alternatives, modifications and variations and it is not intended that the invention be limited, except as by the following claims.

I claim:

1. In an iontophoresis delivery system, penetration enhancers to increase the depth of penetration or conversely, penetration inhibitors to limit the depth of penetration of an active drug.

2. A method of treatment, comprising:

using charged chemicals such as negative sulfonic acid or positive quantinary amine either in solution with botu-

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- linum or as a pre-treatment to botulinum infusion to limit the depth of penetration of potent botulinum when indicated.
3. A method of treatment, comprising:
using cationic penetration enhancers with collagen or other fillers saturating a charged membrane intervenor between electrode and skin.
4. A method as recited in claim 3, wherein when the filler is negatively charged, an anionic penetration enhancer is provided to enhance depth of penetration.
5. A method of treatment, comprising:
using penetration enhancers with collagen or other drugs saturating a charged membrane intervenor between a non-metallic electrode such as conductive silicone and the skin.
6. A system as recited in claim 7 and further including enhancement or inhibition of penetration of a drug saturating a reservoir composed of charged membranes.
7. A method comprising:
using reverse iontophoresis or electro-osmosis with a penetration enhancer at the positive pole to increase water flow to the negative pole for analyte pickup.
8. A method of treatment, comprising:
the use of a cationic penetration enhancer with other active elements such as aluminum chlorhydrate or other aluminum derivatives, atropine, or the equivalent drug or chemical for sweat inhibition.
9. A method comprising:
use of a cationic penetration enhancer saturating charged membranes for limiting skin damage from high currents.
10. A method comprising:
use of an anionic penetration enhancer saturating charged membranes for limiting skin damage from high currents.
11. A method comprising:
use of a penetration enhancer such as cetyltrimethylammonium bromide (CTAB) as an additive to an antiperspirant.
12. A method comprising:
using CTAB as a penetrant in an electroosmotic device to be driven by the positive pole.
13. A device, comprising:
a cationic or anionic penetration enhancer or limiter saturating a wool nib felt such as those used in pen markers, said wool felt nib intervenor providing a reservoir for an active drug to be driven into the skin from an iontophoretic device.
14. A method of treatment, comprising:
simultaneous infusion of botulinum and collagen or other fillers with penetration enhancers, each drug in a separate positive output using a common negative return.
15. A method of treatment, comprising:
infusion of botulinum with charged chemicals in solution or as a pre-treatment and simultaneously, but with another applicator, infusion of collagen with a penetration enhancer, with the collagen in a negatively charged liposome and driven by the negative polarity; and driving the botulinum into the skin by the positive polarity.
16. A method, comprising:
using cationic or anionic penetration enhancers or limiters in passive or unpowered drug delivery patches; and drug propulsion into the skin being accomplished by charged membranes which also may be used to store the drug.
17. A system and/or method as recited in any of claims 1-16 wherein automatic dosimetry control is provided.
18. A system and/or method as recited in any of claims 1-17 wherein iontophoretic electrical current is applied as an initial ramp up to mitigate shock.
19. A system and/or method as recited in any of claims 1-18, and further comprising:
an electronic control system for iontophoretic delivery of electrical current over time to a biological subject including means for determining the magnitude of said electrical current delivered to the biological subject;
means for controlling the time period over which electrical current is supplied to the biological subject;
adjustable means for selecting the dosage to be delivered to the biological subject;
means for electrically measuring the actual dosage applied to the biological subject as a function of said electrical current and time; and
means for terminating said electrical current delivered to the biological subject when said function equals said desired total dosage to be administered as established by said adjustable means.
20. Each and every novel feature and/or combination of features herein disclosed.

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United States Patent [19]

Tapper

[11] Patent Number: 5,224,927
[45] Date of Patent: Jul. 6, 1993

- [54] IONTOPHORETIC TREATMENT SYSTEM
[76] Inventor: Robert Tapper, 1935 Armacost Ave., Los Angeles, Calif. 90025
[21] Appl. No.: 607,874
[22] Filed: Nov. 1, 1990
[51] Int. Cl.⁵ A61N 1/30
[52] U.S. Cl. 604/20; 128/803; 128/898
[58] Field of Search 604/20, 783; 128/798, 128/802, 803
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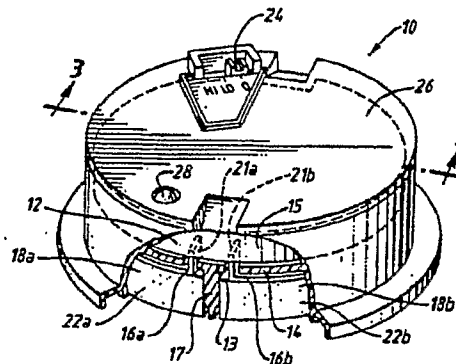
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[57]

ABSTRACT

A method and apparatus for applying iontophoretic treatment to a biological subject wherein electrical treatment current between a pair of electrodes is periodically reversed at very low frequencies, substantially in the range of approximately 0.0027 Hz to approximately 10 Hz, to mitigate tissue damage, enable long term dosimetry with single and multiple drugs of any polarity and at higher concentrations, and eliminate the need for buffering agents and the like, all in a relatively simple, economical and compact physical packaging configuration. The system delivers treatment substances with large and/or small molecular size and weight and can be adjusted to control pH at the delivery site. A method of lowering resistance and enhancing permeability at the delivery site is also provided.

19 Claims, 4 Drawing Sheets



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FIG. 1

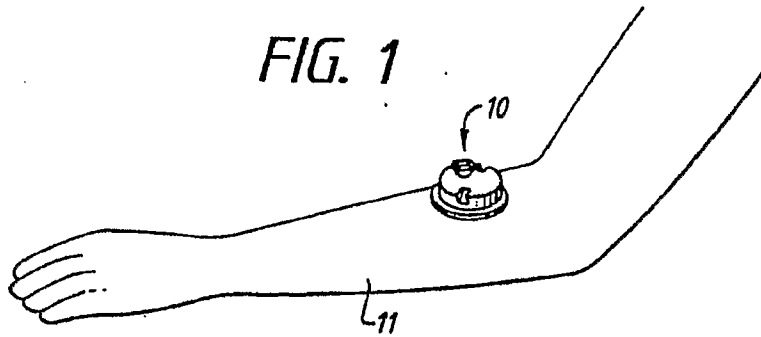


FIG. 2

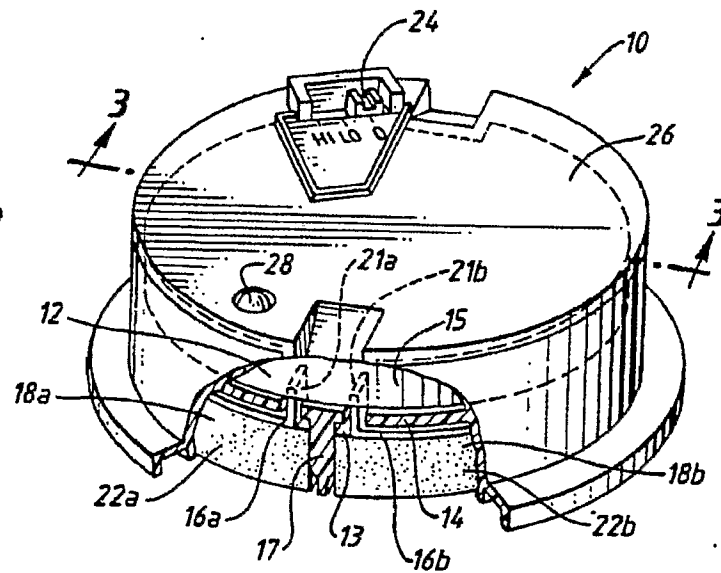


FIG. 3

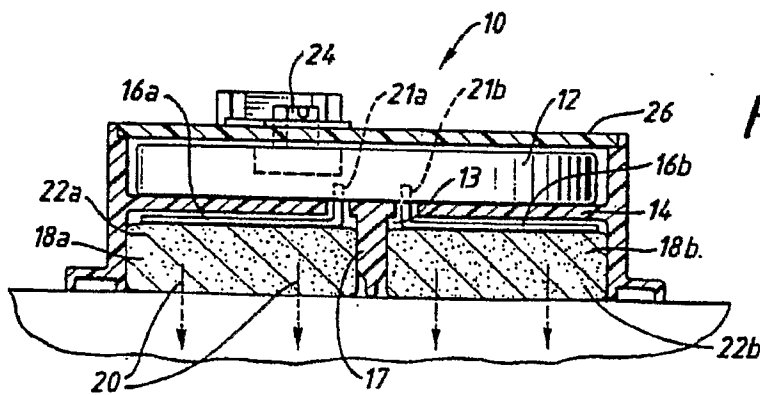


FIG. 4

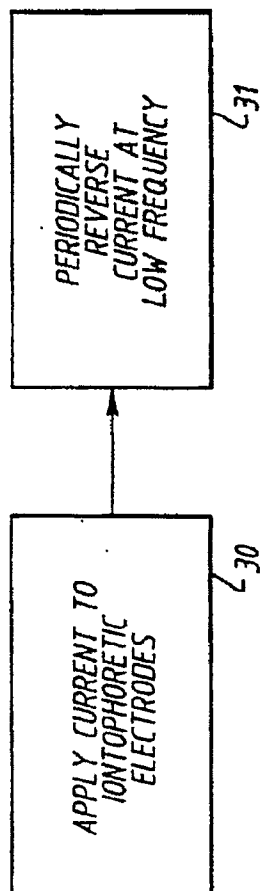


FIG. 5

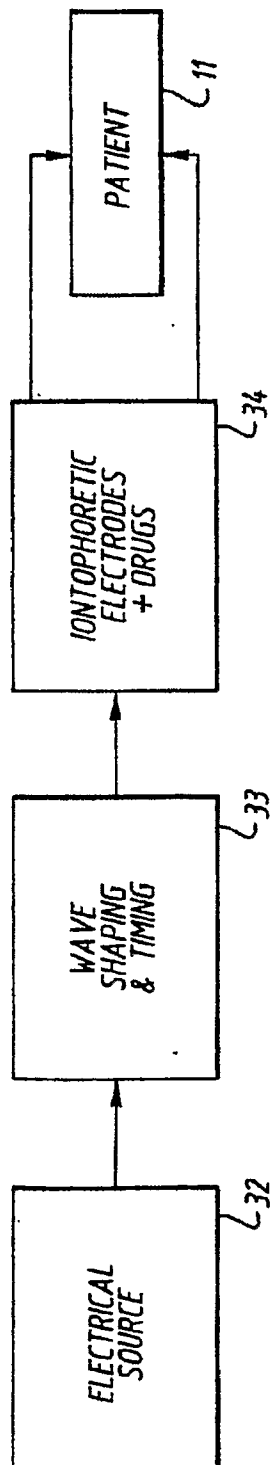


FIG. 6

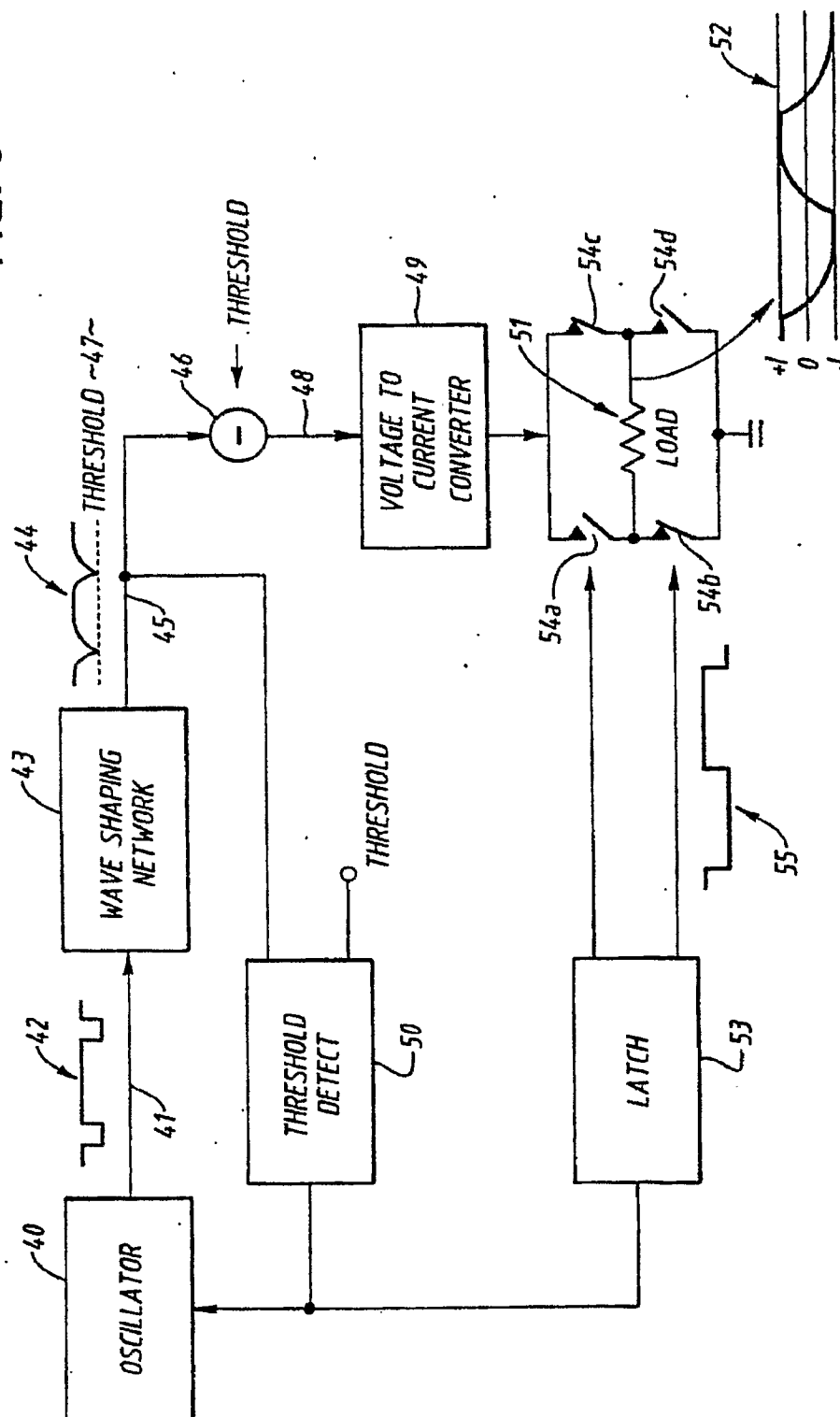
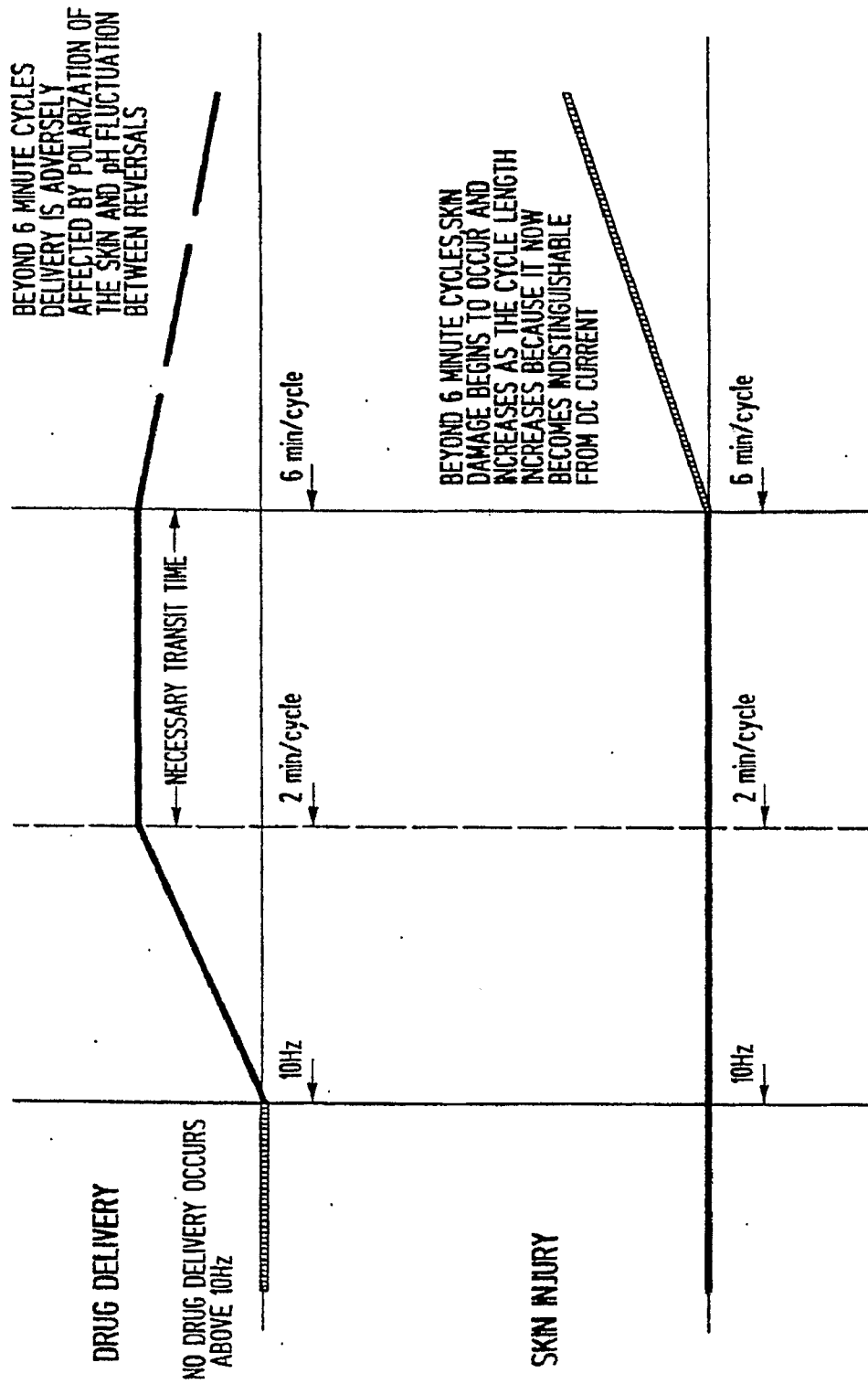


FIG. 7



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IONTOPHORETIC TREATMENT SYSTEM

BACKGROUND OF THE INVENTION

This invention relates generally to improvements in methods and apparatus for effecting an electrotherapeutic treatment on a biological subject, such as iontophoretic delivery of medicaments and, more particularly, to a new and improved system for the application of an iontophoretic treatment topically to the skin of a human body.

Around the turn of the century there was disclosed a plethora of electrode types for applying "electric treatments" to the human body. The electrodes were normally placed upon the body in relation to the position of the organ to be treated. Such "electric treatments" encompassed a wide range of applications. For example, galvanic (direct current) treatments have been popular in the past for their polar effects on ionized molecules, causing the ionized molecules to be driven through the skin, usually superficially. This phenomenon is known as iontophoresis or ion transfer, and it has been employed for the introduction of medicaments or even simply moisture, into the skin of a patient.

More specifically, and by way of example, some ions of zinc and copper can be employed in the treatment of various skin infections, and chlorine ions have been employed for the loosening of superficial scars. Further, vasodilating drugs can be used in rheumatic and peripheral vascular affections, and skin anesthesia can be produced by iontophoresis of local anesthetic drugs. Moreover, iontophoretic administration of drugs typically avoids the gastrointestinal side effects sometimes associated with direct ingestion of such drugs.

Although the aforementioned iontophoretic treatments have been found to be effective, they are also known to be accompanied by a number of undesirable side effects, such as the occurrence of skin injury in the form of iontophoretic burns and irritation in the treated area, as well as the formation of undesirable vesicles and bulla, on the skin in the treated area. Various complicated or compromised methods for preventing these iontophoretic burns have been developed. However, such methods and apparatus have generally been found not to be adequately effective for preventing irritation and the formation of vesicles or bulla on the skin in the treated area. Consequently, iontophoretic treatments have usually been limited to relatively low electrical currents and relatively short periods of administration of, typically, twenty minutes or less.

Iontophoretic drug delivery systems of the prior art have also been primarily limited to delivering a drug of only a single polarity at a time to a given area, at relatively low concentrations, and have not been suitable for simultaneous delivery of multiple drugs. Furthermore, there were virtually no satisfactory iontophoretic devices which were relatively simple, economical, compact, portable and capable of safe, long term delivery over several days, once applied to the patient and placed into operation. Attempts to meet these needs have involved rather complex buffering, electrical or other compensatory systems which have not proven entirely practical or satisfactory.

In addition to the foregoing difficulties, iontophoretic systems of the past have not proven effective in the administration of drugs embodying relatively large and/or heavy molecular structures. Moreover, drug formulations intended for iontophoretic therapeutic drug de-

livery have oftentimes required buffering agents for pH control. Control of pH at the delivery site of the therapeutic drug has been essentially unknown. Furthermore, difficulties in obtaining sufficiently high rates of infusion, due to relatively high electrical resistance and/or poor permeability at the delivery site, have also been encountered with iontophoretic systems.

The aforementioned difficulties and undesirable side effects of iontophoretic treatment have resulted in a sometimes less than enthusiastic reception of iontophoretic techniques by the medical community, in spite of the potentially great and varied advantages to be realized through their use and development.

Hence, those concerned with development and use of iontophoretic systems in the medical field have long recognized the need for a convenient and effective apparatus and method for preventing burns, irritation and the formation of vesicles and bulla on the skin in an area subjected to an iontophoretic treatment over extended periods of continuous treatment, for systems which can be physically packaged in a relatively simple, economical and compact configuration, can deliver therapeutic drugs at a relatively high rate and at higher concentrations, without the need for buffering agents and the like, which are capable of delivering large molecular substances such as insulin and the like, can deliver a plurality of drugs simultaneously in a relatively simple manner without matching drug polarity, can be used to lower resistance and increase permeability, and can be used to reliably control pH at the drug administration site. As will become apparent from the ensuing discussion, the present invention clearly fulfills all of these needs and more.

SUMMARY OF THE INVENTION

Briefly, and in general terms, the present invention provides a method and apparatus for applying electrical energy topically to a suitable surface of a biological subject, such as the skin of a human body, particularly for the long term administration of medicaments and the like or for other electrotherapeutic treatment, and by which the aforementioned deficiencies and undesired side effects are greatly minimized and may be eliminated. Moreover, the system of the present invention is relatively inexpensive to manufacture, can be physically packaged in a completely self-contained, relatively simple and compact configuration, trouble free and reliable in use, is capable of higher drug administration rates and drug concentrations, can deliver multiple drugs simultaneously in a simple manner, can control pH at the delivery site, is capable of delivering large and/or heavy molecule drugs, is a more effective bactericidal, and is arranged to be safely, simply and reliably operated for self-treatment by an average person in normal home use, even for extended periods of several days at a time. Furthermore, it is contemplated in the practice of the invention that electrical impedance at the administration site on the patient can be substantially reduced to vastly improve permeability and penetration and thereby further enhance medicament delivery.

Basically, the present invention is directed to a new and improved system for iontophoretic drug administration which includes conducting direct electrical current through the skin of a body, and periodically reversing the electrical current and conducting the current through the skin in the opposite direction, to effectively deliver very low frequency AC current, substantially in

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the critical range of approximately 0.0027 Hz to 10 Hz. It has been discovered that, within this substantially critical frequency window between approximately six minutes per full cycle and approximately ten cycles per second, a dramatic cancellation of skin damaging ions takes place. At frequencies higher than approximately 10 Hz, no substantial effective delivery takes place. At frequencies lower than approximately 0.0027 Hz, the risk of skin injury increases substantially.

It is well known that the positive iontophoretic electrode, in addition to its primary function of driving like polarity ionic substances into the skin of a subject, unfortunately produces skin damaging hydrochloric acid as well. Likewise, the negative iontophoretic electrode, in addition to its primary function of driving like polarity ionic substances into the skin, unfortunately also produces skin damaging sodium hydroxide. However, within the aforesaid frequency range of the present invention, either driving polarity delivers the desired ionic therapeutic substances, but also cancels the undesired skin damaging ions with the reverse portion of the electrical cycle. The reason for neutralization of the harsh injury producing chemicals, i.e., hydrochloric acid and sodium hydroxide, is that both of these chemicals require a finite period of time on the skin to cause damage. Hence, these damaging chemicals are made to cancel each other before damage takes place, by critical frequency selection, in accordance with the invention, of the AC driving signal. Therefore, optimization of a long sought therapeutic device with reduced side effects has been achieved.

In accordance with the invention, electronic circuitry is provided to automatically impose the reversal of electrical current at regularly repeating intervals of time, in accordance with the aforescribed substantially critical frequency range, and the system can be adjusted to conduct the iontophoretic treatment at any desired level of electrical current.

More specifically, the present invention is directed to a novel concept in overcoming the unwanted ions generated at the negative and positive electrodes of an iontophoretic drug delivery system, that lead to skin damage among other undesirable effects during iontophoresis. In attempting to replicate the drug delivery capability of an IV unit that would be used continuously over days, iontophoretic devices of the past are generally unsatisfactory because of their impracticality, complexity and/or the substantial skin damage they would cause. When the demand is for use over days, the new, simplified and improved technology of the present invention is required to overcome the skin damaging acid and alkali generated at the electrodes. This new technology that results in the hydrochloric acid and the sodium hydroxide canceling each other, was achieved with the aforementioned extremely low frequency alternating electrical current that mimics the drug delivery of a direct current system because it is so slow, but deposits otherwise harmful ions on the same skin area to offset or neutralize each other before skin damage can take place.

In accordance with the invention, a basic AC generator delivers a drug into the skin of a patient, but neutralizes opposing harmful chemicals that are inherently developed at the output electrodes when in an aqueous solution or gel form in contact with the skin during electrical current flow. It has been discovered that, when the electrical current is reversed at the slow rate of approximately 0.0027 Hz to 10 Hz, the behavior of

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the drug is to react as if it were a DC signal in that the polarity at any given moment will drive a like polarity drug component into the skin. The benefit achieved is that the unwanted chemical that was generated at the electrode was neutralized when the signal polarity reversed and developed an opposing chemical to cancel each other at the skin interface.

This non-invasive, minimal side effects system, in accordance with the invention, is designed to deliver drugs either systemically, locally or both, and is also appropriate for other iontophoretic treatment, such as sweat inhibition and the like. It can be made in two or more forms, i.e., a long lasting iontophoretic patch with self-contained electronics, or a larger unit that contains an electronics package for power and control and which terminates into output jacks. The user then plugs an electrical extension cable into these jacks and applies the other end of the cable, which terminates in a remote applicator housing suitable iontophoretic electrodes and drug reservoirs, to the patient. This larger, more powerful unit is generally intended for shorter term use. Large units, employing the frequency range of the present invention, may also be used for treating areas such as the foot which may soak in a liquid surfactant combined with an antifungal agent or the like.

Previous DC iontophoretic devices necessarily required an "inactive" or ground return electrode to electrically complete the circuit. Often, this electrode was remotely connected ("distal" electrode) adding to an unwieldy, space devouring component. Even if the inactive electrode were adjacent to the active, drug driving electrode, it normally occupied at least fifty percent of the space of the device for its simple, one dimensional purpose—to complete an electrical circuit. With the AC system of the present invention, the so-called "inactive" electrode is made active, in that it contributes to driving the drug into the skin when its alternating polarity changes to be the same polarity of the therapeutic medicament. Hence, both electrodes are used to infuse therapeutic drugs into the patient. This has another advantage from the practitioner's view. The polarity of the drug need no longer be known in order to place it in the correct polarity drug reservoir, since the polarity of each reservoir reverses regularly. Otherwise an error could be made. The practitioner also need not stock applicators with two different capabilities—one for positive and one for negative. In effect, the applicator size is doubled because of the presence of the AC signal in accordance with the invention.

The system of the present invention also uses relatively inexpensive silicone/carbon electrodes. While this material is in common use with TENS devices (Transcutaneous Electrical Nerve Stimulators), it is not used for both electrodes for common DC iontophoretic devices. This is because these non-metallic electrodes typically show a high resistance after short use, with a consequent substantial drop in load current (especially the positive electrode). With a slow AC signal, it has been discovered that this build-up of resistance does not take place and both electrodes maintain the desired low electrical resistance. The alternative to these low cost electrodes would be pure and extremely expensive palladium, platinum or rhodium electrodes to minimize corrosion, but with the consequent possibility of metal ions being driven into the skin and further adding to "clutter".

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The presence of hydrochloric acid and sodium hydroxide does have a beneficial value in that these chemicals have a bactericidal effect. Each of these chemicals kill different groups of bacteria. In the conventional DC device, only one chemical is present at one electrode and, therefore, attacks only a particular group of microbes. With an AC signal, in accordance with the present invention, the antibacterial effect takes place against the groups of microbes effected by both polarities and, within the substantially critical frequency range of the invention, also avoids damage to the skin.

Heretofore, it was commonly accepted that drugs delivered by iontophoretic systems necessarily had to be limited to approximately one to two percent concentration. Increasing the concentration of the drug not only would not show an increase in drug concentration in the skin, but could actually decrease the amount of drug delivered because of "clutter" and competition to enter a very minute passageway (the eccrine duct). With the slow AC signal of the present invention, drug concentration can now be increased substantially beyond two percent with very important benefits that include enhanced therapeutic value and shortened treatment time.

The reason that the slow AC signal facilitates increased drug dosage or concentration above two percent is as follows: If, for instance, a positively charged drug was in the drug reservoir when the positive half of the AC signal was driving that same reservoir, then the positive component of the drug would be repelled and driven into the skin. Since all drug molecules also contain a negative component that, in this instance, would be left behind in the reservoir (in a DC device) as non-productive "clutter", when the AC signal swings negative on the other half of the signal, the negative component also will be driven to the skin, thereby eliminating the aforementioned "clutter" from the reservoir. This "cleansing" of the area, by removal of otherwise delivery inhibiting clutter, enables increased drug concentrations.

A further feature of the present invention resides in the ability to deliver drugs embodying large and/or heavy molecular structures, such as insulin, since the frequency of operation of the system of the present invention both removes "clutter" as a drug transfer impediment and also provides adequate molecular transport times.

In a presently preferred embodiment, the control signal generated by the system of the present invention is usually equal and opposite in all respects so that opposing unwanted chemicals cancel each other and maintain a neutral pH of approximately 7. The electrical circuitry may also be modified to favor the positive portion of the electrical cycle, rather than being exactly the same amplitude as the negative portion of the cycle. Since the skin is naturally acidic at approximately 5.6 pH, the amplitude of the positive signal would be adjusted upward to provide the pH more compatible with the skin. Of course, the opposite effect could be obtained, whenever desired, by increasing the amplitude of the negative portion of the electrical cycle relative to the positive portion.

It may be desirable to maintain a neutral pH of a drug for drug stability, permeability and irritation control among other reasons. In monopolarity DC iontophoretic devices where extremes of acid or alkaline are generated at the electrodes, the drug would quickly reach either extreme. Using an AC signal, in accordance

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with the invention, with substantially equal and opposite half cycles, both in amplitude and duration, would, as previously indicated, make the pH at the drug delivery site essentially neutral. However, there may be circumstances where it is desirable to controllably alter the pH from neutral. By adjusting the zero reference line, or electrical bias, of the aforescribed symmetrical AC signal up or down (by switch), the positive signal can be increased or decreased in amplitude relative to the negative signal and vice versa, and, therefore, raise or lower the pH relative to neutral. Ancillary chemicals that are commonly included in drug formulations, such as buffers and isotonic drugs should be dropped from an iontophoretic drug formulation to further reduce clutter.

Modern treatment often demands the simultaneous infusion of different drugs. This is known as multi-therapy and is typically performed by inserting two catheters from two different IV units containing different medications to treat multiple problems within one patient. With a non-invasive (no catheter) iontophoretic patch, this is easily accomplished with the two reservoir system utilized by the simplified, more economical and reliable construction and method of the present invention, by placing a different drug into each reservoir. The drugs may be of the same or opposite polarity. The economy of one unit offering two distinct treatments is obvious.

In addition, since both electrodes are "active" with the arrangement of the present invention, the system can deliver twice the amount of drug compared to a comparable DC iontophoretic device. For example, if the drug to be delivered is positive and the signal in one drug reservoir were positive at any given instant, then that reservoir will deliver the drug to the skin. Simultaneously, the other reservoir will be negative and the same drug will ordinarily not flow. However, if a negative "carrier drug" is made part of the formulation, then this carrier drug would flow on the negative half of the electrical cycle while pulling along the desired positively charged active drug. Thus, even though the desired drug is polarity sensitive, the system of the present invention will double the amount of drug delivered. Another embodiment utilizing the same concept is to employ an amphoteric (dipole) surfactant as part of the drug formulation. Not only does the drug flow continuously, but flow rate efficiency is very substantially enhanced because of the permeation qualities of the surfactant.

In addition to the foregoing features, the practice of the present invention may also include the preparatory process of infusing an ionic surfactant, either amphoteric or cationic, at the drug delivery site to lower load resistance by increasing permeability and penetration, and thereby enable higher levels of electrical current and drug delivery with relatively lower driving voltage. This process increases the permeability of the skin, especially the palms and soles. Electrically driving in the surfactant at the delivery site is much more effective than any presoak or swabbing.

Hence, those concerned with development and use of iontophoretic systems in the medical field have long recognized the need for a convenient and effective method and apparatus for preventing skin injury and the formation of vesicles and bulla on the skin in an area subjected to an iontophoretic treatment over extended periods of continuous treatment, which can be physically packaged in a compact and economical configuration.

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tion, can deliver therapeutic drugs to deeper levels of penetration at a high rate and at higher concentrations, without the need for buffering agents, are capable of delivering large and/or heavy molecular substances, can deliver a plurality of drugs of the same or different polarity simultaneously, and can be used to control pH at the drug administration site.

These and other objects and advantages of the invention will become more readily apparent from the following more detailed description of the invention, when taken in conjunction with the accompanying drawings of illustrative embodiments.

DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates an iontophoretic patch administration device constructed in accordance with the invention, and shown installed upon the arm of a human subject;

FIG. 2 is an enlarged, perspective view of a presently preferred embodiment of an iontophoretic patch constructed in accordance with the invention, portions being broken away to illustrate internal structure;

FIG. 3 is a sectional view, taken substantially along the line 3—3 in FIG. 2;

FIG. 4 is a flow chart illustrating a process embodying features of the present invention;

FIG. 5 is a flow chart illustrating a more expanded process in accordance with the invention;

FIG. 6 is a combined overall block diagram and electrical schematic, including waveforms, of a presently preferred iontophoretic administration system embodying features of the present invention; and

FIG. 7 is a graphical representation illustrating the appropriate frequency window for simultaneous drug delivery and prevention of skin injury.

DESCRIPTION OF THE PREFERRED EMBODIMENT(S)

Referring now to the drawings, and more particularly to FIG. 1, there is shown an iontophoretic patch administration device 10, of relatively simple, economical, reliable and compact construction, embodying features of the present invention, and shown installed upon the arm 11 of a suitable biological subject so that the patch contacts the skin of the subject for appropriate administration of therapeutic treatment by iontophoretic delivery of medicaments or the like.

While the device 10 is shown in its presently preferred embodiment as a compact patch, it will be appreciated by those of ordinary skill in the art that a larger structural and/or physical packaging unit (not shown) may be utilized, including a terminal electrode applicator for contact with the skin, and also embodying various features of the present invention.

As best observed in FIGS. 2 and 3 of the drawings, the iontophoretic patch 10 is a very compact, circular, cylindrical device fabricated primarily of an outer plastic shell with internal, preferably integrally molded, baffles. The plastic shell and baffles are typically molded of an electrically insulating, flexible vinyl material or the like.

The internal baffles divide the interior of the iontophoretic patch 10 (to be marketed under the trademark LECTRO PATCH by General Medical Company of Los Angeles, Calif.) into upper and lower, hollow internal chambers 12 and 13, respectively, more specifically, by means of an interior baffle member 14. The upper chamber 12 contains a compact electronics package 15,

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including a suitable microchip and battery power supply. This upper chamber 12 is electrically insulated from the lower chamber 13 by the plastic baffle member 14.

The lower chamber 13 contains a pair of iontophoretic electrodes, 16a and 16b, typically of electrically conductive silicone/carbon material, and which are separated from each other by an electrically non-conductive plastic divider baffle 17 forming a separator wall which divides the lower compartment 13 into a pair of semi-circular electrode chambers and reservoirs 18a and 18b. The chambers 18a and 18b house the electrodes 16a, 16b and contain the therapeutic substances to be ultimately infused into the biological subject, the drug infusion path being indicated generally by the arrows 20 in FIG. 3.

The iontophoretic electrodes 16a, 16b are suitably connected electrically into the electronics package 15 via electrically conductive tabs 21a and 21b, respectively, extending through appropriate slotted openings in the chamber dividing baffle member 14. The silicone/carbon electrodes 16a, 16b are typically fabricated of 1-2 ohm per square centimeter conductive plastic material. While the electrodes 16a, 16b are preferably of silicone/carbon in a presently preferred embodiment of the invention, they may be fabricated of other electrically conductive, non-corrosive materials as well. With the AC signal used in the system of the present invention, there is little or no resistance build-up in the silicone/carbon electrodes.

The drug reservoirs 18a and 18b are filled either with a gel containing the therapeutic substances to be administered or a pair of felt pads 22a and 22b which have been appropriately saturated with the substances to be dispensed.

In addition, an electrical slide switch 24, allowing selection of dosage, schedule and treatment duration, projects physically, for access by an operator, through an upper plastic cover plate 26 adhered to the top of the outer shell of the iontophoretic device 10. The switch 24 is electrically connected in the chamber 12 to the electronics package 15. The switch 24 may be selectively moved between a "0" (off) position, to either a "LO" (low current or lower rate of drug delivery) or "HI" (high current or higher rate of drug delivery) switch positions, to either turn the device 10 "off" so as to cease electrical operation, or to set the device for either high or low electric current rate operation which can remain in such a state on the patient, continuously if desired, for typically either 7 days or 10 days, respectively.

The function of the switch 24 in FIG. 1 with markings "0" (meaning off), "LO" and "HI" is as follows:

1) The "0" position keeps the device from functioning. It may also be used to schedule an "off" interval after leaving one of the other drug delivery positions.

2) The "LO" treatment position infuses the drug at the lowest current level at a continuous, controlled rate. This position can be used for drugs with a narrow therapeutic index for low level infusion. Another use for this position could be a drug with a long half-life with a schedule of intermittent "0" positions to avoid an accumulation that might otherwise result in toxicity.

3) The "HI" treatment position of the switch 24 infuses the drug at a current level typically twice as high as the "LO" setting. This position may be used to maintain efficacy for drugs with a short half-life, such as peptides. Also, the "HI" position can be used for a bolus

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dose coming off the "LO" position, when therapeutically indicated.

If desired, a second switch (not shown), similar to the slide switch 24, may also be provided and similarly disposed to project through the cover plate 26 of the outer shell of the iontophoretic device 10 and, likewise, be connected to the internal electronics package 15, to selectively vary the frequency of the low frequency duty cycle of operation of the iontophoretic patch 10, as where different size molecules are to be infused into the patient. In this regard, varying frequencies would be used for separation of heavier molecules, such as insulin and the like, to allow for increased drug transport times during the portion of the electrical duty cycle where the particular molecule is delivered from the drug reservoirs 18a, 18b into the skin of the subject being treated. If desired, the electrical system may be modified, in a manner well known to those of ordinary skill in the art, to automatically vary the signal frequency periodically.

In addition, a third switch (also not shown) similar to the switch 24 may be used, in the manner to be subsequently described in connection with the more detailed description of the iontophoretic control system and circuitry, to vary the ratio of the amplitude of the forward to reverse portions of the overall low frequency AC electrical duty cycle, for purposes of controlling the effective pH at the surface, e.g. the skin, of the patient for a variety of medical reasons.

An LED test indicator 28 extends from the electronics package chamber 13 below the cover plate 26, through an appropriate opening in the cover plate, and is observable from the top of the iontophoretic patch 10 to confirm proper electrical operation of the system for the user. An additional switch, such as a membrane switch located inside the patch 10 below the cover plate 26, and operable by pressure on the flexible cover plate, (not shown) may be included to selectively connect the indicator 28 into and out of the electrical circuit, so as to minimize power drain when the indicator is not needed.

Of course, as previously indicated, the invention is not limited to being physically packaged as a patch 10. A larger electronics package may be housed in a remote instrument containing the electronics package, and either battery or plug-in electrical power may be utilized. A local applicator would then be electrically connected by cable to the remote instrument. The applicator would house suitable iontophoretic electrodes and drug reservoirs akin to the chamber 13 of the patch 10 in FIGS. 1-3.

Referring now to FIG. 4 of the drawings, the overall process which facilitates the numerous advantages of the present invention is broadly illustrated and defined. In this regard, the process calls for the step 30 of applying electrical current to a pair of iontophoretic electrodes, such as the electrodes 16a and 16b in the iontophoretic patch 10 illustrated in FIGS. 1-3. The electrical polarity and, therefore, the direction of the electrical current flowing from the electrodes and through the patient is then, in step 31, periodically reversed (twice per AC cycle) at low frequencies in the substantially critical range of approximately 10 Hz to once every three minutes, or a low frequency limit of approximately 0.0027 Hz, to achieve the plethora of advantages previously and subsequently described herein in connection with the practice of the present invention. In the practice of the invention, using lidocaine, the system is optimally operated between one cycle per minute and

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one cycle every six minutes, with one cycle every two minutes being typical.

FIG. 5 is a basic block diagram illustrating the invention, wherein an electrical source 32 is directed to appropriate waveshaping and timing circuitry 33 for generating the aforescribed low frequency AC duty cycle which is then directed as electrical current to iontophoretic electrodes 34 to administer drugs to the patient 11 which is the electrical load in the system. The system illustrated in FIG. 5 may be implemented, in a presently preferred embodiment of the invention, by the more detailed system shown in FIG. 6 of the drawings.

Referring now more particularly to FIG. 6 of the drawings, there is shown a presently preferred embodiment of an overall system for providing a regulated and periodically reversible electrical current into a variable load resistance (the patient), the electrical current reversing polarity and direction of flow periodically at a very low frequency. In the embodiment shown in FIG. 6, a smooth transition without discontinuity in slope, is made between polarities, thus avoiding a shock sensation to the patient when reversing the electrical current. The magnitude and duty cycle of the positive and negative currents are substantially the same. The system of FIG. 6 utilizes a conventional DC power supply.

In FIG. 6, the timing of current reversals is determined by an oscillator 40, which produces at its output 41 sharp transitions between two levels, as illustrated by the waveform 42. The electrical output 41 is applied to a waveshaping network 43 to produce gradual electrical transitions, as shown by the output waveform 44 available on line 45. The electrical output of the oscillator 40, and thus the sense of the smoothed waveform, is reversed when the waveform crosses a predetermined threshold 47 determined at junction 46 under the control of a threshold detection subsystem 50. The voltage waveform 44, less the threshold 47, is applied over line 48 to a suitable voltage-to-current converter subsystem 49.

The polarity of the electrical current through a floating load 51 (e.g. the patient) reverses at the threshold crossing time, when the instantaneous electrical load current is zero, as illustrated by the waveform 52 in FIG. 6. A latch subsystem 53 controls a plurality of switches 54a-54d, as shown by the waveform 55, to maintain this polarity until the next threshold crossing, producing smooth transitions between electrical current levels which are, by design, substantially equal in magnitude but opposite in sign. The relatively slow rise and decay evident from leading and trailing edges of the waveform 52 provides the desirable electrical ramping up and down of each half cycle to minimize shock sensations.

One example of specific electrical circuitry, suitable for implementing the system shown in FIG. 6, is set forth in Appendix A attached hereto and which is specifically incorporated by reference herein.

With the slow AC signal utilized in the system of the present invention, drug concentration can now be increased substantially beyond two percent with very important benefits that include enhanced therapeutic value and shortened treatment time. The reason for this is, if, for instance, a positively charged drug is in the drug reservoir when the positive half of the AC signal is driving that same reservoir, then the positive component of the drug is repelled and driven into the skin. Since all drug molecules also contain a negative component, that negative component would normally be left

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behind in the reservoir as non-productive "clutter". However, when the AC signal swings negative on the other half of the signal, the negative component will then also be driven into the skin, thereby eliminating "clutter" from the reservoir. This "cleansing" of the area, by removal of otherwise delivery inhibiting "clutter", enables substantially increased drug concentrations.

It may be desirable to maintain a neutral pH of a drug for drug stability, permeability and irritation control among other reasons. In monopolarity DC iontophoretic devices where extremes of acid or alkaline are generated at the electrodes, the drug would quickly reach either extreme. Using an AC signal, in accordance with the invention, with substantially equal and opposite half cycles, both in amplitude and duration, would make the pH at the drug delivery site essentially neutral. However, as previously indicated, there may be circumstances where it is desirable to controllably alter the pH from neutral. By adjusting the zero reference line, or electrical bias, of the aforescribed symmetrical AC signal up or down (by switch), the positive signal can be increased or decreased in amplitude relative to the negative signal and vice versa, and, therefore, raise or lower the pH relative to neutral. Ancillary chemicals that are commonly included in drug formulations, but should be dropped from an iontophoretic drug formulation, are buffers and isotonic drugs.

Introducing a positive or negative bias into the waveform 52 in FIG. 6 consists of adding a separate DC current of appropriate polarity through the load 51. This bias current cannot be added directly to the alternating current whose waveform 52 is shown in FIG. 6, because it, too, would then alternate. One example of specific electrical circuitry, suitable for modifying the electrical system shown in FIG. 6 and implemented by the electrical circuitry of Appendix A, is shown in Appendix B which is also attached hereto and is specifically incorporated by reference to form part of the present description. By shifting the amplitude of the electrical current during one portion of the duty cycle relative to the other portion of the duty cycle, pH balance is also shifted and this provides an effective method for controlling the pH at the drug delivery site in the patient.

In addition, since both electrodes are "active" with the simplified arrangement of the present invention, the system can deliver twice the amount of drug compared to a comparable DC iontophoretic device. For example, if the drug to be delivered is negative and the signal in one drug reservoir were negative at any given instant, then that reservoir will deliver the drug to the skin. Simultaneously, the other reservoir will be positive and the same drug will ordinarily not flow. However, if a positive "carrier drug" is included as part of the drug formulation, then this carrier drug would flow on the positive half of the cycle while pulling along the desired negatively charged active drug as well. A typical "carrier drug" would be 4% lidocaine hydrochloride. Hence, even though the desired drug is polarity sensitive, the arrangement described above will double the amount of drug delivered. As will subsequently be explained herein, the "carrier" medium may also be an ionic surfactant, and preferably an amphoteric surfactant.

The iontophoretic electric patch 10 of the present invention is capable of infusing a broad range of drugs up to and including some of the large molecular pep-

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tides. This non-invasive system offers increased efficacy with little or no side effects compared to traditional administrative methods. Generally, drugs formulated for iontophoretic delivery should be ionized either negatively or positively, free of causing local irritation or a high rate of hypersensitivity, and have an absence of isotonic and buffer drugs. Used as directed, the iontophoretic patch 10, or the larger version system with a remote applicator, in accordance with the present invention, produces a systemic result as well as a localized effect at the point of application.

The presence of hydrochloric acid and sodium hydroxide also has a beneficial value in that these chemicals have a bactericidal effect. Each of these chemicals kill different groups of bacteria. In the conventional DC device, only one chemical is present at one electrode and, therefore, attacks only a particular group of microbes. With an AC signal, operating in the critical low frequency range in accordance with the present invention, the antibacterial effect takes place against the groups of microbes effected by both polarities, all without damage to the skin and the drug delivery site.

Another application of the AC signal to sterilize is to send this signal down conductive catheter tubes. Infection of the wound that the catheter enters is of major concern and a common problem with dialysis users, IV patients, etc.

As previously suggested, unique features of the iontophoretic patch 10 of the present invention include: no tissue damage, rapid onset of action, long term dosing at selected levels, compatibility with either polarity drug, capability for delivery of two separate drugs at the same time (multitherapy) and ability to deliver higher drug concentration. These and other features of the iontophoretic patch 10 greatly enhance drug therapy. Operating ease comes through the selection switch 24 to provide programmed input. Selection assures consistent dosing within the general population, thereby maintaining effective plasma concentrations.

Referring now more particularly to FIG. 7 of the drawings, there is shown, in graphical form, an illustration of the manner in which drug delivery and skin injury typically vary over the substantially critical frequency window between approximately six minutes per full cycle and approximately ten cycles per second. In this frequency range, there is a dramatic cancellation of skin damaging ions. At frequencies higher than approximately 10 Hz, no substantial effective drug delivery takes place, and other factors such as skin polarization and pH fluctuation may typically reduce drug delivery beyond six minutes per full cycle. At frequencies lower than six minutes per cycle, or approximately 0.0027 Hz, the risk of skin injury increases substantially.

The iontophoretic patch 10 of the present invention is capable of delivering drugs at a continuous, controlled rate. This allows the physician/pharmaceutical manufacturer to titrate drug dosage to the most effective concentration with minimum or no side effects. Significantly elevated concentrations can be obtained in 60 minutes or less after start of treatment. Thus, a steady-state concentration of the drug can be maintained during the dosing interval. The physician specifies the duration of application and has a variety of treatment regimens from which to select.

In addition to the treatment regimens previously described, and solely by way of example and not by way of limitation, other possible regimens may include: A scheduled switching regimen between "LO" and

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"HI" positions of the switch 24 for a wide therapeutic index drug, to avoid building a tolerance to a fixed, static level. Another therapeutic opportunity may be where multi-therapy is indicated with drugs of similar half-lives. This application would allow total drug separation (one drug in each of the reservoirs 18a, 18b of the patch 10), for infusion of drugs of the same polarity (alternate delivery) or opposite polarity (simultaneous delivery). Still another therapeutic variation could be to halve the infused dosage (intermittent dosing) in the "LO" position of the switch 24 by filling only one reservoir with the drug of choice and the other reservoir with common tap water. Conversely, drug delivery can be doubled if a compatible "carrier" drug of opposite polarity to the active drug is included in the reservoirs. When the signal reverses, so as to now block transport of the active drug, the oppositely charged carrier drug would flow with the piggy-backed active drug.

The iontophoretic patch 10, in accordance with the invention, is designed to infuse either positively or negatively charged drugs at a constant rate, by way of example in connection with a presently preferred embodiment of the invention, for up to seven days in the "HI" position of the switch 24 or ten days in the "LO" position. The clinician fills a hypodermic syringe with approximately 6 cc of the appropriate drug and then proceeds to fully saturate both felt pads 22a, 22b in each drug reservoir 18a, 18b, respectively. Care must be taken to avoid wetting the bottom of the wall 17 separating the reservoirs 18a, 18b and that the pads 22a, 22b are slightly above this separator wall (see FIG. 3) and recessed within the housing before application to the skin of a patient. Pad fibers must not cross over this separator wall 17 because they may otherwise cause the device to malfunction.

Suitable skin preparation must precede iontophoretic patch surface adhesion. One possibility is to prepare application areas by swabbing with approximately fifty percent isopropyl alcohol. At higher concentrations, permeability is decreased due to the precipitation of tissue proteins.

Iontophoretic treatment should preferably be preceded by a skin preparation process that strongly enhances permeability. It has long been a desire in iontophoretic drug delivery to infuse drugs anywhere on the human body. Penetrating the palms of the hands or the soles of the feet is virtually impossible because the skin in these areas is about forty times thicker than other areas of the body. Additionally, other areas of the body, as well as differences in skin resistance among different human beings, often limits the sites for infusion. This is especially true when using the low power of an iontophoretic patch 10 as compared to the relative high power of a full-sized instrument where five times or more voltage could be available to overcome high skin resistance. It is, therefore, a great advantage to be able to treat any area without having to be selective.

Historically, the art calls for preparing the skin with alcohol, acetone or surfactants by swabbing the area to be treated with these chemicals to remove oils and other debris to enhance electrical contact for the iontophoretic applicator. Obviously, these traditional methods of skin preparation were not satisfactory in overcoming the limits of drug delivery to many parts of the body. There have also been some efforts to enhance delivery of metallic ions by means of an anionic surfactant, as well as in vitro experiments to deliver certain drugs using an anionic surfactant.

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In accordance with the invention, it has been discovered that using an appropriate ionic surfactant and driving the surfactant into the skin with the iontophoretic device (or an equivalent current source), prior to drug delivery, greatly lowers skin resistance and increases skin permeability thereby allowing treatment to take place anywhere on the human body. An alternate arrangement could allow the ionic surfactant to be included in the treatment drug formulation where compatible. Forms of the ionic surfactant can be liquid, gel or equivalent. Suitable ionic type classifications for such surfactants would be cationic and amphoteric. Amphoteric surfactants appear to work best only with an AC signal, such as that used in the system of the present invention. With cationic monopolarized surfactants, both AC and DC signals work. In this regard, the amphoteric surfactant can be the "carrier" medium for another drug to be delivered.

The use of amphoteric and cationic surfactants, electrically delivered into the treatment site, to enhance permeability and penetration at the site, can be effectively utilized as a skin preparation technique for both iontophoretic and non-iontophoretic drug delivery at that site.

In the practice of the present invention, it has been discovered that amphoteric surfactants performed much more efficiently than cationic surfactants, while cationic surfactants were considerably more effective than anionic surfactants such as sodium lauryl sulfate. Suitable examples of such surfactants successfully utilized in the practice of the invention are:

SURFACTANT PREPARATION SOLUTIONS

(1) AMPHOTERIC

Product Name:	AMPHOTERIC-L
Chemical Name:	COCO AMIDOPROPYL BETAINE
Physical Appearance:	Clear Liquid
Manufacturer:	Exxon Chemical Company Performance Products Group Tomah Products 1012 Terra Drive (P.O. Box 388) Milton, Wisconsin 53563

(2) CATIONIC

Product Name:	DEHYQUART A
Chemical Name:	CETYL TRIMETHYL AMMONIUM CHLORIDE
Physical Appearance:	Clear Liquid
Manufacturer:	Henkel Corporation Chemical Specialties Division 300 Brookside Avenue Ambler, Pennsylvania 19002

Surfactants may include suitable functional materials such as coupling agents, antimicrobials, chelating agents and the like.

Of course, it will be appreciated that the aforementioned ionic surfactants are presented only by way of example, and those of ordinary skill in the art may substitute other amphoteric or cationic surfactants, currently known or unknown, without departing from the spirit and scope of the invention.

The vastly increased permeability and penetration capability at the treatment site, made possible by use of an appropriate ionic surfactant, and particularly an amphoteric surfactant, yields yet another embodiment of the invention relating to sweat control by iontophoresis. In this regard, sacrificial aluminum electrodes may be substituted for the silicone/carbon electrodes 16a, 16b, to direct ions into the eccrine duct for sweat control.

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The aluminum ions precipitate the skin protein therefore causing a plug that lasts weeks (no sweat period). The treatment site is either first prepared using an appropriate surfactant, as outlined above. Thereafter, tap water is placed in the reservoirs 18a, 18b. Alternatively, an appropriate ionic, and preferably amphoteric, surfactant is placed into the reservoirs 18a, 18b adjacent the aluminum electrodes for delivery into the treatment site.

In general, placement for systemic infusion is the volar surface of the forearm near the elbow. If the use is to treat a lesion or any other specific site, the patch 10 should be placed over that site for target delivery. If the application site is contoured, the iontophoretic patch 10 may be bent to conform with this irregular surface. The bend should take place in line with the separation wall 17 running down the center of the patch 10.

In normal operation, the switch 24 is moved from the "0" position to either "LO" or "HI" as prescribed. The user may feel a gentle tingle for only the first approximately thirty seconds to one hour (priming period) of treatment, depending to some extent upon the permeability at the delivery site. Treatment is then continued for the prescribed period of time. The patch 10 is switched to the "0" position when not in use.

After completion of treatment, the iontophoretic patch 10 should normally be discarded. The hands and drug application site should be washed with soap and water and then dried to remove any remnant drug.

In normal use, after the patch 10 has been applied and working for approximately one hour, the following procedures can be used throughout the seven day ("HI") or ten day ("LO") treatment to prove workability. If the green indicator 28 lights when switched into the electrical circuitry (in accordance with the circuitry of Appendix A), it means the batteries are fresh and the device is delivering the medication. If the indicator 28 fails to light, it means that the batteries are dead and the device must be replaced. If the green indicator 28 flashes on and off continuously, it can mean one of the following malfunctions: a) that the drug is leaking from one side of the separation wall 17 to the other (oversaturation of pads), b) that the drug level is too low and more must be added to the felt pad 18a or 18b, or that the patch 10 itself is not firmly adhered to the skin surface (especially a contoured surface) and c) (for investigators) that an unproven formulation is non-ionic or of such poor conductivity that minimum current needs for the "LO" position (approximately 0.5 ma by way of example) or the "HI" position (approximately 1.0 ma by way of example) cannot be met. Under these conditions, the investigator may consider adding another drug to act as a "carrier" for the substantially non-ionic drug. Electroosmotic transport of water or solvent also enhances penetration of non-electrolytes.

It will be apparent that the various electrical subsystems indicated in FIGS. 5 and 6 of the drawings can be implemented readily by those of ordinary skill in the art without the exercise of inventive skill.

Hence, those concerned with development and use of iontophoretic systems in the medical field have long recognized the need for a convenient and effective apparatus and method for preventing iontophoretic burns and irritation and the formation of vesicles and bulla on the skin in an area subjected to an iontophoretic treatment over extended periods of continuous treatment, which can be physically packaged in a simple, reliable, relatively inexpensive and compact configuration, can

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increase permeability and penetration at the treatment site, can deliver therapeutic drugs at a high rate and at higher concentrations, without the need for buffering agents, are capable of delivering large molecular substances, can deliver a plurality of drugs of the same or different polarity simultaneously, and can be used to control pH at the drug administration site.

Accordingly, it will be apparent from the foregoing that, while particular forms of the invention have been illustrated and described, various modifications can be made without departing from the spirit and scope of the invention. Therefore, it is not intended that the invention be limited, except as by the appended claims.

I claim:

1. A method of applying iontophoretic treatment to a biological subject, said method including the steps of:

conducting an electrical current through a surface of said subject in a first direction from a first electrode to a second electrode on said subject; and

intermittently reversing, at a relatively low frequency which prevents skin damage, between approximately 20 times per second and approximately once every three minutes, the polarity of said electrodes to cause said electrical current to flow in a second direction opposite to said first direction, whereby iontophoretic treatment may be continuous for extended periods of time.

2. A method as set forth in claim 1, including the step

of: selectively varying the amplitude of the electrical current in one direction relative to the amplitude of the electrical current in the opposite direction to control pH at the surface of said subject.

3. A method as set forth in claim 1, including the step

of: selectively varying the frequency of the electrical current to accommodate the transport times of different size molecules.

4. A method as set forth in claim 1, wherein multiple drugs are delivered.

5. A method as set forth in claims 1 or 4, wherein drugs of the opposite polarity are delivered simultaneously.

6. A method as set forth in claim 1 or 4, wherein drugs of the same polarity are driven alternately from different electrodes.

7. A method as set forth in claim 1, wherein a carrier of opposite polarity is added to a drug to be driven by at least one of said electrodes.

8. A method of clearing ionic clutter from an iontophoretic drug administration system, said method including the steps of:

conducting an electrical current through a surface of a subject being treated, in a first direction from a first electrode to a second electrode on said subject; and

periodically reversing, at a relatively low frequency which avoids damage to said subject, between approximately 20 times per second and approximately once every three minutes, the polarity of said electrodes to cause said electrical current to flow in a second direction opposite to said first direction, whereby the resulting very low frequency alternating current eliminates ionic clutter and facilitate continuous drug administration for extended periods of time.

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9. A method of iontophoretic infusion of medical substances into a biological subject, comprising the steps of:

locating a pair of electrically conductive electrodes adjacent to a surface of said subject to be treated; placing at least one medical substance between at least one of said electrodes and said surface of said subject to be treated;

conducting an electrical current through said surface of said subject in a first direction from a first of said electrodes to a second of said electrodes on said subject; and

periodically and regularly reversing, at a relatively low frequency, between approximately 20 times per second and approximately once every three minutes, the polarity of said electrodes to cause said electrical current to flow in a second direction opposite to said first direction, whereby skin damage to said subject is avoided and drug infusion may be continuous for extended periods of time.

10. A method as set forth in claim 9, including the step of:

selectively varying the amplitude of the electrical current in one direction relative to the amplitude of the electrical current in the opposite direction to control pH at the surface of said subject.

11. A method as set forth in claim 9, including the step of:

selectively varying the frequency of the electrical current to accommodate the transport times of different size molecules.

12. A method as set forth in claim 9, wherein multiple medical substances are delivered.

13. A method as set forth in claims 9 or 12, wherein medical substances of the opposite polarity are delivered simultaneously.

14. A method as set forth in claims 9 or 12, wherein medical substances of the same polarity are driven alternately from different electrodes into said surface.

15. A method as set forth in claim 9, wherein a carrier substance of opposite polarity is added to a medical substance to be driven by at least one of said electrodes.

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16. A method as set forth in claim 9, including the additional step of:

iontophoretically delivering a surfactant material into said surface to lower electrical resistance and enhance drug penetration.

17. A method as set forth in claim 9, including the additional step of:

iontophoretically delivering an amphoteric surfactant material into said surface to lower electrical resistance and enhance drug penetration.

18. A method as set forth in claim 9, including the additional step of:

iontophoretically delivering a cationic surfactant material into said surface to lower electrical resistance and enhance drug penetration.

19. A method of iontophoretic infusion of medical substances into a biological subject, comprising the steps of:

locating a pair of electrically conductive electrodes upon said subject to be treated;

placing at least one medical substance between at least one of said electrodes and a surface of said subject to be treated;

conducting an electrical current through said surface of said subject in a first direction from a first of said electrodes to a second of said electrodes on said subject; and

intermittently reversing the polarity of said electrodes to cause said current to flow in a second direction opposite to said first direction, at a relatively low frequency which prevents skin damage to said subject and simultaneously provides adequate molecular transport time for said medical substance to be delivered into said surface of said subject, whereby infusion of said medical substance may be continuous for extended periods of time and wherein the polarity reversal occurs after the accumulated time periods of actual substantial electrical current flow in either direction equal a selected period of time between approximately 0.05 seconds and approximately 3 minutes.

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United States Patent [19]

Tapper et al.

[11] **4,340,047**[45] **Jul. 20, 1982****[54] IONTOPHORETIC TREATMENT APPARATUS**

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[73] Assignee: Robert Tapper, Los Angeles, Calif.

[21] Appl. No.: 119,844

[22] Filed: Feb. 8, 1980

Related U.S. Application Data

[62] Division of Ser. No. 952,341, Oct. 18, 1978, Pat. No. 4,301,794.

[51] Int. Cl.³ A61N 1/30

[52] U.S. Cl. 128/207.21; 128/419 R

[58] Field of Search 128/207.21, 419 R, 419 S, 128/420 R, 421, 422, 423 R, 803

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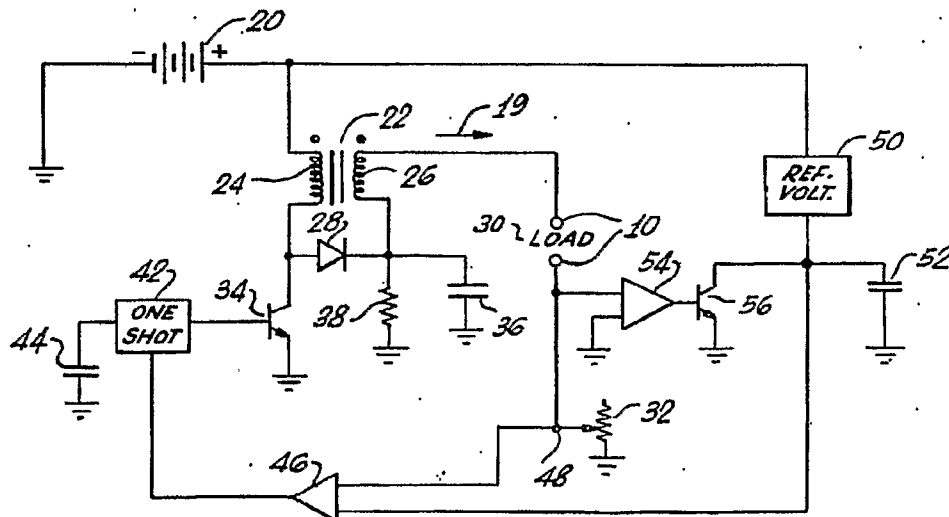
Primary Examiner—Lee S. Cohen

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[57] ABSTRACT

A method and apparatus for applying iontophoretic treatment to a living body is provided by which a unidirectional treatment current is periodically interrupted by a relatively short pulse of current in the opposite direction in order to prevent the formation of undesirable vesicles and bulla in the skin being treated. The apparatus and method are arranged to impose the treatment current gradually at the beginning of each treatment.

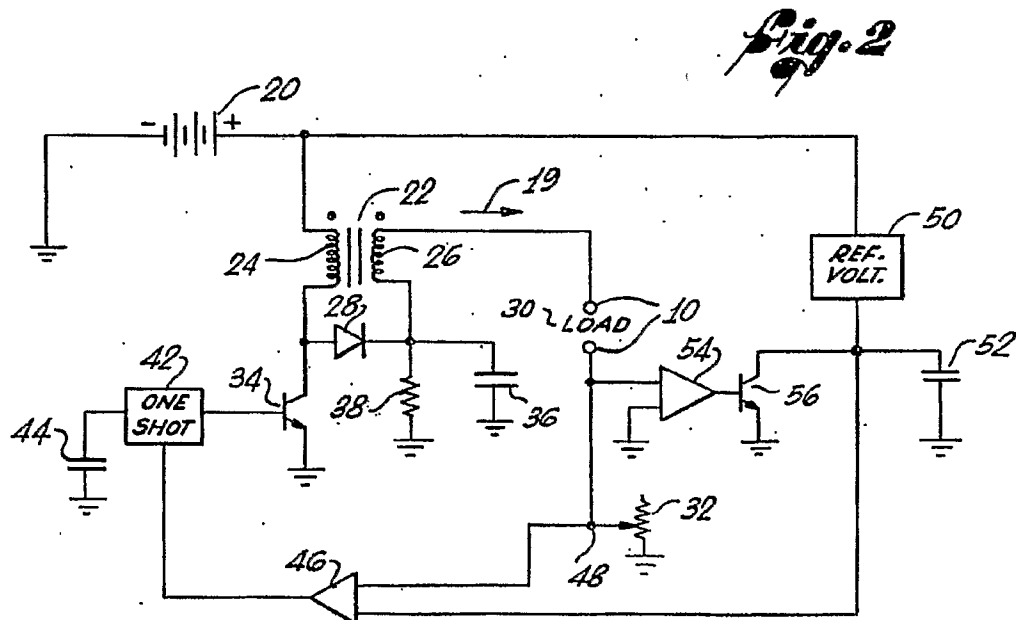
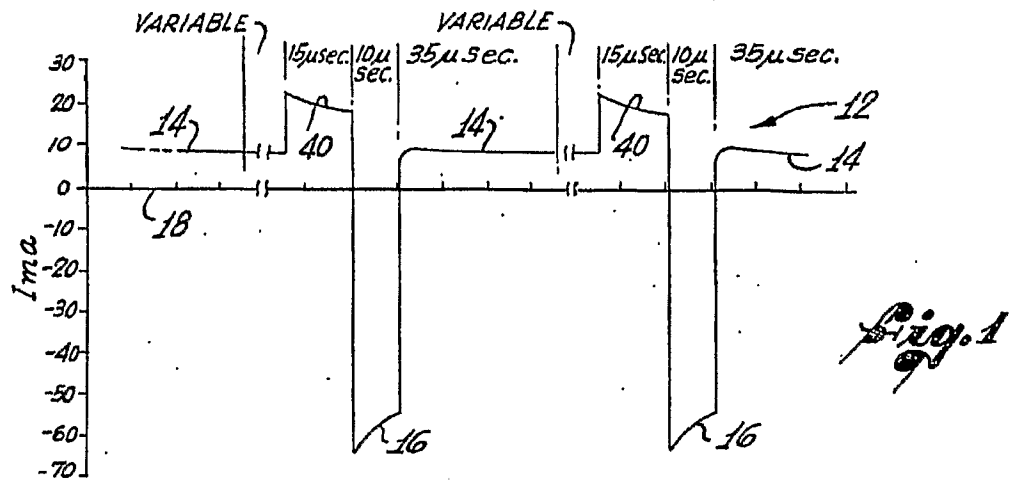
7 Claims, 2 Drawing Figures



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IONTOPHORETIC TREATMENT APPARATUS

This is a division, of application Ser. No. 952,341, filed Oct. 18, 1978, now U.S. Pat. No. 4,301,794.

BACKGROUND OF THE INVENTION

This invention relates to apparatus for effecting an electrotherapeutic treatment on a living body, and more particularly, to the application of an iontophoretic treatment topically to the skin of a human body.

Direct current electrotherapeutic treatments have been employed in the past for their polar effects on ionized molecules, causing the ionized molecules to be driven through the skin, usually superficially. This phenomenon is known as iontophoresis, and it has been employed for the introduction of medicants, or even simply moisture, into the skin of a patient.

More specifically, some ions of zinc and copper can be employed in the treatment of some skin infections, and chlorine ions have been employed for the loosening of superficial scars. Further, vasodilating drugs can be used in rheumatic and peripheral vascular infections, and skin anesthesia can be produced by iontophoresis of local anesthetic drugs. It has been suggested that application of direct current to carefully selected areas of a living body can produce anesthetic effects (see Limoge, *An Introduction To Electroanesthesia*, 1975, University Park Press).

Further, F. Levitt in "Archives of Dermatology", Vol. 98 No. 5, November 1968, reports on pp. 505-507 the production of long term anhidrosis by iontophoretic treatment of the feet or hands. His test results indicate that the treatment inhibits perspiration where the electric current is applied.

Although the above-mentioned iontophoretic treatments have been found to be effective, they are also known to be accompanied by undesirable effects such as the occurrence of iontophoretic burns in the treated area as well as the formation of undesirable vesicles and bulla, and redness of the skin in the treated area. An apparatus and method for preventing these iontophoretic burns are disclosed in copending applications Ser. Nos. 806,393 filed June 13, 1977 and 940,777 filed Sept. 8, 1978, now U.S. Pat. Nos. 4,164,226 and 4,211,222, respectively. However, the apparatus and method disclosed in those applications have been found not to be adequately effective for preventing the formation of vesicles, bulla and redness of the skin in the treated area.

Accordingly, there has existed a need for a convenient and effective apparatus and method for preventing the formation of vesicles, bulla and redness of the skin in an area subjected to an iontophoretic treatment. As will become apparent from the following, the present invention satisfies that need.

SUMMARY OF THE INVENTION

The present invention resides in a means for applying electrical energy topically to the skin of a human body, and by which undesired side effects are greatly minimized and may be eliminated. Moreover, the device of the present invention is relatively inexpensive to manufacture, is trouble free and reliable in use, and is arranged to be safely operated for self-treatment by an average person in normal home use.

More specifically, the present invention provides apparatus for applying an iontophoretic treatment which includes conducting direct current through the

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skin of the body, and periodically reversing the current and conducting a relatively short pulse of current through the skin in the opposite direction. It has been discovered that by intermittently including relatively short pulses of current in a direction opposite the direction of the normal direct current treatment, the undesirable formation of vesicles, bulla and reddening of the skin in the treated area is greatly reduced or even eliminated.

Electronic circuitry is provided to automatically impose the reverse pulse of current at regular intervals of time, and the device can be adjusted to conduct the iontophoretic treatment at any desired direct current level. According to a further feature of the invention, the apparatus and method are arranged to impose the treatment current gradually at the beginning of each treatment period so that the invention can be safely employed for self-treatment by an average person in the home.

Other features and advantages of the present invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, the principles of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing a current waveform which can be used in the present invention; and

FIG. 2 is a schematic diagram of a preferred apparatus for accomplishing the method of the present invention.

DETAILED DESCRIPTION

As shown in the exemplary drawings, the present invention is embodied in apparatus for applying iontophoretic treatment to a living body. In this treatment, direct current is applied topically to the skin by a pair of electrodes 10, illustrated diagrammatically in FIG. 2.

In order to accomplish the desired results, the iontophoretic treatment generally consists of a constant flow of unidirectional current between the electrodes. Depending upon the kind of iontophoretic treatment being applied, this current can be applied to the body at a rate of between a small fraction of a milliamper (ma) and about fifty ma. In an iontophoretic treatment for the production of anhidrosis, for example, a treatment current of between about four and fifteen ma is preferred.

A current versus time waveform, indicated generally by reference numeral 12 in FIG. 1, is illustrated as having a treatment portion 14 which, in this instance, is a relatively long steady current of about eight ma. in the positive or forward direction. Heretofore, iontophoretic treatments have been effected by application of a pure direct current to a user.

In accordance with the present invention, the iontophoretic treatment portion 14 of the waveform 12 is periodically interrupted by a relatively short pulse 16 of current in the opposite direction in order to prevent the formation of undesirable vesicles, bulla or redness of the user's skin in the treated area. It should be understood that the reference to a short reverse pulse 16 is not to be construed as referring to a conventional alternating current waveform. Rather, the waveform 12 represents a substantially direct current treatment interrupted at regular intervals of time by the reverse pulse 16, thereby forming the asymmetrical waveform 12.

As will be described in greater detail hereinafter, the apparatus of the present invention is further arranged to

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impose the treatment current gradually at the beginning of each treatment period. By this arrangement, inadvertent electric shocks to the user are prevented so that the invention can be safely employed for self-treatment in the home by an average person of ordinary intelligence. Further, the apparatus of the present invention is relatively inexpensive to manufacture, and is trouble free and reliable in use.

It has been discovered that the undesirable formation of vesicles, bulla and redness of the skin in an area subjected to an iontophoretic treatment can be greatly reduced or even eliminated by periodic inclusion of the reverse pulse 16 into the waveform 12. More specifically, it has been found that these undesirable phenomena are completely eliminated when the waveform 12 is adjusted so that the energy indicated by the waveform above the zero current reference line 18 is substantially equal to the energy indicated by the waveform below the reference line 18.

The portions of the waveform 12 above and below the reference line 18 indicate the amount of energy applied in the forward direction and the reverse direction, respectively.

Unfortunately, when the reverse energy is arranged to be substantially equal to the forward energy, thereby eliminating the above-mentioned undesirable effects, it has been found that the desirable iontophoretic treatment is also eliminated. As a corollary to this discovery, it has been determined that whenever the waveform 12 is adjusted so that the forward energy exceeds the reverse energy, some desirable treatment occurs.

With the forward energy only slightly greater than the reverse energy, the undesirable vesicles and redness of the skin are eliminated, but the period required to achieve the desired results of the iontophoretic treatment becomes so long that the apparatus would not be considered practical by many. Accordingly, it has been found that a satisfactory compromise is achieved between forward energy for treatment and reverse energy for prevention of undesirable effects when the ratio of forward energy to reverse energy is between about 2:1 and 7:1.

More specifically, when operating at a treatment current of about fourteen ma, a ratio of forward energy to reverse energy of about 2.3:1 has been found to achieve the desired results. Naturally, other ratios can be employed in practicing this invention, but ratios within the above-mentioned range have been found to be satisfactory in reducing or preventing vesicle formation and reddening of the user's skin.

In order to impose the waveform 12 on the electrodes 10, electronic circuitry is provided, as illustrated in the schematic diagram of FIG. 2. It will be appreciated that various electronic means can be provided to interrupt a steady unidirectional flow of current with a relatively short reverse pulse of current at regular intervals of time. The circuit represented by the diagram of FIG. 2 is an example of such an electronic means, and is the presently preferred embodiment of this invention.

For providing a steady flow of unidirectional current across the electrodes 10, in a forward direction indicated diagrammatically by an arrow 19, a source of direct current, herein illustrated as a battery 20, is connected to a transformer 22 having a primary winding 24 and a secondary winding 26. The battery is connected to one terminal of the primary winding 24, and a diode 28 is coupled between the other terminal of the primary winding and one terminal of the secondary winding

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with the anode connected to the primary terminal and the cathode connected to the secondary terminal. A storage capacitor 36, and a resistor 38 are coupled in parallel between the cathode of the diode and ground, whereby a direct current path is formed from the battery 20 to the capacitor 36, via the primary winding 24 and the diode 28.

When a load 30 is imposed across the electrodes 10, a steady flow of direct current is permitted to flow from the battery 20 through the primary winding 24, the diode 28, the secondary winding 26, the load 30, and to ground through a variable resistor 32. The variable resistor 32 is used to control the amount of current which is permitted to flow across the load 30.

The apparatus includes switch means for imposing a succession of reverse current pulses 16 on the load 30. The switch means includes the transformer 22, the diode 28, and a shunt transistor 34, the shunt transistor being connected to the end of the primary winding 24 opposite the battery 20. When the transistor 34 is turned on for a short period of time, a surge of current will flow through the primary winding 24 inducing a similar increase in current through the secondary winding 26 and across the load 30, discharging the capacitor 36. Upon abruptly turning the transistor 34 off, the magnetic flux generated by the surge of current through the transformer 22 will collapse, causing a temporary reversal of current through the secondary winding 26, to charge the capacitor 36.

As illustrated in the exemplary waveform 12 in FIG. 1, when the shunt transistor 34 is turned on for 15 microseconds, a period of increased current 40 appears in the waveform 12. This increased flow continues while the shunt transistor 34 is on, and decays slightly due to a gradual decrease in the rate of change of current in the primary winding 24 of the transformer 22 and to a gradual discharging of the capacitor 36.

The above-mentioned reverse flow of current through the secondary winding 26 appears in the waveform 12 as the reverse pulse 16. The amplitude of this reverse pulse is also shown as decaying because of a gradual decrease in the rate of change of current in the primary winding 24 as the magnetic flux in the transformer collapses, and because the load 30, which is ordinarily human skin, is known to have some capacitance. An electronic model of human skin showing this capacitance can be found in an article by Erich A. Pfeiffer entitled: "Electrical Stimulation of Sensory Nerves With Skin Electrodes For Research, Diagnosis, Communication and Behavioral Conditioning: A Survey", Medical and Biological Engineering, Vol. 6, pp 637-651; 1968.

The shunt transistor 34 is turned on by a one-shot 42 which is arranged to turn the transistor on for a short period of time, and as mentioned above, in this example the transistor is turned on for 15 microseconds and then abruptly turned off. The one-shot 42 is further arranged, by connection with an external timing capacitor 44, to wait for an additional period of time after the transistor 34 has been turned off before the one-shot can again be triggered to turn the transistor on. The value of the timing capacitor 44 can be chosen to impose any desired waiting period on the one-shot 42, and in the example illustrated in FIG. 1, a 45 microsecond waiting period is shown. This waiting period consists of the reverse pulse 16, having a width of about 10 microseconds, and a minimum iontophoretic treatment period of 35 microseconds.

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The one-shot 42 is triggered by frequency adjusting means that includes a control comparator 46 and the variable resistor 32. The control comparator compares the voltage at a terminal 48 on the variable resistor 32 to a prescribed internal reference voltage maintained by a voltage reference device 50. The comparator 46 triggers the one-shot 42 whenever the voltage at the terminal 48 drops below the voltage supplied by the reference 50.

By this arrangement, when the device is being operated at a relatively high treatment current 14, the voltage at the terminal 48 will drop below the reference voltage before the waiting period has elapsed, and therefore, the one-shot will always be triggered immediately after the waiting period. Conversely, when the device is operated at a relatively low treatment current 14, the above-mentioned inherent capacitance in the load 30 will cause the voltage at the terminal 48 to drop more slowly, and the comparator 46 will trigger the one-shot at some time after the waiting period has elapsed.

Accordingly, it will be appreciated that the period of time between triggering the one-shot 42 to turn on the transistor 34 will vary according to the level of treatment current chosen by the user and the actual capacitance of the skin represented by the load 30. This variable period of time is illustrated in the waveform 12 by a broken time scale and the legend "variable".

Further, it will be appreciated that this arrangement provides for relatively frequent occurrences of reverse pulses 16 when a high treatment current 14 is employed, and relatively infrequent occurrence of reverse pulses 16 when a lower treatment current 14 is employed. This variance in frequency of reverse pulses 16 results in a varying ratio of forward energy to reverse energy at different treatment currents 14, but the value of the timing capacitor 44 is chosen to maintain this ratio within a range that has been found to be satisfactory, as described above.

Another important feature of the present invention is its facility to be safely employed in the home by an average person of ordinary intelligence. This feature is desirable because, if the treatment current 14 is imposed on the user too rapidly, the user may experience discomfort in the form of an electric shock. Accordingly, the present apparatus of the invention includes delay means arranged to impose the treatment current gradually whenever a load 30 is placed across the electrodes 10 and the device is activated. Further, if the load is removed from the electrodes during operation of the device and subsequently reimposed thereon, the delay means of the apparatus is arranged to gradually increase the current until the treatment current 14 is again achieved.

Toward the foregoing ends, when the device is originally activated with a load 30 across the electrodes 10, the voltage reference device 50, which is connected to the battery 20, slowly charges a delay capacitor 52 up to the reference voltage. Consequently, the current flowing from the battery 20 through the load 30 will rise slowly as the capacitor 52 charges. Preferably, the value of the delay capacitor 52 is chosen so that the current through the load 30 will rise to the treatment level in about two seconds. When the delay capacitor has fully charged, the prescribed reference voltage will be applied to the control comparator 46, and normal operation of the present invention can proceed as described above.

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If the load 30 is removed during operation of the apparatus thereby creating an open circuit between the electrodes 10, a window comparator 54 will detect the open circuit and rapidly discharge the delay capacitor 52 through a transistor 56. The discharge of the delay capacitor 52 will bring the reference voltage on the control comparator 46 to zero and inhibit the one-shot 42 from being triggered. When the load is reimposed across the electrodes 10, the delay capacitor 52 will once again be charged gradually to the prescribed reference voltage, thereby causing the current across the load to gradually rise correspondingly.

From the foregoing, it will be appreciated that the present invention provides an effective apparatus for applying an iontophoretic treatment to the skin of a living body while greatly reducing or preventing the formation of undesirable vesicles, bulla or redness of the skin in the treated area. Further, the present invention is arranged to be safely employed for self-treatment by a person of ordinary intelligence, and the apparatus of this invention can be manufactured conveniently and economically, and is trouble free and reliable in use.

While a particular form of the invention has been illustrated and described, it will be apparent that various modifications can be made without departing from the spirit and scope of the invention.

I claim:

1. An apparatus for applying an iontophoretic treatment to a living body, comprising:
 - a pair of electrodes adapted to contact the skin of the body, in spaced relationship to each other;
 - a supply capacitor coupled across the electrodes for supplying electrical current for conduction through the body, from one electrode to the other;
 - switch means for charging the supply capacitor at regular intervals of time; and
 - means for controllably adjusting the frequency at which the switch means operates to charge the supply capacitor, to adjust the magnitudes of the voltage on the capacitor and the electrical current supplied by the capacitor, correspondingly.
2. An apparatus as defined in claim 1, wherein the means for controllably adjusting includes delay means, operable when the iontophoretic treatment is initiated by the apparatus, for slowly increasing the frequency at which the switch means operates, whereby application of full treatment current is delayed for a prescribed time duration.
3. An apparatus as defined in claim 2, wherein:
 - the delay means includes
 - a delay capacitor, and
 - means for charging the delay capacitor to a prescribed reference voltage; and
 - the frequency at which the switch means operates to charge the supply capacitor varies in accordance with the charge on the delay capacitor.
4. An apparatus as defined in claim 1, wherein the switch means charges the supply capacitor by a substantially constant amount each time it operates.
5. An apparatus for applying an iontophoretic treatment to a living body, while minimizing concomitant vesicle formation, the apparatus comprising:
 - first and second electrodes adapted to contact the skin of the body, in spaced relationship to each other;
 - direct current means electrically coupled to the two electrodes for conducting direct current through

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the body, from the first electrode to the second electrode; and
 reverse pulse means electrically coupled to the two electrodes for conducting a short duration pulse of current through the body, from the second electrode to the first electrode, at regular intervals of time; the reverse pulse means including
 a transformer having a primary winding and a secondary winding, the secondary winding being electrically coupled to the two electrodes, and
 means electrically coupled to the primary winding of the transformer for conducting a primary current pulse of prescribed magnitude and duration through the primary winding, at regular intervals of time, termination of each primary current pulse inducing in the secondary winding the short duration pulse of current for conduction through the body.

6. An apparatus for applying an iontophoretic treatment to a living body, while minimizing concomitant vesicle formation, the apparatus comprising:
 first and second electrodes adapted to contact the skin of the body, in spaced relationship to each other;
 direct current means electrically coupled to the two electrodes for conducting direct current through the body, from the first electrode to the second electrode;
 reverse pulse means electrically coupled to the two electrodes for conducting a short duration pulse of current through the body, from the second electrode to the first electrode, at regular intervals of time; and
 delay means for delaying the conduction of a full treatment current through the body, the delay means including

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a delay capacitor electrically coupled to the direct current means, the current conducted by the direct current means varying in accordance with the voltage on the delay capacitor,
 means for charging the delay capacitor in a prescribed fashion, whereby the direct current means conducts a full treatment current through the body only after a prescribed time duration,
 means for detecting an open circuit between the two electrodes and for generating a corresponding control signal, and
 means responsive to the control signal for rapidly discharging the delay capacitor.

7. In an apparatus for applying an iontophoretic treatment to a living body, the apparatus including a pair of electrodes adapted to contact the skin of the body, in spaced relationship to each other, and current means for conducting a treatment current through the body, from one electrode to the other, in a prescribed fashion, an improvement comprising:
 delay means for delaying the conduction of a full treatment current through the body, the delay means including
 a delay capacitor electrically coupled to the current means, the current conducted by the current means varying in accordance with the voltage on the delay capacitor;
 means for charging the delay capacitor in a prescribed fashion, whereby the current means conducts a full treatment current through the body only after a prescribed time duration,
 means for detecting an open circuit between the two electrodes and for generating a corresponding control signal; and
 means responsive to the control signal for rapidly discharging the delay capacitor.

* * * * *

CLAIMS

1. A method of applying electrical currents to a biological subject for electrotherapy, said method including the steps of:
 - conducting an electrical current through a surface of said subject in a first direction from a first electrode to a second electrode on said subject; and
 - intermittently reversing, at a relatively low frequency which prevents skin damage, the polarity of said electrodes to cause said electrical current to flow in a second direction opposite to said first direction, whereby electrical currents may be continuous for extended periods of time and circulation is improved.
2. The method of claim 1, wherein said intermittently reversing, at a relatively low frequency which prevents skin damage, is between approximately 20 times per second and approximately once every three minutes.
3. A method as recited in either of claims 1 or 2 wherein a slow AC or DC signal supplies non-metallic conductive electrodes.
4. A method as recited in any of claims 1-3 wherein the electrodes are powdered carbon electrodes.
5. A method as recited in claim 4 wherein the carbon particles range in size from micron to nano.
6. A method as recited in any of claims 1-3 wherein the electrodes include copper particles.
7. A method as recited in any of claims 1-3 wherein the electrodes include a metal powder such as aluminum, copper, zinc, magnesium and/or stainless steel.

8. A method as recited in claim 7 wherein the metal powder is mixed with a saline gel.
9. A method of applying electrical currents to a subject for electrotherapy, comprising:
 - using charged membranes for solution storage and prevention of harmful chemicals emitted from electrodes from reaching the skin; and
 - a water solution between the electrode and skin to complete the circuit, whereby the device acts as stimulation to increase capillary blood flow in an osteoarthritic joint, typically the knees.
10. A method as recited in claim 9, wherein a DC electrical power source is connected to said electrodes.
11. A method as recited in any of claims 1-10, wherein the system is used for wound healing.
12. A method as recited in any of claims 1-10, wherein the system is used for restoring blood circulation.
13. A method as recited in any of claims 1-10, wherein the system is used for speeding tissue growth.
14. A method as recited in any of claims 1-13, wherein a slow AC or DC signal is also provided for bactericidal treatment.
15. A method for wound healing in a biological subject for electrotherapy, said method comprising:
 - conducting an electrical current through a surface of said subject in a first direction from a first electrode to a second electrode on said subject; and
 - intermittently reversing, at a relatively low frequency which prevents skin damage, the polarity of said electrodes to cause said electrical current to flow in a second

direction opposite to said first direction, whereby electrical currents may be continuous for extended periods of time and circulation is improved.

16. A method for restoring blood circulation to a biological subject for electrotherapy, said method comprising:

conducting an electrical current through a surface of said subject in a first direction from a first electrode to a second electrode on said subject; and intermittently reversing, at a relatively low frequency which prevents skin damage, the polarity of said electrodes to cause said electrical current to flow in a second direction opposite to said first direction, whereby electrical currents may be continuous for extended periods of time and circulation is improved.

17. A method for enhancing tissue growth in a biological subject for electrotherapy, said method comprising:

conducting an electrical current through a surface of said subject in a first direction from a first electrode to a second electrode on said subject; and intermittently reversing, at a relatively low frequency which prevents skin damage, the polarity of said electrodes to cause said electrical current to flow in a second direction opposite to said first direction, whereby electrical currents may be continuous for extended periods of time and circulation is improved.

18. A DC treatment device, comprising:

a powdered stainless steel negative electrode, said electrode being located within a porous membrane, whereby sodium hydroxide is prevented from reaching the skin of the subject being treated.

19. A DC treatment device, comprising:

a positive electrode utilizing powdered metals selected from aluminum, aluminum zirconium, copper, zinc, magnesium and the like, said electrode being located within a porous pouch to prevent hydrochloric acid from damaging the skin of the subject being treated.

20. A method of applying electrical currents to a subject for electrotherapy, comprising:

using charged membranes for prevention of harmful chemicals emitted from electrodes from reaching the skin, whereby skin injury is mitigated.

21. A method as recited in claim 20, wherein the electrical current is AC utilized for drug delivery.

22. A method as recited in claim 20, wherein the electrical current is DC utilized for drug delivery.

23. A method of applying electrical currents to a subject for electrotherapy, comprising:

using electrodes which include a metal powder such as aluminum, copper, zinc, magnesium and/or stainless steel, mixed with saline gel, for preventing skin injury.

24. A method as recited in claim 23, wherein the electrical current is AC utilized for drug delivery.

25. A method as recited in claim 23, wherein the electrical current is DC utilized for drug delivery.

26. A method as recited in any of the previous claims, wherein the stimulative electrical currents are applied therapeutically to benefit the problems selected from the group consisting of osteoarthritis, treating knee joints as well as other joints, carpal tunnel syndrome, decubitus ulcers, tremors, diabetic feet, aging skin, and any other problems and/or disabilities that may benefit from increased blood circulation.

27. Use of the method and/or DC treatment device as recited in any one of the previous claims.

28. Each and every novel feature and/or novel combination of features herein disclosed.

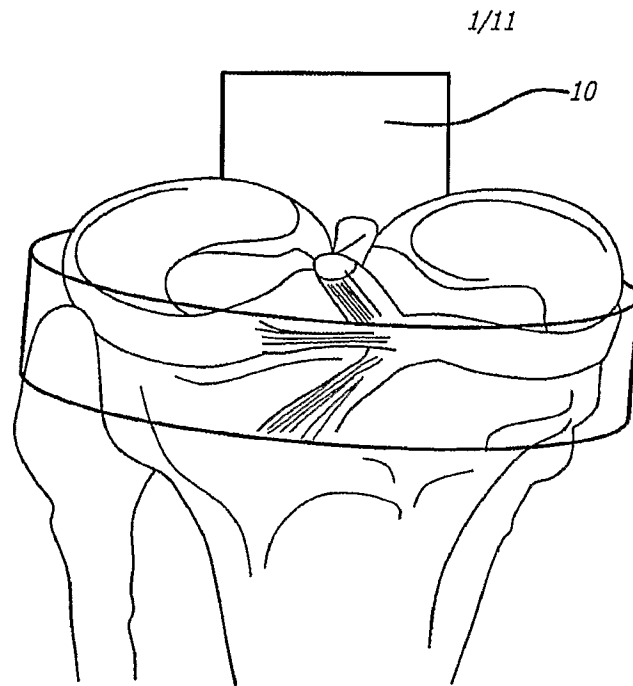


FIG. 1

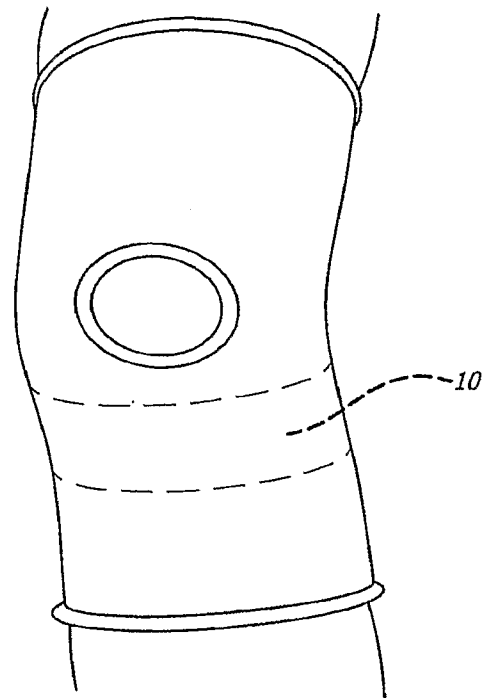


FIG. 2

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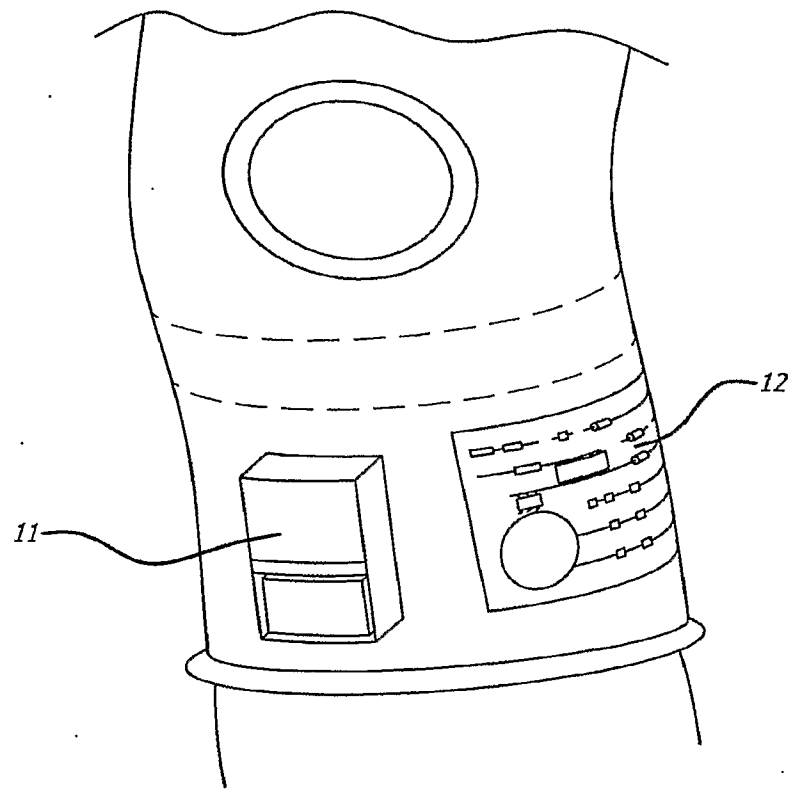
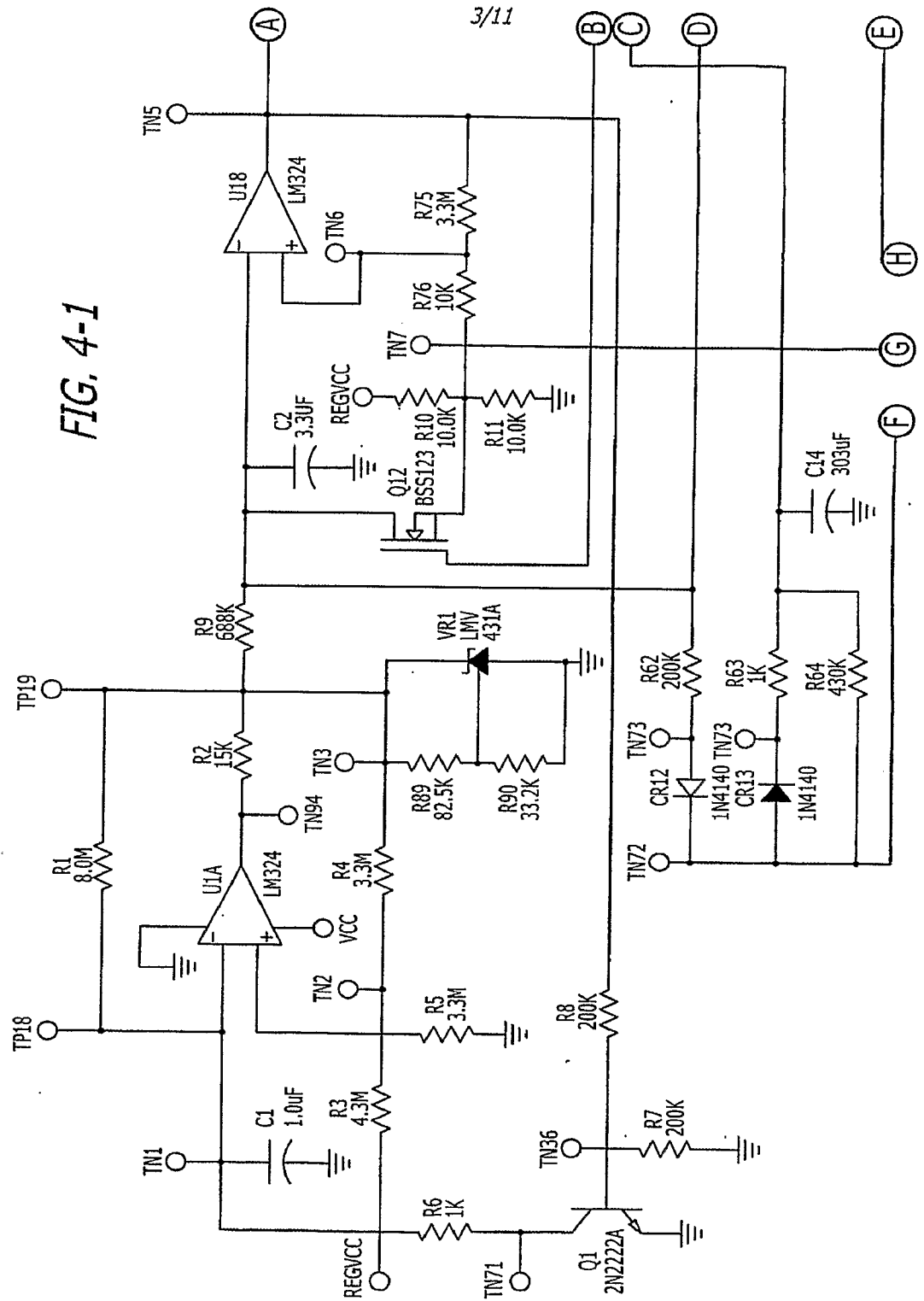


FIG. 3

FIG. 4-1



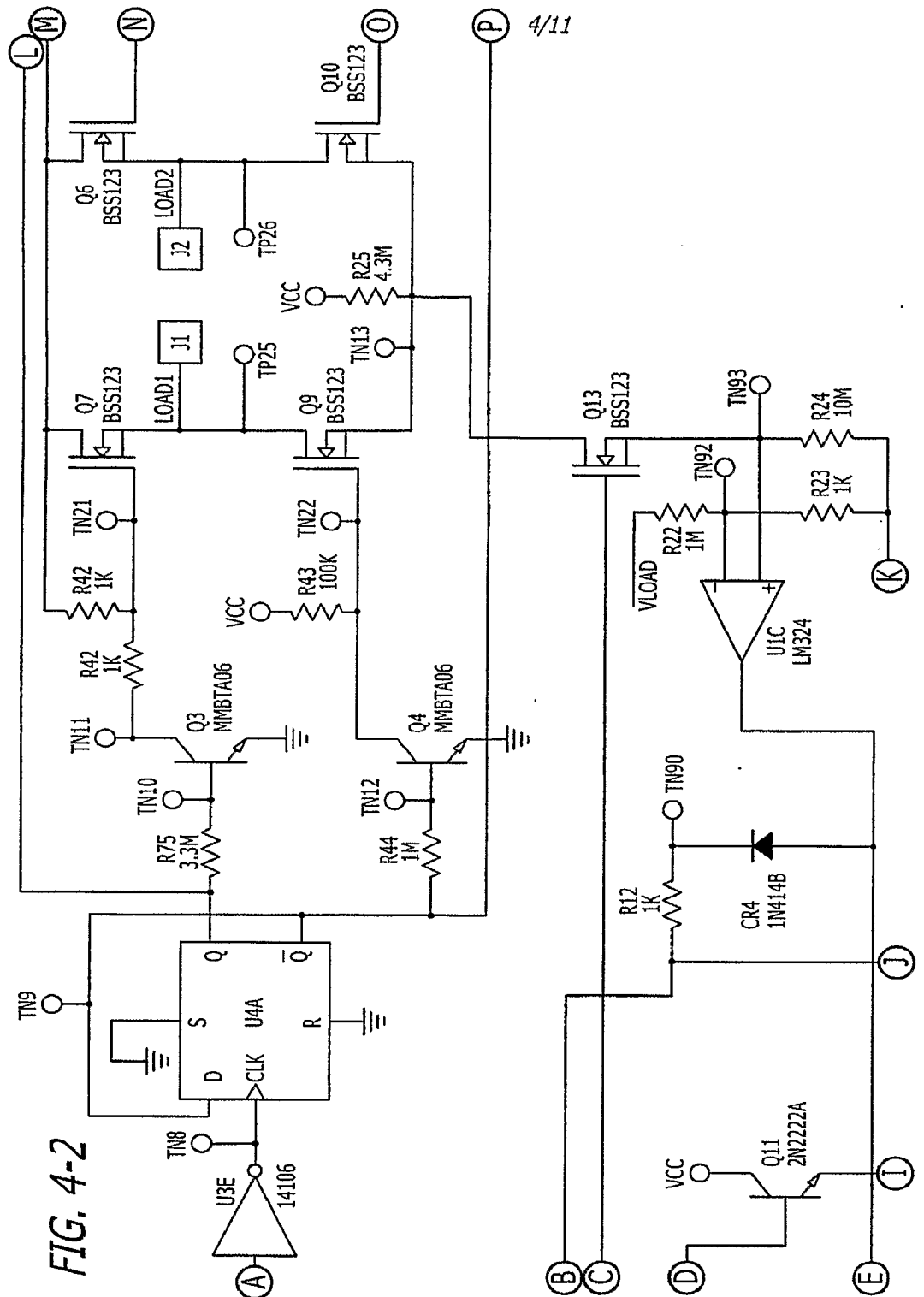


FIG. 4-3

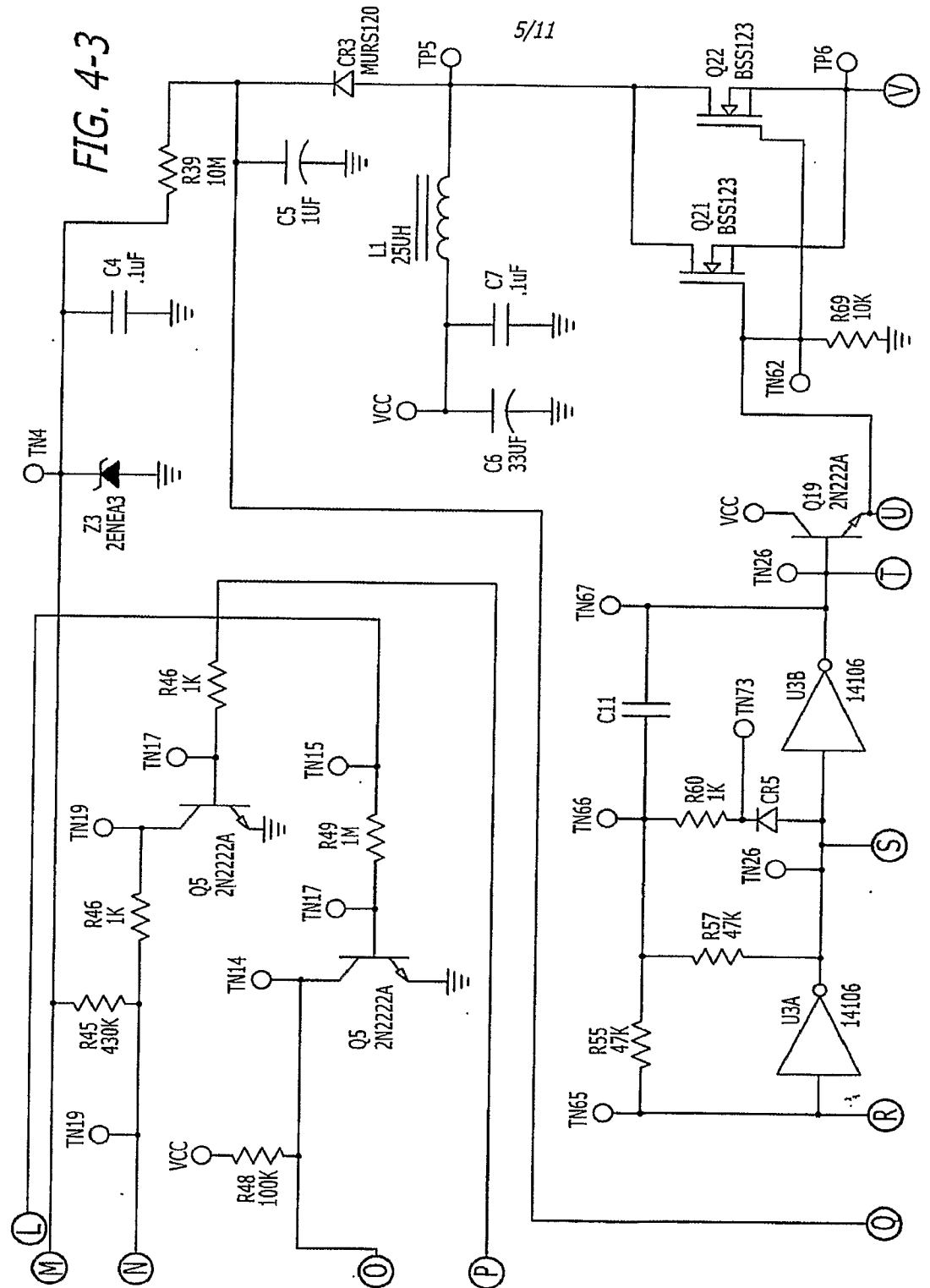
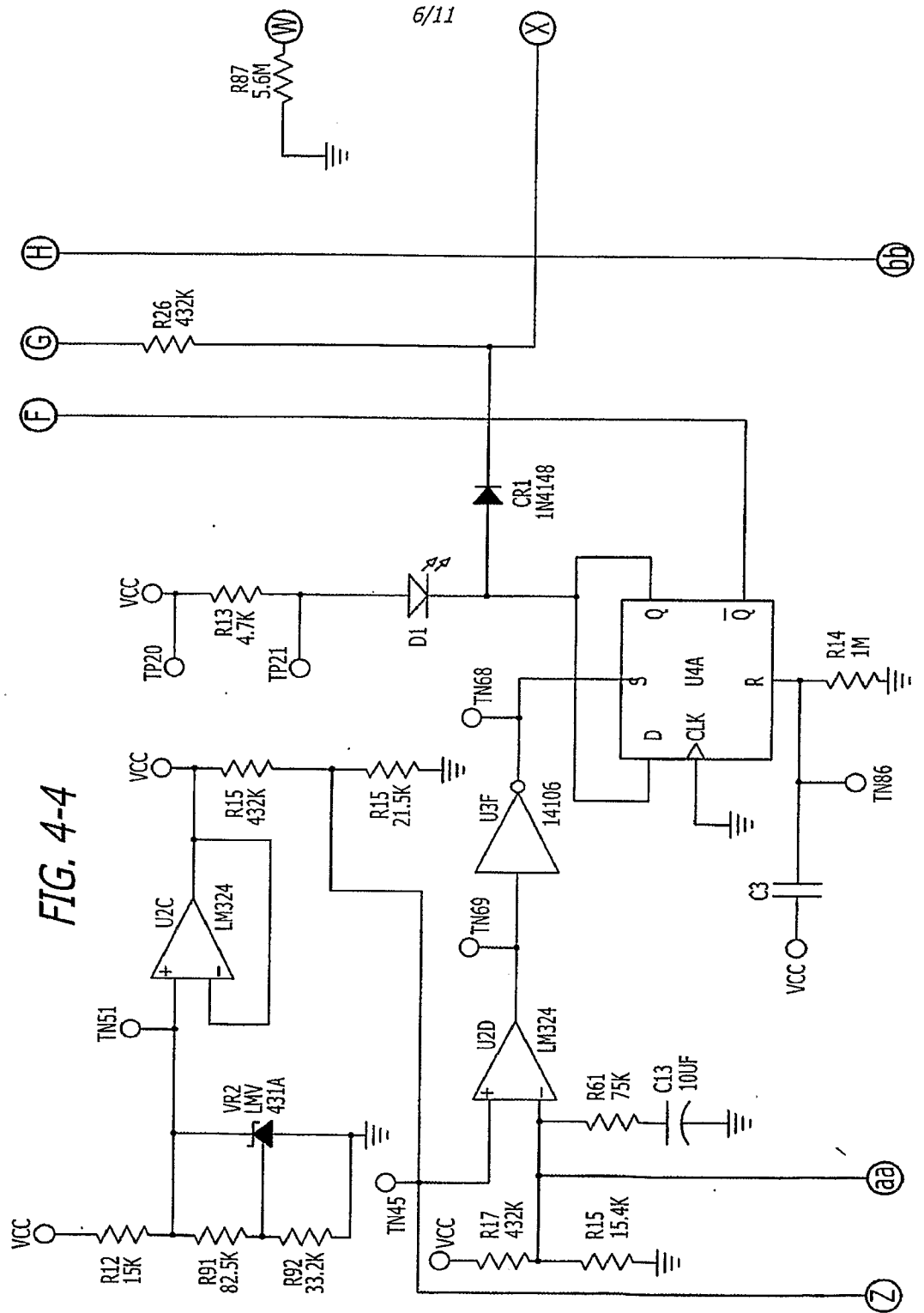


FIG. 4-4



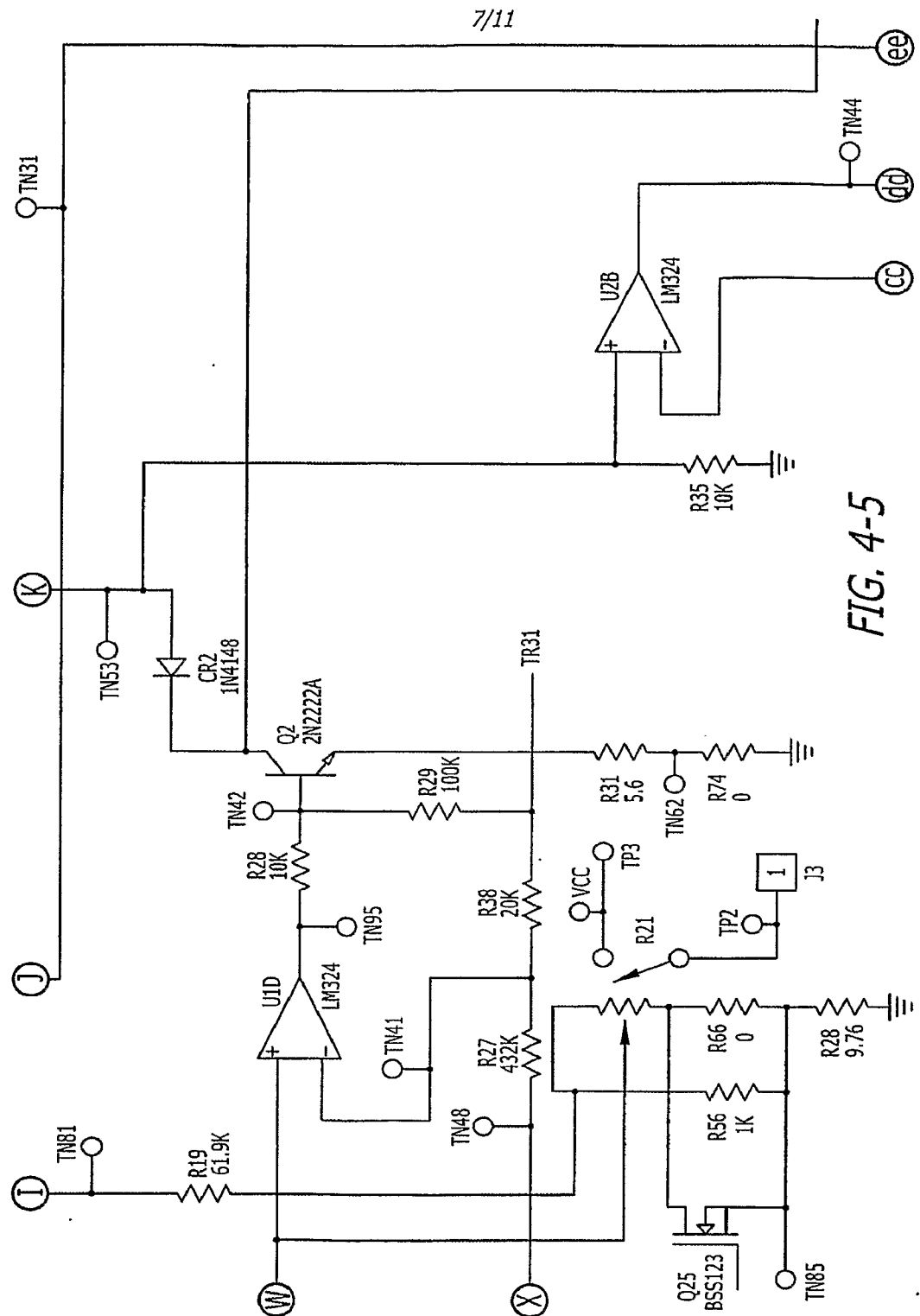


FIG. 4-5

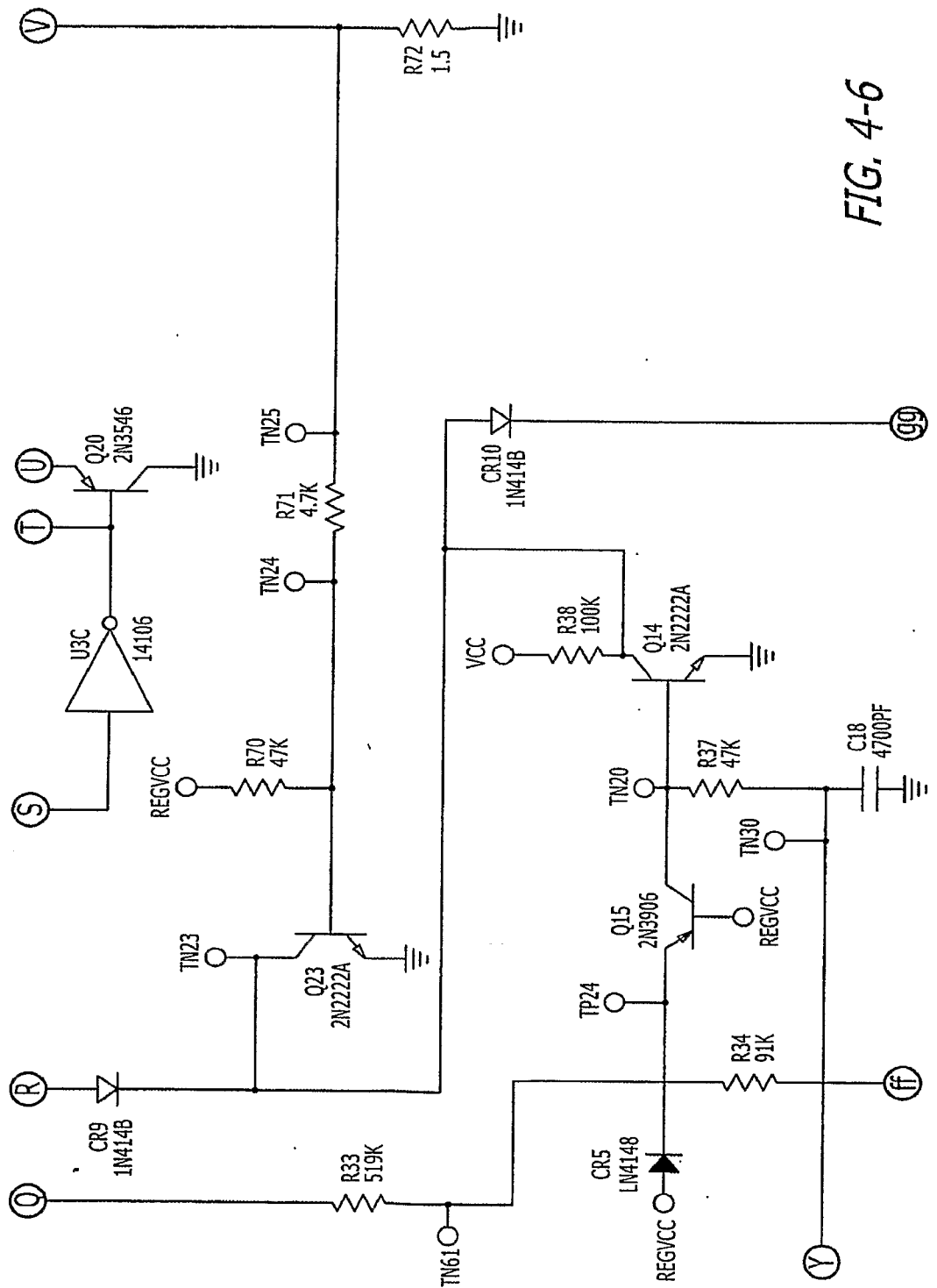
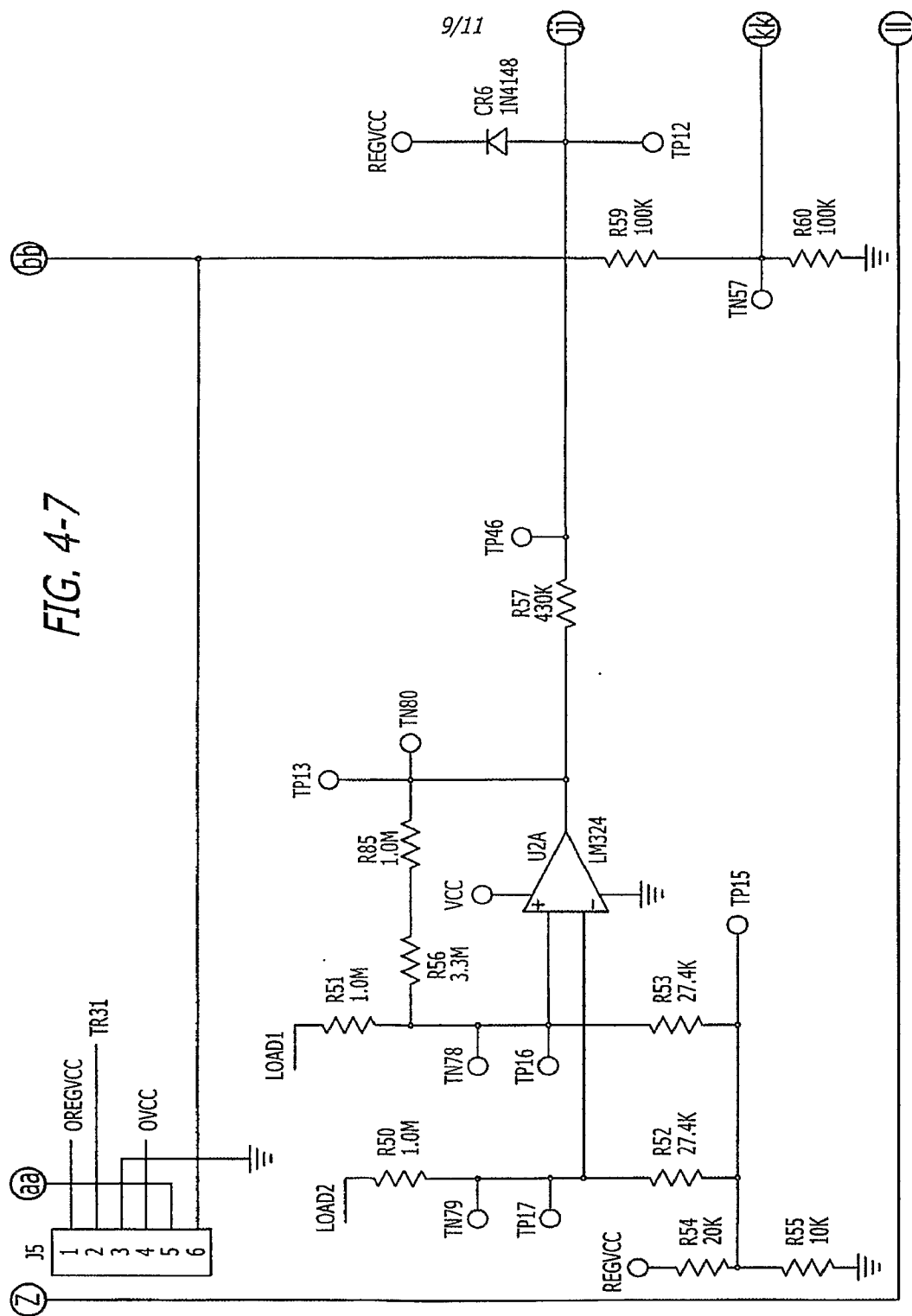


FIG. 4-6



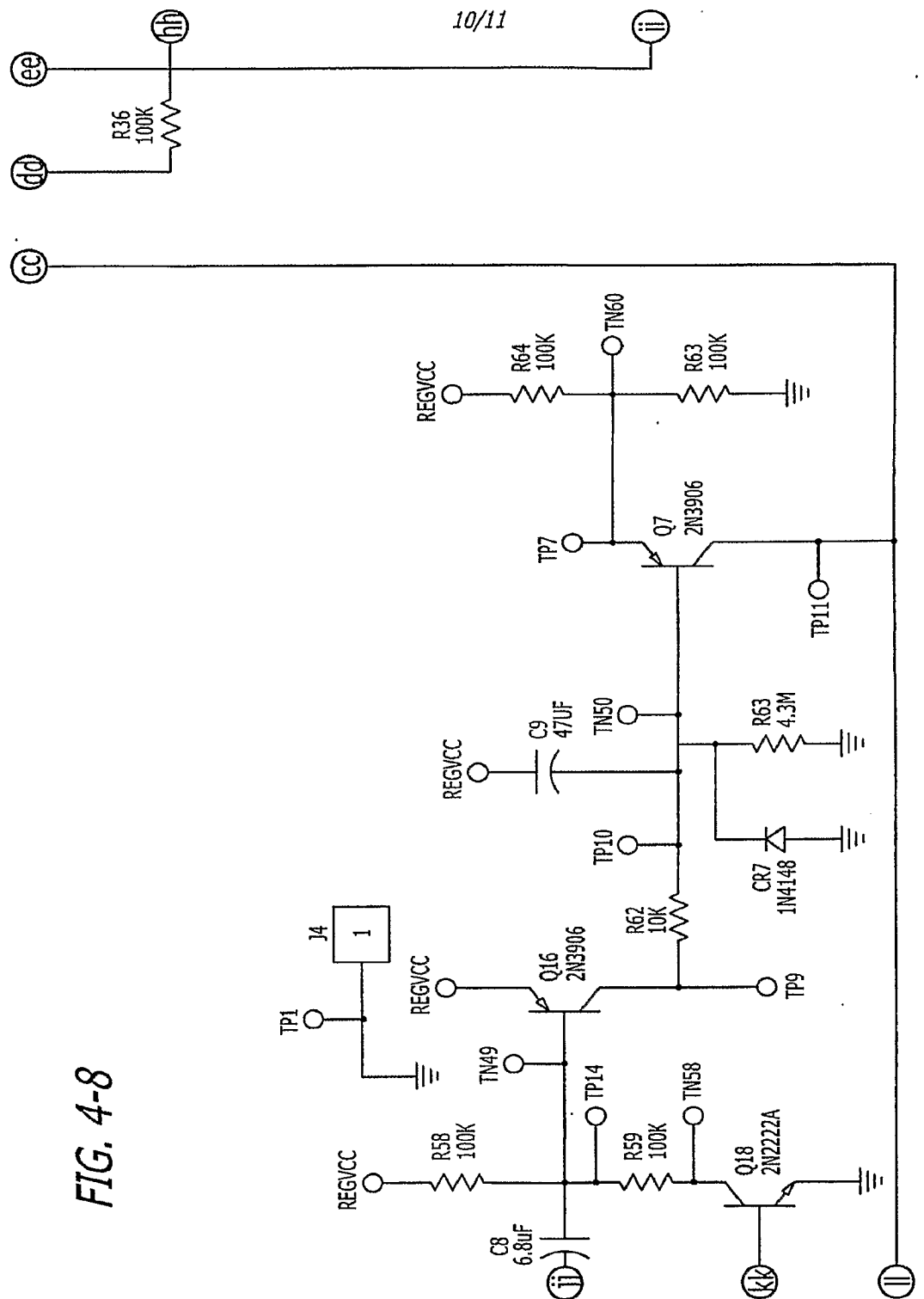


FIG. 4-8

FIG. 4-9

