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(54) **Title**: ELECTROTRANSPORT FENTANYL DELIVERY DEVICE WITH CONSISTENT DELIVERY

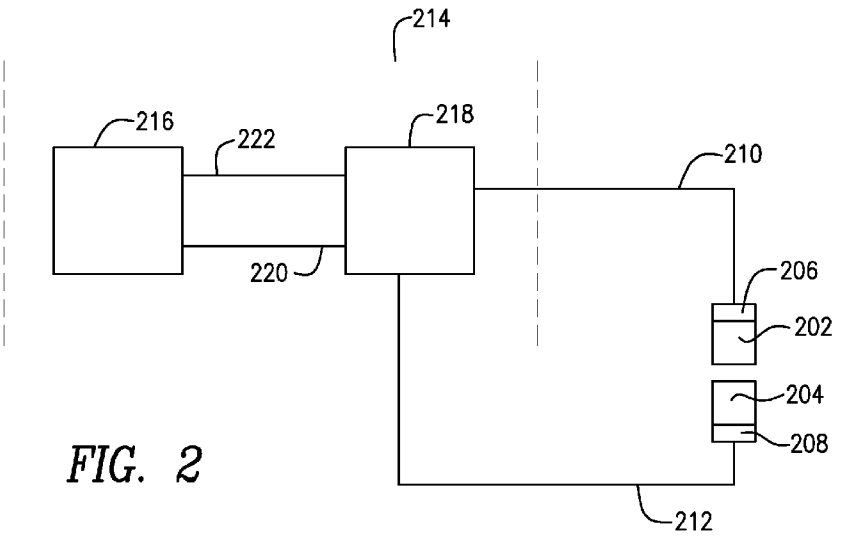


FIG. 2

(57) **Abstract**: A transdermal electrotransport fentanyl delivery system having relatively stable fentanyl flux. The system has a controller that controls a current through a donor reservoir wherein the current generally changes with time nonlinearly and non-exponentially to result in a relatively stable fentanyl flux.

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ELECTROTRANSPORT FENTANYL DELIVERY DEVICE WITH CONSISTENT DELIVERY

TECHNICAL FIELD

[0001] The present invention relates to an electrotransport drug delivery system for driving fentanyl across a body surface or membrane. In particular, the invention relates to a system that delivers a current that generally changes with time to result in a relatively stable fentanyl flux.

BACKGROUND

[0002] The delivery of active pharmaceutical agents through the skin provides many advantages, including comfort, convenience, and non-invasiveness. Gastrointestinal irritation and the variable rates of absorption and metabolism including first pass effect encountered in oral delivery are avoided. Transdermal delivery also provides a high degree of control over blood concentrations of any particular active agent.

[0003] In transdermal drug delivery, the natural barrier function of the body surface, such as skin, presents a challenge to delivery therapeutics into circulation. Devices have been invented to provide transdermal delivery of drugs. Transdermal drug delivery can generally be considered to belong to one of two groups: transport by a "passive" mechanism or by an “active” transport mechanism. In the former, such as DUROGESIC® fentanyl transdermal systems available from Janssen Pharmaceuticals and other drug delivery skin patches, the drug is incorporated in a solid matrix, or a reservoir with rate-controlling membrane, and/or an adhesive system.

[0004] Passive transdermal drug delivery offers many advantages, such as ease of use, little or no pain at use, disposability, good control of drug delivery and avoidance of hepatic first-pass metabolism. However, many active agents are not suitable for passive transdermal delivery because of their size, ionic charge characteristics, and hydrophilicity. Most passive transdermal delivery systems are not capable of delivering drugs under a specific profile, such as by ‘on-off’ mode, pulsatile mode, etc. Consequently, a number of alternatives have been proposed in which the flux of the drug(s) is driven by various forms of energy. Some examples include the use of iontophoresis, ultrasound, electroporation, heat and microneedles. These are considered to be “active” delivery systems.

[0005] One method for transdermal delivery of such active agents involves the use of electrical current to actively transport the active agent into the body through intact skin by

electrotransport. Electrotransport techniques may include iontophoresis, electroosmosis, and electroporation. Electrotransport devices, such as iontophoretic devices are known in the art, see, e.g., EP0939659 A1 and US patents 6,049,733, 6,181,963 and 6,216,033. One electrode, called the active or donor electrode, is the electrode from which the active agent is delivered into the body. The other electrode, called the counter or return electrode, serves to close the electrical circuit through the body. In conjunction with the patient's body tissue, e.g., skin, the circuit is completed by connection of the electrodes to a source of electrical energy, and usually to circuitry capable of controlling the current passing through the device. If the substance to be driven into the body is ionic and is positively charged, then the positive electrode (the anode) will be the active electrode and the negative electrode (the cathode) will serve as the counter electrode. If the ionic substance to be delivered is negatively charged, then the cathodic electrode will be the active electrode and the anodic electrode will be the counter electrode. A prior system for delivery of fentanyl is the IONSYS™ fentanyl iontophoretic transdermal system (Janssen-Cilag), hereinafter the "IONSYS" system. Characteristics of the IONSYS system can be found in Annex I (Summary of Product Characteristics) of the Product Information (24/01/2006 Ionsys-H-C-612-00-00) of IONSYS system, available from the European Medicines Agency (EMEA).

[0006] A prior iontophoretic system similar to that of US 6,181,963 is shown in FIG. 1. FIG. 1 shows a perspective exploded view of an electrotransport device 10 having an activation switch in the form of a push button switch 12 and a display in the form of a light emitting diode (LED) 14. Device 10 includes an upper housing 16, a circuit board assembly 18, a lower housing 20, anodic electrode 22, cathodic electrode 24, anodic reservoir 26, cathodic reservoir 28 and skin-compatible adhesive 30. Upper housing 16 has lateral wings 15 that assist in holding device 10 on a patient's skin. Upper housing 16 is preferably composed of an injection moldable polymer.

[0007] Printed circuit board assembly 18 includes an integrated circuit 19 coupled to discrete electrical components 40 and battery 32. Printed circuit board assembly 18 is attached to housing 16 by posts (not shown) passing through openings 13a and 13b, the ends of the posts being heated/melted in order to heat weld the circuit board assembly 18 to the housing 16. Lower housing 20 is attached to the upper housing 16 by means of adhesive 30, the upper surface 34 of adhesive 30 being adhered to both lower housing 20 and upper housing 16 including the bottom surfaces of wings 15. Shown (partially) on the underside of printed

circuit board assembly 18 is a battery 32, preferably a button cell battery and most preferably a lithium cell. Other types of batteries may also be employed to power device 10.

[0008] The circuit outputs (not shown in FIG. 1) of the circuit board assembly 18 make electrical contact with the electrodes 24 and 22 through openings 23,23' in the depressions 25,25' formed in lower housing, by means of electrically conductive adhesive strips 42,42'. Electrodes 22 and 24, in turn, are in direct mechanical and electrical contact with the top sides 44', 44 of reservoirs 26 and 28. The bottom sides 46', 46 of reservoirs 26,28 contact the patient's skin through the openings 29', 29 in adhesive 30. The skin-facing side 36 of the adhesive 30 has adequate adhesive property to maintain the device on the skin for the duration of the use of the device.

[0009] Recently, there have been suggestions to control the current of drug delivery with more sophisticate current or voltage profiles. See, for example, US5207752, US5983130, US6219576, and EP941085B1. However, there has not been an electrotransport system that has been shown to deliver fentanyl with relatively stable flux over time.

[0010] What is needed is an electrotransport device that can deliver fentanyl with relatively stable flux over time.

SUMMARY

[0011] The present invention relates to an electrotransport device for delivering fentanyl through the skin of an individual with a relatively stable fentanyl flux. The present invention provides such electrotransport devices and methods of making and using such electrotransport devices.

[0012] In one aspect, the device has a donor compartment (e.g., reservoir) containing the fentanyl salt (a therapeutic agent for analgesic effect) for delivery through the body surface by electrotransport. The device has at least two electrodes for driving fentanyl ions (from the ionized salt) from the donor reservoir. A controller is connected to the electrodes to control the current delivery for driving the fentanyl ions such that in use the amount of current, i.e., charge delivered per unit time, generally decreases with time. In an embodiment, in use the current is controlled to have a current that would decrease in amplitude with time in a way that is neither exponential nor linear. In an embodiment, a transdermal electrotransport system for administering fentanyl through the skin of a user for a predetermined period of time includes a donor reservoir and a counter reservoir, the donor reservoir containing a fentanyl salt for delivery of fentanyl by means of fentanyl ions. A controller in the device controls the current

delivery that drives the fentanyl ions such that the amount of charge per dose period of the current passing through the donor reservoir decreases with time nonlinearly and nonexponentially. The average amount of charge per dose period during the first hour in the predetermined delivery period differs from the average amount of charge per dose period during the final hour by not more than 60% of the average amount of charge of the first hour.

[0013] It has been shown that if a constant current is used for electrotransport of fentanyl, the flux tends to be low initially and slowly increases with time. Since a more stable flux over time is desirable for controlling pain, we have shown that it is beneficial to start fentanyl delivery with a larger amount of current. With the present invention, we have shown that we could deliver fentanyl without the initial period of low flux by way of starting with a higher current and decreasing the current flow with time. In this way, we were able to deliver fentanyl with an adequate flux initially and further without the fentanyl flux having to slowly increase with time. In fact, with adequate fentanyl flux initially, the fentanyl flux did not slowly increase with time.

[0014] In an aspect, the controller in the present invention controls the current to be within about 20% of the value I, wherein $I = I_f / y$, and $y = 0.4454 + 0.0587t - 0.0016t^2$, wherein I_f is the average current for a targeted final hour of use, t is time in hour after initial application of the device on the skin.

[0015] An electrotransport device that administers adequate drug in the initial period and throughout the time of use of the device provides significant advantage over devices that start out with low flux and trend up with time, in that with the devices of the present invention, adequate analgesia is possible from the beginning hour of use, and would reduce the likelihood that a supplemental dose of analgesic by injection or other route of administration may be needed. In certain embodiments of the invention, the amount of current used is always equal or larger than the current used in the commercial IONSYS system, it provides even better analgesic effect than the IONSYS system, in that during certain period where the IONSYS system fentanyl is slightly low, the devices of the present system will deliver a larger amount of fentanyl to effect better analgesia. We have demonstrated in clinical trials that such relatively level delivery of fentanyl can be achieved safely.

[0016] The present invention also provides methods of making and methods of using the above electrotransport devices.

BRIEF DESCRIPTION OF THE FIGURES

[0017] The present invention is illustrated by way of examples in embodiments and not limitation in the figures of the accompanying drawings in which like references indicate similar elements. The figures are not shown to scale unless indicated otherwise in the content.

[0018] FIG. 1 illustrates an exploded perspective view of a prior art typical electrotransport system.

[0019] FIG. 2 illustrates a schematic view of an embodiment of an electrotransport system of the present invention.

[0020] FIG. 3 is a graph showing data that illustrate normalized fentanyl flux as a function of time and predicted fentanyl flux if the current is controlled according to an embodiment of the present invention.

[0021] FIG. 4 is a graph showing data of normalized fentanyl flux as a function of time from three human trials and curve fitting to model the data of normalized fentanyl flux as a function of time from the three human trials.

DETAILED DESCRIPTION

[0022] The present invention is directed to an electrotransport drug delivery system that has delivers fentanyl with an average amount of charge per dose period that trends down with time to result in a more stable fentanyl flux over time. In particular, the system has a controller that controls the average amount of charge per dose period so that it decreases in a nonlinear and nonexponential way to drive fentanyl ions from the donor reservoir transdermally.

[0023] The practice of the present invention will employ, unless otherwise indicated, conventional methods used by those skilled in the art of mechanical and electrical connections in drug device development.

[0024] In describing the present invention, the following terminology will be used in accordance with the definitions set out below.

[0025] The singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a polymer” includes a single polymer as well as a mixture of two or more different polymers.

[0026] The term "AUC" means the area under the curve obtained in a subject by plotting blood plasma concentration of the beneficial agent in the subject against time, as measured from the time of start of dosing, to a time "t" after the start of dosing. AUC_{inf} is the area under the curve extended to time of infinity. For steady state, the AUC_n is the area under the curve

for a single dose normalized for doses administered. The AUC can be obtained by assaying samples from a patient.

[0027] As used herein, the term "C_{max}" refers to the peak blood or plasma concentration of the drug, e.g., fentanyl.

[0028] As used herein, the term "C_{min}" refers to the valley blood or plasma concentration of the drug, e.g., fentanyl.

[0029] As used herein, the term "bioavailability", refers to the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. The rate and extent are established by the pharmacokinetic parameters, such as, the peak blood or plasma concentration (C_{max}) of the drug and the area under the blood or plasma drug concentration-time curve (AUC). To be bioequivalent to a prior transdermal drug delivery system, the 90% confidence interval of the steady state C_{max} ratio of a new transdermal system to that of the prior system needs to be within 80% to 125% and the 90% confidence interval of the steady state AUC_{ss} ratio of a new transdermal system to that of the prior system of the same dose strength needs to be within 80% to 125%. All delivery doses for fentanyl here are expressed in terms of fentanyl base equivalent unless specified otherwise in the content.

[0030] As used herein, "dose period" refers to a period of time during which the device delivers a nominal dose that the device has been designed to deliver. Such a nominal dose is typically a target amount of drug that the device is specified to deliver according to regulatory approval by a competent government drug administration agency. Typically such a dose is delivered each time the device is activated for delivery of a dose.

[0031] As used herein, the "trending down" of charge delivery (e.g., current) refers to a delivery profile in which during the delivery time the system is designed to be used, the averaged charge per dose of the second half of delivery is less than that of the first half of delivery.

MODES OF CARRYING OUT THE INVENTION

[0032] The present invention provides an electrotransport device that is for electrotransport delivery of ionic fentanyl through a surface, such as skin.

[0033] Electrotransport devices, such as iontophoretic devices are known in the art, e.g., US6216033. The structures, drugs, and electrical features of US6216033 and in FIG. 1 can be adapted to equivalents to be used in the present invention, as can be understood by one skilled

in the art. In an iontophoretic drug delivery device, there is a drug reservoir and a counter reservoir.

[0034] FIG. 2 shows a schematic representation of an embodiment of an electrotransport device of the present invention. The fentanyl electrotransport device 200 includes a drug reservoir 202 and a counter reservoir 204 connected by means of donor electrode (here the anode) 206 and counter or return electrode (here the cathode) 208 and conductors 210, 212 respectively to the electronic circuitry 214 of the device. The electronic circuitry 214 includes power source (e.g., battery) 216 and a controller 218 that controls the current flow through the electrodes 206, 208 during electrotransport. Conductors 220, 222 provide for electrical communication between the power source 216 and the controller 218.

[0035] The controller 218 controls the dose of fentanyl delivered by transdermal electrotransport from about 20 μg (mcg) to about 60 μg (i.e., 40 μg of fentanyl) over a delivery time of up to about 20 minutes (delivery period or dose period, e.g., 10 min) in human patients having body weights of 35 kg or greater. Preferred is about 20 μg to 60 μg of fentanyl per dose. Preferred is a dosage of about 35 μg to about 45 μg, and most preferred is a dosage of about 40μg for the delivery period. The device of the invention further preferably includes means for delivering about 10 to 100, and more preferably about 20 to 80 additional like doses over a period of 24 hours in order to achieve and maintain the analgesic effect. When a user initiates (i.e., activates) the device, a dose is delivered. After the dose delivery is completed, if the device is initiated (or activated) again, another dose is delivered. The device can be made such that the controller cannot be activated for a second dose during the delivery of a first dose, and only a certain maximum number of doses can be activated per hour or per day, such as a maximum of six 10-minute doses per hour and 80 doses per day as in the IONSYS system. For example, the reservoir contains an amount of fentanyl salt (e.g., fentanyl halide, such as fentanyl hydrochloride) adequate for this dosing regime and the controller controls the delivery for such dosing practice.

[0036] The fentanyl salt-containing anodic reservoir formulation for transdermally delivering the above mentioned doses of fentanyl by electrotransport is preferably comprised of an aqueous solution of a water soluble fentanyl salt such as halide salt (e.g., HBr, HI, or HCl) or citrate salts. Most preferably, the aqueous solution is contained within a hydrophilic polymer matrix such as a hydrogel matrix. The fentanyl salt is present in an amount sufficient to deliver the above mentioned doses transdermally by electrotransport over a delivery period

of up to about 20 minutes, to achieve a systemic analgesic effect. The fentanyl salt typically comprises about 1 to 10 wt % of the donor reservoir formulation (including the weight of the polymeric matrix) on a fully hydrated basis, and more preferably about 1 to 5 wt % of the donor reservoir formulation on a fully hydrated basis. Although not critical to this aspect of the present invention, the applied electrotransport current density is typically in the range of about 50 to 150 $\mu A/cm^2$ and the applied electrotransport current is typically in the range of about 150 to 240 μA, depending on the analgesic effect desired. In the initial period of use of the device on a patient, the current can be slightly higher. The current can be up to about 380 μA. A smaller current can be used for a device of lower dose. For example, a device for 25 μg per dose can have a current of about 100 μA in the later part of delivery. In the initial periods of delivery, the current will correspondingly be slightly higher according to the present invention.

[0037] A suitable electrotransport device includes an anodic donor electrode, e.g., one that contains silver, and a cathodic counter electrode, e.g., one that contains silver chloride. The donor electrode is in electrical contact with the donor reservoir containing the aqueous solution of a fentanyl salt. The donor reservoir is preferably a hydrogel formulation. The counter reservoir also preferably comprises a hydrogel formulation containing a (e.g., aqueous) solution of a biocompatible electrolyte, such as citrate buffered saline. Typically the donor and the counter reservoir each would have a surface area for contacting skin of about 0.8 cm^2 to 10cm^2. Preferably the anodic and cathodic hydrogel reservoirs preferably each have a skin contact area of about 1 cm^2 to 5 cm^2 and more preferably about 2 cm^2 to 3 cm^2, even more preferably about 2.7 cm^2 to 2.8 cm^2. The anodic and cathodic hydrogel reservoirs preferably have a thickness of about 0.05 to 0.25 cm, and more preferably about 0.15 cm. Most preferably, the applied electrotransport current is substantially constant DC current during the dosing interval.

[0038] Preferably, the concentration of fentanyl in solution in the donor reservoir is maintained at or above the level at which the transdermal electrotransport fentanyl flux is independent of drug concentration in the donor reservoir during the electrotransport drug delivery period. Transdermal electrotransport fentanyl flux begins to become dependent upon the concentration of the fentanyl salt in aqueous solution as the fentanyl salt concentration falls below about 11 to 16 mM. The 11 to 16 mM concentration is calculated based only on the volume of liquid solvent used in the donor reservoir, not on the total volume of the reservoir. In other words, the 11 to 16 mM concentration calculation does not include the volume of the

reservoir which is represented by the reservoir matrix (e.g., hydrogel or other matrix) carrier material. For fentanyl HCl, the 11 to 16 mM concentration is equivalent to about 4 to 6 mg/mL. Other fentanyl salts (e.g., fentanyl citrate) will have slightly differing weight based concentration ranges based on the difference in the molecular weight of the counter ion of the particular fentanyl salt in question. As the fentanyl salt concentration falls to about 11 to 16 mM, the fentanyl transdermal electrotransport flux begins to significantly decline, even if the applied electrotransport current remains constant. Thus, to ensure a predictable fentanyl flux with a particular level of applied electrotransport current, the fentanyl salt concentration in the solution contained in the donor reservoir is preferably maintained above about 11 mM, and more preferably above about 16 mM. Since fentanyl is a base, the salts of fentanyl are typically acid addition salts, e.g., citrate salts, hydrochloride salts, etc. The acid-addition-salts of fentanyl typically have water solubilities of about 25 to 30 mg/mL. When these salts are placed in solution (e.g., aqueous solution), the salts dissolve and form protonated fentanyl cations and counter (e.g., citrate, bromide or chloride) anions. As such, the fentanyl cations are delivered from the anodic electrode of an electrotransport delivery device. In accordance with the teachings in these patents, the cationic fentanyl is preferably formulated as a halide salt (e.g., hydrochloride salt) so that any electrochemically-generated silver ions will react with the drug counter ions (i.e., halide ions) to form a substantially insoluble silver halide.

[0039] The reservoirs of the electrotransport delivery devices generally can contain a gel matrix, with the drug solution uniformly dispersed in at least one of the reservoirs. In IONSYS systems, the gel was made from poly(vinyl alcohol). Obviously, other types of reservoirs such as membrane-confined reservoirs are possible and contemplated. The application of the present invention is not limited by the type of reservoirs used. Gel reservoirs are described, e.g., in US patents 6039977 and 6181963. Such reservoirs, devices, and methods of using and making are well known in the art. Suitable polymers for the gel matrix can contain essentially any synthetic and/or naturally occurring polymeric materials suitable for making gels. A polar nature is preferred when the active agent is polar and/or capable of ionization, so as to enhance agent solubility. Optionally, the gel matrix can be water swellable nonionic material.

[0040] Examples of suitable synthetic polymers include, but are not limited to, poly(acrylamide), poly(2-hydroxyethyl acrylate), poly(2-hydroxypropyl acrylate), poly(N-vinyl-2-pyrrolidone), poly(n-methylol acrylamide), poly(diacetone acrylamide), poly(2-hydroxylethyl methacrylate), poly(vinyl alcohol) and poly(allyl alcohol). Hydroxyl functional

condensation polymers (i.e., polyesters, polycarbonates, polyurethanes) are also examples of suitable polar synthetic polymers. Polar naturally occurring polymers (or derivatives thereof) suitable for use as the gel matrix are exemplified by cellulose ethers, methyl cellulose ethers, cellulose and hydroxylated cellulose, methyl cellulose and hydroxylated methyl cellulose, gums such as guar, locust, karaya, xanthan, gelatin, and derivatives thereof. Ionic polymers can also be used for the matrix provided that the available counterions are either drug ions or other ions that are oppositely charged relative to the active agent.

[0041] The reservoir formulation for transdermally delivering cationic drugs by electrotransport is preferably composed of an aqueous solution of a water-soluble salt, such as HCl or citrate salts of a cationic drug, such as fentanyl. More preferably, the aqueous solution is contained within a hydrophilic polymer matrix such as a hydrogel matrix. The drug salt is preferably present in an amount sufficient to deliver an effective dose by electrotransport over a delivery period of up to about 20 minutes, to achieve a systemic effect. The drug salt typically includes about 0.05 to 20 wt % of the donor reservoir formulation (including the weight of the polymeric matrix) on a fully hydrated basis, and more preferably about 0.1 to 10 wt % of the donor reservoir formulation on a fully hydrated basis. In one embodiment the drug reservoir formulation includes at least 30wt % water during transdermal delivery of the drug. Delivery of fentanyl has been described in US6171294. The parameter such as concentration, rate, current, etc. as described in US6171294 can be similarly employed here, since the electronics and reservoirs of the present invention can be made to be substantially similar to those in US6171294.

[0042] A preferred hydrophilic polymer matrix is polyvinyl alcohol such as a washed and fully hydrolyzed polyvinyl alcohol (PVOH), e.g. MOWIOL 66-100 commercially available from Hoechst Aktiengesellschaft. A suitable buffer is an ion exchange resin which is a copolymer of methacrylic acid and divinylbenzene in both an acid and salt form. One example of such a buffer is a mixture of POLACRILIN (the copolymer of methacrylic acid and divinyl benzene available from Rohm & Haas, Philadelphia, Pa.) and the potassium salt thereof. A mixture of the acid and potassium salt forms of POLACRILIN functions as a polymeric buffer to adjust the pH of the hydrogel to about pH 6. Use of a humectant in the hydrogel formulation is beneficial to inhibit the loss of moisture from the hydrogel. An example of a suitable humectant is guar gum. Thickeners are also beneficial in a hydrogel formulation. For example, a polyvinyl alcohol thickener such as hydroxypropyl methylcellulose (e.g. METHOCEL

K100MP available from Dow Chemical, Midland, Mich.) aids in modifying the rheology of a hot polymer solution as it is dispensed into a mold or cavity. The hydroxypropyl methylcellulose increases in viscosity on cooling and significantly reduces the propensity of a cooled polymer solution to overfill the mold or cavity.

[0043] Polyvinyl alcohol hydrogels can be prepared, for example, as described in US6039977. The weight percentage of the polyvinyl alcohol used to prepare gel matrices for the reservoirs of the electrotransport delivery devices, in certain embodiments can be about 10 % to about 30 %, preferably about 15 % to about 25 %, and more preferably about 19 %. Preferably, for ease of processing and application, the gel matrix has a viscosity of from about 1,000 to about 200,000 poise, preferably from about 5,000 to about 50,000 poise. In certain preferred embodiments, the drug-containing hydrogel formulation includes about 10 to 15 wt % polyvinyl alcohol, 0.1 to 0.4 wt % resin buffer, and about 1 to 30 wt%, preferably 1 to 2 wt % drug. The remainder is water and ingredients such as humectants, thickeners, etc. The polyvinyl alcohol (PVOH)-based hydrogel formulation is prepared by mixing all materials, including the drug, in a single vessel at elevated temperatures of about 90 °C to 95 °C for at least about 0.5 hour. The hot mix is then poured into foam molds and stored at freezing temperature of about -35 °C overnight to cross-link the PVOH. Upon warming to ambient temperature, a tough elastomeric gel is obtained suitable for ionic drug electrotransport.

[0044] Including fentanyl, a variety of drugs can also be delivered by electrotransport devices. In certain embodiments, the drug is a narcotic analgesic agent and is preferably selected from the group consisting of fentanyl and related molecules such as remifentanil, sufentanil, alfentanil, lofentanil, carfentanil, trefentanil as well as simple fentanyl derivatives such as alpha-methyl fentanyl, 3-methyl fentanyl and 4-methyl fentanyl, and other compounds presenting narcotic analgesic activity such as alphaprodine, anileridine, benzylmorphine, beta-promedol, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dimenoxadol, dimeheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, meperidine, meptazinol, metazocine, methadone, methadyl acetate, metopon, morphine, heroin, myrophine, nalbuphine, nicomorphine, norlevorphanol, normorphine, norpipanone, oxycodone, oxymorphone, pentazocine, phenadoxone, phenazocine, phenoperidine,

piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, and tilidine.

[0045] Some ionic drugs are polypeptides, proteins, hormones, or derivatives, analogs, mimics thereof. For example, insulin or mimics are ionic drugs that can be driven by electrical force in electrotransport.

[0046] For more effective delivery by electrotransport salts of such analgesic agents are preferably included in the drug reservoir. Suitable salts of cationic drugs, such as narcotic analgesic agents, include, without limitation, acetate, propionate, butyrate, pentanoate, hexanoate, heptanoate, levulinate, chloride, bromide, citrate, succinate, maleate, glycolate, gluconate, glucuronate, 3-hydroxyisobutyrate, tricarballylicate, malonate, adipate, citraconate, glutarate, itaconate, mesaconate, citramalate, dimethylolpropinate, tiglicate, glycerate, methacrylate, isocrotonate, β-hydroxibutyrate, crotonate, angelate, hydracrylate, ascorbate, aspartate, glutamate, 2-hydroxyisobutyrate, lactate, malate, pyruvate, fumarate, tartarate, nitrate, phosphate, benzene, sulfonate, methane sulfonate, sulfate and sulfonate. The more preferred salt is chloride.

[0047] A counterion is present in the drug reservoir in amounts necessary to neutralize the positive charge present on the cationic drug, e.g. narcotic analgesic agent, at the pH of the formulation. Excess of counterion (as the free acid or as a salt) can be added to the reservoir in order to control pH and to provide adequate buffering capacity. In one embodiment of the invention, the drug reservoir includes at least one buffer for controlling the pH in the drug reservoir. Suitable buffering systems are known in the art.

METHOD OF MAKING

[0048] A device according to the present invention can be made by forming the various parts of the device (e.g., the parts as shown in FIG. 1) and assembling the parts into an assembled device. The polymeric layers such as the housing parts can be made by molding. Some of the layers can be applied together and secured. Some of the parts can be affixed together by adhesive bonding or mechanical anchoring. Such chemical adhesive bonding methods and mechanical anchoring methods are known in the art. A device that delivers fentanyl with a more stable flux can be made as a single unit as shown in FIG. 1. Such a device is made by assembling the parts together to form a unit and then the assembled unit is packaged and stored until it is to be removed from the packaging for use. Alternatively, a device can be made by first making an electronic module and a reservoir module separately, wherein the two modules

can be stored separately (e.g., in protected packages). The electronic module contains the control electronics and the reservoir module contains the reservoirs. The electronic module can be coupled with the reservoir module just before use by a medical professional, e.g., by inserting one module into the other module or by pressing the modules together. For example, the electronic module can be reusable whereas the reservoir module is disposable. After the system has been used, the reusable electronic module can be separated from the reservoir module and reused again by coupling with a fresh reservoir module. The used reservoir module can be discarded according to proper standard procedure. Iontophoretic drug delivery systems each with a separate drug reservoir unit and controller unit have been described in the past in patent and scientific literature. Such prior separate systems can be adopted for the electronic modules and reservoir modules of the present invention. For example, such assemble-before-use systems (electrotransport devices having parts being connected together before use) include those described in US4731926 (Sibalis) and US5919155 (Lattin et al.).

[0049] General methods of making gels for reservoirs and incorporating drugs in the gels are known in the art. General methods for making electrodes, printed circuit boards, adhesives, housing, and other kind of iontophoretic device components are known. General methods for making electrotransport devices from their components are known in the art. Generally, components such as the reservoirs, the electrodes, the printed circuit boards, the housing parts, adhesive, displays are made and then the components are assembled by connecting the electrical connections and affixing the separate pieces together. For example, the reservoir gel can be laid into a depression in the lower housing to contact the electrode and the lower housing is fitted with the upper housing to enclose the printed circuit between the lower and upper housing. An adhesive, protected by a peelable release liner, is laid on the lower housing to provide adhesion when the device is to be used.

[0050] General methods of using electrotransport devices are known in the art. Generally, a user, such as a patient, more often a care giver (e.g., doctor, nurse, etc.) will open a package pouch, remove the device from the pouch, check the device for proper functioning, remove the peelable protective release liner and apply the device on the body surface of the patient for the device to adhere thereto. During the use period, the control button on the device is manipulated to control the delivery of doses of the drug and display of information.

Decreasing Amount of Charge Flow with Time

[0051] We have discovered that for a constant current delivery of fentanyl for a set length of time, the amount of fentanyl delivered changes depending on the time after the device has been put into use. The following pharmacokinetic evaluation demonstrated that the fentanyl flux is dependent on the time after the initial application. All fentanyl flux is determined in terms of flux of fentanyl base equivalent, which is well understood by those skilled in the art.

Pharmacokinetic Evaluation

[0052] Fentanyl HCl patient-controlled transdermal analgesia (PCTA) system that delivers each requested dose over 10 minutes after initiation of dose was used. The 40 microgram (μg) PCTA systems were 40 μg dose IONSYS systems. The IONSYS system is structurally similar to that shown in FIG. 1 in general. IONSYS systems were designed to deliver 40 μg per dose with a duration of 10 minutes per dose with a maximum of 6 doses per hour for a maximum of 80 doses with a constant current of about 170 μA of current over a hydrogel reservoir of contacting surface area of about 2.7 to 2.8 cm^2. Each 25μg system had a fentanyl HCl reservoir surface area of about 1.4 cm^2, with reduced current of about 100μA.

[0053] Three studies were done, all 3 studies were single-center, open-label, randomized, and crossover, and the PCTA system was applied to the upper outer arm. Study I (25-μg system, n=30) evaluated 3 treatments: with different dosing frequencies: (1A) 2 sequential doses hourly for 23.33 hours; (1B) 6 sequential doses every 3 hours over 23.33 hours, and (1C) 72 sequential doses continuously. Study II (40-μg system, n=31) evaluated 3 treatments with different dosing frequencies: (2A) 2 sequential doses hourly for 23.33 hours; (2B) 6 sequential doses every 3 hours over 10 hours; and (2C) continuous sequential 80 doses. In Study III (40-μg system, n=28), subjects received 4 treatments (3A, 3B, 3C, and 3D): involving 6, 18, 36, and 80 continuous sequential doses over 1, 3, 6, and 13.33 hours, respectively. In treatment 3A only, two systems were used on a single individual simultaneously on two different locations on the skin. Thus a total of 12 doses (counting the two systems together) targeting 40μg each were delivered in 1 hour to the individual. Naltrexone was used to block fentanyl opioid effects. The mean weight of the individuals were 74.5Kg, 72.6Kg, and 70.4Kg for Studies I, II, and III respectively. The nonparametric PK parameter area under concentration-time curve (AUC) was determined. Table 1 shows the treatment conditions.

Table 1. Fentanyl HCl Treatments Used Studies I, II, and III

STUDY	TREATMENT	DESCRIPTION
I	1A	2 sequential doses/hour for 23.33 hours (total doses = 48)
	1B	6 sequential doses every 3 hours for 22 hours (total doses = 48)
	1C	72 continuous doses over 12 hours
II	2A	2 sequential doses/hour for 23.33 hours (total doses = 48)
	2B	6 sequential doses every 3 hours for 10 hours (total doses = 24)
	2C	80 continuous doses over 13.33 hours
III	3A	2 systems each of 6 continuous doses over 1hour
	3B	18 continuous doses over 3 hours
	3C	36 continuous doses over 6 hours
	3D	80 continuous doses over 13.33 hours

[0054] Table 2 shows AUC_t (the AUC for the time period t) and how the AUC_n (which is the AUC normalized per dose) values were estimated from AUC_t.

Table 2

TREATMENT	AUC_t	AUC_n (FOR SINGLE DOSE)
1A	AUC_{23-24}	$AUC_{23-24}/2$
1B	AUC_{21-24}	$AUC_{21-24}/6$
1C	AUC_{inf}	$AUC_{inf}/72$
2A	AUC_{23-24}	$AUC_{23-24}/2$
2B	AUC_{inf}	$AUC_{inf}/24$
2C	AUC_{inf}	$AUC_{inf}/80$
3A	AUC_{inf}	$AUC_{inf}/12$
3B	AUC_{inf}	$AUC_{inf}/18$
3C	AUC_{inf}	$AUC_{inf}/36$
3D	AUC_{inf}	$AUC_{inf}/80$

[0055] In Table 2, AUC_t is defined in the AUC_t column. AUC_{inf} is the AUC for the whole treatment. AUC_{23-24} is the AUC after the 23rd hour and throughout the 24th hour. AUC_{21-24} is the AUC after the 21st hour up to and including the 24th hour. The AUC_n gives the estimate of

how plasma fentanyl AUC might increase per dose of delivery for the dose that was delivered at the time corresponding to the period in AUC_t. The AUC_{21-24} and AUC_{23-24} reflect the delivery rate at the end of the 24-hour period, whereas AUC_{inf} reflects the delivery rate averaged over the entire delivery period the system was worn. .

[0056] Table 3 shows the pharmacokinetic data of Study I. C_{max} is the maximum serum fentanyl concentration as fentanyl base equivalent. T_{max} is the time at which C_{max} occurred. $T_{1/2}$ is the half life in hours. Ka is the elimination rate constant. The numbers are the mean values with the standard deviation in the parentheses.

Table 3 Pharmacokinetic Data of Study I

PARAMETER	TREATMENT		
	Fentanyl HCl PCTA 25 µg (1A) n = 25	Fentanyl HCl PCTA 25 µg (1B) n = 25	Fentanyl HCl PCTA 25 µg (1C) n = 25
C_{max}, (µg/L)	0.86 (0.30)	0.97 (0.23)	1.32 (0.31)
T_{max}, (h)	23.11 (1.69)	22.04 (0.19)	10.56 (1.44)
$t_{1/2}$, (h)	—	—	15.3 (12.0)
Ka (h^{-1})	—	—	0.067 (0.34)
AUC_t (µg·h/L)	0.75 (0.24)	2.19 (0.54)	22.58 (7.88)
AUC_n (µg·h/L)	0.374	0.365	0.314

[0057] In Table 3, it can be seen that the AUC_n for treatment 1A and 1B, 2 doses per hour every hour for 23.33 hours and 6 doses every 3 hours for 22 hours, respectively, indicates that the dose amount toward 24 hours, 0.374 and 0.365 µg/h/L, was approximately equal, despite the differences in dose frequency. Conversely, the dose for the continuous 80 doses, averaged over the 12 hours of system application in treatment 1C was only 0.314 µg/h/L. This indicates that the dose was lower, on average, in the first 12 hours of treatment compared to the dose toward the end (approximately 24 hours) of treatment. Thus, doses were higher at 24 hours compared to over the first 12 hours in spite of the larger number of doses and the higher frequency of dosing in the continuous treatment 1C compared to 1A or 1B.

[0058] Table 4 shows the pharmacokinetic data of Study II.

Table 4 Pharmacokinetic Data of Study II

PARAMETER	TREATMENT		
	Fentanyl HCl PCTA 40 µg (2A) n = 23	Fentanyl HCl PCTA 40 µg (2B) n = 23	Fentanyl HCl PCTA 40 µg (2C) n = 23
C_{max} (µg/L)	1.30 (0.30)	0.91 (0.39)	1.94 (0.43)
T_{max} (h)	22.74 (1.46)	10.07 (0.69)	12.11 (1.24)
$t_{1/2}$ (h)	16.1 (5.5)	15.1 (7.4)	22.00 (10.0)
ka (h^{-1})	0.048 (0.015)	0.061 (0.038)	0.037 (0.014)
AUC_t (µg·h/L)	1.14 (0.26)	10.3 (3.8)	40.8 (12.7)
AUC_n (µg·h/L)	0.57	0.43	0.51

[0059] In Table 4, it can be seen that the AUC_n for treatment 2A, 2 doses per hour every hour for 24 hours at the 23rd hour is 0.57, higher than the AUC_n for treatment 2B with 6 doses every 3 hours for 10 hours or for treatment 2C for 6 doses every hour for 13.33 hours, 0.43 and 0.51 µg-hr/L, respectively. This indicates that again the dose amount at approximately 24 hours is higher than doses over the initial period of the wear time, 10 or 13.33 hours for studies 2A and 2C respectively.

[0060] Table 5 shows the pharmacokinetic data of Study III.

Table 5 Pharmacokinetic Data of Study III

PARAMETER	TREATMENT			
	Fentanyl HCl PCTA 40 µg (3A) n = 20	Fentanyl HCl PCTA 40 µg (3B) n = 20	Fentanyl HCl PCTA 40 µg (3C) n = 20	Fentanyl HCl PCTA 40 µg (3D) n = 20
C_{max} (µg/L)	0.27 (0.18)	0.72 (0.20)	1.08 (0.48)	2.00 (1.24)
T_{max} (h)	1.86 (1.79)	3.45 (0.33)	6.12 (0.68)	13.00 (1.93)
$t_{1/2}$ (h)	19.2 (6.0)	10.5 (2.5)	10.4 (4.6)	20.5 (7.2)
ka (h^{-1})	0.040 (0.013)	0.070 (0.016)	0.076 (0.025)	0.038 (0.015)
AUC_{inf} (µg·h/L)	2.79 (1.43)	5.75 (2.13)	12.87 (5.32)	36.44 (18.34)
AUC_n (µg·h/L)	0.23	0.32	0.36	0.50

[0061] From Table 5, it can be clearly seen that the mean dose amount increases as the duration of the study increases (as shown by the increase in value of AUC_n). The data in Table 5 can be analyzed to determine the mean dosing at different dose intervals. Subtracting the AUC_{inf} for treatment 3A (0 to 1 hour) divided by 2 (to account for 2 systems applied in that study) from treatment 3B (0 to 3 hours) gives the AUC_{inf} for the 1 to 3 hour interval. Dividing that by the number of doses (12 in this case), gives the AUC_n over the 1 to 3 hour interval. Similarly, the AUC_n over the 3 to 6 and 6 to 13.33 hour intervals can be determined. The ratio of the dose for each interval compared to an estimate of the dose at 24 hours (estimated from data from a separate cohort of subjects at 23 to 23.33 hours) is given in the following table (Table 5A).

Table 5A

Time interval (hours)	Flux Ratio (Flux in interval compared to flux at 23 to 23.33 hours)
0 to 1	0.41
1 to 3	0.64
3 to 6	0.69
6 to 13.33	0.97

[0062] The results of the Studies I, II, and III indicated the fentanyl amount absorbed from the PCTA system increases as a function of time and is independent of dosing frequency and total number of doses delivered.

[0063] The AUC_n values from Study III were used to derive a mathematical model as a function of time. Data from the 4 points at t = 0.5, 2, 4.5, and 9.66 hours (the midpoint of each measuring interval, i.e., 0 to 1 hour, 1 to 3 hour, 3 to 6 hour, and 6 to 13.33 hour) of Study III were used to construct a graph of delivery vs. time. Values were fitted to a curve and the best-fit curve was found to be nonlinear and nonexponential. Modeling the data with a second order polynomial fit lead to the following Equation (1). The per-dose flux, y(t), of fentanyl delivered expressed as a decimal fraction of the targeted dose size or nominal dose size (e.g., 40 μg in a 40 μg per dose device) is the following Equation (1), wherein t is the time in hours the system is in use, for example, being turned on or after the initial activation of the system.

$y(t) = 0.4027 + 0.0873t - 0.0031t^2$ (1)

for $t < 12$ hours; and

$y(t) = 1$ for $t \geq 12$ hours.

[0064] Thus, the experimental data show that actual fentanyl flux tends to increase with time for the same current flow in the same system; y(t) is an indication of how effective the current is producing flux of the drug.

[0065] At a constant current, the flux F(t) as related to the nominal dose flux Fo (e.g., 40 μg per 10 min in a 40 μg per 10-min dose device) is:

$F(t) = Fo \cdot y(t)$ (2)

Decreasing Current as with Time for More Consistent Flux

[0066] Since the experimental data of Studies I, II, and III show that the actual fentanyl flux tends to decrease with time for the same current flow (between the donor and counter electrodes), to provide an actual flux that is more consistent or stable over time, it is preferred that the current used for driving drug flux is adjusted with time to have a generally downward trend. In other words, it is preferred that as a whole, the current at the later part of the use of the device be smaller (delivering less charge per unit time) than the current at the start. Based on Equation (1), it was found that the average current for the first hour of use is preferably between 1.7 and 2.7 times, more preferably 1.8 to 2.3 times, the average of the current to be applied at the final hour of designed use (e.g., hour 24 (i.e., after the 23rd hour before the end of the 24th hour) for a device designed for 24 hour use) if the device is projected to deliver current for a particular period (e.g., for 24 hours). The current would trend down (i.e., be adjusted downward) in general in a particular manner, even if the device (e.g., a 24 hour device) is taken off the skin before the end of the 24 hour period, e.g., because patient needed an MRI (magnetic resonance Image) and the presence of an iontophoretic system in MRI is not desirable. If I_f is assumed to be the average current for a steady state delivery of the targeted dose (in most cases, e.g., for applications more than 12 hours, the final hour of use can be assumed to be the steady state), the current at time t that is needed to result in a stable flux (i.e., a per-dose flux in decimal fraction equal 1) is I(t):

$I(t) = I_f / y(t)$ (3)

[0067] Thus, Equation (3) is a profile for the drug delivery current to follow to achieve a more stable flux over time. In Equation (3), y(t) is $y(t) = 0.4027 + 0.0873t - 0.0031t^2$ as stated above in Equation (1). In Equation (3) I(t) is related to the average amount of charge passing

through the donor reservoir during a dosing period at time t and I_f is related to the average amount of charge passing through the donor reservoir during a dosing period at the final period of use. Because the sizes of the reservoirs in the device are constant, Equation (3) can also apply to the current density such that I(t) and I_f are current densities.

[0068] As an example, if a device is designed for 24 hour use with a constant dose period (e.g., 10 min) throughout the use of the device, and the target dose is 40 μg/dose, the average current at the 24^{th} hour is taken to be I_f. The fentanyl flux in decimal fraction of the target dose of 40 μg is y(t) according to Equation (1) at any time t. Thus, y(t) is a representation of the effectiveness of the current delivery in resulting in fentanyl flux as compared to the steady state (approximate by the final period of delivery) in the use of the device. Experimental data have shown that after about 10 hours of use, the effectiveness does not change substantially and can be assumed to be close to about 100%. At about 24 hours, the effectiveness can be assumed to be 100%.

[0069] To test for the current delivery profile with time, the device can be activated at maximum use for a period to test for the current and the amount of charge delivered. The term "at maximum use" means that the device is activated to deliver as many doses as the device is designed to deliver during a specific period. For example, if a device is designed to deliver 6 doses per hour, then at maximum use, no matter how often the device is activated during the period of one hour, the device delivers a maximum of 6 doses per hour. As long as the device can be operated at maximum use for time periods (e.g., for 1 hour, 2 hours, 3 hours, etc.) for the average flux per hour to be determined at various time periods during use, it is not necessary that the device be in fact in operation at maximum use for the whole period of time the device is in use.

[0070] To show whether a device behaves similar to Equation (1) and Equation (3), an average current passing through the donor reservoir over a period of time (e.g., one hour, 2 hour, 3 hour, etc.) can be estimated by obtaining the current-time graph under maximum use and dividing the area under the curve of the current time graph by time over the period. Similarly, the average amount of charge passing through per dosing period over a multi-dose period (e.g., one hour, 2 hour, 3 hour, etc.) can be estimated by obtaining a current-time graph for each dose, summing up the total area under the curves for the doses and dividing by the number of doses during the period. Preferably, the estimations are done for a device under maximum use to obtain information about the characteristics of the device.

[0071] It is noted after a device has been used over the length of time it is designed to operate, the device is removed. If analgesia is still needed and a fresh device is to be applied to the skin, the fresh device is applied to a new location. Since the skin at the new location is not accustomed to fentanyl delivery by the fresh device, the current profile needs to be implemented all over again on the fresh device at the new location on the skin.

[0072] According to an embodiment of the present invention, in the downward trend of current delivery, a useful device wherein the fentanyl flux through human skin is relatively stable, the average amount of charge per dose of fentanyl flux differs from the average amount of charge per dose in an immediately subsequent hourly period by not more than 40%, preferably not more than 30%, more preferably by not more than 25% of that of the earlier hourly period. In an embodiment designed for at least 12 hours of use, preferably designed for 1 day of use, or for more than one day of use, in which the duration (per dose) of the dosing current flow remains unchanged over time but the current is changed, the average charge flow per dose period averaged over an earlier hourly period preferably differs from the average charge flow per dose period of an immediately subsequent hourly period by not more than 40%, more preferably not more than 30% of that of the earlier hourly period. It is also preferred that the average current (or the average charge flow per dose period) at the last hour (e.g., the 24th hour for a 24 hour device) of designed use differs from the average current (or the average charge flow per dose period) of the initial hour of use by not more than 60%, preferably not more than 55%, more preferably not more than 50% of the average current of the initial hour of use. It is also preferred that the average current (or the average charge flow per dose period) at the last hour of designed use differs from the average current (or the average charge flow per dose period) of the initial hour of use by not less than 25%, preferably not less than 40% of the average current of the initial hour of use. It is also preferred that the average current (or the average charge flow per dose period) from the fourth hour through the sixth hour (i.e., after the third hour, through the sixth hour averaged over 3 total hours) of use differs from the average current (or the average charge flow per dose period) of the initial hour by not more than 50%, preferably not more than 40% of the average current of the initial hour (i.e., the first hour). It is also preferred that the average current (or the average charge flow per dose period) from the seventh hour through the ninth hour of use differs from the average current (or the average charge flow per dose period) from the tenth hour through the twelfth hour of use by not more than 30%, preferably not more than 20% of the average current of the

seventh hour through the ninth hour of use. It is also preferred that the average current (or the average charge flow per dose period) from the seventh hour through the ninth hour of use differs from the average current (or the average charge flow per dose period) of the last hour of use by not more than 30%, preferably not more than 20% of the average current of the seventh hour through the ninth hour of use. It is also preferred that the average current (or the average charge flow per dose period) from the tenth hour through the twelfth hour of use differs from the average current (or the average charge flow per dose period) of the last hour of use by not more than 25%, preferably not more than 15% of the average current of the tenth hour through the twelfth hour of use. It is noted that it is not necessary to have the electrotransport current continuously decreasing with time. If desired, the current for a period of time can remain unchanged, or even go up in amplitude so long as the average current trends down as described in the above. Also, it is to be understood that when it is mentioned that the current having a particular profile with time with a dose period that remains constant, the invention can be practiced by providing the corresponding coulombs of charge per dose of drug via changing the duration of dose period and/or the current amplitude.

[0073] It is possible that during the period of use of the device on the skin, in any given period of time the user would refrain from activating the device or choose to activate only sparingly (e.g., during the first hour of use) and thus rendering the average current use per hour in reality to be zero or near zero during this period. However, the device is made in such a way that if it is activated for maximum use during a period (e.g., one hour or more) it can deliver current (or amount of charge passing through per dose period) that trends down as described above to provide stable fentanyl flux. The operational characteristics of a device can be determined by determining the current flow or charge delivery profile over a period of time by assuming maximum use over that period of time. It is not necessary that the device in fact be activated for maximum use or if activated for maximum use that it does so all the time during which the device is in use.

[0074] Although the charge delivery (e.g., current or duration or both) of the transdermal electrotransport device can be controlled manually, it is preferable that the control is electronic by a controller to provide the time-varied rate of charge delivery (such as by current change). First, in certain embodiments, the charge delivery (e.g., current) is controlled to deliver in discrete periods of constant current for fentanyl delivery for at least a portion of the whole period or episode of use. Thus, for a period of time, the current is held constant until after the

end of that period the current is changed to a different amplitude for another set period of time, etc. For Example, the current is held at a constant current of A μA for one hour and then immediately is switched to B μA for a period of two hours, before being switched to a constant current of C μA for another period of 3 hours thereafter. Alternatively, the current can be controlled, typically electronically, e.g., by means of hard wired circuitry, application-specific integrated circuit (ASIC), programmable circuitry (such as microprocessor(s)), microcomputer, etc., to continuously change the current with time. Such implementation of circuitry for control of current delivery is known to those skilled in the art of electrical control of medical devices. As used herein, if the device has discrete steps of current amplitude change and the number of stepping periods of different current amplitude exceeds 50 for the designed length of delivery, it is considered to be changing the current substantially continuously. If the number of stepping periods exceeds 100, the current can be considered to change continuously. Techniques and electronics on programming current control in medical devices are known to those skilled in the art. Thus, such skilled persons will be able to design and implement current control, either in discrete steps or with continuous change for electrotransport based on the present disclosure. For example, the "stepped-down" current control required to achieve a more stable fentanyl delivery (to approach a zero-order profile, zero-order meaning that the amount of fentanyl delivered per dose remains constant with time) can be accomplished with a programmable 8-bit microprocessor, the simplest computer architecture found in commercial applications. Examples of 8-bit microprocessors include the INTEL™ 8051 family, and the MOTOROLA™ 6800 family, which are familiar to those skilled in the art of programming control of drug delivery devices. Further, although the above examples are selected as programmable microcontrollers to provide both the required product functions and flexibility for implementing a multigenerational iontophoretic fentanyl delivery product line, there are other means that could provide the current control required for zero-order fentanyl delivery. Some examples of such other means include an uncommitted logic array (ULA), a field programmable gate array (FPGA), or even an analog circuit.

[0075] With the current controlled to deliver more current during the first part of the fentanyl delivery than in the later part to overcome the inefficiency of fentanyl delivery initially (i.e., regarding flux per current use), the current density as a consequence also decreases with time. However, even with increased current initially, it is preferred that the device is controlled to deliver the current at an average current density of less than about 400

$\mu A/cm^2$ averaged over an hour, during the whole period of use for a 40 μg per 10 minute device. For a device that delivers a different dose strength dose, e.g., 25 μg per 10 minutes, 50 μg per 10 minutes, or 60 μg per 10 minutes, etc., the current density can be proportionally scaled to increase the charge delivery. More preferably, the averaged current density for any one hour is controlled to be less than about 200 $\mu A/cm^2$, preferably less than about 150 $\mu A/cm^2$ averaged over an hour at all time of use.

[0076] FIG. 3 is a graph showing data that illustrates fentanyl flux in human trial Study III, described above as a function of time and shows predicted fentanyl flux if the current is controlled according to an embodiment of the present invention. The ordinate of the graph shows the fentanyl flux as a percentage of target flux (e.g., a target flux of a 40 μg device is 40 μg/(10 min) of fentanyl). In FIG. 3, the squares are data points derived from Study III above. The smooth curve with x's is the modeled line correspond to Equation (1). The open circles are the predicted flux at the time indicated in the graph with current that trended downward in amplitude stepwise, the steps occurring at the end of the 1st hour, 3rd hour, 6^{th}, and 9^{th} hour. The flux is predicted by Equation (1), multiplying the flux by the ratio of the current at the time interval to the current at 24 hours. The solid disks represent the average predicted flux that would be observed at the mid point of each period of stepwise current change. This predicted flux was calculated by using a trapezoidal approximation to determine the areas underneath the graph and dividing by time.

[0077] The following modeling method was used. A prediction based on the available clinical data from delivery rates for a 5-step current profile was made. This prediction was made in the following way:

- Data from the 4 points at t = 0.5, 2, 4.5, and 9.66 hours (the midpoint of each measuring interval) was used to construct a graph of delivery vs. time. Values were fitted to a second order polynomial fit of the data. The equation (Equation (1) curve-fitting to the data of Study III) was: $y = 0.4027 + 0.0873t - 0.0031t^2$, where t is time in hours and y is a unitless ratio, i.e., the fraction of the 40 μg dose delivered during the 10 minutes dose period. Time points after 12 hours were assumed to be at 100% delivery rate (40 μg).
- Delivery was assumed to be directly proportional to current; i.e., a linear relationship with an intercept of zero was assumed for the relationship between dose delivered and current. Current step intervals of 0 to 1 (i.e., 1 hour through

Hour 1 before Hour 2), 1 to 3 (i.e., 2 hours starting after Hour 1 through Hour 3), 3 to 6, and 6 to 9, and 9 to 24 were used. These were selected from the observation that change occurred more rapidly immediately after system activation than later in the application period. The intervals are therefore 1, 2, 3, 3, and 15 hours long.

- The current level was determined by locating the percent delivered in the original IONSYS at the mid point of each interval (i.e., 1, 3, 6, and 9 hours) and dividing that into 170 μA, which is the current applied by the IONSYS system. The current to be applied is estimated by the equation $I = I_f / y$, wherein I_f is current where the value of the ratio y is estimated to be 1, which we have found to be generally about the average current for a targeted final hour of use (for a 24 hour system, it is the final hour of the day, i.e., time from Hour 23 to Hour 24, i.e., end of Hour 23 through Hour 24). The time variable, t, is time in hour after initial application on the skin. For example, from the graph, at 1 hour, delivery was 44% of the 40 μg dose. To increase the flux at the first hour to a level about equal to the desired flux (which is about equal to flux at the final hour), the current chosen for the 0 to 1 hour interval was about 170 μA / 0.44 = 382 μA.

[0078] Thus, the model predicts the current use to result in a fentanyl flux that is more stable. The following Table 6 shows the current levels and stepped changes used in the simulation.

Table 6

Time (hrs)	Deliver % midpoint from fit	current (μA)	current density (μA/cm^2)
0 to 1	44%	383	136
1 to 3	56%	301	108
3 to 6	73%	232	83
6 to 9	88%	193	69
9 to 24	100%	170	61

EXPERIMENT

Experiment 1 (Human Trial PK1)

[0079] The system used in this study includes a clinical controller (which includes microcontroller that was programmed to direct the delivery of a stepped-down current profile as well as a boost converter with feedback to operate as a current source that can be controlled by the microcontroller). The drug unit controlled by the controller included a fentanyl reservoir and a counter ion reservoir similar to the IONSYS system. The fentanyl reservoir hydrogel had an area of about 2.8 cm^2. The controller in this system was controlled by a programmable microprocessor and delivered the stepped-down current profile, ranging from a 380-μA maximum to a 170-μA minimum. The currents and intervals are shown in the table below. This profile was designed to target near-zero-order absorption of a 40-μg fentanyl dose over a 24-hour period. The controller (Model 1508-BD, a custom programmable current controller and includes a Microchip 16F84 8-bit microprocessor, and a Linear Tehcnologies LT1109 boost converter) had a pre-programmed current profile that set the current during the clinical study. The drug unit was a minor modification of an existing design of an electrotransport (fentanyl HCl) 40 μg System (IONSYS System). The fentanyl reservoir hydrogel at the anode had an area of about 2.8 cm^2. The composition of the anode and cathode (counterion) hydrogels was identical to that of IONSYS. The housing for the drug unit had conductive snaps to make electrical contact with the controller. Effectively, the reservoirs, except being connected to a controller that controlled the current to be stepped down with time, had the same structure and ingredient, and electrical connection as the IONSYS system.

[0080] This study included 40 healthy adult subjects, 34 of which completed an intravenous (IV) treatment of fentanyl and all 4 electrotransport treatments of fentanyl: a 1-hour treatment, a 3-hour treatment, a 6-hour treatment, and either a 9-hour treatment or a 12-hour treatment. During each treatment the serum fentanyl was measured periodically so the amount of fentanyl absorbed by each subject could be calculated. The serum fentanyl measured during electrotransport measurements was normalized using the serum fentanyl measured during the intravenous treatment. The desired delivery of fentanyl is 240 μg/hour, which is equivalent to six 10-minute 40 μg doses, with 60 minutes per hour. During the treatments, the controller recorded battery voltage, output voltage, and load current once per minute.

[0081] The modeled % efficiency at mid period is the estimated % effectiveness by the system to achieve the desired flux for the current delivered at the mid period of a period according to the model of Equation (1). In order to achieve a stable fentanyl flux with time with the estimated % effectiveness, the current applied was increased at the first part of the delivery according to Equation (3) as compared to the later part of the delivery. With the applied current and the resulting current density as shown in the table, the resulting measured average fentanyl flux (in μg/hr) data for each of the periods of the stepped current are listed in Table 7. The result indicated the fentanyl flux was more stable with time than the result of fentanyl delivery without stepped down current as observed in Study III (see the flux ratio in Table 5A for comparison).

Table 7 Data of Human Trial PK1

Time elapsed, hr	Modeled % efficiency at mid period	Current applied, μA	Current density μA/cm^2	Measured averaged flux, μg/hr	Flux as ratio to 40 μg per 10 min
0-1	44	380	136	299	1.25
1-3	56	300	108	250	1.05
3-6	73	230	83	175	0.73
6-9	88	190	69	230	0.96
9-12	100	170	61	198	0.82

[0082] It is noted that with the application of current according to Table 7, the fentanyl flux during the first periods, i.e., for the 0-1 and 1-3 hour periods, the flux was slightly higher than

the later periods. Thus, it is estimated that to provide an even more stable fentanyl flux with time, the initial current to be used would be slightly less initially and slightly more during the 3-6 hour period part of the use of the device compared to the delivery directed by Equation (1) and Equation (3). Therefore, preferably, the difference between the initial and later part of the use of a device in the rate of charge delivery(e.g., current), as well as in flux is less pronounced that those shown in Table 7. For example, the following Table 8, in which the current applied was precalculated to bring the ratio of normalized flux (relative to dose of 40 μg per 10 min) as various dose periods close to a value of 1, would result in a more stable flux, preferably for a reservoir of about 2 cm^2 to 3 cm^2, even more preferably about 2.7 to 2.8 cm^2.

Experiment 2 (Human Trial PK2)

[0083] Similar process as used in Experiment 1 was used in a study in studying the variation of the current applied. In this study, Treatment B involved using 2 systems each of which delivered about 160 μg per 40 minutes beginning at Hour 0 (thus a total of 320 μg per 40 minutes Hour 0. Treatment C involved using 2 systems each of which delivered about 160 μg per 40 minutes beginning at Hour 0 and 80 μg per 20 minutes beginning at Hour 2 (thus a total of 320 μg per 40 minutes at Hour 0 and 160 μg per 20 minutes at hour 2). Treatment D involved using 2 systems each of which delivered about 160 μg per 40 minutes beginning at Hour 0 and 80 μg per 20 minutes beginning at Hour 2 and at Hour 4. Treatment E involved using only 1 system to deliver about 80 μg per 20 minutes every hour for 23 hours and 20 minutes beginning at Hour 0. In Treatments B to D, the drug delivery during the delivery of the dose was 40 μg per 10 minutes, same as that in Study III above. The following Table 8 shows the drug flux results of the treatments. Data were not collected from after Hour 6 to Hour 23. One of the 28 subjects in the study provided data that were very different from the others (outlier) probably because of experimental error. In Table 8, the data marked with ** were based on calculation in which the data from that outlier subject was not included in the calculation.

Table 8 Human Trial PK2

Time elapsed, hr	Number of subjects, N	Current applied, μA	Drug flux in 20 min mean & (Std Div)	Flux as ratio to 40 μg per 10 min	Drug flux in 20 min mean & (Std Div)**	Flux as ratio to 40 μg per 10 min**
0-1	N=28	380	83.8(26)	1.05	80.6(20)	1.01
1-3	N=28	300	97.8(46)	1.22	101.3(44)	1.27
3-6	N=28	300	112.6(71)	1.40	116.5(69)	1.46
6-9		270				
9-23		170				
23-24	N=27	170	74.7(13)	0.93	74.7(13)	0.93

** where one outlier-data subject was removed from the calculation

[0084] Table 8 shows that from Hour 0 to Hour 6 the current applied was a little high to result in drug flux higher than what would be needed to provide flux of 40 μg per 10 minutes, whereas the current applied from Hour 23 to Hour 24 was a little too low.

[0085] Calculating the normalized flux per normalized current for the experimental data from the Study III, PK1 and PK2 human trials, it was found that the normalized flux per normalized current data fell together about a pattern to a large extent. As stated, the normalized flux per normalized current is a unitless number obtained by dividing the flux (μg) per 10 minutes by the expected flux per normalized current, i.e., (40μg per 10 minutes/current used/170μA). FIG. 4 shows the normalized flux per normalized current data for all three human trials. The square data points represent PK1 data points. The triangle data points represent PK2 data points. The diamond data points represent Study III data points. The Study III trial was assumed to have flux of 37 μg for the 10-minute dose period at 23 to 23.33 hour, based on data from the PK2 trial indicating that the dose at 23 to 23.33 hours is closer to 37 μg than 40 μg.

[0086] The data points of FIG. 4 are modeled with mathematical curve fitting to obtain a polynomial equation: $y = -0.0016t^2 + 0.0587t + 0.4454$, as shown by the curve line in FIG. 4, in which t is the time in hours after the system is in use up to 24 hours. To bring the ratio of drug flux to 40 μg per 10 minutes, based on the data of all three human trials, y can be used as a factor to raise the current for each dose period. Since we found that the major part of the

current change should appear in that first part of the use, it is preferred that during at least the first 12 hour period of use, the current profile follows substantially the polynomial equation. "Substantially" here means if the charge delivery rate per dose were averaged out hourly, during at least 90% of the hours the charge delivery rate per dose is within a difference of a ratio p from the hourly averaged values calculated according to the polynomial equation shown in FIG. 4. During the last few hours of use, for example, a 24 hour delivery period, the charge delivery rate per dose can follow the polynomial equation and/or remain relatively constant. Preferably p is 25% or less, more preferably 20% or less, even more preferably 15% or less, even more preferably 10% or less. Based on the data and curve of FIG. 4, by calculating the current that is needed to raise the value of the normalized flux (y ratio) at various times to a value of 1, an exemplary current profile as shown in Table 9 below should be able to produce a more level flux close to about 40 μg per 10 minutes dose for about 24 hours. The transdermal patch preferably has a drug reservoir of about 2 cm^2 to 3 cm^2, even more preferably about 2.7 to 2.8 cm^2.

[0087] It is preferred that the current applied at a dose period be not different from the value predicted from the y ratios from the above equations by 20% or more, more preferably by 10% or more. In Table 9, the difference between the average current for the first hour and the last hour is about 53%, which is no greater than 60%. However, the difference between the average current (i.e., charge delivery rate) for the first hour and the average current for the last hour is above 25%, and in fact, above 40%.

Table 9

Time elapsed, hr	Current applied, μA
0-1	360
1-3	305
3-6	250
6-9	215
9-15	185
15-24	170

[0088] Based on the above experimental results, it is contemplated that ranges of current can be used according the following Table 10 to provide a stable fentanyl flux in iontophoretic delivery with fentanyl flux within 80% to 125% of 40 μg per 10 minutes, preferably for a

reservoir of about 2 cm^2 to 3 cm^2, even more preferably about 2.7 to 2.8 cm^2. It is noted that for systems designed for different dose strengths (e.g., 25 μg per 10 minutes, 50 μg per 10 minutes, 60 μg per 10 minutes, 80 μg per 10 minutes, etc.), the current can be scaled accordingly to increase or decrease the flux. In Table 10, the difference between the average current for the first hour and the last hour is generally no greater than 60%, preferably no greater than 55%, preferably no greater than 50%, more preferably no greater than 40% of the average first hour value. Even with a current profile that have more than 6 steps, the average current for a period can be found by integrating the area under the curve of the current-time graph and dividing by the time in the period.

Table 10

Time elapsed, hr	Current range applied, μA	Preferred Current range applied, μA
0-1	300 to 390	330 to 380
1-3	250-350	270-340
3-6	200- 300	220-290
6-9	185-245	200-230
9-15	170-220	170-210
15-24	150-190	160-180

[0089] Further, to control the current with more steps, more time periods can be used each to have current picked for that time period based on the value of the normalized flux (ratio y). For example, Table 11 show semi-hourly and hourly time periods (up to Hour 16) and the desired average current for each of the time periods to achieve a more level resulting flux.

Table 11

Time (hour)	Ratio y	Desired current (μA)
0	0.45	382
0.5	0.47	358
1	0.50	338
1.5	0.53	321
2	0.56	306
2.5	0.58	292

3	0.61	280
3.5	0.63	269
4	0.65	260
4.5	0.68	251
5	0.70	243
5.5	0.72	236
6	0.74	230
6.5	0.76	224
7	0.78	219
7.5	0.80	214
8	0.81	209
8.5	0.83	205
9	0.84	201
9.5	0.86	198
10	0.87	195
10.5	0.89	192
11	0.90	189
12	0.92	185
13	0.94	181
14	0.95	178
15	0.97	176
16	0.98	174

[0090] Other than controlling the current so that the current generally trends down with time to result in a more stable fentanyl flux with time, it is understood that the device can be controlled so that the current (i.e., amount of charge per time) passing through the donor reservoir per dose generally trends down with time to produce the same result. For example, instead of decreasing the current with time according to Equation (1) and Equation (3), the average number of coulombs of electricity that traverses through the donor reservoir per dose or per unit time can trend down with time. In this case in Equation (1), I is the averaged charge flow per dose, and I_f is the charge flow per dose at the final stage of the use of the designed use of the device. For example, to deliver a dose (e.g., 40 μg) initially the current can be turned on

for a longer duration per dose, and as time progresses, the dose time is shortened according to Equation (1) and Equation (3).

[0091] Further, the fentanyl dose can be delivered with the trending down of charge transferred by a combination of current decrease and dose duration decrease with time. Thus, the trending down of the number of coulombs of electricity that traverses through the donor reservoir per dose or unit time according to Equation (1) and Equation (3) can be effected by a combination of current decrease and dose duration decrease with time. Such systems in which the duration of current flow per dose changes with time is practicable if the system is designed to deliver a dose with a maximum dose periods of equal or less than the dose period at the initial level of delivery. In this way, the dose period will only decrease to result in decreasing charge delivery per unit time, never exceeding the maximum number or duration permissible in the device. At maximum use, even if the device is activated as much as possible, in such devices with shortened dose periods in the later periods of use, the doses will not be delivered immediately one after the other.

[0092] Although a useful embodiment of the present invention is one in which a DC (direct current) of a constant amplitude is applied for a period of time that is minutes long (e.g., 30 min, 60 min, 180 min, etc.) for each of the stepped down current levels, devices in which the current is applied as pulsed current of constant amplitude for each of the periods with stepped down amplitude can also be used. Typically the pulses have duty cycles in terms of milliseconds, e.g., shorter than 1 second per cycle. For example, the pulses can be 500 msec on and 500 msec off. The pulse amplitude for all the cycles in the "on" phase is the same during a period of a particular step in the stepped down delivery. When the device is at a particular step in the stepped down delivery, the current is at a constant level in the "on" phase of a duty cycle remains the same during that particular step, and so on. The amplitude, the length of the duty cycle, and the length of the "on" phase can be controlled to provide the charge delivery or current profile desired.

[0093] All patent publications cited above are incorporated by reference in their entireties herein. The above-described exemplary embodiments are intended to be illustrative in all respects, rather than restrictive, of the present invention. Thus the present invention is capable of many variations in detailed implementation that can be derived from the description contained herein by a person skilled in the art, e.g., by permutation or combination of various features. Although specific iontophoretic devices are described in detail as illustration, other

modifications are possible by one skilled in the art. All such variations and modifications are considered to be within the scope of the present invention.

What is Claimed is:

1. A transdermal electrotransport system for administering fentanyl through the skin of a human user for a predetermined period of time to effect analgesia, comprising:

(a) donor reservoir comprising fentanyl salt;

(b) at least two electrodes for conducting a current to drive fentanyl ions from the donor reservoir transdermally to deliver a dose of fentanyl in a dose period;

(c) a controller for controlling current delivery that drives the fentanyl ions such that the amount of charge per dose period of the current passing through the donor reservoir trends down with time nonlinearly and nonexponentially, wherein the average amount of charge per dose period during a first hour differs from the average amount of charge per dose period during a final hour the device is designed to be used by not more than 60% of the average amount of charge of the first hour.

2. The system of claim 1 wherein an average amount of charge per dose period averaged over an earlier hourly period differs from an average amount of charge per dose period of an immediately subsequent hourly period by not more than 40% of the average amount of charge per dose period of the earlier hourly periods.

3. The system of claim 2 wherein the controller controls the device to deliver from 25μg to 60μg of fentanyl per dose and the donor reservoir contains fentanyl HCl.

4. The system of claim 3 wherein an average current delivery at the last hour of use differs from an average current delivery of the first hour by not less than 25% of the average current delivery of the first hour.

5. The system of claim 4 wherein an average current delivery from the fourth hour through the sixth hour of use differs from the average current delivery of the first hour by not more than 40% of the average current delivery of the first hour.

6. The system of claim 4 wherein an average current delivery from the seventh hour through the ninth hour of use differs from the average current delivery of the last hour of use

by not more than 20% of the average current delivery from the seventh hour through the ninth hour.

7. The system of claim 3 wherein the controller controls the device to deliver from 35μg to 50μg of fentanyl per dose.

8. The system of claim 3 wherein the donor reservoir has a surface area for contacting skin of 0.8 cm^2 to 10cm^2.

9. The system of claim 3 wherein the donor reservoir comprises fentanyl halide.

10. The system of claim 3 wherein the donor reservoir comprises fentanyl hydrochloride.

11. The system of claim 3, wherein the controller controls the current delivery such that the current delivery is not constant during the use of the device, the resulting current delivery being within 20% of the value $I = I_f / y$, and $y = -0.0016t^2 + 0.0587t + 0.4454$ for at least substantially the first 12 hours of use, wherein t is the time in hours the system is in use, If is an average current delivery for a targeted final hour of use.

12. The system of claim 3 wherein the average amount of charge delivered for a dose period at the last hour of use differs by not less than 25 % from the average amount of charge delivered for the same dose period at the first hour.

13. The system of claim 3 wherein the controller controls the current delivery to discrete periods of constant current delivery for at least a period of fentanyl delivery.

14. The system of claim 3 wherein the controller controls the current delivery to substantially continually change with time for at least a period of fentanyl delivery.

15. The system of claim 3, wherein the controller controls the current to at an average current of less than 400 μA averaged over an hour at all time the device is in use.

16. The system of claim 3, wherein the controller controls the current delivery to an average current density of less than 150 μA/ cm^2 averaged over an hour at all time of use.

17. A method for transdermal electrotransport of fentanyl through the skin of a human to effect analgesia, comprising:

(a) controlling current delivery to a fentanyl reservoir of an electrotransport device to drive fentanyl ions therefrom through the skin such that the average amount of charge passed per dose period decreases with time nonlinearly and nonexponentially to result in a more stable fentanyl delivery than delivery with a constant amount of charge per dose period, wherein the average amount of charge per dose period during a first hour differs from the average amount of charge per dose period during a final hour the device is designed to be used by not more than 60% of the average amount of charge of the first hour.

18. The method of claim 17, comprising controlling the current delivery such that an average amount of charge per dose period averaged over an earlier hourly period differs from an average amount of charge per dose period of an immediately subsequent hourly period by not more than 40% of the average amount of charge per dose period of the earlier hourly periods.

19. The method of claim 18, comprising controlling the current delivery to deliver from 30μg to 60μg of fentanyl per dose.

20. The method of claim 19, comprising controlling the current delivery such that an average current delivery at the last hour of use differs from an average current delivery of the first hour by not more than 55% of the average current delivery of the first hour.

21. The method of claim 20, comprising controlling the current delivery such that an average current delivery from the fourth hour through the sixth hour of use differs from an average current delivery of the first hour by not more than 40% of the average current delivery of the first hour.

22. The method of claim 20, comprising controlling the current delivery such that an average current delivery from the seventh hour through the ninth hour of use differs from an average current delivery of the last hour of use by not more than 20% of the average current delivery from the seventh hour through the ninth hour.

23. The method of claim 19, comprising controlling the current delivery to deliver from 35μg to 50μg of fentanyl per dose.

24. The method of claim 20, comprising delivering fentany through a donor reservoir having a surface area for contacting skin of 0.8 cm^2 to 10cm^2.

25. The method of 20, comprising delivering fentany from a donor reservoir that comprises fentanyl halide.

26. The method of 20, comprising delivering fentany from a donor reservoir that comprises fentanyl hydrochloride.

27. The method of claim 20, comprising controlling the current delivery such that the current delivery is not constant during the use of the device, the resulting current delivery being within 20% of the value $I = I_f / y$, and $y = -0.0016t^2 + 0.0587t + 0.4454$ for at least substantially the first 12 hours of use, wherein t is the time in hours the system is in use, I_f is the average current delivery for a targeted final hour of use.

28. The method of claim 20, comprising controlling the current delivery such that an average amount of charge delivered for a dose period at the last hour of use differs by not more than 55% from an average amount of charge delivered for the same dose period at the first hour.

29. The method of claim 20, comprising controlling the current delivery to result in discrete periods of constant current delivery for at least a period of fentanyl delivery.

30. The method of claim 20, comprising controlling the current delivery to substantially continually change with time for at least a period of fentanyl delivery.

31. The method of claim 20, comprising controlling the current delivery to result in an average current of less than 400 μA averaged over an hour at all time the device is in use.

32. The method of claim 20, comprising controlling the current delivery to result in an average current density of less than 150 μA/ cm^2 averaged over an hour at all time the device is in use.

33. A method for making a transdermal electrotransport system for administering fentanyl through the skin of a human to effect analgesia, comprising:

(a) providing at least two electrodes, one of which for conducting a current to drive fentanyl ions from a fentanyl reservoir having fentanyl salt;

(b) connecting a controller to the at least two electrodes for controlling electrical charge delivery that drives the fentanyl ions to deliver a dose of fentanyl in a dose period such the average amount of charge passing through the donor reservoir per dose period trends down with time nonlinearly and nonexponentially for doses at different time periods to result in a more stable fentanyl delivery over time than delivery with a constant average amount of charge per dose period, wherein the average amount of charge per dose period during a first hour differs from the average amount of charge per dose period during a final hour the method is to predetermined to last by not more than 60% of the average amount of charge of the first hour.

34. A transdermal electrotransport system for administering fentanyl through the skin of a human user for a predetermined period of time to effect analgesia, comprising:

(a) donor reservoir comprising fentanyl salt;

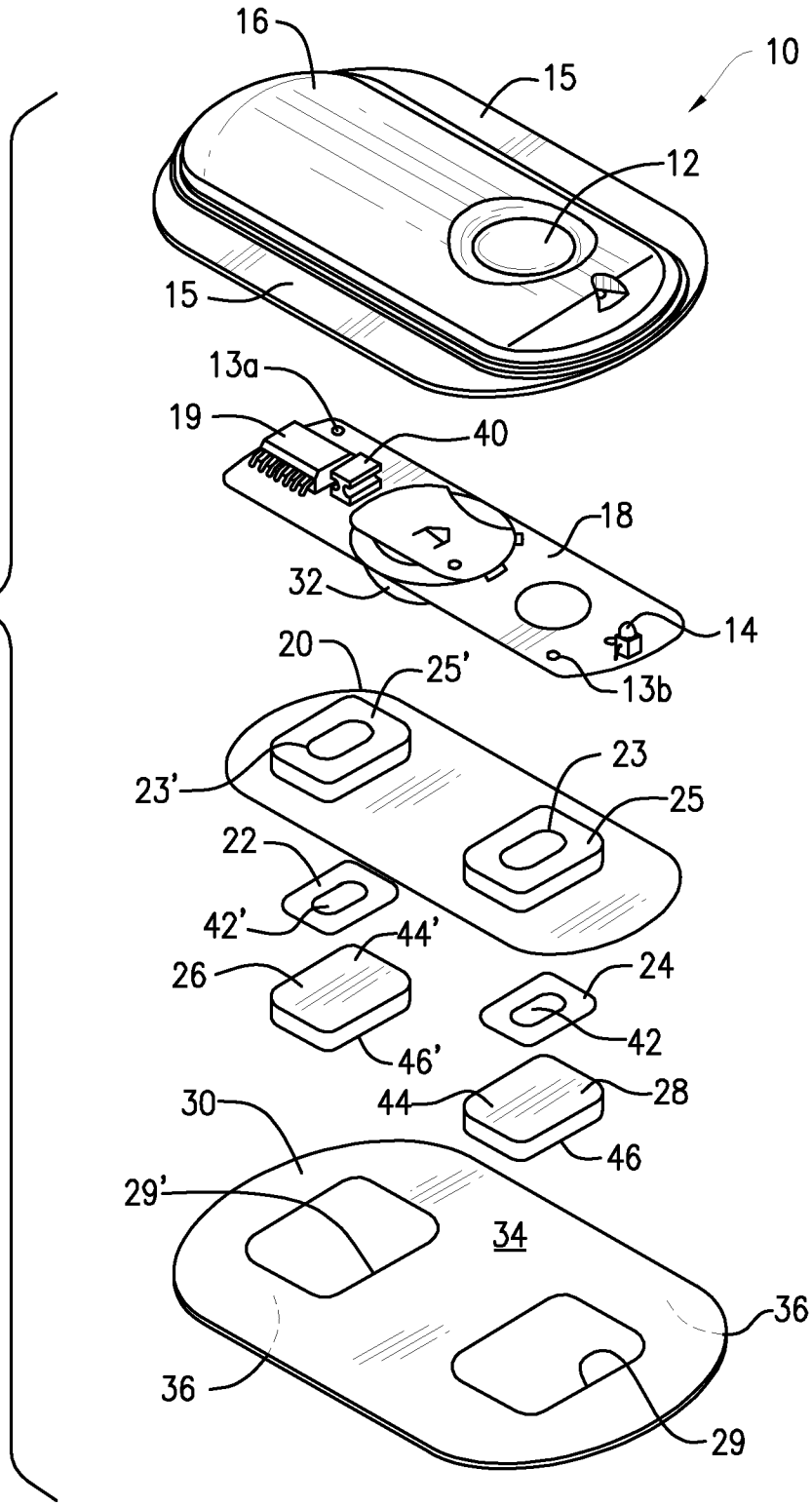
(b) at least two electrodes for conducting a current to drive fentanyl ions from the donor reservoir transdermally to deliver a dose of fentanyl in a dose period;

(c) a controller for controlling electrical charge delivery that drives the fentanyl ions such that the amount of charge per dose period of the current passing through the donor reservoir trends down with time nonlinearly and nonexponentially, wherein the average amount of charge per dose period during a first hour differs from the average amount of charge

per dose period during a final hour the device is designed to be used by not more than 60% of the average amount of charge of the first hour.

(Prior Art)

FIG. 1



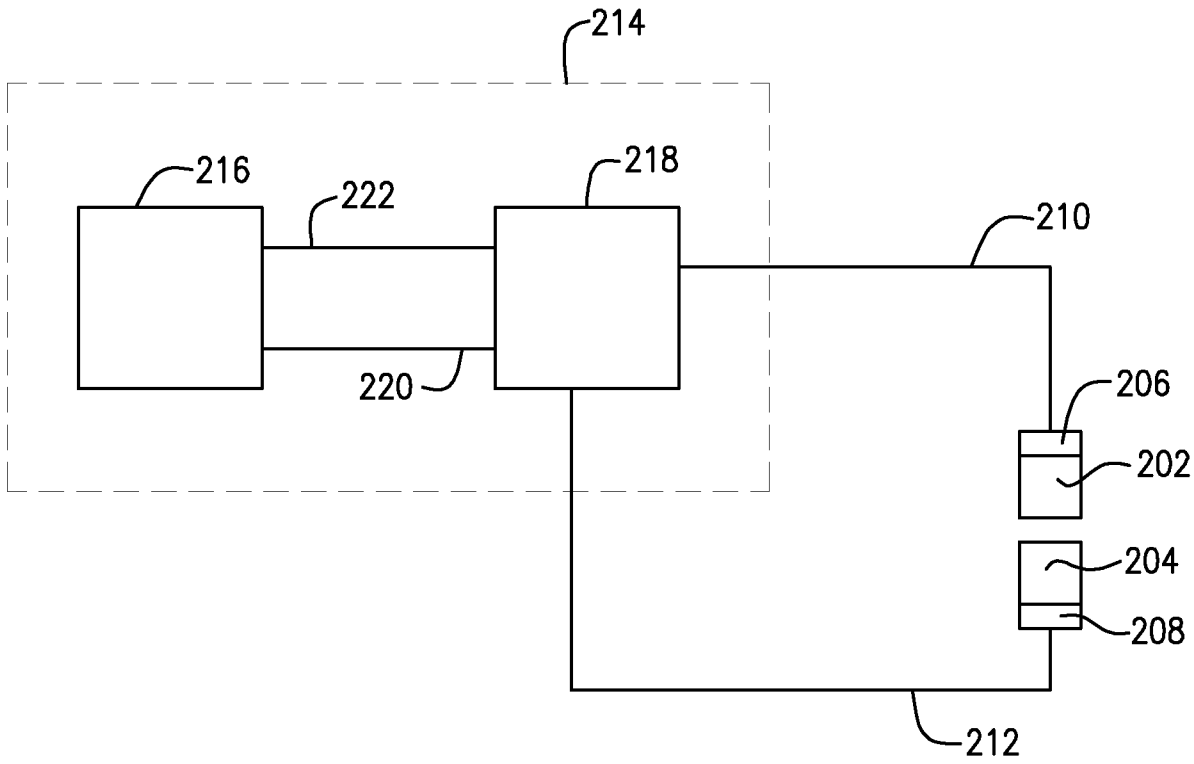


FIG. 2

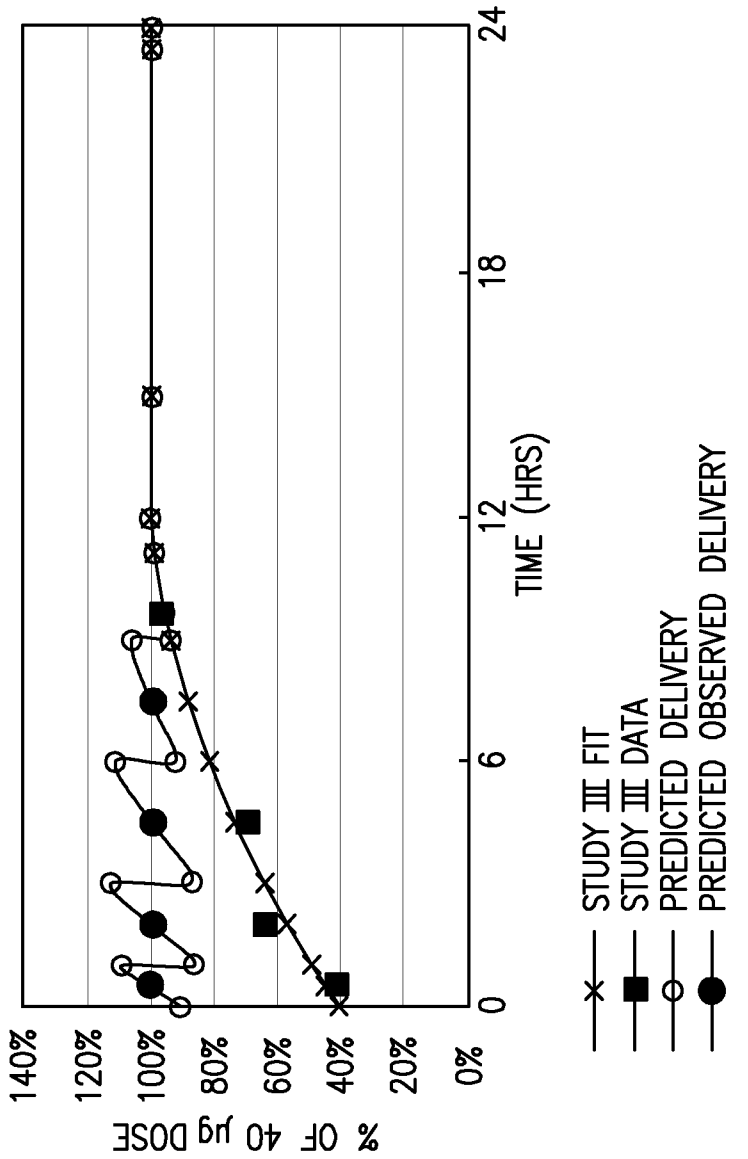

% OF 40 µg DOSE
140%
120%
100%
80%
60%
40%
20%
0%
0
6
12
18
24
TIME (HRS)
STUDY III FIT
STUDY III DATA
PREDICTED DELIVERY
PREDICTED OBSERVED DELIVERY

FIG. 3

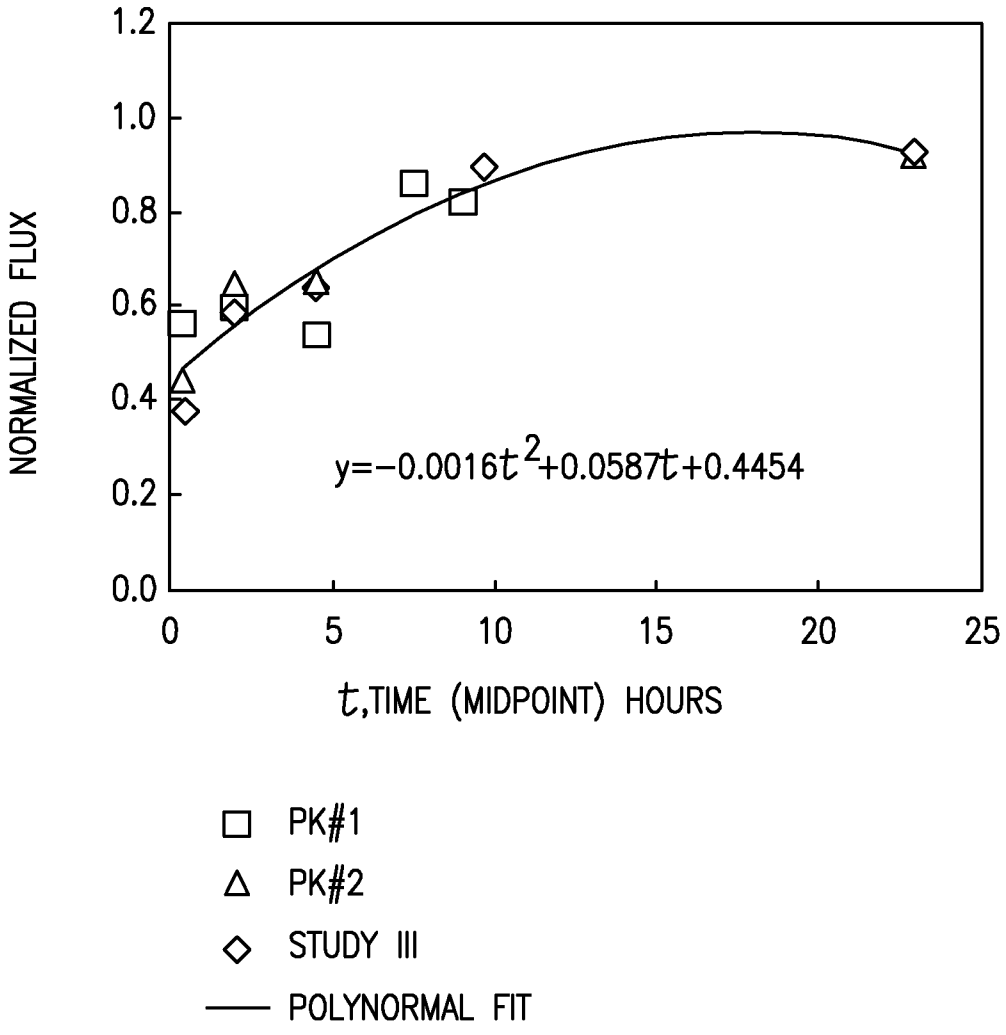

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0.8
0.6
0.4
0.2
0.0
NORMALIZED FLUX
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0
5
10
15
20
25
t,TIME (MIDPOINT) HOURS
PK#1
PK#2
STUDY III
POLYNORMAL FIT

FIG. 4