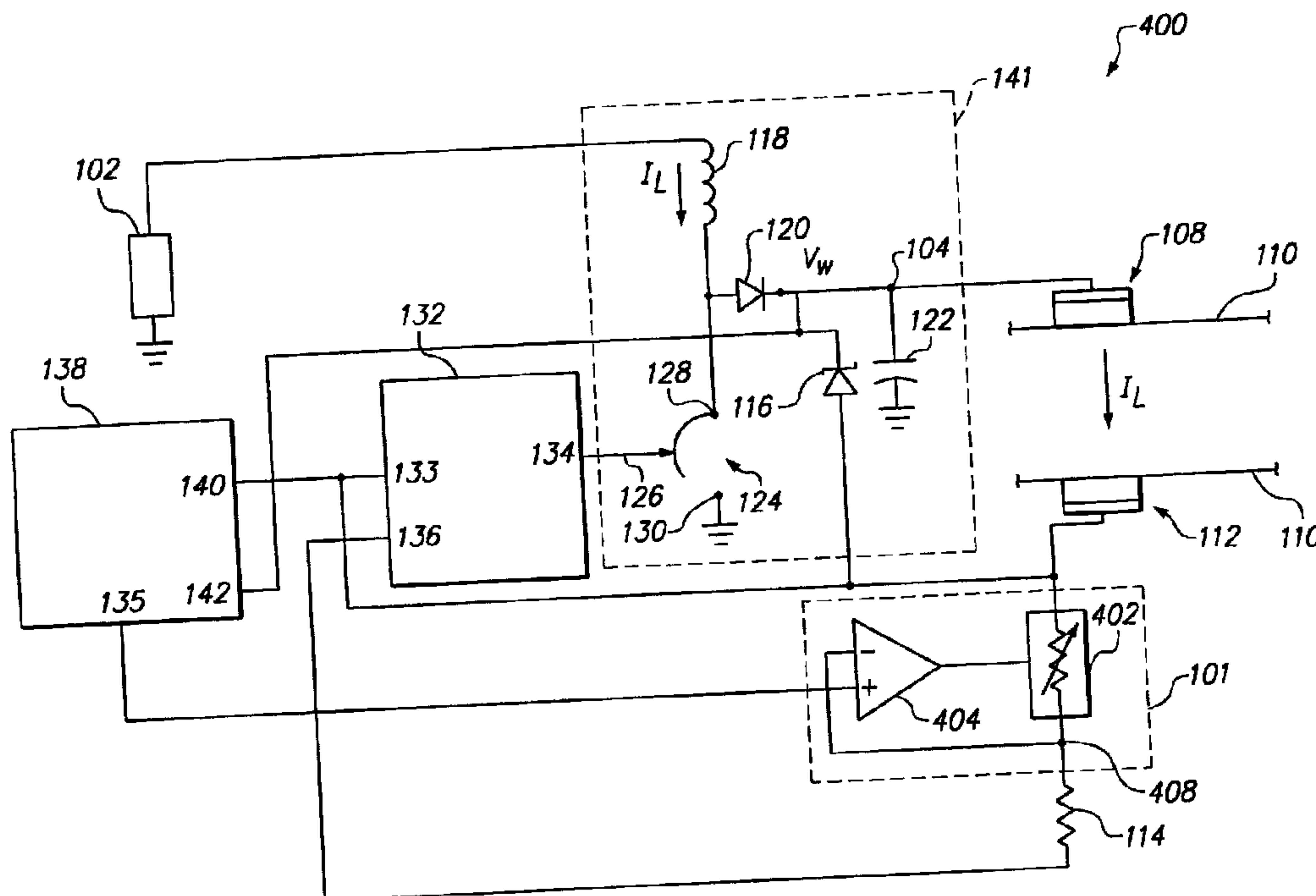




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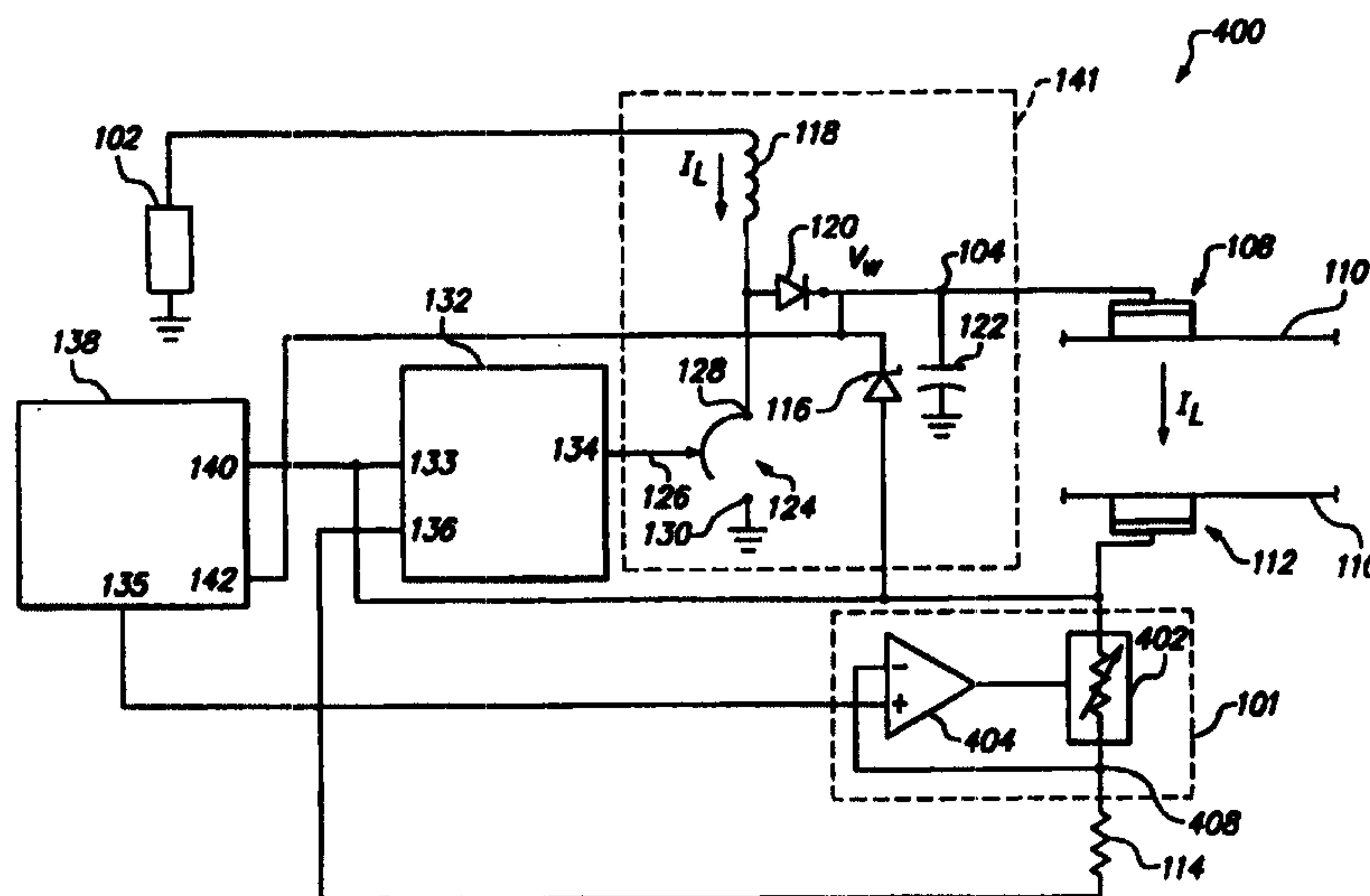
An electrotransport device with a drug delivery regulating apparatus delivers a proper drug dosage rate over time by adapting to variable skin resistance values. The electrotransport device adapts to a decline in skin resistance over a time that the electrotransport device is used, and to different skin resistances at different skin surface locations. One drug delivery regulating apparatus includes a voltage booster, a serially connectable artificial impedance, and a feedback sensor, which are all connected to a controller. This apparatus outputs a load voltage across two electrodes. The controller monitors the output of the feedback sensor to determine the skin resistance, or a load current, or the load voltage. Based on the monitored value, the load voltage across the electrodes is controlled, so that a targeted drug dose rate is maintained even as the initial skin resistance drops over the period that the electrotransport device is used. The artificial impedance is selectively controlled to prevent overdose where the skin resistance falls below a predetermined resistance, such that a load voltage greater than a supply voltage could result in an overdose.



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(54) Title: REGULATOR WITH ARTIFICIAL LOAD TO MAINTAIN REGULATED DELIVERY**(57) Abstract**

An electrotransport device with a drug delivery regulating apparatus delivers a proper drug dosage rate over time by adapting to variable skin resistance values. The electrotransport device adapts to a decline in skin resistance over a time that the electrotransport device is used, and to different skin resistances at different skin surface locations. One drug delivery regulating apparatus includes a voltage booster, a serially connectable artificial impedance, and a feedback sensor, which are all connected to a controller. This apparatus outputs a load voltage across two electrodes. The controller monitors the output of the feedback sensor to determine the skin resistance, or a load current, or the load voltage. Based on the monitored value, the load voltage across the electrodes is controlled, so that a targeted drug dose rate is maintained even as the initial skin resistance drops over the period that the electrotransport device is used. The artificial impedance is selectively controlled to prevent overdose where the skin resistance falls below a predetermined resistance, such that a load voltage greater than a supply voltage could result in an overdose.

REGULATOR WITH ARTIFICIAL LOAD
TO MAINTAIN REGULATED DELIVERY

FIELD OF INVENTION

5 The present invention relates generally to an electrotransport device for transdermally or transmucosally delivering a beneficial agent (e.g., a drug) to a patient. More particularly, the present invention relates to a portable or patient-worn electrotransport delivery device having a voltage booster and an artificial load to maintain regulated delivery of the beneficial agent.

BACKGROUND OF THE INVENTION

10 The term "electrotransport" as used herein refers generally to the delivery of an agent (e.g., a drug) through a membrane, such as skin, mucous membrane, or nails, in which the delivery is at least partially induced or aided
15 by the application of an electric potential. For example, a beneficial therapeutic agent may be introduced into the systemic circulation of an animal (e.g., a human) by electrotransport delivery through the skin.

 The electrotransport process has been found to be useful in the transdermal administration of drugs including lidocaine hydrochloride,
20 hydrocortisone, fluoride, penicillin, dexamethasone sodium phosphate, and many other drugs. Perhaps the most common use of electrotransport is in diagnosing cystic fibrosis by delivering pilocarpine salts iontophoretically. The pilocarpine stimulates production of sweat. The sweat is then collected and analyzed for its chloride content to detect the presence of the disease.

25 Presently known electrotransport devices use at least two electrodes, positioned in intimate contact with some portion of the animal's body (e.g., the skin). A first electrode, called the active or donor electrode, delivers the therapeutic agent (e.g., a drug or a prodrug) into the body by electrotransport.

 The second electrode, called the counter or return electrode, closes an
30 electrical circuit with the first electrode through the animal's body. A source of electrical energy, such as a battery, supplies electric current to the body through the electrodes. For example, if the therapeutic agent to be delivered

into the body is positively charged (i.e., a cation), the anode will be the active electrode and the cathode will serve as the counter electrode to complete the circuit. If the therapeutic agent to be delivered is negatively charged (i.e., an anion), the cathode will be the donor electrode and the anode will be the counter electrode.

Alternatively, both the anode and cathode may be used to deliver drugs of opposite electrical charge into the body. In this situation, both electrodes are considered donor and counter electrodes. For example, the anode can simultaneously deliver a cationic therapeutic agent and act as a "counter" electrode to the cathode. Similarly, the cathode can simultaneously deliver an anionic therapeutic agent into the body and act as a "counter" electrode to the anode.

A widely used electrotransport process, electromigration (also called iontophoresis), involves the electrically induced transport of charged ions. Another type of electrotransport, electroosmosis, involves the flow of a liquid solvent from the donor reservoir, which liquid contains the agent to be delivered, under the influence of the applied electric field.

Still another type of electrotransport process, electroporation, involves the formation of transiently existing pores in a biological membrane by the application of high voltage pulses. A therapeutic agent can, in part, be delivered through the skin by passive diffusion by reason of the concentration difference between the concentration of the drug in the donor reservoir of the electrotransport device and the concentration of the drug in the tissues of the patient's body. In any given electrotransport process, more than one of these processes may be occurring simultaneously to a certain extent. Accordingly, the term "electrotransport", as used herein, should be given its broadest reasonable interpretation so that it includes, for example, the electrically induced or enhanced transport of at least one therapeutic agent, whether charged, uncharged, or a mixture thereof. Further, the terms load current and the current flowing through the skin are defined as the current flowing between the two electrodes.

Electrotransport devices generally require a reservoir or source of the

agent, or a precursor of such agent, that is to be delivered into the body by electrotransport. Examples of such reservoirs or sources of, preferably ionized or ionizable, agents include a pouch as described in Jacobsen U.S. Patent 4,250,878, or a pre-formed gel body as disclosed in Webster U.S. Patent 4,383,529. Such reservoirs are electrically connected to the anode or the cathode of an electrotransport device to provide a fixed or renewable source of one or more desired therapeutic species.

Recently, a number of U.S. Patents have issued in the electrotransport field, indicating a continuing interest in this mode of drug delivery. For example, Vernon et al U.S. Patent 3,991,755, Jacobsen et al U.S. Patent 4,141,359, Wilson U.S. Patent 4,398,545, Jacobsen U.S. Patent 4,250,878, Sorenson et al. U.S. Patent 5,207,752, Lattin et al. U.S. Patent 5,213,568, and Flower U.S. Patent 5,498,235 disclose examples of electrotransport devices and some applications thereof.

More recently, electrotransport delivery devices have become much smaller, particularly with the development of miniaturized electrical circuits (e.g., integrated circuits) and more powerful light weight batteries (e.g., lithium batteries). The advent of inexpensive miniaturized electronic circuitry and compact, high-energy batteries has meant that the entire device can be made small enough to be unobtrusively worn on the skin of the patient and under clothing. This allows the patient to remain fully ambulatory and able to perform all normal activities, even during periods when the electrotransport device is actively delivering drug.

However, disadvantages remain in prior art electrotransport devices that restrict the wider application of these valuable devices. One such limitation is the difficulty in regulating the amount of the drug delivered. The correct delivery is complicated by the fact that the electrical resistance of the patient's body surface (e.g., skin) is not constant during the electrotransport delivery. Since the voltage (V) necessary to drive a particular level of electric current (I) through the patient's skin is proportional to the resistance (R) of the skin (i.e., according to Ohm's Law, wherein $V = I R_{\text{skin}}$), the voltage requirements of the power supply are not constant during electrotransport

delivery. For example, when electrotransport drug administration starts, the patient's initial skin resistance is relatively high, requiring the power supply to produce relatively high voltage to deliver a predetermined level of electrotransport current. However, after several minutes (i.e., after about 1 to 5 30 minutes of current being applied through the skin) the skin resistance drops, such that the voltage required to deliver a particular level of electric current becomes significantly less than the voltage required at the start of electrotransport delivery.

Another complicating factor regarding the regulation of an
10 electrotransport delivery device is that although skin over the entire body has a fundamentally similar structure, there are many local variations in thickness, mechanical strength, softness, and most importantly, skin resistance.

The prior art transdermal electrotransport delivery devices supply set voltages indiscriminately to any skin surface, irrespective of the resistance of
15 the skin. Further, in some other prior art transdermal electrotransport delivery devices, the voltage of the power supply and/or the boost multiple of the voltage boosting circuit, are chosen to be large enough to overcome the high skin resistance present at the start of operation. However, once operation had reached a steady state, with the attendant drop in skin resistance, the
20 prior art devices have excess working voltage. Accordingly, by supplying a higher voltage than required, these prior art devices deliver more drug dosage than required, once the skin resistance drop from its initial high level.

Hence, there is a need for an improved electrotransport device and method, that can maintain a target drug delivery rate while the skin resistance
25 drops from its initial value, and which can be applied to deliver the targeted drug delivery rate to different areas of the skin with different resistances.

SUMMARY OF THE INVENTION

One embodiment of the present invention is an electrotransport device
30 with a drug delivery regulating apparatus which delivers the proper drug dosage rate over time by adapting to variable skin resistance values, particularly the decline in skin resistance over the time that the

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electrotransport device is used, and to different skin resistances at different skin surface locations.

In another embodiment, a drug delivery regulating apparatus includes a voltage booster, a serially connectable
5 artificial impedance, and a feedback sensor, which are all connected to a controller. This apparatus outputs a load voltage across two electrodes. The controller monitors the output of the feedback sensor to determine (a) the skin resistance, or (b) a load current, or (c) the load voltage,
10 and based on the monitored value, controls the load voltage across the electrodes, so that the targeted drug dose rate is maintained even as the initial skin resistance drops over the period that the electrotransport device is used. The artificial impedance is generated and applied to prevent
15 overdose where the skin resistance falls below the battery voltage of the apparatus.

In accordance with an aspect of the invention, there is provided an electrotransport transdermal agent delivery regulator comprising: a voltage booster circuit
20 coupled to a first electrode for providing a load voltage to the first electrode; control circuitry coupled to the voltage booster circuit for regulating the load voltage in response to a load resistance between the first electrode and a second electrode; and a variable resistance circuit
25 coupled in series with the load resistance, wherein the variable resistive circuit is coupled to the control circuitry for adjusting a current through the load resistance, and wherein the variable resistive circuit comprises: a first current path having a first resistance; a
30 second current path having a second resistance; and a switch circuit coupled to the first and second current paths for selectively coupling either the first or second resistance

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in series with the load resistance in response to the control circuitry.

In accordance with another aspect of the invention, there is provided an electrotransport transdermal delivery regulator delivering a beneficial agent through an animal skin surface by supplying a load voltage and load current across a first electrode assembly and second electrode assembly using an electrical power source, the regulator comprising: a controller; a voltage booster electrically connected to the controller, the electrical power source and the first electrode assembly; a control enabler electrically connected to the second electrode assembly; a control enabler switch for adjusting the load current, the control enabler switch being connected to the controller and capable of being connected to the second electrode assembly or the control enabler, the control enabler switch being controlled by the controller; and a sensor connected to the controller and the control enabler switch, wherein the controller determines a feedback value from the sensor and the controller regulates the load voltage using the voltage booster, the control enabler, the control enabler switch and the feedback value.

In accordance with another aspect of the invention, there is provided an electrotransport transdermal delivery regulator comprising: a controller; a voltage booster connected to the controller, an electrical power source and a first electrode assembly, the voltage booster comprising: an inductor coupled to the electrical power source; and an inductor switch connected to the inductor and a capacitor, the inductor switch being coupled to and controlled by the controller; a controllable impedance connected to a second electrode assembly, the controllable impedance provides first or second impedance paths in series with the first and second electrode assemblies in response to the controller; and a voltage limiter

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connected to the first electrode assembly for limiting a load voltage to a predetermined maximum value.

In accordance with another aspect of the invention, there is provided the use of the electrotransport transdermal agent delivery regulator as defined in any one of the previous three paragraphs for delivering a beneficial agent through an animal skin.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a perspective view of an electrotransport drug delivery device of this invention.

Figure 2 is an exploded view of an electrotransport device of this invention.

Figure 3 is a graph illustrating the decline of patient skin resistance with time.

Figure 4 is a graph of an exemplary current-time profile of load current supplied by an electrotransport device of this invention. The graph is an example of a current-time profile.

Figure 5 is a time line graph of a load voltage of an electrotransport device of this invention.

Figure 6 is a schematic block diagram of a drug delivery regulator of this invention.

Figure 7 is a schematic logic circuit diagram of a drug delivery regulator of this invention.

Figure 8 is a timing diagram of the operation of the circuit of Figure 7.

Figure 9 is a schematic logic circuit diagram of another drug delivery

regulator of this invention.

Figure 10 is a timing diagram of the operation of the circuit of Figure 9.

Figure 11. is a perspective view of an electrotransport drug delivery device which includes a disposable drug unit.

5 Figure 12 is an exploded view of an electrotransport device of Figure 11.

Figure 13 is a schematic logic circuit diagram of another drug delivery regulator of this invention.

10 DETAILED DESCRIPTION OF THE INVENTION

Embodiments of electrotransport drug delivery devices which include the electrotransport drug delivery regulator of the present invention are illustrated in Figs. 1-2 and 11-12.

15 Figure 1 shows a perspective view of an electrotransport delivery device 10 having an optional activation switch in the form of a push button switch 12 and an optional light emitting diode (LED) 14 which is turned on when device 10 is in operation.

Figure 2 is an exploded view of a second device 10 of this invention. The device 10 of Figure 2 differs from device 10 of Figure 1 in the location of a LED 14. Device 10 of Figure 2 comprises an upper housing 16, circuit board assembly 18, lower housing 20, anode electrode 22, cathode electrode 24, anode reservoir 26, cathode reservoir 28 and skin-compatible adhesive 30. Upper housing 16 has lateral wings 15 which assist in holding device 10 of Figure 2 on a patient's skin. Upper housing 16 can be composed of an injection moldable elastomer (e.g., ethylene vinyl acetate). Upper housing 16 can also be composed of rubber or other elastomeric material. Printed circuit board assembly 18 comprises an integrated circuit 19 coupled to discrete components 40 and battery 32. Circuit board assembly 18 is attached to housing 16 by posts (not shown in Figure 2) passing through openings 13a and 13b, the ends of the posts being heated/melted in order to heat stake circuit board assembly 18 to housing 16. Lower housing 20 is attached to upper housing 16 by an adhesive 30, an upper surface 34 of adhesive 30

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being adhered to both lower housing 20 and upper housing 16 including the bottom surfaces of wings 15.

Shown (partially) on the underside of circuit board assembly 18 is a button cell battery 32. Other types of batteries may also be employed to power device 10. Device 10 is generally comprised of battery 32, electronic circuitry 19, 40, electrodes 22, 24, and drug/chemical reservoirs 26, 28, all of which are integrated into a self-contained unit. The outputs (not shown in Figure 2) of the circuit board assembly 18 make electrical contact with the electrodes 24 and 22 through openings 23, 23' in depressions 25, 25' formed in lower housing 20, by electrically conductive adhesive strips 42, 42'. Electrodes 22 and 24, in turn, are in direct mechanical and electrical contact with top sides 44', 44 of drug reservoirs 26 and 28. Bottom sides 46', 46 of drug reservoirs 26, 28 contact the patient's skin through openings 29', 29 in adhesive 30.

Lower housing 20 can be composed of a plastic or elastomeric sheet material (e.g., polyethylene) which can be easily molded to form depressions 25, 25' and cut to form openings 23, 23'. The assembled device 10 is preferably water resistant (i.e., splash proof) and is most preferably waterproof. The system has a low profile that easily conforms to the body, thereby allowing freedom of movement at, and around, the wearing site. Reservoirs 26 and 28 are located on the skin-contacting side of device 10 and are sufficiently separated to prevent accidental electrical shorting during normal handling and use.

Any agent may be used, so long as it is at least partly ionized. The terms "drug" and "agent" are used interchangeably and are intended to have their broadest reasonable interpretation, namely any therapeutically active substance that is delivered to a living organism to produce a desired, usually beneficial, effect. For example, the terms "drug" and "agent" include therapeutic compounds and molecules from all therapeutic categories including, but not limited to, anti-infectives (such as antibiotics and antivirals), analgesics (such as fentanyl, sufentanil, buprenorphine, and analgesic combinations), anesthetics, antiarthritics, antiasthmatics (such as terbutaline),

anticonvulsants, antidepressants, antidiabetics, antidiarrheals, antihistamines, anti-inflammatories, antimigranes, antmotion sickness preparations (such as scopolamine and ondansetron), antineoplastics, antiparkinsonisms, antipruritics, antipsychotics, antipyretics, antispasmodics (including
5 gastrointestinal and urinary), anticholinergics, sympathomimetrics, xanthine and derivatives thereof, cardiovascular preparations (including calcium channel blockers such as nifedipine, beta-agonists (such as dobutamine and ritodrine), beta blockers, antiarrhythmics, antihypertensives (such as atenolol), ACE inhibitors (such as lisinopril), diuretics, vasodilators (including general,
10 coronary, peripheral and cerebral), central nervous system stimulants, cough and cold preparations, decongestants, diagnostics, hormones (such as parathyroid hormones), hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetrics, prostaglandins, proteins, peptides, psychostimulants, sedatives and tranquilizers.

15 The electrotransport device of the present invention can deliver drugs and/or agents including baclofen, beclomethasone, betamethasone, buspirone, cromolyn sodium, diltiazem, doxazosin, droperidol, encainide, fentanyl, hydrocortisone, indomethacin, ketoprofen, lidocaine, methotrexate, metoclopramide, miconazole, midazolam, nicardipine, piroxicam, prazosin,
20 scopolamine, sufentanil, terbutaline, testosterone, tetracaine and verapamil.

The electrotransport device of the present invention may also deliver peptides, polypeptides, proteins and other macromolecules. Such molecules are known in the art to be difficult to deliver transdermally or transmucosally due to their size. For example, such molecules may have molecular weights
25 in the range of 300-40,000 daltons and include, but not limited to, LHRH and analogs thereof (such as buserelin, goserelin, gonadorelin, naphrelin and leuprolide), GHRH, GHRF, insulin, insulinotropin, heparin, calcitonin, octreotide, endorphin, TRH, NT-36 or N-[[[(s)-4-oxo-2-azetidiny]carbonyl]L-histidyl-L-prolinamide], liprecin, pituitary hormones (such as HGH, HMG,
30 HCG, desmopressin acetate), follicle luteoids, α -ANF, growth factor releasing factor (GFRF), b-MSH, somatostatin, bradykinin, somatotropin, platelet-derived growth factor, asparaginase, bleomycin sulfate, chymopapain,

cholecystokinin, chorionic gonadotropin, corticotropin (ACTH), erythropoietin, epoprostenol (platelet aggregation inhibitor), glucagon, hirulog, hyaluronidase, interferon, interleukin-2, menotropins (such as urofollitropin (FSH) and LH), oxytocin, streptokinase, tissue plasminogen activator, urokinase, vasopressin, desmopressin, ACTH analogs, ANP, ANP clearance inhibitors, angiotensin II antagonists, antidiuretic hormone agonists, antidiuretic hormone antagonists, bradykinin antagonists, CD4, ceredase, CSF's, enkephalins, FAB fragments, IgE peptide suppressors, IGF-1, neurotrophic factors, colony stimulating factors, parathyroid hormone and agonists, parathyroid hormone antagonists, prostaglandin antagonists, pentigetide, protein C, protein S, renin inhibitors, thymosin alpha-1 antitrypsin (recombinant), and TGF-beta.

Device 10 optionally has a feature which allows the patient to self-administer a dose of drug by electrotransport. Upon depression of push button switch 12, the electronic circuitry on circuit board assembly 18 delivers a predetermined DC current to electrodes/reservoirs 22, 26 and 24, 28 for a delivery interval of predetermined length. Push button switch 12 is conveniently located on the top side of device 10 and is easily actuated through clothing. A double press of push button switch 12 within a short time period, e.g., three seconds, can be used to activate the device for delivery of drug, thereby minimizing the likelihood of inadvertent actuation of device 10. The device can transmit to the user a visual and/or audible confirmation of the onset of the drug delivery interval by LED 14 becoming lit and/or an audible sound signal from, e.g., a "beeper". Drug is delivered through the patient's skin by electrotransport, e.g., on the arm, over the predetermined delivery interval.

Anodic electrode 22 can be comprised of silver, and cathodic electrode 24 can be comprised of silver chloride. Both reservoirs 26 and 28 can be comprised of polymer hydrogel materials. Electrodes 22, 24 and reservoirs 26, 28 are retained within the depressions 25', 25 in lower housing 20.

Device 10 adheres to the patient's body surface (e.g., skin) by a peripheral adhesive 30 which has upper side 34 and body-contacting side 36.

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Adhesive side 36 has adhesive properties which assures that device 10 remains in place on the body during normal user activity, and yet permits reasonable removal after the predetermined (e.g., 24-hour) wear period. Upper adhesive side 34 adheres to lower housing 20 and retains lower housing 20 attached to upper housing 16.

Reservoirs 26 and 28 generally comprise a gel matrix, with the drug solution uniformly dispersed in at least one of the reservoirs 26 and 28. Drug concentrations in the range of approximately 1×10^{-4} M to 1.0 M or more can be used, with drug concentrations in the lower portion of the range being preferred. Suitable polymers for the gel matrix may comprise essentially any nonionic synthetic and/or naturally occurring polymeric materials. A polar nature can be implemented where the active agent is polar and/or capable of ionization, so as to enhance agent solubility. Optionally, the gel matrix will be water swellable. 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-methylolacrylamide), poly(diacetone acrylamide), poly(2-hydroxyethyl 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.

Thus, the polypeptide analogs of the present invention will be incorporated into the drug reservoir, e.g., a gel matrix as just described, and administered to a patient using an electrotransport drug delivery system, optionally as exemplified hereinabove. Incorporation of the drug solution can be done any number of ways, i.e., by imbibing the solution into the reservoir

matrix, by admixing the drug solution with the matrix material prior to hydrogel formation, or the like.

Figures 11-12 show another embodiment of an electrotransport drug delivery device of the present invention. This embodiment includes a reusable electronic controller and a drug unit. The reusable controller in
5 Figures 11-12 usually houses a drug delivery regulator and is designed to be used in conjunction with the drug unit for transdermally delivering the drug stored in the drug unit.

Figure 11 is a perspective view of electrotransport device 320 having a
10 reusable electronic controller 322 which is adapted to be coupled to and uncoupled from, drug-containing unit 324. The reusable electronic controller 322 is reusable, i.e., it is adapted to be used with a plurality of drug units 324, e.g., a series of similar and/or very different drug units 324. On the other hand, drug unit 324 typically has a more limited life and is adapted to be
15 discarded after use, i.e., when the drug contained therein has been delivered or depleted. Thus, after the drug contained in drug unit 324 becomes depleted after a predetermined operational life (e.g., 24 hours), drug unit 324 is uncoupled from reusable electronic controller 322 and replaced with a fresh drug unit 324 of the same or different structure and/or composition. Reusable
20 electronic controller 322 is designed to provide one of a plurality of different predetermined electrical outputs which can be set at the time the controller is

manufactured. The different electrical outputs of the reusable electronic controller 322 are designed to be used with different drug units 324.

25 For purposes of illustration, the reusable electronic controller 322 can be designed to be used with at least two different drug units 324, both of which units are adapted to be used with the same reusable electronic controller 322 to continuously deliver drug over a period of 12 hours. The two different drug units 324 contain the same drug in their respective donor
30 reservoirs but each contains a different amount of the drug. The drug unit 324 which contains a greater amount of drug is a "high dose" drug unit which is adapted to be used with a higher DC current (e.g., 2 mA) output from the

reusable electronic controller 322. The drug unit 324 which contains a lesser amount of drug is a "low dose" drug unit which is adapted to be used with a lower DC current (e.g., 1 mA) output from the reusable electronic controller 322. Thus, the reusable electronic controller 322 is designed to apply one of
5 two different DC currents (i.e., 1 mA or 2mA) depending upon whether a low dose or a high dose drug unit 324 is coupled thereto.

The present invention signals to reusable electronic controller 322 which type of drug unit (e.g., either a high dose or a low dose drug unit) is being coupled thereto and for appropriately setting the output of the controller
10 (i.e., setting either the high current output or the low current output) to match the coupled drug unit. In the device illustrated in Figs. 11 and 12, drug unit 324 signals reusable electronic controller 322 by an optical signal, which optical signal is automatically sent and then read (i.e., decoded) by reusable electronic controller 322 upon coupling drug unit 324 thereto (i.e., by the snap
15 connectors 326, 328). Upon reading the signal, the controller appropriately selects the correct electrical output to apply to the coupled drug unit 324.

With reference to Figure 12, there is shown an exploded view of both drug unit 324 and reusable electronic controller 322. Reusable electronic controller 322 is comprised of an upper housing 368 and a lower housing 350,
20 both typically formed of a molded plastic such as polypropylene. Upper housing 368 is joined to lower housing 350 by a contiguous splash proof and preferably water proof peripheral seal. The seal can be made by heat sealing or ultrasonic welding of the joint between housings 350, 368, by gluing the housings together at their common joint using a water proof adhesive, and the
25 like. Lower housing 350 has an opening 352 for receiving battery 354. Battery contacts 364, 366 are provided to make electrical contact with the respective poles of battery 354. A removable cover 360 screws into the opening 352 to retain battery 354 in place. Cover 360 has a slot 362 for inserting a coin or a screw driver blade to turn cover 360 and remove it from
30 opening 352 in order to access (i.e., replace) battery 354. Reusable electronic controller 322 includes a battery 354, e.g. a button cell battery, for powering the electrical circuit (not shown) on circuit board 359. Circuit board

359 is formed in a conventional manner, having conductive traces patterned for interconnecting electrical component(s) thereon which control the magnitude, timing, frequency, waveform shape, etc., of the electrical output (e.g., voltage and/or current) of reusable electronic controller 322. The conductive traces on circuit board 359 may be deposited with a conventional silk screen printing process or a conventional solder coated copper plated mask and etch process. The insulating substrate of circuit board 359 may be made of standard FR-4 or the like. Although not critical to the invention, reusable electronic controller 322 includes a push button switch 374 which can be used to start operation of device 310 and a liquid crystal display 356 (Figure 11) which can display, through a window 358 (Figure 12), system information such as the particular type of drug unit 324 that is coupled to the controller, the applied current level, the dosing level, number of doses delivered, elapsed time of current application, battery strength, etc.

Lower housing 350 is provided with holes 375a, 375b which hold electrically conductive receptacles 330, 332. Receptacles 330, 332 protrude through respective holes 375a, 375b in lower housing 350. The ends of receptacles 330, 332 are held in place, and make electrical contact with the outputs of the electronic circuit on circuit board 359, by respective conductive gripping fasteners 376a, 376b.

Drug unit 324 is configured to be removably coupled to reusable electronic controller 322, with the top of drug unit 324 adjacent to and facing the bottom of reusable electronic controller 322. Top drug unit 324 is provided with the male parts of two snap type connectors, the male parts being posts 326 and 328 which extend upwardly from drug unit 324. Receptacle 330 is positioned and sized to receive donor post 326 and receptacle 332 is positioned and sized to receive counter post 328. One snap connector pair, for example receptacle 332 and post 328, may be made larger than the other snap connector pair (i.e., receptacle 330 and post 326) in order to provide a polarity specific connection of drug unit 324 to reusable electronic controller 322. Receptacles 330, 332 and posts 326, 328 are made from an electrically conductive material (e.g., a metal such as silver, brass,

stainless steel, platinum, gold, nickel, beryllium-copper, etc., or a metal coated polymer, e.g., ABS with a silver coating). Donor post 326 is electrically connected to donor electrode 390, which in turn is electrically connected to donor reservoir 401 which typically contains a solution of the therapeutic agent (e.g., a drug salt) to be delivered. Counter post 328 is electrically connected to counter electrode 388, which in turn is electrically connected to counter reservoir 399 which typically contains a solution of a biocompatible electrolyte (e.g., buffered saline). Electrodes 388 and 390 are typically comprised of electrically conductive materials, which can be a silver (e.g., silver foil or silver powder loaded polymer) anodic electrode and a silver chloride cathodic electrode. Reservoirs 399 and 401 typically include hydrogel matrices which hold the drug or electrolyte solutions and are adapted to be placed in contact with the body surface (e.g., skin) of a patient (not shown) when in use. Electrodes 388, 390 and reservoirs 399, 401 are isolated from each other by foam member 396. The bottom (i.e., patient contacting) surface of foam member 396 can be coated with a skin contact adhesive in order to secure drug unit 324 on the patient's body. A release liner 402 covers the body contacting surfaces of the two reservoirs 399 and 401 and the adhesive coated surface of foam member 396 before drug unit 324 is put in use. Release liner 402 in one embodiment is a silicone coated polyester sheet. Release liner 402 is removed when device 320 is applied to the skin of a patient (not shown).

Thus, post 326 and receptacle 330 comprise a snap type connector which electrically connects an output 378a of the circuit on circuit board 359 to electrode 390 and reservoir 401. Similarly, post 328 and receptacle 332 comprise a snap type connector which electrically connects an output 378b of the circuit on circuit board 359 to electrode 388 and reservoir 399. In addition to providing the above described electrical connections, the two snap connectors also provide a separable (i.e., not permanent) mechanical connection of drug unit 324 to reusable electronic controller 322. Thus, electrically conductive snap connectors 326, 330 and 328, 332 simultaneously provide the functions of (i) mechanically coupling drug unit

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324 to connector 322, and (ii) electrically connecting electrical output of reusable electronic controller 322 to drug unit 324.

In accordance with this embodiment of the present invention, drug unit 324 provides an optical signal to reusable electronic controller 322 in order to properly set the electrical output of the controller to a predetermined output which is appropriate for the specific drug unit 324 and the specific drug unit 324 and the specific drug contain therein. As is clearly shown in both Figs. 11 and 12, the mating surface of drug unit 324 has two surface areas 340, 342. Surface area 340 is shown as "white" for high light reflectivity while surface area 342 is shown as "black" for low light reflectivity. Areas 340, 342 may be provided (e.g., by printing or painting) directly on backing layer 344 of drug unit 324 or alternatively on a thin strip of paper or mylar 343 which is mounted on backing layer 344 by a suitable adhesive.

Reusable electronic controller 322 has a pair of light reflection switches 334, 336 mounted on circuit board 359 and oriented so as to project through holes 337a, 337b in lower housing 350. Switches 334, 336 are directed toward and adjacent to drug unit 324. Reflective areas 340, 342 are positioned on drug unit 324 such that areas 340, 342 are located closely adjacent to reflection switches 336, 334, respectively, when reusable electronic controller 322 and drug unit 324 are coupled.

Light reflection switches 334, 336 are arranged to illuminate the light reflective areas 340, 342 respectively. Reflective areas 340, 342 are arranged such that the illumination from switch 334 is independently reflected by area 342 back to switch 334. Similarly, the illumination from switch 336 is independently reflected by area 340 back to switch 336. In a one embodiment, switches 334 and 336 are each provided with a respective illumination source in the form of a photo emitter, 346a and 346b, and a respective matching light sensitive photodetector in the form of a phototransistor, 348a and 348b, such as the SFH901 or SFH902 available from Siemens Optoelectronics Division, Cupertino, CA. The phototransistors 348a and 348b are connected in a circuit (described below) which generates signals responsive to incident light.

Switches 334, 336 are mounted on circuit board 359 and respective traces (not shown) by conventional means such as through holes and solder connections.

Flexible backing layer 344, which can be made of a material (e.g., polyethylene sheet) which is impermeable to the passage of liquid water, forms the top-most layer of drug unit 324. Holes 384a, 384b are provided through backing layer 344 and perforations 382a, 382b through strip 343 in an aligned arrangement. Conductive base rivets 326a, 328a project through openings 384a, 384b and perforations 382a, 382b, respectively, and engage posts 326, 328 to fix backing layer 344 therebetween.

Electrodes 388, 390 are composed of electrically conductive materials such as a carbon powder/fiber loaded polymer matrix, a metal powder loaded polymer matrix or a metal foil. Electrodes 388, 390 make contact with the base rivets 326a, 328a. A carbon filled or silver particle filled conductive adhesive is used to bond electrodes 388, 390 to base rivets 326a, 328a. Electrodes 388, 390 are in electrical contact with reservoirs 399, 401, respectively. An insulating closed cell foam layer 396 has cavities 398, 400 therein, which cavities contain reservoirs 399, 401, respectively. Typically, one of reservoirs 399, 401 is the donor reservoir which contains a liquid solution of the therapeutic agent to be delivered by electrotransport while the other is the counter reservoir which contains a solution of a bio-compatible electrolyte (e.g., saline). The matrix of reservoirs 399, 401 can be a gel.

Transmitting information about drug unit 324, via the optical signal transmitted to reusable electronic controller 322, is accomplished by providing reflective areas 340, 342 with different levels of reflectivity. For example, area 340 may be a standard white having about 90% reflectivity, while area 342 may be a flat black having between about 10 to 15% reflectivity at the wavelength of illumination from the switches 334, 336. With two light reflective surface areas, each area having one of two possible light reflectivities, drug unit 324 may transmit to reusable electronic controller 322 up to four differently coded optical signals based on following "reflectivity code"; (1) a first optical signal when both areas 340 and 342 have low

reflectivities; (2) a second optical signal when both areas 340 and 342 have high reflectivities; (3) a third optical signal when area 340 has a low reflectivity and area 342 has a high reflectivity; and (4) a fourth optical signal when area 340 has a high reflectivity and area 342 has a low reflectivity. The areas 340, 342 may be encoded by simply painting with a paint having suitable reflectivity. The areas 340, 342 may also be encoded by printing or by applying adhesive tape with suitable reflectivity.

An apparatus, e.g., electronic circuitry, which implements the method of regulating the drug delivery of the present invention is installed in the electrotransport drug delivery devices of the present invention described above. More specifically, electronic circuitry fabricated on circuit board assembly 18 of Figure 2, or circuit board 359 of Figure 12, is implemented to regulate the drug delivery of the present invention. The electronic circuitry is referred as a regulator hereinafter.

The regulator initiates the drug delivery only if the delivery device is attached to the patient's skin surface and when the push button switch is pressed in a particular sequence, e.g., a double click. Now referring to the current (i) verses time (t) graph of Figure 4, the regulator then starts a step-up period T_0 , during which the regulator supplies an initial current (i) with a boosted voltage to overcome the high initial skin resistance. The regulator, during the step-up period T_0 , maintains the voltage seen at the skin to be between a maximum (24 V) and a minimum (0 V) to reduce the irritation patient's sensation of the initial applied current. The voltage is supplied by the regulator between two electrodes, for example, 22 and 24 of Figure 2 or 388 and 390 of Figure 12. After the step-up period, the regulator controls the boosted voltage to maintain a delivery current (i_d) during a delivery period (T_d). This provides the steady state operation of the device, providing the drug delivery rate, with a delivery current, provided by a controlled variable voltage.

Even though the initial skin surface resistance is relatively high, after a period of time, the skin resistance drops appreciably. Figure 3 illustrates this characteristic graphically, showing that the decline of skin resistance R is substantially asymptotic to a steady state value. For a discharge rate of 0.1

ma/cm², this steady state value is typically on the order of 20 to 30 kohm-cm², while the initial value of skin resistance is several or many times as much.

When the skin resistance is sufficiently lowered, the anode voltage (V_a) may fall below the battery voltage (V_b). This causes the regulator to enter, at time T1, into an over dose mode during which an excess load current flows through the skin even when the battery voltage is supplied without the boosted voltage. This is shown in Figure 5, where the anode voltage, V_a , is shown on the y-axis, and time (t) is shown on the x axis.

If the over dose mode continues for longer than a first maximum low load detection period, e.g., 10 seconds, then a control enabler, that is an artificial impedance, is serially connected to the skin surface. When the control enabler's impedance value is sufficiently high, it lowers the current supplied to the skin and also enables the regulator to control the load current by the boosted voltage.

Further, if the low load condition of the skin persists, even after connecting the artificial impedance, for longer than a second maximum low load detection period, e.g. 10 seconds, then the regulator cuts off the voltage supplied to the electrodes.

The preceding regulating method is illustrated with reference to Figure 6 which depicts a block schematic of a one apparatus embodiment implementing the method. A regulator 50 includes a controller 53 connected to a battery 51. Controller 53 is also connected to a voltage booster 55, an impedance connecting switch 77, and two terminals of a regulating resistor 59. In this exemplary embodiment an artificial impedance 57 (e.g., a resistor) is serially connected between a cathode electrode assembly 65 and impedance connecting switch 77. However, artificial impedance 57 and impedance connecting switch 77 can be serially connected between voltage booster 55 and an anode electrode assembly 63. This structure is not shown in Figure 6.

Impedance connecting switch 77 connects artificial impedance 57 serially between electrode assembly 65 and regulating resistor 59 only during

an over dosage mode, otherwise switch 77 connects electrode assembly 65 directly to resistor 59.

During a set-up period, controller 53 activates voltage booster 55 to supply boosted voltage across two electrodes 63 and 65 which are attached to a skin surface 61. The boosted voltage is required because, initially, skin surface 61 inhibits the current flowing between electrodes 63 and 65 by having a high resistance value.

During the set-up period and a dose period, a load current flows from electrode assembly 63, through skin 61, to the electrode assembly 65, to regulating resistor 59, and to a system ground port 73. A feedback input port 71 having a sufficiently high resistance prevents the load current from flowing into port 71. The load current path allows controller 53 to monitor the load current between electrodes 63 and 65 using the voltage value sensed at feedback input port 71. In other words, by using the resistance value of regulating resistor 59, which is known in advance, and by using the voltage value at feedback input port 71, controller 53 is designed to determine the current flowing through regulating resistor 59. The determined current is an accurate approximate of the load current.

Using the approximated load current, controller 53 regulates voltage booster 55 to supply sufficient voltage to maintain the dose current. This is accomplished by boosting the supplied voltage by turning on voltage booster 55 when the feedback voltage falls below a target voltage, and by turning off voltage booster 55 when the feedback voltage is equal to or more than the target voltage. When voltage booster 55 is turned off the voltage from battery 51 is supplied without being boosted. The target voltage can be set to be equal to the voltage across regulating resistor 59 when the load current is equal to the dose current.

When the feedback voltage is higher than a preset voltage, then the regulator enters into an over dose mode. The preset voltage can be set such that it precisely determines when the skin resistance is too low to cause the anode voltage to drop below the battery voltage. As an example, the preset voltage can be set to 10% over the target voltage.

After the first maximum low load detection period from an onset of an over dose mode, controller 53, using an impedance switch control 75, causes impedance 57 to be serially connected between electrode assembly 65 and regulating resistor 59. This step stops the over dose current and allows
5 controller to regulate the load current using voltage booster 55.

However, if the over dose mode persists for longer than the second maximum low load detection period, even after serially connecting artificial impedance 57, then controller 53 cuts off the voltage supplied to electrode assembly 63.

10 A voltage limiter 79 is connected between electrode assembly 63 and a terminal of regulating resistor 59 as a safety measure. When the voltage booster builds up more than a safe level, e.g., 25 V, voltage limiter stops further boosting of the voltage supplied to electrode 63.

The apparatus described above with reference to Figure 6 can be
15 implemented in an ASIC or using logic circuits. Further, the embodiment depicted in Figure 6 is only one embodiment, hence the components, controller 53, voltage booster 55, artificial impedance 57, and regulating resistor 59, can be implemented in one integrated circuit or using separate integrated circuits. Implementing the functions of each of the above
20 described components as software modules and programming them into a microprocessor may also embody this invention.

Figure 7 illustrates a detailed schematic diagram of one embodiment depicted in Figure 6. A regulator 100 is electrically connected to a power source in the form of a battery 102, and a voltage controlled electrical junction
25 104 which is connected to an electrode assembly 108. The electrode assembly 108 is attached to one region of a skin surface 110 by conventional devices such as adhesive, straps, belts or the like. The skin surface is shown schematically as a variable resistance load, R_v , to indicate the variation of load resistance typical of the skin when applying electric current I_L , there
30 through. An electrode assembly 112 is similarly attached to another region of skin surface 110.

Electrode assembly 112 is serially connected to a regulating resistor

114. Electrodes 108 and 112, skin surface 110 and regulating resistor 114 form a load current path for conducting the load current, I_L .

A voltage booster 141 includes an energy storage inductor 118 being connected between battery 102 and the anode of rectifying diode 120. The cathode of diode 120 is connected to voltage controlled electrical junction 104. Voltage booster 141 further includes a filter capacitor 122 being connected to junction 104 and a controlled switch 124, having a control input 126. Controlled switch 124 has one terminal 128 connected to the junction of the anode of diode 120 and inductor 118, and another terminal 130 connected to the system ground. Control input 126 can alternately open and close switch 124 creating a low resistance connection between terminals 128 and 130, thereby connecting or disconnecting the inductor 118 through a low resistance path to the system ground. Switch 124 may be an electronic switch device such as a bipolar or field effect transistor (FET).

A control circuit 132 has a control output 134 connected to switch control input 126. Control circuit 132 includes a feedback input 133 for controlling the control output 134 and a ground input 136.

Regulator 100 is provided with a microcontroller 138. Microcontroller 138 is idle until a threshold voltage is seen at regulating resistor 114. This threshold voltage develops when the controller is attached to a patient and a variable skin resistance develops between electrode assemblies 108 and 112. Microcontroller 138 uses an internal counter and software routine to time a low current delivery, e.g., 0.1mA. This time duration is programmable. After this time has expired, microcontroller 138 then delivers a dose current, e.g., 0.5mA, for a second programmable time period. Microcontroller 138 can deliver another dose current, e.g., 0.1mA, for a third programmable time period. The time periods may vary from 0 seconds to a time determined by the limitations of microcontroller 138 memory or battery life.

In addition, microcontroller 138 receives feedback at input 140 which senses the current I_L through the skin 110, by sensing voltage drop of regulating resistor 114, and compares the sensed voltage drop against a preset limit therefor. Microcontroller 138 also receives an input 142 which

senses the voltage drop accross the skin 110 and compares the sensed voltage against a preset maximum limit therefor. An artificial impedance includes a control enabling resistor 123, which is serially connected between a control enabling switch 127 and electrode assembly 112. Control enabling switch 127 is controlled by load control output 135 of microcontroller 138.

When the feedback voltage sensed by microcontroller 138 at feedback input 140 is higher than the preset voltage limit for longer than a predetermined time, then control enabling switch 127 connects control enabling resistor 123 to regulating resistor 114. When the high feedback voltage condition persists even after connecting control enabling switch 127 is closed, then microcontroller shuts down control circuit 132 and also stops load current I_L . At other times, load switch connects electrode assembly 112 directly to regulating resistor 114.

The microcontroller 138 monitors the resistance of the skin 110 by the voltage input 142 and the current input 140 and shuts down the voltage boosting function of regulator 100 when the resistance of skin 110 exceeds a predetermined upper limit or decreases below a predetermined lower limit in accordance with stored programs. The first maximum low load detection period and the second maximum low load detection period mentioned above are measured by microcontroller 138, e.g., by tracking the number of timer overflow interrupts.

Microcontroller 138 also monitors system events. A low battery signal from control circuit 132 (not shown in Figure 7) notifies microcontroller 138 of a low battery condition. Microcontroller 138 then causes an LED (light emitting diode, not shown in Figure 7) to flash notifying the caregiver.

Normal operation of voltage boost circuit 141 in connection with other circuits of regulator 100 can be understood with reference to Figure 8. After initiation of regulator 100, for example, by a push button switch 12 illustrated in Figure 1, control circuit 132 is adapted to first connect input 136 to system ground. This enables regulating resistor 114 to begin conducting load current, I_L , from load 110.

Control circuit 132 is configured to toggle control output 134 so that

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switch 124 connects the one end of inductor 118 to ground for a period of time T_1 . During the time T_1 , the inductor current I_L , driven by battery 102, increases to a maximum value, I_p . Here, T_1 is a part of the set-up period.

At the end of time T_1 , the control circuit is adapted to change output 134 to toggle switch input 126 again which opens switch 124 for a time period, T_2 . During T_2 , the inductor current, I_L , will not flow toward ground, but is forced to conduct through diode 120 into electrical junction 104. Filter capacitor 122 provides a low impedance path for the instantaneous current, I_L , which then decays toward zero during the time period T_2 , as the voltage at electrical junction 104 is boosted by the charging of capacitor 122. Here, T_2 is another part of the set-up period.

During the time T_1 , inductor 118 stores energy by charging with the current. During the period T_2 , inductor 118 discharges energy into filter capacitor 122 through diode 120. Inductor 118 thereby transfers energy from battery 102 into capacitor 122 with low loss, limited only by the voltage drop across diode 120 and the negligible series resistance of inductor 118, battery 102 and the electrical connections. Thus, the energy source for load current I_L is not directly the battery 102 but rather either capacitor 122 (i.e., during time T_1) or a combination of the capacitor 122 and inductor 118 (i.e., during time T_2).

Control circuit 132 is adapted to repeat the T_1 , T_2 cycle indefinitely or when stopped as described below. The voltage, V_w , at junction 104 is thereby boosted to an adjustable multiple of battery 102 voltage depending on the values of the time periods T_1 and T_2 . The voltage boost thus can be adjusted by adjusting the values of T_1 and T_2 .

Dotted lines in Figure 8 indicate missing or delayed pulses as controlled by the control circuit 132. This may occur when pulses are not necessary to replace charge depleted from the capacitor 122, for example, when the therapeutic current, I_L , demanded is relatively low. The dotted lines in Figure 8 indicate that the voltage boost control may be by pulse width modulation (PWM), pulse frequency modulation (PFM), pulse skipping, or some combination thereof.

The adjustable working voltage, V_w , causes the load current I_L to flow through skin surface 110, through regulating resistor 114 to the system ground at switch input 136.

Feedback input 133 senses the voltage across regulating resistor 114 caused by the load current, I_L . Control circuit 132 is adapted to respond to feedback input 133 to regulate the working voltage either boosting, V_w , by adjusting the time periods, T1 and T2 or connecting load resistor 123 by controlling loading switch 127. This is accomplished by comparing the voltage sensed at input 133 with set reference voltages within control circuit 132, e.g., the target voltage.

If the voltage sensed at input 133 is less than a first reference voltage, then control circuit 132 opens and closes switch 124 at a high frequency until V_w is boosted to the appropriate level. In general, the longer switch 124 is closed (i.e., the longer is T1), the greater the voltage which is developed in inductor 118 and the greater the voltage boost. Battery 102 voltage can be boosted by reason of inductor 118. The voltage (V_{ind}) developed in inductor 118 is equal to the inductance value (L) multiplied by the rate of change of the current flow through the inductor:

$$V_{ind} = L * (d_i/dt) \quad \text{Eq. 1}$$

Thus, a higher voltage (which is determined in part by the inductance value of inductor 118 and in part by the rate of change of current flow through inductor 118, which is controlled by the values of T1 and T2) is output from inductor 118 at a lower current, since the power into inductor 118 must equal the power out of inductor 118.

Electrode assemblies 108 and 112, and thus skin surface 110, are not exposed to high peak voltages, but instead experience only the minimum, constant value sufficient to drive the desired load current I_L .

The time periods T1 and T2 are adjusted by the control circuit 132 to boost V_w to the minimum absolute value to provide the load current I_L , to maintain a desired predetermined value. If the resistance of the skin surface

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110 is too high to allow the predetermined value of I_L to be attained without having V_w exceed a safe level, then a voltage limiting device, such as a zener diode 116 connected across the electrode assemblies 108 and 112, limits the voltage applied to skin 110. A typical safe maximum limiting value for V_w is about 24 volts. Other values of limiting voltage can be achieved by zener diodes 116 having different breakdown voltages, or by using other protection as described further below.

Once the resistance of skin surface 110 decreases sufficiently to allow the load current, I_L , to reach the desired predetermined level at the maximum safe voltage, the control circuit 132 will respond to the feedback at feedback input 133 and will adjust T1 and T2 to boost V_w to a multiple just sufficient to maintain the current at the predetermined level. Further, when the skin resistance becomes too low so that the load voltage falls below the battery voltage, control enabling resistor 123 is serially connected to allow controller to regulate the load voltage using voltage booster 141.

The working voltage, V_w , at the controlled electrical junction 104 is thus boosted to a boost multiple of the battery 102 voltage just sufficient to maintain the load current, I_L , at the predetermined value as long as the load voltage is less than the limiting voltage set by the zener diode 116.

The low loss transfer of energy from the battery 102 to the skin 110 and capacitor 122 maximizes the useful life of the battery 102, for a given battery capacity. This allows smaller batteries to be used for a given therapeutic regimen, or extends the lifetime of therapeutic treatment at a given cost.

The predetermined current applied across skin 110 may be constant or varying with time in accordance with a current-time profile. In either event, the control circuit 132 establishes a predetermined current-time profile to be applied. This may be accomplished by means well known in the art, such as a differential comparator having one input connected to the regulating resistor 114, a constant reference voltage connected to the other input, or having the other input connected to the output of a D to A converter driven by a clocked ROM having a pre-programmed pattern (not shown in Figure 6).

The control circuit 132 is additionally adapted such that, in combination with the values of inductor 118, the value of the load resistance across skin 110, the capacitance value of capacitor 122, the time periods, T1, T2, and load resistor 123 are arranged in response to the voltage at feedback input 5 133 such that filter capacitor 122 smooths and adjusts the voltage V_w , to provide a load current, I_L , of an essentially constant (DC) current of predetermined value.

Figure 13 is a schematic diagram of an alternate drug delivery 10 regulator circuit 400. Regulator 400 is similar to the drug delivery regulator circuit 100 described above with reference to Figure 7, where like elements are numbered similarly. Referring to regulator circuit 100 of Figure 7, microcontroller 138 detects a decrease in the skin resistance between electrodes 108 and 112. When the skin resistance approaches a first pre- 15 determined minimum resistance, switch 127 is activated to couple resistance 123 in series with electrode 112 and resistor 114. As such, the resistance between node 102 and input 136 of control circuit 132 is increased. It will be appreciated that this combined resistance can be further reduced below the first pre-determined minimum resistance. For example, the skin resistance 20 may decrease to substantially zero ohms. Regulator circuit 100 is shut off when this condition is experienced. An alternate embodiment of a drug delivery regulator 400 (Figure 13) compensates for skin resistance which is reduced below the first pre-determined minimum resistance.

The drug delivery regulator circuit 400 includes battery 102, voltage 25 booster circuit 141, electrodes 108 and 112, microcontroller 138 and control circuit 132. The regulator circuit also includes a variable resistor 402, and resistor control circuit 404. The variable resistor can be, in one embodiment, a field effect transistor (FET) having a channel resistance and the resistor control circuit 404 can be an operational amplifier (op-amp) coupled to a gate 30 electrode of the FET. Referring again to regulator 100, as described above with reference to Figure 7, capacitor 122 in combination with the series resistance defined through skin 110 and resistor 114 form an RC circuit.

When the skin resistance decreases too low, such that a voltage at node 104 falls below the battery voltage, resistor 123 is coupled in series with the skin resistance and resistor 114 to effectively increase the resistance of the RC circuit. If the skin resistance continues to decrease, it is possible that node 104 can again fall below the battery voltage. To alleviate this potential problem, regulator 400 includes a variable resistance 402.

In operation, during times T1 and T2 when a current is conducted through the skin, a voltage drop is provided across resistor 114. In effect, a resistor divider circuit is provided by the skin resistance, variable resistor 402 and resistor 114. The value of the skin resistance and the resistance through variable resistor 402, therefore, determine the voltage at node 408. Operational amplifier 404 receives an input voltage from microcontroller 138 via output node 135. When a voltage at node 408 exceeds the voltage provided at node 135, the operational amplifier adjusts a control voltage provided to variable resistor 402. In one embodiment where variable resistor 402 is a field effect transistor, operational amplifier 404 reduces the gate voltage such that a resistance across the transistor source and drain is increased. It will be appreciated by those skilled in the art, that proper selection of the FET allows the regulator to provide a constant current between electrodes 108 and 112 even when the skin resistance approaches zero. The regulator of Figures 7, 9 and 13 include a variable resistance circuit 101. This circuit allows the regulator to vary a resistance path through the electrodes. Each embodiment allows the control circuitry 132 and 138 to control a series resistance. In Figures 7 and 9 include different resistance paths, while the embodiment of Figure 13 includes a variable resistance circuit. The variable resistance circuit 101 is shown in Figure 7 as having either a low resistance path (essentially zero ohms) or resistor 123 coupled in series with the load resistance. Figure 9 illustrates a variable resistance circuit 101 which has both the low resistance path (through switch 274) and resistor 272 coupled in parallel to form a low resistance path. Thus, those skilled in the art, having the benefit of the present disclosure, will appreciate different ways to implement the variable resistance circuit.

Figure 9 shows a variation of the embodiment of the regulator for the present invention depicted in Figure 7. A regulator circuit 200 includes a battery 202, an inductor 204, a diode 206, a voltage controlled electrical junction 207, a low resistance filter capacitor 208, and electrode assemblies 210, 212 which are attached by conventional means to spaced apart regions of skin surface 213. Skin surface 213 is represented schematically as a variable load resistance R_v to emphasize the fact that the resistance of the skin 213 does vary with time and current. At least one of the electrode assemblies 210, 212 contains a therapeutic agent in a form suitable for electrotransport delivery into skin surface 213.

Regulator 200 includes an N-channel field effect transistor (FET) switch 218, for switching inductor current I_L , an inductor current sense resistor 220, and a regulating resistor 214. The circuit also includes a high efficiency, adjustable DC-DC step-up controller 216.

An adjustable DC-DC step-up controller 216 can be the Maxim MAX773 controller made by Maxim Integrated Products, Inc. of Sunnyvale, CA. Figure 9 also shows a simplified schematic of the MAX773 controller which is sufficient for purposes of the present invention. A more detailed schematic of the MAX773 controller can be found in the MAX773 data sheet 19-0201; Rev 0; 11; 93, incorporated herein by reference. A simplified block diagram version of the MAX773 data sheet information is shown in Figure 9. The MAX773 controller 216 includes a reference voltage pin 256, a ground pin 258, a feedback input 264, a shut down input 266, a current sense input 268, and a power bus input 270.

MAX773 controller 216 also includes a first two-input comparator 230 having an output 231, a second two-input comparator 232 having an output 233, a first reference voltage 242, a second (e.g., 1.5 volt) reference voltage 244, a PFM/PWM driver circuit 240 having a switch control output 252, and a switch control output 254.

In addition, regulator 200 includes a boost monitoring comparator 273, an over voltage monitoring comparator 275, control enabling switch 274, a control enabling resistor 272, and a cut-off switch 276. A microcontroller (not

shown in Figure 9) is also included in regulator 200. A boost monitoring signal 277, an over voltage monitoring signal 279, a feedback signal 265 and a pair of reference voltages (not shown in Figure 9) are connected to the microcontroller as inputs thereto. In turn, the microcontroller controls the control enabling switch 274, cut-off switch 276, and a shut-down signal 271.

A microcontroller for the present invention can be the PIC16C620-SSOP microcontroller, available from Microchip Technology, Inc. of Chandler, AZ. This microcontroller is discussed in more detail in the PIC 16/17 Microcontroller Data Book, May 1995, pages 2-203 through 2-212, which are incorporated herein by reference. Normal operation of regulator 200 can be understood by reference to Figure 9 and Figure 10. The circuit 200 uses the MAX773 controller 216 to provide a high efficiency conversion of energy from the battery 202 into an adjustably boosted voltage V_w at the voltage controlled electrical junction 207, and simultaneously control the load current I_L .

Unlike traditional pulse frequency (PFM) converters, which use an error voltage from a voltage divider circuit to control the output voltage of the converter to a constant value, MAX773 controller 216 is connected to use regulating resistor 214 to generate an error voltage to control the average load current I_L . MAX 773 controller 216 also operates with high frequencies, (up to 300 kHz) allowing the use of small external components.

With reference to Figure 9, in accordance with this invention, a portion of the load current I_L is fed back to feedback input 264. Electrode assemblies 210 and 212 are attached to skin surface 213 which is represented as a variable resistance load. MAX773 controller 216 is an integrated circuit having internal components connected by conductive traces formed during the integrated circuit manufacturing process. External pins are provided for electrical connection to external components by conventional printed circuit features such as plated or deposited copper or other conductors deposited and formed on insulating substrates. Reference to electrical connections in the description herein are understood to be internal or external as shown in Figure 9. References to the components of the MAX773 controller 216 circuit

are illustrative for the purposes of describing the function of circuit 216.

One terminal of regulating resistor 214 is connected to feedback input 264. This same terminal of regulating resistor 214 is also connected to electrode assembly 212 for receiving the load current I_L . The other terminal of regulating resistor 214 is connected to the system ground. Input 264 connects to the inverting input of comparator 232. Non-inverting input of comparator 232 is connected to reference voltage 244. Output 233 of comparator 232 is connected to PFM/PWM driver circuit 240.

Output 231 of comparator 230 is connected to PFM/PWM driver circuit 240. Inverting input of comparator 230 is connected to reference voltage 242. Non-inverting input of comparator 230 connects to current sense input 268. Input 268 is connected to one terminal of inductor current sense resistor 220. The other terminal of resistor 220 connects to the system ground. The ground pin 258 of the MAX773 controller 216 is also connected to the system ground.

One output of PFM/PWM driver circuit 240 connects to output 252. Input 270 is connected to one terminal of battery 202. The other terminal of the battery 202 is connected to the system ground. One output of PFM/PWM driver circuit 240 connects output 254. Outputs 252 and 254 are both connected to the gate of the external N-channel switch 218. The drain of the switch 218 is connected to a joint connection of one end of energy storage inductor 204 and the anode of rectifying diode 206. The source of switch 218 is connected to the one terminal of inductor current sense resistor 220 which is connected to current sense input 268.

The other terminal of the inductor 204 is connected to power bus input 270 and to the terminal of battery 202. A filter capacitor 276 is connected between input 270 and the system ground. A filter capacitor 278 is connected between voltage pin 256 and the system ground. Filter capacitors 276 and 278 have low dynamic impedance at the pulse frequencies of interest.

Cathode of diode 206 is connected to an electrical junction 207. Junction 207 is also connected to one terminal of a filter capacitor 208, the

cathode of a zener diode 280 and electrode assembly 210. The anode of zener diode 280 and the other terminal of capacitor 208 are connected to ground. Junction 207 completes circuit 200 which boosts the working voltage, V_w , at junction 207 by an adjustable multiple of the voltage of the power source, i.e., battery 202. Zener diode 280 limits the peak voltage across the electrode assemblies 210 and 212, and thus the maximum voltage experienced by the skin 213.

With reference to Figure 9 and Figure 10, normal operation of regulator 200 can be understood. When power is applied by battery 202 to power bus 262 via power input 270, and shut-down input signal 271 is of the correct logic level, the MAX773 controller 216 and the microprocessor begin operating.

As with traditional PFM converters, switch 218 is not turned on until voltage comparator 232 senses that the output current is out of regulation. However, unlike traditional PFM converters, the MAX773 controller 216 uses the combination of the peak inductor current limit sense resistor 220, reference voltage 242 and comparator 230 along with the maximum switch on-time and minimum switch off-time generated by PFM/PWM driver circuit 240; there is no oscillator. The typical maximum switch on-time, T_1 , is 16 micro seconds. The typical minimum switch off-time, T_2 , is 2.3 micro seconds.

Once off, the minimum off-time holds the switch 218 off for time T_2 . After this minimum time, the switch 218 either (1) stays off if the output current I_L is in regulation, or (2) turns on again if the output current I_L is out of regulation.

While switch 218 is off, the inductor current I_L flows through diode 206 into capacitor 208 at junction 207, replenishing any charge drawn off by skin 213. It can be seen that this method of switching the charging current I_L provides an adjustable boost multiple of battery 202 voltage to a working voltage V_w at junction 207, just sufficient to supply the desired constant current I_L . The peak voltage delivered by inductor 204, will be just that required to overcome the diode drop of the diode 206 and the working voltage V_w and thus minimizes energy loss from the battery 202.

The MAX773 controller 216 circuitry allows circuit 200 to operate in continuous-conduction mode (CCM) while maintaining high efficiency with heavy loads. When power switch 218 is turned on, it stays on until either (1) the maximum on-time turns it off (typically 16 microseconds later), or (2)
 5 inductor current I_L reaches the peak current limit I_p set by the inductor current limit resistor 220, reference voltage 242 and comparator 230. In this event, the on time will be less than the maximum on time, T_1 . Limiting the peak inductor current, to a predetermined maximum, I_p , avoids saturating inductor 204 and allows the use of smaller inductor values, thus smaller components.

10 The average load current I_L is equal to the value of reference voltage 244 V_{ref} divided by the value of regulating resistor 214 R_s , that is:

$$I_L = V_{ref} / R_s$$

Eq. 2

15 If the average load current I_L is below the desired value as set by the value of reference voltage 244 V_{ref} and the value of regulating resistor 214 R_s , then PFM/PWM driver circuit 240 will automatically adjust the on time T_1 and off time T_2 , and alternately turn the switch 218 on and off, until load current I_L is at or above the desired value.

20 During the normal operation, the current flows from the boosted voltage at electrode assembly 210 through the variable skin resistance R_v to electrode assembly 212, through control enabling switch 274 to cut-off switch 276, and finally, to regulating resistor 214. Thus, in normal operation, both switches 274 and 276 are closed and current flows through control enabling
 25 switch 274, bypassing control enabling resistor 272.

The current delivered through electrode assemblies 210 and 212 is regulated by the MAX773 controller 216 maintaining a voltage, e.g., 1.5V, across regulating resistor 214. For example, when MAX 773 controller 216 controller maintains 1.5V across regulating resistor 214, e.g., 1.5 KW, the
 30 regulated current is $(15/15000 = 0.1mA)$.

However, if the variable skin resistance R_v between electrodes 210 and 212 falls low enough that the voltage seen at feedback input 264 of the

MAX773 controller 216 rises above a reference voltage, e.g., 1.5V, Max773 controller 216 does not provide a boosted voltage and thus the current is not regulated and causes the entire battery voltage (battery 202) minus voltage drop of diode 206 to be applied to electrode assembly 210 causing boost monitoring comparator 273 to be activated. Regulator 200 then goes into an over dose mode. When the over dose mode continues longer than a preset period, e.g., the first maximum low load detection period, measured by the microcontroller, the microcontroller turns off control enabling switch 274. The current is then forced to flow through the additional impedance of control enabling resistor 272. This additional (or artificial) load, added in series with the variable skin resistance, insures a regulated current from electrode 210 to electrode 212 even if the skin resistance falls to 0W. However, if the over dose condition continues for longer than another preset period, e.g., the second maximum load detection period, measured by the microcontroller, then the microcontroller opens the cut-off switch 176 thereby cutting off the load current I_L .

In alternate embodiments of this invention, the current I_L may be programmed to follow a predetermined profile by programming the value of the load current through regulating resistor 214. Regulating resistor 214 value may be programmed by switching additional resistors in parallel or series with the load current I_L .

Although this invention has been described with some particularity in respect to embodiments thereof which, taken together, comprise the best mode known to the inventors for carrying out their invention, many changes could be made, and many alternative embodiments could thus be derived without departing from the scope of the invention. Consequently, the scope of the invention is to be determined only from the following claims.

For example, in the present invention, the electrotransport controller may also be disposable. Also, the functions executed in the embodiments herein by circuits (see Figures 7 and 9) may alternatively be done by software in programmable components, in a digital environment.

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CLAIMS:

1. An electrotransport transdermal agent delivery regulator comprising:

5 a voltage booster circuit coupled to a first electrode for providing a load voltage to the first electrode;

control circuitry coupled to the voltage booster circuit for regulating the load voltage in response to a load resistance between the first electrode and a second
10 electrode; and

a variable resistance circuit coupled in series with the load resistance,

wherein the variable resistive circuit is coupled to the control circuitry for adjusting a current through the
15 load resistance, and

wherein the variable resistive circuit comprises:

a first current path having a first resistance;

a second current path having a second resistance;

and

20 a switch circuit coupled to the first and second current paths for selectively coupling either the first or second resistance in series with the load resistance in response to the control circuitry.

2. The electrotransport transdermal agent delivery
25 regulator of claim 1 wherein the second resistance is greater than the first resistance.

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3. The electrotransport transdermal agent delivery regulator of claim 1 wherein the second current path is defined by a resistor having the first resistance coupled in parallel with a switch of the switch circuit to provide the
5 second resistance.

4. The electrotransport transdermal agent delivery regulator of claim 1 wherein the voltage booster circuit comprises:

an inductor circuit coupled to a power supply; and

10 a capacitor coupled to the inductor circuit,
wherein the control circuitry controls the inductor circuit to generate a peak current, and the control circuitry selectively couples the inductor circuit to the capacitor to discharge the peak current and charge the capacitor to the
15 load voltage.

5. An electrotransport transdermal delivery regulator delivering a beneficial agent through an animal skin surface by supplying a load voltage and load current across a first electrode assembly and second electrode assembly using an
20 electrical power source, the regulator comprising:

a controller;

a voltage booster electrically connected to the controller, the electrical power source and the first electrode assembly;

25 a control enabler electrically connected to the second electrode assembly;

a control enabler switch for adjusting the load current, the control enabler switch being connected to the controller and capable of being connected to the second

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electrode assembly or the control enabler, the control enabler switch being controlled by the controller; and

a sensor connected to the controller and the control enabler switch, wherein the controller determines a
5 feedback value from the sensor and the controller regulates the load voltage using the voltage booster, the control enabler, the control enabler switch and the feedback value.

6. The regulator of claim 5, wherein the controller regulates the load voltage to make the load current to
10 follow a predetermined current-time profile.

7. The regulator of claim 5, wherein the control enabler switch connects the second electrode assembly to the sensor, and a closed electrical circuit is established from the electrical power source to the controller via the
15 voltage booster, the two electrode assemblies and the sensor without the control enabler being connected.

8. The regulator of claim 5, wherein the controller determines at least one of the load voltage, the load current and an electrical resistance of the animal skin
20 surface from the feedback value.

9. The regulator of claim 5, wherein the controller boosts the load voltage using the voltage booster when the feedback value is lower than a target value.

10. The regulator of claim 5, wherein the control enabler switch connects the control enabler serially between
25 the second electrode assembly and the sensor when the feedback value is higher than a predetermined value for longer than a first predetermined period.

11. The regulator of claim 10, wherein the controller
30 shuts off the load voltage when the feedback value is higher

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than the predetermined value even after the control enabler is connected serially for longer than a second predetermined period.

12. The regulator of claim 5, further includes a voltage limiter connected between the first electrode assembly and the sensor for limiting the load voltage to a predetermined value.

13. The regulator of claim 5, wherein the sensor includes a resistor.

14. The regulator of claim 5, wherein the control enabler is an artificial impedance.

15. The regulator of claim 5, wherein the voltage booster includes:

an inductor coupled to the electrical power source; and

an inductor switch connected to the inductor and a capacitor, the inductor switch being coupled to and controlled by the controller, wherein the controller controls the inductor switch to connect the inductor to the electrical power source, thereby charging the inductor to a peak instantaneous current, and then to connect the capacitor to the inductor for discharging the current in the inductor into the capacitor.

16. An electrotransport transdermal delivery regulator comprising:

a controller;

a voltage booster connected to the controller, an electrical power source and a first electrode assembly, the voltage booster comprising:

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an inductor coupled to the electrical power source; and

an inductor switch connected to the inductor and a capacitor, the inductor switch being coupled to and
5 controlled by the controller;

a controllable impedance connected to a second electrode assembly, the controllable impedance provides first or second impedance paths in series with the first and second electrode assemblies in response to the controller;
10 and

a voltage limiter connected to the first electrode assembly for limiting a load voltage to a predetermined maximum value.

17. Use of the electrotransport transdermal agent
15 delivery regulator as defined in any one of claims 1-16 for delivering a beneficial agent through an animal skin.

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PATENT AGENTS

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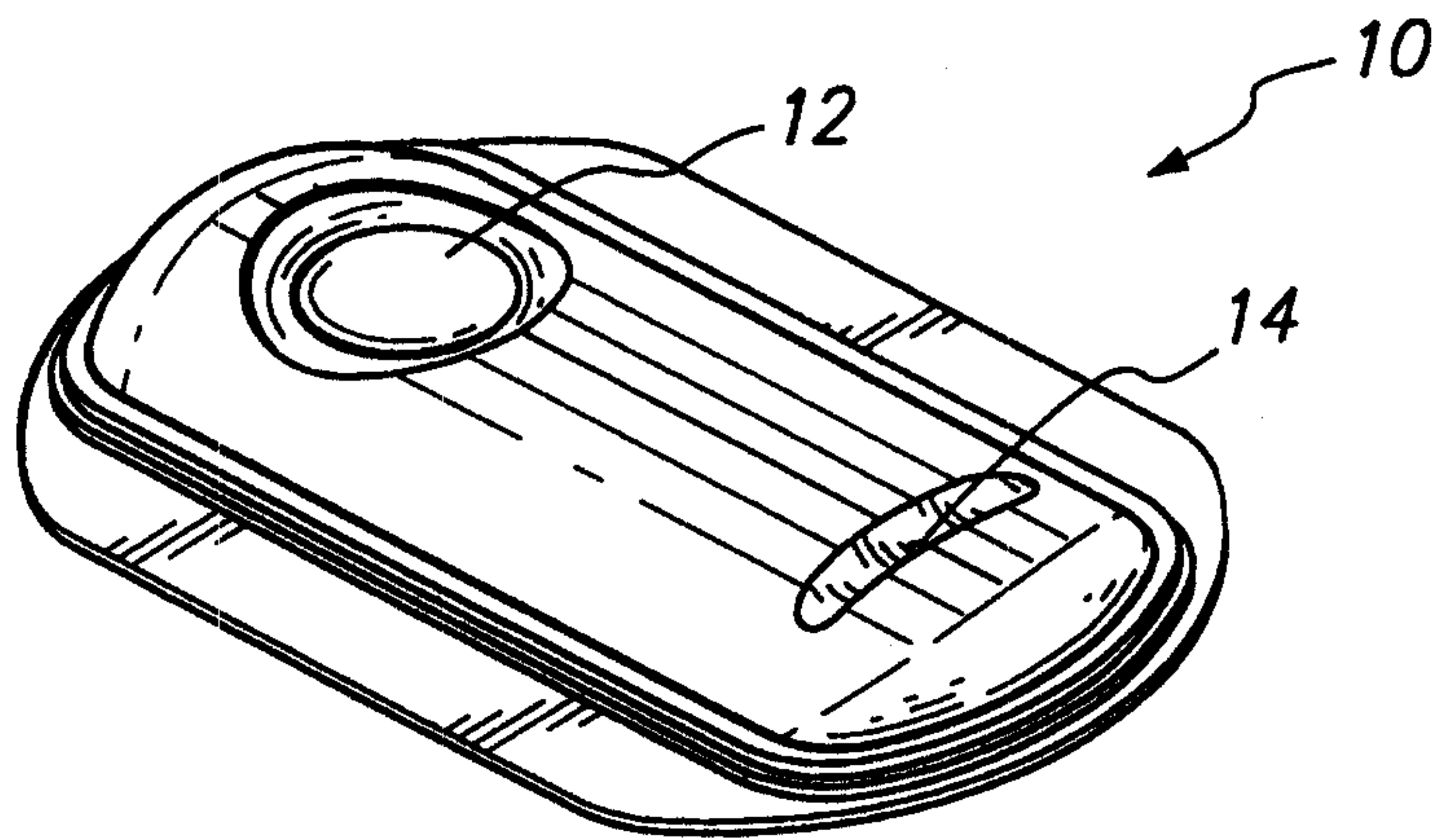
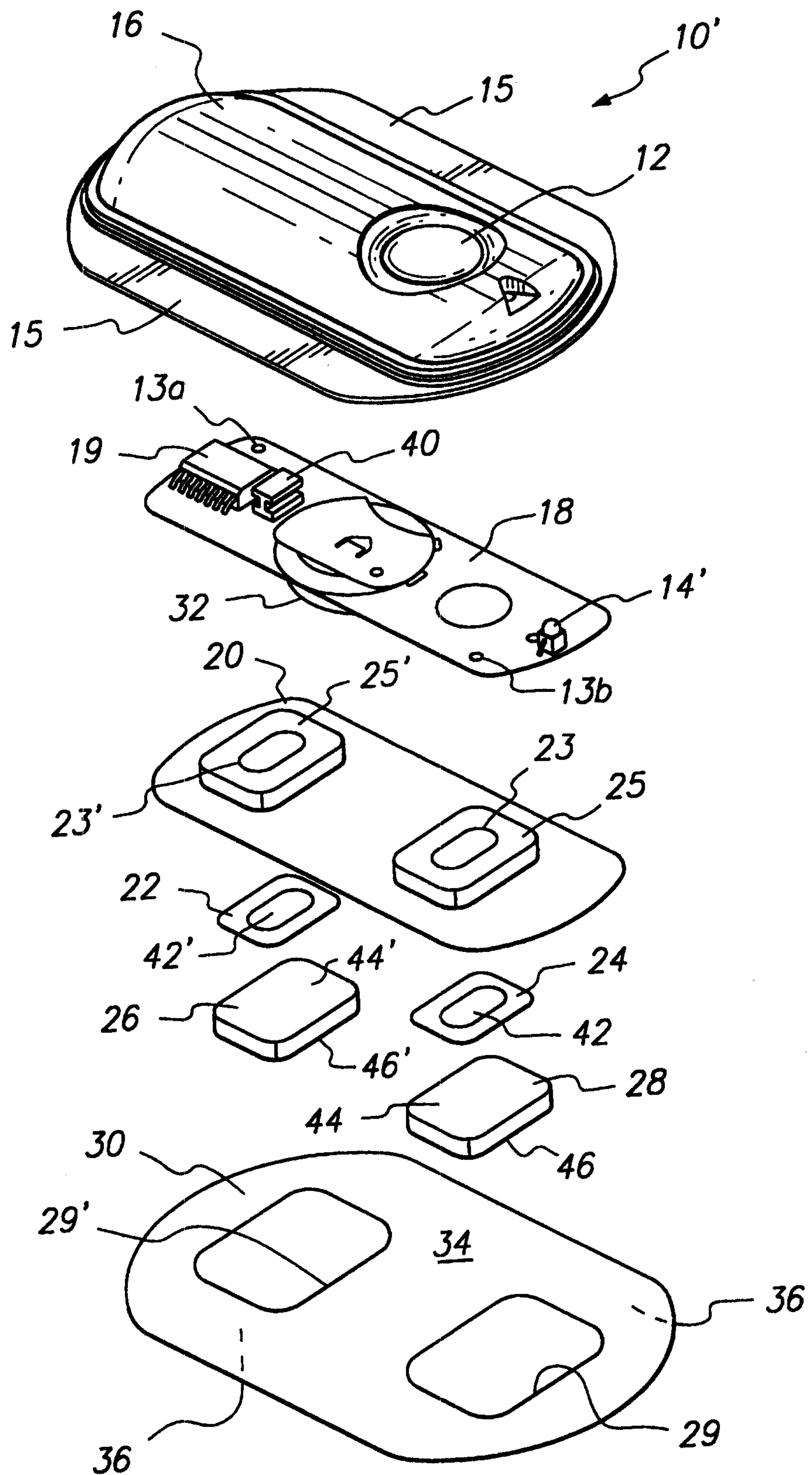


FIG. 1

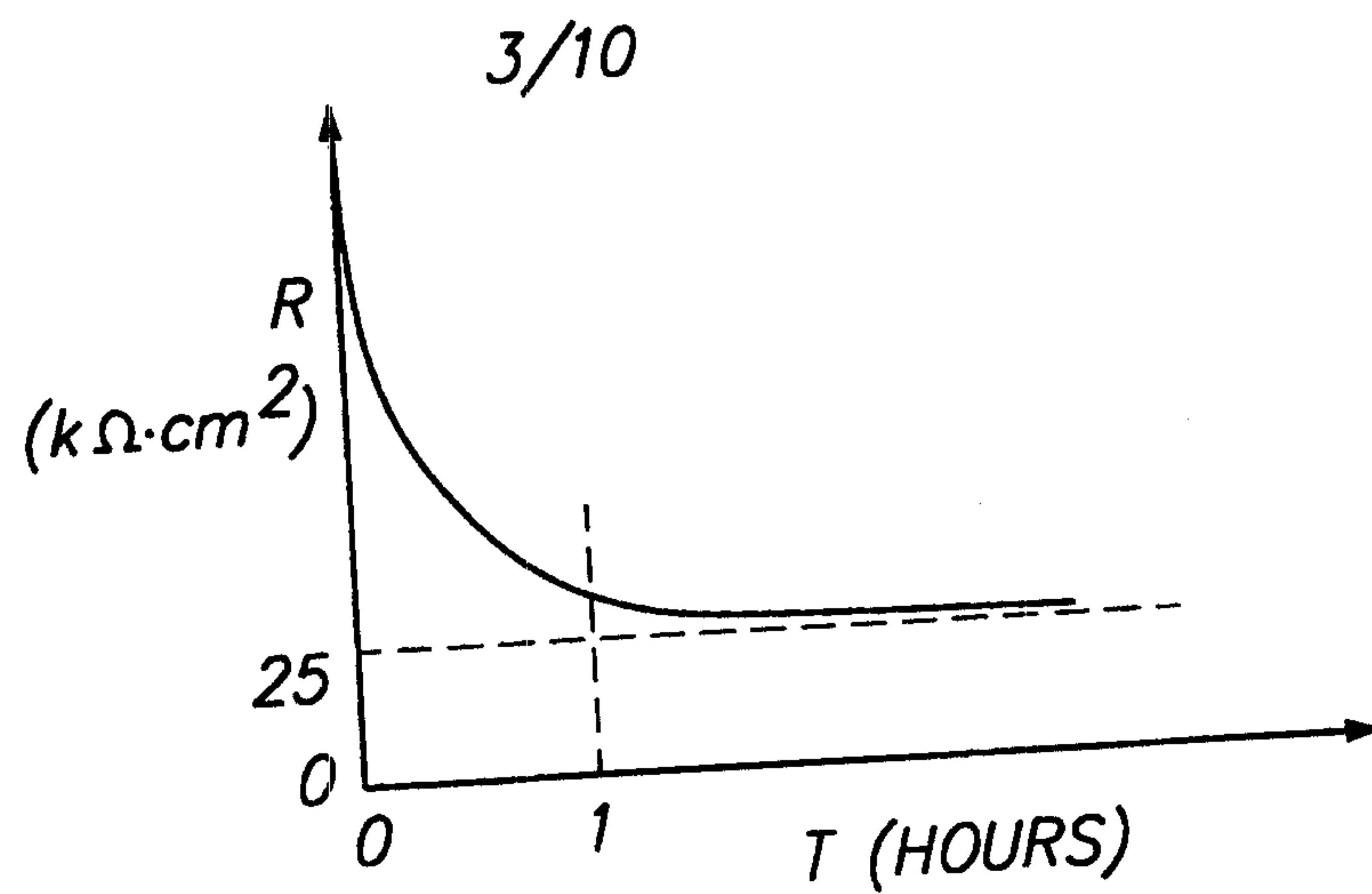
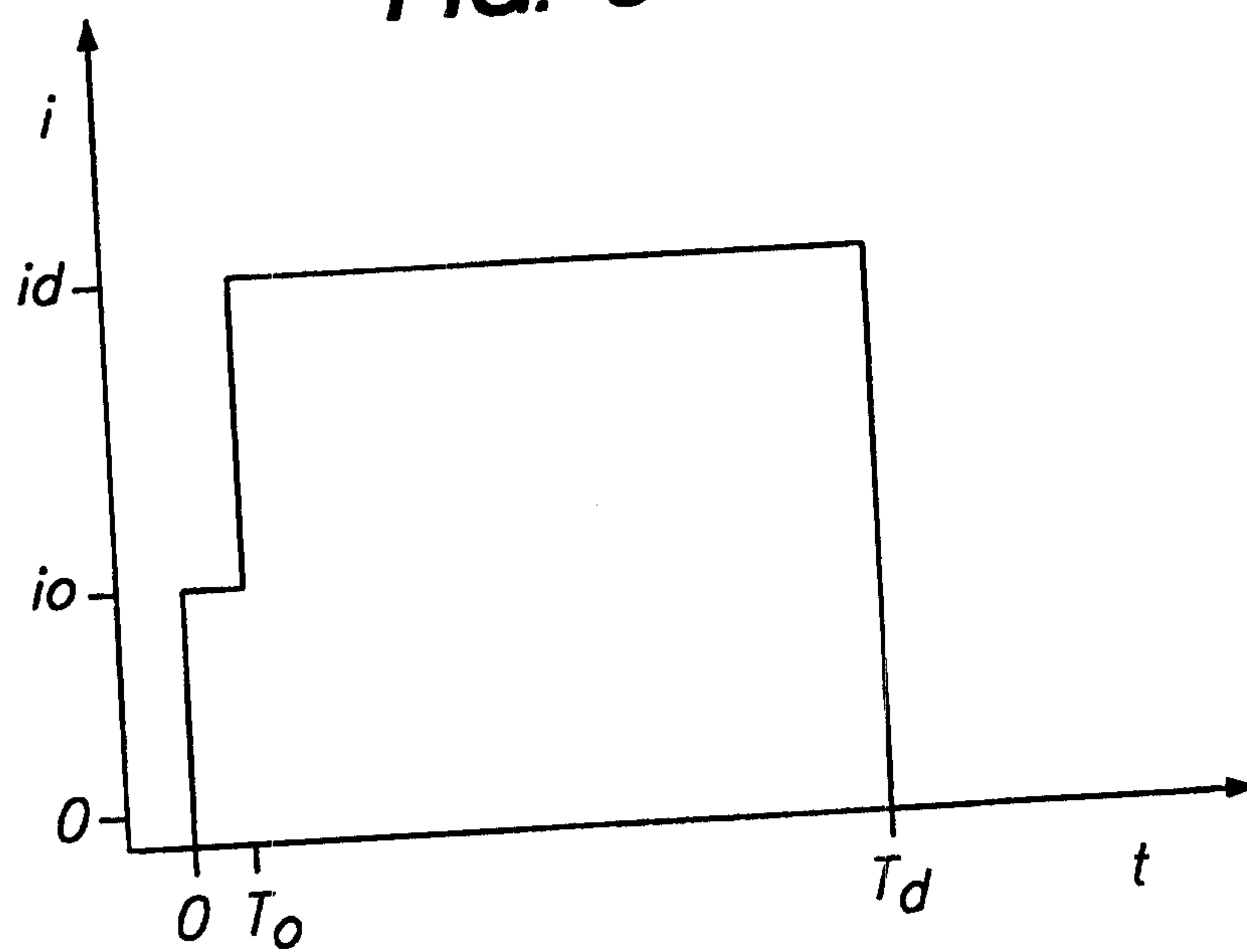
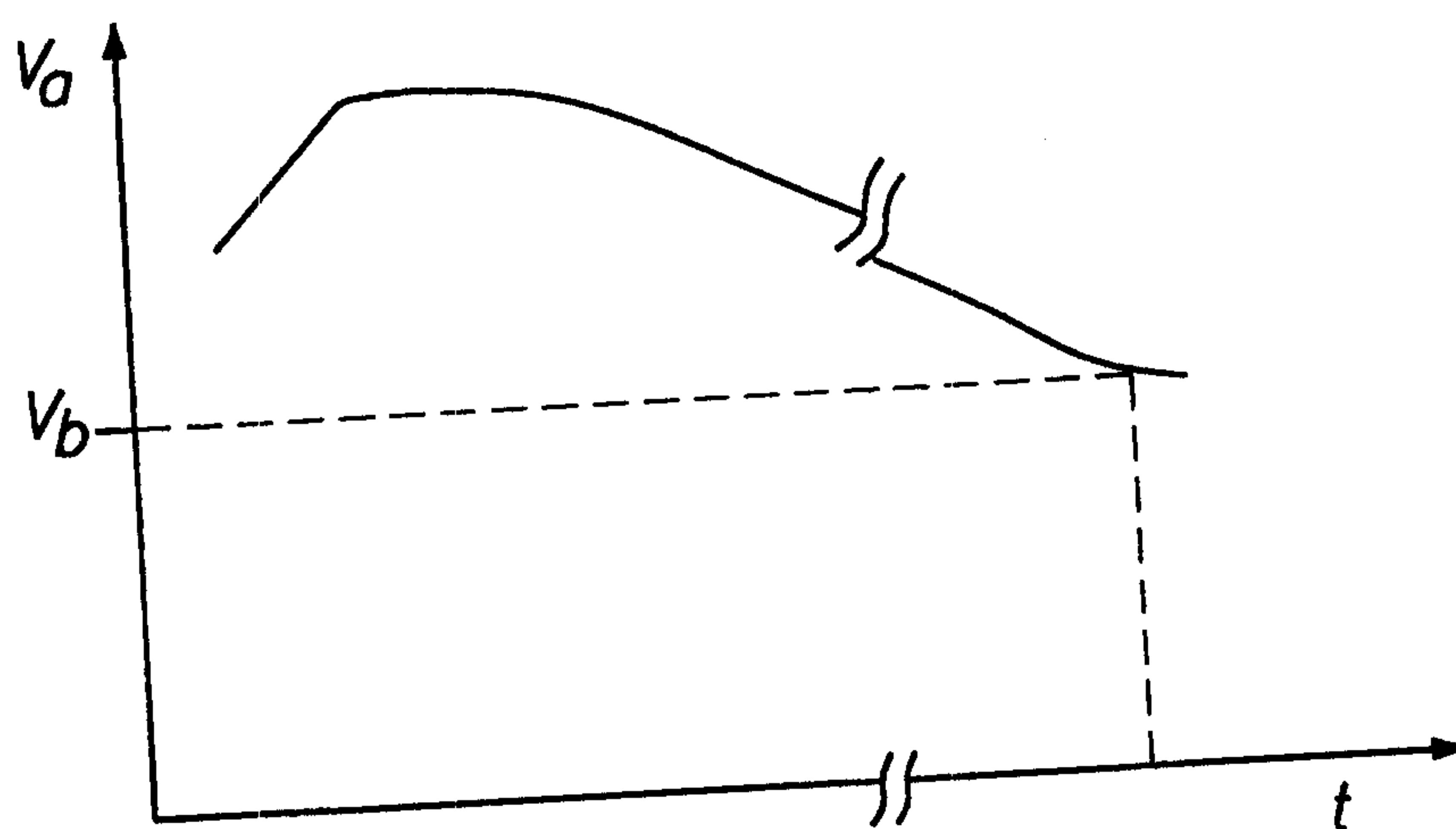
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FIG. 2

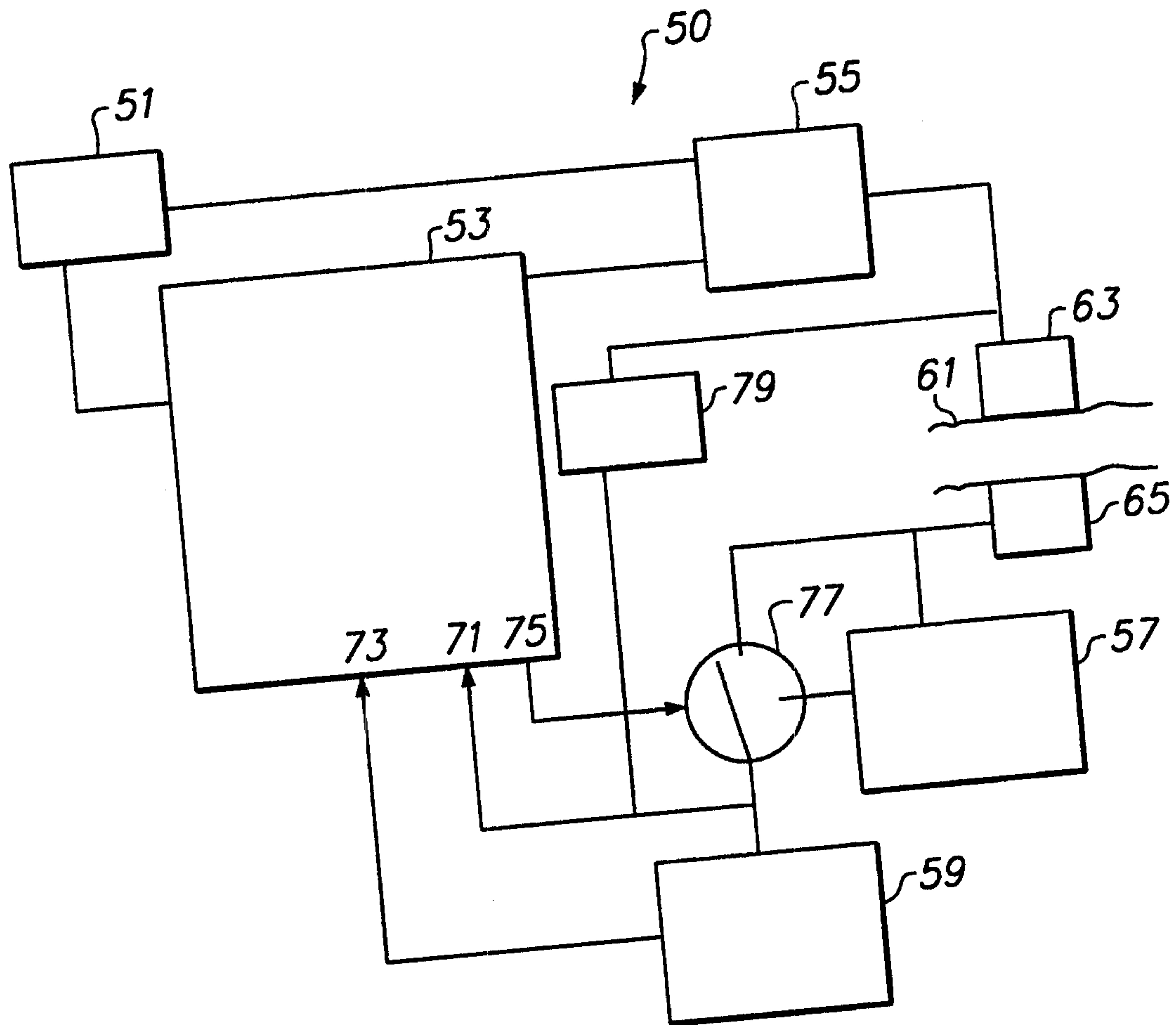


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**FIG. 3****FIG. 4****FIG. 5**

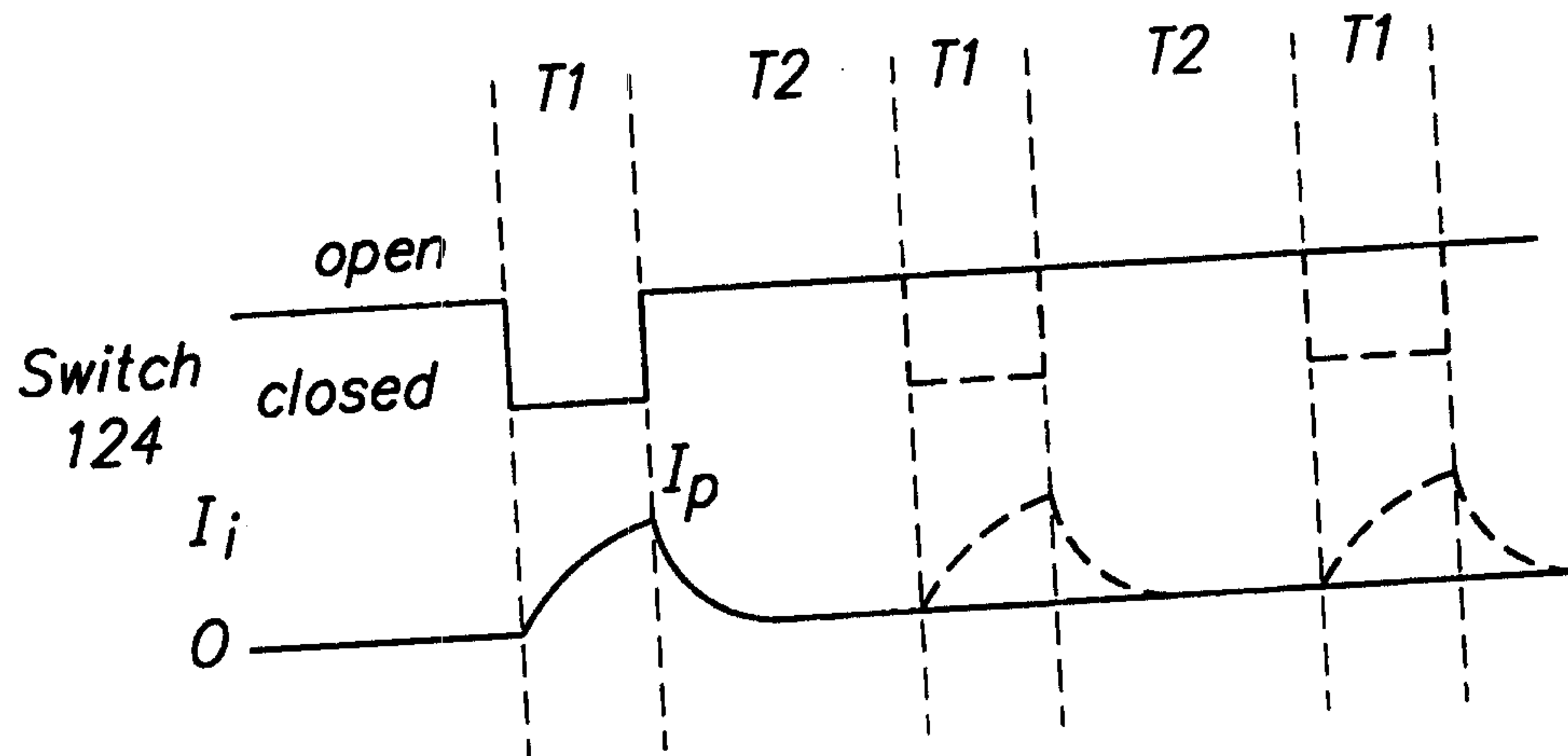
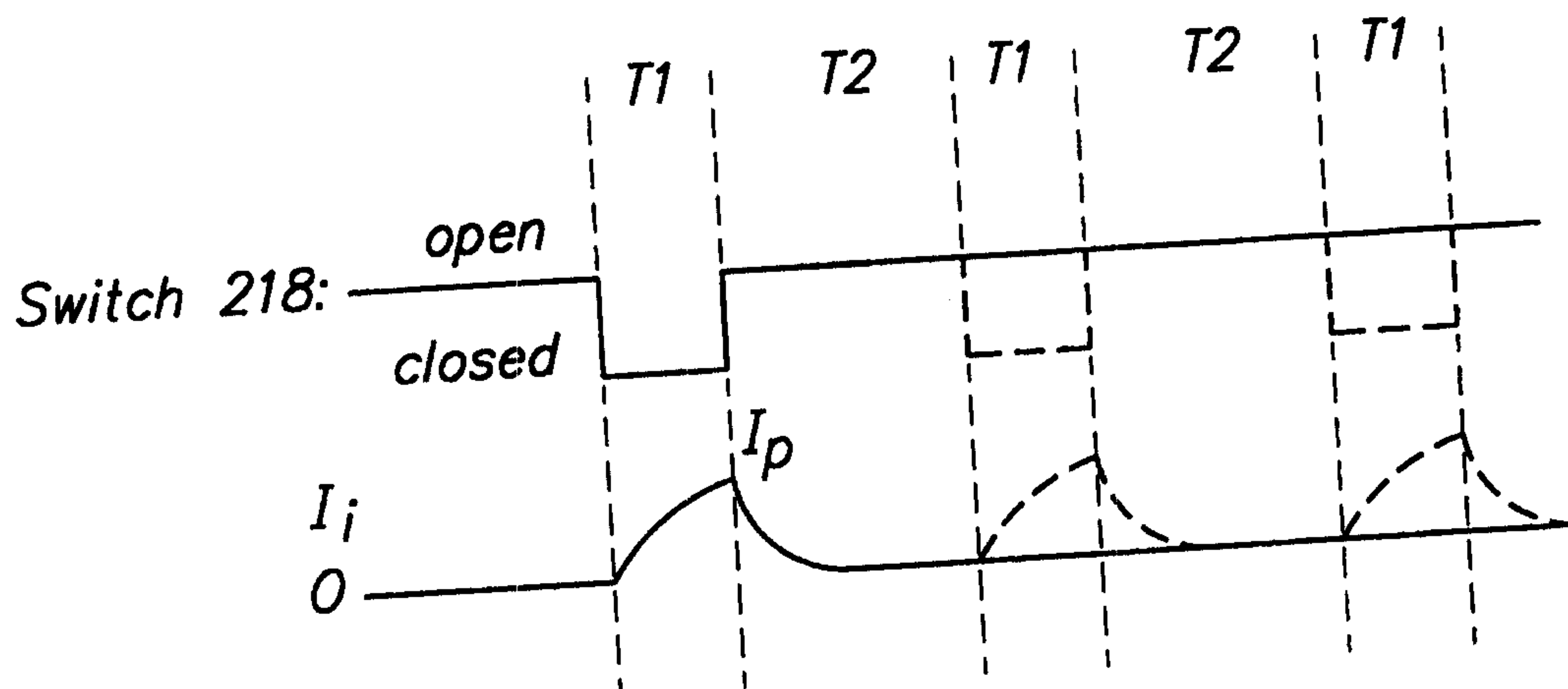
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**FIG. 6**

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**FIG. 8****FIG. 10**

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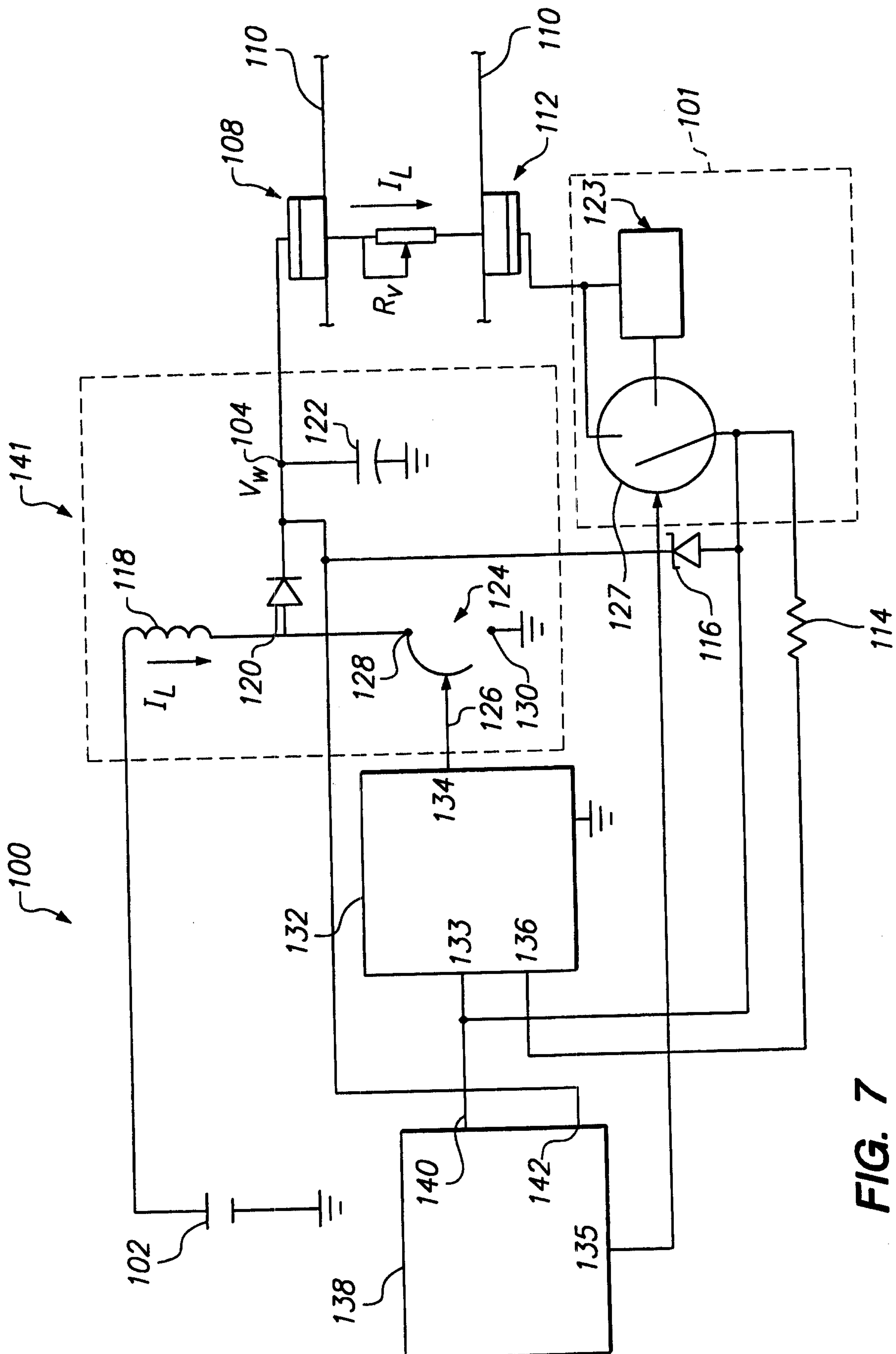


FIG. 7

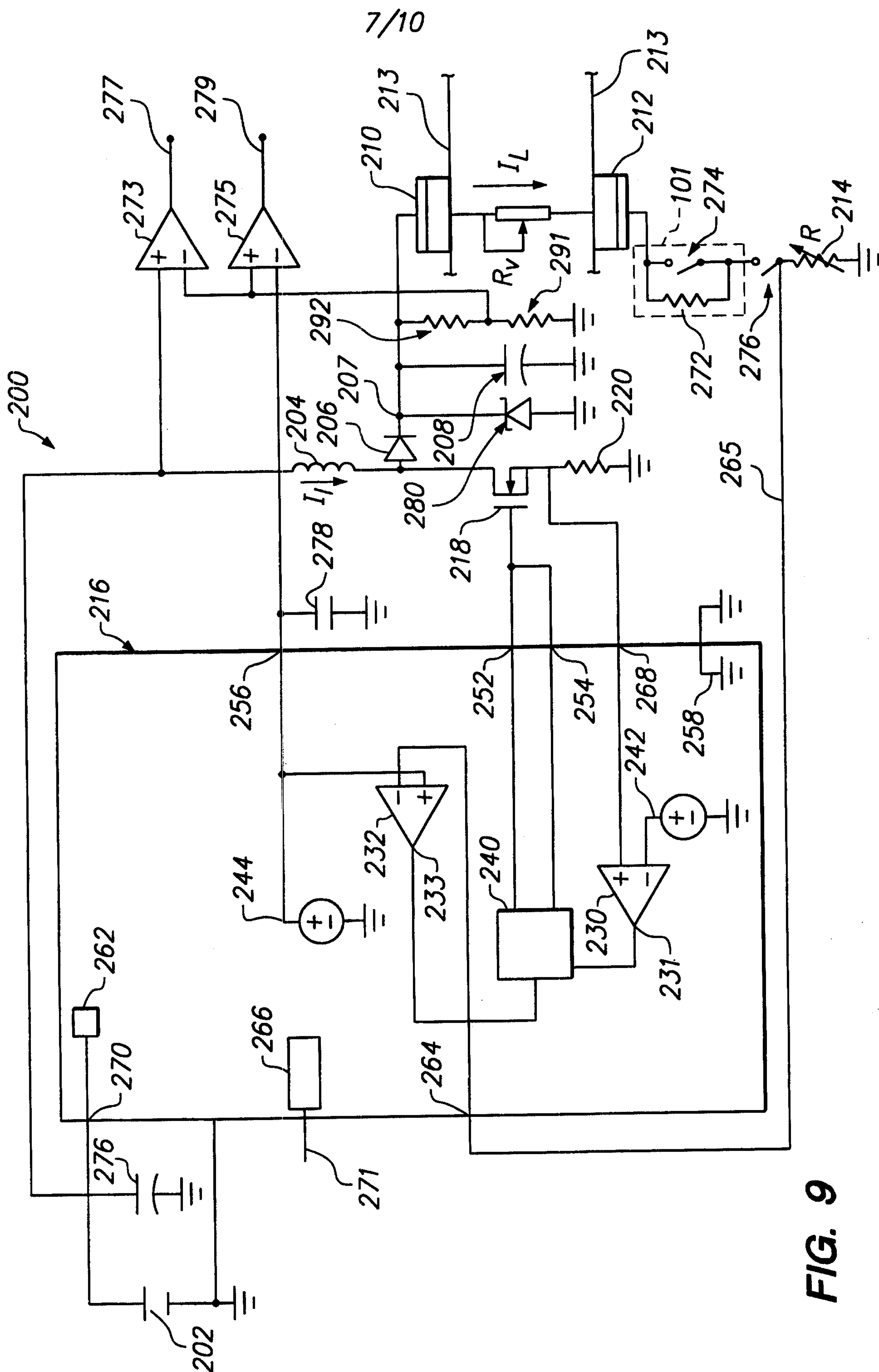
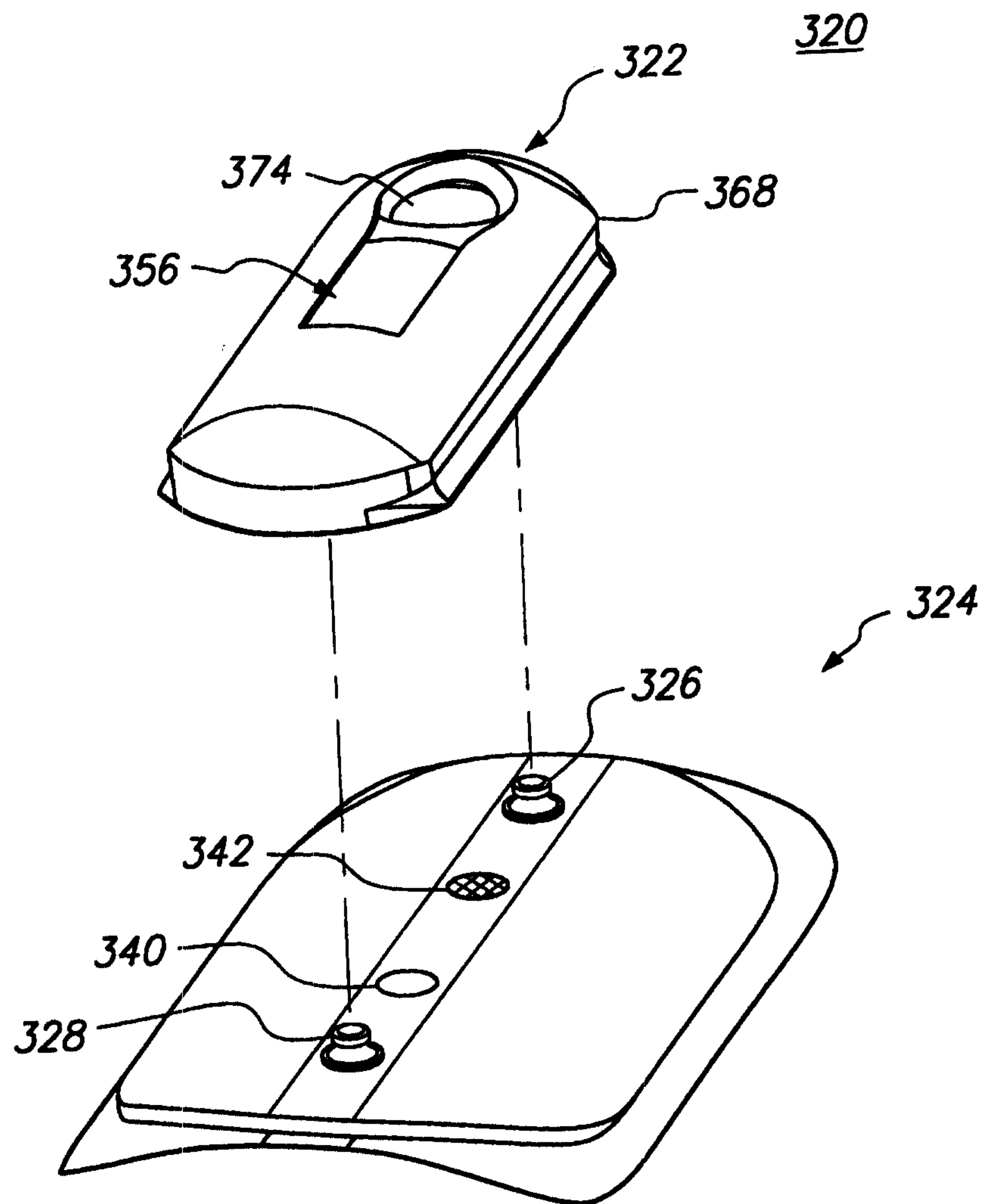


FIG. 9

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**FIG. 11**



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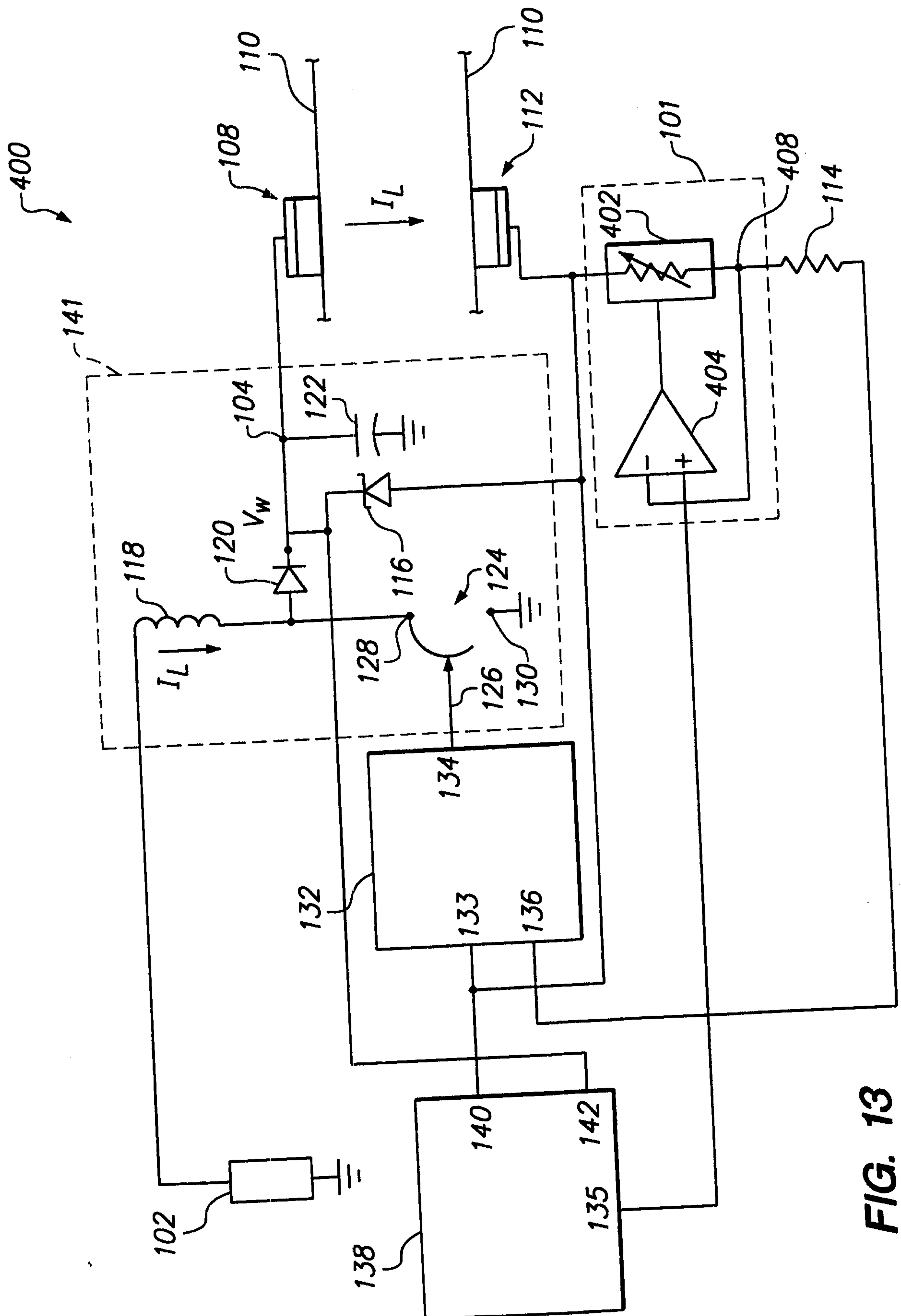


FIG. 13

