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CA 2183875 C 2003/10/14

(11)(21) **2 183 875**

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) **Date de dépôt PCT/PCT Filing Date**: 1994/03/18
(87) **Date publication PCT/PCT Publication Date**: 1995/09/28
(45) **Date de délivrance/Issue Date**: 2003/10/14
(85) **Entrée phase nationale/National Entry**: 1996/08/21
(86) **N° demande PCT/PCT Application No.**: US 1994/002985
(87) **N° publication PCT/PCT Publication No.**: 1995/025562

(51) **Cl.Int.^{6}/Int.Cl.^{6}** A61N 1/30

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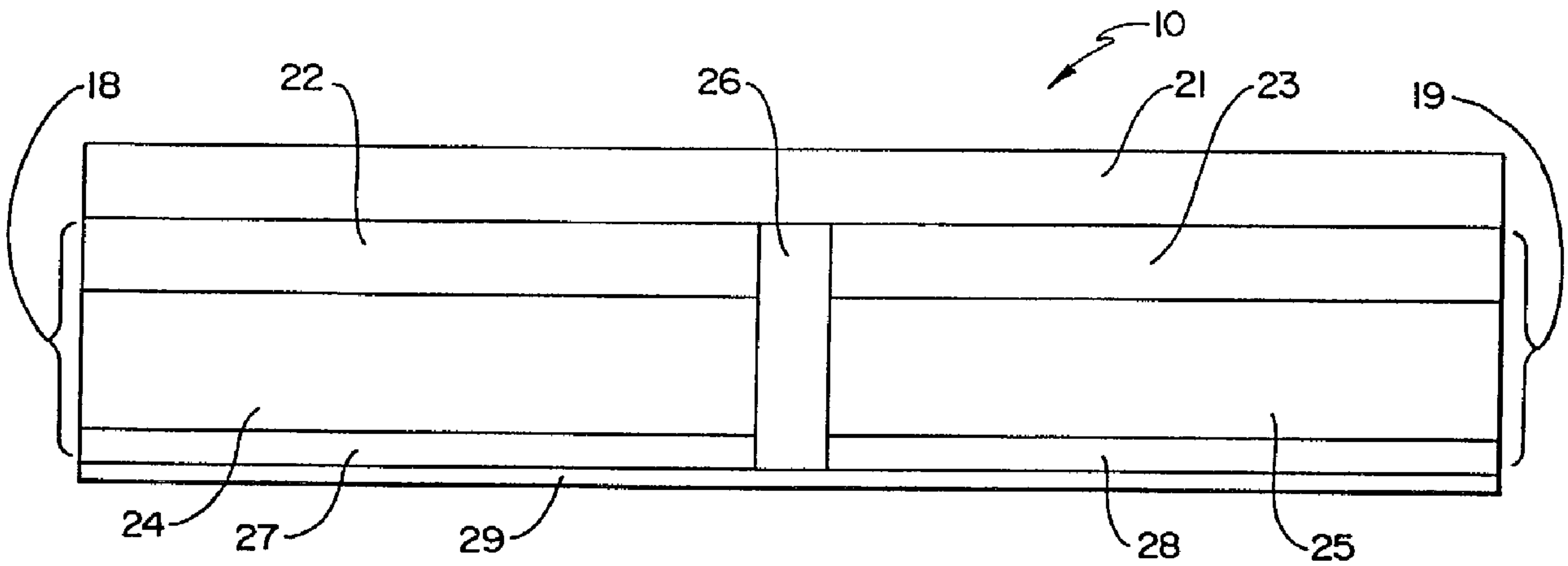
(54) Titre : DISPOSITIF POUR L'ADMINISTRATION D'UN MEDICAMENT PAR ELECTROTRANSPORT
(54) Title: ELECTROTRANSPORT DRUG DELIVERY DEVICE



(57) **Abrégé/Abstract**:
An electrotransport agent delivery device (10) having a simplified structure and ease of manufacture is provided. The device (10) utilizes an electrical circuit (40) disposed upon one of two opposing sides (43, 45) of a flexible, non-conductive substrate (42). The electrical circuit (40) comprises a source of electrical energy (46), one or more electrically conductive circuit pathways (44) and a circuit output means (48). The circuit output means (48) are connected directly or indirectly, e.g., by means of an electrically conductive adhesive (34), to the remaining components of the device such as current distribution members, lead wires, or electrodes (60, 62). In this arrangement, the circuit (40) is inverted from that of conventional electrotransport devices such that the surface (45) of the flexible substrate (42) having the electrical circuit (40) disposed thereon faces the body surface through which the drug or other agent is delivered by electrotransport. Economical, reel-to-reel methods of manufacturing a one-sided electrotransport circuit (40) are disclosed.

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61N 1/30

A1

(11) International Publication Number: WO 95/25562

(43) International Publication Date: 28 September 1995 (28.09.95)

(21) International Application Number: PCT/US94/02985

(22) International Filing Date: 18 March 1994 (18.03.94)

(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

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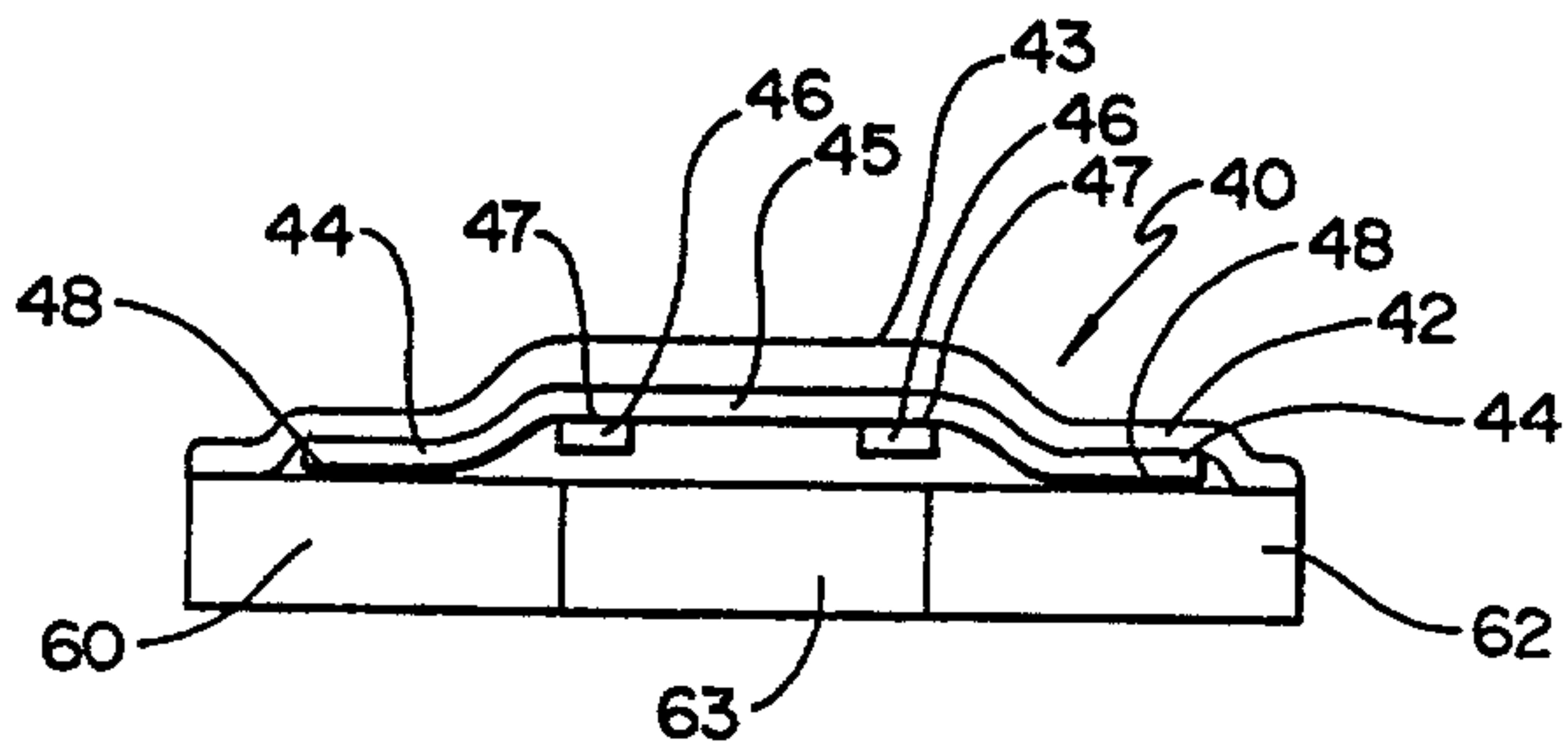
2183875

(54) Title: ELECTROTRANSPORT DRUG DELIVERY DEVICE

(57) Abstract



An electrotransport agent delivery device (10) having a simplified structure and ease of manufacture is provided. The device (10) utilizes an electrical circuit (40) disposed upon one of two opposing sides (43, 45) of a flexible, non-conductive substrate (42). The electrical circuit (40) comprises a source of electrical energy (46), one or more electrically conductive circuit pathways (44) and a circuit output means (48). The circuit output means (48) are connected directly or indirectly, e.g., by means of an electrically conductive adhesive (34), to the remaining components of the device such as current distribution members, lead wires, or electrodes (60, 62). In this arrangement, the circuit (40) is inverted from that of conventional electrotransport devices such that the surface (45) of the flexible substrate (42) having the electrical circuit (40) disposed thereon faces the body surface through which the drug or other agent is delivered by electrotransport. Economical, reel-to-reel methods of manufacturing a one-sided electrotransport circuit (40) are disclosed.

ELECTROTRANSPORT DRUG DELIVERY DEVICE

Technical Field

The present invention generally concerns a device for the electrically assisted administration of therapeutic agents or species. This invention also concerns methods for making such a device.

More specifically, this invention concerns low cost, generally disposable, electrically-assisted drug or therapeutic agent delivery systems. Yet more specifically, this invention relates to devices for electrotransport drug delivery in which, preferably flexible circuits are electrically connected or coupled to other, separate components or sub-assemblies of the device in an inexpensive yet rapidly manufacturable manner. Lastly, this invention relates to disposable electrotransport drug delivery devices.

Background of the Invention

The present invention concerns devices for transdermal delivery or transport of therapeutic agents by electrotransport. Herein the term "electrotransport" is used to refer to methods and devices for transdermal delivery of therapeutic agents, whether charged or uncharged, by means of an applied electromotive force to an agent-containing reservoir. The particular therapeutic agent to be delivered may be completely charged (i.e., 100% ionized), completely uncharged, or partly charged and partly uncharged. The delivery of ionic agents under the influence of an electric field is also sometimes referred to as iontophoresis. The therapeutic agent or species may be delivered by electromigration, electroosmosis or a combination of the two. In general, electroosmosis of a therapeutic species into a tissue results from the migration of solvent, in which the species is contained, as a result of the application of electromotive force to the therapeutic species reservoir. Still another type of electrotransport process, electroporation, involves the formation of transiently-existing pores in a biological membrane by the application of an electric field, through which pores an agent can be delivered either passively (ie, without electrical assistance) or actively (ie, under the influence of an electric potential). However, in any given electrotransport process, more than one of these processes may be occurring simultaneously to a certain extent. Accordingly, the term "electrotransport", as used herein, should be given its broadest possible interpretation so that it includes the electrically induced or enhanced transport of at least one agent, which may be charged, uncharged, or a mixture thereof, regardless of the specific mechanism or mechanisms by which the agent actually is transported.

Electrotransport devices have been known since the early 1900's. British patent specification No. 410,009 (1934) describes an iontophoretic device which overcame one of the disadvantages of such early devices known to the art at that time, namely the requirement of a special low tension (low voltage) source of current. That current requirement meant that the patient needed to be immobilized near the current source. The device of that British specification was made by forming a galvanic cell from the electrodes and the material containing the medicament or drug to be transdermally delivered. The galvanic cell produced the current necessary for iontophoretically delivering the medicament. This portable device thus permitted iontophoretic drug delivery with substantially less interference with the patient's daily activities.

More recently, a number of United States patents have issued in the electrotransport field, indicating a renewed interest in this mode of drug delivery. For example, Vernon et al. U.S. Patent No. 3,991,755; Jacobsen et al. U.S. Patent No. 4,141,359; Wilson U.S. Patent No. 4,398,545; and Jacobsen U.S. Patent No. 4,250,878 disclose examples of electrotransport devices and some applications thereof. The electrotransport process has been found to be useful in the transdermal administration of medicaments or drugs including lidocaine hydrochloride, 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. Iontophoretically delivered pilocarpine stimulates sweat production, the sweat is collected, and is analyzed for its chloride ion content. Chloride ion concentration in excess of certain limits suggests the possible presence of the disease.

In presently known electrotransport devices, at least two electrodes are used. Both of these electrodes are disposed so as to be in intimate electrical contact with some portion of the skin of the body. One electrode, called the active or donor electrode, is the electrode from which the ionic substance, agent, medicament, drug precursor or drug is delivered into the body via the skin by electrotransport. The other electrode, called the counter or return electrode, serves to close the electrical circuit through the body. In conjunction with the patient's skin contacted by the electrodes, the circuit is completed by connection of the electrodes to a source of electrical energy, e.g., a battery. For example, if the ionic substance to be driven into the body is positively charged, then the anode will be the active electrode and the cathode will serve to complete the circuit. If the ionic substance to be delivered is relatively negatively charged, then the cathodic electrode will be the active electrode and the anodic electrode will be the counter electrode.

Alternatively, both the anode and the cathode may be used to deliver drugs of appropriate charge, or drugs of neutral charge, into the body. In such a case, both electrodes are considered to be active or donor electrodes. For example, the anodic electrode can drive positively charged and/or neutral substances into the body while the cathodic electrode can drive negatively charged and/or neutral substances into the body.

Furthermore, existing electrotransport devices generally require a reservoir or source of the species (or a precursor of such species) which is to be delivered or introduced into the body. Examples of such reservoirs or sources of species include a pouch as described in the previously mentioned Jacobsen U.S. Patent No. 4,250,878, a pre-formed gel body as disclosed in Webster U.S. Patent No. 4,382,529 and a generally conical or domed molding of Sanderson et al., U.S. Patent No. 4,722,726. Such drug reservoirs are electrically connected to the anode or to the cathode of an electrotransport device to provide a fixed or renewable source of one or more desired species or agents.

Recently, the transdermal delivery of peptides and proteins, including genetically engineered proteins, by electrotransport has received increasing attention. Generally speaking, peptides and proteins being considered for transdermal or transmucosal delivery have a molecular weight in the range of about 300 to 40,000 Daltons (or more). These high molecular weight substances are usually too large to diffuse passively (i.e., without electromotive force) through skin at therapeutically effective rates. Since many peptides and proteins carry either a net positive or net negative charge and because of their inability to diffuse passively through skin at therapeutically useful rates, they are considered likely candidates for electrotransport delivery.

Several approaches have been suggested to couple components of an electrotransport device such as the power source and associated current generating and/or control circuitry to the electrodes. One suggested approach is to use a two-sided circuit board. A two-sided circuit board has electrically conductive traces or circuit pathways on both major opposing surfaces of a non-conductive substrate (ie, the board). The two-sided circuit board also uses connective, conductive conduits or "through holes" running through the board to electrically connect the two sets of circuit pathways on the opposing surfaces of the board. The circuit pathways on one surface (ie, the underside of the board) are then placed in physical and electrical contact with the remaining components of the device. Producing a two-sided circuit board with connective conduits is relatively costly.

Another approach is to use a single-sided circuit assembly or board and folding, by 180°, the board so that the circuit outputs are folded beneath the main part of the circuit board. This permits physical contact between the circuit outputs and the underlying portions of the device, (e.g., the electrodes). Unfortunately, folding the circuit board tends to produce stress points at the folds which can cause electrical failure (ie, breaking) of the circuit pathways at the fold lines.

From a commercial standpoint, it is generally desirable for an electrotransport apparatus to be manufacturable in a cost effective manner, preferably in large quantities. This invention provides devices and methods of manufacture capable of achieving both objectives.

Disclosure of the Invention

Briefly, in one aspect, the present invention is an electrotransport device comprising a single-sided, preferably flexible, electrical circuit. The single-sided electrical circuit is coupled to a source of electrical energy, such as a battery, and further is coupled to further components of the device such as electrodes as described above. "Coupled," as the term is used herein, means connected physically or electrically, directly or indirectly, i.e., through further components or connector means. A flexible circuit of this invention comprises a relatively non-conducting flexible substrate having opposing first and second major surfaces. An example of such a substrate is a segment of flexible film. The substrate has at least one conductive (or at least controllably conductive) electronic circuit trace or pathway printed, deposited, or adhered on one of the opposing major surfaces thereof. At least a portion of the electrical circuit is in electrical contact with the rest of the device structure, e.g., the electrodes. In a preferred embodiment, the electrical circuit has one or more circuit outputs in direct physical and electrical contact with the electrodes. This arrangement requires the electrical circuit to be on the same side of the substrate as the electrodes or other components of the electrotransport device to which the circuitry is coupled. In a preferred embodiment, the other or remaining major surface of the flexible substrate is juxtaposed against or is overlain by a protective backing layer.

Thus, in a preferred embodiment, the arrangement of components in a device of this invention from its top (or outside) to its bottom (or skin-side) is optional protective film, flexible substrate - first opposing surface, flexible substrate - second opposing surface, at least one electrically conductive pathway (the substrate and electrically conductive pathway(s) comprise a one-sided circuit) and the rest of the electrotransport structure such as electrodes. Generally speaking, a source of electrical energy will be coupled to the electrically conductive pathway (e.g., a battery output terminal will be connected to a circuit input terminal) and be located on the same side of the flexible substrate. In order for the various layers to adhere to each other, suitable adhesives can be disposed therebetween. Alternatively, thermoplastic materials or layers can be sealed to each other, e.g., by heat sealing.

Describing the above invention in another manner, the device comprises an electrotransport medicament or agent delivery device comprising a single-sided circuit means having a top or exterior side and a bottom or interior side. The frame of reference of the previous sentence is that the first, top, or upper side of the single-sided circuit would be the exterior side or the side furthest away from the site at which drug is to be delivered by electrotransport. The second, bottom, or underside then would be the interior side of the one-sided circuit or the side of the circuit closest to the site to which drug is to be delivered. In either instance, in this embodiment, the conductive, flexible electrically conductive pathway (which would include input means and output means) would be disposed on the second or bottom side of the substrate. In a preferred practice, the substrate comprises a segment of film which optionally may include a plurality of sprocket holes located along one or both sides thereof, similar to 35mm photographic film. In common terms, the electrically conductive pathways including current generating means, current controlling means and current output means, are "upside down" or inverted with its top toward the patient. Completing the device, the circuit is coupled to a source of electrical energy such as a battery. In order to obtain the least complex structure, electrical energy sources, such as batteries, will generally be located on the same side of the non-conductive member or substrate as the electrically conductive pathways. The circuit output means is coupled to the rest of the electrotransport drug delivery device structure, generically referred to as electrode means. This would mean, for example, the electronic circuit output means could be coupled to electrode current distribution members or other electrode structures. This means, for example, that the electronic circuit output means could be in direct physical and electrical contact with, e.g., a current distribution member of an electrode.

In another construction of the present invention, the one-sided, upside-down circuit can be coupled to the rest of the device by means of an electronically conductive adhesive means such as that described in published International Application WO 93/24178. An electrically conductive adhesive permits indirect electrical coupling between circuit output means and, e.g., electrode means. In its broadest application, the present invention permits simplification of electrotransport device structure by providing electrical coupling of the circuit output and the electrode without folding electrical connectors or "through hole" electrical connections.

According to a broad aspect of the invention there is provided an electrotransport agent delivery device having at least two electrodes, at least one of the electrodes containing the agent to be delivered by electrotransport, the device having an electronic circuit for generating and controlling electric current applied by the device, the electronic circuit including an electrically conductive pathway disposed on one of a first and a second opposing surfaces of a substantially non-conductive, flexible substrate, the circuit including a source of electrical power and a circuit output, the circuit output being electrically connected to at least one of the electrodes, the device characterized by the electronic circuit, the electrically conductive pathway and the circuit output all being disposed on the first opposing surface which first opposing surface faces at least one of the electrodes with the circuit output being electrically connected thereto.

According to another broad aspect of the invention there is provided an electrotransport agent delivery device having at least two electrodes, at least one of the electrodes containing the agent to be delivered by electrotransport, the device having an electronic circuit for generating or controlling electric current applied by the device, the electronic circuit including an electrically conductive pathway disposed on one of a first and a second opposing surfaces of a substantially non-conductive, flexible substrate, the circuit including a source of electrical power and a circuit output, the circuit output being electrically connected to at least one of the electrodes, the device characterized by the electronic circuit, the electrically conductive pathway and the circuit output all being disposed on the first opposing surface which first opposing surface faces at least one of the electrodes with the circuit output being electrically connected thereto.

According to a further broad aspect of the invention there is provided a method of manufacturing an electrotransport agent delivery device including a flexible electronic circuit and other components, the method comprising providing an electronic circuit on one of two opposing surfaces of a flexible, substantially non-conductive, substrate of a suitable size to support and contain the electronic circuit, the electronic circuit being capable of generating and controlling electric current applied by the device, the electronic circuit including a source of electrical power, at least one electrically conductive pathway and a circuit output; the method being characterized by disposing the electronic circuit, the electrically conductive pathway and the circuit output on only one of the two opposing surfaces, which surface faces an at least one electrode; and coupling the circuit output to the at least one electrode.

According to a further broad aspect of the invention there is further provided a method of manufacturing an electrotransport agent delivery device including a flexible electronic circuit and other components, the method comprising providing an electronic circuit on one of two opposing surfaces of a flexible, substantially non-conductive, substrate of a suitable size to support and contain the electronic circuit, the electronic circuit being capable of generating and controlling electric current applied by the device, the electronic circuit including a source of electrical power, at least one electrically conductive pathway and a circuit output; the method being characterized by disposing the electronic circuit, the electrically conductive pathway and the circuit output on only one of the two opposing surfaces, which surface faces an at least one electrode; and coupling the circuit output to the at least one electrode.

"Flexible" as the term is used herein, means being capable of conforming to the contours of a portion of the body to which the device is attached or to which it most closely approaches, i.e., to be conformable to a highly contoured body surface such as an arm, a leg, or the chest. "Flexible", as used herein, also means being capable of bending, twisting, or deforming so as to continue to conform to the contours of the area of the body to which the device is attached throughout the normal range of movement of the body area.

"Conductive" as the term is used herein means having a bulk electronic conductivity of greater than about 1 ohm-cm.

"One-sided" or "single-sided" circuit or circuitry as those terms are used herein means lying or being disposed upon substantially a single side of a support substrate, member, or film. In its preferred usage, this definition requires that the circuit elements of a device to which it applies would be substantially co-planar.

Brief Description of the Drawings

A better understanding of the present invention as well as other objects and advantages thereof will become apparent upon consideration of the following detailed description especially when taken with the accompanying drawings, wherein like numerals designate like parts throughout, and wherein:

FIG. 1 is a side sectional view showing the primary components of an electrotransport delivery device as described above;

FIG. 2 is a side, sectional view of an electrotransport device of the invention;

FIG. 3 is a sectional view of a second electrotransport device of the present invention;

FIG. 4 is a sectional view of a preferred electronically conductive adhesive material useable in this invention; and

FIG. 5 is an overhead view of a constant current circuit useable in the present invention.

Modes of Carrying Out the Invention

Thus, FIG. 1 is a side sectional depiction of an electrotransport delivery device 10. It is to be understood that device 10 can have essentially any convenient size or shape, whether square, oval, circular, or tailored for a specific location on the skin. As depicted, device 10 is applied to the skin of a patient by means of a suitable bio-compatible adhesive material. Device 10 is preferably flexible as defined herein.

Device 10 has a top layer 21 which contains a source of electrical energy (e.g., a battery or a series of batteries) as well as control circuitry for current regulation, e.g., a resistor or a transistor-based current control circuit, an on/off switch, and/or a microprocessor adapted to control the current output of the power source over time. Layer 21 generally contains all components necessary to deliver current of predeterminable characteristics to the rest of the components of the device. Layer 21 is "flexible" as defined above, and generally is comprised of an electronic circuit disposed upon a thin, flexible substrate or support such as, for example, a film or polymeric web as will be described in greater detail below.

Device 10 further comprises electrode assemblies indicated by brackets 18 and 19. Electrode assemblies 18, 19 may contain further electrode structure such as current distribution members or electrodes 22, 23 to eliminate "hot spots". Electrode assemblies 18 and 19 are separated from one another by an electrical insulator 26, and form therewith a single, self-contained unit. For purposes of illustration, the electrode assembly 18 is sometimes referred to as the "donor" electrode assembly while electrode assembly 19 is sometimes referred to as the "counter" electrode assembly. These designations of the electrode assemblies are not critical and may be reversed in any particular device or in operation of the device shown.

In the embodiment of FIG. 1, a donor electrode 22 is positioned adjacent a drug reservoir 24 while a counter electrode 23 is positioned adjacent a reservoir 25 which contains an electrolyte. Electrodes 22 and 23 may comprise metal foils, or a polymer matrix loaded with metal powder, powdered graphite, carbon fibers, or any other suitable electrically conductive material. Reservoirs 24 and 25 can be polymeric matrices or gel matrices. Natural or synthetic polymer matrices may be employed. Insulator 26 is composed of an electrically insulating and non-ion-conducting material which acts as a barrier to prevent short-circuiting of the device 10. Insulator 26 can be an air gap, a non-ion-conducting and electrically insulating polymer or adhesive, or other suitable barrier to ion and charge flow. The device 10 optionally can be adhered to the skin by means of ion-conducting adhesive layers 27 and 28. The device 10 also optionally includes a strippable release liner 29 which is removed just prior to application of the device to the skin. Alternatively, device 10 can be adhered to the skin by means of an adhesive overlay of the type which are conventionally used in transdermal drug delivery devices. Generally speaking, an adhesive overlay contacts the skin around the perimeter of the device to maintain contact between reservoirs 24 and 25 and the patient's skin. Thus, for purposes of orientation, the top, exterior, or outside of device 10 would be closest to the top of FIG. 1. Conversely, the bottom, interior or inside of the device would be in the direction of the bottom of FIG. 1.

In a typical device 10, the drug reservoir 24 contains a supply of the drug or agent to be delivered, and preferably in an ionized or ionizable form, and the counter reservoir 25 contains a suitable electrolyte such as, for example, sodium chloride, sodium phosphate, or other biocompatible salt. Alternatively, device 10 can contain an ionizable, or neutral supply of drug in both reservoirs 24 and 25 and in that manner both electrode assemblies 18 and 19 would function as donor electrode assemblies. For example, positive drug ions could be delivered through the skin from the anode electrode assembly, while negative drug ions could be delivered from the cathode electrode assembly. Generally, the combined skin-contacting area of electrode assemblies 18 and 19 can range from about 1 cm^2 to about 200 cm^2, but typically will range from about 5 cm^2 to about 50 cm^2.

In accordance with the present invention, the drug reservoir 24 and return reservoir 25 of the electrotransport delivery device 10 must be placed in agent or drug transmitting relation with the patient so as to deliver agent or drug by electrotransport. Usually this means the device is placed in intimate contact with the patient's skin after removal of any release liner. Various sites on the human body may be selected depending upon the physician's or the patient's preference, the drug or agent delivery regimen, or other factors such as cosmetic.

FIGs. 2 and 3 illustrate, in schematic section, two embodiments of the present invention. FIG. 2 illustrates an embodiment of the present invention wherein the "upside down" or inverted flexible circuit of the invention is placed in direct physical/electrical contact with the rest of the apparatus structure. Flexible, one-sided or single-sided circuit 40 comprises a substantially non-conductive, flexible substrate 42 on which there is disposed a conductive pathway 44. Substrate 42 has opposed first and second surfaces 43, 45, respectively. Pathway 44 is disposed on second surface 45. Batteries 46 are electrically connected to conductive pathway 44 (at interface 47).

Batteries 46, in this embodiment, comprise button cells. Many other sources of electrical energy (including flexible polymeric or sheet batteries) could be utilized without departing from the scope or intent of this invention. Conductive pathway 44 has output means, e.g., output pads, 48. Output pads 48 directly touch and therefore physically and electrically couple to electrode means 60, 62, respectively. Electrically and ionically non-conductive separator 63 is disposed between electrode means 60 and 62. While not critical, electrode means 60 is the anode and electrode means 62 is the cathode. Depending upon preference there may be a further layer (eg, a water-proof backing layer) or layers overlying flexible substrate 42. Also the apparatus may comprise additional structure, e.g., a drug reservoir and an electrolyte reservoir, coupled to electrode means 60, 62, respectively. These further structures have been intentionally omitted so as not to detract from illustration of the invention.

FIG. 3 illustrates an embodiment of the present invention in which an electrically conductive adhesive means 34 is used to electrically connect output pads 48 to electrode means 60, 62, respectively. In this embodiment, electrically conductive adhesive means 34 comprises flexible electrically conductive adhesive (ECA). ECA 34 can be of simple or complex structure depending upon the particular application, as long as the structure is electrically conductive, adhesive and, preferably, flexible. As shown, ECA 34 couples circuit output means or pads 48 and electrode means 60, 62. ECA 34 creates an efficient coupling of the circuit output pads 48 and at least the back side of anode 60 and cathode 62, respectively. The present invention is not limited, however, to the use of an ECA and other types of coupling means or connectors may be used to electrically connect output pads 48 and electrode means 60, 62 without deviating from the teachings of the present invention.

The ECA 34 may have substantially any structure or composition which provides acceptable electrical conductivity and flexibility. However, one particularly preferred ECA is formed by laminating one or more layers 52, 54 of an adhesive material to one or more electrically conductive webs, mats or meshes 50 to form a composite ECA 34 as shown in FIG. 4. One particularly useful composite ECA 34 is formed by laminating, between opposing laminating rollers 40, a single conductive mat or mesh 50 between two adhesive layers 52, 54. Lamination is conducted at a suitable temperature and pressure to ensure that layers 52 and 54 "flow" into the interstitial spaces between the fibers/strands of mesh 50 and intimately contact and adhere to the fibers/strands of mesh 50 so that the entire composite ECA 34 is flexible, adhesive, conductive and has a substantially uniform cross-section. A composite ECA (not shown) formed by laminating a single adhesive layer 52 to a single conductive mesh 50 is also suitable. An alternative composite ECA 34 (not shown) can be formed by laminating two conductive meshes 50 with a single layer 52 of adhesive sandwiched therebetween.

Mat or mesh 50 may be of any suitable conductive, flexible structure. For example, mat or mesh 50 can have an open weave design which approximates a screen. One preferred mat is made of 100% nylon strands, type 6-6, 40 denier, 13 filaments per end and has a thickness of approximately 0.064 cm (0.025 inches). This open-weave material has its interwoven strands coated with an electrically conductive material such as graphite, carbon, silver, silver oxide, aluminum powder, or gold. The mat has a resultant surface resistance of less than 1.6 ohms/cm^2 (10 ohms/in^2), a tensile strength in excess of 8.79 kg/cm^2 (125 lbs/in^2) and a tear strength in excess of 0.7 kg/cm^2 (10 lbs/in^2). This material may be obtained from Tecknit Corporation, Cranford, N.J. Other electrically conductive adhesive materials are disclosed in published International Application WO 93/24178.

A particularly preferred composite ECA is formed by laminating at least one layer of an intermingled, non-woven, carbon fiber matting and at least one other layer of an adhesive polyisobutylene matrix. The non-woven carbon fiber matting comprises about 1 to 10 volume percent, and preferably about 2 to 5 volume percent, of the total volume of the ECA. This ECA is made by laminating the polyisobutylene (PIB) into the carbon fiber mat so that the PIB flows therein and becomes intimately admixed therewith. Within the above limits, various equivalent formulations will become apparent to one of ordinary skill in this art. The preferred composite ECA may be produced by laminating the conductive mesh to one layer, or between two layers, of adhesive matrix. For example, sheet PIB, in rolled form, and kept usable by wrapping it with two release liners, is unrolled and laminated onto one or both major surfaces of a non-woven, conductive carbon mesh. In this manner, an ECA in sheet form, such as that shown in FIG. 4, is produced. The sheet can then be cut or otherwise processed into suitable lengths, shapes or configuration(s) for use in an electrotransport device.

FIG. 5 is an illustration of a specific flexible, one-sided circuit assembly of the present invention. Circuit 40 comprises non-conductive flexible substrate 42 and a series of components which comprise the electrical pathway generally designated 44 in FIGs. 2 and 3. Substrate 42 is preferably a segment of flexible film, similar to the film base used in 35mm photographic film. Circuit 40 is a constant current device useable in an electrotransport drug delivery device where variable load resistances and supply voltages occur. Circuit 40 comprises output pads 48a and 48b. Output pad 48a is adapted to be electrically connected (either directly as shown in FIG. 2 or indirectly through ECA layer 34 as shown in Fig. 3) to anode 60. Similarly, output pad 48b is adapted to be electrically connected to cathode 62. As shown, output pad 48a is electronically coupled to 100 ohm resistor 64, a 0-22 kilo-ohm variable resistor 66 and to field effect transistor 68. Three 3-volt button cell lithium batteries 46 complete circuit 40. Continuity test points 70, 72, 74 are indicated on the circuit.

Shown cross-hatched in FIG. 5 is a "keep out" or excluded zone 80. Zone 80 provides a perimeter space in which or on which, for example, sprocket holes 43 or other film transport means (not shown) may optionally be provided. Sprocket holes provide a means by which circuits 40 can be rapidly and cheaply processed in a continuous fashion.

In this manner low cost, relatively inexpensive flexible circuits can be produced. Typical dimensions of a one-sided circuit assembly 40 would be a total film width of approximately 1.4 cm, a circuit repeat distance of approximately 4.0 cm, and "keep out" zone width of approximately 0.2 cm. Sprocket holes 43 can be separated a distance determined by the ease or difficulty of advancing the film substrate during processing. Typically, sprocket holes 43 are separated a distance of about 0.5 cm.

Flexible, relatively thin, electrically conductive circuit pathways can be applied to a flexible film substrate using standard flex circuit processing techniques. For example, printing, depositing, or etching processes can be used to create copper or silver circuit pathways on flexible film substrates. Reel-to-reel processes can be used to rapidly mate the flexible film substrate which carries the electrically conductive circuit to one or more additional device components (e.g., a backing layer or donor and/or counter electrode assemblies. For example, flexible film substrates with printed, deposited or etched circuits can be received in reel form or rolled form. A polymeric film backing material can also be received in reel or rolled form. After appropriate alignment, the electrical circuits are then mated with the backing material to create a bi-layer (e.g., backing layer and circuit layer) composite work piece in continuous ribbon form in a rapid manner. For example, the circuits can be mated with the backing material by application of roller pressure. If necessary, a pressure sensitive adhesive can be used to adhere the circuit layer to the backing layer. The bi-layer composite material is then cut to produce individual units each comprised of a flexible circuit layer and a backing layer. After inversion, the output means (48) of the individual circuit units are coupled to the donor and counter electrode assemblies to form completed electrotransport devices again, using automated (e.g., pick-and-place) processes. In this manner, automated manufacture and concomitant cost savings can be achieved.

As noted, a source of electrical energy, e.g., one or more batteries, is incorporated into the electrical circuit before or at the time of assembly of the circuit. Batteries also can be included as part of the flexible circuit before it is applied to the substrate. Alternatively batteries can be connected or coupled to the circuit later, e.g., at the time of actual patient use, using known mechanical or electrical contacts. The complete device then can be activated by medical personnel or the patient depending upon the drug or agent delivery protocol.

The power source may comprise a group of cells, connected in parallel or series, to obtain the desired capacity and/or voltage necessary to obtain the desired current output needed for electrotransport delivery of the particular medicament. The polarity orientation of a battery depends on the ionic charge of the drug ions. If the drug is negatively charged in solution or suspension then the battery or batteries are oriented so that the negative battery terminal is connected to the donor electrode and the positive battery terminal is connected to the counter electrode. The converse applies if positively charged species are to be delivered. Any conventional miniaturized battery cells, e.g., button cells, now generally available can be employed, arranged and connected in series to obtain the desired operating voltage.

In addition, the technology now exists for batteries which are made up of very thin, flexible sheets of a conductive polymer with high surface areas relative to thickness to provide adequate current densities. One such so-called plastic battery is described in "Batteries Today", Autumn 1981, pages 10, 11, and 24. When such a battery is employed, sheets may be layered to place the cells in series. Of course, battery selection ultimately depends on such factors as the degree of flexibility or conformability desired, current density required for a specific application, and time of discharge. Whether miniature batteries or sheet batteries are employed, battery output terminals can be directly or indirectly connected, e.g., by conventional means such as clips, wires, printed circuitry or by an electrically conductive adhesive, to the circuit 40.

The terms "agent" or "drug" are used extensively herein. As used herein, the expressions "agent" and "drug" are used interchangeably and are intended to have their broadest interpretation as any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial, effect. In general, this includes therapeutic agents in all of the major therapeutic areas including, but not limited to, anti-infectives such as antibiotics and antiviral agents, analgesics and analgesic combinations, anesthetics, anorexics, antiarthritics, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine preparations, antimotion sickness preparations, antinauseants, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, including gastrointestinal and urinary, anticholinergics, sympathomimetrics, xanthine derivatives, cardiovascular preparations including calcium channel blockers, beta-blockers, antiarrythmics, antihypertensives, diuretics, vasodilators, including general, coronary, peripheral and cerebral, central nervous system stimulants, cough and cold preparations, decongestants, diagnostics, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetrics, proteins, peptides, polypeptides and other macromolecules, psychostimulants, sedatives and tranquilizers.

It is believed that an apparatus of the present invention can be used to deliver the following drugs: baclofen, betamethasone, beclomethasone, buspirone, cromolyn sodium, dobutamine, doxazosin, droperidol, fentanyl, sufentanil, ketoprofen, lidocaine, metoclopramide, methotrexate, miconazole, midazolam, nicardipine, prazosin, piroxicam, scopolamine, testosterone, verapamil, tetracaine, diltiazem, indomethacin, hydrocortisone, terbutaline and encainide.

This invention is also believed to be useful in the iontophoretic delivery of peptides, polypeptides and other macromolecules typically having a molecular weight of at least about 300 Daltons, and typically a molecular weight in the range of about 300 to 40,000 Daltons. Specific examples of peptides and proteins in this size range include, without limitation, LHRH, LHRH analogs such as buserelin, gonadorelin, naphrelin and leuprolide, insulin, heparin, calcitonin, endorphin, TRH, NT-36 (chemical name: N=[[(s)-4-oxo-2-azetidinyl]carbonyl]-L-histidyl-L-prolinamide), liprecin, pituitary hormones (e.g., HGH, HMG, HCG, desmopressin acetate, etc.,), follicle leutoids, αANF, growth factor releasing factor (GFRF), βMSH, somatostatin, bradykinin, somatotropin, platelet-derived growth factor, asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic gonadotropin, corticotropin (ACTH), erythropoietin, epoprostenol (platelet aggregation inhibitor), glucagon, hyaluronidase, interferon, interleukin-2, menotropins (urofollitropin (FSH) and LH), oxytocin, streptokinase, tissue plasminogen activator, urokinase, vasopressin, 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, parathyroid hormone and agonists, parathyroid hormone antagonists, prostaglandin antagonists, pentigetide, protein C, protein S, renin inhibitors, thymosin alpha-1, thrombolytics, TNF, vaccines, vasopressin antagonist analogs, alpha-1 anti-trypsin (recombinant).

Generally speaking, it is most preferable to use a water soluble salt of the drug or agent to be delivered. Drug or agent precursors, i.e., species which generate the selected species by physical or chemical processes such as ionization, dissociation, or dissolution, are within the definition of "agent" or "species" herein. "Drug" or "agent" is to be understood to include charged and uncharged species as described above.

In certain cases, it may be desirable to deliver the drug or agent with one or more skin permeation enhancers. A skin permeation enhancer can be selected from any of a wide variety of known materials capable of enhancing transdermal drug flux. Known permeation enhancers include, for example, surfactants, alkyl substituted sulfoxides, alkyl polyethylene glycols, lower alcohols and the permeation enhancers disclosed in U.S. Patent Nos. 3,989,816; 4,405,616; 4,415,563; 4,424,210; 4,722,726; and 5,023,085.

The above disclosure will suggest many alternatives, permutations, and variations of the invention to one of skill in this art. This disclosure is intended to be illustrative and not exhaustive. All such permutations, variations and alternatives suggested by the above disclosure are to be included within the scope of the attached claims.

CLAIMS:

1. An electrotransport agent delivery device having at least two electrodes, at least one of the electrodes containing the agent to be delivered by electrotransport, the device having an electronic circuit for generating and controlling electric current applied by the device, the electronic circuit including an electrically conductive pathway disposed on one of a first and a second opposing surfaces of a substantially non-conductive, flexible substrate, the circuit including a source of electrical power and a circuit output, the circuit output being electrically connected to at least one of the electrodes,

the device characterized by the electronic circuit, the electrically conductive pathway and the circuit output all being disposed on the first opposing surface which first opposing surface faces at least one of the electrodes with the circuit output being electrically connected thereto.

2. An electrotransport agent delivery device having at least two electrodes, at least one of the electrodes containing the agent to be delivered by electrotransport, the device having an electronic circuit for generating or controlling electric current applied by the device, the electronic circuit including an electrically conductive pathway disposed on one of a first and a second opposing surfaces of a substantially non-conductive, flexible substrate, the circuit including a source of electrical power and a circuit output, the circuit output being electrically connected to at least one of the electrodes,

the device characterized by the electronic circuit, the electrically conductive pathway and the circuit output all being disposed on the first opposing surface which first opposing surface faces at least one of the electrodes with the circuit output being electrically connected thereto.

3. The device of claim 1 or claim 2, further comprising a covering means in intimate contact with the second opposing surface of the substrate.

4. The device of any one of claims 1 to 3, wherein the substrate is substantially planar.

5. The device of any one of claims 1 to 4, wherein the circuit output is coupled to at least one of the electrodes by means of an electrically conductive adhesive.

6. The device of claim 5, wherein the electrically conductive adhesive comprises a laminate of an adhesive material and an electrically conductive web, mat or mesh.

7. The device of any one of claims 1 to 4, wherein the circuit output is in physical contact with at least one of the electrodes.

8. The device of any one of claims 1 to 7, wherein the non-conductive substrate comprises a segment of film.

9. The device of any one of claims 1 to 8, wherein one of the first and the second opposing surfaces is oriented to face a body surface of a patient, the other of the first and the second opposing surfaces is oriented to face away from the patient body surface and wherein the electrically conductive pathway is disposed on the opposing surface facing the patient body surface.

10. The device of any one of claims 1 to 9, wherein the substrate and the electrically conductive pathway comprise a one-sided circuit.

11. The device of any one of claims 1 to 10, wherein the circuit output is coupled to at least one of the electrodes by means of a separate coupling means.

12. A method of manufacturing an electrotransport agent delivery device including a flexible electronic circuit and other components, the method comprising providing an electronic circuit on one of two opposing surfaces of a flexible, substantially non-conductive, substrate of a suitable size to support and contain the electronic circuit, the electronic circuit being capable of generating and controlling electric current applied by the device, the electronic circuit including a source of electrical power, at least one electrically conductive pathway and a circuit output;

the method being characterized by disposing the electronic circuit, the electrically conductive pathway and the circuit output on only one of the two opposing surfaces, which surface faces an at least one electrode; and

coupling the circuit output to the at least one electrode.

13. A method of manufacturing an electrotransport agent delivery device including a flexible electronic circuit and other components, the method comprising providing an electronic circuit on one of two opposing surfaces of a flexible, substantially non-conductive, substrate of a suitable size to support and contain the electronic circuit, the electronic circuit being capable of generating or controlling electric current applied by the

device, the electronic circuit including a source of electrical power, at least one electrically conductive pathway and a circuit output;

the method being characterized by disposing the electronic circuit, the electrically conductive pathway and the circuit output on only one of the two opposing surfaces, which surface faces an at least one electrode; and

coupling the circuit output to the at least one electrode.

14. The method of claim 12 or claim 13, wherein the electronic circuit is located between the substrate and the at least one electrode.

15. The method of any one of claims 12 to 14, wherein the coupling step is accomplished using an automated process.

16. The method of claim 15, wherein the automated process is a pick-and-place process.

17. The method of any one of claims 12 to 16, wherein the circuit output means is coupled to the at least one electrode using an electrically conductive adhesive.

18. The method of 17, wherein the electrically conductive adhesive comprises a laminate of an adhesive material and an electrically conductive web, mat or mesh.

19. The method of any one of claims 12 to 18, wherein the electronic circuit provides a constant current to the circuit output means.

20. The method of any one of claims 12 to 19, wherein the electronic circuit is assembled by providing a plurality of identical circuits in series on a continuous rolled

substrate; cutting the substrate between adjacent circuits; and coupling the output means of an individual circuit to donor and counter electrode assemblies.

21. The method of claim 20, including adhering the continuous rolled substrate to a backing material in continuous rolled form.

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PATENT AGENTS

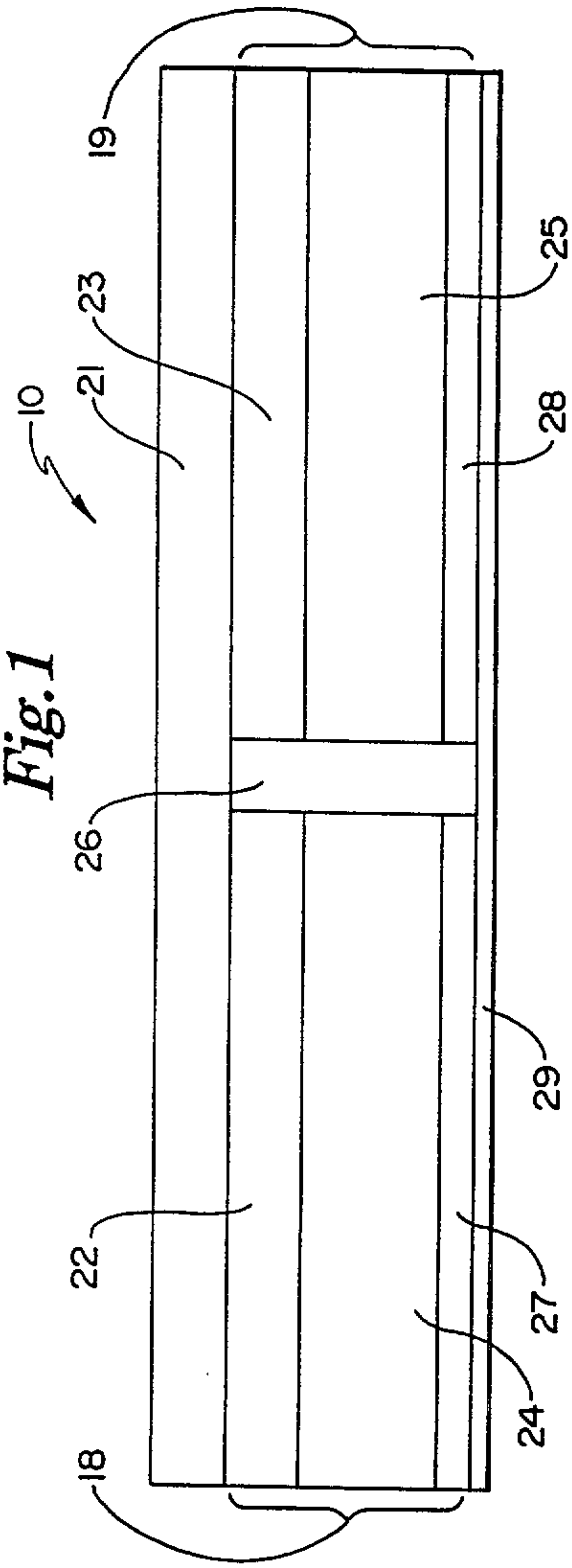


Fig. 1

Fig.2

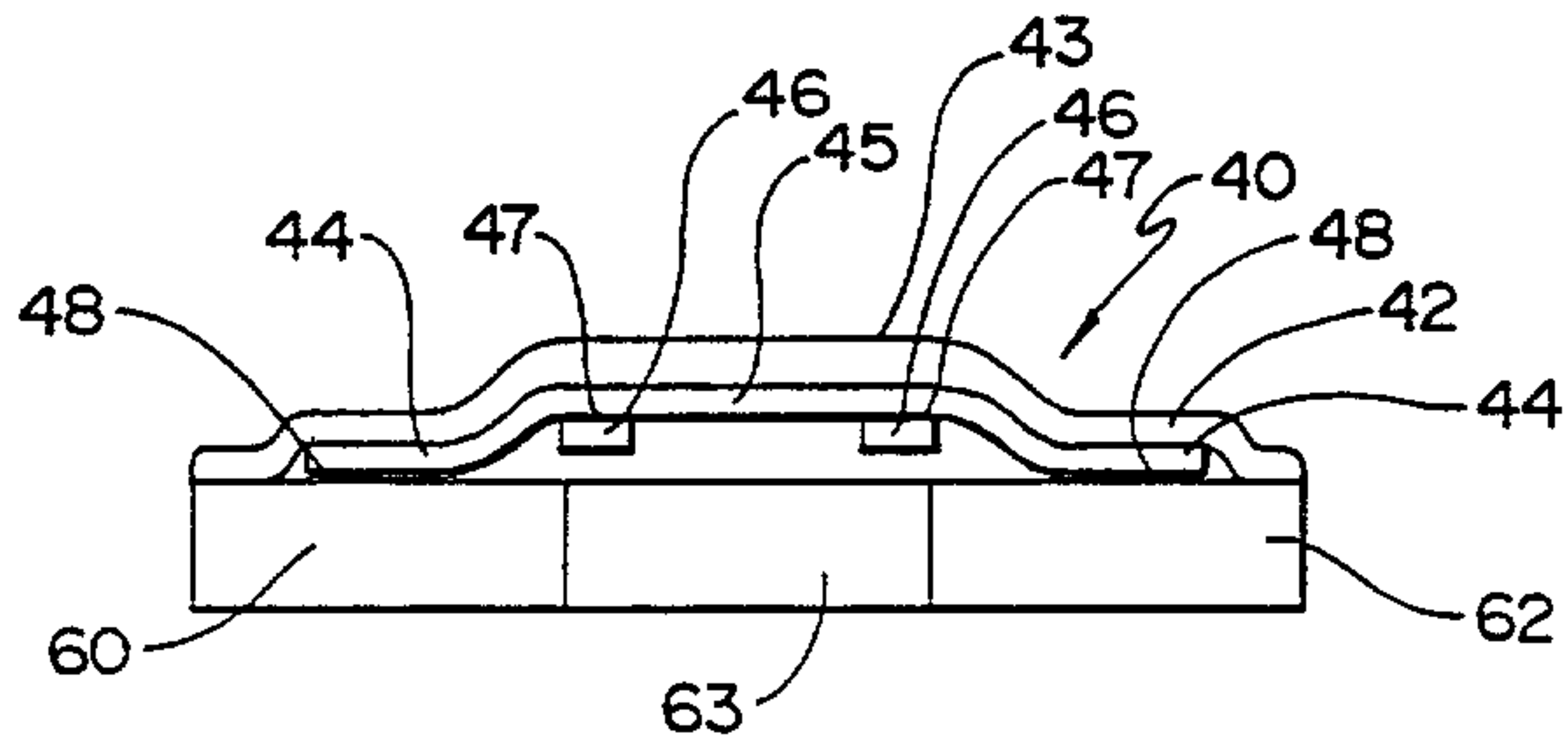


Fig.3

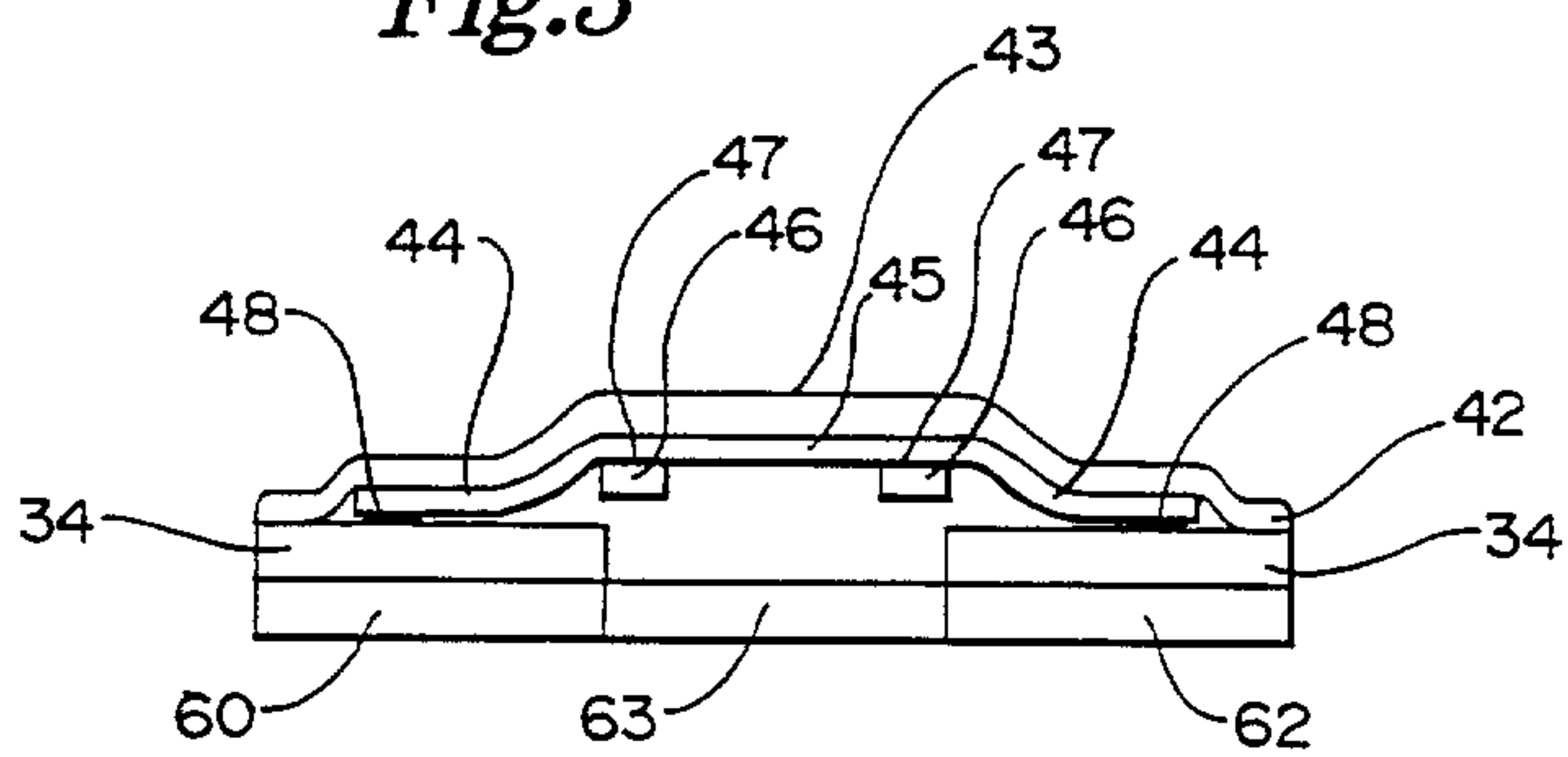
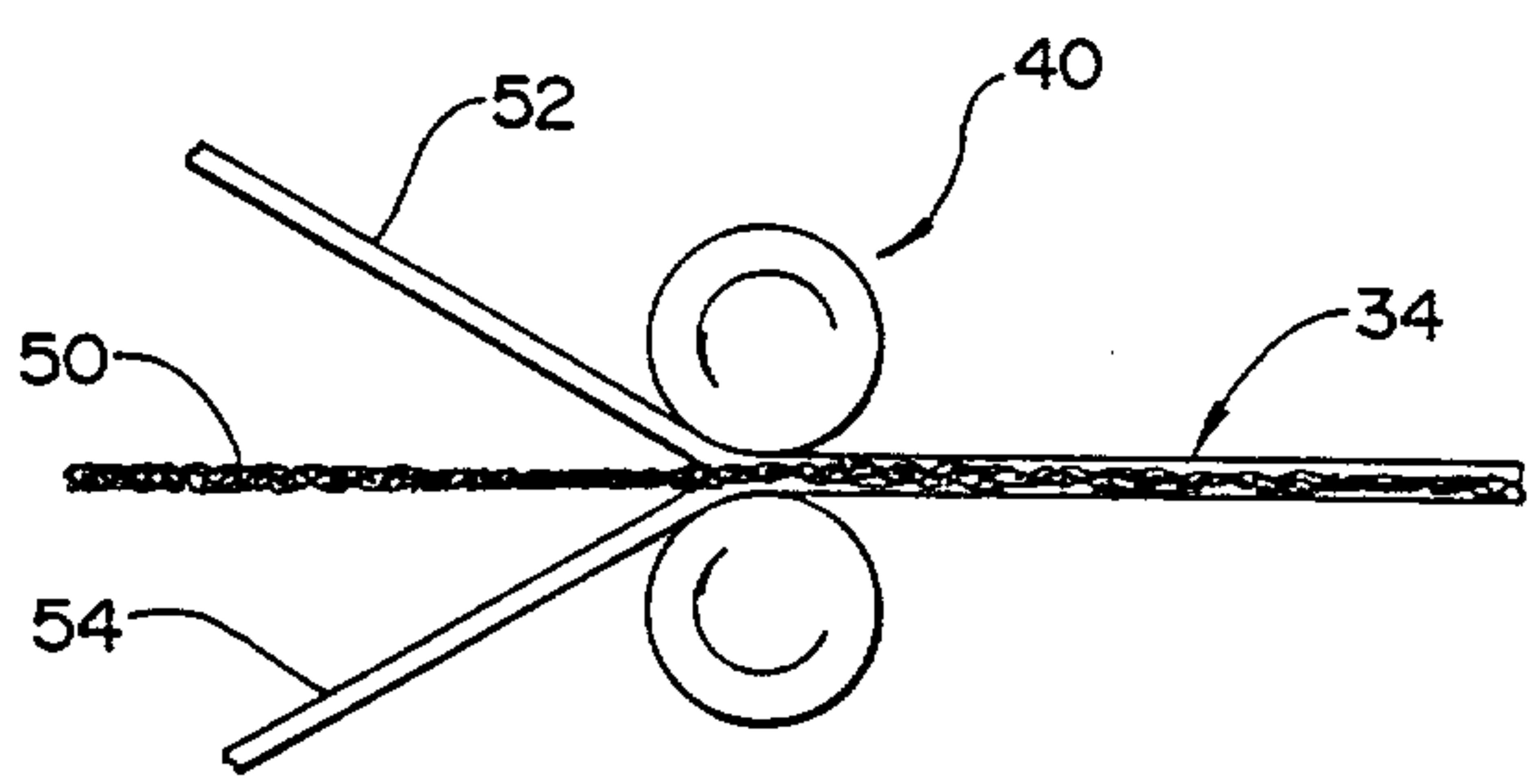


Fig.4



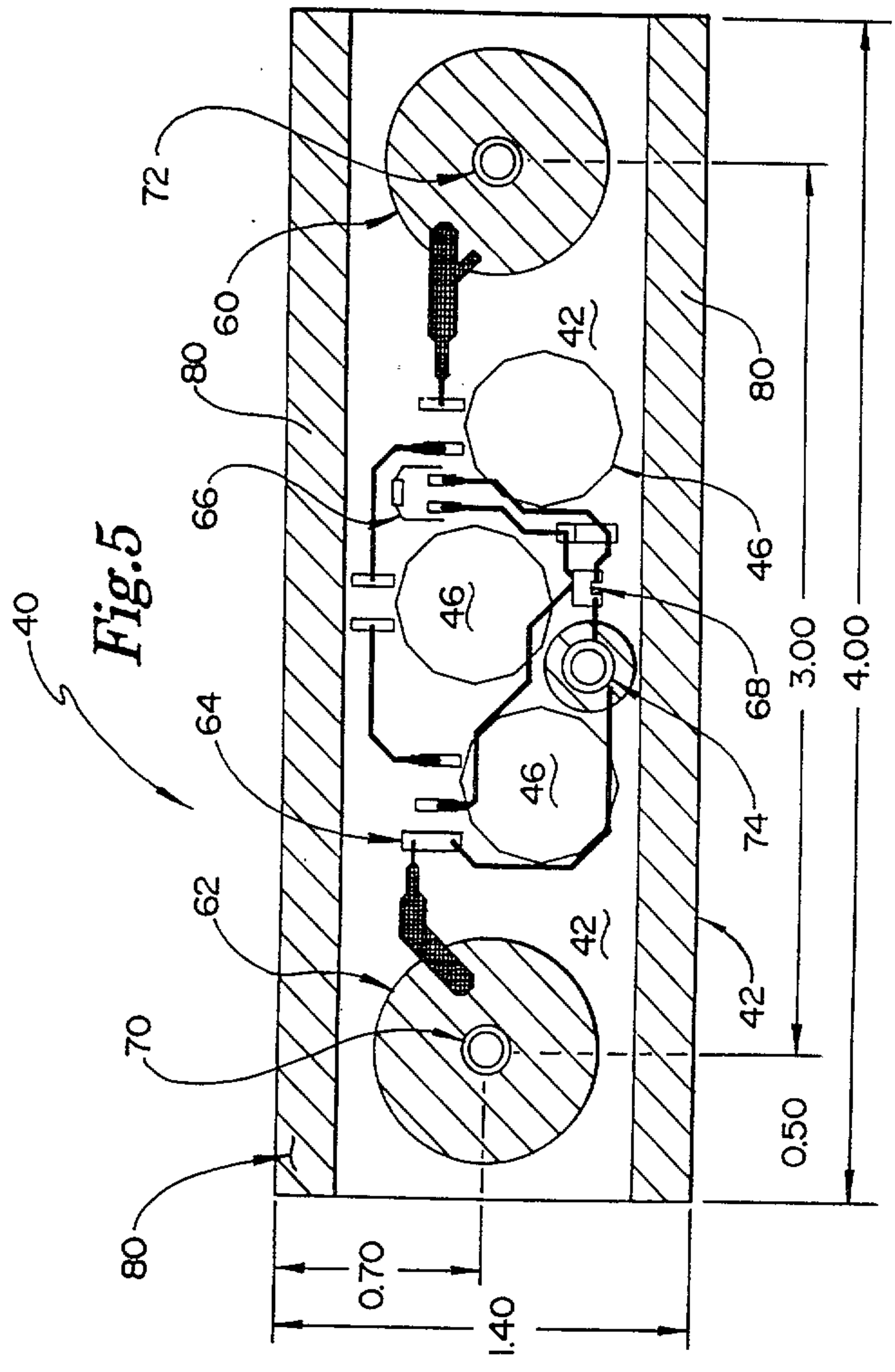


Fig.5

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