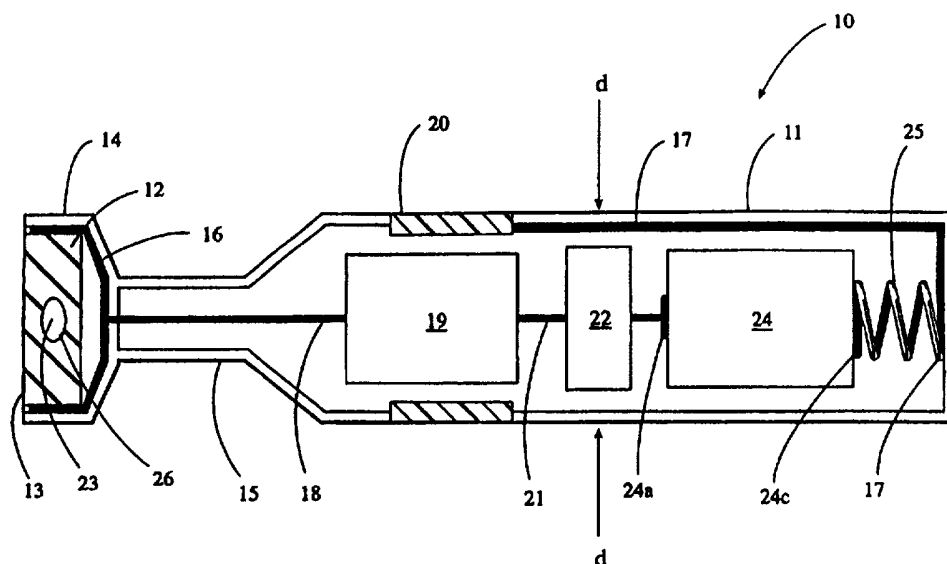




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<p>(21) International Application Number: PCT/US97/07590</p> <p>(22) International Filing Date: 5 May 1997 (05.05.97)</p> <p>(30) Priority Data: 08/646,853 8 May 1996 (08.05.96) US</p> <p>(71) Applicant: THE APS ORGANIZATION, LLP [US/US]; 49 Miles River Road, South Hamilton, MA 01982 (US).</p> <p>(72) Inventor: HENLEY, Julian, L.; 38 Munger Road, Guilford, CT 06437 (US).</p> <p>(74) Agent: RADACK, David, V.; Eckert Seamans Cherin & Mellott, 42nd floor, 600 Grant Street, Pittsburgh, PA 15219 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>

(54) Title: IONTOPHORETIC DRUG DELIVERY APPARATUS AND METHOD FOR USE



(57) Abstract

This invention is a portable iontophoresis apparatus (10) for facilitating delivery of medication across the cutaneous membrane into adjacent underlying tissues and blood vessels. The apparatus employs a modular, detachable non-reusable medicament containing applicator electrode (12) which is adapted to attach to a base assembly (11). The apparatus is designed to be hand held, and includes a circumferential tactile electrode band (20) on the base assembly (11) which provides electrical connection between the skin of the user's hand and one pole (24c) of a bipolar power source (24) housed within the base assembly (11). The opposing pole (24a) of the power source is connected to the applicator electrode (12). The user's body completes the electrical circuit between the applicator and tactile electrodes. A method for using the device for the treatment of Herpes simplex infection, and related viral infections, which produce similar cutaneous lesions, is presented. The apparatus, when used in accordance with the method described herein, demonstrated >90% treatment efficacy in clinical trials.

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**IONTOPHORETIC DRUG DELIVERY APPARATUS
AND METHOD FOR USE**

Inventor: Julian L. Henley, M.D.

BACKGROUND OF THE INVENTION

1. **Field of the Invention:**

This invention relates generally to the transdermal electrokinetic mass transfer of medication into a diseased tissue, and, more specifically, to a portable apparatus for the iontophoretic delivery of medication across the skin and incorporation of the medication into diseased tissues and blood vessels adjacent to the delivery site. The apparatus provides a new method for treating and managing disease presenting cutaneous lesions.

2. **Prior Art:**

Iontophoresis has been employed for several centuries as a means for applying medication locally through a patient's skin and for delivering medicaments to the eyes and ears. The application of an electric field to the skin is known to greatly enhance the skin's permeability to various ionic agents. The use of iontophoretic transdermal delivery techniques has obviated the need for hypodermic injection for many medicaments, thereby eliminating the concomitant problems of trauma, pain and risk of infection to the patient.

Iontophoresis involves the application of an electromotive force to drive or repel oppositely charged ions through the dermal layers into a target tissue. Particularly suitable target tissue include tissues adjacent to the delivery site for localized treatment or tissues remote therefrom in which case the medicament enters into the circulatory system and is transported to a tissue by the blood. Positively charged ions are driven into the skin at an anode while negatively charged ions are driven into the skin at a cathode. Studies have shown increased skin penetration of drugs at anodic or cathodic electrodes regardless of the predominant molecular ionic charge on the drug. This effect is mediated by polarization and osmotic effects.

Regardless of the charge of the medicament to be administered, a iontophoretic delivery device employs two electrodes (an anode and a cathode) in conjunction with the

patient's skin to form a closed circuit between one of the electrodes (referred to herein alternatively as a "working" or "application" or "applicator" electrode) which is positioned at the delivered site of drug delivery and a passive or "grounding" electrode affixed to a second site on the skin to enhance the rate of penetration of the medicament into the skin
5 adjacent to the applicator electrode.

Recent interest in the use of iontophoresis for delivering drugs through a patient's skin to a desired treatment site has stimulated a redesign of many of such drugs with concomitant increased efficacy of the drugs when delivered transdermally. As iontophoretic delivery of medicaments become more widely used, the opportunity for a consumer/patient to
10 iontophoretically administer a transdermal dosage of medicaments simply and safely at non-medical or non-professional facilities would be desirable and practical. Similarly, when a consumer/patient travels, it would be desirable to have a personal, easily transportable apparatus available which is operable for the iontophoretic transdermal delivery of a medication packaged in a single dosage applicator. The present invention provides a portable
15 iontophoretic medicament delivery apparatus and a unit-dosage medicament-containing applicator electrode which is disposable and adapted for use with the apparatus for self-administering medicament.

SUMMARY OF THE INVENTION

20 The present invention discloses a portable iontophoretic transdermal or transmucosal medicament delivery apparatus and a unit dosage medicament applicator electrode adapted for use with the apparatus for the self-administration of a unit dose of a medicament into the skin. The apparatus is particularly suited for the localized treatment of herpes infections. Recurrent herpetic infections (fever blisters or herpes labialis) are very common and usually
25 involve the mucocutaneous juncture. The established treatment for recurrent herpetic lesions (oral or genital) has been primarily supportive; including local topical application of anesthesia. Severe cases have been treated with systemic Acyclovir® (Zovirax Burroughs-Wellcome). Some cases the condition is managed with prophylactic long-term dosing administration with a suitable antiviral agent at great expense. Systemic treatment of acute
30 herpetic flare-ups may reduce the normal 10-12 day course of cutaneous symptoms into a 6-8

day episode. Topical treatment of lesions with Acyclovir® has not been as effective as in vitro studies would suggest. A compound which is not presently available to clinicians but has demonstrated significant anti herpetic activity is 5-iodo-2 deoxyuridine (IUDR). Both of those agents have shown limited clinical efficacy when applied topically to the herpetic lesion. It is the present inventor's contention that the limited efficacy of topical administration previously observed is, at least in part, due to the poor skin penetration of these medicaments when applied topically. The present invention provides improved transdermal delivery of these medicaments and demonstrates improved clinical results in the case of Herpes.

Oral Herpes (most commonly Herpes simplex I infection) as well as genital Herpes (usually Herpes Simplex II infection) afflict many people, cause discomfort, shame, and may contribute to more severe and costly illnesses such as cervical cancer, prostate cancer, and perinatal blindness from herpetic conjunctivitis. The present invention discloses a portable, user-friendly transdermal delivery device and a method for using the device with Acyclovir® (or similar antiviral agent) to greatly benefit these afflicted patients. The present inventor has constructed embodiments of this device and conducted human clinical trials which clearly demonstrate improved therapeutic efficacy using iontophoretically administered antiviral agents when compared to unassisted topical application of the agent.

It is an object of the present invention to provide an iontophoretic medicament delivery apparatus which is portable and operable for self-administration of medicament into the skin of a person.

It is another object of the present invention to provide an improved iontophoretic transdermal drug delivery apparatus having a medicament-containing application electrode which disperses a single dosage and is disposable and non-reusable.

It is a feature of the present invention that the iontophoretic medicament delivery apparatus is easily maneuverable and operable when hand-held.

It is another feature of the present invention that the iontophoretic medicament delivery apparatus is battery powered and conveniently transported by a person.

It is a further feature of the present invention that the iontophoretic medicament delivery apparatus employs a tactile electrode which is in electrical contact with the skin of a user's hand when the apparatus is held in the user's hand, obviating the need for a separate

grounding electrode connector or wire.

It is still another feature of the present invention that the iontophoretic medicament delivery apparatus is adapted to be operable with a disposable medicament containing applicator electrode which applicator electrode includes an absorbent, inert, non-corrosive
5 portion containing a therapeutic agent.

It is yet another feature of the present invention to provide an embodiment of an iontophoretic transdermal delivery device wherein the disposable iontophoretic medicament-containing applicator electrode is adapted for releasable attachment to use with a hand-held base assembly housing a grounding electrode.

10 It is yet another feature of the present invention that the disposable iontophoretic medicament applicator electrode include indicator means operable for enabling a user to determine when the medicament within the removable applicator electrode has been released in delivery and/or depleted.

It is yet another feature of the present invention that the circuitry employed in the
15 disposable iontophoretic medicament applicator include current limiting means operable for limiting the electrical current flowing between the surface of the applicator and the skin to less than about one milliamperere per square centimeters of application electrode skin-contacting surface.

It is another advantage of the present invention that the iontophoretic medicament
20 delivery apparatus employs a disposable application electrode which conducts the electrical current to the tissue through the solution in which the medicament is dissolved.

It is still another advantage of the present invention that the improved disposable iontophoretic medicament applicator is inexpensive, safe to use and greatly increases the therapeutic efficacy of a medicament administered thereby.

25 The apparatus in accordance with the present invention provides a means for topically administering medicament directly and with high efficiency into a diseased tissue thereby providing a novel method for treating clinical conditions presenting mucocutaneous symptoms and particularly mucocutaneous Herpes Simplex viral eruptions and sequelae associated therewith.

The above objects, features and advantages of the invention are realized by the
30 improved monopolar iontophoretic medicament applicator which is easily transportable. The

applicator employs a detachable medicament containing application electrode. The objects, features and advantages of the invention will become apparent upon consideration of the following detailed disclosure of the invention, especially when it is taken in conjunction with the accompanying drawings wherein:

5

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side elevational plan view of the iontophoretic medicament delivery apparatus showing the circumferential tactile ground electrode on the outer surface of the base housing and a disposable iontophoretic application electrode;

10 FIG. 2 is a side elevational view of the disposable non-reusable iontophoretic application electrode with a portion broken away to view the medicament dose packet;

DESCRIPTION OF THE PREFERRED EMBODIMENT

FIG 1 shows, in side elevation, a preferred embodiment of the hand-held iontophoretic
15 transdermal medicament delivery apparatus of the present invention. The apparatus, indicated generally by the numeral 10, has an elongate base assembly 11 the major portion of which is preferably formed of plastic and shaped to conform to and comfortably fit within a users hand. An applicator electrode module 12, containing a unit dose of medicament 23, is releasably attached to a applicator electrode receptacle 14 on the distal end of the base
20 assembly 11. The application electrode 12 is preferably a "clip-on" type of electrode similar in configuration to an electrocardiogram electrode. In the drawing presented in Figures 1 and 2, electrically conductive elements such as wires and busses are presented as heavy lines. A wire 16 provides electrical connection between the applicator electrode receptacle 14 and wire 18 within the neck 15 of the base assembly 11. Connecting wire 18, in turn, provides
25 electrical connection between the wire 16 and the current driver unit 19 housed within the base assembly 11. A conductive tactile electrode 20 forms a portion of the exterior skin-contacting surface of the base assembly 11 preferably circumferentially enclosing a portion of the base housing or it may be interrupted or discontinuous on the outer surface. The tactile electrode 20 is in electrical communication with the cathode 24C of battery 24 by
30 means of a buss 17 and conductive urging spring 25 which secures the battery in position

within the base assembly 11. For the self-administration of medicament a user must have skin contact with the tactile electrode 20 for the unit to operate. Current driver 19 underlies the cathodic (ground) tactile electrode 20 and is electrically connected via wire 21 to a voltage multiplier 22. The voltage multiplier 22 receives low voltage power from the anode 5 24a of the battery power source 24 and increases the available voltage for presentation to the application electrode 12. The battery 24 is preferably a size AA or AAA. Battery 24 is held in place by an electrically conductive biasing spring 25 and ensures that electrical power is available at the application electrode 12 when the user grasps and holds the base housing 11 of the apparatus 10 thereby touching the cathodic tactile electrode 20. The application 10 electrode 12 and the tactile electrode 20 thus form a closed circuit in series with the user's skin.

When current flows across the user's skin to the application electrode in response to an applied voltage the current promotes and hastens the penetration of the medicament 23 contained in a reservoir 26 within the working electrode 12 into the skin. The polarity of 15 the working electrode 12 is preferably unidirectional to promote the above described penetration without requiring a separate grounding electrode. The working application electrode 12 will be described in greater detail below.

The base assembly 11 of apparatus 10 serves as a housing to the aforesaid components as a handle. The portion of the base assembly 11, exclusive of the tactile electrode, is 20 preferably made of a plastic such as polyethylene, acrylonitrile, butadiene, styrene or similar durable plastic. The battery portion 24 is connected to a voltage multiplier 22 which steps up the voltage supplied by the battery 24 and applies the stepped up voltage to the current driver 19. Current driver 19 presents a defined current and voltage output at the application electrode 12 the value of the current, which may be empirically determined being sufficient 25 to drive the medicament through the porous, open-celled material 27 (Figure 2) within the application electrode interposed between the skin contacting surface 13 and reservoir 26 containing the unit dose medicament and penetrate the patient's skin. The circuitry limits the maximum current available to the application electrode to preferably to less than about one milliampere per two square centimeters of the skin-contacting surface area 13 of the 30 application electrode 12. However, depending upon working electrode's 12 skin-contacting

surface 13 configuration, the current level can vary from about 0.1 to about 1.2 milliamps. Currents ranging between .1 ma to 5 ma have been used clinically by the present inventor, but the higher currents caused the user minor discomfort and, with chronic use over time, may produce untoward effects.

5 FIG 2 shows a preferred embodiment of the iontophoretic medicament-containing application electrode 12. The application electrode 12 is preferably disposable and non-reusable and is suitable, for example, for transdermally delivering antiviral agents such as Acyclovir® for the treatment of cold sores or genital herpes. The size of the skin-contacting surface 13 of application electrode 12 may vary to accommodate specific clinical
10 applications. The application electrode 12 is detachably housed within a recess within the receptacle 14 which recess presents an electrically conductive interior surface to complete the electrical flow path from the connecting wires 18 and 16 to a conductive element 29 within the application electrode. The electrical current from the current driver 19 is conducted through conductive inner surface of the application electrode receptacle 14 to the electrically
15 conductive element 29 within the applicator electrode which element 29 is in electrical contact with the inner surface of the receptacle in contact therewith to drive the medicament 23 or treatment agent through the open-celled sponge-like matrix material 27 and through the user's skin (not shown). The medicament or treatment agent 23 is contained within a rupturable polymer reservoir 26 until dispensed during treatment. A slight exertion of
20 pressure or squeezing of the reservoir 26 against reservoir puncture means 28 releases the medicament or treatment agent into an open-celled sponge-like material 27 within the application electrode for iontophoretic delivery into the patient's skin. Medicament 23 release can occur at the time of application or upon peruse compression of the electrode 12. Application electrode 12 can be advantageously designed to include a stripping portion
25 adapted so that upon removal of the application electrode 12 from the electrode receptacle 14 a protruding stripping portion (not shown) scrapingly strips the conductive coating from the conductive support arm 29 to prevent reuse of the disposable electrode 12. Application electrode 12 is intentionally packaged with a single dose packet or reservoir 26 of treatment agent or medicament 23. In addition to the medicament, the reservoir 26 can include a
30 coloring agent, such as iodine, which turns dark blue upon contact with starch in the open-

celled material to visibly indicate that the unit dose encapsulation has been used. Other suitable coloring agents can include pH indicators, wet saturation indicators or oxidizable pigments.

The open-celled sponge-like material 27 surrounding reservoir 26 should be inert to the medicament or treatment agent being employed, as well as being non-corrosive and stable when in contact with the treatment agent. Suitable materials include plastic pads, such as polyethylene, paper or cotton, porous ceramics, open-celled porous polytetrafluoroethylene, polyurethane and other inert plastics, and open-celled silicone rubber, such as may be employed with vertically aligned medicament-containing tubes. A typical medicament that can be contained within the rupturable polymer reservoir 26 is xylocaine or similar topical anesthetic.

The disposable electrode 12 possesses the advantages of preventing leaching or migration of the medicament from within the rupturable polymer reservoir, no attendant loss of efficacy, a long shelf life and little or no electrode corrosion. A suitable electrical control circuit for use in the iontophoretic medicament delivery apparatus 12 is shown in U.S. Patent Application, Serial No. 07/157,799, filed September 10, 1990, now US Patent 5,160,316 and hereby specifically incorporated by reference herein in pertinent part.

EXPERIMENTAL CLINICAL TRIALS

The inventor has conducted a clinical study using a prototype iontophoretic device in accordance with the present invention for the treatment of cold sores. The clinical response was promising. A second independent, qualified investigator, a board-certified Urologist, conducted a study using the present apparatus and method for treating male genital herpes lesions with encouraging results. Table 1 summarizes data (discussed below) supporting the claim to unexpected clinical benefits treating disease with this novel method. The method and medicament application device when used together for treating these common, embarrassing, and previously not easily-treatable ailments provide surprising advantages.

The embodiment 1c of the device described hereinabove is a improvement over the prototype used in the clinical study, which was a larger unit, not user friendly, which required physically connecting wires to the patient's body which created anxiety, and could

not be used without attending personnel. Notwithstanding design, the apparatus used in the clinical study summarized in Table 1 employed electronics similar to the apparatus described herein and was used to optimize the clinical performance of the embodiment 12 of the device described herein.

5

TABLE 1			
STAGE I TREATMENT RESULTS			
<u>RESPONSE</u>	<u>IUDR</u>	<u>ACYCLOVIR®</u>	<u>TOTALS</u>
No response	1	1	2
Some response	1	3	4
Major response	26	42	68

The study included a control situation wherein seven patients were found who had simultaneous concurrent herpes lesions at separate locations on their bodies. In each case one lesion was treated with iontophoretic application of antiviral agent (Acyclovir® or IUDR) and the other lesion was treated in the standard method employed in the prior art comprising repeated topical application of the same antiviral agent. The iontophoretically enhanced treated lesion received a single 10-15 minute treatment. All iontophoretically treated lesions demonstrated resolution in 24 hours and none of the unassisted topically treated lesions demonstrated a similar response. The results for the control group are summarized in Table 2.

TABLE 2			
CONTROL GROUP RESULTS			
	<u>No response</u>	<u>Some resp.</u>	<u>Major resp.</u>
<u>IUDR</u>			
Treated lesion	0	0	7
Control lesion	5	2	0
<u>ACYCLOVIR®</u>			
Treated lesion	0	0	1
Control lesion	1	0	0

The clinical studies included patient volunteers with full informed consent who suffered from recurrent cold sores. The study demonstrated greatest treatment efficacy if the herpes lesion received iontophoretic treatment within 36 hours of lesion onset. The treatment incorporated an electrode saturated with Acyclovir[®] ointment (ZOVIRAX[®]) or IUDR
5 (STOXIL[®]) Ophthalmic drops as supplied by the manufacturer. Thus mounted Anodic electrode of the prototype system was used for a 10-15 minute application directly to the lesion with the average current setting of .2 ma-.6 ma which was well tolerated by all patients.

The lesion was evaluated in 24 hours. In 92% of the iontophoretically treated cases
10 (>70 lesions treated) a major response was noted. A major response was categorized by resolution of pain in <6 hours and lesion crusted and healing within 24 hours. The normal course of cold sores involves an average period of 10-12 days before resolution and healing occurs. The present apparatus and clinical method for treatment of mucocutaneous Herpes Simplex (type I and Type II) eruptions presented herein have been described and performed
15 with excellent results. This novel user friendly apparatus in combination with the disclosed clinical treatment method presents a very effective new treatment for Herpes Simplex eruptions.

While the invention has been described above with references to specific embodiments thereof, it is apparent that many changes, modifications and variations in the materials,
20 arrangements of parts and steps can be made without departing from the inventive concept disclosed herein. For example, an impregnated conductive gel can also be used to as medicament containing medium to increase the physical stability and the tissue adhering characteristics of the electrode. Accordingly, the spirit and broad scope of the appended claims is intended to embrace all such changes, modifications and variations that may occur
25 to one of skill in the art upon a reading of the disclosure. All patent applications, patents and other publication cited herein are incorporated by reference in their entirety.

What I claim is:

CLAIMS

1. An iontophoretic drug delivery device for personal use for self-administering a medicament into a person's skin, said device comprising a base assembly and a detachable applicator electrode wherein said base assembly comprises:
- 5 (a) a case having an elongate, substantially cylindrical outer surface having a size and shape adapted to be comfortably grasped within a person's hand and wherein at least a portion of said outer surface is a tactile electrode formed of an electrically conductive material;
- (b) a bipolar electrical power means having a first pole and a second pole; said
10 electrical power means being enclosed within said case and wherein said first pole is an electrical communication with said tactile electrode;
- and wherein said applicator electrode comprises a module containing a porous matrix portion, a unit dose of medicament, an electrically conductive working electrode and attachment means adapted for releasably attaching said applicator electrode to said base assembly to
15 provide electrical connection between said working electrode and said second pole of said electrical power means and wherein said iontophoretic delivery device is operable for releasing said medicament from said porous matrix to a portion of the person's skin in contact with said porous matrix portion of said applicator electrode.
- 20 2. The device in Claim 1 wherein said unit dose of medicament is encapsulated within a rupturable reservoir.
3. The device in Claim 2 wherein said rupturable reservoir further contains a visualizing agent which is released when said reservoir is ruptured thereafter providing a visual signal
25 indicating the release of medicament.
4. The device according to Claim 2 wherein said applicator electrode has an outer treatment surface and a porous material disposed between said reservoir and said treatment surface.

5. The device according to claim 3 wherein said applicator electrode has an outer treatment surface and a porous material disposed between said reservoir and said treatment surface.

5 6. The device according to Claim 4 wherein said reservoir is in fluid communication with said porous material.

7. The device according to Claim 5 wherein said reservoir is in fluid communication with said porous material.

10

8. The device of Claim 4 wherein the porous material is selected from the group consisting of polyethylene, paper, cotton, polytetrafluoroethylene, open-celled polyurethane, open-celled silicone and ceramic.

15 9. The device of Claim 5 wherein the porous material is selected from the group consisting of polyethylene, paper, cotton, polytetrafluoroethylene, open-celled polyurethane, open-celled silicone and ceramic.

10. A method for treating mucocutaneous Herpes Type I and Type II infections present
20 mucocutaneous lesion comprising the iontophoretic transdermal delivery of 9-[(2-hydroxyethoxy)methyl]guanine into tissue overlying said lesion.

11. A method for treating Herpes conditions in accordance with Claim 10 for clinical conditions suspected to be caused by Herpes Simplex virus infection.

25

12. A method for treating lesions associated with cold sores and genital herpes comprising the dispensation, application and transdermal self-application of an active antiviral agent contained within a hand held iontophoretic device to said lesions.

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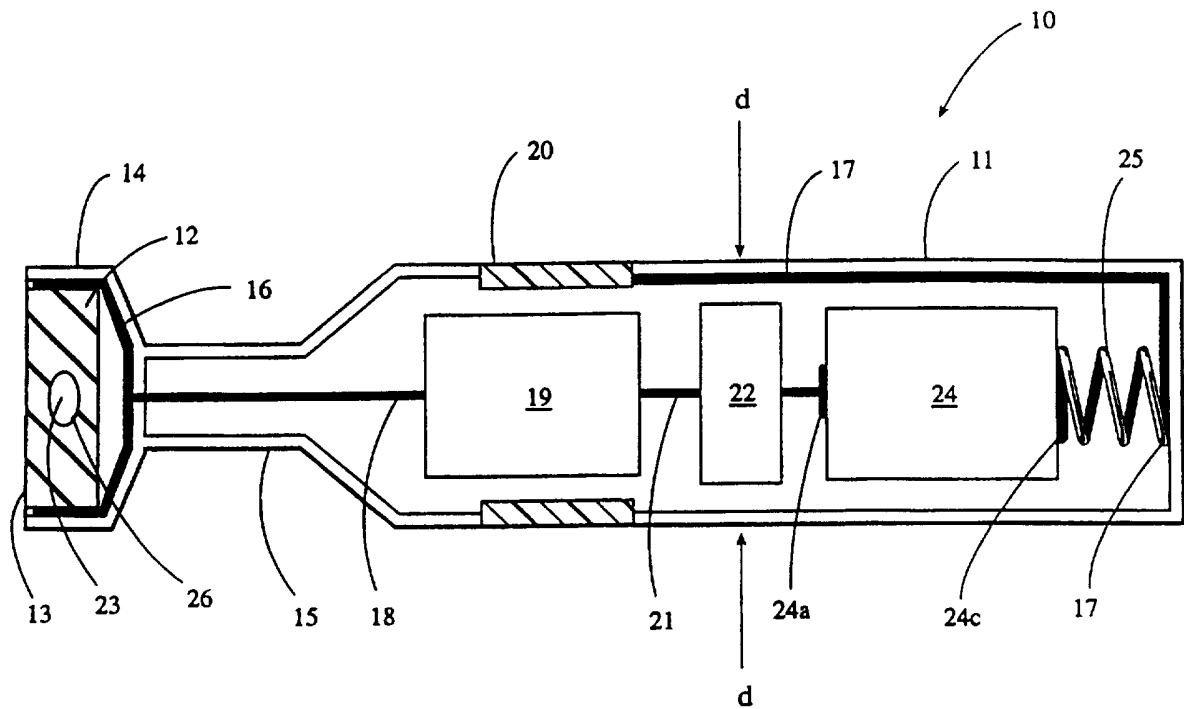


Figure 1

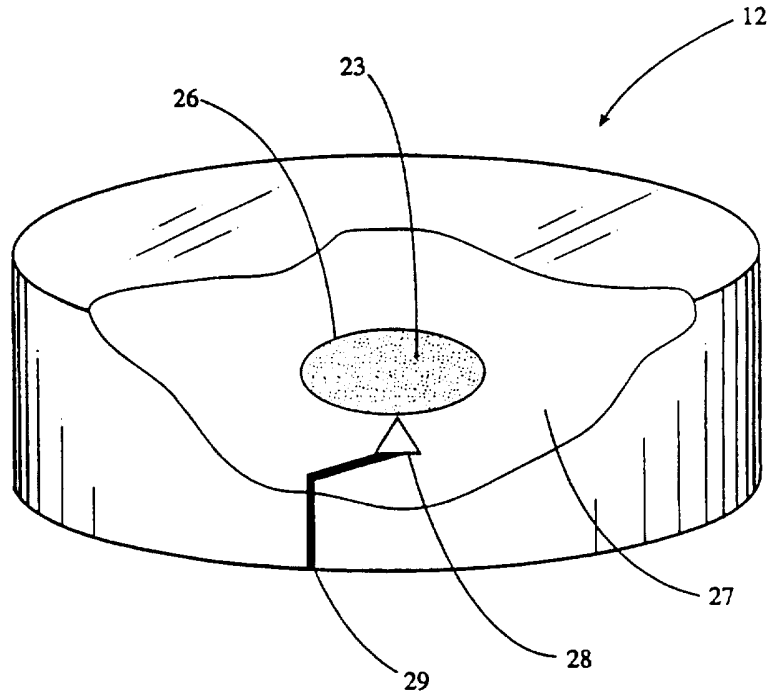


Figure 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/07590

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61N 1/30

US CL : 604/20

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
604/19

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

APS

Search Terms: iontophoresis, herpes, simplex, type I, type II, acyclovir

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	US 3,163,166 A (BRANT et al.) 29 December 1964, entire reference.	12 ----- 1-9
A	US 5,160,316 A (HENLEY) 03 November 1992, Fig. 3, and col. 5.	2-9
Y	US 5,279,543 A (GLIKFELD et al) 18 January 1994, Table 4, line 20.	10-12
Y	US 4,702,732 A (POWERS et al.) 27 October 1987, col. 4, lines 55 and 56.	10-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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