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Review

Iontophoretic Devices for Drug Delivery

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Transdermal drug delivery of ionized drugs can be enhanced by iontophoresis. Drug in the ionic form, contained in some reservoir, can be "phoresed" through the skin with a small current across two electrodes, one above the reservoir and one at a distal skin location. Positive ions can be introduced from the positive pole, or negative ions from the negative pole. The design and development of iontophoretic devices are rather simple. Some of the principles of operation and the advantages/disadvantages and clinical implications associated with these devices are outlined in this review.

KEY WORDS: Iontophoresis; Drug Delivery Devices; Controlled Drug Delivery; Transdermal Drug Delivery; Electroosmosis; Drug Delivery; Devices.

INTRODUCTION

In conventional transdermal drug delivery, the delivery of the drug to the site of action at therapeutic levels is sometimes hindered because many drugs are ionized and, as such, are unable to penetrate the skin surface adequately. The stratum corneum is the main barrier limiting the passive transepidermal diffusion of ionized molecules. The transfollicular and transappendageal (skin pores) routes constitute the major penetration pathways for the ionized molecules (1–5); however, the surface area occupied by these pathways is relatively small (Fig. 1). The only skin appendages applicable are hair follicles, sebaceous glands, and the eccrine sweat glands (1). Penetration of ionic drugs by the transfollicular and transappendageal routes can be facilitated by the application of electricity.

Iontophoresis (or ion transfer) is defined as the migration of ions when an electrical current is passed through a solution containing ionized species. A schematic representation of this phenomenon is shown in Fig. 2. Drugs in the ionic form, containing in some reservoir, can be "phoresed" out with a small current and driven into the body through the skin (6–12). The potential affects ions already present in tissues but, more importantly, also affects ionized drugs at the skin surface and can drive them into the body through the skin pores (1). Electrical potential by itself does not change skin permeability (4,13). Positive ions can be introduced into the tissues from the positive pole, while those of negative charge from the negative pole.

Various reports exist in the literature showing a relative increase in the absorption rate and total amount of drug absorbed when iontophoresis is used compared to the conventional methods of transdermal drug delivery. This noninvasive drug delivery minimizes trauma, risk of infection, and damage to the wound and is an important alternative to the needle.

THERAPEUTIC APPLICATIONS

As early as 1908, LeDuc (14) showed that chemicals could be carried across an avascular membrane using electric potential as an electromotive force. Strohl *et al.* (15) found considerable activity in the blood after electrophoretic introduction of radioactive sodium iodide into the skin of rats, guinea pigs, and rabbits, whereas the penetration by "simple diffusion" (meaning application without electric current) was negligible. Their results are shown in Fig. 3. It is suggested that iontophoresis could markedly facilitate the transdermal transport of ionized drug molecules (10–16). In

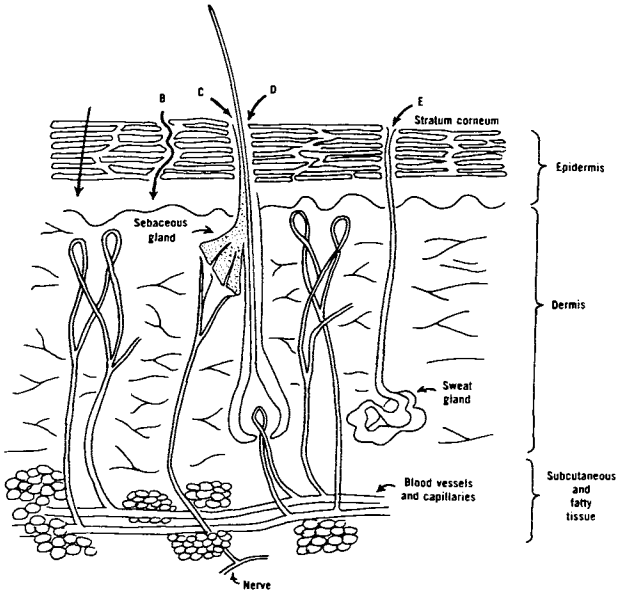

Fig. 1. Schematic presentation of probable routes of penetration. Key to sites of percutaneous penetration: A, transcellular; B, diffusion through channels between cells; C, through sebaceous ducts; D, transfollicular; E, through sweat ducts. (Reproduced with permission from Ref. 78.)

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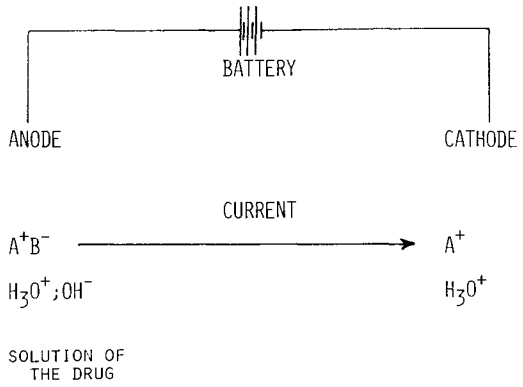

Fig. 2. Movement of active drug ions A^+ from anode to cathode under the influence of current.

other words, percutaneous absorption can be regulated by the strength of the current.

A schematic representation of the complete circuit involved in the process of iontophoresis is shown in Fig. 4. Shelley *et al.* (6) tested nine antihistaminic compounds and concluded that they could be administered transdermally by iontophoresis to achieve local antihistaminic action. Also, the effect of iontophoresis was that of acceleration of absorption. They also concluded that since the acceleration was roughly equivalent for similar compounds, it is possible to correlate the effectiveness of compounds introduced by

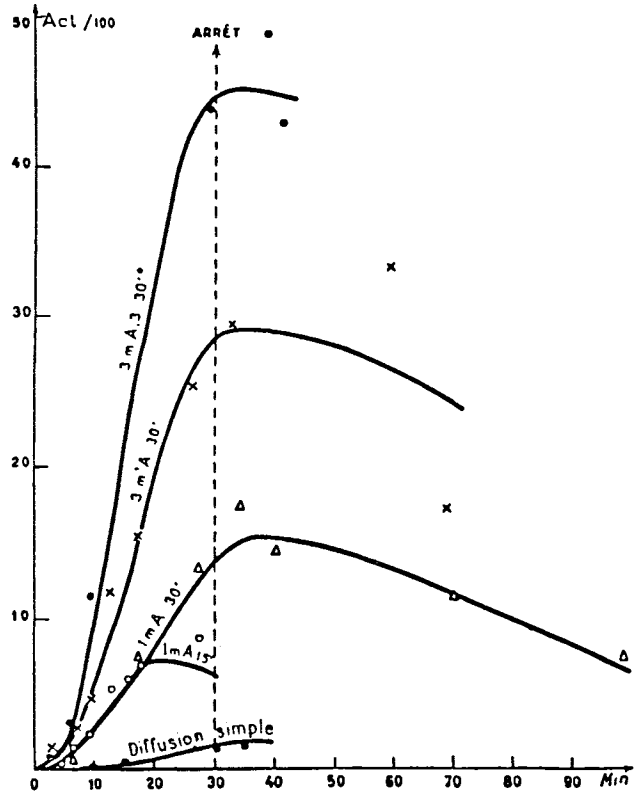

Fig. 3. Development of activity in the blood of rats as a function of intensity of current and length of application after electrophoretic introduction of radioactive sodium iodide into the skin. (Reproduced with permission from Ref. 15.)

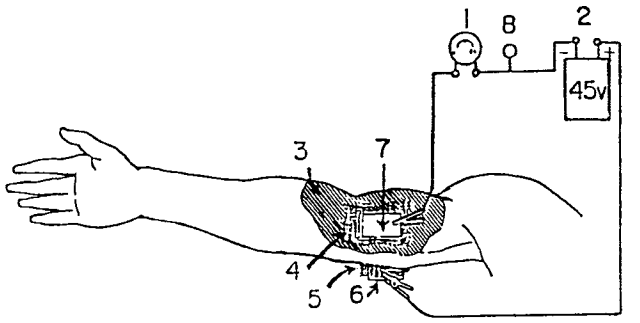

Fig. 4. A schematic representation of iontophoresis circuit. 1, Milliameter; 2, battery; 3, Scar; 4, gauze with drug; 5, gauze with saline; 6, electrode (positive); 7, electrode (negative); 8, potentiometer. (Reproduced with permission from Ref. 10.)

iontophoresis with their effectiveness when applied in topical preparations.

Iontophoresis at some unusual sites has also been reported. Iontophoresis of sulfa drugs, for pyocyaneous infection, was 3 to 12 times greater in the cornea and 3 to 15 times greater in the aqueous humor of the eye than that resulting from diffusion alone (16). The results are shown in Fig. 5. The results of Rapperport *et al.* (10) show that the amount of penicillin deposited through burn eschar and into the avascular tissue was 200-fold greater with iontophoresis compared with simple diffusion.

Harris (17) concluded that iontophoresis is a clinically effective, painless, and safe mode of delivering ionized antiinflammatory drugs to inflamed tissues. Delacerda (18) also showed that the effect of iontophoresis of antiinflammatory drug in shoulder girdle myofascial syndrome is more effective than treatment with muscle relaxant and analgesic medicament or treatment with hydrocollator/ultrasound modalities.

Table I summarizes the various disease conditions in which iontophoretic drug delivery has been used. It should be realized that much of the work done prior to 1960 was based on clinical impressions rather than on a quantitative estimation of the amount of material introduced. Few controlled trials have been undertaken, and even when these approach the "double blind" technique, comparison with results obtained by other methods has not been made.

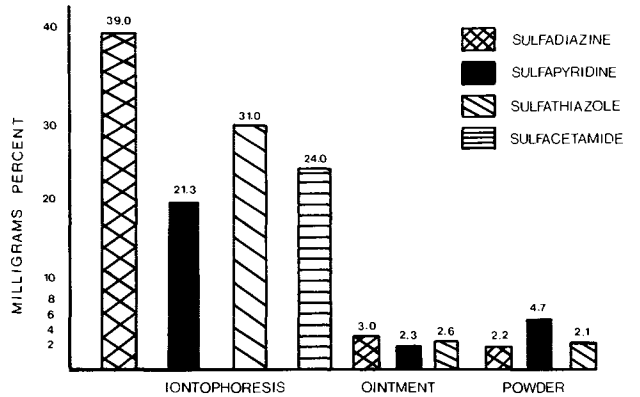

Fig. 5. Comparative concentrations of sulfa drugs in the aqueous of the eye after application by various methods. (Reproduced with permission from Ref. 16. Copyright by the Ophthalmic Publishing Company, Chicago, Illinois.)

Table I. Drugs Used in Various Disease Conditions for Therapy by Iontophoresis

Drug	Condition/disease	Reference (No.)
1. Methylene blue and potassium iodide	Skin disorders (e.g., Demodex infection)	Jenkinson and Walton (7)[a]
2. Pencillin	Burns	Rapperport *et al.* (10)[d]
3. Histamine	Disease conditions of soft tissues, bursae, and tendons	Kling and Sashin (11)[a]
4. Sodium iodide	Electrolytes	Strohl *et al.* (15)[d]
5. Sulfa drugs	Pyocyaneus infection	von Sallmann (16)[d]
6. Dexamethasone, sodium phosphate, xylocaine	Musculoskeletal inflammatory conditions	Harris (17)[a] Delacerda (18)[a]
7. Copper	Contraception	Riar *et al.* (19)[d]
8. Insulin	Diabetes	Kari (21)[d] Stephen *et al.* (22)[d]
9. Pilocarpine	Cystic fibrosis	Webster (23)[d]
10. Ragweed pollen extract	Hay fever	Abramson (31)[a]
11. Phosphorus		O'Malley and Oester (35)[d]
12. Water	Hyperhidrosis	Tapper (43)[a]
13. Citrate	Rheumatoid arthritis	Coyer (51)[a]
14. Dexamethasone Na phos. and lidocaine HCl	Primary tendonitis	Bertolucci (52)[b]
15. Hyaluronidase	Hemorrhages	Boone (53)[a]
16. Vidarabine monophosp. (Ara-AMP)	Keratitis (herpes virus)	Kwon *et al.* (54)[d] Hill *et al.* (56)[d]
17. Lignocaine HCl or lidocaine	Topical analgesia	Comeau *et al.* (9,28)[d] Russo *et al.* (12)[b] Echols *et al.* (27)[a] Siddiqui *et al.* (38)[c] Petelenz *et al.* (55)[b] Schleuning *et al.* (59)[a] Gangarosa (60,61)[a] Arvidsson *et al.* (62)[a]
18. Acetyl beta methylcholine Cl	Arteriosclerosis	Cohn and Benson (57)[a]
19. Acetyl beta methylcholine	Arthritis	Martin *et al.* (58)[a]
20. Idoxuridine	Herpes simplex, keratitis	Gangarosa *et al.* (60,63)[b]
21. Sodium floride	Dentin	Gangarosa (60)[a]
22. Methylprednisolone succinate	Postherpetic neuralgia	Gangarosa *et al.* (64)[a]
23. Lidocaine, epinephrine, and corticosteroid	Temporomandibular joint–myofascial pain dysfunction syndrome	Ganagrosa and Mahan (65)[a]
24. Sodium salicylate	Planter warts	Gordon and Weinstein (66)[a]
25. Calcium	Myopathy	Kahn (67)[a]
26. Acetic acid	Calcium deposits	Kahn (68)[a]
27. Zinc	Nasal disorders	Weir (69)[a]
28. Esterified glucocorticoids	Peyronie's disease	Rothfeld and Murray (70)[a]
29. Vasopressin	Lateral septal neuron activity	Marchand and Hagino (71)[c]
30. Alkaloids	Chronic pain	Csillik *et al.* (73)[a]
31. Optidase	Arthrosis	Ulrich (74)[a]
32. Natrium salicylicum butazolindin	Acute thrombophlebitis	Kostadinov *et al.* (75)[a]
33. Penicillin	Pneumonia and abscesses of lungs	Sokolov *et al.* (76)[d]
34. Papaverine and nicotinic acid	Cervical osteochondrosis with neurological symptoms	Ostrokhovich and Strelkova (77)[d]
35. Grasses	Allergy	Shilkret (80)[a]
36. 6-Hydroxydopamine	Ocular infection	Caudil *et al.* (81)[d]
37. Metoprolol	Beta-blocker (angina pectoris)	Okabe *et al.* (82)[d]

[a] Based on clinical impressions (qualitative).
[b] Based on double-blind study (well-controlled study).
[c] Based on *in vitro* experiments.
[d] Based on controlled comparative study (quantitative, but not double blind).

Table II shows the effect of duration of iontophoresis, at a fixed current, on the rate of sweat production (23,24). The drug used was 0.5% pilocarpine in the diagnosis of cystic fibrosis. The optimum sweating rate was attained when the quantity of electrical charge delivered reached a value of about 47 mC/cm^2 of skin. This deposits approximately 0.1 mg pilocarpine/cm^2, which is the recommended dosage for the diagnosis of cystic fibrosis. This technique is reported as reliable and more advantageous than other methods of collecting sweat because it is rapid, with minimal discomfort, and accurate, and the chance of producing hyperpyrexia in critically ill infants or children is eliminated (22).

Riar *et al.* (19) found that copper iontophoresis is a promising method for male contraception. Copper was deposited in the form of a depot from where it is released into the lumen and acts as a spermicidal agent. One deposition was sufficient for 9 months. Copper was deposited by iontophoresis into vasa deferentia of animals, using a 1-mA current for 30–90 sec in rats and a 3-mA current for 60 sec in rabbits. Gangarosa *et al.* (20) measured electrical conductivities, *in vitro,* of several local anesthetics, vasoconstrictors, corticosteroids, anticancer drugs, and antiviral agents and found them suitable for iontophoretic delivery.

Recently, macromolecules have been delivered iontophoretically for systemic action. Cathodal iontophoresis, with currents of 0.2–0.8 mA, was used to deliver insulin transdermally in rabbits from reservoirs containing regular pork insulin concentrations of 10–500 U/ml in aqueous solution (21). Regardless of the level of current used, a decrease in blood glucose levels and an increase in serum insulin levels within 1 hr were observed. A representative graph is shown in Fig. 6. The amount of insulin delivered was observed to be limited by the current (<0.4 mA) and the amount of insulin available for iontophoresis. The delivery of this protein can open an entire new era in the pharmaceutical industry and an alternate therapy for diabetes. Stephan *et al.* (22) also proved trancutaneous administration of insulin by iontophoresis in pigs. However, their attempts in human volunteers failed because regular soluble insulin is only weakly charged and much of it is present in a polymeric form.

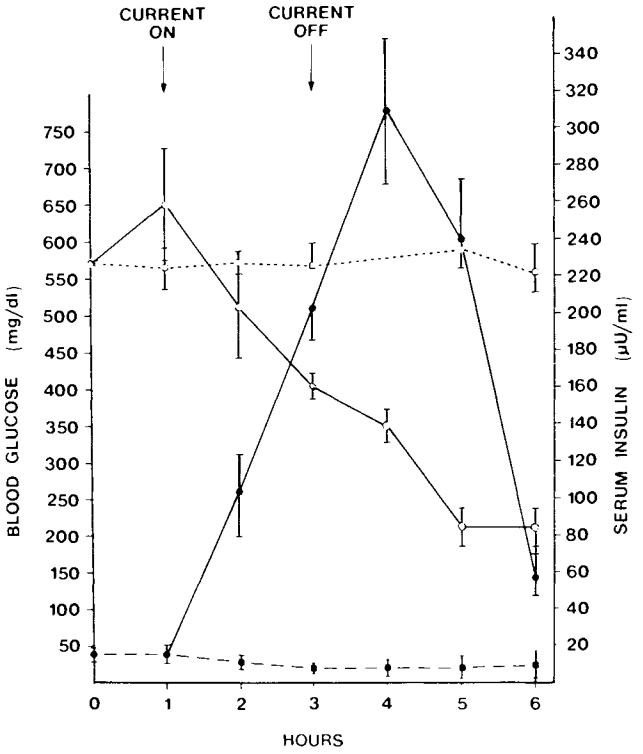

Fig. 6. Alloxan-diabetic rabbits were given insulin by iontophoresis using a current of 0.4 mA for 2 hr and reservoirs containing 300 U of regular pork insulin. In control experiments, animals were prepared in the same manner and a drug reservoir was placed on the iontophoresis site; however, no current was applied. Control blood group level (BGL), □·····□; control serum insulin concentration (SIC), ■·····■; BGL in experimental animals, ○——○; and SIC in experimental animals, ●——●. All experimental values represent the mean ± SE of four different experiments using four different animals. (Reproduced with permission from Ref. 21.)

Local Anesthetic Agents. A typical local anesthetic drug is a weakly basic tertiary amine which is soluble in lipids but poorly soluble and unstable in water (25). Conversely, salts of these bases are readily soluble in water and

Table II. Effect of the Duration of Iontophoresis, at a Fixed Current, on the Subsequent Rate of Production of Sweat[a]

Iontophoresis duration (min)	Volume of sweat (μl)	Rate of sweat production (g/m^2/min)	Quantity of electricity delivered to skin (mC/cm^2)	Pilocarpine deposited at skin surface (mg/cm^2)
1	26	3.0	15.7	0.03
2	30	3.5	31.4	0.07
2.5	50	5.8	39.3	0.09
3	60	7.0	47.1	0.10
5	61	7.1	78.5	0.17
7	66	7.7	109.9	0.24

[a] Experimental conditions: iontophoresis, using 0.5% pilocarpine, at a fixed current of 1.5 mA, applied to a circular area of skin (5.73 cm^2) on the flexor surface of the forearm. The same area of skin was stimulated for each experiment to ensure identical sweat-gland contribution; 15-min collection under heated cup, immediately following iontophoresis. Reprinted with permission from Ref. 23 Copyright CRC Press, Inc., Boca Raton, Florida.)

stable in solution. The usual local anesthetic solution contains a salt (commonly the hydrochloride) of the base. In this aqueous solution, the positively charged quaternary amine species is in equilibrium with the uncharged base according to (25)

$$R \equiv NH^+(\text{cation}) \rightleftarrows R \equiv N(\text{base}) + H^+$$

Since the *p*Ka of most local anesthetics lies between 7.5 and 9.0, the solution at tissue pH [isoelectric range, 3–4; pH of skin surface is 3.78 (26)] contains more cations than base, as derived from the Henderson–Hasselbalch equation. Because of their *p*Ka, hydrochloride salts of local anesthetics conduct iontophoretically best at pH 5. This pH keeps almost all local anesthetic molecules in the positively charged form. Increasing the pH tends to lower the conductivity by converting positively charged molecules to unionized molecules. However, iontophoresis of local anesthetics can be performed successfully even when the pH is close to the *p*Ka since there will be adequate numbers of local anesthetic ions to carry the current (20).

Lidocaine (*p*Ka, 7.86) is one of the most widely used local anesthetic agents. The marketed solutions of lidocaine hydrochloride are mostly ionized (27). Anesthetizing a person can be painful if done by the conventional intradermal injection method and time-consuming if done by using topical ointments. On the other hand, iontophoresis of a compound of this nature may be virtually painless, as well as bring in a more uniform concentration throughout the skin area of interest. By this method, the drug, lidocaine hydrochloride, can be applied to the skin by means of a sponge which has been soaked in its solution. The positive electrode can then be placed over it and current passed. The negative electrode contacts the skin at some distant point to complete the circuit. To ensure good electrical contact, the negative electrode is coated with electroencephalograph electrode paste. Complete coating is important here as well, to prevent minor direct current burns resulting from metal-to-skin contact. A sponge rubber cuff which prevents any possibility of metal-to-skin contact can also be used. Drug penetration should occur at least through the stratum corneum, a result that cannot be obtained presently from the topical application of conventional solutions or ointments of either the ionized or the unionized forms of lidocaine. Various reports showing the effectiveness of lidocaine hydrochloride by iontophoresis exist (see Table I). Russo *et al.* (12) found that when lignocaine was administered topically by iontophoresis to volunteers, it produced a local anesthesia of significantly longer duration than did administration by swabbing, thus avoiding the use of needles. Comeau and co-workers (9,28) showed the relationship between the duration of anesthesia with different concentrations of lidocaine and the duration of iontophoresis. Problems of physical retention of drug and controlled release can also be solved.

MECHANISM OF ACTION AND THEORY

Skin consists of 15–20% lipids (triglycerides, free fatty acids, cholesterol and phospholipids), 40% proteins (mostly keratin), and approximately 40% water (29,37). The isoelectric point of skin is between 3 and 4, which is another way of saying that pores have a positive charge below pH 3 and a negative charge above pH 4 (26,29,37). Because of this original negative charge in the superficial skin layers, it is relatively "easy" to introduce basic drugs (e.g., methylene blue) through the skin (1). Electroosmosis, the transport of the liquid water as a whole, can interfere with the mechanism of iontophoresis. This causes migration of undissociated molecules in solution (4). Because the skin has a negative charge, iontophoresis will effect the movement of water into the body from the positive pole electroosmotically toward the outer surface of the skin at the negative pole. This leads to shrinkage of the skin pores at the positive pole and causes swelling at the negative pole after intensive iontophoresis (29). This process is helpful in case of cation transfer from the postive pole, as it acts in the same direction, facilitating absorption of the cationic drugs. Electroosmosis is highest in solutions with a low conductivity; iontophoresis, on the other hand, is greatest in fluids with a high electrolyte concentration (4). Gangarosa *et al.* (30) postulated that increased penetration of the drug idoxuridine after anodal iontophoresis may result from the water movement associated with the sodium ion transfer. They adopted the term "iontohydrokinesis" to describe water transport during iontophoresis, with no specific mechanism implied by the term. In addition to ionic conduction and electroosmosis, other phenomena such as solute–solvent and solute–solute coupling may account for observed enhancement of drug absorption when an electric field is present. Although a number of equations have been used to describe the observed rate of iontophoretic drug delivery, an exact relationship has not been defined, primarily because of the differences in the experimental conditions used by various authors.

The iontophoretic procedure involves a number of variables that must be controlled in the interest of patient safety and optimal stimulation. Faraday's law has been used by some authors to provide dependable information concerning the rate of deposition of the drug at the skin surface. Faraday's law, in essence, states that the amount of material deposited at either electrode is proportional to the quantity of electricity passed through the system. However, due to the complexity of the factors involved during the process of iontophoresis, theoretical predictions based on Faraday's law and their correlations with experimental data are virtually impossible. Abramson (31) used Coulomb's law for predicting an electrophoretic treatment unit, independent of the area of the electrode.

Abramson and Gorin (1) defined an equation relating the iontophoretic dosage to the various components contributing to it. These included contributions due to electrical mobility, electroosmosis, and simple diffusion. Another equation, defining the iontophoretic current, I, passing through an electrode tip, having a resistance, R_E, and surrounding tissues release energy, P, in the form of heat is given by (32)

$$P = I^2(R_E + R_e) \quad (1)$$

where R_e is the resistance of the tissues. This relationship is not very practical and can be used only in *in vitro* experiments.

Masada *et al.* (33) used the following equation for describing their *in vitro* studies using a four-compartment diffusion-cell electrode system.

$$E = (Y/Y_o) = (FZ\Delta\vee) * \{RT\,[\exp-(FZ\Delta\vee/RT-1)]\}^{-1} \quad (2)$$

where

E = flux enhancement ratio,
Y = flux with an electric field,
Y_o = flux with no electric field,
$\Delta\vee$ = potential drop,
Z = molecular charge,
F = Faraday's constant,
R = universal gas constant, and
T = absolute temperature.

The authors found that at a low voltage, 0–0.25 V, the data obtained by iontophoretic transport of benzoic acid, sodium benzoate, and tetraethylammonium bromide were in agreement with the theoretical flux enhancement. These experiments were done using a cellulose acetate membrane and hairless mouse skin. At high voltages, however, they observed a faster experimental flux enhancement than the theoretical predications. Burnette and Marerro (34) studied the iontophoretic transport of thyrotropin releasing hormone (TRH), a trepeptide, using hairless mouse skin. They found that the steady-state transport results were in agreement with their predictions based on the Nernst–Planck flux equations.

EXPERIMENTAL VARIABLES

The technique of iontophoresis depends upon several randomized physicochemical variables i.e., electrolyte concentration, pH, vehicle type and composition, ionic strength, solubility of the drug, viscosity of the vehicle, drug concentration, duration and strength of the current, resistance of the skin, and size of the electrodes. The role of these parameters in the iontophoretic delivery of drugs and in optimization of the technique are of utmost interest to the medical device and pharmaceutical industry. It might be mentioned here that a review of the literature indicated that various investigators had attempted to ascertain what effects these various physicochemical factors had on iontophoresis. However, their results were based mostly on clinical observations rather than on scientific experiments.

pH. Changes in the pH of the fluid at the driving electrode produced only minor changes on the uptake of radioactive phosphorus by various tissues in rats (35). Release of histamine from aqueous media during iontophoresis also showed a similar behavior (36). Harpuder has, however, shown a significant dependence on pH during electrophoretic therapy (37). The change in flux for lignocaine hydrochloride during iontophoresis was related to the degree of ionization (38). The results obtained with the iontophoresis of sulfa drugs (16) were also shown to be paralleled by the degree of ionization.

Ionic Strength. Only a few papers in the literature relate to the concern of ionic strength during iontophoresis. A report on a decrease in the uptake of phosphorous by tissue has been published (35).

Size and Charge of Electrodes. Electrode material used should be harmless to the body and sufficiently flexible to be applied closely to the body surface. Tin/steel plates are known to be the best for this purpose (8). The electrode pad/sponge chosen should be about 1–2 cm in thickness. One should avoid direct contact of electrode with the body. The charge of the electrode under which the drug will be kept depends on the charge of the active drug species. In the case of lidocaine HCl, the positive electrode is used, so that the positive lidocaine ions will migrate toward the negative electrode. The distribution of active drug species within the skin depends on the size and position of electrodes. They are usually selected according to individual needs. The literature indicates that greater amounts of drugs are introduced by larger electrodes. Results negating this observation are also published (31,35).

Nature of Electrodes. Disposable electrodes capable of conforming to irregular skin surfaces comprising a flexible material having one surface coated with a skin adhesive adapted to be applied directly to the skin of the patient and the nonconductive planar body having a tab to which an electrical connection can be made are highly desirable (39).

Duration and Intensity of Current. From Faraday's law we know that in an electrolytic solution the transported quantity of electricity depends on the strength of the current and the duration of its passage (5). The same number of ions will be transported at different strengths of current if the time for current flow is inversely related to their strengths. The rate at which the ions are introduced into the body with various current strengths can play an important role. When the current is stronger, more ions penetrate at one time, and their accumulation produces the desired local effect and may even build up a reserve of ions that will later be diffused more deeply into the tissues, perhaps resulting in a prolonged drug effect. The strength of the current used depends also on the sensitivity of the patient (40). Using benzoate as a model ion, it is reported (41) that increases in the applied current produced a linear increase in benzoate flux. However, upon current termination, benzoate flux does not return to the control values, suggesting compromised barrier integrity of a variable nature. The authors speculated that the diffusional path followed specifically by ionized species undergoes sporadic current-related changes.

Iontophoretic technique is based on a direct current source. It is designed to increase the current slowly and to remain at a predetermined level as long as the treatment requires, following which the current is slowly decreased to zero. The time for iontophoresis ideally is 1 min for the increasing phase and 30 sec for the decreasing phase. The intensity of the current used is between 40 μA and 10 mA regulated with a 25,000-Ω potentiometer (10). Currents ranging from 5 to 10 mA have been found to be painless (10). The intensity of the current should not exceed 0.5 to 1 mA/in.^{2} for large electrodes (11,40). This current can be distributed in the case of stimulation treatment of a number of areas, by branching wires connected with the desired pole. The relationship between the duration of the iontophoresis and the time until the effect is perceived is not widely investigated.

Resistance. The electrical resistance of the skin area where the iontophoretic application is desired can vary widely. The electrical resistance of the human epidermis was measured with a minute electrode (42). When the electrode was placed over the skin, the resistance was much lower on sweat pores, especially when they discharged sweat (42). When the electrode was gradually inserted into the epidermis, no marked change in resistance was found in the

outermost layer, followed by a thin layer where a slight fall in resistance began to occur.

Concentration. Increased uptake by the skin after iontophoresis with an increase in drug concentration has been the subject of many reports (35,36). Increased uptake of radioactive phosphorus by various tissues after iontophoresis with an increase in the concentration of ^{32}P is demonstrated by O'Malley and Oester (35).

DISADVANTAGES

Iontophoretic burns are often produced by low voltages and are caused without the sensation of pain. Tapper (43) has tried to pinpoint the cause and source of these burns. A thick pad/gauge usually prevents these types of burns. Tapper (44) has described a method for an iontophoretic burn-protection electrode structure. He suggests the use of a felt-like material, preferably moistened, having a thickness in excess of 3 mm covering at least the area of the negative electrode in contact with the skin. Compliance with a current-time limitation according to the method essentially avoids iontophoretic burns. Formation of undesirable vesicles and bullae in the skin being treated can be avoided by periodically interrupting a unidirectional treatment current with a relatively short pulse of current in the opposite direction (45). Electric shocks are caused by a high current density at the skin surface. This situation can easily be avoided by conditioning the body to the current in a stepwise fashion. This would require an operator first to secure the patient to the device and then slowly advance the output control from zero to permit patient accomodation to the signal. After a given treatment period, the operator would then slowly turn the output control down to zero and release the patient from contact with the output (43). The literature contains reference to the use of brass, copper, zinc, gold, conductive plastic, and steel for avoiding this problem. The resistance contributed by the electrode in infinitesimally low compared with that of the skin and is not, per se, a factor potentially predisposing toward burns (23).

The limitations of iontophoresis depend on the properties of the drug species. The drug solution must be of a sufficiently ionized concentration to carry a measurable current (in excess of 10^{-10} A) in biological systems (32).

EQUIPMENT AND DEVICES

The design and construction of equipment for iontophoresis are not unduly complex. The development of prototype devices which could deliver small amounts of therapeutically active materials is under way at various research laboratories. Some of these devices are also available on the market today. The limitations of an iontophoretic device are governed by three major factors—safety, convenience, and predictability. Many devices in the past used household current to power the devices and these caused the patient shock hazard should the device malfunction (22). These devices were modified to function with a constant voltage so that the current can be varied, depending upon the resistance of the skin area being treated. This decreased the possibility of electric shocks. At present there is a need for devices with high patient compliance and acceptability.

Many types of devices for the delivery of drugs, enzymes, dyes, and other ions have been employed. These vary in complexity from the simple battery and rheostat type

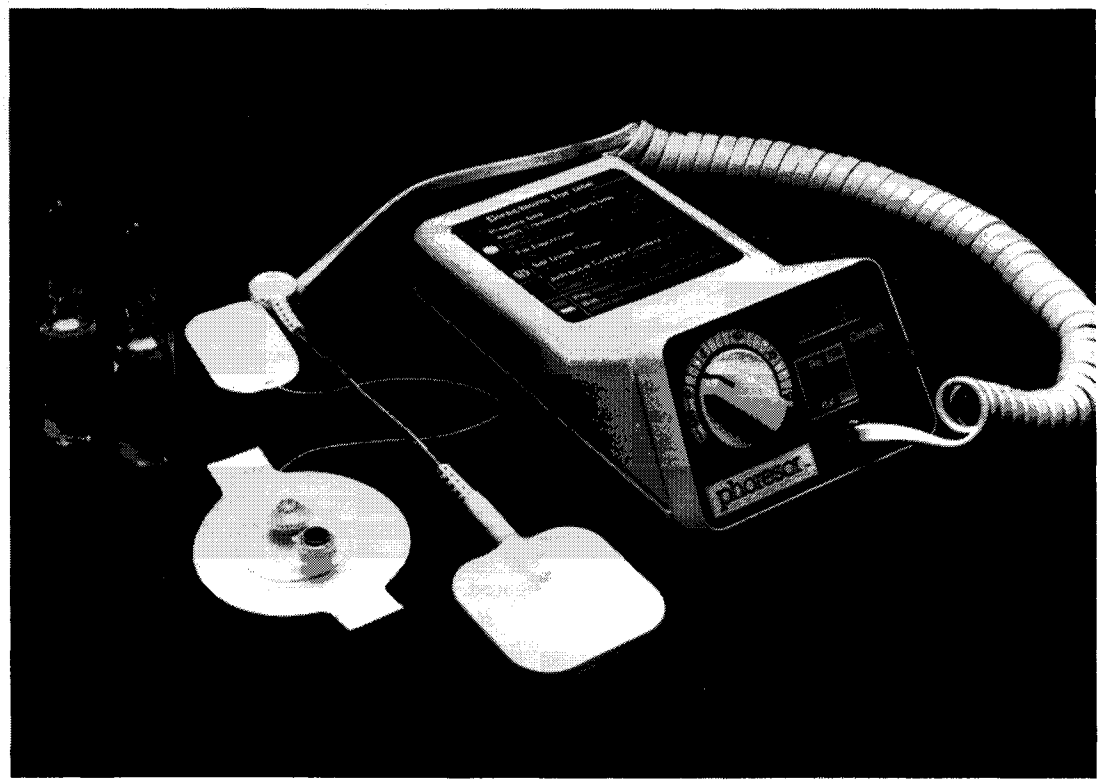

Fig. 7. The control unit and the electrode system of the Iontophoretic device. (Phoresor) manufactured by Motion Control, Inc., Salt Lake City, Utah.

Table III. Circuit Characteristics of Commercial Iontophoresis Systems[a]

	Manufacturer						
	Farrall Model IPS-6D	Orion Model 417	Medtherm	Sherwood	Wescor Model 3600	Phoresor Model PM600	Drionic
Power source	Battery	Battery	AC line-operated	AC line-operated	Electronic charge displacement	Battery	Battery
Automatic current rate-of-change limitation	No	Yes, 20-sec rise	No	Yes, <10-sec rise	Yes, 30-sec rise decay	Yes, 20-sec rise	Yes, 2.5-sec rise
Current control	Manual (limit at 4 mA)	Automatic (1.0 or 1.5 mA)	Manual	Automatic	Automatic (0.25 mA/cm^2)	Manual	Automatic variable resistor
Circuit resistance sensor	Voltage limited, no shutdown	No	No	No	Audio signal automatic shutdown, >18 kΩ	No	Voltage-limited capacitor
Open-circuit sensor	Ammeter indication, no shutdown	Ammeter indication, no shutdown	Ammeter indication, no shutdown	Ammeter indication, no shutdown	Audio signal automatic shutdown	Audio signal automatic shutdown	Delay capacitor discharge

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to modern electronic circuit devices (79). The optimal features of these devices for control of the amount of the drug delivered should include regulation of parameters such as current density, voltage, and time. One of the devices currently on the market is the Phoresor, manufactured by Motion Control (Fig. 7). The device is designed to deliver drugs such as lidocaine and dexamethasone. The features incorporated in this device and some other devices are listed in Table III (23,24). This device features control for a slow increase in current to avoid any discomfort caused by changes in skin resistance. LecTec Corporation uses a wafer-thin membrane to push positively charged ions of a drug through the stratum corneum of the skin (46). Based on patient safety, Webster (23) outlined some recommendations for the desired safety features in an iontophoretic device. Jochem *et al.* (47) have described a high-voltage electrometer for iontophoresing dyes or enzymes through extremely fine micropipettes. This device incorporates a controlled current source, direct current monitoring, balance bridge, electrode resistance, and capacitance compensation test circuits. A device for iontophoretic application of fluoride on teeth is discussed by Ishikawa *et al.* (48).

Another iontophoretic based device, the Drionic, was recently released by the Food and Drug Administration (FDA) for the market and has gained wide acceptance among consumers and medical professionals in its very short life (43,49). The device is currently sold by prescription for about $100; it takes 30 min to soak the Drionic pad and another 20 min for the application. The device has been designed for home self-use, primarily for antiperspirant action. Clinical studies showing the safety and effectiveness of the device have been reported (43). The device is presently being developed for drug delivery purposes (43).

The FDA has classified iontophoretic devices for specialized uses (for the diagnosis of cystic fibrosis, fluoride uptake acceleration in dentistry, and anesthesia of the intact tympanic membrane) into class II (performance standards) and for all other uses into class III (50).

In summary, iontophoresis is a very effective and viable technique for drug delivery. However, its therapeutic applications are not based soundly on clinical experiments but remain based considerably on clinical impressions. Therefore, future controlled clinical experiments are necessary to quantitate the contribution of this technique, relative to transcellular diffusion.

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