

Iontophoresis - An Approach for Controlled Drug Delivery: A Review

Nitin Dixit, Vikas Bali, Sanjula Baboota*, Alka Ahuja and Javed Ali

Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, (Hamdard University), New Delhi-110062, India

Abstract: The recent approval of lidocaine hydrochloride and epinephrine combined iontophoretic patch (Lidosite[®] Vysteris Inc.) for localized pain treatment by FDA has invigorated the gaining interest in iontophoretic drug delivery systems for the transdermal delivery of drugs. This technique of facilitated movement of ions across a membrane under the influence of an externally applied electric potential difference, is one of the most promising physical skin penetration enhancing method. The rationale behind using this technique is the capability of this method to increase the systemic delivery of high molecular weight compounds with controlled input kinetics and minimum inter-subject variability, which is otherwise achieved only when parenteral route of administration is used. Recently, good permeation of larger peptides like insulin has been achieved through this technique in combination with chemical enhancers. This review briefly describes the factors which affect iontophoretic drug delivery and summarizes the studies conducted recently using this technique in order to achieve higher systemic absorption of the drugs having low passive diffusion otherwise. The effect of permeation enhancers (chemical enhancers) on iontophoretic flux of drugs has also been described. Present review also provides an insight into reverse iontophoresis. Various parameters which affect the transdermal absorption of drugs through iontophoresis like drug concentration, polarity of drugs, pH of donor solution, presence of co-ions, ionic strength, electrode polarity etc. have also been reviewed in detail.

Keywords: Iontophoresis, electric current, potential difference, transdermal, permeation enhancers.

INTRODUCTION

The skin has been investigated for several decades as a route of drug administration and so far many drug delivery techniques which utilize alternative forms of energy have been explored to facilitate permeation of drugs across the skin. Amongst these, iontophoresis, which is the facilitated movement of ions across a membrane under the influence of an externally applied small electrical potential difference (0.5 mA/cm² or less), is one of the most promising novel drug delivery system, which has proved to enhance the skin penetration and the release rate of a number of drugs having poor absorption/permeation profile through the skin [1-4]. It is a localized, non-invasive, convenient and rapid method of delivering water soluble, ionized medication into the skin. This technique has already been reviewed by Banga and Chien [5] and Banga *et al.* [6]. Recently it was reviewed by Kalia *et al.* [7]. Wang *et al.*, described an overview of improved permeation of hydrophilic as well as the lipophilic drugs using iontophoresis in combination with several strategies like permeation enhancers, sonophoresis etc. [8]. Iontophoresis provides the usual advantages of a transdermal route like, therapeutic efficacy improvement by bypassing hepatic "first pass" metabolism, avoidance of inconvenience caused by parenteral drug delivery and prevention of variation in the absorption seen with oral administration. Besides this, it also reduces the chance of dosing variation by providing programmed delivery of the drug. Iontophoresis also provides a therapeutic regimen leading to better patient compliance. It

permits the use of a drug with a short biological half life since the drug is delivered to the target area without the need to recirculate in the blood. Moreover, the drug is delivered into the bloodstream directly without any delay. It also provides a rapid termination of the effect by turning off the iontophoretic delivery system. Thus, because of many advantages associated with this system, it has been an area of growing interest in the local and the systemic delivery of drugs.

Iontophoresis is gaining wide popularity in the area of pain relief as it provides a non invasive means of systemic administration of minute amount of drugs. The potential of this technique has been exploited for the transdermal delivery of many drugs with poor penetration properties e.g., high molecular weight electrolytes such as proteins, peptides and oligonucleotides which are normally difficult to administer except through parenteral route. It also offers a great potential for the delivery of charged peptides used as drugs. Although iontophoresis has been able to achieve significant increase in the transdermal absorption of many drugs, it has not been able to show significant permeation of larger peptides like insulin. This has led to many studies involving the use of various chemical enhancers (permeation enhancers) along with iontophoresis [9]. Such combination approaches have been found to significantly improve the absorption of insulin and many other drugs, which could not be delivered using iontophoresis alone. The permeation rate of thiocolchicoside, a muscle relaxant used in the treatment of orthopedic, traumatic and rheumometallogic disorders, which can not permeate the skin easily due to high molecular weight and low octanol /water partition coefficient, has been enhanced using iontophoresis in combination with chemical enhancer like lauric acid. This produced a significant increase in the

*Address correspondence to this author at the Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, (Hamdard University), New Delhi-110062, India; Tel:/Fax: 26059663; E-mails: sbaboota@rediffmail.com or sbaboota@jamiyahamdard.ac.in

ment [23]. In a recently conducted study Chaturvedula *et al.*, showed that iontophoretic patch of salmon calcitonin, a modified WEDD[®] iontophoretic system delivered therapeutically relevant concentrations of the drug in the body which was comparable to conventional route like subcutaneous besides providing improved patient compliance [24].

Hence, iontophoresis is an area which has wide scope for expansion. There are several devices, reusable or disposable available to help suit the individual needs and to improve patient compliance. Factors affecting the iontophoretic process and the studies conducted recently are now described in detail.

FACTORS INFLUENCING IONTOPHORETIC PROCESS

The factors influencing iontophoretic delivery of a drug can be broadly classified into operational and biological factors [6, 25]. These factors are enlisted in Table 1.

Operational Factors

Composition of Formulation

Concentration: Concentration of drug is one of the most important factors affecting iontophoretic process. The effect of the concentration has been studied on a number of drugs. An increase in concentration was shown to increase the apparent steady state flux of a number of drugs e.g., AVP [26], metoprolol [27], butyrate [28], diclofenac sodium [29], dopamine agonist 5-OH DPAT [30], rotigotine [31], atenolol HCl [32] and ketorolac [33]. All these drugs showed a proportional increase in flux with an increase in concentration. With drugs like benzoate [34] and LHRH [35], a modest increase was observed. But this is not the general observation since, an increase in concentration increases flux upto a point, after which the flux becomes independent of the donor concentration. This is probably due to the charge saturation of the aqueous conducting pathways of skin also called as

boundary layer saturation [36]. Methyl phenidate showed a little change in flux when concentration was increased beyond 0.1M [37].

pH: Since iontophoresis is widely used for peptide delivery, pH plays a vital role and it determines the ionization of peptides, which depends upon isoelectric point and respective pK_a of charged amino acid. Moreover, skin permeability is also dependent upon pH e.g., AVP (pI - 10.8) showed maximum flux when donor having a wide range of pH (4-8) were used [38, 39] but calcitonin (pI -6.5) showed optimum flux at pH 4.0 and not at higher pH [40]. 5-OH DPAT showed enhanced flux when pH was increased from 3 to 5 but not at higher pH [30]. In case of leuprolide (LHRH agonist) a two fold increase in flux at pH 7.2 was observed than at pH 4.5 [41]. There was a three fold increase in flux of buprenorphine at pH 4.0 than at pH 5.0 [42]. Glibenclamide, when given by pulsed iontophoresis, showed higher flux at pH 8.5 than at pH 7.4 or 8.0 [43]. Since pH influences the charge on protein, polarity of electrodes is an important factor to be taken into consideration during drug delivery e.g. anodal delivery of insulin is preferred [44] but below its isoelectric point [45] whereas in case of pilocarpine a moderate pH of 5.98 is required to achieve maximum permeation [46]. Thus, the optimum pH for iontophoretic delivery of a compound is one where it exists predominantly in an ionized form. The effect of pH of aqueous vehicle on rate and extent of iontophoretic delivery of lidocaine was investigated. The rate was found to be maximum when the drug was in an ionized form [47]. Thus, pH is an important factor governing the iontophoretic delivery of drugs. Moreover, it also influences the chemical stability of the drug involved.

Ionic strength & presence of other ions: In iontophoresis the main aim is that the drug ion should carry maximum charge across the membrane. It follows that an increase in ionic strength will decrease drug delivery, as extraneous ions compete with the drug ions. The buffering agents used to maintain pH of the donor medium is a source of co-ions.

Table 1. Factors Affecting Iontophoretic Delivery of the Drug

Operational Factors	Biological Factors
<p>I. Composition of formulation: Concentration of drug solution pH of donor solution Ionic strength Presence of co-ions</p> <p>II. Physicochemical properties of the permeant: Molecular size Charge Polarity Molecular weight</p> <p>III. Experimental conditions: Current density Current profile Duration of treatment Electrode material Polarity of electrodes</p>	<p>I. Intra and inter subject variability II. Regional blood flow III. Skin pH IV. Condition of skin</p>

These co-ions are generally more mobile and smaller in size than the drug ions itself and can dominate the penetration into the skin thereby causing a decrease in transdermal flux of the drug. Many peptides widely studied for ionic strength showed a higher flux occurring at low electrolyte concentration [26, 38, 48-50]. Similarly, drugs like ketorolac showed increased flux with decrease in ionic strength [33]. A 50% reduction in benzoate flux occurred when an approximately equimolar amount of NaCl was added to donor compartment [35]. Salicylic acid flux was found to decrease with the increase in concentration of HEPES buffer [51] and 5-OH DPAT flux decreased with addition of NaCl [30]. But occasionally an increase in ionic strength leads to an increased flux e.g., iontophoresis facilitated an increased skin permeation of AVP as the ionic strength of donor solution increased [52].

Physicochemical Properties

Molecular size and molecular weight: The molecular size of the solute is a major factor governing its feasibility for iontophoretic delivery and hence the amount transported. When the iontophoretic delivery of carboxylate ions was studied, flux for acetate was found to be more than that of hexanoate and dodecanoate. This suggests that smaller and more hydrophilic ions are transported at a faster rate than larger ions [53, 54]. Many studies correlating flux as a function of molecular weight have been conducted and it was concluded that for electro repulsive iontophoresis, when all other conditions were kept constant, transport of compounds decreased with increase in molecular weight (chloride>amino acid>nucleotide>tripeptide>insulin) [55-59]. But due to the use of advanced techniques like iontophoresis, electroporation and phonophoresis, delivery of even large molecule like peptides is possible now.

Charge: Charge on a molecule is an important physicochemical property governing iontophoretic transport, since the sign of the charge determines the mechanism by which iontophoresis will proceed e.g., electrorepulsion or electrorepulsion and electroosmosis [60]. Although the transport of cations has been shown to be better than anions for amino acids and peptides [55, 56, 61], this however is not so simple because an increase in charge will require pH to be decreased, which in turn shall directly decrease the electroosmosis and electrotransport process. An increased positive charge on peptide, cause it to bind tightly to the membrane creating a reservoir which in turn can decrease the rate at which the steady state flux will be achieved [60].

Polarity: Generally, the compounds which are hydrophilic are considered ideal candidates for optimum flux e.g., nalbuphine and its ester showed an increased flux as the lipophilicity of the compound decreased [62].

Experimental Conditions

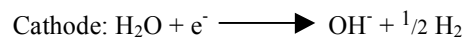
Current strength: Since current can easily be controlled by the use of electronics, it is a convenient mean to control delivery of drugs to the body. However, a large increase beyond the permissible limits causes irritation and can damage the skin. A linear relationship has been observed between the apparent flux of a number of compounds and the applied current. Methyl phenidate showed a linear relationship be-

tween the applied current and its iontophoretic flux [37]. A linear increase in the flux with current has also been found for TRH [63], verapamil [64], GRH [35], diclofenac [65] and ketorolac [33]. In general, 0.5 mA/cm² is often stated to be the maximum iontophoretic current which should be used on human beings [13].

Current profile: Mostly, in the studies conducted on animals *in vitro*, current is kept constant and very low voltage of about 10 V is applied.

Pulsed current: The persistent use of direct current (DC), proportional to time, can reduce the iontophoretic flux because of its polarization effect on the skin [66]. This can be overcome by the use of pulsed DC which is a direct current delivered in a periodic manner [5]. During "off stage" the skin gets depolarized and returns to the initial polarized state. However, Bagniefski and Burnett showed that enhanced skin depolarization can decrease the efficiency of drug transport, if the frequency of pulsed current is very high [67]. A two fold increase in the transdermal flux of vasopressin was observed when pulsed current was used *in vivo* in rabbits [68]. Enhanced transport of proteins and peptides has been reported using pulsed DC e.g., insulin [69]. But in many cases like sufentanil [70], fentanyl [71] and ketorolac [33], a decreased flux was observed when pulsed current was used as compared to constant direct current.

Electrode material: Iontophoretic studies have been conducted using both platinum wire and Ag/AgCl wires. However, platinum electrodes or other inert electrodes like nickel or stainless steel have been found to cause pH drift and gas bubbling due to decomposition of water and thus causing production of H⁺ and OH⁻ ions [26] in the following manner:



Thus, Ag/AgCl electrodes with redox potential lower than that of water which help to maintain electroneutrality at both anode and cathode have been used for this purpose.

Phipps *et al.* [72] studied the electrode material selection in optimizing the delivery of lithium across polyvinyl alcohol (PVA) hydrogel membrane. They showed use of platinum anode in donor caused a pH decrease due to production of hydronium ion as shown above, which are more mobile and no efficient delivery of lithium was observed while the use of Ag/AgCl electrodes in place caused no pH drift and a significant increase in lithium flux almost double of the above case was observed.

Regional blood flow: During iontophoresis, the dermal blood supply determines the systemic and underlying tissue solute absorption. Blood supply however, does not appear to affect the drug penetration fluxes through the epidermis during iontophoretic delivery. Cross and Roberts [73] showed that solute in the upper layer of the skin following iontophoresis was comparable in anaesthetized rats and sacrificed rats. It can thus be presumed that the blood did not affect the penetration through the epidermis since the latter has no blood supply.

Condition of skin: In iontophoresis, skin condition also affects the penetrating properties of permeant. Roberts *et al.*, studied the *in vivo* passive diffusion of methyl salicylate us-

ing skin from different areas of human body and observed the following rank order: abdomen > forearm > instep > heel > planter, for all subjects [74]. Feldman *et al.*, showed that the passive diffusion of hydrocortisone occurred maximally from the area with numerous hair follicle while lesser in area with thickest stratum corneum [75].

Table 2 enlists the drugs which have been studied recently for iontophoretic drug delivery.

Use of Chemical Enhancers in Iontophoresis

For a transdermal delivery system to be successful, it should make the drug permeate through the skin to the systemic circulation in quantities sufficient to show the therapeutic effect. In many cases, iontophoresis itself has been able to show an increased permeation of the drug molecule but, in many others, iontophoresis alone has not given desired results which have led to the use of various chemical enhancers along with iontophoresis to enhance the delivery of drugs especially larger peptide molecules. By both chemical and physical alteration of stratum corneum barrier, the extent of drug absorption can be increased dramatically. Iontophoresis, thus, has been used along with chemicals like permeation enhancers to produce a synergistic effect on the permeation of many drugs. Table 3 provides some of the studies conducted using iontophoresis along with chemical enhancers.

OTHER IONTOPHORETIC DELIVERY SYSTEMS

1. PULSATILE/SWITCHING IONTOPHORESIS

Many studies have been conducted where instead of using constant DC iontophoresis; DC in the form of short pulses has been used. Table 4 summarizes the list of studies conducted recently.

2. IONTOPHORESIS (IP) AND ELECTROPORATION (EP) COMBINATION

Iontophoresis has also been used along with other skin penetration enhancing techniques like electroporation, which involves the application of high voltage (> 100 V) pulses for short duration (μ s-ms) to increase the permeability through the skin [6]. Electroporation is usually applied before iontophoresis, which causes the creation of permeabilized skin due to exposure to high voltage pulses. Iontophoresis thus, when applied after electroporation helps in extending the permeabilized state of the skin resulting in the rapid onset (which is not possible with iontophoresis alone) and sometimes increased flux. Optimum time for electroporation is desired since if it is not applied for proper time, it may not reduce the lag time sufficiently to produce the desired permeabilized skin state which would otherwise facilitate the flux of the drug [76]. The increased transport by electroporation has been found due to creation of electropores as well as local field induced electrophoretic drift [94, 95]. Fang *et al.*, studied the effect of electroporation on the delivery of buprenorphine [76]. They showed that application of 300 V or 500 V pulses increased the buprenorphine flux by several folds over passive transport. Despite the pulsing time of 10 min, the cumulative amount of buprenorphine in the receptor compartment increased constantly till the end of 8 h. This sug-

gested that a drug reservoir was created within the skin from where the drug was able to permeate to receptor site after 10 min of application, at a constant rate, thus authenticating the studies conducted previously [96-100]. Table 5 shows the drugs where iontophoresis and electroporation have been used in combination.

3. REVERSE IONTOPHORESIS

Reverse iontophoresis, a technique in which low electric current is applied to draw intestinal fluid through the skin, is widely applied now a days in devices meant for diagnostic application. This provides a convenient and non-invasive method for sampling of body fluids so as to permit simultaneous measurement of the desired substance in the body fluid and thus to monitor them efficiently e.g., devices like GlucoWatch[®] uses the reverse iontophoretic process to continuously monitor the glucose level in the blood. This system provides a needleless means of monitoring blood glucose levels in diabetic patients and uses an electrical signal that is proportional to the amount of glucose in the extracellular fluid. The GlucoWatch[®] technology requiring calibration with traditional finger-stick glucose measurements is able to provide readings every 20 min for 12 h. This is a patient friendly mechanism as regular finger pricks are avoided. GlucoWatch[®] is approved for use in children and adults, and is currently indicated only as an adjunctive therapy to conventional blood glucose monitoring. The technique of reverse iontophoresis provides a feasible method for rapid, linear extraction of phenylalanine and for easy detection (by instrument like biosensors) of monitoring diseases like phenylketonuria [103]. This technique not only provides non-invasive sampling but also provides filtered samples free from large molecules. Although this technique provides for less tedious sampling, for it to be successful, it needs a very sensitive analytical method since the amount extracted is very low.

Table 6 lists recent applications of reverse iontophoresis in extraction of drug substances for diagnostic purposes.

CONCLUSION

Iontophoresis, the technique of facilitated movement of ions across a membrane under the influence of an externally applied electrical potential difference, is one of the most promising methods to enhance delivery of drugs with poor permeation profile through the skin. This is especially true for high molecular weight compounds e.g. proteins, peptides, and oligonucleotides, which can only be administered through parenteral route having many obvious disadvantages. Iontophoresis dramatically enhances both the rate of release and the extent of penetration of the salt form of the drugs. Without iontophoresis, such charged species are largely incapable of transdermal penetration due to the skin's lipophilic nature. Iontophoresis is gaining wide popularity as it provides a non invasive and convenient means of systemic administration of drugs with poor bioavailability profile, short half life and with multiple dosing schedules. Iontophoresis, in comparison to oral route, definitely provides benefits of improved efficacy and/or reduction in adverse effects. For topical delivery of drugs like lidocaine (Lidosite[®]), iontophoresis provides an obvious advantage of getting quicker

Table 2. List of Drugs Investigated Recently for Iontophoretic Delivery

Drug	Animal/ Membrane Model Used	Experimental Conditions	Results	References
Thiocolchicoside	Rabbit and human skin	<i>In vitro</i> : Glass-Franz type cell.	Enhanced flux of the drug over passive control.	[10]
Salbutamol	Non rate limiting artificial membrane	<i>In vitro</i> : Release of drug from a liquid crystalline vehicle was studied.	Enhanced flux from the vehicle.	[77]
Timolol maleate (TM)	Excised rat, rabbit, guinea pig, mouse and human skin	<i>In vitro</i> : Valia-Chien side by side diffusion cell. Studied effect of species.	Iontophoretic transport highest in human skin and lowest in rabbits.	[78]
Dextran sulphate	Full thickness pig skin or epidermis separated from human cadaver skin	<i>In vitro</i> : Valia-Chien cell; 500 V; Current- 0.5mA/cm ² ; Time – 6 h.	Cumulative amount fluxed from cathode was approximately 300 times more over passive and from anode it was 15 times more.	[79]
Diclofenac	Guinea Pig skin	<i>In vitro</i> : Current- 0.2 and 0.5 mA/cm ² ; Time- 6 h. Studied effect of current on drug delivery.	Full plasma concentration achieved in 1 h. Drug delivery was proportional to current (371± 141 µgm / lt at 0.5 mA/cm ² and 132 ± 62 µ gm/ lt at 0.2 mA/ cm ²).	[65]
Rotigotine	Human stratum corneum	<i>In vitro</i> : Side-by-side diffusion cell; Studied effect of drug concentration and effect of co-ions (triethylamine (TEA) & tributylamine (TBA) on flux; 0.05mA/ cm ² .	Flux increased with drug concentration. With co-ions viz.TEA, flux of rotigotine increased while TBA showed no effect on flux.	[31]
Leuprolide (LHRH agonist)	Human epidermal skin	<i>In vitro</i> : Conducted using buffers with pH- 4.5 and pH- 7.2; Current- 0.5-2.3 mA/cm ² .	Iontophoretic permeation was found to be double at pH-7.2 than at pH-4.5 (increased transference number was observed).	[41]
5-Amino Levulinic acid (Ala) & its methyl ester (m-Ala).	Porcine skin	<i>In vitro</i> : Anodal iontophoresis for 15 h at 0.4 mA/cm ²	Ala - steady state - 10-12 h. Flux- 65 nmole/cm ² . m-Ala - steady state - 2.5-4.0 h flux- 145 nmole/cm ² .	[80]
Nalbuphine (Nb) & prodrug Nalbuphine pivalate, decanoate and enduthate.	Intact skin, stratum corneum stripped skin, dilipidised skin, Wistar rat skin.	<i>In vitro</i> : Done to asses the effect of prodrug lipophilicity on passive and iontophoretic permeation.	Enhancement ratio highest for Nb & decreased as the lipophilicity of the prodrug increased.	[62]
Arginine & Vasopressin (AVP)	Rat skin	<i>In vitro</i> : Franz diffusion cell; Ionic strength - 0.05 M and 0.5M; Current- 0.5 mA/cm ² ; Time- 4h. Studied the effect of ionic strength	Enhancement ratio was found to be 6 folds at 0.5 M compared to 0.05 M ionic strength.	[52]
Atenolol hydrochloride	Porcine buccal mucosa	<i>In vitro</i> : Horizontal three chamber permeation cell; Current densities - 0.1, 0.2, 0.3, 0.4 mA/cm ² ; Time-8h Studied the effect of donor concentration.	Delivery of atenolol hydrochloride increased with increase in donor concentration.	[32]

(Table 2) contd...

Drug	Animal/ Membrane Model Used	Experimental Conditions	Results	References
Buprenorphine	Human epidermal membrane	<i>In vitro</i> : Franz (vertical) diffusion cell. 0.5 mA/cm ² ; Time- 4h.	8 fold increase in delivery by anode than cathode.	[42]
Piroxicam	Ventral forearm surface of human volunteer	<i>In vivo</i> : Two glass chambers ; Current-0.3 mA/cm ² applied via Phoresor II (tape stripped stratum corneum).	10 fold increased permeation.	[81]
Chlorhexidine dihydrochloride	Excised human skin	<i>In vitro</i> : Side by side diffusion cell; Constant iontophoresis for 1h; 0.5 mA/cm ² .	Cumulative amount of drug permeated showed a 7 times increase in drug flux by iontophoresis.	[82]
Gentamycin	White rabbits	<i>In vivo</i> : 1 mA; Time-60 sec.	Concentration achieved in cornea and aqueous humour was 12-15 times higher than the topical eye drop.	[83]

Table 3. Iontophoresis & Chemical Enhancer Combination

Drug	Animal/Membrane Model	Permeation Enhancers Used (in italics)	Results	References
Insulin	Sprague Dawley rats	<i>Ex vivo & in vivo</i> : Gel formulation of Insulin in Poloxamer 407 and <i>Linoleic acid & menthone</i> .	Synergistic effect on skin permeation of the drug but increased skin irritation.	[84]
Insulin	Full thickness rat skin	<i>Ex vivo</i> : Experiment conducted after 2 h treatment of skin with 5% <i>menthol, menthone, cineole, pulegone</i> (all in ethanol); 0.5 mA/cm ² ; Time-6h.	Synergistic enhancement obtained which was dependent on the type and concentration of terpenes.	[85]
Bupirone Hydrochloride	Human skin	<i>In vitro</i> : Low current iontophoresis (0.025 mA/cm ²) along with enhancers like <i>azone, oleic acid, menthone, cineole, and terpineol</i> .	Iontophoresis with Enhancers caused a synergistic effect over each technique alone	[86]
Thiocolchicoside	Rabbit and human skin	<i>In vitro</i> : Glass-Franz type cell; Donor- saturated solution of drug and 0,2 and 4% of <i>lauric acid</i> .	Enhanced flux of the drug by a factor of 200 and 300 with 2 % and 4 % of lauric acid respectively was observed.	[10]
LHRH	Human skin (HEM)	<i>Ex vivo</i> : Iontophoresis with <i>oleic acid / propylene glycol</i>	30 fold increase in flux was seen when combination was used as compared to passive alone.	[87]
Timolol Maleate (TM)	Albino rabbits	<i>In vivo</i> : Pretreatment with Azone [®] (<i>laurocapram</i>) (3% v/v emulsion) and iontophoresis (0.375 mA/cm ² ; 2h)	The required transport rate achieved with low drug concentration and AUC was comparable to intravenous TM (30 µg/Kg). Azone [®] pretreatment eliminated the lag time and prolonged the duration of action of iontophoresis.	[88]
Insulin	Dorsal skin portion of female Sprague-Dawley rats	<i>In vitro</i> : Investigated the pretreatment with vehicles: <i>ethanol, propylene glycol</i> , water and their binary combinations, <i>dimethyl acetamide (DMA), ethyl acetate (EtAC), isopropyl myristate (IPM)</i> .	DMA, EtAC and EtOH having skin barrier altering potential produced synergism with iontophoresis.	[9]

(Table 3) contd...

Drug	Animal/Membrane Model	Permeation Enhancers Used (in italics)	Results	References
R- Apomorphine	Dermatomed human skin	<i>In vitro</i> : Iontophoresis and penetration enhancers e.g. <i>lauric acid</i> (anionic), <i>DTAB</i> (cationic), <i>laureth-3-oxyethylene ether</i> (non ionic).	Lauric acid- increased passive transport but affected iontophoretic transport slightly. DTAB- Inhibited both type of transport. Laureth-3-oxyethylene ether- Increased iontophoretic transport 2-3 fold (most effective).	[89]
Acetaminophen (non-ionic), buspirone (cationic), ibuprofen (anionic).	Rabbit ear skin	<i>In vitro</i> : Iontophoretic and <i>lauric acid</i> combination.	Lauric acid was found to enhance ibuprofen (anionic) flux.	[90]

Table 4. Studies Done Using Pulsed Iontophoresis

Drug	Animal/ Membrane Model	Experimental Conditions	Results	References
Human Para thyroid hormone	Sprague-dawley hairless rats; beagle dogs	<i>In vivo</i> : iontophoresis given in pulses; current- 0.05, 0.1 and 0.15 mA/cm ² for 20/30 min with a rest period of 40-90 min	Increase in HPTH hormone in all animals, creating a pulsatile pattern without the need of frequent drug administrations.	[91]
Glibenclamide	Excised rat abdominal skin	<i>In vitro</i> : Donor containing 0.2M TRIS buffer of pH-7.4, 8.0, 8.5; Switching IP -1h; DC-10 V. Studied the effect of buffer pH.	Solution of pH-8.5 gave higher absorption rate than other two buffers.	[43]
Phthalic acid (PA), benzoic acid (BA), Verapamil (VR).	Dorsal portion of Sprague Dawly female rats	<i>In vitro</i> : Electric current in pulsed waveform for 2 h; 10 V; switching at 5, 10 and 15 min.	For PA, BA and VR, the cumulative permeated amount was higher at short pulses.	[92]
LHRH and Nafareline	Stratum corneum or epidermal/dermal human skin	<i>In vitro</i> : Pulsed DC iontophoresis.	Higher flux obtained for pulsed waveform compared to constant DC.	[93]
Ketorolac	Rat skin	<i>In vitro</i> : Pulsed DC iontophoresis.	Flux reduced when pulsed current was used.	[33]

Table 5. Iontophoresis and Electroporation Combination

Drug	Animal/ Membranemodel	Experimental Conditions	Results	References
Salmon calcitonin (SCT) and PTH combination	Human epidermal skin	<i>In vitro</i> : Franz TD diffusion cell; Current(IP) – 0.5 mA/cm ² ; Electroporation (EP)- 1 pulse/min.; 500V; Pulse length- 200 msec.	EP enhanced IP induced drug permeation by 17 fold in PTH and 3.5 fold in SCT.	[101]
Buprenorphine	Cellulose membrane and stratum corneum stripped skin of female mouse	<i>In vitro</i> : Horizontal glass diffusion cell; 500V pulses followed by iontophoresis (Current- 0.3mA/cm ² ; Time-8 h).	Increased permeation of the drug from its solution by a factor of 14.27 compared to passive diffusion with shortened lag time and rapid onset.	[76]
Tacrine Hydrochloride	Intact and stripped rat skin	<i>In vitro</i> : Electroporation followed by iontophoresis (6 h).	Iontophoresis with electroporation and stripped skin produced greatest flux compared to each technique alone.	[102]

Table 6. Reverse Iontophoresis in Diagnostic Applications

Drug	Animal Model	Experimental Conditions	Results	References
Caffeine, Theophylline	Porcine ear skin (intact and tape stripped)	<i>In vitro</i> : Three compartment vertical diffusion cell; 0.3 mA/cm ² ; Time-5 h.	Better extraction through stratum corneum than the stratum corneum stripped skin.	[20]
lithium	Dermatomed pig ear skin	<i>In vitro</i> : Extraction via electro migration to cathode.	Excellent correlation between subdermal lithium and iontophoretic extraction flux and iontophoresis tracked sudden changes in lithium concentration.	[104]
Phenytoin	Dermatomed pig ear skin	<i>In vitro</i> : Extraction of ionized solution at anode by electromigration and neutral at cathode by electroosmosis.	Ratio of extracted amount correlated well with subdermal concentration.	[105]

onset of action and minimization of side effects due to avoidance of large oral doses to get local action on the skin. Many characteristics of iontophoresis must be controlled to achieve successful drug delivery. These include mainly the factors which can affect the iontophoretic delivery of drugs like the operational factors and the biological factors. The charge, concentration, and drug combinations must be compatible with the entire process of iontophoresis. Besides this, preservatives, buffers, osmotic agents, stability and conductivity of the vehicle, are also important for the process of iontophoresis to be successful. Many studies involving the use of combination approaches like use of various chemical enhancers along with iontophoresis have lead to significant improvement in the absorption of insulin and many other drugs, which could not be delivered using iontophoresis alone. Use of pulsed waveform of DC has also been used and has shown to produce significant and rapid delivery of drugs. Other types of iontophoretic techniques like reverse iontophoresis, have opened a new era in the diagnostic field, as it provides a non-invasive and less tedious sampling of body fluids. The major advantages of iontophoretic delivery system which makes its future use hopeful on large scale are the accurate control over drug input kinetics and optimization of drug input rates. In the future, this system might be used to deliver therapeutic proteins or vaccines transdermally. Even though iontophoresis has so many advantages, a considerable amount of research and judicious use of technology is needed to make further improvement in these microelectronics devices and to make the iontophoretic delivery products available to public on a large scale. Thus, iontophoresis may prove to be an important alternative method of drug delivery in the near future.

REFERENCES

- [1] Tyle, P. *Pharm. Res.* **1986**, 3 (6), 318-26.
- [2] Green, P.G.; Flanagan, M.; Shroot, B.; Guy, R.H. In *Physical Skin Penetration Enhancement*, Walters, K.A.; Hadgraft, J. Eds.; Marcel Dekker Inc.: New York, **1993**, 311-33.
- [3] Green, Philip G. *J. Control. Release*, **1996**, 41(1-2), 33-48.
- [4] Sage, B.H. In *Encyclopedia of pharmaceutical Technology*, Swarbrick, J.; Boylan, J.C., Eds.; Marcel Dekker Inc.: New York, **1993**, Vol. 8, 217-47.
- [5] Banga, A.K.; Chien, Y.W. *J. Control. Release*, **1988**, 7(1), 1-24.
- [6] Banga, A.K.; Bose, S.; Ghosh, T.K. *Int. J. Pharm.* **1999**, 179(1), 1-19.
- [7] Kalia, Y. N.; Naik, A.; Garrison, J.; Guy, R.H. *Adv. Drug Deliv. Rev.* **2004**, 56(5), 619-58.
- [8] Wang, Y.; Thakur, R.; Fan, Q.; Michniak, B. *Eur. J. Pharm. Biopharm.* **2005**, 60(2), 179-91.
- [9] Pillai, O.; Nair, V.; Panchagnula, R. *Int. J. Pharm.* **2004**, 269(1), 109-20.
- [10] Artusi, M.; Nicoli, S.; Colombo, P.; Bettini, R.; Sacchi, A.; Sanli, P. *J. Pharm. Sci.* **2004**, 93 (10), 2431-8.
- [11] Chou, W.-L.; Cheng, C.-H.; Yen, S.-C.; Jiang, T.-S. *Drug Dev. Ind. Pharm.* **1996**, 22(9&10), 943-50.
- [12] Lai, P. M.; Roberts, M. S. In *Dermal absorption and toxicity assessment*, Roberts, M.S.; Walters, Kenneth A., Eds.; Marcel Dekker Inc.: New York, **1998**, Vol. 91, pp. 371-414.
- [13] Banga, A.K. *Electrically assisted transdermal and topical drug delivery*, Taylor and Francis, London, **1998**.
- [14] Singh, J.; Bhatia, K.S. *Med. Res. Rev.* **1996**, 16, 285-96.
- [15] Singh, J.; Maibach, H.I. *Crit. Rev. Ther. Drug Carr. Syst.* **1994**, 11, 161-213.
- [16] Pikal, M.J. *Adv. Drug. Deliv. Rev.* **1992**, 9(2-3), 201-37.
- [17] Huang, Y.-Y.; Wu, S.-M.; Wang, C.-Y. *Pharm. Res.* **1996**, 13(4), 547-52.
- [18] Clemessy, M.; Couaraze, G.; Bevan, B.; Puisieux, F. *Int. J. Pharm.* **1994**, 101(3), 219-26.
- [19] Rao, G.; Glikfeld, P.; Guy, R.H. *Pharm. Res.* **1993**, 10(12), 1751-5.
- [20] Sekkat, N.; Naik, A.; Kalia, Y.N.; Glikfeld, P.; Guy, R.H. *J. Control. Release* **2002**, 81(1-2), 83-9.
- [21] Kavanagh, G. M.; Oh, C.; Shams, K. *Brit. J. Dermatol.* **2004**, 151, 1093-95.
- [22] Alza product literature, www.alza.com.
- [23] Iomed product literature, http:// www.iomed.com.
- [24] Chaturvedula, A.; Joshi, D. P.; Anderson, C.; Morris, R. L.; Sembrowich, Walter L.; Banga, A. K. *Int. J. Pharm.* **2005**, 297(1-2), 190-6.
- [25] Turner, N. G.; Guy, R.H. *J. Pharm. Sci.* **1997**, 86(12), 1385-9.
- [26] Lelawongs, P.; Liu, J-C; Siddiqui, O.; Chien, Y. W. *Int. J. Pharm.* **1989**, 56(1), 13-22.
- [27] Thysman, S.; Pr at, V.; Roland, M. *J. Pharm. Sci.* **1992**, 81(7), 670-5.
- [28] Delterzo, S.; Behl, C.R.; Nash, R.A. *Pharm. Res.* **1989**, 6(1), 89-90.
- [29] Koizumi, T.; Kakemi, M.; Katayama, K.; Inada, H.; Sudeji, K.; Kawasaki, M. *Chem. Pharm. Bull.* **1990**, 38(4), 1022-3.
- [30] Nugroho, A. K.; Li, L.; Dijkstra, D.; Wikstr m, H.; Danhof, M.; Bouwstra, J.A. *J. Control. Release* **2005**, 103(2), 393-403.

- [31] Nugroho, A. K.; Li, G.; Arne, G.; Danhof, M.; Bouwstra, J. A. *J. Control. Release* **2004**, *96*(1), 159-67.
- [32] Jacobsen, J. *J. Control. Release* **2001**, *70*(1-2), 83-95.
- [33] Tiwari, S. B.; Udupa, N. *Int. J. Pharm.* **2003**, *260*(1), 93-103.
- [34] Bellantone, N.H.; Rim, S.; Francoeur, M.L.; Rasadi, B. *Int. J. Pharm.* **1986**, *30*(1), 63-72.
- [35] Miller, L.L.; Kolaskie, C.J.; Smith, G.A.; Rivier, J. *J. Pharm. Sci.* **1990**, *79*(6), 490-3.
- [36] Sanderson, J.E.; Riel, S.D.; Dixon, R. *J. Pharm. Sci.* **1989**, *78*, 361-64.
- [37] Singh, P.; Boniello, S.; Liu, P.; Dinh, S. *Pharm. Res.* **1997**, *14*(suppl.), S309-10.
- [38] Morimoto, K.; Iwakura, Y.; Miyazaki, M.; Natakani, E. *Int. J. Pharm.* **1992**, *81*(2-3), 119-25.
- [39] Iwakura, Y.; Morimoto, K. *S.T.P. Pharm. Sci.* **1991**, *1*, 387.
- [40] Morimoto, K.; Iwakura, Y.; Nakatani, E.; Miyazaki, M.; Tojima, H. *J. Pharm. Pharmacol.* **1992**, *44*(3), 216-8.
- [41] Kochhar, C.; Imanidis, G. *J. Control. Release* **2004**, *98*(1), 25-35.
- [42] Bose, S.; Ravis, W.R.; Lin, Y.-J.; Zhang, L.; Hofmann, G.A.; Banga, A.K. *J. Control. Release* **2001**, *73*(2-3), 197-203.
- [43] Takahashi, Y.; Iwata, M.; Mahila, Y. *Yakugaku Zasshi*, **2001**, *121*(2), 161-6.
- [44] Pillai, O.; Nair, V.B.; Ramarao, P.; Panchagnula, R. *J. Pharm. Pharmacol.* **2000**, *52*(suppl.), 92.
- [45] Siddiqui, O.; Sun, Y.; Liu, J.-C.; Chien, Y.W. *J. Pharm. Sci.* **1987**, *76*(4), 341-5.
- [46] Huang, Y.-Y.; Wu, S.-M.; Wang, C.-Y.; Jiang, T.-S. *Drug Develop. Ind. Pharm.* **1995**, *21*(14), 1631-48.
- [47] Siddiqui, O.; Roberts, M.S.; Polack, A.E. *J. Pharm. Pharmacol.* **1985**, *37*(10), 732-5.
- [48] Craane-Van, Heinsberg, W.H.M.; Bax, L.; Flinterman, N.H.M.; Verhoef, J.; Junginger, H.E.; Boddé, H.E. *Pharm. Res.* **1994**, *11*(9), 1296-1308.
- [49] Knoblauch, P.; Moll, F. *J. Control. Release* **1993**, *26*(3), 203-12.
- [50] Fu, L.M.; Lee, D.; Carlson, R.; Rao, G.S.; Hui, H.W.; Adjei, L.; Herrin, M.; Sunberg, D.; Hsu, L. *Drug Develop. Ind. Pharm.* **1993**, *19*(13), 1557-71.
- [51] Yoshida, N.H.; Roberts, M.S. *J. Pharm. Pharmacol.* **1995**, *47*(11), 883-90.
- [52] Nair, V.B.; Pillai, O.; Ramarao, P.; Panchagnula, R. *J. Pharm. Pharmacol.* **2000**, *52*(Suppl.), 79.
- [53] Miller, L.L.; Smith, G.A.; Chang, An-Chang.; Zhou, Q.-X. *J. Control. Release* **1987**, *6*(1), 293-6.
- [54] Miller, L.L.; Smith, G.A. *Int. J. Pharm.* **1989**, *49*(1), 15-22.
- [55] Green, P.G.; Hinz, R.S.; Cullander, C.; Yamane, G.; Guy, R.H. *Pharm. Res.* **1991**, *8*(9), 1113-20.
- [56] Green, P.G.; Shroot, B.; Bernard, F.; Pilgrim, W.R.; Guy, R.H. *J. Control. Release* **1992**, *20*(3), 209-17.
- [57] Langkjaer, L.; Brange, J.; Grodosky, G.M.; Guy, R.H. *Proc. Int. Symp. Control. Rel. Biact. Mater.* **1994**, *21*, 172.
- [58] Vander-Geest, R.; Hueber, F.; Szoka, F.C. Jr.; Guy, R.H. *Pharm. Res.* **1996**, *13* (4), 553-8.
- [59] Burnett, R.R.; Ongpipattanakul, B. *J. Pharm. Sci.* **1987**, *76*(10), 765-73.
- [60] Berner, B.; Dinh, S.M. *Electronically assisted controlled drug delivery*, CRC: Washington DC. **1998**.
- [61] Green, P.G.; Hinz, R.S.; Kim, A.; Cullander, C.; Yamane, G.; Szoka, F.C. Jr.; Guy, R.H. *J. Control. Release* **1992**, *21* (1-3), 187-190.
- [62] Sung, K.C.; Fang, J.-Y.; Hu, O.Y.-P. *J. Control. Release* **2000**, *67* (1), 1-8.
- [63] Burnett, R.R.; Marrero, D. *J. Pharm. Sci.* **1986**, *75*(8), 738-43.
- [64] Wearley, L.; Liu, J.-C.; Chien, Y.W. *J. Control. Release* **1989**, *8*(3), 237-50.
- [65] Hui, X.; Anigbogu, A.; Singh, P.; Xiong, G.; Poblet, N.; Liu, P.; Maibach, H.I. *J. Pharm. Sci.* **2001**, *90*(9), 1269-76.
- [66] Lawler, J.C.; Davis, M.J.; Griffith, E. *J. Invest. Dermatol.* **1960**, *34*, 301-8.
- [67] Bagniefski, T.; Burnett, R.R. *J. Control. Release* **1990**, *11*(1-3), 113-22.
- [68] Singh, P.; Puchun, L.; Dinh, S.M. In *Percutaneous Absorption Drug-cosmetic-mechanism and methods*, Bronaugh, R.L.; Maibach, H.I. Eds.; 3rd edition, Marcel Dekker Inc., New York, **1998**.
- [69] Chien, Y.W.; Lelawong, P.; Siddiqui, O.; Sun, Y.; Shi, W.M. *J. Control. Release* **1990**, *13*(2-3), 263-78.
- [70] Prétat, V.; Thysman, S. *Int. J. Pharm.* **1993**, *96*(1-3), 189-96.
- [71] Thysman, S.; Tasset, C.; Prétat, V. *Int. J. Pharm.* **1994**, *101*(1-2), 105-13.
- [72] Phipps, J.B.; Padmanabham, R.V.; Lattin, G.A. *J. Pharm. Pharmacol.* **1989**, *78*, 365.
- [73] Cross, S.E.; Roberts, M.S. *J. Pharm. Sci.* **1995**, *84*, 584-92.
- [74] Roberts, M.S.; Favretto, W.A.; Meyer, A.; Rechmann, M.; Wongseelashote, T. *Aust. N.Z. J. Med.* **1982**, *12*, 305.
- [75] Feldman, R.H.; Maibach, H.I. *Arch. Dermatol.* **1967**, *48*, 181.
- [76] Fang, J.-Y.; Sung, K.C.; Wang, J.-J.; Chu, C.-C.; Chen, K.-T. *J. Pharm. Pharmacol.* **2002**, *54*(10), 1329-37.
- [77] Nolan, L.M.A.; Corish, J.; Corrigan, O.I.; Fitzpatrick, D. *Int. J. Pharm.* **2003**, *257*(1-2), 41-55.
- [78] Kanikannan, J.N.; Singh, J.; Ramarao, P. *J. Control. Release* **2001**, *71*(1), 99-105.
- [79] Badkar, A.V.; Banga, A.K.; *J. Pharm. Pharmacol.* **2002**, *54*(7), 907-12.
- [80] Merclin, N.; Bramer T.; Edsman, K. *J. Control. Release* **2004**, *98*(1), 57-65.
- [81] Curdy, C.; Kalia, Y.N.; Naik, A.; Guy, R.H. *J. Control. Release* **2001**, *76*(1-2), 73-9.
- [82] Amini, T.; Conway, B.R.; Irwin, W.J.; Lambert, P.A.; Elliot, T.S.J. *J. Pharm. Pharmacol.* **2000**, *52*(Suppl.), 25.
- [83] Esther, E.-B.; Raiskup, F.; Stepensky, D.; Domb, A.J. *J. Invest. Ophthalm. Vis. Sci.* **2004**, *45*, 2543-8.
- [84] Pillai, O.; Panchagnula, R. *J. Control. Release* **2003**, *89*(1), 127-40.
- [85] Pillai, O.; Panchagnula, R. *J. Control. Release* **2003**, *88*(2), 287-96.
- [86] Meidan, V. M.; Al-Khalili, M.; Michniak, B. B. *Int. J. Pharm.* **2003**, *264*(1-2), 73-83.
- [87] Smyth, H.D.C.; Becket, G.; Mehta, S. *J. Pharm. Sci.* **2002**, *91*(5), 1296-1307.
- [88] Kanikkannan, N.; Singh, J.; Ramarao, P. *Int. J. Pharm.* **2000**, *197*(1-2), 69-76.
- [89] Li, G.L.; Van der Geest, R.; Chanet, L.; Zanten, E. V.; Danhof, M.; Bouwstra, J. A. *J. Control. Release* **2002**, *84*(1-2), 49-57.
- [90] Sebastiani, P.; Nicoli, S.; Santi, P. *Int. J. Pharm.* **2005**, *292*(1-2), 119-26.
- [91] Suzuki, Y.; Iga, K.; Yanai, S.; Matsumoto, Y.; Kawase, M.; Fukuda, T.; Adachi, H.; Higo, N.; Ogawa, Y. *J. Pharm. Pharmacol.* **2001**, *53*(9), 1227-34.
- [92] Ishikawa, O.; Kato, Y.; Onishi, H.; Nagai, T.; Machida, Y. *Int. J. Pharm.* **2002**, *249*(1-2), 81-8.
- [93] Johanna, R.; Majja, k.; Katri, H.; Risto, K.; Jouni, H. *Eur. J. Pharm. Sci.* **2004**, *21*(2-3), 371-7.
- [94] Prausnitz, M.R. *J. Control. Release* **1996**, *40*(3), 321-6.
- [95] Riviere, J. E.; Heit, M.C. *Pharm. Res.* **1997**, *14*(6), 687-97.
- [96] Vanbever, R.; Demorre, N.; Prétat, V. *Pharm. Res.* **1996**, *13*(9), 1360-6.
- [97] Bose, S.; Ravis, W.R.; Lin, Y.J.; Zhang, L.; Hofmann, G.A.; Banga, A.K. *J. Control. Release* **2001**, *73*(2-3), 197-203.
- [98] Jadoul, A.; Lecouturier, N.; Mesens, J.; Caers, W.; Prétat, V. *J. Control. Release* **1998**, *54*(3), 265-72.
- [99] Regnier, V.; De Moore, N.; Jadoul, A.; Prétat, V. *Int. J. Pharm.* **1999**, *184*(2), 147-56.
- [100] Merino, V.; Kalia, Y.N.; Guy, R.H. *Trends. Biotech.* **1997**, *15*, 288-90.
- [101] Chang, S.L.; Hofmann, G.A.; Zhang, Lei; Deflor, L. J.; Banga, A.K. *J. Control. Release* **2000**, *66*(2-3), 127-33.
- [102] Hirsch, A.C.; Upasani, R.S.; Banga, A.K. *J. Control. Release* **2005**, *103*(1), 113-21.
- [103] Merino, V.; López, A.; Hochstrasser, D.; Guy, R.H. *J. Control. Release* **1999**, *61*(1-2), 65-9.
- [104] Leboulanger, B.; Fathi, M.; Guy, R.H.; Delgado-Charro, M.B. *Pharm. Res.* **2004**, *21*(7), 1214-22.
- [105] Leboulanger, B.; Guy, R. H.; Delgado-Charro, M.B. *Eur. J. Pharm. Sci.* **2004**, *22*(5), 427-33.