Expert Opinion

Transdermal iontophoresis

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Iontophoresis is a technique used to enhance the transdermal delivery of compounds through the skin via the application of a small electric current. By the process of electromigration and electro-osmosis, iontophoresis increases the permeation of charged and neutral compounds, and offers the option for programmed drug delivery. Interest in this field of research has led to the successful delivery of both low (lidocaine) and high molecular drugs, such as peptides (e.g., luteinising hormone releasing hormone, nafarelin and insulin). Combinations of iontophoresis with chemical enhancers, electroporation and sonophoresis have been tested in order to further increase transdermal drug permeation and decrease possible side effects. In addition, rapid progress in the fields of microelectronics, nanotechnology and miniaturisation of devices is leading the way to more sophisticated iontophoretic devices, allowing improved designs with better control of drug delivery. Recent successful designing of the fentanyl E-TRANS® iontophoretic system have provided encouraging results. This review will discuss basic concepts, principles and applications of this delivery technique.

Keywords: electro-osmosis, electrorepulsion, iontophoresis, skin, transdermal

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1. Introduction

The skin has been used as an alternative route for the systemic delivery of drugs to circumvent the hepatic first-pass metabolism and the chemical degradation of compounds in the gastrointestinal (GI) tract. Transdermal drug delivery has been extensively researched in past decades to deliver many therapeutic agents using various formulations and delivery systems, the most popular being patches. However, the stratum corneum, which forms the outermost layer of the skin and serves to limit water loss from the body, presents a tough barrier to the penetration of molecules. The presence of flattened corneocytes (terminally differentiated keratinocytes) embedded in layers of intercellular lipid lamellae renders the stratum corneum impermeable and tortuous, thus restricting skin permeation to small lipophilic molecules [1]. This barrier effect has somewhat limited the success of transdermal delivery of molecules such as clonidine, fentanyl, oestradiol, nicotine, nitroglycerin, testosterone, scopolamine, oxybutynin and the combination products norelgestromin/ethinyl oestradiol and oestradiol/norethindrone acetate, which are active at low blood concentrations [2].

Nevertheless, it is the extensive study of the stratum corneum that has led to the manipulation of its components in order to facilitate the permeation of compounds. Penetration enhancement of the stratum corneum has been achieved through the application of chemical and physical enhancement techniques. Chemical enhancers have been widely explored and they serve to increase the partitioning and diffusion of drugs through the skin [3-5]. Although many chemical enhancers work through a combination of mechanisms, they either increase permeation by insertion into and alteration of the stratum corneum lipids (i.e., they enhance paracellular diffusion), or they interact with the cellular proteins in the corneocytes to

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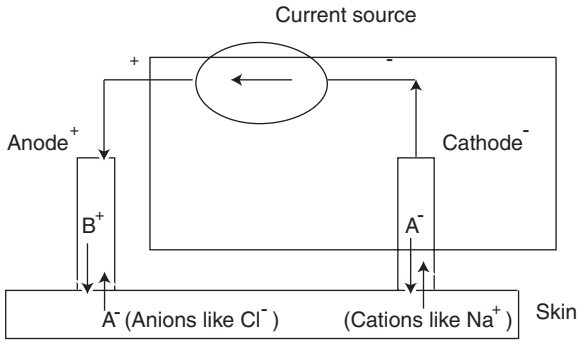

Figure 1. An anodal iontophoretic system.

increase the partitioning and the transcellular permeation [6,7]. Although chemical enhancers can increase the partitioning of the drug into the skin, they can also cause skin irritation that can limit the number and the amount of enhancers that can be used. Various physical approaches to permeation enhancement, such as iontophoresis [8], phonophoresis [9], electroporation [10] and microneedle arrays [11], have been widely investigated for transdermal permeation enhancement. In addition, combinations of physical and chemical enhancements have been examined and shown to further enhance the permeation of the skin [12].

Transdermal iontophoresis is defined as the administration of soluble ionic/charged therapeutic agents through the skin by the application of a low-level electric current. It is a noninvasive technique and enables programmed drug delivery through the skin. Aside from the water-soluble ionic drugs, the delivery of macromolecules, including peptides, through the skin can also be enhanced by this technique [13]. Drug molecules are transported from the drug solution/device into the skin from where they move into the systemic circulation through the blood capillaries.

Over the years, the development of iontophoretic delivery systems, in addition to a surge in the development of transdermal patches, has led to extensive research in the field of iontophoretic transdermal drug delivery. The technique delivers therapeutic agents to the skin with improved permeability, and various drugs that have been successfully tested are described in this article. In addition, successful transdermal iontophoretic delivery of peptides such as luteinising hormone releasing hormone (LHRH), nafarelin and insulin has shown that this method can be used successfully for peptide delivery [14,15]. A recent application of iontophoresis is the fentanyl hydrochloride patient-controlled transdermal system that delivers small doses of fentanyl by iontophoresis with electrotransport delivery platform technology (E-TRANS®, ALZA Corp.) [16]. Reverse iontophoresis has also been used to develop the GlucoWatch® Biographer (Cygnus, Inc.), a wrist-worn device that monitors glucose continuously for up to 13 h.

2. Advantages and limitations of iontophoresis

In addition to increasing the permeation and delivery of ionic molecules in a noninvasive fashion, iontophoresis permits the control of the delivery rate in a determined and preprogrammed manner [17]. This control over delivery, and the proportionate relationship of the drug delivered to the current applied, facilitates the reduction of intra- and interpatient variability [17,18].

This technique is particularly advantageous for macromolecules including peptides, which do not achieve therapeutically relevant concentrations through oral delivery. Transdermal iontophoresis also shares the advantages of passive transdermal delivery, namely the avoidance of hepatic first-pass effect and the GI tract environment, improved patient compliance, and ease of terminating drug delivery as soon as the device is removed. On demand delivery is also possible allowing better patient control.

Although the technique is considered safe, the application of higher levels of current involved in this method may cause discomfort, painful burning sensations, skin irritation, along with blisters and necrosis [19,20]. For example, initial iontophoresis treatment takes ~ 30 min/treatment site for at least 4 days/week. There is a potential for skin irritation, and it is not usually recommended for underarm or facial/head hyperhidrosis. The feasibility of designing a practical dosage form for everyday use, especially when other techniques such as ultrasound are used with iontophoresis, is also questionable.

3. Principles of iontophoresis

3.1 Basic principles

Iontophoresis is based on the general principles of electricity and charges (i.e., like charges repel each other). An electrode with a defined charge is used to repel a drug with a similar charge, which is attracted by an oppositely charged electrode placed elsewhere on the body. Thus, an anodal iontophoretic device consists of a current source, an electronic device to control the current, positively charged drug/ion in solution, an anode reservoir system (with the anode electrode) and the cathode reservoir system (with the cathode electrode). The positively charged drug is placed in the anode reservoir system at the desired site of application, whereas the cathode is placed on a different site on the skin. On application of an electric current, all cations, including the positively charged drug, move away from the anode and into the skin. At the same time, negatively charged ions in the body move from the body into the donor reservoir [18]. A typical anodal iontophoretic system is shown in Figure 1.

3.2 Electrode system in iontophoresis

The electrodes chosen should be of a shape and form that contour well on the skin surface and produce minimal changes in the pH of the skin. Silver/sliver chloride (Ag/AgCl) electrodes

have been commonly used in iontophoretic systems [21,22]. The silver present at the anode oxidises and reacts with the chloride ions to form insoluble AgCl. At the same time, the AgCl at the cathode gets reduced to Ag^+ and releases the Cl^-. The reactions do not involve the electrolysis of water, thus avoiding sharp changes in the pH that have been seen with other metallic electrodes (platinum) [23]. Phipps *et al.* studied the delivery of lithium across a polyvinyl alcohol hydrogel membrane. Although the use of a platinum anode caused a pH decrease from 5.9 to 2.6 after 6 h with a lithium delivery efficiency of only 20.2%, using the silver anode caused virtually no change in pH and increased the efficiency to ~ 37% [21].

3.3 Theory of drug transport by iontophoresis

Iontophoretic transport across the skin can occur by the process of electrorepulsion or electromigration (as described in Sections 3.1 and 3.2). However, due to the permselective properties of the skin, drugs can also be transported by the process of electro-osmosis [19,24].

At pH 7.4, the skin is negatively charged and cation permselective [19]. Thus, the passage of current can cause a net convective solvent flow in the anode-to-cathode direction. This can facilitate cation transport, inhibit the transport of anions and enhance the transport of neutral and polar solutes (electro-osmotic flow). The negatively charged skin under iontophoresis can therefore cause electro-osmotic flow of water into the body, which facilitates the transfer of cations.

Thus, iontophoretic transport can occur through a combination of electrorepulsion and electro-osmosis, and the balance between both methods will depend on the pH and the electric properties of the membrane and of the drug that is permeating. Formulation strategies for the drug will depend on the contribution of electrorepulsion or electro-osmosis to its transport. If the predominant method is electrorepulsion, then the transport of a charged drug can be increased by decreasing the amount of competing ions. On the other hand, for larger ions, where the predominant method can be electro-osmosis, different strategies are warranted [25].

The total iontophoretic flux across a membrane can be considered to be the sum of electrorepulsion and electro-osmosis (assuming here that passive diffusion is negligible) [26].

$$J_{Total} = J_e + J_c \qquad (1)$$

where J_{Total} is the total flux of a cationic drug. J_e is the flux due to electrorepulsion and is given as:

$$J_e = \left(\frac{1}{Z_x F}\right) \frac{z_x u_x c_x}{\sum_{n=0}^{i} z_i u_i c_i} I_D \qquad (2)$$

where I_D is the applied current density, F is the Faraday's constant, and z_X, u_X and c_X refer to the charge, mobility and concentration of the drug in the membrane, respectively. The denominator here is the sum of the products of these parameters for each ion in the system contributing to charge transfer across the membrane.

From Equation 2, it can be seen that the presence of competing ions can reduce the drug flux and thereby the delivery efficiency. The competition of drug transport will also depend on the mobility and the concentration of all species in the membrane, indicating that the delivery of a less mobile species can be enhanced by increasing its concentration. J_c is the flux due to convective transport (electro-osmosis) and is given as:

$$J_c = \nu C_x \qquad (3)$$

where ν is the electro-osmotic solvent velocity.

Thus, electro-osmosis can be defined as solvent velocity, which is equivalent to a permeability coefficient in units of cm/h. If solvent flow occurs from anode to cathode, it can deliver neutral molecules by anodal iontophoresis. As previously mentioned, this mode of transport also benefits cations, which can be transported along with the solvent [26].

The contribution of electrorepulsion and electro-osmosis in the iontophoretic transport of a drug is difficult to determine. However, it has been suggested that the transport of small mobile ions such as Na^+ occurs predominantly by electrorepulsion, whereas larger bulkier species of high molecular weights (≥ 1000 Da) seem to be primarily transported by electro-osmosis [27,28].

Recent advances in understanding iontophoretic delivery have been due to the development of the ionic mobility–pore model. Here, the determinants for iontophoresis have been solute size [29,30] (defined by solute molecular volume, molecular weight or radius); solute mobility; solute shape; solute charge; the Debye layer thickness; total current applied; solute concentration; fraction ionised; solute conductivity (governed by presence of extraneous ions); epidermal permselectivity; partitioning rates to account for the interaction of unionised or ionised lipophilic solutes with the wall of the pore; and electro-osomosis.

The solute size affects the flux due to a pathway restriction in the transport. There are two models considered for pathway restriction: the free volume model in which molecules jump into limited space through pores, and the pore restriction model in which entry into the pore and movement through it are restricted due to stearic hindrance and friction with the pore wall. The second model has been found to be more predictive for model/experimental data correlations. The final equation for this theoretical model is given as follows:

$$PC_{j,\,iont,\,overall} = \frac{2\mu_j f i_j F z_j I_T \Omega P R T_j}{(k_{s,a} + k_{s,c})[1 + f\mu_j \theta_{ju} + (1 - f\mu_j)\theta_{ji}]} \pm (1 - \sigma_j)\nu_m \qquad (4)$$

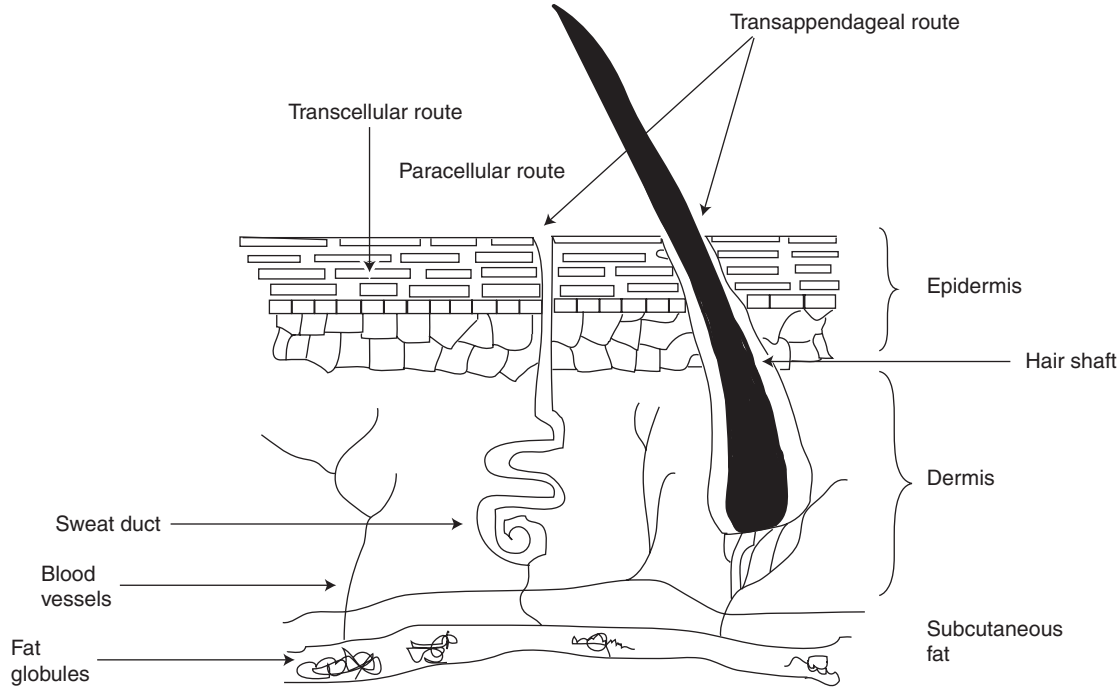

Figure 2. Pathways of drug transport through the skin.

where $PC_{j,iont,overall}$ is the overall iontophoretic permeability coefficient of a solute *j*; μ_j is the ionic mobility of the solute; fi_j and fu_j are the fraction of the solute ionised and unionised, respectively; *F* is Faraday's constant; z_j is the charge of the solute; I_T is the current; $k_{s,a}$ and $k_{s,c}$ is the conductivity of the solution in the anodal and cathodal chamber, respectively; θ_{ju} and θ_{ji} is a function of the interfacial clearance of the solute and other factors of unionised and ionised solutes, respectively; Ω is the permselectivity factor; PRT_j is the pathway restriction term; σ_j is the reflection coefficient and is related to the electro-osmotic component of iontophoretic transport; and v_m is the velocity of flow across the membrane.

Other interesting investigations include the mechanistic studies of flux variability of neutral and ionic permeants conducted by Li *et al.* [31] during constant direct current (DC) iontophoresis. It was observed that although pore size and pore charge density led to these variations, the later factor contributed more significantly to the flux drifts. In addition, the flux variability was smaller for ionic variants as compared with neutral molecules. The study also established that if the permeability coefficient of one neutral permeant is known, the flux of the other neutral permeant can be predicted.

3.4 Routes of transport

Applying an electric current to transport ions across the skin will cause them to move by pathways that offer the least amount of electrical resistance. The application of current can also create changes in the skin permeability and create new pathways for drug permeation [32]. Although there are three routes for a drug to permeate through the skin (transcellular, paracellular and transappendageal, as indicated in Figure 2), iontophoretic delivery is said to occur primarily through the transappendageal and the paracellular route. The major route is believed to be the appendageal pores in the skin, including the hair follicles and sweat glands [33]. Ionised drugs can also move in through damaged pieces of the skin.

Cullander and Guy [34] used a vibrating probe electrode to identify the routes taken by charged substances through hairless mouse skin during iontophoretic drug delivery at clinically relevant current densities. They found that iontophoretic currents passed primarily through the appendages. In addition, certain appendages such as small hairs seemed to carry most of the current. They also detected the movement of ions where no appendageal structures and skin injuries were present, suggesting the involvement of the paracellular route. Visualisation of transport pathways by iontophoresing mercuric chloride showed that the compound penetrated the skin through appendageal pathways and a paracellular route [35]. In addition, a potential dependant pore formation in the stratum corneum due to a 'flip-flop' gating mechanism has also been reported [36]. On the application of electric potential, the polypeptide helices in the stratum corneum undergo a flip-flop motion and can form a parallel arrangement, leading to the repulsion of the neighbouring dipoles and opening of the

pores. Ions flow in through these opened pores to neutralise the generated dipole moments.

4. Factors affecting iontophoretic transport

Modifications/alterations of the three components in iontophoretic delivery (the formulation, the iontophoretic system and the membrane) can affect the iontophoretic transport of a drug and subsequently its permeation. Some of the factors that affect iontophoretic delivery are discussed in this section.

4.1 pH

As discussed earlier, ionised species pass through the membrane by electrorepulsion (or electromigration) under the influence of an electric current. Thus, the ideal pH will be one where a large proportion of the drug is in the ionised form. Siddiqui *et al.* [37] demonstrated the effect of pH on the iontophoretic transport of lidocaine. In the absence of iontophoresis, the rate of penetration was found to be greatest at the high pH values where the molecule exists mainly in the unionised form. However, at pH values of 3.4 and 5.2, the flux increased by ~ 8.5- and 4-times, respectively, under the influence of iontophoresis, relative to that occurring without iontophoresis. Thus, iontophoresis was found to be most effective at lower pH values where the drug was predominantly ionised.

During the process of iontophoresis, oxidation and reduction reactions occur at the electrodes, which produce a lowering of pH at the anode and an increase at the cathode [21]. These changes in pH can alter drug transport by an electro-osmotic effect. In addition, the pH of the membrane can also affect the charge on the skin and, subsequently, the electro-osmotic flow.

4.2 Concentration and ion competition

The flux of a drug diffusing passively through the skin is a function of its concentration. Del Terzo *et al.* [38] showed that the iontophoretic flux of butyrate increased with the increase in drug concentration. Nevertheless, in iontophoresis, it is not only the concentration of the drug but also the concentration of the counterions (other ions with the opposite charge) or co-ions (other ions with the same charge) that play a role. The electromigration of the drug ions can be negatively influenced by competition with these ions. In addition, ions from buffers added to donor solutions in order to maintain the pH may be mobile enough to compete with drug ions for transport, and thus affect the efficiency of the delivery.

4.3 Molecular size

Studies conducted with different drug molecules have established relationships between the size and iontophoretic delivery. Yoshida *et al.* [39] investigated the effect of molecular size of a series of positively charged, negatively charged and uncharged solutes on their iontophoretic transport across excised human skin. They observed that a linear relationship exists between the logarithm of the iontophoretic permeability coefficient and the molar volume of the solutes. Molecular size has also shown to have a significant effect on the electro-osmotic flow of ions. The electro-osmotic flow increases in importance as the size of the drug ion increases; for monovalent ions with Stokes radii > ~ 1 nm, electro-osmotic flow is the dominant flow mechanism [40].

4.4 Current: strength and choice of continuous versus pulsed

Equation 2 shows that the electromigratory flux for a charged drug should be proportional to the current applied. Investigations regarding this effect have shown that the flux does increase with an rise in the amount of applied current as shown with methylphenidate HCl [41] and thyrotropin releasing hormone (TRH) [42]. However, a plateau has been seen with further increase in the current, which indicates that a saturation phenomenon may exist [43]. Application of higher currents may also cause skin burning and discomfort.

The use of continuous currents may lead to a buildup of charge, which may cause the skin to be polarised, thus decreasing the efficiency of delivery [44]. The use of pulse currents has been found to be equally effective or better for iontophoretic transport efficiency [45,46]. With pulsed current, less current is required to reduce the skin resistance, and the time between two pulses allows the skin to depolarise and return to its original state, thus minimising side effects due to minimal accumulation of charges. Chien *et al.* showed that the *in vivo* transdermal delivery of vasopressin was improved twofold using pulsed current as compared with simple DC current with the same current density and for the same time [46]. Pulsed direct current profile was also shown to be the most efficient in transporting both LHRH and nafarelin across the human epidermis. It was found that the percentage of intact LHRH in the receiver phase was slightly higher with the pulsed current, thus indicating better transport and stability [14].

All the above factors, as well as physiological factors, such as the permselectivity of the skin, injuries and blood flow, may affect the efficacy and efficiency of iontophoresis. Optimisation will thus depend on the nature of the permeant and combinations of the factors discussed above.

5. Transdermal iontophoresis: applications

5.1 Transdermal iontophoresis of small molecules

Iontophoresis as a technique for permeation enhancement has been found to be useful for the delivery of small molecules such as apomorphine [47,48], rotigotine [8,49], 5-fluorouracil (5-FU) [50], and buspirone hydrochloride [51]. Apomorphine, a dopamine agonist used for the treatment for Parkinson's disease, exhibits minimal oral absorption, high first-pass metabolism, chemical instability and local toxicity. Currently, the subcutaneous route is the main choice for administration but often leads to the appearance of subcutaneous nodules. This has lead to the investigation

of alternative routes of administration, such as transdermal iontophoretic delivery of apomorphine, which has been studied both *in vitro* and *in vivo* [47,48,52]. In the *in vivo* studies, [47] two groups of five patients were each treated with the passive application of an apomorphine formulation followed by the application of iontophoresis. The first group was exposed to a current density of 250 µA/cm^2 and the second to 375 µA/cm^2, and the plasma concentration levels, current-induced irritation and skin resistance were measured. The maximum plasma concentrations obtained were 1.3 ± 0.6 ng/ml at 250 µA/cm^2 and 2.5 ± 0.7 ng/ml at 375 µA/cm^2. The flux values for the *in vivo* studies (69 ± 30 nmol/cm^2·h) were slightly lower than those reported for the *in vitro* steady-state flux (101 ± 13 nmol/cm^2·h) across the stratum corneum [48]. The studies were performed using Ag/AgCl electrodes at 37°C and in both the studies, a donor formulation of apomorphine 15 mM at pH 5 was used. The commonly reported side effects with subcutaneous administration, such as prolonged inflammation and green colouring, (as a result of oxidation of apomorphine) were not observed with iontophoretic delivery. The iontophoresis application, however, did cause a mild and transient erythema. The achieved concentrations in the *in vivo* study remained just below therapeutically significant concentrations of 3 – 6 ng/ml at the applied current density. In conclusion, the *in vivo* studies correlated well with the *in vitro* studies, and the *in vivo* delivery was dependent on applied current, which opens up the attractive option of individual titration of administered dose. Depending on the extent of any side effects that may occur, lower drug concentrations could be applied together with the addition of chemical enhancement or formulation modifications.

This was investigated by Li *et al.* [52] who changed various parameters, including temperature, current density and type of tissue, for *in vitro* delivery of *R*-apomorphine. Surfactant skin pretreatment was employed as a strategy to improve the permeation. Laureth-3 oxyethylene ether ($C_{12}EO_3$), laureth-7 oxyethylene ether ($C_{12}EO_7$) and sodium sulfosuccinate in a molar ratio of 70:30:5 were used as surfactants. Ascorbic acid was used as an antioxidant and tetraethylammonium chloride (TEACl) as a source of Cl^-, which was seen to favourably affect the transdermal iontophoretic transport rate. Increasing temperature from 22 to 32°C, increasing current density and using stratum corneum instead of dermatomed skin also increased the iontophoretic flux. The flux obtained across stratum corneum at a current density of 500 µA/cm^2 with a formulation containing 15 mM drug, TEACl 137.9 mM, ascorbic acid 1 g/l at pH 5.0, and with surfactant pretreatment was reported to be 362 ± 46 nmol/cm^2·h. Assuming a one-to-one relationship between *in vivo* and *in vitro* studies, and taking into account the clearance values of apomorphine in the body, it was calculated that a patch of 20 cm^2 would give plasma concentrations of ~ 10 ng/ml, which would reach the required therapeutic levels of drug. Controls used phosphate buffer pretreatment in which sodium metabisulfite and sodium chloride were used in place of ascorbic acid and TEACl, and there was no pretreatment with surfactants.

Such combination strategies (chemical enhancers plus iontophoresis) have also expanded to the use of more than two chemical/physical enhancement methods. Ketorolac tromethamine, with a molecular weight of 364 Da, is a non-steroidal agent with potent analgesic and moderate anti-inflammatory activities. Oral administration of this drug suffers from drawbacks such as severe GI side effects and the short biological half-life of 4 – 6 h, making it unsuitable for parenteral administration. Chemical enhancement [53] and prodrug approaches [54] have been investigated, and transdermal delivery of this drug achieved the desired plasma concentrations [55]. However, concerns regarding the lag time and the inability to modulate the rate of the release warrant the use of other delivery enhancement techniques such as iontophoresis, which provide better delivery control. Tiwari and Udupa [56] studied the transdermal iontophoretic permeation flux of ketorolac in four different combinations of iontophoresis with:

- chemical enhancer pretreatment with ethanol
- 5% D-limonene in combination with ethanol
- physical enhancer pretreatment (ultrasound)
- combination of chemical and physical enhancer pretreatment (ultrasound plus 5% D-limonene in ethanol)

In all cases, ketorolac 2 mg/ml and current density of 0.5 mA/cm^2 was used. The enhancer pretreatment was conducted for 2 h, and the ultrasound treatment was conducted at 1 MHz, 1.4 W/cm^2 for 30 min. Delivery with ethanol/iontophoresis (flux: 64.21 ± 5.93 µg/cm^2·h) and ultrasound /iontophoresis (flux: 64.25 ± 5.84 µg/cm^2·h) did not provide significant enhancement over iontophoresis alone (flux: 62.80 ± 6.78 µg/cm^2·h). The highest flux was provided by a combination of all the four variables (flux: 136.11 ± 9.10 µg/cm^2·h), which was significantly different from iontophoresis alone, ethanol, ultrasound pretreatment ($p < 0.01$) or D-limonene/ethanol pretreatment ($p < 0.05$). As a result, there was a 45% reduction in patch area with the application of D-limonene/ethanol with ultrasound pretreatment followed by iontophoresis when compared with iontophoresis without pretreatment. Another example of combined enhancement techniques was the study of the effect of iontophoresis and enhancers on the delivery of buspirone hydrochloride (molecular weight 422 Da) [51]. Meidan *et al.* observed that although Azone® and iontophoresis at 0.025 mA/cm^2 gave a synergistic enhancement of the flux, terpenes had antagonistic effects on the iontophoretic delivery. In the study, the researchers could achieve a threefold higher delivery for Azone/iontophoresis combination as compared with iontophoresis alone and the enhancement ratio from the combination was 87-fold above control (no physical or chemical enhancement).

5.2 Transdermal iontophoresis of macromolecules

Iontophoretic delivery is also generating interest for the delivery of macromolecules such as peptides, the most widely studied being insulin. Pillai *et al.* [15,57-60] studied the various

factors affecting iontophoretic delivery of insulin, as well as additional methods to improve its permeation. They found that extraneous ions have a pronounced effect on the fraction of peptide transported, and increasing the amount of applied peptide in order to increase iontophoretic flux is an expensive option. An alternative approach could be to use an optimal concentration of the competing ions. Pillai and colleagues [57] observed that although the buffer salt concentration affected the iontophoresis of insulin, no direct correlation between solution conductivity of varying concentrations of buffer salts and flux was observed. With the two buffers studied, insulin was observed to have a lower flux if applied in potassium biphthalate as compared with citrate-phosphate buffer. Thus, the transport efficiency may be improved by optimising co-ions and counterions. An optimum concentration of sodium chloride would increase the overall permeation of large peptides, such as insulin, by ion-induced convective flow. In two other studies, the influence of chemical enhancers on insulin iontophoresis was studied [59,60]. The following binary compositions were investigated: EtOH:water (2:1); propylene glycol (PG):water (1:1); PG:EtOH (1:1) and 10% v/v dimethyl acetamide (DMA), 5% v/v menthone in EtOH, 5% v/v pulegone in EtOH, 5% v/v cineole in EtOH, 5% v/v menthol in EtOH, as well as single components: EtOH, ethanol, ethyl acetate, isopropyl myristate (IPM), DMA and PG. Amongst the terpenes, neat menthone application with iontophoresis provided the highest flux followed by ethanol treatment with iontophoresis. Pulegone, menthol and cineole seemed to reduce the flux as compared with ethanol applied alone with iontophoresis. IPM and DMA also improved iontophoretic permeation. In summary, all the chemical enhancer compositions improved the transdermal iontophoresis of insulin when compared with insulin applied alone. These data support the hypothesis that chemical enhancement used in conjunction with iontophoresis enables the reduction in current and enhancement of peptide flux.

5.3 Stability of peptides

The challenge with transdermal iontophoresis of proteins and peptides is the stability of these molecules during delivery. Although the skin has less proteolytic enzymes than other mucosa, degradation of peptides during transdermal iontophoresis needs to be considered. Degradation kinetics of two major peptides, TRH and insulin, were studied *in vitro* [61] with different current densities. At a small current density (< 0.32 mA/cm^2), TRH was stable at 37°C in citrate buffer at pH 4. Increasing the current density increased the degradation rate, with > 75% of the drug degrading with 10 h of iontophoresis at 0.64 mA/cm^2. The same was true with insulin, which showed linear degradation kinetics in the skin. In fact all the insulin had degraded by the end of 24 h, irrespective of the experimental conditions. Likewise, insulin maintained its integrity at 4°C but showed incremental degradation at 23 and 37°C. Another significant issue with iontophoretic delivery is that peptides containing closely juxtapositioned cationic and lipophilic residues find it difficult to traverse the skin even under the influence of iontophoretic current (for example nafarelin) [14]. This occurs due to the neutralisation of the negative charge in the skin by the adsorption of the positively charged peptide. The net result is a shut down of the electroosmotic flow, which is responsible for the absorption of peptides in the skin. In an attempt to resolve these problems (the instability and decreased permeation), Raiman *et al.* studied the iontophoretic permeation of two decapeptides, LHRH and nafarelin [14]. A pulsed delivery (direct current with varying on/off ratios) approach was tried *vis-à-vis* the conventional DC signal. Five different current profiles (100% DC, 75/25% or 50/50% pulsed DC and 75+/25%- or 50+/50%- alternating current) were compared in delivering LHRH and nafarelin across the human epidermis. Pulsed DC was the most efficient method to transport both LHRH and nafarelin and 75% pulsed DC resulted in the highest flux. In the stability experiments, no degradation was recorded with nafarelin. LHRH on the other hand degraded completely when in contact with the dermis but no degradation was observed during the current application process (current duration 12 h). The pulsed current protocol thus seemed to prevent the peptides from adsorption/desorption processes (electrostatic and hydrophobic interactions) in the bilayers of stratum corneum, which may have protected the peptide structure from the hydrolytic degradation and improved drug permeability. Alternating current (50+/50%-) with back and forth transport of drug causes the most deterioration of the peptide.

5.4 Novel mechanistic approaches

One of the more promising combination techniques (as described above) is the use of iontophoresis and electroporation. 5-Aminolaevulinic acid, timolol, atenolol, 5-FU, buprenorphine and insulin [50,62-66] have been studied using this approach. Due to the hydrophobicity and overall negative charge of the skin, it is difficult to deliver hydrophilic molecules across the skin. Fang *et al.* [50] studied various physical enhancement techniques for the delivery of 5-FU, which is a negatively charged hydrophilic substance. Although no passive permeation was observed due to the weakly acidic (negatively charged) and hydrophilic nature of the drug, iontophoresis with current application of 0.5 mA/cm^2 for 3 h across mouse skin resulted in a flux of 31.41 µg/cm^2·h. The permeation remained elevated even after cessation of current, implying that a reservoir of drug may have formed in the skin. Although iontophoresis follows the principle of repulsion of like charges to drive molecules into the skin, electroporation leads to the formation of micropores in the skin. The authors also studied the influence of electroporation pretreatment followed by iontophoresis. The protocol consisted of the application of 1 pulse/30 s applied for 10 min. The pulse voltage was 300 V and pulse length was 200 ms followed by iontophoresis after 10 min. It was observed that at pH 8.5 and electroporation of positive polarity, the combination of electroporation pretreatment and subsequent

iontophoresis resulted in a higher permeation of 5-FU than either technique alone.

Larger molecules such as human parathyroid hormone (PTH) have also shown improved permeation using this approach. The combination of electroporation at 100 and 300 V followed by iontophoresis at 0.2 mA/cm^2 was able to produce a 10- and 5-fold increase in the flux of the hormone, respectively [67]. Another study with PTH also demonstrated a synergistic effect of the two methods on the delivery of the hormone [63]. PTH solution 100 µg/ml was applied to the skin, which was then exposed to electroporation 1 pulse/min, at a pulse voltage of 500 V and pulse length of 200 ms, followed by iontophoresis with a 0.5 mA/cm^2 current density applied for 4 h. An enhancement ratio of 17 was observed for the combined approach compared with iontophoresis alone. In the same study the effect of high current density and continuous voltage pulsing on the delivery of salmon calcitonin was investigated. In the continuous pulse experiments, the highest flux was obtained with 15 pulses (1 ppm) of 500 V (200 ms) followed by iontophoresis (0.5 mA/cm^2). The flux was found to peak at 0.5 h, and a long pulse length lead to a quick input of the drug and high flux (achieved within 15 min of the iontophoresis). As expected from the previous data, electroporation reduced the lag time.

Low frequency sonophoresis has also been explored as a potential technique to be used in combination with iontophoresis, and it is postulated to be a better approach for the enhancement of iontophoretic delivery than other physical enhancement techniques. In a study comparing ultrasound/iontophoresis, electroporation/iontophoresis and laser/iontophoresis [68], it was found that electroporation only accelerated the onset of transdermal iontophoresis of sodium nonivamide acetate (SNA) but it did not have any enhancing effect on iontophoretic delivery. SNA (sodium *N*-nonanoyl vanillyl-4′-*O*-acetate) is a recently designed derivative of capsaicin, which has an antinociceptive potency higher than that of capsaicin and indomethacin, respectively.

Sonophoresis on the other hand was shown to increase the iontophoretic flux 1.5-fold as compared with iontophoresis alone. As SNA was thought to permeate the skin by shunt routes during iontophoresis, pretreatment of low frequency ultrasound on the skin may enhance this effect by reducing the threshold voltage required for drug transport in the presence of an electric field. Accordingly, a lower voltage may be able to deliver an effective current during iontophoresis of SNA compared with that of controls. The erbium:yttrium–aluminum–garnet laser treatment at 0.35 J with subsequent iontophoresis showed a synergistic effect, but higher energy laser treatment showed a reduced flux as compared with iontophoresis alone. However, safety considerations with laser treatment will probably hinder the frequent use of this technique.

For sustained iontophoretic delivery and improved stability of certain drugs, it is customary to use polymers as vehicles for electrically assisted delivery. The use of polymers instead of simple solutions also improves patient compliance and improves ease of application. Polyvinylpyrrolidone (PVP) or hydroxypropylcellulose (HPC) have been observed to promote a zero-order iontophoretic delivery of SNA, showing potential for application in sustained iontophoretic delivery [69]. Binary systems (combination of two polymers, such as cellulose and PVP) were seen to improve the mechanical properties of the hydrogel carrier. The flux of SNA from these binary systems increased in the order of: methylcellulose (MC) + PVP < hydroxypropyl methylcellulose (HPMC) < PVP < HPC + PVP. For individual polymer formulations, the flux of SNA increased with the decrease of viscosity, as viscous solutions hinder the free movement and reduce conductivity of ions. PVP and HPC showed the highest flux values for SNA among six formulations studied (chitosan, PVP, HPC, MC, HPMC and Plastoid®). This was probably due to the superior crystal growth retarding properties of both, which would stabilise the supersaturated solutions. A binary mixture of PVP and HPMC has also been shown to be the best vehicle for diclofenac sodium delivery as compared with each individual polymer [70]. *In vitro* studies were conducted using rat and human skin with PVP, HPMC and PVP/HPMC as vehicles and iontophoresis of 0.5 mA/cm^2 for 6 h. The flux (µg/cm^2·h) for PVP-based iontophoresis was 6.6 ± 1.78 (human skin), and 74.8 ± 7.75 for rat skin. For HPMC-based experiments, flux was 8.13 ± 1.25 (human skin) and 82.50 ± 19.17 (rat skin), whereas for the combination of HPMC and PVP, it was 11.71 ± 2.98 (human skin) and 128.57 ± 19.66 (rat skin). The reason for the higher flux with the 1:1 mixture of polymers was probably due to lower hydrogen bonding and entanglement density between PVP and HPMC, as compared with PVP and HPMC polymer alone. The use of a cellulose membrane showed that the drug delivery was membrane controlled rather than vehicle-matrix controlled as observed with skin.

In vivo studies conducted with the same drug were divided into three main stages. In stage I, passive diffusion of diclofenac without applying current was studied for 6 h. In stage II, a 0.5 mA/cm^2 current density was used for 6 h and in the last 4.5 h of stage III, the current density was turned off. The combination of PVP/HPMC with cardamom oil pretreatment and the above regimen (stages I – III) showed the highest peak within the first few hours of stage II. Thus, the combination of the binary mix of polymers together with enhancer pretreatment and iontophoresis may be explored further for successful transdermal delivery of hydrophilic molecules.

Another approach is the use of nanospheres, which are gaining attention as carriers in iontophoretic delivery, especially for peptides. Nicoli *et al*. studied nanoparticles of triptorelin, a decapeptide analogue of LHRH [71]. Nanospheres were prepared with the double emulsion:solvent evaporation technique, with or without drug. The zeta potential was recorded in order to ensure that the drug was not localised at the surface of the particles. Of the three different polymers used, Resomer®RG 756 and Resomer®RG 752 nanospheres were almost neutral, whereas Resomer®RG 503 H nanospheres were negatively charged, due to the presence of free carboxylic groups. To obtain

Table 1. Commercially applicable iontophoretic devices.

Device/system	Company	Application	Ref.
GlucoWatch® Biographer	Cygnus, Inc.	Minimally invasive technique for monitoring glucose via the skin	[77]
Phoresor®	Iomed, Inc.	Delivery of water-soluble ionic medications. Can be used to deliver Iontocaine® (brand of lidocaine hydrochloride 2% and adrenaline 1:100,000 topical solution)	[101]
Iontophor®, Microphor®	Life-Tech, Inc.	Delivery of ionic drugs. Can be used for pain management	[102]
Macroduct® Nanoduct®	Wescor, Inc.	Sweat collection in the diagnosis of cystic fibrosis Sweat collection for cystic fibrosis diagnosis in neonates Both systems use Pilogel® (pilocarpine) iontophoretic discs for sweat induction	[78]
Dupel®	Empi, Inc.	Delivery of water-soluble ionic medications	[103]
Drionic®	General Medical Co.	Treatment of hyperhidrosis	[79]

positively charged particles more suitable for iontophoresis, the nanoparticles were magnetically stirred with a solution of cetyltributylammoniumbromide overnight. The application of current did not affect the release kinetics of the nanospheres as no burst effect was recorded. In conclusion, nanospheres suitable for iontophoretic delivery could be formed, and are being studied as a future strategy for transdermal permeation enhancement.

Transferosomes™ are ultradeformable liposomal vesicles that adapt to external stresses by rapid shape transformations requiring low energy. They are known to successfully deliver hydrophilic and lipophilic compounds, proteins and other macromolecules through the skin. Iontophoresis of these liposomes has been another interesting development in transdermal delivery. Reduced degradation and enhanced transdermal delivery were observed for drugs delivered using this technique. Drugs studied include enkephalin [72,73], colchicines [74] and oestradiol [75].

6. Commercial applications

Widespread application of iontophoresis has led to successful commercial applications that, although few in number, offer unique advantages in their own right. One of the key areas for commercialisation today is designing an efficient and portable device. An iontophoretic device typically contains a current-controlling mechanism, a timer, a pulse controller and electrodes [76]. Table 1 contains a list of commercially applicable iontophoretic devices.

ALZA Corp's E-TRANS iontophoretic system has been tested for the delivery of the analgesic fentanyl, in conjunction with Johnson & Johnson. A credit-card sized system, it has electrodes, an electronic controller and a battery. A drug reservoir at one electrode and a donor reservoir, containing a salt solution to restore the electrochemical balance at the other, deliver the drug. The major advantage is the ability to preprogramme the device to deliver fixed amounts and also features an on-demand button enabling the patient to administer the drug when needed [104,105].

Clinical trial results of a unique iontophoretic patch developed by Vyteris, Inc. have shown successful delivery of peptides up to a molecular weight of 3,500 Da. Skin effects were minimal and transient due to the use of low current and a proprietary current profile to reduce irritation. Vyteris has received approval for delivery of lidocaine through its iontophoretic patch [104]. The patch is made of a flexible adhesive pad with a reservoir of lidocaine and adrenaline (a vasoconstrictor), with an electronic dose controller that is reusable and battery powered. On current application, the positively charged drug molecules are forced away from the anode through the skin to the capillary bed below, in exchange for chloride ions.

7. Expert opinion and conclusion

The skin, the largest organ in the body, provides an attractive interface for transdermal drug delivery as its use overcomes first-pass effects of the liver and increases patient compliance. However, after about three decades of research only a few transdermal delivery systems (patches) are marketed globally, all based on low molecular weight lipophilic drugs (< 500 Da). This, in part, is due to the fact that the uppermost layer of the skin, the stratum corneum, poses an effective physical barrier to drug permeation. Several methods have been studied over the years that overcome this barrier and enhance the permeability of drugs. Examples of approaches include chemical enhancement through additives to the formulations applied, application of ultrasound, photoacoustic waves, microneedles to the skin, as well as electrical techniques such as electroporation, and iontophoresis. With all these techniques, the resulting safety levels are always questioned, as high levels of electric fields as well as high percentages of many chemical enhancers result in unwanted skin irritation, burning or irreversible skin damage. All of these techniques provide a certain level of enhancement but the future lies in combinations of these approaches as this may result in a more gentle skin barrier modification with fewer side effects. In addition, this may also open up the possibility of some success with higher molecular weight compounds. Although significant enhancement has

been reported for functional peptides of ~ 4 kDa, insulin is still posing a challenge with its physicochemical properties, as well as the dose that needs to be delivered for effective therapy. Iontophoresis has been studied together with chemical enhancement, ultrasound and electroporation. The application of electroporation prior to iontophoresis has been shown in some cases to increase drug permeation and/or reduce the value of the lag time. Iontophoresis in particular has the advantage of controlled drug delivery with customised drug input rates, an improved inset time and also a more rapid off-set time (when the current is switched off, drug transport ceases). The rapid progress in the fields of microelectronics, nanotechnology and miniaturisation of devices will also allow the design of these iontophoretic patches to become more sophisticated, allowing improved novel designs with even more control of drug delivery ('dial-a dose' approach). The next few years are expected to bring even more therapeutic agents in patch form to the market for both transdermal as well as topical drug delivery.

We are already seeing some recent progress with the lidocaine iontophoretic patch from Vyteris, Inc. as well as the fentanyl system for postoperative pain from ALZA Corp. However, progress in this area will also depend on a paradigm shift in the pharmaceutical industry away from the traditional oral delivery approaches to a higher acceptance of novel routes for delivery for the new generation of drugs forthcoming from the pharmacogenomic/nanotechnology era.

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