

Iontophoretic Transport Mechanisms and Factors Affecting Electrically Assisted Delivery

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5.1 Introduction

Molecular transport during iontophoresis can be attributed to three component mechanisms: passive diffusion, electromigration (EM), and convective solvent flow, also called electroosmosis (EO). In physical terms, the flux of a molecule, J_i , across the skin, in the presence of an applied electric field, E , depends on both the concentration and potential gradients and can be described by a modified form of the Nernst-Planck equation that also takes into account the convective solvent flow (Pikal 2001) when an electric potential is applied to a membrane that contains fixed negative charges (e.g., the skin with isoelectric point (pI) of ~4–4.5 (Marro et al. 2001a)) (Srinivasan and Higuchi 1990; Kasting 1992):

$$J_i = - \left[D_i \frac{\partial c_i}{\partial x} + u_i c_i \frac{\partial \varphi}{\partial x} \right] \pm v_w c_i \quad (5.1)$$

$$J_{\text{TOT}} = J_p + J_{\text{EM}} \pm J_{\text{EO}}$$

where D_i , c_i , and u_i are the diffusion coefficient, concentration, and electrical mobility of ion i and v_w represents the linear velocity of the convective solvent flow (Gratieri and Kalia 2013). The diffusion coefficient and the electric mobility are related by the Nernst-Einstein equation:

$$u_i = \frac{z_i D_i F}{RT} \quad (5.2)$$

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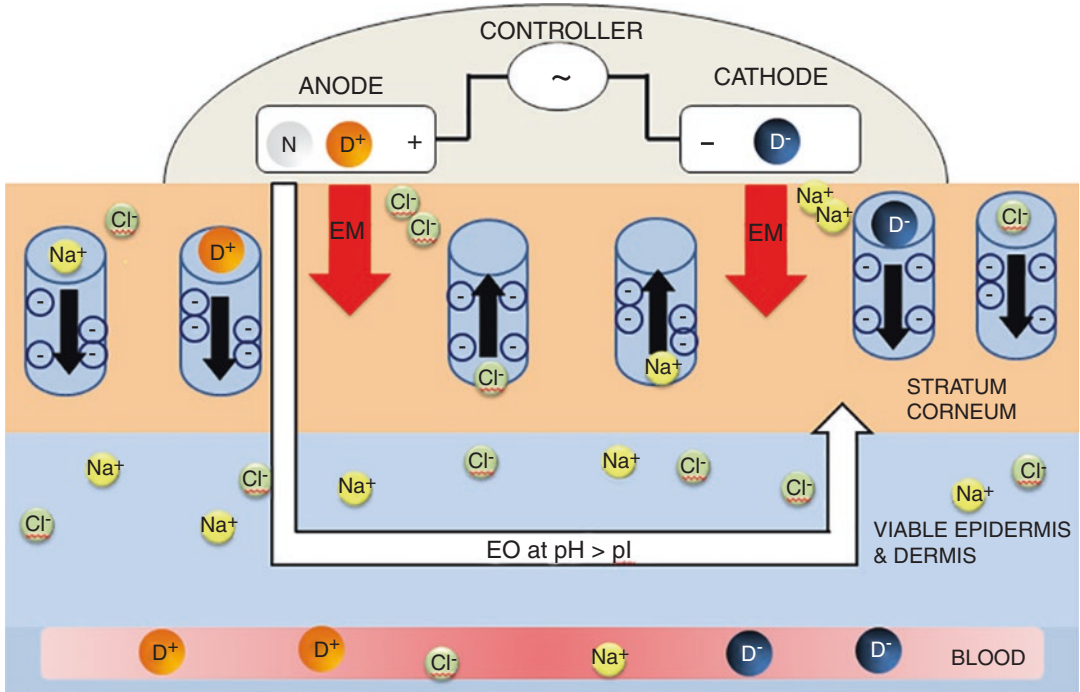


Fig. 5.1 Schematic representation of iontophoresis including the representation of transient pores created in the skin during current application. Under the influence of the applied field, it is envisaged that ions electromigrate through these pores – the presence of the fixed negative

charges in the pore walls gives rise to electroosmotic phenomena (Pikal 1990). (Modified from (Gratieri and Kalia 2013). D is the drug, which can be either positively (D⁺) or negatively (D⁻) charged. N represents a neutral molecule. EM is the electromigration and EO the electroosmosis)

Thus, the electric mobility represents an “ordered” diffusion dictated by the electric field – it competes against thermal disordering (RT term in the denominator) which will act to decrease its magnitude. It is clear that the higher the valence (z_i), the higher is the electrical mobility. For charged molecules, passive diffusion across the stratum corneum is limited or negligible, meaning that molecular transport during iontophoresis is attributed to EM and EO – their relative contributions depending on the experimental conditions and the physicochemical properties of the molecule (Gratieri and Kalia 2013).

The penetration pathways of such charged molecules during iontophoresis may also be different from those during passive diffusion. Instead of following the tortuous intercellular lipid pathway between the corneocytes, it has been suggested that under the influence of an electric current, ions will follow the path of the least electrical resistance, e.g., they will

preferentially take the appendageal pathways (i.e., hair follicles, sweat glands) (Cullander and Guy 1991). However, in addition to transport via these “shunt” pathways, structural changes in the membrane, which may correspond to transient reorientation of SC proteins and lipids in the presence of the electric field, may also facilitate ion transport (Jadoul et al. 1999). Lipids and proteins have dipole moments and will align themselves to the direction of the applied electric field. The reorientation of these SC components under the influence of the electric field may result in the formation of transient conduction pathways (“pores”) in the bulk SC (Gratieri and Kalia 2013). Therefore, although the appendageal structures are probably involved in iontophoretic transport, smaller negatively charged (given the skin’s permselectivity at physiological pH) transient “nano-pores” with estimated pore radii of ~20 nm may also be present (Aguilella et al. 1994) (Fig. 5.1).

5.2 Factors Influencing Electrically Assisted Drug Delivery

5.2.1 Current Density

Electromigration refers to the ordered movement of the ions in the presence of the applied electric field in a process that can be described by Faraday's law (Phipps et al. 1989; Phipps and Gyory 1992; Sage and Riviere 1992; Delgado-Charro and Guy 2001; Kalia et al. 2004):

$$J_{EM} = \frac{I t_D}{A F z_D} \quad (5.3)$$

where I is the applied current (amperes); t_D is the transport number of the drug; A is the cross-sectional area through which transport occurs; F is the Faraday constant (Coulombs/mole); and z_D is the drug valence.

It is evident from the equation that the applied current (I) is a parameter that can directly affect the rate and extent of drug delivery. The introduction of the second driving force – the electrical potential gradient – in addition to the concentration gradient across the skin (Gratieri and Kalia 2013), means that drug delivery is enhanced, and the flux can be strictly correlated with duration, intensity, and profile of current application. As such, complex drug delivery kinetics – determined solely by the current profile – are feasible. This was demonstrated in studies carried out in Yorkshire swine investigating the feasibility of delivering zolmitriptan (MW 287.4 Da) – used for the treatment of migraine. An iontophoretic patch system and a complex multistep current profile were used. The study showed that the drug levels in the blood (7.1 ± 1.7 and 11.9 ± 2.0 ng/ml at $t=30$ and $t=40$ min, respectively) closely followed the variations in the applied current (four-step profile with current intensities ranging from 0.35 to 0.05 mA/cm²) (Patel et al. 2009).

Many other studies have demonstrated that the iontophoretic flux of a drug can be enhanced by increasing the applied current (Green et al. 1992; Lau et al. 1994; Abla et al. 2005; Panzade et al. 2012); linear correlations between flux and current density have been reported either small molecules

as thyrotropin (362 Da) (Burnette and Marrero 1986) or for larger molecules, e.g., triptorelin (1311.5 Da) (Schuetz et al. 2005). In this way, the modulation of the applied current and the patch size enables easy individualization of therapy (Djabri et al. 2012a). This was recently observed with rasagiline (RAS) and selegiline (SEL), which are dose-dependent selective irreversible inhibitors of monoamine oxidase B (MAO-B), with therapeutic applications for the treatment of Parkinson's disease and in the treatment of major depressive disorder (Kalaria et al. 2012). Permeation experiments performed across porcine and human skin in vitro demonstrated that while passive delivery from aqueous solution was minimal, drug delivery was directly correlated with current density ($I_d=0.15, 0.3,$ and 0.5 mA/cm²) producing a linear increase in steady-state iontophoretic flux (J_{ss} , RAS=49.1 I_d +27.9 ($r^2=0.96$) and J_{ss} , SEL=27.8 i_d +25.8 ($r^2=0.98$)). Drug extraction from the skin showed that there was also a statistically significant increase in the amounts of RAS and SEL retained within the membrane as a function of current density (Fig. 5.2).

However, straightforward linear correlations are not always observed. For example, a poor correlation was observed between 9-desglycinamide-8-arginine-vasopressin (DGAVP) flux and applied current; a more than sixfold increment in current density did not even double the flux (Craanevanhinsberg et al. 1994).

It is also evident from Eq. 5.3 that a drug's transport number influences the electromigration efficiency. This parameter is related to the ability of the drug to function as a charge carrier, and the transport number represents the fraction of the total charge carried by each species ($0 < t_D < 1$) (Mudry et al. 2006a, b, c). It depends on how drug concentration, mobility, and valence compare with those of the other ions present in the pharmaceutical formulation (buffering agents, viscosity modifiers, and preservatives) generated by electrode reactions and present in the skin (Mudry et al. 2006a). Specifically,

$$J_{EM} = \left(\frac{1}{z_D F} \right) \frac{z_D u_D c_D}{\sum_{i=0}^i z_i u_i c_i} \cdot I_d \quad (5.4)$$

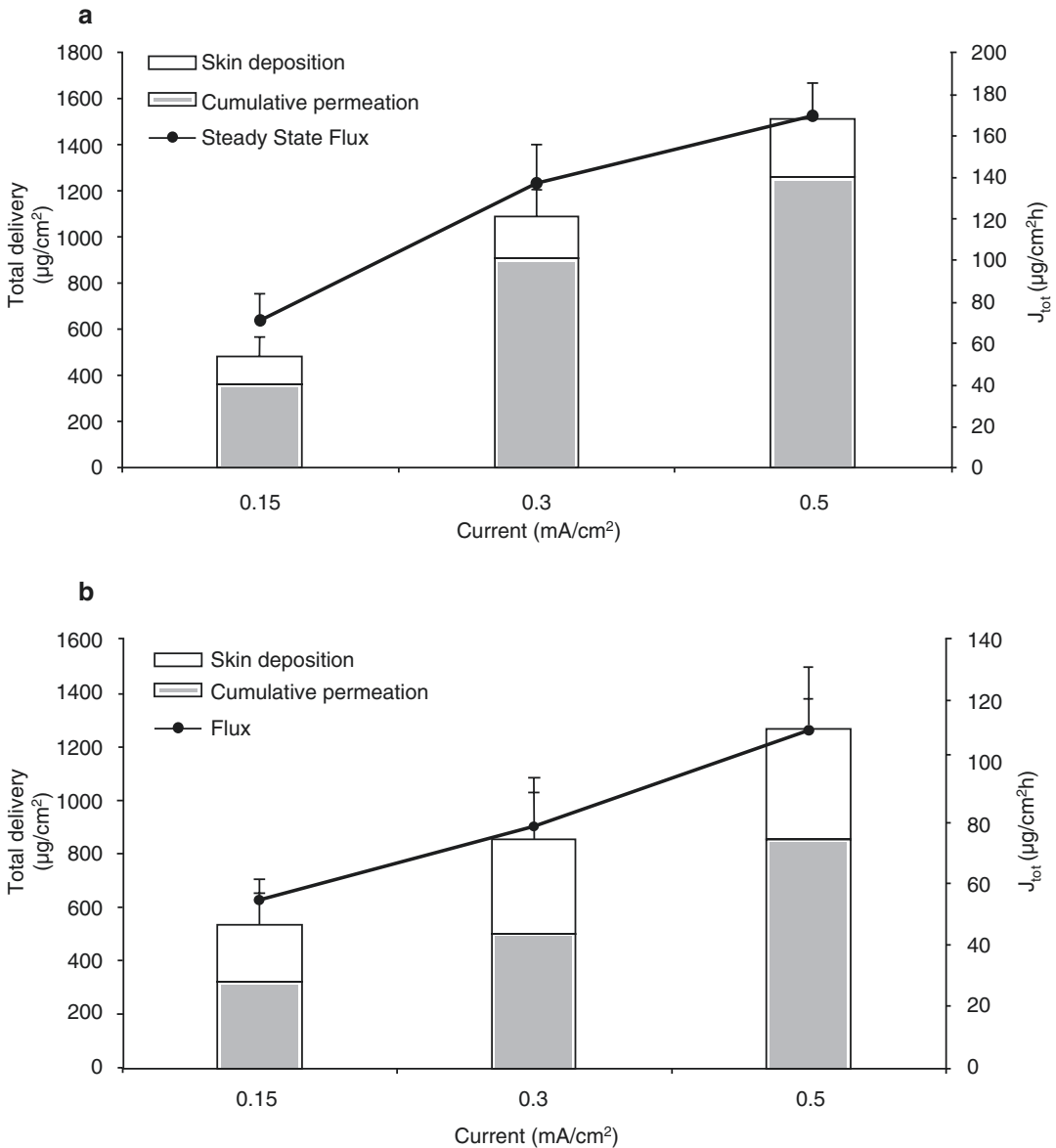


Fig. 5.2 Total delivery (cumulative permeation+skin deposition) and steady state flux (J_{tot}) of (a) RAS (20 mM) and (b) SEL (20 mM) as a function of current density

(at 0.15, 0.3, and 0.5 mA/cm²) across porcine skin after 7 h of transdermal iontophoresis (mean ± SD; n ≥ 5). (Adapted and reproduced with permission from Kalaria et al. 2012)

where I_d is the applied current density ($= I/A$) and z_D , u_D , and c_D refer to the charge, mobility, and concentration of the drug in the membrane, respectively; the denominator is the sum of the products of these parameters for each ion in the system contributing to charge transfer across the membrane (Kalia et al. 2004; Kasting and Keister 1989). It is obvious that the presence of endogenous competing

counterions decreases the iontophoretic transport of the drug.

5.2.2 Formulation

5.2.2.1 Drug Concentration

Drug concentration is a commonly studied experimental parameter in iontophoretic experiments,

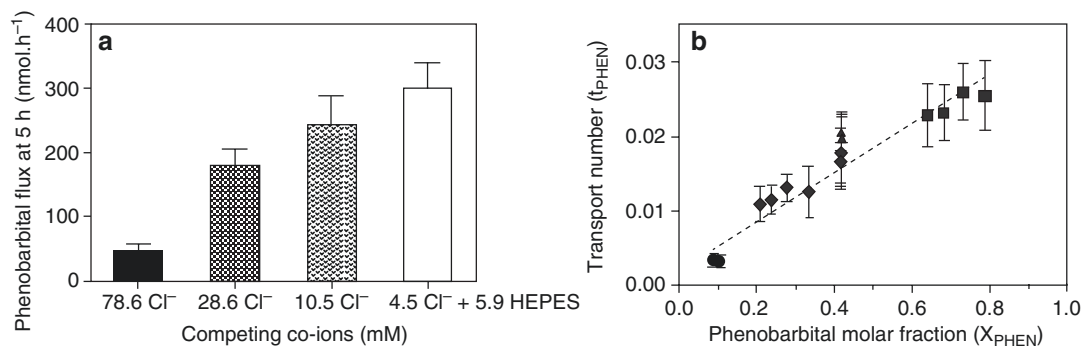


Fig. 5.3 Cathodal delivery of phenobarbital from different donor solutions (pH 7.4) containing various amounts of competing co-ions. (a) Flux values (mean \pm SD) determined after 5 h of iontophoresis (0.4 mA). (b) Transport number of phenobarbital (t_{PHEN} , mean \pm SD) as a function of molar fraction (X_{PHEN}). Values of the latter parameter were calculated from the concentrations of phenobarbital, HEPES, and chloride.

The sources of Cl⁻ included NaCl (used as background electrolyte), HCl (used to adjust the donor solution pH), and the electrode electrochemical reaction. The dashed line is the linear regression through all data points except those obtained with HEPES: $t_{\text{PHEN}} = 0.002 (\pm 0.001) + 0.033 (\pm 0.002) X_{\text{PHEN}}$ ($r^2 > 0.8$). Adapted and reproduced with permission from Djabri et al. (2012b)

as it might be envisaged that an increase in the amount of drug in the formulation would result in increased drug delivery. However, linear correlations are not always encountered, and behavior is complicated by drug-membrane interactions. For certain molecules, the flux-concentration profiles reach a plateau above which further increases in concentration have only a limited or negligible effect on flux.

A key factor is the presence or absence of competing ions (Kasting and Keister 1989). Studies have described the use of a salt bridge to eliminate the presence of competing cations in the donor compartment rendering delivery independent of drug concentration. For example, it was observed that cumulative permeation of RAS after iontophoresis for 7 h using a salt bridge at 0.5 mA/cm² was independent of drug concentration. For the three concentrations studied (10, 20 and 40 mM), the cumulative permeation was statistically equivalent (1200.4 ± 154.6 , 1262.6 ± 125.0 and 1321.5 ± 335.2 $\mu\text{g}/\text{cm}^2$, respectively); similar behavior was observed for SEL (the corresponding values were 748.3 ± 115.2 , 848.8 ± 108.3 , and 859.8 ± 230.1 $\mu\text{g}/\text{cm}^2$, respectively) (Kalaria et al. 2012). Although the use of salt bridges precluded the presence of competing cations in the donor compartment, chloride ions present in the receptor were the principal charge carrier due to their high mobility and concentration as they migrated

across the skin toward the anode – as would be the case in vivo (Kalaria et al. 2012).

In cases where a salt bridge is not used, Eq. 5.4 suggests that the increase of the drug concentration, or drug molar fraction, should enhance the transdermal flux via an increase in t_D , therefore, increasing EM. This was recently demonstrated with the cathodal iontophoresis of phenobarbital in vitro across porcine skin. The results showed that drug fluxes were inversely related to the Cl⁻ concentration present in the donor solution after 5 h of current application (0.5 mA/cm²) (Fig. 5.3a). Therefore, the lower the co-ion concentration, the greater the drug molar fraction in the vehicle and the greater the drug transport number in a linearly proportional manner ($r^2 \approx 0.80$) (Fig. 5.3b) (Djabri et al. 2012b).

It may also be assumed that an increase in drug concentration would result in an increased EO flux, according to Eq. 5.5, which expresses the EO drug flux:

$$J_{\text{EO}} = v_w \cdot c_D \quad (5.5)$$

where v_w is the electroosmotic solvent flow, and c_D is the concentration of the drug in the vehicle (Pikal 1992). This should have a direct impact on the delivery of positively charged and neutral molecules. However, the real situation may be far more complex than the cited equations suggest, as other factors may be involved: not only the

existence of competing ions, as mentioned before, but also the effect of drug physicochemical properties and their impact on the ability of the molecule to interact with structures along the iontophoretic transport pathway.

Studying the anodal iontophoresis of granisetron (GST; MW: 348.9, pKa 9.4) across porcine skin *in vitro*, it was demonstrated that cumulative delivery from 5 to 10 mM solutions was statistically equivalent; however, statistically significant increases were seen when drug concentration was raised to 20 or 40 mM (Cazares-Delgado et al. 2010). The reduced delivery efficiency at lower concentrations could be explained by the presence of Na⁺ in the formulation, which possesses higher mobility than granisetron, effectively negating the effect of any increase in formulation concentration (Kasting 1992). As the formulation pH (6.6–6.8) was higher than the skin's pI, there was an EO contribution to delivery. However, co-iontophoresis of acetaminophen, a neutral molecule used to report on convective solvent flow, showed that EM was the predominant transport mechanism accounting for 71–86% of total granisetron delivery. It was also observed that a fourfold increase in granisetron concentration from 10 to 40 mM resulted in a twofold reduction in acetaminophen permeation indicating that skin permselectivity was decreased (Cazares-Delgado et al. 2010). As for other lipophilic cations, including the peptides, leuprolide, and nafarelin, it is likely that the positively charged molecules were bound to skin structures along the iontophoretic transport pathway neutralizing the intrinsic negative charges, thereby reducing the volume of solvent flow (Lu et al. 1993; Delgado-Charro and Guy 1994; Hoogstraate et al. 1994; Delgado-Charro and Guy 1995; Delgado-Charro et al. 1995; Hirvonen et al. 1996; Rodriguez Bayon and Guy 1996; Hirvonen and Guy 1997; Nair and Panchagnula 2003). In these cases, the impact on drug delivery can depend on the relative contribution of EM and EO to the iontophoretic transport of the molecule in question (Hirvonen and Guy 1997; Marro et al. 2001b).

5.2.2.2 pH

In principle, the ionization state of the skin will determine the EO solvent flow, and *in vitro* studies have tried to use modification of

formulation pH as a means to change skin pH. However, this is a strategy more suited to enhancing the ionization state of the drug and so affects mobility and hence EM, since manipulation of skin ionization state is rather more difficult to achieve *in vivo* due to the skin's intrinsic buffering capacity (Levin and Maibach 2008). Although modulation of formulation pH can certainly be used to improve transport, in practice, extreme pH values need to be avoided to prevent irritation or chemical burns. Acceptable pH values for skin application have a mildly acidic to neutral pH (5–7.4).

Acyclovir, for example, is an antiviral agent used in the treatment of cutaneous viral infections caused by herpes simplex virus (HSV-1). Although it is a small molecule (225.20 Da), it is unable to diffuse efficiently through the SC and subsequently enter into the basal epidermis, where viral replication occurs. In order to enhance the permeation of this molecule, iontophoresis has been applied by many authors (Volpato et al. 1995; Volpato et al. 1998; de Jalon et al. 2001; Stagni et al. 2004; Padula et al. 2005; Morrel et al. 2006; Shukla et al. 2009; Siddoju et al. 2011). However, it has been shown that at pH 7.4, the amount of drug recovered in the stratum corneum and epidermis after iontophoresis was similar to that obtained after passive diffusion (Volpato et al. 1998). This is because acyclovir is essentially uncharged at physiological pH (pKa1 2.27; pKa2 9.25); hence EO is the only enhancing mechanism. However, even delivery by EO is compromised due to its low aqueous solubility (1.3 mg/ml at pH 7.4, 25 °C). For this reason, other studies employed formulations with extreme pH to have the drug molecule in an ionized state (Fig. 5.4). For example, after 10 min cathodal iontophoresis of acyclovir gel at pH 11 to hairless rats *in vivo*, fourfold more ACV was detected in the SC as compared with passive delivery (30.70 ± 4.83 and 7.83 ± 1.59 µg/cm², respectively) (Siddoju et al. 2011). Improved delivery to the dermis was observed in rabbits *in vivo* after 1 h of cathodal iontophoresis at pH 11 (Shukla et al. 2009). However, although the authors reported there were no additional signs of skin irritation on the conditions used, it is rather implausible that a formulation with such an irritant pH can be of practical use.

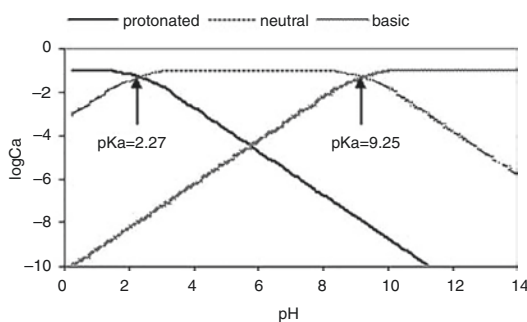


Fig. 5.4 Acyclovir ionization state, assuming an analytical concentration of Ca of 0.1 M. (Reproduced with permission from Shukla et al. (2009))

5.2.3 Delivery System

The iontophoretic delivery system comprises a microprocessor/power source and two electrode compartments. The “active” electrode contains the drug formulation, and the circuit is completed by the return electrode placed at an adjacent area on the skin. The system design may have an impact on patient compliance and hence on the efficiency of the treatment. However, the formulation and the electrodes may also affect drug delivery rates and safety.

The ideal formulation for iontophoretic application would be easy to apply, have good electrical conductivity, have good bioadhesion avoiding leakage, be compatible with the electrodes and the device, promote high drug stability, not be irritant to the skin, and not contain competing ions. In this way, hydrogels have been proposed as base formulations for iontophoretic delivery because of the high water content and consequent good electrical conductivity (Fang et al. 1999; Fang et al. 2001; Fang et al. 2002; Merclin et al. 2004; Jyoung et al. 2009; Taveira et al. 2009) but also because of their adhesiveness and biocompatibility (Alvarez-Figueroa and Blanco-Mendez 2001; Haak et al. 1994). However, in some cases anti-adherent hydrogel films that could be easily removed might be desirable. Such a formulation, composed of the polyelectrolyte poly(methyl vinyl ether-co-maleic acid) cross-linked in a 2:1 ratio with PEG 10,000, was investigated as a potential rapid photodynamic antimicrobial chemotherapy treatment for

infected wounds using iontophoresis for the delivery of the photosensitizers meso-Tetra (N-methyl-4-pyridyl) porphine tetra tosylate (TMP), methylene blue (MB), and TMP with sodium dodecyl sulfate. The study demonstrated that formulation properties such as hydrogel hardness, compressibility, adhesiveness, and ionic conductivity could be influenced by the concentration of a component in the formulation. The authors concluded that hydrogels prepared from aqueous blends containing 10% of the polymer loaded with TMP or MB were the most flexible (should conform most easily to wounds), least adhesive (reducing the potential trauma to the wound upon removal), and released the greatest amount of photosensitizer (ensuring the greatest extent of microbial kill in the wound) (Fallows et al. 2012). Indeed, studies demonstrate that network structure and composition can be manipulated to influence the permeation and diffusion characteristics of a drug within the hydrogel (Banga and Chien 1993), changes that should take into account the charge of both the polymer and the drug. Normally, drug release is reduced when the molecule has the opposite charge to the polymer and favored when they have the same charge (Tatavarti et al. 2004).

To improve iontophoretic delivery efficiency, the use of ion-exchange materials, such as ion-exchange membrane, has been proposed (Patel et al. 2007; Patel et al. 2009; Xu et al. 2009). The membranes used should have the opposite charge to that of the ionized drug, and when placed between the skin and the donor electrode, they would hinder the migration of competing counterions, selectively enhancing drug transport across the skin (Xu et al. 2009). A recent study showed that the use of drug in a complex with ion-exchange fibers might be more promising than the use of ion-exchange membranes. It was observed that when cathodal iontophoresis of diclofenac across rat skin *in vitro* and *in vivo* was carried out, drug bound to ion-exchange fibers with an ionic bond had a higher transference number than those having the drug bound to other ion-exchange materials or simply in solution (Che et al. 2012). Further studies with other molecules should be performed to confirm the promising results. As the field is constantly evolving,

novel ion-exchange materials with higher efficiency on enhancing drug permeation may also be developed in the future.

Conclusion

The work performed to date using many different molecules has given us a better understanding of the advantages and limitations of the technique and the principal factors that impact on its efficiency. Analysis of the molecular properties is a first step in trying to predict feasibility of drug delivery and in identifying which parameters might affect transport rates. First, if it is positively charged, the relative contributions of EM and EO to the total flux need to be determined. If EO plays an important role, conditions that might reduce interactions with the skin penetration pathway should be used. If EM is the main transport mechanism, the pH should preferably favor drug ionization. Second, the impact of drug concentration in the formulation and current density must be evaluated since these would help to determine the treatment conditions; if the amount of compound delivered is directly proportional to the applied current or concentration, the duration of current application and the area of the skin surface in contact with the active electrode compartment can be calculated to deliver a specific dose of the drug molecule. In this way, it is possible to control drug delivery kinetics and allow individualization of the therapy. Although a better understanding of iontophoretic transport mechanisms is essential, it must be accompanied by progress in the enabling technologies required to develop iontophoretic patch systems. Only then will it be possible to create the patient-friendly, safe therapeutic systems that will enable the clinical applications described in the next chapter to be realized.

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