Review Article

Transdermal drug delivery by iontophoresis: Mechanistic aspects

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ABSTRACT

The passive diffusion of drugs in transdermal delivery is hindered by the stratum corneum and limits the scope of deliverable molecules through the skin. The evolution of novel electrical and physical enhancement techniques can enable the delivery of hydrophilic and larger molecules such as proteins and peptides through the skin. Iontophoresis utilizes small amounts of direct current to push charged drug molecules through and across the skin. Several drug categories have been investigated over the years as possible drug candidates for this mode of delivery. It enables the delivery of more hydrophilic molecules in contrast to conventional transdermal delivery and has an advantage of modulating the rate of delivery by changing the electrical parameters.

Keywords: Drug delivery, electrotransport, iontophoresis, pathways, transdermal

Iontophoresis

Iontophoresis involves the delivery of ionic drug molecules under electric fields. The drug molecules will be taking the least resistance pathways such as hair follicles. There are two components to the iontophoretic delivery, electrorepulsion, and electroosmosis.

$$J_{Iontophoresis} = J_{electrorepulsion} \pm J_{electrosmosis}$$

Electrorepulsion is the simple repulsive force between similar charges. Electroosmosis is the convective solvent flow in the direction of the anode to cathode because of the current passage. Burnette and Ongpipattanakul hypothesized that skin is negatively charged at pH 7.4. They observed that electroosmosis is changed by altering the membrane electrical properties by preferential binding of cations to the fixed negative charges in the membrane.[1] Electroosmosis facilitates the passage of cationic species but inhibits the anionic species. Electroosmosis can be used to deliver polar and neutral solutes. The relative importance of electrorepulsion and electroosmosis depends on the physicochemical and electrical characteristics of the membrane.[2] Mannitol flux can be used as a marker for electroosmotic flow.

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Factors Affecting Iontophoretic Drug Delivery Iontophoretic and Electrochemistry

Iontophoretic patch essentially consists of two electrodes, anode and cathode, and a drug reservoir. Patch will be connected to a current source. Commonly used electrode materials include platinum (Pt) electrodes and silver-silver chloride (Ag-AgCl) couples. The latter are considered to be better because Pt electrodes require voltages higher than water electrolysis voltage. Thus, during the iontophoretic process, electrolysis of water creates protons responsible for pH drifts and can significantly influence the iontophoretic flux.[3] Ag- AgCl electrodes require Cl^- ions for the oxidation of Ag at the anode. This could be achieved by either adding NaCl or using a chloride salt form of the drug in the donor formulation.

Effect of Concentration

In contrast to conventional passive transdermal delivery, iontophoretic flux generally increases with the increase in the drug concentration only up to a certain level, and then it reaches a plateau. This is due to a lack of increase of the drug molecules in the membrane by increasing the amount of drug in the formulation, effect of competing ions in the

formulation and the possible structural interactions of drug molecules with the transport pathways. Marro *et al.* investigated the effect of donor concentration (100-fold) on the iontophoretic flux of lidocaine, propranolol, and quinine in the presence and absence of background electrolyte. They observed that in the presence of background electrolyte, flux was linearly increased with the donor concentrations for the least hydrophobic lidocaine. In contrast, for propranolol and quinine, flux was nonlinearly increased. This was explained by the more competing tendency of lidocaine with the background ion to transport the current with increasing concentration. In the absence of background electrolyte, there was no effect of concentration on the iontophoretic flux of any of the three drugs used.[4]

Effect of current

Electrorepulsion contributes almost 90% of the iontophoretic flux which is directly related to the current applied. Apparently, increase in the current will increase the electromigration but it does show a saturation point at a certain current density. The dependence of the delivery on the current density is again a function of physicochemical properties of the drugs. Conjeevaram *et al.* showed an increase in the iontophoretic flux of p-blockers *in vitro* and *in vivo*.[5]

Effect of pH

Charge is the major attribute of a molecule to be delivered by iontophoresis, yet uncharged molecules can be delivered by electroosmosis. Charge on any molecule or a membrane is a function of pH of the environment. Drugs will be 50% ionized at its pKa and they assume a positive charge when they are present in an environment with pH less than its pKa and vice versa. In case of proteins and peptides, the charge will be dictated by the isoelectric point (pI) and pH of the formulation. Extreme pH values of the formulation can produce hydronium or hydroxide ions with high electrical mobilities which in turn will reduce the iontophoretic flux of drug molecules. Skin acts as a permselective membrane depending on the pH conditions.

Marro *et al.* showed that pI of human skin is around 4.8 and at pH values lower than pi, skin assumes a positive charge and acts as anion-selective, net positively charged membrane. However, at physiological pH, it acts as cation-selective, net negatively charged membrane. The direction of the electroosmotic flow can be altered by changing the electrical properties of the membrane.[4]

Iontophoretic flux of lysine (pKa, 10.8) was higher at pH 7.4 than pH 4.0 because of the contribution of electroosmosis. In contrast, histidine showed an increased iontophoretic flux at pH 4.0 than 7.4. At this pH, lysine is mostly uncharged, and flux increase is mainly due to electroosmosis than electromigration.[6]

Mechanistic Aspects of Iontophoretic Transport

Iontophoretic transport pathways

Three major routes of drug transport through skin include intercellular, intracellular, and transappendageal routes. Cullander and Guy showed that largest currents were observed near the vicinity of residual hair using a vibrating probe electrode which can measure the currents on the skin surface.[7] It was suggested that the electroporation of the hair follicles at the epidermal cells allow the transport of drug molecules from the appendages.[8] Monteiro-Riviere *et al.* investigated the iontophoretic delivery of mercuric chloride to identify the pathways of transport by microscopy. They concluded that intercellular routes were predominantly responsible for the iontophoretic transport. Even in the follicular transport, final pathway will still be intercellular between hair follicle epidermal cells.[9] Hikima *et al.* investigated the role of appendages on iontophoretic flux by comparing the flux through human stratum corneum (consists appendages) and shed snakeskin (lacks skin appendages). They concluded that the appendageal pathways contribute less for the flux for relatively small ionic species with high mobility. However, for larger molecules such as peptides, most likely follows appendageal channels.[10] Turner and Guy showed the dependence of iontophoretic transport pathways on the penetrant physicochemical properties using confocal microscopy. Iontophoretic delivery of calcein for 1 h, resulted in the delivery of fluorophore deep (>20 μm below the skin surface) into the pilary canal of the hair follicle and intercellular penetration was also observed.[11]

Uitto and White *et al.* showed that the electroosmotic transport of neutral molecules in human skin occurs through shunt pathways identified as hair follicles or sweat glands. They speculate the possible involvement of gap junctions in the epidermis to induce electroosmotic flow.[12]

Transport number

A transport number is the fraction of total current carried by a given ionic species, which can be regarded as the efficiency of the electrophoretic transport of that species.[13]

$$t_n = \frac{JzF}{I} \quad (1)$$

Where, t_n is the transport number, J is the transdermal flux, z is the valence of the ionic species, F is Faraday's constant, and I is the total current passes across the skin.

Theories of Electrotransport

Modified Nernst-Planck model

Iontophoretic transport of monovalent cations and anions can be approximately predicted by the modified Nernst-Planck model which is modified to account for the influence of convective solvent flow.

The steady state flux ($J_\Delta\psi$) during iontophoresis in a porous membrane can be written as follows:

$$(J_{\Delta\psi}) = \varepsilon\left\{-\left(D\frac{dC}{dX} + \frac{CzF}{RgasT}\frac{d\varphi}{dx}\right) \pm vC\right\} \quad (2)$$

Where,
ϕ = Electric potential in the membrane
F = Faraday's constant

Rgas = Gas constant
T = Temperature
v = Average velocity of the convective flow
ε = Combined porosity and tortuosity factor of the membrane
C = Concentration
x = Position in the membrane
z = Charge number
D = Diffusion coefficient.

The predictions of the fluxes from this equation are consistent with the induction of pores in iontophoresis.

In case, where the permanent molecular radius is of the order of magnitude of the membrane pore radius, hindrance considerations must be included, and Equation (2) can be rewritten as follows:

$$(J_{\Delta\Psi}) = \varepsilon\left\{-\left(HD\frac{dC}{dX}+\frac{CzF}{RgasT}\frac{d\varphi}{dx}\right)\pm WvC\right\} \quad (3)$$

Where, H is the hindrance factor for simultaneous Brownian diffusion and migration driven by the electric field and W is the hindrance factor for permanent transport through convective solvent flow.

Equation (3) is called Modified Nernst-Plank equation[14]

The steady state flux for passive transport ($J_{passive}$) across a porous membrane can be expressed as:

$$\left(J_{passive}\right) = \frac{DCd\,\varepsilon H}{\Delta x} \quad (4)$$

Where,
H = Hindrance factor for passive diffusion
C_d = Concentration of the solute on the donor side
Δx = Effective thickness of the membrane.

After integration of Equation (2), the steady-state flux can be expressed as:

For anions

$$\left(J_{\Delta\Psi}\right) = \frac{C_D\varepsilon HD\{[Wv/(HD)]+[K/\Delta x]\}}{\exp\{[Wv(\Delta x)/(HD)]+k\}-1} \quad (5)$$

For Cation $$(J\Delta\psi) = \frac{C_D\varepsilon HD\{[Wv/(HD)]-[K/\Delta x]\}}{1-\exp\{[K-Wv(\Delta x)/(HD)]} \quad (6)$$

Where, $K = \frac{zF\Delta x}{(RgasT)}$ and

Δx = Applied voltage across the membrane.

Enhancement factor (E_{total}) due to iontophoresis can be determined by the following equation:

$$E_{total} = \frac{J_{\Delta\Psi}}{J_{passive}} \quad (7)$$

In another study by Li *et al.*, the average effective pore sizes induced by electrical field was measured around 12 °A, which were of the same order of magnitude as those of pre-existing pores determined from the conventional passive diffusion experiments.[15] Li *et al.* showed the correlation between the electromobilities predicted and observed by the model. They suggested that the Modified Nernst-Planck model's predictions are satisfactory only when the electromobilities and the effective molecular size of the molecule are known.[16]

Kontturi and Murtomaki proposed a model with two penetration routes: An aqueous and lipoid pathway for iontophoresis. The mathematical form of the model is as follows:

$$J_p = J^W + J^\circ \quad (8)$$

$$Jif = E \times J_p + J^\circ \quad (9)$$

Where, J^w and J° are the fluxes across the aqueous and organic pathways, respectively. J_p and J_{if} are the total passive and iontophoretic fluxes, respectively, and E represents the iontophoretic transport.[17] Hirvonen *et al.* confirmed the predictability of the model and confirmed the idea that hydrophilic drugs experience the greatest benefit from iontophoretic delivery, whereas the flux enhancement of lipophilic drugs remains low.[18]

Manabe *et al.* proposed hydrodynamic pore theory for iontophoretic drug transport. They assumed parallel permeation pathways, pore and lipid pathways. Pore pathways are the main route for hydrophilic drugs, as explained by the pore theory, and the net flux of a drug at steady state (J) can be described as the sum of each pathway flux:

$$J = J_L + J_P \quad (10)$$

Where, J_L and J_P represent the flux through lipid and pore pathways, respectively.[19]

Conclusion

With the advancement in technologies, iontophoresis serves as a great tool for delivery drugs which are otherwise difficult to transfer by traditional transdermal route. Therefore, it serves as a major pathway for delivery of drugs through various transport mechanisms. Iontophoresis has been demonstrated as a good mode for delivering larger molecules by various reports in the literature for delivering insulin, calcitonin, human parathyroid hormone, luteinizing hormone-releasing hormone, vasopressin and analogs, somatorelin and analogs and somatostatin analogs, etc. The technique dramatically reduces the lag times associated with conventional transdermal delivery. Iontophoretic delivery of opioids, nonsteroidal anti-inflammatory drugs, local anesthetics, migraine medications, and medications for neurodegenerative conditions such as Alzheimer's disease, dermatological applications, antiemetic agents, antiviral agents, cardiovascular agents, and steroids has been reported.

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