Iontophoresis: Modeling, Methodology, and Evaluation

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Iontophoresis is a noninvasive and painless means of delivering various drugs into the body. Many drugs, in particular peptides, proteins, and hormones are given parenterally either through intravenous, subcutaneous, or intramuscular injections. Transdermal delivery using iontophoresis circumvents hepatic clearance and breakdown by the gastric juices thus allowing local high concentrations of active compounds. Local delivery of these compounds is much safer than parenteral routes since lower concentrations are necessary to reach the target sites. The present analysis focuses on previously overlooked areas including skin impedance, iontophoretic waveforms, skin modeling, optimization of delivery parameters, and their effects on iontophoretic delivery. Particular emphases are placed on modeling, methodology, and evaluations of the efficacy of iontophoresis.

Key words: iontophoresis; transdermal drug delivery; skin impedance model; optimal waveforms.

INTRODUCTION

Iontophoresis is a transport phenomenon that has been known for sometime but has found renewed interest over the past 20 years. Iontophoretic delivery results when an electric field is placed across a permeable or semipermeable membrane. In transdermal applications, skin is the membrane of choice. Moreover, iontophoresis stems from the movement of ions in solution due to an electric field across two electrodes. Positive drug ions are repelled from the positive electrode (anode) and the negative drug ions are repelled from the negative electrode (cathode). The additional driving force created by the electric field functions separately from the passive diffusion forces. The electronic current resulting from the electric field is transformed into an ionic current at the electrode/liquid or electrode/skin interface. This ionic current carries the drug ions into the skin while endogenous ions that are more mobile complete the electrical circuit.

The amount of drug delivery is modulated by the following parameters: electric field intensity, drug solution pH, drug concentration, current duration, current amplitude, and intrinsic properties of the drug ion and skin membrane (Behl et al., 1989). Because of the complex list of parameters affecting drug delivery, many researchers have been unable to generally optimize iontophoretic drug delivery and have opted to maximize delivery for specific compounds (Gupta et al., 1994; Huang et al., 1995; Lelawongs et al., 1990).

Iontophoresis is a noninvasive and painless means of delivering various drugs into the body. Many drugs, in particular peptides, proteins, and hormones are given parenterally either through intravenous, subcutaneous, or intramuscular injections. Proteins, peptides, and hormones are degraded by the acids in the stomach and therefore cannot reach systemic concentrations when taken orally. In addition, many of these drugs are rapidly eliminated from the body due to hepatic clearance. Enteral degradation and rapid first-pass hepatic clearance coupled with drug rapid half-lives makes oral delivery impractical and potentially dangerous due to the high concentrations needed to reach systemic therapeutic levels. Transdermal delivery using iontophoresis circumvents hepatic clearance and breakdown by the gastric juices thus allowing local high concentrations of active compounds. Local delivery of these compounds is much safer than parenteral routes since lower concentrations are necessary to reach the target sites, and high systemic concentrations of these compounds can be detrimental to other body tissues and organs.

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Although Iontophoretic delivery has been proven safe, some detrimental effects can occur including erythema, burns, insufficient delivery, and blisters. Most of these occurrences can be eliminated or minimized if proper care is taken when using Iontophoresis.

Some applications of iontophoretic transdermal delivery consist of lidocaine for analgesia (Allen et al., 1999), heparin for anticoagulation, metoprolol for treatment of hypertension and angina pectoris (Okabe et al., 1997), fentanyl for chronic pain management (Thysman et al., 1994; Vanbever et al., 1998), insulin (Langkjaer et al., 1998; Siddiqui et al., 1987; Sun et al., 1990) procaainamide for antiarrhythmic therapy (Avitall et al., 1992), heparin and more recently, hindulin for combating restenosis (Fernandez-Ortiz et al., 1994, 1995; Mitchel et al., 1997; Scott, 1995). Furthermore, several researchers have investigated the iontophoretic delivery of various peptides, proteins, and amino acids (Banga et al., 1997; Scott, 1995). Furthermore, several researchers have investigated the iontophoretic delivery of various peptides, proteins, and amino acids (Banga et al., 1997; Scott, 1995). Advances in the biotechnology sector have helped ignite a new vigor in exploring iontophoretic delivery as a non-invasive means of drug delivery especially since most biotechnology drugs cannot be delivered orally because of degradation from gastric juices.

Several thorough reviews have been written which further discuss iontophoretic applications (Banga et al., 1988; Costello et al., 1995; Nair et al., 1999; Riviere et al., 1997; Singh et al., 1989; Tyle, 1986). The present analysis focuses on previously overlooked areas including skin impedance, iontophoretic waveforms, skin modeling, optimization of delivery parameters, and their effect on iontophoretic delivery. Particular emphasis are placed on modeling, methodology, and evaluations of the efficacy of iontophoresis. We investigated the physical principles governing iontophoresis and provided an analysis of the current approaches. We also presented suggestions for future experimentation related to modeling, methodologies, and efficacy of iontophoresis.

**PHYSICAL PRINCIPLES AND GOVERNING EQUATIONS**

Iontophoresis is based on the Nernst–Planck equation that is shown in Eq. (1) below (Riviere et al., 1997):

\[
J_i = -D_i \frac{dc_i}{dx} - \frac{D_i z_i F c_i \Phi}{RT} \frac{d\Phi}{dx} \tag{1}
\]

where \(J_i\) is the flux across the membrane of species \(i\), \(D_i\) is the diffusion coefficient, \(c_i\) concentration of species \(i\), \(z_i\) charge on species \(i\), \(F\) is the Faraday constant (96,500 C/mol), \(R\) is the gas constant (8.31 J/(mol K)), \(T\) is absolute temperature (K), \(x\) is distance, and \(\Phi\) is the electric potential.

The overall flux in Eq. (1) consists of two components, one related to concentration and the other related to the voltage across the membrane. In the event that the drug is uncharged (\(z_i = 0\)) or the voltage is zero (\(d\Phi/dx = 0\)) the Nernst–Planck equation simplifies to

\[
J_i = -D_i \frac{dc_i}{dx} \tag{2}
\]

which is simply Fick’s first law of diffusion. Passive diffusion results from a concentration gradient across a membrane. Substances flow down a concentration gradient or from higher concentrations to lower concentrations.

Also, if the concentration on either side of the membrane is equal (\(dC_i/dx = 0\)) resulting in the Nernst–Planck equation simplifying to the electrical driving component (electrotransport) only:

\[
J_i = -\frac{D_i z_i F c_i \Phi}{RT} \frac{d\Phi}{dx} \tag{3}
\]

Electrotransport results when an electric potential or voltage is applied across a membrane as shown by Eq. (3).

Three principal mechanisms of delivery may occur during iontophoretic delivery. The first two mechanisms involving passive diffusion and electrotransport were discussed above. The third mechanism of transport that may occur during iontophoretic delivery is called convective flux. Others have called convective flux electroosmosis or iontophoretic flux (Gangarosa et al., 1980; Pikal, 1992; Sims et al., 1991). Convective Flux occurs when drug ions are dragged or pulled along when water transport occurs. For instance, ions such as Na\(^+\) are hydrated in solution meaning they are surrounded by water molecules. When Na\(^+\) is delivered iontophoretically, its movement causes the surrounding water molecules to flow in the direction of Na\(^+\) movement. Any drug ions adjacent to hydrated Na\(^+\) ions will be pulled along with the solvent in the direction of Na\(^+\) movement. Therefore, the Nernst–Planck equation can be modified to include all three components of iontophoretic delivery:

\[
J_a = J_q + J_{zc} + J_e = J_i = -\frac{D_i z_i F c_i \Phi}{RT} \frac{d\Phi}{dx} + c_i v \tag{4}
\]