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# Mathematical models to describe iontophoretic transport in vitro and in vivo and the effect of current application on the skin barrier ☆

Taís Gratieri, Yogeshvar N. Kalia *

*School of Pharmaceutical Sciences, University of Geneva & University of Lausanne, 30 Quai Ernest Ansermet, 1211 Geneva, Switzerland*

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ABSTRACT

The architecture and composition of the stratum corneum make it a particularly effective barrier against the topical and transdermal delivery of hydrophilic molecules and ions. As a result, different strategies have been explored in order to expand the range of therapeutic agents that can be administered by this route. Iontophoresis involves the application of a small electric potential to increase transport into and across the skin. Since current flow is preferentially via transport pathways with at least some aqueous character, it is ideal for hydrosoluble molecules containing ionisable groups. Hence, the physicochemical properties that limit partitioning and passive diffusion through the intercellular lipid matrix are beneficial for electrically-assisted delivery. The presence of fixed ionisable groups in the skin (pI 4–4.5) means that application of the electric field results in a convective solvent flow (i.e., electroosmosis) in the direction of ion motion so as to neutralise membrane charge. Hence, under physiological conditions, cation electrotransport is due to both electromigration and electroosmosis—their relative contribution depends on the formulation conditions and the physicochemical properties of the permeant. Different mathematical models have been developed to provide a theoretical framework in order to explain iontophoretic transport kinetics. They usually involve solutions of the Nernst–Planck equation – using either the constant field (Goldman) or electroneutrality (Nernst) approximations – with or without terms for the convective solvent flow component. Investigations have also attempted to elucidate the nature of ion transport pathways and to explain the effect of current application on the electrical properties of the skin—more specifically, the stratum corneum. These studies have led to the development of different equivalent circuit models. These range from simple parallel arrangements of a resistor and a capacitor to the inclusion of the more esoteric "constant phase element"; the latter provides a better mathematical description of the "non-ideal" behaviour of skin impedance. However, in addition to simply providing a "mathematical" fit of the observed data, it is essential to relate these circuit elements to biological structures present in the skin. More recently, attention has also turned to what happens when the permeant crosses the epidermis and reaches the systemic circulation and pharmacokinetic models have been proposed to interpret data from iontophoretic delivery studies in vivo. Here, we provide an overview of mathematical models that have been proposed to describe (i) the effect of current application on the skin and the implications for potential iontophoretic transport pathways, (ii) electrotransport kinetics and (iii) the fate of iontophoretically delivered drugs once they enter the systemic circulation.



**Contents**



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* Corresponding author at: School of Pharmaceutical Sciences, University of Geneva, 30 Quai Ernest Ansermet, 1211 Geneva 4, Switzerland.
*E-mail address:* yogi.kalia@unige.ch (Y.N. Kalia).

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## 1. Introduction

The stratum corneum (SC), the outermost layer of the epidermis, is the principal barrier to molecular transport across the skin and into the body [1,2]. Its structure consists of protein rich anucleated corneocytes embedded in a lipidic intercellular matrix. In addition to providing mechanical protection against the external environment, the SC also has a homeostatic function in that it regulates transepidermal water loss [3]. This is achieved through a combination of its architecture (the high degree of tortuosity increases the diffusional pathlength) and composition. Its efficacy is evidenced by its ability to maintain a water concentration gradient of ~55 M between the body's interior and the external environment across a barrier which is typically only 10–20 μm thick [4]. Given that the SC has evolved over millions of years to prevent water loss, it follows that it is also extremely effective at liming the entry of water-soluble, polar molecules into the body.

Iontophoresis is a technique that involves application of a small potential across the skin to drive ions into and across the membrane [5]. Since ion flow is facilitated by transit through aqueous pathways, the physicochemical properties that mitigate against passive diffusion through the intercellular lipidic space favour electrically-assisted delivery. Iontophoretic transport rates are governed by the intensity, duration and profile of current application—as such iontophoresis can be used for the controlled delivery of therapeutic molecules including peptides and proteins and it has been compared to a “needle-less” infusion pump.

In physical terms, the one-dimensional 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 takes into account the convective solvent flow due to the skin permselectivity [6,7]:

$$J_i = -\left[D_i \frac{\partial c_i}{\partial x} + u_i c_i \frac{\partial \varphi}{\partial x}\right] \pm v_w c_i \tag{1}$$

Passive + Electromigration ± Electroosmosis

where $D_i$, $z_i$, $c_i$ and $u_i$ are the diffusion coefficient, valence, concentration and electrical mobility of ion $i$ and $v_w$ represents the linear velocity of the convective solvent flow (N.B., the sign conventions used by authors can vary depending on the direction of increasing $x$ (i.e., whether $x=0$ is defined at the skin's external or internal surface)). The diffusion coefficient and the electric mobility are proportionality constants between the flux and the concentration and potential gradients, respectively. They are related by the Nernst–Einstein equation:

$$u_i = \frac{z_i D_i F}{RT}. \tag{2}$$

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. The product ($z_iF/RT$) serves effectively as a constant of proportionality between the electric mobility and the diffusion coefficient; it is clear that, depending on the valence, there can be order of magnitude differences between the two parameters and hence between passive and electrically-assisted delivery (Fig. 1). Since passive diffusion of these molecules is limited or negligible, electrotransport is due to electromigration and electroosmosis—the relative contributions depending on the experimental conditions and the physicochemical properties of the molecule.

In the following sections we present mathematical models that have been developed to describe (i) the effect of iontophoretic current application on the electrical characteristics of the skin, (ii) iontophoretic transport either in terms of electrical/formulation parameters or as a function of permeant properties and (iii) the pharmacokinetic behaviour of iontophoretically delivered molecules in the body.

## 2. Equivalent circuit models of the skin barrier

The electrical impedance properties of the skin can be attributed almost entirely to the stratum corneum. As for most biological membranes, they are most simply described by a parallel arrangement of a resistor ($R_m$) and a capacitor ($X=C_m$) and the skin impedance ($Z$) is given by (Fig. 2A) [8,9]:

$$Z = \frac{R_m}{1 - j\omega R_m C_m} \tag{3}$$

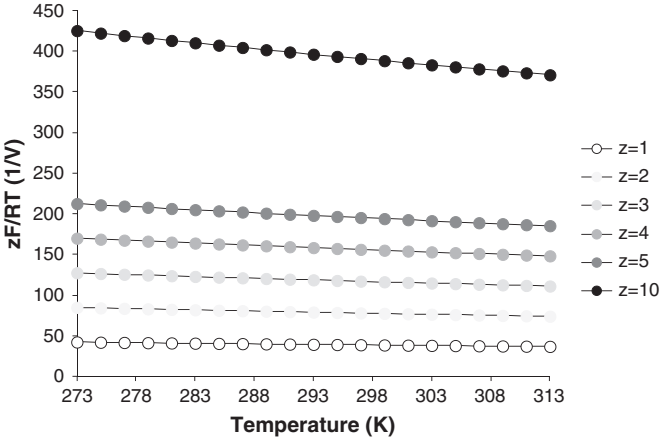


**Fig. 1.** Use of the Einstein relation (Eq. (2)) to determine the variation of the pre-multiplier, $zF/RT$, as a function of temperature (K) provides an approximate measure of the relative magnitude of the electric mobility and diffusion coefficient for ions with different valences (z).