Overcoming hurdles in iontophoretic drug delivery: is skin the only barrier?

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Iontophoresis consists of the application of a mild electric field across a biological membrane to facilitate the transport of drug molecules. The proof-of-concept that an electric current could drive molecules across the skin dates from 1900, but it was over the past 30 years that considerable achievements were reached on understanding the mechanisms governing drug transport. Today's interest in this technique can be explained by the fact that, besides the known benefits of the transdermal route itself (e.g., patient-friendly administration, ease of therapy cessation, avoidance of first-pass metabolism, low-dose administration, and fewer adverse effects), iontophoresis offers unique advantages to therapy, such as control over drug-input kinetics, meaning that bioavailability can be modulated by the intensity and duration of the applied current profile and easily modified according to specific needs [1]. Therapeutic concentrations are generally achieved faster than from passive delivery [2] and, because it acts principally on the molecule by introducing a second driving force – the electrical potential gradient – in addition to the concentration gradient across the membrane [3], there are no considerable physiological modifications to the tissue barrier function after treatment termination, hence irritation and risk of infection are possibly minimized in comparison to other more aggressive physical enhancement methods. Additionally, recent studies have been challenging preconceived notions demonstrating that iontophoresis not only enhances the delivery of small molecular weight therapeutics, but also enables the non-invasive delivery of peptides and proteins across the skin. A remarkable example was the demonstration that biologically active human basic fibroblast growth factor, a 17.4 kDa protein, was delivered into and across the skin in therapeutically relevant amounts corresponding to those used in clinical trials and animal studies for the treatment of burns, incisional wounds, recalcitrant ulcers and peripheral arterial disease [4]. Our group has also demonstrated that in addition to topical and transdermal delivery, iontophoresis applied to the skin enables local enhanced delivery to subjacent muscle, which may provide alternative clinical treatments for localized inflammation and pain [5]. Recently, a US FDA advisory panel considered a less-restrictive category for iontophoresis devices used for local drug administration, based in part on a literature review and analysis of safety information from the FDA's databases [6]. With such a relief for the manufacturers and continuous expansion of drug candidates, new investments can be expected in the future. It is possible that we will soon witness new products reaching the market.

The more the field advances, the more possibilities arise. After all, is skin the only barrier to which iontophoresis can be applied? Could the mechanisms governing iontophoretic drug delivery to the skin apply to other biological tissues?

Iontophoretic mechanisms applied to other membranes

In the last decade researchers have been trying to answer the question of whether iontophoretic drug delivery to other barriers

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is possible. Iontophoretic transport across several other biological tissues has been investigated for either local or systemic delivery; for example, the buccal [7,8] and nasal mucosae [9], the sclera [10,11], the cornea [12] and the nail [13,14]. The particularities of each therapy can be better comprehended by addressing the basic principles of iontophoresis. Molecular transport during iontophoresis can be attributed to three component mechanisms: passive diffusion, electromigration (EM) and electroosmosis (EO) [1].

Mucous membranes do not possess a permeability barrier as effective as the stratum corneum. For example, the oral mucosa, depending on the site, can be 4000-times more permeable than the skin [15]. The nail plate, conversely, is approximately 10- to 100-fold thicker than the stratum corneum [16]. Therefore, the passive component will obviously provide different contributions to total drug delivery depending on the membrane for diffusion.

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EM refers to the ordered movement of the ions in the presence of an electric field applied by a power source and is often the dominant mechanism accounting for delivery enhancement into and across the skin [3]. Most of the factors influencing EM (e.g., the physicochemical characteristics of the drug molecule, formulation composition and pH, current density, etc) are not directly correlated to the biological membrane to which the active electrode is applied. Hence, it is expected that EM can also enhance drug delivery across other biological membranes such as as the cornea, sclera, buccal mucosa and the nail plate. Even though lipid and aqueous content may vary enormously when comparing membranes such as the skin, the sclera and the nail plate, all of them were found to be suitable to conduct iontophoresis [10,16]. The extent of delivery due to EM to each membrane, however, may vary depending on the membrane, as a function of composition and mainly as a function of concentration of competing counter ions.

The other concern when applying iontophoresis to tissues other than the skin is the risk of irritation at the application site. Generally, until a certain level, EM is proportional to the current density applied [2]. However, the maximal current supported by each tissue depends on the resistance of the tissue to current flow, given by Ohm's law: $I = V/R$, where I is the current applied through the tissue in amperes, V is the potential difference measured across the tissue in volts, and R is the resistance of the tissue in ohms.

Tissues with greater aqueous content offer a lower resistance to current flow, and higher current densities can be applied requiring lower voltages, thus reducing the risk of irritation or pain. The maximum current density generally applied on the skin is 0.5 mA/cm^2 [17], while tolerability studies in humans demonstrated the maximum current density tolerated by the sclera was 5.5 mA/cm^2 applied for 20 min [18]. This translates to faster onsets for tissues with higher aqueous content [8]. On the other hand, protocols designed for application sites with higher resistance, for example, the nail plate, may need to compensate the low current density with longer application times (i.e., 0.1 mA/cm^2 for 6–8 h [12]).

The third component responsible for molecular transport during iontophoresis, EO, can be described as an electrically induced convective solvent flow, the direction of which is dependent on the membrane's ionization state, that is, in the anode (positively charged electrode) to cathode (negatively charged electrode) direction for negatively charged membranes [1,3]. The skin has an isoelectric point of ~4.5 and at physiological pH it is negatively charged and acts as a cation-selective ion-exchange membrane. Hence, at physiological pH, both charged and neutral molecules placed at the anode are driven towards the skin following this convective solvent flow.

In recent years, several groups have demonstrated the permselective nature of tissues such as the nail plate [19], sclera [11] and the buccal mucosa [20], highlighting the potential of iontophoresis for the delivery of both charged and neutral molecules through these tissues driven by EO. Even though the significance of EO contribution for drug transport to the nail plate remains unclear [21], it has been demonstrated to be considerable for other membranes. It can reach between 3.2 and 5.4 μl/cm^2/h under a current density of 2.9 mA/cm^2 applied *in vitro* across the sclera for 2 h [11]. A possible concern that may arise is whether this solvent flow could disturb the homeostasis and affect transparency of the cornea. Although we have demonstrated *in vitro* that corneal integrity was maintained after 6 h of iontophoresis [12], animal and clinical studies are required to assure the safety of the procedure and to establish *in vivo* protocols.

The clinical scenario

Today, clinical studies have advanced for the use of scleral iontophoresis. EyeGate Pharmaceuticals Inc. (MA, USA) recently announced positive results from a Phase III study of dexamethasone phosphate

applied with the EyeGate® II Delivery System in the lead indication of noninfectious anterior uveitis. According to the company, the study demonstrated that two iontophoretic treatments over a 4-week period achieved the same response rate as 154 drops of prednisolone acetate 1%. Other ocular iontophoresis systems under investigation for transscleral iontophoresis include Ocuphor (Iomed Inc., USA) and Visulex (Aciont Inc., USA).

Apart from *in vitro* and animal studies, there are still few clinical studies applying iontophoresis to membranes other than the skin and sclera.

The transbuccal delivery of naltrexone from an intraoral device termed IntelliDrug has been proven effective in humans offering the possibility of using small drug doses to achieve therapeutic blood concentrations [22]. Although previous studies with this device showed an iontophoretic component [23], it is not clear from the publication what electric current application protocol was used, and if such a component indeed remained present.

Nail iontophoresis of terbinafine [13] and dexamethasone [14] has been clinically used to treat onychomycosis and psoriasis, respectively. Although the feasibility of nail iontophoresis was clearly demonstrated, more studies covering safety and tolerance aspects are needed.
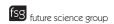
Future perspective

In conclusion, iontophoresis holds great potential to be applied in tissues other than the skin. Component mechanisms governing iontophoretic delivery to the skin seem to apply to other membranes, in variable degrees of relevance. While ocular applications seem to be advanced with products completing Phase III clinical trials, buccal and nail iontophoresis still require more work to establish the best protocols and device design.

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