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Iontophoresis—Recent Developments*

RICHARD H. GUY

Centre Interuniversitaire de Recherche et d'Enseignement, 'Pharmapeptides', Campus Universitaire, F-74166 Archamps, France

Abstract

This paper addresses the development and optimization of the technology of iontophoresis as a non-invasive approach to transdermal diagnosis and therapy. The rationale for this work is that the skin offers a unique and easily accessible body surface through which drugs can be delivered and general clinical monitoring information can be extracted.

The architecture and biology of the skin is directed towards the construction of a highly efficient barrier to the outward loss of water (Potts & Francoeur 1990, 1991; Elias & Menon 1991). From a structural and compositional standpoint the most superficial and least permeable skin layer, the stratum corneum, provides uniquely impressive resistance to molecular transport both from and into the body. This is why transdermal delivery requires potent drugs—it is simply not possible to transfer very many micrograms of any compound through a relatively small surface area in the period of a few hours (Merino et al 1997). Because the principal function of the skin is to minimize trans-epidermal water loss, the stratum corneum is a lipophilic barrier that is particularly (passively) impermeable to hydrophilic drugs (including charged species) (Flynn 1990). Enhancing technologies always elicit their greatest effects upon compounds of inherently low permeability.

Thus, the skin's barrier function severely constrains the number, the type, and the control of molecules that can cross the membrane at diagnostically or therapeutically useful rates. Importantly, many chemical classes of considerable current interest, for example peptides and oligonucleotides with regard to drug delivery, and glucose, metabolites and electrolytes with regard to monitoring and diagnosis, have extremely low intrinsic transdermal permeabilities (Cleary 1993; Merino et al 1997). To overcome the problem of poor transport, the use of chemicals which alter skin permeability has been examined in some detail (Smith & Maibach 1995). However, the unpredictable extent of permeation enhancement and the local skin irritation often induced by these agents can limit their practical application, particularly in chronic usage (for example in non-invasive monitoring). Iontophoresis, on the other hand, represents a bioengineering technology which has the potential to satisfy the following key criteria for success: reproducible enhancement of transdermal permeability at a level sufficient to increase dramatically the number of diagnostic and therapeutic opportunities via the skin; close control of the kinetics and extent of transport enhancement, including rapid reversibility; and a minimum of biological and histological effects on the skin (i.e. little or no irritation or current-induced cell damage) (Sage 1995; Merino et al 1997).

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Iontophoresis—The State of the Art

Assessment of the feasibility of enhancement of transdermal delivery for a particular substance (and optimization of its delivery or extraction) requires that: the pathways of percutaneous penetration are characterized; the rate-limiting steps in transdermal absorption are identified; pertinent structure-penetration relationships are understood; and the effects of the approach on the skin itself are evaluated.

The iontophoretic enhancement of drug delivery through the skin has been studied for over 100 years (Sage 1995). The key areas of concern with iontophoresis are: the permselectivity of skin; the relationship between iontophoretic transport of solutes and their properties; the paths of ion transport; the possibility of tissue alteration as result of passage of current; and the electrical properties of the skin.

During iontophoresis, what pathways do the ions follow through the skin?

The imposition of a transdermal potential gradient creates, or substantially amplifies, ion-conducting

pathways through the skin. Recent research using laser-scanning confocal microscopy (LSCM) and the vibrating-probe electrode technique have confirmed that iontophoretic transport occurs at discrete sites and that an association of these sites with specific appendageal structures (sweat glands, hair follicles and sebaceous glands) can be established (Cullander & Guy 1992). Despite the persuasive nature of these findings, however, it must be emphasized that transport might also occur, at an enhanced level, through other pathways; for example, although a study by Scott et al (1992), using scanning electrochemical microscopy, supported the importance of discrete iontophoretic transport sites, the density of the sites was calculated to be approximately an order of magnitude greater than the number of appendages.

What are the important structure–activity relationships in iontophoresis?
Patterns are emerging of the behaviour relating electro-transport to the structure and physicochemical properties of the permeant (Roberts et al 1997). Given the permselectivity of skin at physiological pH (Sage 1995) it is true that, all other things being equal, during iontophoresis cations cross the skin better than anions. For anions of molecular mass from 35 to 500 Da the efficiency of iontophoretic delivery seems to decrease with increasing molecular size (Roberts et al 1997). The enhanced flux of neutral solutes by electroosmosis is less than that achieved for charged species, which are driven by electrostatic repulsion. Electroosmosis plays an important role in the transport of charged, high-molecular-weight species. For relatively small uncharged compounds (MW < 400 Da) iontophoretic permeability seems to be quite insensitive to lipophilicity (Green et al 1992b). The implication of this is clearly that the transport path is not lipophilic in nature, a situation in complete contrast to passive percutaneous penetration. Transdermal migration of ions is very sensitive to the ionic composition and pH of the drug-containing medium applied. The pH, for example, can affect the extent of ionization of the drug and the permselectivity of the skin (Kim et al 1993) and the tenacious binding of a positively-charged permeant can also elicit a similar effect and thereby alter its own iontophoretic delivery profile (Delgado-Charro & Guy 1994; Hoogstraate et al 1994; Hirvonen et al 1996). Counter-ions to the drug within or beneath the stratum corneum and, in particular, the presence of ions of like charge to the drug (co-ions) can compete to carry the current across the membrane (Sage & Riviere 1992). The efficiency of drug delivery depends, therefore, upon the relative transport numbers of the ions present in the system.

What happens to skin tissue when a current is passed through it for a significant period of time?
An important question related to this issue is 'what is the maximum acceptable (discernible or tolerable) current that can be safely passed through the skin?' The literature (Ledger 1992) provides an incoherent picture. It is certainly true that 'tolerable' current density decreases with increasing electrode area, and this is useful information to be considered when evaluating the feasibility of iontophoretic drug delivery (Sage & Riviere 1992). In addition, alterations in the electrical and transport barrier properties of the skin have been observed during and after iontophoresis (Sage 1995). This predominantly in-vitro work has shown that when the level of current passed reaches a threshold value, changes in the skin occur which are not fully reversible; these include, for example, a diminution of skin resistance and an increase in passive permeability. Pre-treatment of the skin with an iontophoretic current can also increase passive transport (Green et al 1992a), and the application of current for only a brief period might be sufficient to elicit substantial enhancement effects.

To what extent can the electrical properties of the skin be modeled to deduce the mechanism of iontophoretic enhancement?
An important experimental development in the modeling and prediction of iontophoresis is the isolated perfused porcine skin flap as a tool for electro-transport research (Sage & Riviere 1992). This system has been shown to be an excellent (albeit complex, labour-intensive and expensive) model for iontophoretic studies that can be used to predict in-vivo absorption. From a theoretical standpoint, model development has progressed in terms of ion transport, electrodiffusion and electroosmosis (Kasting 1992; Pikal 1992). Kasting developed the classic equations of Nernst-Planck, Poisson and Butler-Volmer into a kinetic theory of iontophoresis which provides new hypotheses for experimental testing. Pikal demonstrated the importance of electroosmotic flow and how it can become dominant as permeant size increases. The existence of a heterogeneous distribution of 'pores' within the skin has been postulated on the basis of this theoretical and experimental work, placing new emphasis on the development of tools for closer definition of the pathways of ion transport across the skin (see above). Useful adjunct information to this area of research is emerging from impedance

spectroscopy measurements (Burnette & DeNuzzio 1997); these which are refining electric-circuit models of the skin beyond the parallel capacitor and resistor analogy originally proposed. By observing the response of the skin's impedance, as a function of frequency, to carefully selected perturbations (including applied direct current, ionic strength of the bathing electrolyte, pH and temperature), it is becoming increasingly possible to correlate electrical properties with structure and function—significantly, the ability to perform these measurements reliably in-vivo in man has been developed (Kalia & Guy 1995), thereby maximizing the potential relevance of a model based upon the proposed experimental studies and their outcome.

Iontophoresis for Drug Delivery

Iontophoresis uses a low-level current (< 0.5 mA cm^{-2}) to drive charged and highly polar (yet neutral) compounds through the skin at rates very much greater than their passive permeabilities. The principal mechanisms of enhancement are electrorepulsion and electroosmosis (Sage 1995). Irrespective of mechanism, flux is proportional to the applied current, thereby enabling the necessary control. Problems with the delivery of the new 'biotechnology' drugs (i.e. peptides, small proteins, oligonucleotides, etc.) explain, in large part, the renaissance of interest in iontophoresis. The highly polar and frequently charged nature of these compounds has provoked a considerable amount of new research into the mechanism and application of electrically-controlled drug delivery through the skin (Merino et al 1997). In particular, because of the complicated pharmacology of some of these agents, the potential of iontophoresis to control the drug input rate is a singular advantage. There is good evidence that the current profile can be manipulated to vary the kinetics and extent of drug absorption (Sage 1995). The 'downside' is that iontophoresis is not necessarily very efficient; that is, of the total charge introduced, only a small fraction is translated into drug delivery (Sage & Riviere 1992). There is an important question of the economics of iontophoresis, therefore, in addition to other concerns, for example those of drug stability in an iontophoretic patch and of the extent of skin metabolism and of local irritation (Ledger 1992). It should be noted that the low efficiency of iontophoresis constrains even this quite effective means of enhancement (after all, very large relative increases in permeation are possible) to potent drugs, emphasizing the need to optimize formulations which interface with the bioengineering technology (Sage 1995).

Iontophoresis—Non-invasive Diagnosis and Monitoring

'Reverse' iontophoresis can also be used for diagnosis and non-invasive clinical monitoring (i.e. not for drug delivery but instead for the relatively non-invasive extraction of 'information' from the body for the purpose of classical clinical chemistry). The symmetry of iontophoresis means that current passage causes ions and other molecules to move in both directions under both electrodes (Merino et al 1997). Thus, with an appropriate level of assay sensitivity, iontophoresis can be used to 'sample' an analyte within the body; it therefore has the potential to be a key component of a true closed-loop system. The idea has been initially applied, not surprisingly, to glucose monitoring (Guy 1995). Although glucose is not charged, iontophoresis can dramatically increase the passage of this polar sugar across the skin by electroosmosis (Merino et al 1997). After initial feasibility studies (Rao et al 1993, 1995) it has recently been shown that 'reverse iontophoresis' can be used for non-invasive monitoring of diabetics' blood glucose levels as efficiently as the currently-used 'finger-stick' methodologies (Tamada et al 1995). Several key issues must be addressed and solved in the development of useful, practical systems (Guy 1995); important among these are an 'on-board' sensor that can measure small analyte concentrations precisely and reliably, and calibration of the system so that the measurement of an analyte at the level of the skin reflects the serum concentration even when the system is removed and replaced at a different skin site.

Conclusions

In the past decade, iontophoresis has undergone serious re-examination, and considerable achievements have been recorded such that commercial products can be reasonably expected before the turn of the century. In comparison with the historical development of other novel delivery technologies, this is healthy progress. Future applications in therapy require, at least, that delivery options be considered early in drug development, even at the level of drug design and structural optimization. In particular, the importance of drug potency and manageable molecular properties must be impressed upon the medicinal chemist and the molecular biologist; insoluble 'rocks' the daily doses of which are 100 mg or more, and giant, multiply negatively-charged oligonucleotides, for example, are not going to be 'saved' by iontophoresis in its current configuration (or any other non-injectable dosage form, for that matter).

At the level of non-invasive clinical chemistry,

the success of the glucose story promises further applications of 'reverse iontophoresis' technology. The pharmaceutical scientist must convince colleagues in analytical chemistry to think about much lower levels of detection and the elimination of interfering signals. For the patient, the possibility of probing the systemic circulation continuously and, in particular, without the requirement of a needle is too attractive to ignore.

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