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TRANSDERMAL DRUG DELIVERY BY IONTOPHORESIS. I. FUNDAMENTALS AND THEORETICAL ASPECTS.

R. Pignatello, M. Fresta and G. Puglisi
Cattedra di Tecnologia, Socio-Economia e Legislazione Farmaceutiche,
Istituto di Chimica Famaceutica e Toss., Università di Catania, Viale A. Doria, 6
I-95125 Catania (Italy)

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Synopsis

Although the skin can represent an useful pathway for the local and systemic administration of drugs, its barrier properties strongly limit the efficacy of conventional topical delivery systems. Electrically-enhanced drug release, or iontophoresis, offers a valid mean for the transdermal delivery of charged and hydrophilic, or high-molecular weight substances at a controlled rate. This technique consists of the application of a known current field between two electrodes placed on the skin surface. A drug solution is layered beneath one of the electrodes and, by controlling the duration and intensity of current flow, a predetermined amount of the drug can be released into epidermis and dermal tissues.
In this review, the theories underlaying this technique of drug administration are analyzed, along with a brief description of skin structure and the effects of iontophoretic therapy on skin integrity.

Riassunto

La cute rappresenta una utile via per la somministrazione locale e sistemica di molti farmaci, per i diversi vantaggi che può fornire, rispetto ad altre possibili vie di somministrazione tradizionali; tuttavia, le eccellenti proprietà di barriera che la pelle offre, limitano l'efficacia delle formulazioni dermatologiche tradizionali a poche molecole lipofile e dotate di una elevata attività.
Tra i diversi approcci terapeutici proposti, la iontoforesi si è dimostrata un'attraente alternativa, in quanto è in grado di permettere il rilascio transdermico di farmaci carichi e altamente idrofili, come pure di molecole ad alto peso molecolare (polipetidi e proteine). Tramite l'applicazione di due elettrodi sulla superficie della pelle, al di sotto di uno dei quali viene posta una soluzione contenente un farmaco, viene creato un campo elettrico di intensità nota; in questo modo, controllando la durata e l'intensità del flusso elettrico, è possibile assicurare il rilascio di quantità predeterminate di farmaco nell'epidermide e nei tessuti sottostanti.
In questa prima parte di una rassegna sulle tecniche iontoforetiche finora sviluppate, vengono presentate alcune considerazioni teoriche sulle quali tale metodica e le sue applicazioni pratiche si basano. Per una migliore discussione del processo di trasporto transdermico indotto dall'applicazione di corrente, viene rapidamente discussa l'importanza dei vari costituenti della pelle sulle sue proprietà di permeazione, nonché gli effetti provocati dalla iontoforesi sull'integrità della pelle stessa.

Introduction

The penetration of compounds through the skin has both pharmacological and toxicological significance. The possibility of using the intact skin as the pathway for drug administration has been investigated for many decades: in fact, transdermal delivery of drugs shows some advantages over other administration pathways, in particular the avoidance of gastrointestinal incompatibility and liver "first-pass" effect. On the other hand, the skin represents a very efficacious barrier to the transport of many substances, and the conventional topical delivery devices are thereby limited to drugs with a local action or to highly potent, small and lipophilic molecules for a systemic effect. Contrarely, it is very difficult to transport charged or at least hydrophilic compounds as well as high-molecular weight molecules through the skin.
Among the various therapeutical approaches recognized to overcome such limitations, including chemical enhancers (1), transdermal drug delivery devices (2), use of ultrasonic and thermal energy (3), or application of ointments containing skin delipidizing compounds (3), iontophoresis can represent a valid method for the transdermal delivery of many substances at a controlled rate. Iontophoresis (or ion transfer) is defined as the migration of ions when an electric current is passed through a solution containing ionic species. In particular, the applied electric field imposes a force on ionized drugs which adds to the "diffusion force" or concentration gradient; this additional force drives the ion through the membrane into the body, more efficiently than in the case of pure diffusion or "passive" transdermal drug delivery. Since the preliminary studies of Leduc in early 1900 (4), iontophoresis has been used to transport drugs across several biological membranes including the skin (5), tooth mucosa (5, 6), the eyes (8-12), mucosae (13, 14), and cervix (15-17), in many pathological conditions. Recent extensive collections of drugs used by this administration tecnique have been reported by Yoshida and Roberts (18), Singh and Roberts (19), and Gangarosa and Hill (7). Barner (20) have described an iontophoretic device for the introduction into the skin of pigments for tattooing.
In this first part of a review upon iontophoresis, the theories underlaying such a procedure of drug administration will be discussed, along with a brief description of skin structure and the effects of iontophoretic therapy on skin integrity. In the forthcoming papers, the experimental procedures and the in vitro-in vivo models described in the literature will be reviewed, together with the present clinical applications and the future possibilities offered by this tecnique.

Structure of human skin and passive diffusion of topically applied compounds

Anatomical and physiological properties of skin have to be accurately considered to better understand and then conveniently exploit the potential of iontophoresis as a drug delivery device.
Mammalian skin is a multi-layered epithelium, supported by connective tissue and containing complex structures as eccrine and apocrine sweat glands, hair follicles with sebaceous glands, and nails, all of them referred to as skin appendages. Three main histological layers compose the skin: epidermis, dermis, and subcutaneous tissue (Fig. 1). The epidermis is further subdivided into several strata, which are characterized by hystological and functional differentiation of keratinocytes, as they move up from the lowest stratum basale to the outer surface, where they form the stratum corneum (SC), which consists of some layers of keratin-filled dead cells (corneocytes), that are anucleate, dehydrated, flattened and compacted (Fig. 1). Corneocytes are surrounded by lipid lamellae, mainly consisting of a mixture of cholesterol and its esters, fatty acids, phospholipids, glycerol and sphingosine esters and, in particular, ceramides, which represent about 50% of the SC

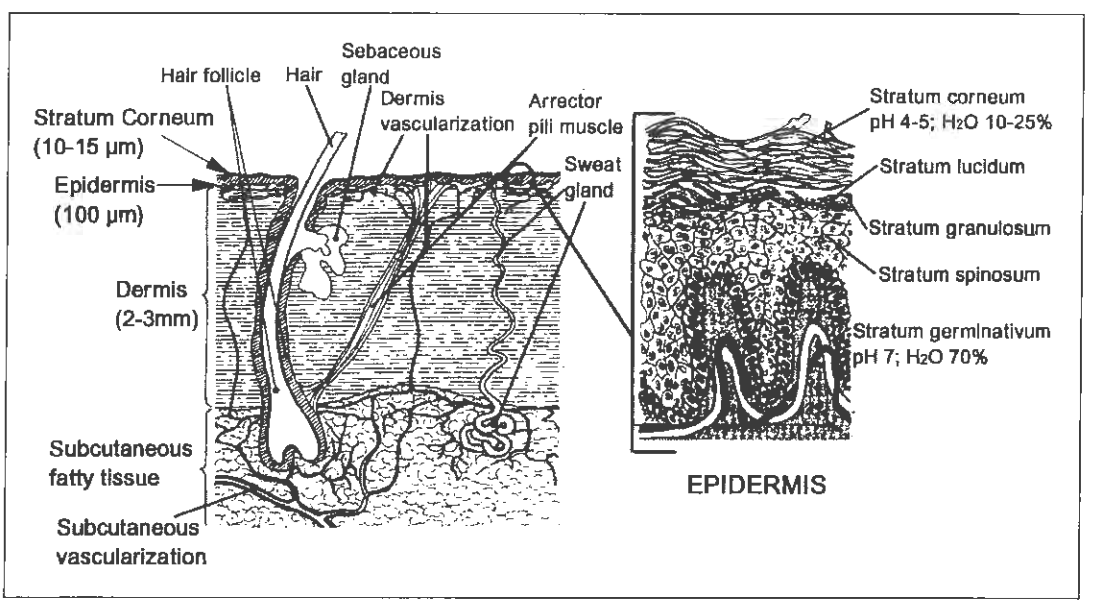
lipids; this lipid matrix forms a continuous medium through the SC and represents the primary barrier to the permeation of water and other hydrophilic substances, as well as the pathway for penetration of lipophilic compounds (21-23); moreover, these lipids are able to form multiple lipid bilayers and become important for the mechanical properties and desquamatory process of the SC (24). Corneocytes are connected together by desmosomes, proteinaceous structures which ensures an excellent mechanical protection for the underlaying, more sensitive viable tissues. The presence of these thight junctions suggest the possibility of a transcellular pathway of penetration through the SC (25).

The stratum corneum has a water content of only 20% as compared to 70% of other viable skin layers. Its mean thickness is around 10-50 µm, but significative differences are observable as a function of the rate of hydration of SC and between different areas of the body (17). The pH of the skin surface is between 3 and 4, which is about the isoelectric point of keratin in the SC (26); namely, skin surface has a positive charge below pH 3 and a negative one above pH 4. This aquires a great importance in predicting the permeation behaviour of basic or acidic substances.

The four layers situated under the SC (lucidum, granulosum, spinosum and germinativum, from the upper toward dermis), constitute the viable epidermis; this is an aqueous solution of proteins encapsulated into cellular compartments by thin cell membranes, fused together by tonofibrils. Epidermis has a thickness of about 100-150 µm and is avascular, performing all nutrition and waste exchanges by diffusion with the capillary beds inside the papillary layers of the dermis (Fig. 1). The convolute interface between the two layers enhances the contact area with dermal capillary loops, then facilitating epidermal metabolism.

The dermis consists of connective tissue and contains the inner portions of skin appendages, all of them highly vascularized. Dermis is 2-3 mm thick and is made of a fibrous protein matrix, mainly formed by collagen, elastin, and reticolin, embebbed in an amorphous colloidal polysacharidic ground substance. A papillary layer in contact with epidermis and a deeper

Figure 1: Sectional structure of the skin and, in particular, of epidermis components.



coarse reticular layer (the main structural layer of the skin) form the dermis (27). The dermis also contains blood vessels, sensory nerves and lymphatic structures. At its basis, a subcutaneous fat layer protects the body from shock and injuries (mainly heat), provides flexibility and strenght, acts as a barrier to infection and as a water-storage tissue (28). It has no effect on drug percutaneous permeation, since it is placed below the dermal vascular system.

Skin appendages

Human skin contains hair follicles and sebaceous glands as well as eccrine, apocrine and apoeccrine sweat glands (29). Skin surface contains, on the average, 40-70 hair follicles and 200-500 sweat ducts per square centimeter (17). Thermoregulatory eccrine glands are distributed in humans all over the body surface but are particularly concentrated in the hand palms and feet soles; the sweat secretion of the apocrine glands is limited to the axillae, breast areola and genital perianal areas. It is noteworthy that no completely homologous animal model exists for human skin: porcine and hairless rodent skin lacks eccrine sweat glands, while other mammals, including primates, show them only in the palmar and plantar regions.

Vellus or terminal hairs are present over the entire body, except for the red part of the lips, the palmar and plantar surfaces, and parts of sex organs. The follicles of terminal hairs can extend deep to the subcutaneous fatty tissue, while vellus follicles may only reach the upper dermis.

Sebaceous glands are more numerous on the face, forehead, in the ear, on the midline of the back, and in the perianal area. They produce an oily secretion, known as sebum, deriving from cell disintegration and acting as a skin lubrificant and a source of SC plasticizing lipids and maintains the acidic conditions on the skin's outer surface (27).

Passive diffusion of topically applied compounds

The process of percutaneous absorption can be viewed as the movement of a substance from the skin surface into the systemic circulation. It requires the penetration into the SC, diffusion through each layer of the skin, uptake by the capillary network at the interface between epidermis and dermis, and finally transport by the blood circulation to the action sites.

For a substance dissolved in the vehicle, a modification of Fick's law describes the passage through the SC:

$$J = \frac{dQ}{dt} = \frac{P C_v D A \alpha}{h}$$

(Eqn. 1)

where dQ/dt is the amount of drug appearing in the viable epidermis (i.e., the flux J), P is the partition coefficient of the drug between vehicle and skin surface, D is the diffusion coefficient of the drug, i.e., the ability of penetrate the SC, A and h the surface area and thickness of this latter, the fraction of drug which is in a non-ionized (liposoluble) form, and Cv the bulk concentration of drug in the vehicle.

The percutaneous absorption can occur by means of two different pathways, transfollicular (hair follicles, sweat ducts and secretory glands) and transepidermal (across the SC, intracellularly or intercellularly) routes (Fig. 2). The occurrence of percutaneous absorption through human skin is attributed to the passive diffusion of the drugs from a vehicle placed on the skin surface. Such a simple diffusion, regulated by a chemical (concentration) gradient, is strongly influenced by a number of factors which have to be accurately considered before executing a transdermal permeation study or application. These factors includes both physico-chemical characteristics of the drug (concentration, solubility, relative affinity for skin and vehicle, ionization rate, molecular weight and size) and of the vehicle or carrier (viscosity, solvent properties, affinity for skin

surface) as well as a number of physiologic or pathologic conditions of the skin, like individual or species-related variability in skin permeability and sensitivity to the systems applied (17).

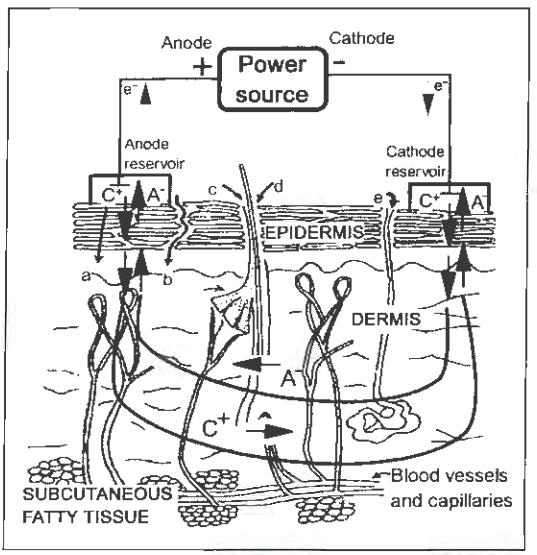


Figure 2: A schematic representation of charged species flow in an iontophoretic circuit, along with the possible routes of penetration through the skin: a) transcellular; b) diffusion between intercellular pores; c) through sebaceous gland duct; d) transfollicular; e) through sweat gland ducts. For simplicity, it is assumed that both aqueous solutions under the electrodes (reservoir) contains only one positively charged drug (C+) and one negatively charged counterion (A-), respectively.

There are some but discordant data in the literature showing that hair follicles and sebaceous glands act as routes (pores) for the passive absorption of polar substances (30). The use of appendage-free (hairless rat skin regrown after scalding and newborn rat skin) as models for both neutral (hydrocortisone and caffeine) and ionized drugs (niflumic acid and p-aminobenzoic acid) (31, 32) would suggest that the presence of hair follicles positively influence the permeation. However, because of the fact that all the skin shunts (follicles plus sweat glands) represent only 0.1% of the total human skin surface area (33), it is generally assumed that they normally give only a minor contribution to the passive flux of substances through intact skin after topical application.

Iontophoresis: definition and advantages

Although the impermeability of skin to ionic and polar species, it would seem that pathways ('pores') for the transport of small ions exist within the skin, particularly via the transfollicular and transappendageal routes. Paracellular transport also takes place and all of these forms of transport can be enhanced by the application of an exogenous transdermal potential.

When an electrical potential gradient is imposed across the skin, ions and charged compounds will move along the pathways of lowest electrical resistance. By repulsion of ions at the active electrode, they are driven into skin tissues: negative ions are delivered by cathode [cathodal (-) iontophoresis] and positive ions by anode [anodal (+) iontophoresis] (34) (Fig. 2).

Practically, a battery is used to create an electric field; the electrodes are placed at two adiacent sites on the skin: battery anode is at the highest potential, while the cathode is the lowest potential point. The electric field induces a migration of electrons toward the anode and the contemporary movement of ions within the ionic solution portion of the circuit, which consisted of the skin surface under the anode reservoir, the hydrated skin tissues between the two electrodes and the surface under the cathode. Positive ions (C^+) migrate toward the cathode and negative ions (A^-) toward the anode. If the solution in the anode reservoir contains a cationic drug, it will move in the direction of the cathode across the circuit and, hence, into the skin. Before it reaches the cathode, it is partitioned into the different skin tissues and/or removed by dermal blood circulation away from the site of permeation. Similarly behaves a drug which is an anion, when delivered by the cathodic reservoir (Fig. 2).

Many evidences indicate that the transport of ionic substances takes place both via a paracellular (along interconnections among cells) and skin pore routes. Cullander and Guy used confocal microscopy to visualize that two fluorescent

ions, calcein and NBD-diethanolamine, after iontophoresis into mouse skin, are distributed both in the follicular spaces and between cells, whereas no transcellular diffusion was observed (30). Similarly, mercuric chloride iontophoresis both in nude mouse, pig and human skin, indicated that the compound permeates through the intact SC via an intercellular route and was mainly localizated in the extracellular spaces (30, 35).

Other experiments clearly demonstrated that many ionic species cross the outer skin layers through pores, which are usually, but not necessarily, associated with appendages (30, 36). Iontophoresis of pilocarpine is routinely used to induce sweating in the diagnosis of cystic fibrosis (37); Abramson et al. (38, 39) and Grimnes (40) employed charged dyes to individuate the position of sweat glands within the epidermis. Experiments with the more sensitive vibrating probe electrodes (30, 41) confirmed that appendages, and particularly sweat pores behave as the highest conductive pathways in the skin. As highlighted by Cullander (30), this could begin a limitation of the efficacy of iontophoresis, when the administered drug has to act within the epidermis, since the rapid transappendageal transport can drive it far from its region of action.

Interestingly, Abrahamson and Gorin (42) have hypotesized that the flux of drugs through sweat glands is limited under normal conditions, because they are not completely filled with fluids. The drug flux is enhanced by the application of an electric current across the skin, which causes a filling of the gland duct, as a consequence of the electro-osmotic phenomenon (see below).

Several reports in the literature (7, 18, 19) indicate the efficacy of iontophoresis in topical and systemic administration of drugs, in particular for polar compounds that can not be applied to other non-iontophoretic transdermal systems. Many studies of model cationic and anionic drugs evidenced a clear increase in transdermal permeation by means of iontophoresis, with respect to passive diffusion. In Fig. 3, the examples of sotalol hydrochloride and sodium salicylate are reported (43).

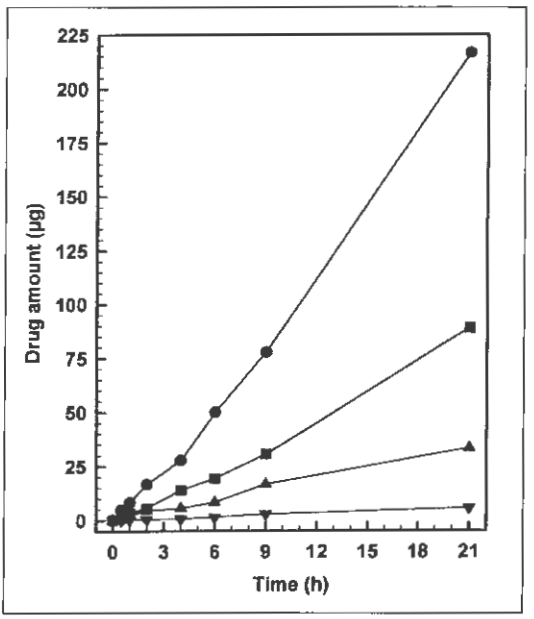


Figure 3: *Passive and iontophoretic in vitro fluxes of two model drugs through excised human skin. Anionic drug (sodium salicilate): passive ▼ and iontophoresis ■ ; cationic drug (sotalol hydrochloride): passive ▲ and iontophoresis ● (adapted from ref. 43).*

This non-invasive method lows the risk of trauma, infections and damage to the wounds. With respect to the oral route, it permits to avoid drug (e.g., peptides and proteins) chemical and/or enzymatic degradation in the gastrointestinal tract and the hepatic first-pass metabolism, and also represents a valid alternative to parenteral route, expecially because a better patient compliance can be achieved.

An aspect of iontophoresis that can be considered as an advantage or a side effect, is the so-called 'epidermal reservoir' phenomenon (42). Different Authors have observed that iontophoresis induces a certain retention of some drugs within skin areas close to the delivery electrode. This fact results in a pharmacological effect limited to the administration site, as described for pilocarpine (37) and bretylium tosylate (44), or a 'depot' effect that allows to prolong or repeat the delivery of the drug during time, as described with insulin (45, 46), histamine (42) and so-

me amino acids (47). However, the accumulation of a drug at the delivery site could also represent a risk, since the prolonged residence time can enlarge its eventual local irritative or toxic effects.

The limits of iontophoresis

The use of iontophoresis has often been associated with more or less severe skin damages (17, 48, 49), although comprehensive studies in this field lack and many Authors tend to underestimate such aspects. Common side effects observed with iontophoresis are erythema, edema and burns produced on the skin. Pain is not generated up to the higher current intensity commonly used (0.5 mA/cm^2). In general, findings showed that a higher skin damage and longer recovery times were observed when lower voltages were applied for longer times to obtain the same decrease in skin electrical resistance than higher voltages at shorter times (50). Burns are caused without any sensation of pain and tend to heal slowly (48, 51, 52). The generation of pain and burns has often been related to the electrochemically induced modification in the pH of the skin surface area under the electrodes. In fact, with many commonly used electrodes, OH^- and H^+ ions are generated at the cathode and anode, respectively, as a consequence of the electrochemical induced hydrolysis of water. As demonstrated by Molitor and Fernandez (53), the contemporary passage of the current through the resulting alkaline and acid layers causes the observed skin damages. Studies of Schwartz et al. (54) confirmed that the lowering of pH is the principal responsible for these effects. In fact, the application upon the skin of 0.1 M HCl without current for 5 min caused no sensation, while the application of 0.01 M HCl with current (2 mA/cm^2) caused pain and blistering within 2 min. More diluted HCl solutions were innocuous. Also with other buffer solutions, pain sensation was not reported until pH went down to 1-2, whereas pH 8.0 solutions did not give pain or blisters beneath the anode.

The problem of avoiding the effects of pH changes during iontophoresis has received much attention, and an useful solution has been attained by modifying the nature of electrodes used; such an argument will be discussed in a forthcoming part of this review.

Erythema has also frequently been observed as a reaction to iontophoresis, probably as a consequence of a mild irritation due to the drug used or to localized cellular damage, which could trigger the stimulation of C-fiber nociceptors and the following release of the usual mediators of inflammation (48). However, irritation and erythema are usually of little duration and do not cause any permanent damage of the skin.

Inada et al. (50) have investigated the effects of current voltage (250-4000 mV) and duration of its application on human epidermis and they found that the observed increase in skin permeability can be referred to the hystological alterations induced by the electrical field, that causes formation of pores.

An experimental approach to measure the effects of iontophoresis upon the skin has recently been described by Oh and Guy (55). They registered the resistance changes of the skin during application of different currents (10, 50 or 100 $\mu A/cm^2$) for increasing times; at the end of current passage, the recovery time of initial resistance was monitored. While skin resistance dropped rapidly (within the first 10 seconds of application) at all the current densities used, the time required for recovery of skin resistance is greater by increasing both time of current application and current density. Thereby, Authors concluded that in vivo measurement of skin impedance, and hence of resistance, can provide a valid assessment of the effects of iontophoresis upon skin surface (55).

Two other potentially limiting aspects must be considered: (i) drug solubility, and (ii) drug stability. The drug solution should have a sufficient concentration to carry the current necessary for permeation through the skin; thus, water solubi-

lity of the drug can be a critical parameter affecting the efficiency of the entire process. The second aspect, is represented by the stability of the drug to the electrical current, since hydrolysis, protein denaturation, racemization and other degradative processes can take place following ionic motion and local temperature raise which occur under iontophoretic application.

Theoretical considerations

The electrically induced transport of an ion across a membrane can be considered as the sum of three factors: simple diffusion, related to a chemical potential gradient; electrical mobility, due to an electric potential gradient; and solute transfer, due to convective solvent flow (electroosmosis) (56):

$$J = Jp + Je + Jc$$

(Eqn.2)

where J is the total flux of the drug, Jp the passive diffusion flux, Je the electrical flux, and Jc the convective flux.

During iontophoresis, the primary contribution to drug transport across the skin derives from electromigration, but electroosmotic flow has been recently reviewed as an important factor affecting the efficiency of iontophoresis (57). Electroosmosis occurs when an electric voltage is applied across a charged porous membrane, like skin, and has to be considered as a bulk fluid flow or 'volume flow'. This flow is not a diffusion: it is a movement of the fluid without concentration gradients; the direction of the flow may be with the current field or against the current flow, depending on the nature of the membrane. Generally, electroosmotic flow occurs in the direction of counterion flow (57): a counterion is an ion with an opposite (in sign) charge to the immobile charges of the membrane. Human skin is negatively charged above pH 4, due to the presence of ionized carboxyl groups. Therefore, electroosmotic flow occurs in the direction of the current, from anode to cathode: thus, anodic delivery is assisted by electroosmosis, while cathodic iontophoresis is hindered (57-59). The main physico-chemical factors which determine the size of electro-osmotic flow are the net charge density of the membrane, the density of the current applied, and the ionic strength and viscosity of the electrolyte (60). Although the role of electroosmotic flux is less significant than ionic transport for small positive ions, it may be dominant when large ions, like polypeptides and proteins, or small negative charged species are iontophoresed (36, 57, 61, 62). However, the effect of convective solvent flow on the iontophoretic flux of a drug is inversely related to the molecular size (diffusion coefficient) of the permeant (60).

Recently, Delgado-Charro et al. (63, 64) have observed that anodic iontophoresis of nafarelin, a cationic peptide, alters the extent and direction of the convective flow, by neutralizing the negative fixed charge on the skin and leading to a reversal (from the anode-to-cathode to the cathode-to-anode direction) of the electroosmotic flow itself. As a consequence, nafarelin transport by electroosmosis is suppressed and an anomalous flux/concentration profile is observed (64).

The migration of ions through the skin under an applied electric field, can be expressed as an ionic current (Eqn. 3). The fraction of current carried by each ion, as a function of its cationic or anionic nature and charge, is called the *transference or transport number*: i.e., a transport number of 0.6 means that the selected ion carries the 60% of the current through the membrane. Importance of such transport number in iontophoresis is analogous to that of permeability coefficient in transdermal passive diffusion (65).

$$J = \frac{Tl}{Z\mathcal{F}}$$

(Eqn. 3)

where J and Z are the flux and the valence (or molecular charge) of the ion, t its transport num-

ber, I the current density resulting from the migration of the ion and $\mathcal{F}$ the Faraday constant (96,500 coulomb mol^{-1}). This equation predicts that the ion flux is linearly dependent on the applied current (66) and, in effects, in most cases iontophoretic penetration of drugs was found to be related to the used current intensity (18, 67). Several laws and theories have been adopetd to optimize the prediction of the experimental iontophoretic behaviour of drugs (68). Among them, the equation proposed by Masada et al. (69) (Eqn. 4) resulted in good agreement with *in vitro* experimental permeation data when a low voltage iontophoresis (0-0.25 V) was performed:

$$E = Y/Y_O = (FZ\Delta V)\ \{RT[\exp-(FZ\Delta V/RT-1)]\}^{-1}$$

(Eqn. 4)

where E is the flux enhancement ratio, that is the ratio between the flux with (Y) and without (Y_O) the electric field, ΔV the potential drop, R the universal gas constant, and T the absolute temperature.

More accurate predictions can be made by using the Nernst-Plank and Poisson equations or also their simplifed approximations (36, 68). Nernst-Plank equation (Eqn. 5) is the most common starting point for the description of the flux of an ion through aqueous pores (J^w), under the influence of both a concentration gradient and an electric field. When the potential gradient is zero, the equation reduces to Fick's passive diffusion law (Eqn. 1).

$$J^w = -D\frac{dc}{dx} - \frac{Z\mathcal{F}}{RT}cD\frac{d\Psi}{dx} + vc$$

(Eqn 5)

Ψ is Galvani's potential at any point x in the membrane, v is the average velocity of the solvent, and vc indicates the transport of ion due to the convective solvent flow: its value is positive for a positively charged permeant, while it is a negative term for negatively charged species. The potential gradient $d\Psi/dx$ can be also approximated with its ohmic resistivity (i/k, where i is the current density and k the conductivity).

Sims and Higuchi (70) developed the following equation for the permeability coefficient of a weak electrolyte under iontophoresis (Eqn. 6):

$$P_T = X_S P_L + X_S P_P + E(1 - X_S)P_P$$

(Eqn. 6)

where P_T is the total permeability coefficient, X_S the fraction of undissociated species, P_L the permeability coefficient for the lipoidal pathway, and P_P the permeability coefficient for the aqueous pore route.

More recently, Srinivasan and Higuchi (60) have proposed an extension of Nernst-Plank model for iontophoresis, including a term for the effect of electrosmotic flow based on the Peclet number Pe:

$$dC/dX + [dV/dX - Pe]\ C = -M$$

(Eqn. 7)

In this equation dimensionless variables are used: the dimensionless distance $X = (x/h)$, h being the membrane thickness; the dimensionless electric potential $V = (Z\Psi/RT)$, and a dimensionless concentration $C = (c/c_d)$, where c is the drug bulk concentration and c_d is the concentration of the permeant at the membrane-donor side interface. The coefficients are: $M = (Jh/Dc_d)$ and Peclet number $Pe = (vh/D)$, where D is the diffusion coefficient of the permeant, and v is the average velocity of the solvent. The same Authors also proposed a method for decoupling and comparing the relative contributions of the applied electric field and induced electroosmotic flow on the observed overall iontophoretic flux. Moreover, rearrangement of such equation allows to obtain the enhancement factor E, the ratio between iontophoretic to passive flux for an ion; it gives a direct impression of the efficacy of iontophoretic flux for a charged species at the applied voltage $\Delta\Psi$. For a positively ion, E is:

$$E = - K[1 - (Pe/K)]/[1 - \exp \{K(1 - Pe/K)\}]$$

(Eqn. 8)

while, for a negatively charged one:

$$E = - K[1 + (Pe/K)]/[1 - \exp \{K(1 + Pe/K)\}]$$

(Eqn. 9)

where $K = (Z\mathcal{F}\Delta\Psi/RT)$.
These two latter equations give the iontophoretic flux enhancement due to both electric potential across the membrane and electroosmotic flow (60). Obviously, none of the mathematical models developed can completely describe all the phenomena experimentally observed during iontophoresis, including convective (electroosmotic) flow and characteristics of the delivery device (thickness of skin or membranes, area of electrodes, pH and concentration of drug solution), but each allows to make good predictive calculations.
In a forthcoming part of this review, the experimental and operational aspects of iontophoresis will be analyzed, along with the description of in vitro and in vivo models (human and animal skin) to date described.

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