

TECH NOTE



Your Partner in Rehabilitation Outcomes

FACTORS AFFECTING THE IONTOPHORESIS PROCESS

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INTRODUCTION

Transdermal administration of drugs has assumed an important place in modern drug therapy. This mode of administration is suitable for non-ionized drugs requiring a relatively small dosage. The drug traverses the skin governed primarily by the laws of passive diffusion of the non-ionized drug through the rate-limiting membrane, the stratum corneum. Ionized drugs, however, do not easily penetrate this barrier and are not generally suitable for routine transdermal dosage forms unless an external source of energy is provided to drive the drug across the skin. In iontophoresis (IP), this external source of energy is in the form of an applied direct electrical current. Electrical energy will assist the movement of ions across the stratum corneum according to the basic electrical principles of "like charges repel each other and opposite charges attract".

There are many advantages for using IP; one of the most important would be that it is noninvasive in nature. Many drugs that currently must be administered parenterally may be suitable for iontophoretic administration and patient acceptability would be high.

THEORETICAL CONSIDERATIONS

Ion Penetration

When salts or drugs are dissolved in aqueous solutions, ionized or electrically charged particles are formed. This process of ion formation is called dissociation or ionization. Ionized drugs do not normally penetrate into surface tissues sufficiently using passive transdermal delivery to achieve a therapeutic level.

The problem of membrane penetration of ionic drugs can be overcome by providing an energy source which increases the rate of penetration. Electrical energy, in the form of a small direct current, will assist the movement of ions. According to electrical principles, as previously mentioned, like charges repel each other and opposite charges attract. Thus, positive drug ions are repelled from a positively charged electrode and negative drug ions are repelled from a negatively charged electrode.

Physics and Mathematical Relationships

There are a few relationships that are important in IP.

Ohm's Law states:

$$V = IR$$

where V is electromotive force in volts, I is current in amps and R is resistance in ohms. The importance of this relationship is that at constant voltage, any change in resistance results in a change in current level. Very often, the resistance decreases during a procedure; as a result the current, in milliamperes, will increase, unless the current device is programmed to deliver a constant current, then the voltage will vary to compensate for changes in resistance.

Coulombs Law states:

$$Q = IT$$

where Q is the quantity of electricity, I is current in amps and T is time in minutes. Thus, "mA•min" is used to describe the "current dosage" used during IP.

Faraday's Law states:

$$D = (IT) (IZI F)$$

where D is the amount of drug delivered (in gm-equivalents), I is current in amps, T is time, IZI is valance and F is Faraday's Constant. From this relationship, the more electricity delivered, the more drug delivered. Faraday's Law has been used by some to provide information concerning the rate of deposition of the drug at the skin surface. However, due to the complexity of the factors involved during the process of IP, theoretical predictions based on it are difficult.

VARIABLES INVOLVED

As can be seen or derived from the above relationships, there are a number of variables that may affect the process of IP; in vitro, or in vivo or both. Each individual variable may impact either the in vivo or in vitro slightly different. The primary differences in the in vitro and in vivo situation concerns the donor cell or electrode system and a receptor cell (in vitro) or patient (in vivo). In the in vitro system, the donor cells are typically glass, plastic or the electrode system; the receptor cells typically are glass or plastic. The membrane is generally an animal skin, although in some studies different artificial membranes have been used. As the current is applied, the drug is generally sampled from the receptor cell and the concentration followed over time. The in vivo situation involves the use of the drug in an electrode system (as the donor "cell") and the patient (as the receptor "cell"). The concentration of the drug in the patient can be determined from the blood level or from skin biopsies. The actual depth of skin penetration can be determined by analyzing different layers of the skin biopsy.

Variables affecting the IP process include: the drug concentration, drug salt form, pH of the drug micro environment, the current intensity and duration, competing ions in the electrode solution/matrix, stability of the drug during the IP process, the type of matrix containing the drug and current density. Additionally, patient anatomical factors and the presence and extent of inflammation can influence the depth of drug penetration.

Drug Concentration: Increased uptake by the skin during and after IP with an increase in drug concentration has been reported.^{1,2} This is generally true until a plateau level is reached at which no further increase in flux is observed.

Drug Salt Form: It has been reported³ that different salt forms have different specific conductivities and that conductivity experiments in vitro will provide information concerning the general suitability of a drug for IP. The salt form of drugs must be considered along with the pH of the solution for determining the amount of drug in the ionized state.

pH of the Drug Micro environment: Laboratory findings vary on the effect of pH and drug behavior. According to the Henderson-Hasselbalch equation, pH is the determining factor governing the amount of drug present in the ionized state. For optimum IP, it is desired to have a relatively large proportion of the drug in the ionized state. However, this must be counterbalanced with delivery of a drug at a pH that is tolerable and safe for the patient.

Current Intensity and Duration: From Faraday's Law we know that in an electrolytic solution the transported quantity of electricity depends on the strength of the current and the duration of its passage.⁴ Thus, this law would suggest that the same number of ions should be transported at different strengths of current if the time for current flow is inversely related to their strengths. However, generally speaking, we also know that in some cases, higher current may deliver more drug than lower current, possibly due to induced changes in skin permeability by the higher current, resulting in a greater flow of drugs. The rate at which the ions are introduced into the body with various current strengths can play an important role. When the current is stronger, more ions penetrate at one time. The strength of the current used also depends on the sensitivity and tolerance of patient.⁵

Competing Ions in the Electrodes: Electrical current is carried by positive and negative ions in solution. There is no major distinction between ions of the same charge even though they are composed of different chemical elements. Therefore, solutions for IP should be as pure as practical and generally contain as few extraneous substances as possible. Drug solutions should be prepared with purified water (deionized, distilled, reverse osmosis). It has been shown that the presence of excipients in dosage forms, i.e. preservatives in injections as well as compounds used as external buffers, will alter the amount of drug delivered. In vitro, the total current will be carried by drug ions along with the same charges as drug ions in the donor cell plus the counter ions present in the receptor cell. Therefore, the competing ions in the donor cell and the counterions in the receptor cell will be affecting the actual current carried by the drug moiety. During IP, there is a shift in pH due to hydrolysis of water which may result in a loss of efficiency of drug transfer due to presumably competing ions. Buffers may be built into the electrode to minimize this effect, but the buffer materials should be bound, or immobile, and not released for IP transport, as they would then compete with the active drug.

Stability of the Drug During the IP Process: The drug undergoing IP must be stable in the solution environment up to the time of IP and also during the iontophoretic process. Oxidation or reduction of a drug not only decreases the total drug available but the degradation compounds, if they possess the same charge as the drug ion, will compete with the drug ion and reduce the overall transmembrane rate of the drug.

Type of Matrix Containing the Drug, Gel Vs. Solution: The migration of the drug under the influence of the electrical current, will be different as the matrices are different. This can be related to differences in viscosities, material electrical charge and porosities.

Current density: Current density is the quantity of current delivered per unit surface area. The following criteria should be considered in selecting proper current densities for IP: (1) the current should be sufficiently high to provide a desired drug delivery rate; (2) it should not produce harmful effects to the skin; (3) there should be a quantitative relationship between the flux and the applied current; and (4) there should be electrochemical stability of the drug.

Patient Anatomical Factors: Patient anatomical factors that influence the depth of penetration that are variable from patient to patient include skin thickness at the site of the application, presence of subcutaneous adipose tissue and the size of other structures, including skeletal muscle. Additionally, the presence and severity of inflammation can influence drug penetration due to the increased temperature (which may increase penetration rate) and the elevated level of blood and fluids present that may serve to transport the drug throughout the body.

SUMMARY

With so many variables affecting IP drug delivery, the clinician can select electrodes, drug solutions and dosage/current parameters which maximize drug delivery as well as select patients and conditions where IP is most efficient. In general, it is best to prepare a simple, stable solution of the drug in water with a minimum number of extraneous substances in order to maximize the efficiency of the drug carried per unit of current conducted.

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For complete instructions for use, indications, contra indications, warnings and precautions, see device instruction manual.



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