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REVIEW ARTICLE

Iontophoresis: Advance Technique in Transdermal Drug Delivery

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ABSTRACT

Transdermal drug delivery route has been found the most effective route in administration of high molecular weight drug through the skin using various techniques. Several transdermal approaches have been used and recently there has been a great attention in using the iontophoretic technique for the transdermal drug delivery of medications, both ionic and non-ionic drugs. Iontophoresis facilitates the movement of ions across the membrane under the influence of applied electric potential. This review describes the mechanism of Iontophoresis, factors affecting iontophoresis also provides application for various disorders.

KEYWORDS

Transdermal drug delivery, Iontophoresis, Chemical enhancer, Electroporation

INTRODUCTION

Skin Anatomy

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. Three main histological layers compose the skin: epidermis, dermis, and subcutaneous tissue. The epidermis is further subdivided into several strata, which are characterized by histological 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. (figure 1) Corneocytes are surrounded by lipid lamellae, mainly consisting of a mixture of cholesterol and its esters, fatty acids, represent about 50% of the sclipids; this lipid matrix forms a continuous medium through the scand represents the primary barrier to the permeation of water and other hydrophilic substances, as well as the pathway for penetration of lipophilic compounds[1,2] moreover, these lipids are able to form multiple lipid bilayers and become important for the mechanical properties and desquarnatory process of these[3] eomeocytes are connected together by desmosomes, proteinaceous structures which ensures an excellent mechanical protection fortheunderlaying, more sensitive viable tissues. The presence of these tight junctions suggests the possibility of a transcellular pathway of penetration through the sc.[4] The stratum corneum has a water content of only 20% as compared to 70% of other viable skin layers. Its mean thickness is around 10-50µm, but significative differences are observable as a function of the rate of hydration of sc and between different areas of the body.[5] The pH of the skin surface is between 3 and 4, which is about the isoelectric point of keratin in the sc[6]; namely, skin surface has a positive charge below pH 3 and a negative one above pH 4.

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This aquires great importance in predicting the permeation behaviour of basic and acidic substance.

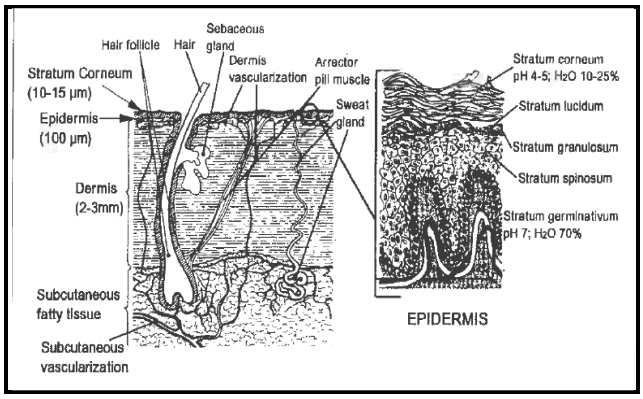

Figure 1: Sectional structure of the skin and parts of epidermis

Transdermal Drug Delivery System

Transdermal delivery of drug through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. In the development of new transdermal drug delivery the object is to obtain controlled, predictable, and reproducible release of the drug into the blood stream of patients. Transdermal device act as drug reservoir and controls the rate of drug transfer.[7] 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 orto 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.[8] Various therapeutical approaches recognized to overcome such limitations, including chemical enhancers, transdermal drug deliverydevices , use of ultrasonic and thermal energy , or application of ointments containing Skin delipidizing compounds , iontophoresis can represent a valid method for the transdermal delivery of many substances at a controlled rate.[9] The method of iontophoresis was described by pivati in 1747. Galvani and vota two scientist working in 18th century combined the knowledge that electricity can move the different metal ions and vice versa.[10]

Iontophoresis

It is a technique which uses an electric current to deliver a medicine or other chemical through the skin. Iontophoresis which is the facilitated movement of ions across a membrane under the influence of an externally applied small electric potential difference (0.5mA/cm^2 or less), is one of the most promising novel drug delivery system, which has proved to enhance the skin penetration and the release rate of number of drugs having poor absorption/permeation profile through skin[11] 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][12] a solution of the drug in pad or gel is placed on the skin. An active electrode is placed on this pad or gel and the return electrode placed elsewhere on the body. A small electric current, usually less than 1 mA, is applied for a time period, usually 15 to 20 min[10] The drug travels through the tissue and is available for its local effect.[13]

Principle of Iontophoresis

The Iontophoretic technique is based on the general principle that like charges repels each other and opposite charge attract. Thus during iontophoresis, if delivery of positively charged drug is desired, the charged drug is dissolved in the electrolyte surroundings the electrode of similar polarity, i.e. anode. An application of electromotive force the drug is repelled and moves across the stratum corneum towards the cathode, which is placed elsewhere on the body.[10] Communication between the electrodes along the surface of the skin has been shown to be negligible. When the cathode is placed in the donor compartment of the Franz diffusion cell

to enhance the flux of an anion, it is termed cathode iontophoresis and for anodal iontophoresis the situation would be reversed. If any neutral molecules are present at the anode at this time the can be transported through the skin along with the water. Such water movement often results in pore shrinkage at the anode and pore swelling at the cathode.[13]

Advantages of Ionotophoresis

1) It is non-invasive technique could serve as a substitute for chemical enhancers.
2) Eliminate problems like toxicity, adverse reaction, and formulation related problem.
3) It may permit lower quantity of drug compared to TDDS; this may lead to fewer side effects.
4) Prevent variation in the absorption of TDDS.
5) Eliminate the chance of over and under dosing by continuous delivery of drug programmed at the required therapeutic rate.
6) Provide simplified therapeutic regimen, leading to better compliances.
7) Permit rapid termination of the modification.
8) It is important in systemic delivery of peptide / protein based pharmaceuticals, which are highly potent

Disadvantages of Iontophoresis

1) Iontophoretic delivery is limited clinically to those applications for which a brief drug delivery period is adequate.
2) An excessive current density usually leads to pain.
3) Burns are caused by electrolyte changes within the tissue.
4) The safe current density varies with electrode size.
5) The high current density and time of application would generate extreme pH, resulting in chemical burns. This change in pH causes the sweat duct plugging which leads to precipitation of protein in ducts.
6) An Electric shock may cause by high current density at the skin surface.
7) Possibility of cardiac arrest due to excessive current passing through heart.
8) High molecular weight results in varying, uncertain rate of Delivery.

Factors Affecting Iontophoretic Drug Delivery of The drug

Physicochemical Properties

Molecular Size and Molecular Weight

The molecular size of the solute is the major factor governing its feasibility for drug delivery. Smaller and more hydrophilic ions are transported at a faster rate than the larger ions, the permeability coefficients of solute across the skin are function of molecular size. When the molecular size increases, the permeability coefficient decreases.[7]

Charge

The charge on molecules is an important physicochemical property governing Iontophoretic transport; sign of the charge determines the mechanism. An increase in the charge will require pH to be decreasing, which in turns directly decreases the eletroosmosis and electro transport process.[13]

Concentration

Concentration of the drug is one of the most important factors. An increase in Concentration was shown to increase the apparent steady flux of the drug. The concentration dependent Iontophoretic delivery has not been fully investigated, some authors reported that as the concentration of drug, increase in the reservoir system then permeation of drug also increases.

Drug formulation related factors

pH

pH is an important factor governing the Iontophoretic delivery of the drug; this affects iontophoresis in two ways. The pH of the donor solution influences the pH of the skin and thus makes the skin a perm selective membrane, especially if the ph of the skin rises above 4. The pH of the donor solution also affects the ionization of the drug itself. Changes in the pH are also considered responsible for the discomfort and skin irritation associated with iontophoresis.[1]

Ionic Strength

The ionic strength of drug delivery system is proportional to the Iontophoretic permeation of drugs. Some authors reported that increasing the ionic strength leads to decreases the rate of permeation, and has no significant effect on penetration up to the 0.5

Presence of co-ions

An ion of equal charge, but of different type is referred as co-ion. The buffering agents used to maintain the pH of the donor medium is source of co-ions. These co-ions are generally more mobile and smaller in size than the drug ions. The presence of co-ions results in competition between the drug and co-ion, a reduction of the fraction of current carried by the drug and thus a reduction in the transdermal Iontophoretic flux of the drug.[7]

Experimental factors

Current Strength

Current can easily be controlled by the use of electronics. Constant direct current has been used in Iontophoretic application, but we contend that constant current generator should be used to provide consistent current flow while the skin resistance is changing. There is a linear relation between the observed fluxes of a $1cm^2$; the current is limited up to 1mA due to patient comfort consideration.[11] This current should not apply for more than 3 min because of local skin irritation and burns. With increasing current, the risk of non specific vascular reactions increased. In general, $0.5mA/cm^2$ is often stated to be the maximum Iontophoretic current.[7]

Current Density

Current density is the quantity of current delivered per unit surface area. The current should be sufficiently high to provide a desired delivery rate. It should not provide harmful effects to the skin. There should be a quantitative relationship between the applied current. The drug should be electrochemically stable.[14]

Pulsed Current

The continuous use of direct current, proportional to time, can reduce the Iontophoretic flux because of its polarization effect on the skin. This can be overcome by the used of pulsed DC which is a direct current delivered in a periodic manner. During off stage the skin gets depolarized and returns to the initial polarized state. However, Burnett showed that enhanced skin depolarization can decrease the efficiency of drug transport if the frequency of pulsed current is very high.[15]

Duration of Application

The transport of drug delivery depends on the duration of the current applied in the iontophoretic drug delivery. TheIontophoretic penetration of the drug linearly increased with increasing application time.[13]

Electrode Material

The electrode materials used for Iontophoretic delivery are to be harmless to body and sufficiently flexible. The most common electrodes are aluminium foil, platinum and silver-silver chloride electrode used for IP. Electrode Ag/AgCl are the most preferred as the resist the change in pH, which is generally seen during the use of platinum or Zn/ZnCl electrodes. The positioning of electrodes in reservoir depends on the charge of the active drug. The distribution of the drug within the skin depends on the size and position of electrodes. These are usually selected according to individual needs. Larger electrode areas introduce the greater amount of drug, but lesser current density is tolerated to the skin.[10]

Limitations of Iontophoresis

Common side effects observed with iontophoresis are erythema, edema and burns produced on the skin. The pain doesn't generate 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.[16] Burns are caused without any sensation of pain and tend to heal

slowIy.[17] The generation of pain and bums 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 *W* ions are generated at the cathode and anode, respectively, as a consequence of the electrochemical induced hydrolysis of water. As demonstrated by Molitorand Fernandez, the contemporary passage of the current through the resulting alkaline and acid layers causes the observed skin damages.[18,19]

Enhancement Technique

Ultrasound and iontophoresis Combined application of ultrasound and iontophoresis also has practical applications. The combination of ultrasound and electric current offers a higher enhancement compared with either used individually under similar conditions. Since ultrasonic pretreatment reduces skin resistivity, a lower voltage is required to deliver a given current during iontophoresis compared with that in controls. This should result in lower power requirements, as well as possibly less skin irritation. Lee and colleagues investigated the effect of ultrasound and iontophoresis on transdermal heparin transport.[20,21]

Iontophoresis with Chemical Enhancers

Chemical enhancers increase the transdermal drug delivery via several ways, which include increased drug solubility, increased drug partitioning into the stratum corneum and by the disruption of the intracellular protein.

Chemical enhancers can be used in combination with iontophoresis to achieve higher drug penetration. A combination of chemical enhancers and electrically assisted delivery should also reduce the side effects, such as irritation caused by high concentration of enhancers or stronger electric forces. The use of chemical enhancer was reported that propylene glycol and oleic acid enhance transdermal transport of AZT in combination of iontophoresis.[14]

Iontophoresis with Electroporation

Electroporation may create new transport pathways in the stratum corneum, thus assist the passage of current during iontophoresis. Electroporation seems more effective for the delivery of some macromolecules such as oligonucleotides, peptides and protein. The mechanism of drug transport is similar to that with sonophorosis. Chang *et al*. studied the effect of iontophoresis and electroporation on transdermal delivery of salmon calcitonin and parathyroid hormone through human epidermis. Author state that a combination of electroporation and iontophoresis induced higher transdermal permeation, than either one technique alone. Electroporation also shortened the lag time of Iontophoretic transdermal delivery of salmon calcitonin.[22]

Applications

Treatment of Hyperhydrosis

It is a condition that most often results in excessive sweating in the hand and feet. Tap water iontophoresis is most popular treatment used in the condition. According to one hypothesis, iontophoresis may induce hyperkeratosis of the sweat pores and obstruct sweat flow and secretion.

Peptide Delivery

This is the most promising application of iontophoresis. TDDs itself gives the advantages of bypassing first pass metabolism as well as patient compliances. An additional advantage that it offers specifically for protein peptides is the avoidance of strong proteolytic condition as found in the GI tract.

Non-invasive Monitoring of Glucose

Electro osmosis flow generated by application of low level current has been used for extraction of glucose through the skin. Reverse iontophoresis with in situ glucose sensors has been used in GLUCO WATCHW BIOGRAPHER (Cygnus Inc .Redwoodcity.USA). This device allows non-invasive extraction glucose across the skin, allowing diabetics glycaemia to be evaluated every 10min.

Dentistry

To the beginning of the 19th century, dentist applied local an aesthetics prior to the oral surgical procedure. Gangarosa described the use of iontophoresis for three basic applications in dentistry: 1) Treatment of hypersensitive dentin using negatively charged fluoride ion. 2) Treatment of oral ulcers using negatively charged corticosteroids and antiviral drugs. 3) Application of local anaesthetics to produce profound topical anaesthesia.

Ophthalmology

Iontophoresis is preferred to deliver antibiotics into the eye. The main disadvantage of this technique is the time required for direct contact of electrode with the eye.[23, 24]

Diagnostic Applications

Iontophoretic application of the Pilocarpine produces intense sweating, allowing a sufficient amount of sweat to be collected and analyzed. This is now accepted as the primary test in the diagnosis of cystic fibrosis. Other drugs such as phenytoin, lithium, caffeine and theophylline are used for the diagnostic application.[25]

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