REVIEW ARTICLE

Iontophoresis for Transdermal Drug Delivery System: A Review on Advancements and Application in Drug Delivery System

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Abstract

In the early twentieth century, the physical medication delivery enhancement method known as iontophoresis was developed. For many years, iontophoresis research was restricted to a few therapeutic uses (such as the treatment of keratitis, psoriasis, and tympanic membrane disease) and concentrated on examining delivery-enhancing mechanisms. But in recent years, new target tissues and organs such as intestinal mucosa, suprachoroidal space, and nibbles have been added to the range of iontophoresis application. The most recent developments in iontophoresis technology with regard to therapeutic applications are included in this review in combinations with alternative methods of administration of medicine. The mechanism of action, different types of iontophoresis such as dermal, transdermal, its use in combination with nanocarriers and the factors affecting its efficacy were studied. To further improve medication delivery, the development of mathematical and computational simulations to forecast iontophoretic drug transport across various tissues has advanced significantly in tandem with this technical breakthrough. The benefits of iontophoresis have been assessed in an increasing number of situations over the past few years, utilizing medications, natural substances or active components used in cosmetics. Its low frequency of adverse effects and ease of coupling with other procedures offer the possibility of several future uses as well as improved cosmetic treatment outcomes.

Key words: Iontophoresis, psoriasis, sonophoresis, transdermal drug delivery

INTRODUCTION

Banga and Chien (1988) have provided a detailed account of the history of iontophoresis (IP), and the idea of using an electric current to promote skin penetration dates back to the 1700s. Among the first and most nonetheless, Ludec carried out well-recorded studies in this area at the start of the 20th century, showing the significance of polarity when he used direct current to give two rabbits strychnine and cyanide (Chien and Banga, 1989). Although IP was extensively studied in the 1930s and 1940s, its use has decreased in the years since. More recent research has concentrated on uses like local anesthesia (lidocaine with epinephrine), hyperhidrosis (tap water, atropine), and sweat testing for the diagnosis of cystic fibrosis (pilocarpine). Furthermore, IP has gained popularity as a technology studied mainly for its application in the systemic circulation of charged ions and macromolecules through the skin in recent decades. On a broad note, the transdermal delivery potential of a variety of medications, including propranolol hydrochloride, apomorphine, buspirone hydrochloride,insulin, thyrotropin-releasing hormone, nafarelin, and luteinizing hormone-releasing hormone (LHRH), has been studied using iontophoresis alone or in combination with other physical and chemical enhancement techniques.[1]

Numerous physical methods, such as IP, electroporation, sonophoresis, and microneedles, have been reported to

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improve the effectiveness of transdermal drug delivery. Among these technologies, we have concentrated on IP utilizing weak electric current (0.3–0.5 mA/cm^2), which provides a straightforward and non-invasive approach in contrast to other approaches because it does not require needles or other complex devices. IP has the potential to facilitate charged compounds' transdermal penetration into skin tissue.[2]

Basic principles and components of iontophoretic system

IP is based on the principle that "like charges repel," while "opposite charges attract." A set of electrodes is used to create these repulsive and attractive forces that provide the external energy to drive the ions through the skin, leading to the enhancement of drug permeation. Two principal system types, anodal and cathodal IP, have been developed based on these concepts. They both include a basic iontophoretic setup with an anode and cathode set of electrodes, drug and salt reservoirs, as well as a current source. Due to repulsion, positively charged ions can be delivered by positioning them beneath the positive electrode (anode). At the same time, an attractive force can be produced by positioning the negative electrode at a distant location on the skin. The body's negatively charged ions, mostly chloride (Cl), are moving in the direction of the anode at the same moment.[2,3]

Figure 1 shows a typical configuration of this system, which is known as anodal IP. The electrodes are switched in cathodal IP such that a medication with a negative charge is administered through the skin. The most widely used electrodes for iontophoretic systems, silver–silver chloride (Ag/AgCl) electrodes, are shown in Figure 1. 1Insoluble AgCl is created at the anode–solution interface by the reaction of Ag and Cl, and it is deposited at the electrode. To keep electroneutrality, either a cation exits this compartment and enters the skin, or the skin's anion is absorbed into this chamber. Likewise, in the cathodal compartment, a Cl ion is released into solution when AgCl is reduced to Agþ at the electrode, requiring the removal of an anion from the chamber or the absorption of a cation from the skin.[4]

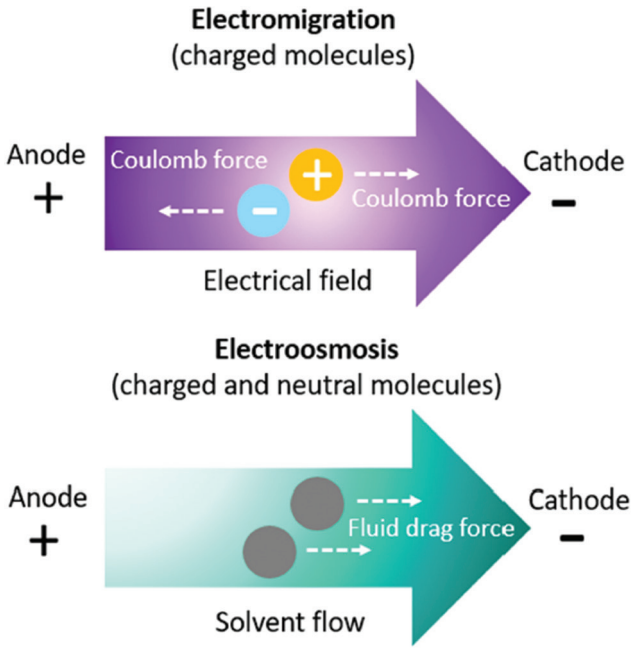

Figure 1: Mechanism of iontophoresis

MECHANISM OF ACTION OF IP

IP is the process of transporting both charged and neutral materials using low-intensity current, typically <0.5 mA/cm^2. Iontophoresis enhances the transport of drug molecules across the skin primarily through two mechanisms: electromigration and electro-osmosis. The foundation of electromigration is the idea that similar charges repel one another. When electromigration occurs, when charged molecules come into touch with an electrode of the same charge, they move under the influence of an electrical field. Therefore, cations are produced when an electrical current is supplied and are driven into the skin from the anode due to electrostatic repulsion, whereas anions are transported from the cathode by a similar repulsive force, thereby enhancing the transdermal permeation of charged drug molecules. A difference in electrical potential across a charged, porous membrane drives a bulk fluid flow in electro-osmosis, also known as solvent flow.[4] Water molecules are carried by the free counter-ions of the charged membrane as they migrate toward the oppositely charged electrode due to the electrical field. This causes a solvent to flow, which then moves both charged and neutral molecules in the same direction. The flow's direction is dependent on affects the biological membrane's charge. It happens in the direction of anode to cathode in the skin at physiological pH. When it comes to neutral and/or bigger water-soluble compounds, including peptides and small proteins, this mode of action is quite helpful. The drug molecules' net flow direction is determined by the respective strengths of electromigration and electro-osmosis.[5]

TYPES OF IP

Dermal and transdermal IP

There is growing interest in using the skin as a drug administration site for both systemic and local drug delivery. Drug administration through the skin is regarded as a secure and efficient method of treating localized skin conditions include acne, psoriasis, and skin cancer. Transdermal drug delivery is a non-invasive method of systemic drug administration that allows medications to be released

gradually and to avoid harmful gastrointestinal disorders. However, the skin, especially the stratum corneum, obstructs both dermal and transdermal drug delivery by preventing the diffusion of hydrophilic and macromolecular medications. Using IP to encourage medication penetration into or through the skin is one method of getting over this barrier. Current developments in dermal and the following are a detailed exploration of transdermal IP.[5]

Dermal IP for skin disease

Psoriasis

To treat psoriasis locally, methotrexate dermal IP has been extensively studied since the turn of the century. Numerous *in vivo* and *in vitro* investigations have been carried out to examine how the formulation and device parameters affect the degree of drug deposition in the tissues of the skin. IP has recently been the subject of clinical research for the treatment of psoriasis. The clinical efficacy and safety of methotrexate cutaneous IP for the treatment of palmoplantar psoriasis have been assessed in a pilot trial in comparison to topical coal tar ointment application.[6]

The electromigration process was the primary driver of methotrexate's cathode-to-anode flow. According to the study, the weekly cathodal IP of methotrexate was higher more efficient than putting coal tar ointment on every 2 days application of an ointment containing 0.05% clobetasol propionate. Along with the markedly increased efficacy, another advantage that enhances patient adherence is the decrease in dosage frequency. In addition, a phase one parallel prospective controlled study is being conducted to examine the efficacy of cutaneous IP with dexamethasone sodium phosphate for the local treatment of psoriasis. The trial, which is expected to be finished in 2021, is being carried out on 20 patients who have heavy plaque psoriasis lesions on their trunk and/or extremities. Based on the findings of these investigations, it is anticipated that advancements in the design of intelligent everyday gadgets will lead to significant advancements in the treatment of psoriasis.[6]

Alopecia

Follicle medication delivery has been demonstrated to be extremely important for the local therapy of several skin disorders. Even though hair follicles have a lesser surface area than the entire surface of the skin, since hair follicles have a significantly lower electrotransport resistance than the stratum corneum, they represent an important channel for iontophoretic drug transport. This fact has led to research into the local therapy of alopecia using IP -enhanced follicular drug delivery of certain medications, such as Adriamycin.[7]

Photodynamic therapy

One form of phototherapy called photodynamic therapy involves applying a photosensitizer medication to the skin, which, when activated by light energy, results in high quantities of reactive oxygen species that kill cells. Acne and skin cancer are two conditions that can be treated with photodynamic treatment. It has been studied that dermal IP of photosensitizing drugs, such as phthalocyanine and porphyrin derivatives, can increase their effectiveness by promoting their skin deposition. Iontophoretic dermal administration of aluminum-chloride phthalocyanine as a photosensitizing agent for photodynamic therapy of skin cancers has been studied recently by Reis *et al*. Aluminum-chloride phthalocyanine was complexed with hydroxypropyl-β-cyclodextrin to increase its solubility before topical administration. The *in vitro* permeation study's findings showed that IP for 6 h enhanced the complex's penetration by 2.3 times compared to passive diffusion for 12 h.[8]

Transdermal drug delivery for neurological disorder

Micro IP and transdermal IP are used in neuroscience to deliver drugs to the brain. First off, micro IP is a commonly used method for the local administration of pharmaceuticals to specific brain sites by ejecting a drug solution from a capillary while being influenced by an iontophoretic current. To do this, a number of investigations into the microiontophoretic injection of different substances into the brain have been carried out, with very encouraging results.[8]

Second, a promising method of drug administration for improving the systemic bioavailability of medications with low bioavailability is transdermal IP. In addition, transdermal by decreasing the frequency of normal drug administration – which is inappropriate for people with neurological conditions like Parkinson's and Alzheimer's – IP may increase patient adherence. Consequently, a lot of recent studies have looked into using transdermal IP to transport drugs to the brain.

Combined use of IP with nanocarriers

As a non-invasive method of improving the cutaneous and transdermal distribution of medications with restricted penetration capacities, such as high molecular weight, nanocarriers are becoming more and more significant medications and hydrophilic medications. Thus, a variety of nanocarrier systems have been investigated, including lipid nanoparticles, polymeric nanoparticles, liposomes, ethosomes, transferosomes, and others. However, numerous investigations showed that only the free drug molecules were able to pass through the layers of the skin; the nanoparticles themselves were only able to deposit onto the skin's surface, especially in the stratum corneum. Therefore, the accumulated nanoparticles on the skin serve as drug reservoirs that regulate the pace at which drugs are released into the skin. Thus, medication transport through the skin has been nearly improved by nanocarriers, but transdermal medication

delivery has not yet been accomplished.[9] The cutaneous and transdermal delivery of the nanocarriers has been improved by a variety of physical and chemical penetration augmentation techniques. To enhance the transdermal delivery of medications, iontophoresis nanocarriers have been thoroughly studied.

IP has generally been thoroughly studied to improve the dermal or transdermal transport of several nanocarriers, such as liposomes, transferosomes, gold nanoparticles, dendrimers, and lipid polymeric nanoparticles, as well as nanoparticles. The majority of published laboratory results and clinical outcomes have shown the important role IP plays in improving nanocarriers' penetration into the skin tissues, despite some reports suggesting that this approach does not improve drug delivery, which makes it controversial and dubious.[10]

FACTORS AFFECTING IP EFFICIENCY

Transcellular, paracellular, and transappendageal are the three main pathways through which passive skin penetration occurs. It is believed that iontophoretic transport mostly happens through the transappendageal (shunt channel) and paracellular pathways, with the main transport pathway being the appendageal pores (such as the sweat glands and hair follicles). Numerous methods, including vibrating probe electrodes and imaging techniques like transmission electron microscopy with mercuric chloride and laser confocal microscopy, have been used to determine the dominance of this transappendageal iontophoretic transport.[10] IP can also improve skin delivery through potential-dependent pore creation in the stratum corneum. Iontophoretic transport can increase a cation's relative molecular size by 100 times compared to passive diffusion. However, the effectiveness of iontophoretic transport is usually <100% due to a number of factors that affect the transport efficiency, namely the permeant characteristics, the vehicle and other formulation elements, the membrane, and system components.

APPLICATIONS OF IP

The administration of medications at therapeutically meaningful levels could be improved through transdermal iontophoretic systems. In addition, they allow the drug kinetics to be programmed or controlled through the device, and consequently, increase patient compliance. Due to these characteristics, the system can deliver a variety of compounds, including those macromolecules with little passive penetration. For a number of small molecules, such as apomorphine, sumatriptan, 5-fluorouracil, rotigotine, buspirone hydrochloride, sodium salicylate, hydrocortisone, lidocaine, and buprenorphine, it has been shown that IP and its combination with other methods can improve transdermal permeation.[11] Enhancing the delivery of macromolecules, including leuprolide acetate, insulin, vasopressin, parathyroid hormone, and peptides, has also sparked interest in iontophoretic drug delivery systems. These kinds of due to their low stability and absorption, molecules that are frequently polar and charged cannot be taken orally. Insulin has been thoroughly studied as a potential iontophoretic delivery agent, primarily in conjunction with chemical enhancer pretreatment or other enhancement methods. The majority of these investigations have resulted in a notable improvement in insulin flow and, frequently, the administration of the recommended dosage.[11,12]

EFFICACY AND SAFETY ISSUES

IP has limitations as a technique, even if it may improve material delivery when compared to traditional passive cutaneous approaches. The iontophoretic Many factors can influence the process, but they can be broadly divided into (a) operational factors, which include the formulation's composition (concentration, pH, ionic strength, and presence of competing ions), the permeant physicochemical properties (molecular size and weight, charge, and polarity), the experimental conditions (treatment duration, current type and density, electrode material, size, and polarity), and (b) biological factors, which include intra- and inter-subject variability, regional blood flow, skin condition, and skin pH.

These elements may have an impact on therapy safety in addition to effectiveness. The operation must be carried out in accordance with the visually acceptable standards to be successful and safe. Therefore, the equipment should be properly configured and treatment parameters, such as current intensity, duration of application, and electrode placement, should be optimized and maintained within established safety standards to ensure effective and safe iontophoretic drug delivery. IP should generally be used on skin that is not injured. The maximum applied current should not be >0.5 mA/cm^2 for safety reasons. For the specified period of time, the current should be applied gradually increasing from zero to the maximum and subsequently falling to zero at a comparable rate. When these conditions are satisfied, there is usually no discomfort or adverse effects other than modest cutaneous erythema, tingling, itching, local vasodilation, or light skin irritation.[13]

CURRENT AND FUTURE DEVELOPMENT

Pharmacological delivery advances are being driven by a number of causes, such as an aging patient population, biological pharmacological therapy for chronic illnesses, and a focus on patient self-monitoring and self-care. Without a doubt, in the coming decades, the skin will emerge as a key medication delivery system. The stratum corneum's formidable barrier has been successfully overcome by iontophoretic systems employing an electrically driven penetration augmentation mechanism, which has demonstrated promise as a way for delivering a variety of

substances, including macromolecules.[4] The bulk of the very small number of physically improved transdermal delivery systems that have been effectively created and marketed to date are iontophoretic drug delivery systems. When combined with other physical improvement techniques such as heat, lasers, blades, ion-exchange materials, chemical enhancers, ultrasound, electroporation, or microneedles, the following outcomes have been observed: much higher flux levels compared to passive transdermal delivery or only one technique. Electrically assisted delivery systems also offer the advantages of regulated drug delivery with changeable drug input rates and the capability to halt drug transport as necessary. However, the skin irritation caused by the combination of strategies may be cause for concern. Smaller substances like fentanyl, lidocaine, metoclopramide + hydrocortisone, cortisone, and vincristine have been the sole focus of most clinical studies conducted too far.[14]

CONCLUSION

One proven, non-invasive method is IP. Utilized to administer bioactive compounds locally or systemically, partially resolving the difficulties associated with cutaneous delivery caused by their partition coefficient and molecular weight. The field of dermato-cosmetics has also used IP in the local administration of active chemicals in an effort to enhance their penetration and activity on the targeted tissues, taking advantage of its many benefits.

The benefits of IP have been assessed in an increasing number of situations over the past few years, utilizing medications, natural substances, or active components used in cosmetics. Its low frequency of adverse effects and ease of coupling with other procedures offer the possibility of several future uses as well as improved cosmetic treatment outcomes.

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