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REVIEW ARTICLE

Influencing factors and drug application of iontophoresis in transdermal drug delivery: an overview of recent progress

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Abstract

Transdermal drug delivery is limited by the stratum corneum of skin, which blocks most molecules, and thus, only few molecules with specific physicochemical properties (molecular weight < 500 Da, adequate lipophilicity, and low melting point) are able to penetrate the skin. Recently, various technologies have been developed to overcome the strong barrier properties of stratum corneum. Iontophoresis technology, which uses a small current to improve drug permeation through skin, is one of the effective ways to circumvent the stratum corneum. This approach not only provides a more efficient, noninvasive, and patient-friendly method of drug delivery but also widens the scope of drugs for transdermal delivery. In this review, the mechanisms underlying iontophoresis and affecting factors are outlined. The focus will be on the latest advancements in iontophoretic transdermal drug delivery and application of iontophoresis with other enhancing technologies. The challenges of this technology for drug administration have also been highlighted, and some iontophoretic systems approved for clinical use are described.

Keywords Iontophoresis · Transdermal · Drug delivery · Electric current · Combination

Introduction

Human skin, the largest organ in the body, can be used for topical and systemic drug administration [1]. However, since skin serves as a natural barrier that protects the body from xenobiotics and hazardous substances, drug transdermal permeation is restrained [2]. The drug transdermal transport is mainly by diffusion through the stratum corneum (SC), viable epidermis, and dermis [3]. And SC, the outermost layer of skin, is the main barrier for drug permeation.

Drugs that are suitable for transdermal delivery fall in a narrow range. They are characterized by low molecular weight (< 500 Da) and high oil–water partition coefficients (log P, > 1.5) [4]. To date, about 17 active pharmaceutical ingredients have been formulated and approved by the Food and Drug Administration (FDA) as transdermal products, all of which are lipophilic drugs with small molecule [5, 6]. Recently, the market of biotechnology drugs is thriving, but most of them barely penetrate the skin because of large molecular weights. Therefore, transdermal delivery of macromolecular drugs is a big challenge. Several technologies have been developed to overcome the barrier of SC and promote skin permeability of drugs, including physical technologies such as sonophoresis, microneedles, and iontophoresis, as well as chemical technologies like penetration enhancers [1, 7].

Of all the technologies adopted to enhance drug transdermal permeation, iontophoresis not only provides ease application but also ensures the delivery of drugs in programmed and controlled manner [8]. Iontophoresis refers to the use of low-density electric current for transdermal drug delivery enhancement [9]. Based on the current flow pattern, iontophoresis can be classified into continuous direct current (CDC) and pulse depolarization current (PDP). CDC iontophoresis is the most common, but its use is sometimes restricted by irritation attributed to the skin polarization. PDP iontophoresis results in a depolarization process between high electric pulses. The depolarization process restores the electrical polarized state of the skin to its initial state and contributes to the elimination of skin irritation [10]. This review summarizes the recent advancements and challenges in the field of transdermal iontophoretic drug delivery.

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Transport mechanisms

Iontophoresis is a method of introducing ionized and neutral drugs into the skin by using electric current [11]. As shown in Fig. 1, during iontophoresis, electromigration and electroosmosis are the principal mechanisms of enhancing drug transport across the skin into systemic circulation [12]. Electromigration refers to the ordered movement of ionized drug molecules in the presence of the applied electric field [13]. Therefore, charged drugs are forced across the skin by electronic repulsion of similar charges. Cationic drugs can permeate through skin by using a positively charged working electrode. Similarly, anionic drugs can cross skin by negatively charged electrodes [8]. Electroosmosis is the fluid moving in a direction in the presence of electric field, forming an electroosmotic flow and driving the movement of hydrated ions [8]. At physiological pH, skin has a slight negative charge. Thus, electroosmotic flow occurs from anode to cathode [14]; that is, the force of introducing cation from the positive electrode includes "the force" generated by electroosmosis [15] in addition to the repulsive force from the electric field. When neutral particles pass through the skin, electroosmotic flow plays a dominant role [11].

In addition, the current induced effect causes a transient, reversible structural disorder in SC, which increases the skin permeability [16]. In vitro iontophoretic studies conducted by Arunkumar have shown an increase in skin permeability by enlarging pores in the skin barrier or creating new pores [17]. This suggests that the change of skin barrier function following iontophoresis is one of the mechanisms of enhancing skin permeability [18].

Factors influencing iontophoretic process

According to the Faraday's law, the iontophoretic flux of a drug molecule (J_{DRUG}) is the sum of the fluxes due to electromigration (J_{EM}), electroosmosis (J_{EO}), and passive delivery (J_p) [19, 20].

$$J_{DRUG} = J_{EM} + J_{EO} + J_p = (i_d * t_{DRUD})/(z_{DRUG} * F) + V_w * c_{DRUG} + k_{DRUG} * c_{DRUG}$$

where i_d is the applied current density and t_{DRUG} and z_{DRUG} are the transport number and charge of the drug, respectively. F is Faraday's constant, V_w is volume of the solvent flow, and c_{DRUG} and k_{DRUG} are the concentration and permeability coefficient of the drug, respectively [19].

From this equation, it would appear that iontophoretic flux should be mainly affected by applied current and drug concentration. Although the equation described above suggests the existence of a fairly straightforward correlation between the amount of drug in the formulation and the observed flux [13], the experimental results demonstrated that this was not the case for every drug. There was not necessarily a direct linear relationship between cumulative permeation amount and concentration for certain drugs, e.g., pramipexole [19], rasagiline [19], buprenorphine hydrochloride (BUP), and naltrexone hydrochloride (NTX) [21], but the experimental results demonstrated that their cumulative permeation amount increased with concentration. Niketkumar et al. also studied the effect of tacrine concentration in iontophoretic patch on pharmacokinetic profile of tacrine [22]. They analyzed the pharmacokinetic parameters, which suggested the concentration-dependent iontophoretic tacrine delivery at lower concentrations and the plateau in tacrine permeation flux at higher concentration.

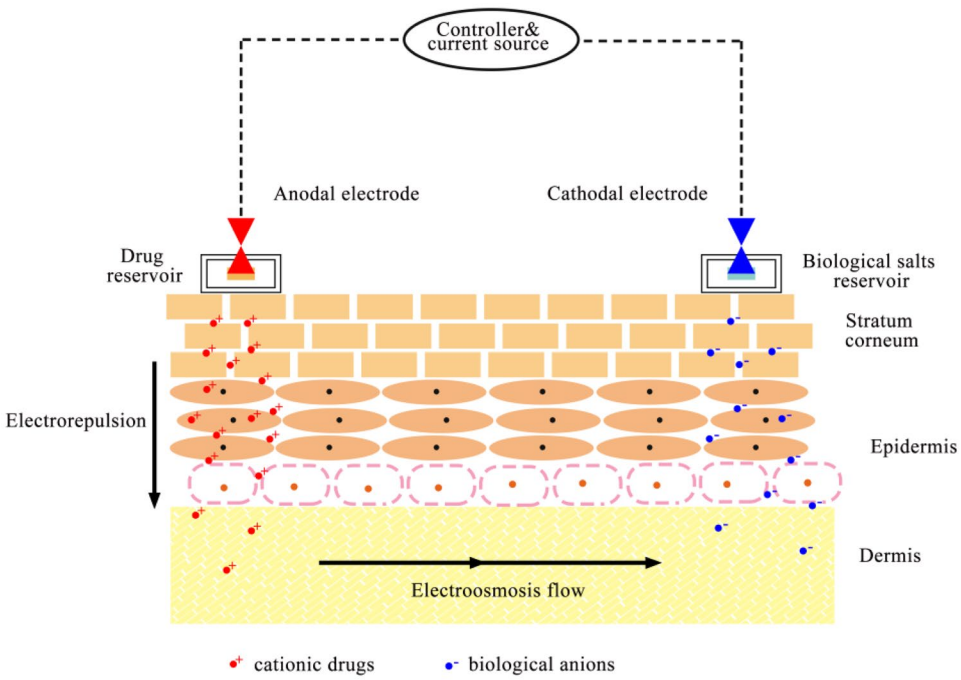

Fig. 1 A schematic diagram of iontophoretic technique: electrorepulsion involves the repulsion of the drug cations and the movements through the skin, while electroosmosis involves the movements towards cathode

Similarly, the effect of current density on iontophoretic flux is similar to drug concentration. Figure 2 shows the effect of current density on the iontophoretic delivery of certain drugs (midazolam [23], penbutolol sulfate [24], BUP, and NTX [21]), and these drug fluxes increased with current density. Although in each case the flux certainly increased, the rate of increase depended on the experimental conditions, formulation conditions, and the physicochemical properties of the molecules [8, 13, 15]. For example, although a significantly higher current density was applied for midazolam [23], the flux was much less than that observed for penbutolol sulfate [24].

The pH of the drug-containing solution is another important factor which can impact on iontophoretic transport. The main mechanism is that pH will affect the degree of ionization of the drug molecule. For weak acids, decreasing pH will reduce the ionized fraction of the molecule and lead to a decreased electromigratory contribution to iontophoretic transport [13]. For example, the iontophoretic flux of midazolam was 18 ± 3.2 nmol·h^{-1} at the pH 4.5 donor solution, which was significantly higher than that with the pH 3 donor (6.0 ± 3.0 nmol·h^{-1}) [23]. Iontophoretic transport of weak acid drugs decreased with decreasing pH. Other important factors affecting iontophoretic delivery including composition of receptor solution, polarity of electrodes, and presence of co-ions are summarized in Table 1 [8, 15, 25].

Iontophoretic device

An iontophoretic device consists of four parts: power source, control circuit, electrodes, and reservoirs. Power source can be connected to the skin through a control circuit and two electrodes—the anode and the cathode [26]. Two electrodes are attached to two reservoirs (one reservoir containing drug ions and the other containing physiologically compatible salts such as NaCl). Recently, Rac et al. found that polyvinyl alcohol (PVA) cryogel was perfectly suitable for a model hydrogel for iontophoretic scientific investigations [27]. The delivery of positively charged drug requires placing in anode compartment and negatively charged drugs in cathode compartment [28]. Generally, Ag/AgCl is selected as the electrode material in iontophoretic systems [12, 29].

In the following part, we present several marketed products based on iontophoresis technology. E-Trans manufactured by Alza, was a patch-sized iontophoretic device used to deliver fentanyl [8]. An electrotransport drug delivery system typically consists of a power supply connected to a pair of electrodes in contact with ionically conductive reservoirs that, in turn, are in contact with the skin. Since the rate of drug delivery is proportional to the applied electric current, electrotransport systems have the potential to provide precise dosing as well as patterned and on-demand delivery. Phoresor iontophoretic drug delivery system from Iomed is used to deliver iontocaine (lidocaine and epinephrine combination) for local dermal

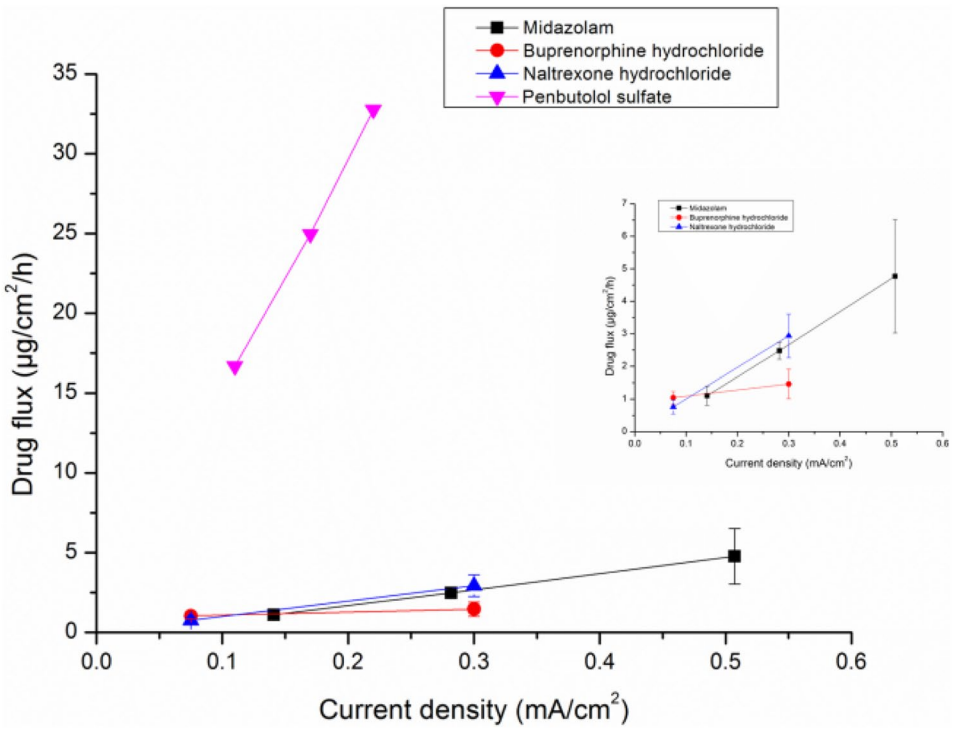

Fig. 2 Effect of current density on the iontophoretic delivery of drugs

Table 1 Factors affecting iontophoretic delivery system

Operational factors			Biological factors
Composition of formulation	Physicochemical properties of drug	Experimental conditions	
Concentration of drug solution	Molecular size	Current density	Intra- and inter-subject variability
pH of donor solution	Charge	Current profile	Regional blood flow
Ionic strength	Polarity	Duration of treatment	Skin pH
Presence of co-ions	Molecular weight	Electrode material	Condition of skin
	Salt form	Polarity of electrodes	Patient anatomical factors
		Composition of receptor solution	
		Temperature of acceptor phase	

anesthesia [8, 9]. Wearable electronic disposable drug delivery (WEDD) developed by BirchPoint Medical Inc. is a portable, disposable patch having a thin, flexible battery having capability to supply variable voltages for versatility in drug delivery and expands the range of drugs which can be delivered by iontophoresis [30].

In anodal iontophoresis of laboratory studies (Fig. 3), the anode electrode is placed in the donor compartment, containing the drug solution or colloid. Another electrode is placed in the receptor compartment filling with buffer, and a small current is applied to delivering the drug through the skin. Usually, a modified Franz diffusion system was used in in vitro experiments, and the glass diffusion cells have additional ports for iontophoresis electrodes [10].

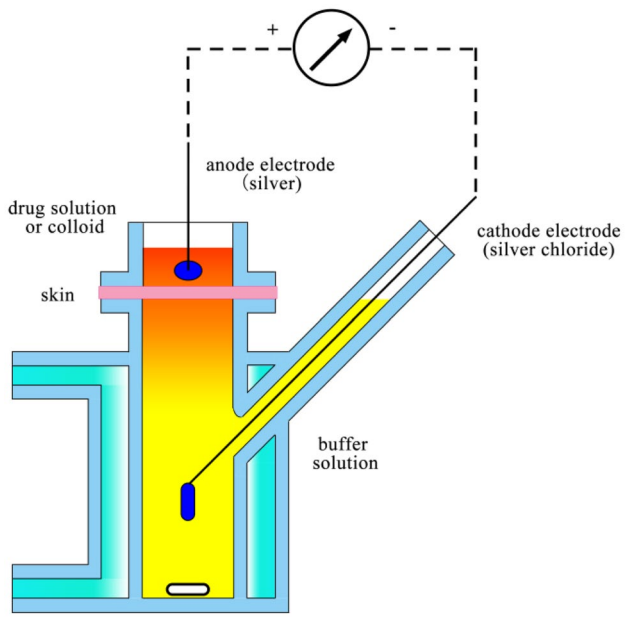

Fig. 3 Experimental setup of anodal iontophoresis with a Franz cell

Application for drug delivery

Small molecules

Transdermal drug delivery offers many advantages, including convenience, painlessness, non-invasiveness, increase in bioavailability, improvement in patient compliance, and avoidance of gastric irritation [31]. However, most drugs cannot penetrate across skin to achieve adequate and therapeutically relevant serum levels due to the limitation of SC. Recent reports have suggested that transdermal iontophoresis may be a promising approach for promoting transdermal drug delivery [9]. The small molecule drugs used in recent years to investigate iontophoretic delivery are shown in Table 2.

Cordery et al. studied the influence of iontophoresis on percutaneous penetration of BUP and NTX [21]. They found that the application of iontophoresis dramatically increased the flux of both drugs compared with passive delivery. The flux of BUP was facilitated from 0.04 ± 0.04 μg/cm^2/h for passive delivery to 25 ± 3 μg/cm^2/h for iontophoresis delivery, and the flux of NTX was also increased 43-fold. Singhal et al. found that drug concentration in formulation and current density could linearly influence drug delivery and steady-state iontophoretic flux [42]. This indicated that modulation of current density and concentration could be used to control drug input rates.

It is known that the partition coefficient is the crucial factor that influences the passive diffusion of small molecule drugs transdermal delivery. Zuo et al. investigated the relationship between iontophoretic delivery efficiency and the physicochemical properties of drugs and explored the enhancement mechanisms of iontophoresis [39]. In the study, aspirin, ibuprofen, and indomethacin were selected as model drugs. They found that dissociation extent was the key factor to determine the enhancement effect of iontophoresis; that is, the higher drugs dissociated, the stronger the iontophoretic enhancement effect was. In this

Table 2 List of small molecule drugs investigated recently for iontophoretic delivery drug

Drugs	Animals/membrane model	Types of iontophoresis	Possible therapeutic indication	References
Tacrine hydrochloride	SD rat skin	Anodal	Dementia of Alzheimer's disease	Patel et al. [22]
Pramipexole and rasagiline	Porcine ear skin	Anodal	Parkinson's disease	Kalaria et al. [19]
Memantine	The porcine skin	Anodal	Alzheimer's disease	Del Río-Sancho et al. [32]
Pizotifen malate	Pig ear skin	Anodal	Antimigraine	Serna-Jiménez et al. [33]
Propranolol	The porcine skin	Anodal	Hypertension	Calatayud-Pascual et al. [34]
3-fluoroamphetamine hydrochloride	Human cadaver skin	Anodal	Substitute-agonist therapies	Puri et al. [35]
Diclofenac potassium	Porcine ear skin	Cathodal	Musculoskeletal disorders	Arunkumar et al. [36]
Polidocanol	Albino rat skin	Anodal	Varicose veins	Murari et al. [37]
Methotrexate	Human cadaver skin	Anodal/cathodal	Psoriasis and rheumatoid arthritis	Nguyen et al. [38]
Aspirin, ibuprofen and indomethacin	SD rat skin	/	Anti-inflammatory	Zuo et al. [39]
Piroxicam	Wistar rat skin	/	Anti-inflammatory	Kazemi et al. [40]
Oxaprozin	The mouse skin	/	Anti-inflammatory	Liu et al. [41]

study, iontophoresis significantly increased drug permeation by disrupting intercellular lipid sequence, increasing fluidity, and loosening the SC structure.

Methotrexate is a folic acid antagonist with a negative charge at physiological pH (pH 7.4) [43]. Generally, cathodal iontophoresis is used for its delivery according to electrorepulsion principle. Nguyen et al. investigated the transdermal iontophoretic transport of methotrexate by employing cathodal iontophoresis and anodal iontophoresis [38]. They found that the amount of methotrexate delivered by anode iontophoresis was significantly higher than that of cathode iontophoresis. Anode iontophorotic delivery was mainly dominated by electroosmosis. The result indicated that anodal iontophoresis provided a stronger driving force for methotrexate delivery than cathodal iontophoresis.

Conventionally, pig skin and rat skin are used to substitute human skin for in vitro study, since they are readily obtainable or have similar histological and biochemical properties to human skin [44, 45]. It was reported that drug permeability varied in different skins, but iontophoresis has been proved to reduce interspecies differences [46]. The roles of different permeation membranes in transdermal iontophoretic delivery of tacrine hydrochloride were investigated by Patel [22] et al. In their study, artificial membrane, in vitro abdominal skin of SD rat and hairless rat, and frozen pig skin were selected as permeation membranes. They investigated the permeation performance of tacrine hydrochloride across different permeable membranes at constant current of 0.1, 0.2, and 0.3 mA. The highest iontophoretic tacrine permeation was observed across artificial membrane, because artificial membrane had no additional resistance to the penetration of tacrine ions compared with animal skin. Under low level of current application (0.1 and 0.2 mA, respectively), the permeation of tacrine depended on the thickness of skin membrane and some properties such as hair follicle strength. Similar iontophoretic delivery amounts were observed under the current application of 0.3 mA, which could be attributed to the disruption of skin structure in all types of skin. That is, the skin played a less prominent role in controlling iontophoretic tacrine permeation under higher current strength application. More significantly, the results indicated that iontophoresis technology could considerably reduce the interspecies differences in transdermal drug delivery.

In the laboratory, drugs are normally formulated into solutions or gels for the study of iontophoretic transdermal drug delivery. Actually, patches are the most common used transdermal drug delivery systems [47]. Talbi et al. designed a controllable transdermal patch for lidocaine delivery and investigated lidocaine permeation amounts at different current density through in vitro experiments by iontophoresis [48]. They found that iontophoretic transport is proportional to current density, which could potentially be used to precisely control drug delivered amounts based on current intensity and duration of treatment. Murari et al. also developed a novel sol-gel patch based iontophoretic drug delivery system for the treatment of varicose veins [37]. They observed that the sol-gel patch could control the release of polidocanol through solvent-filled capillary channels and allowed polidocanol to penetrate through skin under the influence of iontophoretic current.

Combination therapy is a method of treating diseases with two or more drugs to achieve efficacy, gain additive, or synergistic effects and reduce side effects [49], etc. Recently, the combination strategy has attracted lots of

attentions in the field of iontophoresis. Cordery et al. designed an iontophoretic drug delivery system for the co-delivery of NTX and BUP through the skin [21]. They found that the target therapeutic fluxes of both drugs could be achieved by rational controlling experimental conditions. During iontophoresis, BUP and NTX at the same electrode inhibited each other's flux, BUP affected the flux of NTX by suppressing the flow of EO, while NTX altered the flux of BUP by co-ion competition. Kalaria et al. investigated anodal co-iontophoresis of pramipexole and rasagiline [19]. For co-iontophoresis on the same electrode, competitions between the two ions were inevitable and the relative content of two drugs needed to be selected to achieve therapeutic concentration. PRAM had almost four times the dose requirements of RAS. They found that the permeation amounts of PRAM was 3.6-fold greater than RAS when the concentration of PRAM/RAS was 3:1 in the formulation and the permeation amounts of both drugs increased with the applied current density and drugs concentrations. Therefore, iontophoresis could be a very efficient technique in delivering two drug ions with different input kinetics. Cazares-Delgadillo et al. studied the co-iontophoretic delivery of granisetron (GST), metoclopramide (MCL) and dexamethasone sodium phosphate (DEX-P), i.e., simultaneous transdermal delivery of the three antiemetics [50]. The study was performed combining anodal iontophoresis of GST and MCL with cathodal iontophoresis of DEX-P. Similar results of anodal co-iontophoresis were obtained. Besides, the results demonstrated that iontophoresis could be used for providing controlled transdermal poly-pharmacotherapy.

Enhancing transdermal permeation of highly lipophilic compounds by using iontophoresis is a challenge due to poor water solubility and lack of charge, which prevents their absorption into deeper skin layers [51]. Hegde et al. investigated the skin delivery of ketoprofen covalently connected with mildly cationic (2^+ or 4^+) peptide dendrimers [52]. In their study, glycine, arginine, and lysine were chosen to form the peptide dendrimer with ketoprofen since arginine and lysine have ionizable groups, making it easier to perform iontophoresis. They prepared several peptide dendrimer-drug conjugates and evaluated their passive diffusion and iontophoretic permeation across the mouse skin. Compared with ketoprofen, all dendrimeric conjugates of ketoprofen showed improved aqueous solubility and appreciable lipophilicity. They found that in passive diffusion study, dendrimer-conjugated ketoprofen was delivered to a less extent compared with the native form. However, iontophoresis significantly increased transdermal permeation amount from 96.60 ± 5.12 μg/cm^2 for ketoprofen to 711.49 ± 39.14 μg/cm^2 for dendrimeric ketoprofen. Moreover, it was revealed that therapeutic concentrations of ketoprofen could be achieved employing transdermal iontophoresis in vivo studies. Reis et al. studied the transdermal iontophoretic delivery of aluminum-chloride phthalocyanine by complexing it with cyclodextrin [53]. Aluminum-chloride phthalocyanine was complexed with hydroxypropyl-β-cyclodextrin (HP-β-CD), a β-cyclodextrin derivative carrying higher aqueous solubility to increase its loading dose in aqueous medium. Although HP-β-CD is a non-ionizable compound, iontophoresis could improve 2.3-fold aluminum chloride phthalocyanine penetration into skin compared with passive penetration, and the complex penetration mainly benefited from the electroosmotic flow.

In addition to transdermal drug delivery system, iontophoresis is also applied to cosmetics in order to promote the entry of cosmetic ingredients into skin. Redox nanoparticles (RNPs) containing nitroxide radicals were designed as free radical scavengers by Shiota et al. to protect against UV-induced melanin production [54]. They found that RNPs displayed negligible skin permeation by passive diffusion due to its large molecule weight, and RNP accumulated in epidermal layer by iontophoresis. Moreover, UV-induced melanin content in the skin was decreased by combining RNPs with anodal iontophoresis. According to Park et al. a device was designed to perform both sonophoresis and iontophoresis simultaneously, and by using this, glutamic acid could be effectively delivered into skin as model cosmeceutical drug [55]. The device could reduce ultrasound frequency and current density, thus reducing skin irritation and increasing safety, which could be used for self-management in cosmetic field.

Recently, iontophoresis has also attracted the attention of pediatric formulation researchers. Djabri et al. studied cathodal iontophoretic delivery of phenobarbital [18]. They used pig skin as an in vitro model of premature neonatal skin at different levels of maturation, in which the SC was differentially tape-stripped. They found that phenobarbital transport was inversely related to co-ion competition but linearly proportional to the mole fraction of the drug in the carrier. The optimized phenobarbital delivery could be achieved by minimizing the co-ion competition present in formulation. The results showed that therapeutic pediatric doses of phenobarbital could be achieved by iontophoresis, which was able to control drug transport across intact or partially compromised skin. Meanwhile, they investigated the feasibility of delivering midazolam for pediatric treatment by transdermal iontophoresis [23]. It was concluded that a therapeutically relevant dose of midazolam could be delivered transdermally by using an iontophoretic device.

Macromolecules

In recent years, biopharmaceutical technology has achieved rapid development. However, the most effective administration method for biotechnology drugs continues to be injection, which is associated with poor patients compliance [56]. Iontophoresis provides a non-invasive means of systemic drug administration. The technology has been exploited for transdermal delivery of proteins, peptides, and oligonucleotides, all of which are hardly to permeate due to high molecular weight, charge, and hydrophilicity [8]. Lysine-Proline-Valine (KPV) is a C-terminal peptide fragment of α-melanocyte-stimulating hormone with anti-inflammatory activity [57]. Pawar et al. used anodal iontophoresis to enhance transdermal delivery of KPV in Tris buffer [57]. The results showed that in vitro KPV passive permeation was below detectable levels (0.01 μg/mL). However, KPV permeation increased to 35.2 μg/cm^2/h by iontophoresis treatment and the skin retention level of KPV by iontophoresis increased tenfold as compared with passive delivery. They also examined the contribution of different parameter-current intensity, KPV concentration, and duration of current application. With the increase of current density and KPV concentration, iontophoretic transport of KPV was increased. The skin permeation of KPV increased during iontophoresis application, and it was proportional to the time lengths applied. It was demonstrated that the delivery could be controlled by altering the current density and duration of application.

Reverse electrodialysis (RED) technology generates energy from the salinity gradient by contacting waters with different salinity and then produces current by modification [58]. Lee et al. designed a disposable iontophoretic patch using RED system for fluorescein isothiocyanate labeled poly-L-lysine (FITC-PLL) transdermal delivery [59]. They compared the transdermal efficiency of passive diffusion and RED system. The RED system increased the FITC-PLL permeation about 6.7 times more than the passive diffusion. The modified RED system consisting of fabric, salt, and ion exchange membranes was cheap, eco-friendly, and disposable, which could be available for iontophoretic patch. Kim et al. investigated RED system in topical delivery of fluorescein isothiocyanate-hyaluronic acid (FITC-HA), and they found that RED system significantly enhanced the efficiency of topical HA delivery and increased the skin absorption depth [60].

Noh et al. pretreated rat skin with microneedles so as to alter the skin property and then iontophoresis was applied to the pretreated area to further increase skin permeability [61]. Human Growth Hormone (hGH) was chosen as model molecule since it has a molecular weight of approximately 22 kDa. Since hGH is positively charged below its isoelectric point (5.72) and negatively charged above it, they investigated the effects of cathodal iontophoresis and anodal iontophoresis for hGH permeation. The results showed that the steady-state flux was approximately 10 times higher in anodal iontophoresis than that in cathodal iontophoresis. The cumulative permeated amounts of hGH increased 6.73-fold with the combination of microneedle treatment and iontophoresis than with microneedle treatment alone.

In the study of Hashim et al. pulse depolarization iontophoresis was applied to deliver nuclear factor-κB (NF-κB) decoy oligonucleotides (ODN) in the treatment of atopic dermatitis [62]. The decoy strategy used in this study was considered as a useful anti-gene method. The authors found that the skin permeation flux was controllable by varying drug concentration or current density. In in vivo studies, it was revealed that the protein and mRNA expression levels of tumor necrosis factor-α in the ear of the skin inflammation model mice were significantly reduced by iontophoretic delivery of NF-κB decoy ODN. However, ODN molecules accumulated at epidermis and upper dermis and could not penetrate into deep skin. The electrorepulsion in cathodal iontophoresis might be the only driving force for ODN delivery, since the skin was negatively charged and cation selective at physiological pH. Considering the limited transfer of macromolecule and negatively charged molecules across intact skin, combination with microneedles or other approaches might be necessary to achieve transdermal delivery of ODNs [63, 64].

Combination application with other enhancing technologies

There are considerable reports mentioning the combination of iontophoresis with other penetration enhancement techniques such as sonophoresis, chemical penetration enhancers, or microneedle techniques [25]. An easier and more precise delivery of macromolecules and poorly water soluble compounds would be provided by combining iontophoresis with the above techniques compared with iontophoresis alone [25].

Iontophoresis in conjunction with sonophoresis

Sonophoresis refers to the use of low frequency ultrasound for enhancing transdermal drug delivery, and the main mechanism is the disruption of skin barrier properties by ultrasound cavitation [3]. After the disruption of SC lipid bilayer by sonophoresis, transdermal drug delivery can be further increased by iontophoresis.

Tokumoto et al. used iontophoresis combined with low frequency ultrasound to enhance transdermal delivery of mannitol across mouse skin [65]. In this study, the skin was pretreated with low frequency ultrasound (20 kHz, 1.1 W/cm^2),

then 0.4 mA/cm^2 direct current was applied for 4 h. The result indicated that the penetration of mannitol increased apparently compared with iontophoresis alone. Since mannitol was a non-electrolyte drug with no electrorepulsion effect, the iontophoretic delivery of mannitol was mainly dominated by electroosmotic flow. After the application of sonophoresis, the skin surface charge became much more negative, which suggested that the electroosmotic flow was markedly increased by sonophoresis treatment. According to Liu et al. the combination of iontophoresis and sonophoresis showed a synergistic effect, which could improve oxaprozin transdermal permeation [41]. Unlike the above studies in which sonophoresis was applied first followed by iontophoresis, Park et al. designed a device which could perform both iontophoresis and sonophoresis simultaneously to promote drug transdermal delivery, and found that this device could significantly improve drug transdermal permeation [55].

Iontophoresis in conjunction with penetration enhancers

The use of chemical penetration enhancers is one of the most widely studied methods for promoting transdermal drug delivery. It is reported that many enhancers are able to enhance transdermal drug permeation, but only a few have been used in marketed products, limited by theirs toxicity [25]. Higher transdermal drug permeation can be achieved by the combination of chemical penetration enhancer and iontophoresis. At the same time, the combination of the two technologies should also produce a synergistic effect, which can reduce side effects and irritation generated by high concentration of chemical penetration enhancers and current density [25].

Arunkumar et al. investigated three terpene penetration enhances (geraniol, l-menthol and thymol) combined with constant voltage iontophoresis to deliver diclofenac potassium across porcine skin [36]. All three penetration enhancers could significantly promote the permeation efficiency of diclofenac, but only geraniol and l-menthol formulations were found to display high skin deposition. In vivo studies indicated that a therapeutic amount of diclofenac potassium could be transdermally delivered by the combination of iontophoresis with enhancers like geraniol or l-menthol. Moreover, diclofenac sodium was also studied by the authors [17]. Diclofenac sodium hydrogels were formulated with hydroxyethyl cellulose (HEC) as a viscosity imparting agent. The hydrogel matrix would not affect the iontophoretic delivery compared with the aqueous solution, and a comparable level of transdermal permeation could be achieved [66]. The combination strategy could improve transdermal delivery efficiency, which might be able to reduce the size of the patch and enable deliver the drug in a milder and more patient compliant administration manner [36].

A study was conducted by Liu et al. to investigate the effect of the combination of limonene/ethanol and iontophoresis on the permeation of antisense oligodeoxynucleotides through pig ear skin [67]. In their study, sodium fluorescein, an anionic and hydrophilic model drug, was used to investigate the efficiency of different chemical penetration enhancers. It was found that limonene/ethanol showed the highest enhancing effect, and it was used to evaluate the synergistic effect with the combination of cathodal iontophoresis. The results demonstrated that the synergistic effect increased intradermal delivery of oligonucleotides. Regrettably, the permeation across the entire skin was not achieved. Therefore, further combination approaches, such as microneedle-mediated technology in combination with cathodal iontophoresis, might be required to achieve complete permeation across the entire skin.

Iontophoresis in conjunction with microneedles

Microneedles technology is one of the most widely reported physical methods of delivering macromolecules [68]. Microneedles fitted with arrays of microscale needles are able to transport macromolecules and hydrophilic molecules across the epidermis by physical mediated skin microchannels [61]. The combination of microneedles and iontophoresis further enhances diffusion of hydrophilic or charged macromolecules. Iontophoresis utilizing electrorepulsion and electroosmosis can facilitate drug molecules transport through the low electrical resistant channels created by microneedles [69].

Noh et al. designed a Tappy Tok Tok and iontophoresis combined transdermal delivery system for delivering recombinant hGH [61]. The Tappy Tok Tok® array had 20 microneedles on its surface with a 750-μm needle. In this study, the skin was pretreated with the microneedle device for 1 min, and then a constant current of 0.5 mA/cm^2 was applied for 4 h. The results demonstrated that the combination of microneedle and iontophoresis showed synergetic effects, and the enhancement effect was much greater than the method used alone. Considering that combination strategy could obtained a high permeation-enhancing effect and overcame the limitations of iontophoresis that could not disrupt the skin barrier, the combination of iontophoresis and microneedles was a potential strategy for transdermal delivery of macromolecules. Ronnander et al. investigated the combination of dissolving microneedle arrays and iontophoresis for delivering sumatriptan [69]. Dissolving microneedles and iontophoresis combined system was made by assembling the PVP-based dissolving microneedle arrays containing sumatriptan succinate and the iontophoretic electrode. It was found that the dissolving microneedle system aided by iontophoresis was a potential method for the delivery of sumatriptan.

Table 3 Clinical trials based on iontophoresis

Study	Result	Reference
Hospital cases: Assessed tap water iontophoresis in the treatment of hyperhidrosis in a pediatric cohort	A safe and effective method with minimal side effects	Reference [72, 73]
A proof-of-concept study: Compared the use of wearable sensor to the conventional sweat test following sweat induction by pilocarpine iontophoresis	The wearable sensor can provide real-time measurements of sweat chloride with excellent agreement to conventional laboratory testing	Reference [74]
Phase I Clinical Trial: Compared iontophoretic transdermal administration of neostigmine/glycopyrrolate to intravenous administration	Transdermal administration by iontophoresis can induce bowel evacuation safely and effectively in patients with spinal cord injury	Reference [75]
A double-blind study: Tested treprostinil iontophoresis on the finger pad of patients with systemic sclerosis during hand cooling	Treprostinil iontophoresis can improve skin blood flow	Reference [76]
A non-blinded study: Compared the efficacy of topical delivery of methotrexate by iontophoresis to clobetaso propionate 0.05% ointment	Methotrexate iontophoretic is as effective as clobetasol propionate ointment in the treatment of palmar psoriasis	Reference [77]

Clinical use

While a number of researches have been conducted and significant progresses have been made in clinical trials of iontophoresis, only three products (Ionsys®, LidoSite®, and Zecuity®) have been approved by FDA [10]. In Ionsys®, fentanyl was used for post-operative pain. LidoSite®, an iontophoretic drug device, was used to rapidly deliver lidocaine for local anesthesia. Zecuity® containing sumatriptan was used for the management of migraine [10]. In addition, iontophoresis with tap water has been used to treat hyperhidrosis [70], and iontophoretic application of pilocarpine can induce intense sweating, which is available for the diagnosis of cystic fibrosis [71]. Clinical trials involving the use of iontophoresis for the delivery of treprostinil, methotrexate, and neostigmine/glycopyrrolate have also been reported (Table 3). Meanwhile, reverse iontophoresis, which is used for the extraction of a molecule from the body rather than its delivery into the body, has been widely applied in devices for diagnostic application and has shown tremendous potential in glucose monitoring. Glucowatch® is a device that provides a needle-free means of monitoring blood glucose levels in diabetic patients [30].

Challenges

One of the major challenges regarding transdermal iontophoresis is developing low cost and stable devices that can provide efficient transdermal drug delivery. But so far only three iontophoretic products have been approved by FDA, and only Zecuity ® is currently available for purchase because the other two have been withdrawn from the market [6].

Another concern is the safety of transdermal iontophoresis. In iontophoretic delivery, the rate of drug delivery scales with the electric current [78]. However, the potential risk of skin irritation and pain is proportional to current intensity. Therefore, skin irritation remains to be a major problem that needs to be solved. Under low current density, iontophoresis does not disrupt the skin structure that may cause skin damage [79], but the maximum delivery rate is limited [70]. In addition, only molecules approximately 13 kDa molecular weight can permeate through intact skin by iontophoresis [61]. Recently, the number of biotechnology products has a huge increase. In most cases, these compounds possess high molecular weight. Therefore, the contradiction between drug delivery rate and safety needs to be balanced.

The isoelectric point of skin is between 4 and 5 [80], which means that the skin is negatively charged at the physiological condition, and is more selective to cations. Therefore, the transdermal delivery of negative charged drugs such as insulin and hyaluronic acid [60] is limited under physiological conditions. Moreover, only potent molecules can be delivered transdermally to achieve therapeutic levels by iontophoretic transport; for instance, insulin is deliverable ®iontophoretically, but the daily requirements of diabetics cannot be met [81]. The efficiency of iontophoretic transport has to be improved for above group of compounds by combining other technologies.

Conclusion

In recent years, although significant progress in iontophoresis has been recorded and important breakthroughs have been made in the clinic field, there are still some challenges, such as the transdermal delivery of low potent efficiency drugs and biological drugs. Combination of iontophoresis with sonophoresis, chemical enhancers, and microneedles has

been utilized by scientists to solve the limitation. Overall, with more thorough understanding and in-depth research of iontophoresis, more transdermal iontophoretic products will be developed for the benefit of patients.

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