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A novel method to enhance the efficiency of drug transdermal iontophoresis delivery by using complexes of drug and ion-exchange fibers

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ABSTRACT

The main reason for generally low efficiency of the transdermal iontophoretic drug delivery is that the fraction of the total current contributed by the drug ions is very small. The objective of this study was to find a method to increase the fraction of the total current contributed by the drug ions so as to enhance the drug's iontophoretic delivery. Iontophoretic transport of diclofenac solution and diclofenac assisted by ion exchange materials, including ion-exchange resin, ion-exchange membrane and ion-exchange fiber, across the rat skin were investigated. Both in vitro and in vivo iontophoretic transport experiments showed the amount of diclofenac permeated across rat skin from the diclofenac-fibers was highest among those from the diclofenac simple solutions and ion exchange materials complexes. The results of this study suggested that there is an enhancement of drug across rat skin by ion-exchange fibers in ion-exchange fibers assisted iontophoresis. The present study has demonstrated the potential of a new approach using ion-exchange fibers to enhance transdermal iontophoretic transport of an ionizable drug.

1. Introduction

Iontophoresis therapy is a widely used technology in the drug delivery system (DDS) in which ionic or non-ionic drugs are imported in vivo by electric force (Banga, 1998; Kasting, 1992). Iontophoresis devices typically consist of the following components: power supply devices and two electrodes – one is the donor electrode and the other is the receptor electrode. The donor electrode usually has the same polarity as the charge of the permeating drugs. In the process of iontophoresis, the drugs are imported into the body while the other ions in the system also migrate. Ions with the same electrical charge as the drug ions will go the same direction as the drug ions while those with different electrical charges will go the opposite direction. Thus, the total current generated in the electric field is determined by the directional movement of all ions, including drug ions, other ions in the prescription and in vivo endogenous ions (Phipps and Gyory, 1992).

In the iontophoresis therapy the drug ions often have a low efficiency of importation due to their larger volume, weaker electrical charges and slower migration compared with other small ions in the whole system. Hence, the drug's iontophoresis efficiency can be improved in two ways: one is to reduce the existence of ions other than drug ions, and the other is to inhibit the migration rate of these ions. To improve the ionic drug's iontophoresis efficiency, some researchers have purposefully tried to use ion-exchange materials in the process of iontophoresis, such as ion-exchange membrane. When ion exchange membranes were used in transscleral iontophoresis, a two- to three-fold flux enhancement of the permeation was observed (Li et al., 2006; Molokhia et al., 2008). Another report evaluated the ability of anion exchange membranes to enhance transdermal iontophoretic transport of a model permeant salicylate and an antiviralagent acyclovir (Xu et al., 2009). These enhancements of the iontophoretic drug delivery would lead to a lower applied electric current or shorter iontophoresis application times when the delivery of the same amount of drug was carried out (Li et al., 2006).

Although using ion exchange membranes has been proven to be effective in enhancing transdermal iontophoresis, it is still inadequate. We know that ionic drugs usually contain metal ions or acid radical ions, and these small ions' conductivity is much stronger than the drug ions', so their presence will reduce the efficiency of the iontophoresis. In the use of ion exchange membrane assisted iontophoresis, the drug solution contains a large number of acid radical ions or metal ions. If we could remove these small ions we would more effectively enhance the efficiency of the iontophoresis. To rule out these small ions we could bind drug ions in the ion-exchange materials by ionic bond. Consequently the delivery system would contain only drug ions and ion exchange material composites, and no acid radical ions or metal ions. To this end we

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need one kind of ion-exchange material which has a large surface area and a high ion exchange capacity. Ion-exchange fiber fits these requirements.

Given that the ion-exchange fiber's specific surface area is much larger than the ion-exchange resin's and the ion-exchange membrane's, the ion-exchange fiber's exchange capacity will be the largest. Thus, the ion-exchange fiber is more suitable to be used as a carrier of an ionic drug than other ion-exchange materials. Another point which cannot be neglected is that the ion-exchange membrane's small pore size will reduce the passage of drugs. To compensate for this we propose using ion-exchange fibers as ionic drug carriers in an iontophoresis system. Charged drugs are bound onto the ion exchange groups of the fibers, which provides a promising way to achieve controlled drug release and also enhance the stability of drug (Kankkunen et al., 2002a,b; Yu et al., 2006). With the greater permeability and the removal of small ions' interference, this ion exchange fibers assisted iontophoresis whether can improve the efficiency of the iontophoresis to a greater extent will be confirmed in our experiments.

In ion-exchange fibers assisted iontophoresis the ion exchange fibers are used as drug carriers. From the existing literatures we can see that it is not clear whether this technique would be effective in transdermal iontophoretic delivery by using ion exchange fibers as drug carrier materials. Furthermore, in the previous studies, the ion exchange membrane was not used as a material to carry drugs, so in this study we also want to know whether ion exchange fibers can be used as a material to carry drugs and then to enhance the efficiency of transdermal iontophoresis. Transference number is commonly used in assessing the efficiency of iontophoretic drug delivery (Phipps and Gyory, 1992). Therefore, we introduce this concept of transference number in this article. Transference number is the ratio of current carried by the ionized drug to the total current transported across the skin (Kasting, 1992; Phipps and Gyory, 1992; Banga, 1998).

Diclofenac sodium (diclofenac) is an anti-inflammatory agent. In clinical therapy it is often used in percutaneous absorption to get goals of treatment systemically or locally. The main route for the transdermal penetration of diclofenac sodium is the pore pathway in the skin (Maitani et al., 1996). However, the penetration of diclofenac sodium through skin is poor (Nishihata et al., 1987). In order to increase the penetration of diclofenac sodium through skin, people have tried many methods including iontophoretic technique. Based on the literatures, the permeation of ionic drugs such as diclofenac can be facilitated by the application of iontophoretic technique via the shunt route (Tyle, 1986; Varghese and Khar, 1996); nevertheless, iontophoretic transport of diclofenac with the assistance of ion-exchange fibers has not been investigated in any systematic fashion.

The objective of the present study was to examine the effectiveness of ion exchange fiber used as drug carrier materials to enhance the efficiency of transdermal iontophoresis of diclofenac. For this purpose, we design an in vitro experimental facility (see Fig. 1). Direct current (DC) cathodal iontophoresis (cathode in the donor) was conducted using drug anion-exchange fiber complexes and a rat epidermal membrane in a side-by-side diffusion cell. In order to simulate the actual conditions of administration, we also carried out an in vivo test with rats comparing the difference of the drug delivery efficiency between the ion-exchange fiber assisted drug iontophoresis and the other iontophoretic drug delivery methods. The results of this study not only demonstrated the feasibility of this technique on a drug with practical importance, but also provided a broader view in understanding the behavior of drugs in ion-exchange fiber assisted iontophoresis.

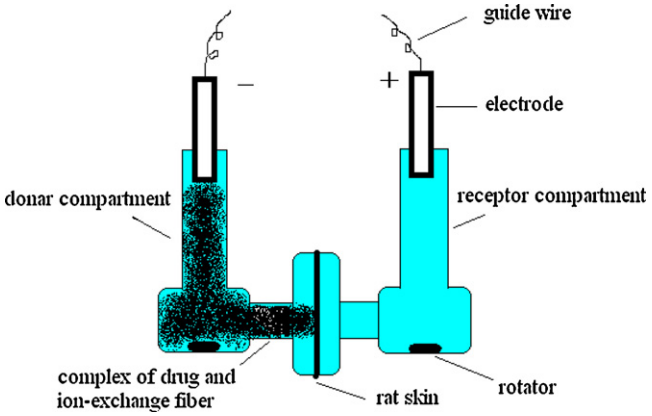

Fig. 1. A conceptual diagram of experimental facility.

2. Materials and methods

2.1. Materials

Diclofenac sodium was a gift from Xing Qi Pharmaceutical Ind. Co. Ltd. (China). Methanol, acetonitrile, HPLC grade, was purchased from Fisher Scientic Co. (USA). Phosphate buffered saline (PBS, pH 7.4; 0.01 M phosphate buffer, 0.0027 M potassium chloride, 0.137 M sodium chloride) was prepared by dissolving PBS tablets purchased from Sigma–Aldrich Co. Ltd. (USA) in distilled deionized water using the method specified by the supplier. Other chemicals used in the present study were of analytical grade.

Side-by-side diffusion cells were custom-made and the area available for diffusion was approximately 1.0 cm^2. The ion exchange materials used were obtained from Guilin Zhenghan Co. Ltd. (Guangxi, China). Maximal ion exchange capacity of the strong anion ion-exchange materials [poly(ethylene-g-styrene-trimethylammonium-chloride)] was about 3.0 mmol/g for all materials. Male Wistar rats of about 250 g were obtained from Shenyang Pharmaceutical University (China). The iontophoretic apparatus used to provide a constant direct current was made by Ruoya Co. Ltd. (Beijing, China). Sliver and silver chloride electrode (purity > 99.99%) were obtained from Green Tree Scientific and Instrument Co. Ltd. (China).

2.2. Preparation of rat skin

Male Wistar rats of about 250 g were sacrificed by excessive ether anesthesia. After the removal of hair using an animal hair clipper, the skins were excised from the abdominal part of the rats, then the residual subcutaneous fat adhering on the dermis side was wiped with scalpel and isopropyl alcohol followed by washing in water and subsequently in PBS pH 7.4. The skins were then packed in aluminum foil and stored in refrigerator at −20 °C. The experimental animal guidelines published by the Chinese Ministry of Science and Technology were followed and this study was conducted in accordance with the guidelines (Jessy and Shripad, 2007).

2.3. Pretreatment of the ion-exchange materials

The ion-exchange materials – resin, membrane, and fiber – were washed consecutively with methanol and double distilled water to remove impurities. Then the ion-exchange materials were activated by three treatments of alternate aliquots of 1 M NaOH and 1 M HCl. Finally the materials were washed with double distilled water and dried.

2.4. Analysis of drugs

Drug concentrations were analyzed by high-performance liquid chromatography (HPLC) (Klimes et al., 2001; Gaudiano et al., 2003). Analyses were performed on a C18 column (5 μm, 250 mm × 4.6 mm, Sigma–Aldrich) with precolumn (5 μm, 20 mm × 4.6 mm, Sigma–Aldrich) by the HPLC system (Jasco, Japan) and analyzed by UV detector. The selected and optimized mobile phase consisted of methanol–water (75:25, v/v) adjusted to an apparent pH 3.5 with H_3PO_4. The mobile phase was pumped at a flow-rate of 1.0 ml/min, and the detection wavelength was 284 nm at ambient temperature. The injection volume was 20 μl. Under these conditions, the retention time of diclofenac was about 7.0 min. Samples collected during the in vitro experiments were injected directly into the HPLC system and blood samples of the in vivo experiments were separated and extracted before being injected into the HPLC system. The concentration of diclofenac was calculated by comparison with the linear regression equation derived from the standard curve. All experiments were carried out at least in triple.

2.5. Loading of the ion-exchange materials

The activated ion-exchange resin and fibers (100 g dry weight) were immersed in diclofenac sodium solution respectively. After commotion at room temperature for 45 min the diclofenac ion-exchange materials complexes formed and were separated from the diclofenac sodium solution. This step was repeated twice or thrice until the amount of diclofenac on the ion-exchange materials reached the materials' ion exchange capacity. The complexes were then washed with a known amount of deionized water to remove unbound drug, squeezed dry at room temperature, and subsequently placed at 40 °C in an oven to constant weight. The amount of adsorbed drug in the ion-exchange materials was determined by HPLC from the different concentrations in the collected washing solutions and the initial solution. The use of ion-exchange membrane was in accordance with previous literature (Xu et al., 2009), in which ion-exchange membranes were not used as a kind of drug carrier but a kind of additive to promote the drug's iontophoresis. So we did not carry out the operation of drug loading for ion-exchange membrane, while we soak the ion-exchange membranes into the drug solution until they reached equilibration according to the report by the previous literature (Xu et al., 2009).

2.6. Equations in the analysis of experimental data

The flux (J_i) for diclofenac was calculated as followed:

$$J_i = \frac{1}{A_D}\frac{\Delta Q}{\Delta t} \quad (1)$$

where $\Delta Q/\Delta t$ was the slope of the curve of the cumulative amount of the diclofenac transported across the membrane into the receptor chamber versus time and A_D was the area of the diffusional surface.

The transference number (t_i) was calculated by the flux of the permeation (J_i):

$$J_i = \frac{t_i I_{total}}{A_D F|z_i|} \quad (2)$$

where I_{total} was the total current, F was the Faraday constant, and z_i was the charge number. The transference number was the fraction of the current carried by the diclofenac (permeation) to the total current carried by all ionic components in the system:

$$t_i = \frac{|z_i|J_i}{\sum_j |z_j|J_j} = \frac{I_i}{I_{total}} \quad (3)$$

where z_j was the charge number of ionic species j, J_j was the flux of all ionic species j in the system, and I_i was the current carried by the diclofenac. Ionic species j in the system represented all ionic components.

2.7. Release studies

The drug release from diclofenac ion-exchange material complexes were studied in a specially designed horizontal-typed diffusion cell at 25 °C. The available diffusion area was 1.0 cm^2 and the volume of both donor and receptor compartments were 10 ml. The transport of diclofenac by diclofenac ion-exchange material complexes was studied across the 0.22 μm cellulose acetate microporous membrane which was used as a synthetic barrier and hydrated with receiver medium before experiments. The membrane was fixed between the two parts of the cell. The diclofenac ion-exchange material complexes (2.0 g) were placed on one side of the membrane. In order to investigate whether the drug ions in the absence of other ions could be released from the drug ion-exchange material complexes by the aid of electric field force in the process of iontophoresis, we choose to put deionized water in the receptor compartment. The donor and receptor compartment were both filled with 10 ml of the deionized water. An externally applied electric field was used (Fig. 1). The direct current was 0.5 mA and sliver and silver chloride electrodes were used. Samples (5 ml) were collected at fixed intervals for up to 8 h (1, 2, 3, 4, 6 and 8 h) and replaced with deionized water (5 ml). The drug concentrations in the samples were determined by HPLC. In order to investigate the influence of amount of the drug in the donor compartment on the results we choose two concentrations of drug solutions 7.0 and 30.0 mg/ml to study.

2.8. Experimental protocol in vitro

The horizontal-typed diffusion cells were the same as that used in release studies. To simulate the in vivo situation, we put phosphate buffer saline in the receptor compartment and still deionized water in the donor compartment. The receptor compartment was filled with 10 ml of PBS (pH 7.4). The rat skin was hydrated for 2 h in PBS (pH 7.4) prior to mounting on the cells with the dermal side of the skin facing the receptor compartment. The distance from electrode to the rat skin was approximately 5 cm while the donor compartment filled with deionized water and the drug ion-exchange materials complex (or drug solution and ion-exchange membranes) and the receptor compartment filled with PBS (pH 7.4). In this step 2.0 g drug ion-exchange resin or fiber complexes were used respectively and ion-exchange membranes were used in a series of five membranes. The direct current was 0.1, 0.5 and 1.0 mA respectively. The transport of diclofenac across the rat skin was studied and samples (5 ml) were withdrawn at 1, 2, 3, 4, 6 and 8 h and replaced with PBS (5 ml). The drug concentrations in the samples were determined by HPLC. Drug's water solution iontophoresis experiments without ion-exchange materials were the controls.

2.9. Experimental protocol in vivo

Male Wistar rats (250–270 g) were supplied by the Animal Experimental Research Centre at the Shenyang Pharmaceutical University, China. Experimental protocols were approved by the Ethical Committee for Animal Experimentation at the Shenyang Pharmaceutical University. The rats were anesthetized by intraperitoneal administration of pentobarbital sodium (40 mg/kg) one day before iontophoresis. The rats' jugular veins were cannulated using medical-grade silicon tubing (Silastic; ID 0.5 mm; OD 0.94 mm). In order to allow iontophoretic administration, rats

were anesthetized and mounted on a wooden support. The surface area of the rat's skin exposed for diclofenac penetration remained the same as the in vitro set up. For in vivo studies we separated the in vitro diffusion cells into two halves. The anode and cathode were placed 3.0 cm apart on the animal's abdomen. The donor compartments contained deionized water and the drug ion-exchange materials complex (or drug solution and ion-exchange membranes). In this step 2.0 g drug ion-exchange resin or fiber complexes were used respectively and ion-exchange membranes were used in a series of five membranes. A power supply delivered a constant, direct current of 0.5 mA (0.5 mA cm^{-2}) for 14 h. Blood samples (0.5 ml) were withdrawn at hourly intervals and immediately centrifuged at 10,000 rpm; the plasma collected was separated and stored at −20 °C until analysis by HPLC. After withdrawing each blood sample, the same volume of saline solution was injected into the rat's blood. At the end of the experiment, the rats were sacrificed by injecting pentobarbital sodium at a dose of 200 mg/kg.

2.10. Plasma extraction

The extraction procedure was based on a one-step liquid–liquid technique (Chmielewska et al., 2006). Diethylether (1 ml) was added to 100 μl of plasma, and the resulting mixture was vortex-mixed for 15 min. After centrifugation at 12,000 rpm and separation, the organic layer was evaporated at 30 °C. The residue was dissolved in 100 μl of mobile phase, and finally 50 μl was injected into the chromatographic column (Pintu et al., 2009).

3. Results and discussion

3.1. Drug content

From the different concentrations of the collected washing solutions and the initial solution, the mean drug contents of the drug fibers and the drug resins were determined to be about 2.965 ± 0.018 mmol/g and 2.917 ± 0.025 mmol/g respectively. It was found that the loading efficiency could achieve about 98.8% and 97.2%, meaning that almost all the active groups of the ion-exchange materials were occupied by the drug ions. We did not carry out the operation of drug loading for ion-exchange membrane, but before the experiments the ion-exchange membranes were still pretreated according to the report of the previous literature (Xu et al., 2009).

3.2. Release studies

The relationship between the drugs bound on ion-exchange materials and the ion-exchange materials can be explained as follows: the drug ions and the ion binding groups of the ion-exchange materials form an ionic bond, which will dissociate positive ions and negative ions in water. However, because of the mutual attraction between the drug ions and the ion binding groups on the ion exchange materials, drug ions would not diffuse into water and then would not appear in the receiver medium. If there are free ions except for drug ions, free ions will be attracted by the ion binding groups of the ion exchanging materials instead of drug ions, and in the same time drug ions will be released into water and will appear in the receiver medium.

The release profiles without the external electrical field of diclofenac ion-exchange fibers complex compared with that of simple diclofenac solutions with the two diclofenac concentrations of 7.0 and 30.0 mg/ml are shown in Fig. 2, respectively. The results showed that the flux of the high concentration solution was larger than that of the low concentration solution in the same interval, but the release percents were similar. This result is consistent

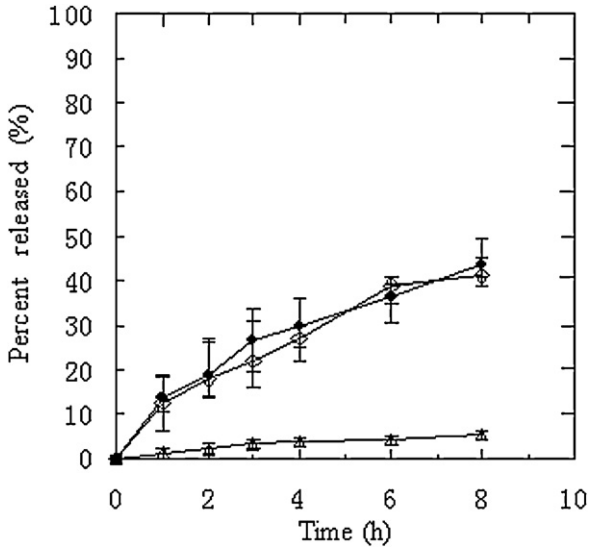

Fig. 2. A comparison of the release profiles across a 0.22 μm cellulose acetate microporous membrane without the external electric field of diclofenac-fibers and simple diclofenac solutions with the diclofenac concentrations of 7.0 and 30.0 mg/ml, respectively. (●) diclofenac solution of 30.0 mg/ml, (◊) diclofenac solution of 7.0 mg/ml, and (△) diclofenac-fibers (0.6 g, equivalent to drug 300 mg) ($n = 5$).

with the rule of concentration-dependent passive diffusion. However, the amount of the diclofenac released from the diclofenac ion-exchange fibers complex was much lower than that from the diclofenac simple solution, which suggested that there was an interaction between diclofenac and ion-exchange fibers that hindered the release of diclofenac from the complexes. On the contrary, Fig. 3 shows the release profiles with the external electrical field of diclofenac ion-exchange fibers complex compared with that of simple diclofenac solutions with the two diclofenac concentrations of 7.0 and 30.0 mg/ml, respectively. The release profiles of the simple diclofenac solutions in Fig. 3 (with the external electrical field) were similar with those of the simple diclofenac solutions in Fig. 2 (without the external electrical field). However, the amount of the diclofenac released from the diclofenac ion-exchange fibers complexes with the external electrical field was higher than that

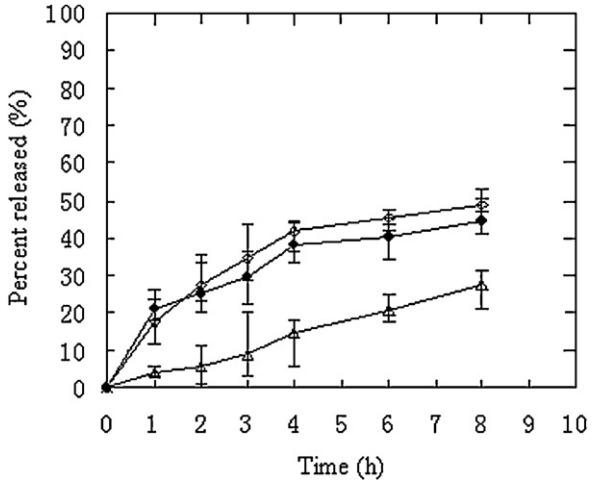

Fig. 3. A comparison of the release profiles across a 0.22 μm cellulose acetate microporous membrane with the external electric field (0.5 mA cm^{-2}) of diclofenac-fibers and simple diclofenac solutions with the diclofenac concentrations of 7.0 and 30.0 mg/ml, respectively. (●) diclofenac solution of 30.0 mg/ml, (◊) diclofenac solution of 7.0 mg/ml, and (△) diclofenac-fibers (0.6 g, equivalent to drug 300 mg) ($n = 5$).

Table 1
Summary of the transference numbers for diclofenac transport across rat skin during 0.1, 0.5 and 1.0 mA constant current DC iontophoresis ($n = 5$).

System	Transference number upon DC current		
	0.1 mA	0.5 mA	1.0 mA
Solution (7.0 mg/ml)	0.12 ± 0.10	0.11 ± 0.12	0.10 ± 0.12
Solution (30.0 mg/ml)	0.11 ± 0.10	0.11 ± 0.09	0.13 ± 0.11
Diclofenac ion-exchange fiber complex	0.63 ± 0.15	0.62 ± 0.16	0.59 ± 0.15
Diclofenac ion-exchange resin complex	0.07 ± 0.4	0.08 ± 0.3	0.07 ± 0.4
Diclofenac with ion-exchange membrane	0.35 ± 0.11	0.38 ± 0.09	0.34 ± 0.12

without the external electrical field, but lower than that of the simple diclofenac solutions. This result suggested that without ion exchanging reaction drug ions could also be released from the drug ion-exchange materials complex by the external electrical field force. The release process of the drug from the drug ion-exchange materials complex by the external electrical field force can be explained as follows: the drug ions and the ion binding groups of the ion-exchange materials were dissociated in the water and formed positive ions and negative ions. The drug ions formed an ionic atmosphere around the ion binding groups of the ion-exchange materials. If there were no free ions in the water, drug ions combined on the ion binding groups of the ion-exchange materials would not dissociate into water by ion exchanging reaction; instead the ion exchanging reaction will occur when the free ions were in water. In the presence of external electrical field, drug ions will overcome the constraint of attraction between the drug ions and the ion binding groups of the ion-exchange materials and move directionally. As a result, the drug ions diffused into water and eventually reached the acceptor compartment.

From Figs. 2 and 3 we can see that although diclofenac ion-exchange fiber complexes released more drug ions with the external electrical field than those without the external electrical field, this amount of the drug released was still less than that of the simple diclofenac solution. The reason of this result is that the inhibition of the microporous membrane is very small compared with the procedure of the drug releasing from the drug ion-exchange fibers complexes, so this inhibition had little influence on the drug's transit amount. Therefore, we can draw a conclusion that in the procedure of the drug permeating through the 0.22 μm cellulose acetate microporous membrane the rate determining step is the procedure of the drug releasing from the drug ion-exchange materials complex under the external electric field. Because of the weak inhibition of the 0.22 μm cellulose acetate microporous membrane for drug, we saw that the release profiles of diclofenac concentrations had no significant difference in Figs. 2 and 3, which means that passive diffusion is the main contribution to drug's migration in these two procedures.

3.3. *In vitro study*

Table 1 presents the transference numbers of diclofenac across rat skin during constant current iontophoresis of 0.1, 0.5 and 1.0 mA. In the case of not using ion-exchange materials the electric current levels did not significantly affect the transference numbers of diclofenac solution, and the average transference numbers of diclofenac was approximately 0.1 under different current levels from 0.1 to 1.0 mA. The relatively low transference numbers are consistent with the reported values in previous transdermal iontophoresis studies of similar anionic drugs (Bellantone et al., 1986; Phipps et al., 1988). Given the different experimental conditions of these previous studies – drug, buffer system and pH – the difference in transference numbers between the previous and present studies is reasonable. Table 1 also presents the diclofenac's 0.1, 0.5 and 1.0 mA iontophoresis data when ion-exchange materials were used in the experiments. The drug ion's transference number was remarkably changed by using ion-exchange materials assisting iontophoresis. Obviously, there was a trend of higher average transference number of diclofenac with ion-exchange fibers assisted than that without fibers (Table 1). On the contrary, the result of the iontophoresis experiment with ion-exchange resin assisted indicated that the drug ions' transference number was reduced. Using ion-exchange membrane can increase drug ions' transference number (Xu et al., 2009). In our comparison tests we also obtained the same results, but this ion-exchange membrane's increasing effectiveness was much smaller than the ion-exchange fiber's. From Table 1 we can also see that in the same method of DC iontophoresis administration the drug's transference numbers had no significant difference when DC iontophoresis with different intensity of current were carried out. A significant increase in the transference number of diclofenac with ion-exchange fibers assisted DC iontophoresis compared with DC iontophoresis was observed, and can be seen more obviously in Fig. 4. From Fig. 4 we can see that the drug's transference numbers of drug-fibers was almost three times of that of the diclofenac solutions.

Transference number represents the proportion of drug ions in the current; the larger the transference number, the more efficient the drug iontophoresis. From Table 1 and Fig. 4 we can see that in the presence of ion-exchange fibers, the drug transference number increased significantly, indicating that the drug-fibers could increase the efficiency of drug ions' iontophoresis. Although the use of ion-exchange membranes can also improve the efficiency of drug iontophoresis, the effect was significantly less than that of the ion-exchange fibers. This may be firstly due to the

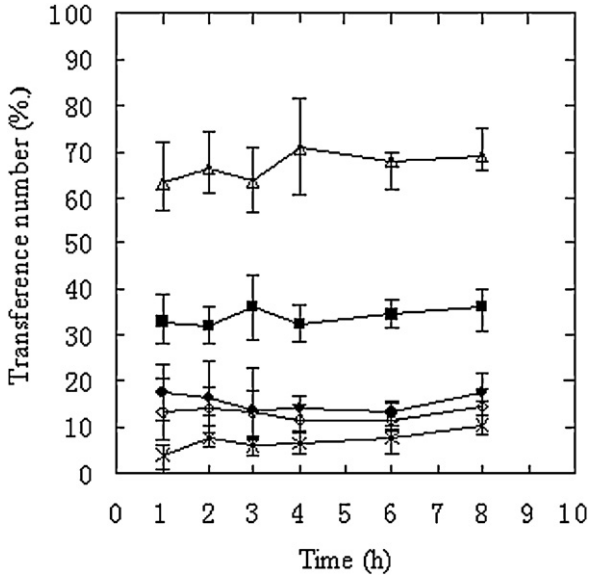

Fig. 4. A comparison of the transference numbers of simple diclofenac solutions and diclofenac with ion-exchange materials across rat skin during DC iontophoresis (0.5 mA cm^{-2}). (●) diclofenac solution of 30.0 mg/ml, (◇) diclofenac solution of 7.0 mg/ml, (△) diclofenac-fibers, (■) diclofenac solution with ion-exchange membrane, and (×) diclofenac-resins ($n = 5$).

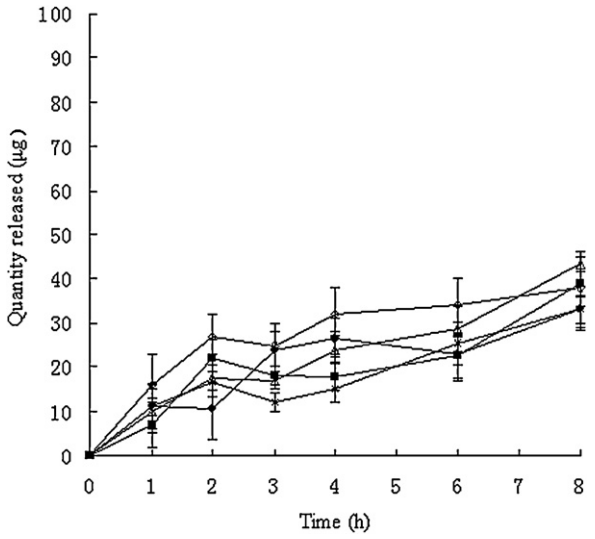

Fig. 5. A comparison of the release profiles across rat skin without the external electric field of diclofenac with ion-exchange materials and that of simple diclofenac solutions of 7.0 and 30.0 mg/ml, respectively. (●) diclofenac solution of 30.0 mg/ml, (◊) diclofenac solution of 7.0 mg/ml, (△) diclofenac-fibers, (■) diclofenac solution with ion-exchange membrane, and (×) diclofenac-resins ($n = 5$).

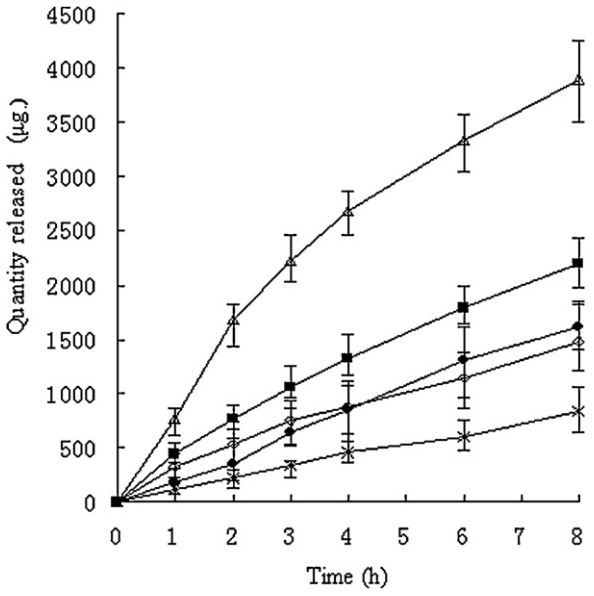

Fig. 6. A comparison of the release profiles across rat skin with the external electric field (0.5 mA/cm^2) of diclofenac with ion-exchange materials and that of simple diclofenac solutions of 7.0 and 30.0 mg/ml, respectively. (●) diclofenac solution of 30.0 mg/ml, (◊) diclofenac solution of 7.0 mg/ml, (△) diclofenac-fibers, (■) diclofenac solution with ion-exchange membrane, and (×) diclofenac-resins ($n = 5$).

fact that ion-exchange membrane's permeability was less than the ion-exchange fibers'. Secondly, the ion-exchange membranes were only a kind of additives in iontophoresis. They did not reduce the amount of the small ions in system at all. There were still a lot of metal ions in the drug solution in the donor compartment. This was the main reason for that the enhancement of the ion-exchange membranes was smaller than that of the ion-exchange fibers. Different from ion-exchange fiber and ion-exchange membrane, the spherical ion-exchange resin in the iontophoresis experiments played a role in delaying drug release. There were two main reasons. One was that most of the ion-exchange resin's ion-exchange groups were within the ball, so the drug release was restricted. The other was that in the process of loading it was difficult to reach the ion-exchange resin's saturated exchange capacity, resulting in small ions in the ion-exchange resins influencing the drug ion's electromigration. From Figs. 5 and 6 we can more clearly observe the behavior of the drug-fibers increasing the efficiency of the drug ions' iontophoresis. All curves in Fig. 5 were the behavior of the drug ions' iontophoresis under the conditions of no external electric field. From Fig. 5 we can see that either of the drug ion-exchange materials composites or of the drug solutions in the drug's passive diffusion experiment using rat skin as a barrier 8 h cumulative amount of drug permeated rat skin were less than 50 μg. This result indicated that it was very difficult for drugs to permeate the rat skin by passive diffusion. In the next trial (Fig. 6) the situation was very different. Fig. 6 shows the release profiles across rat skin with the external electrical field of diclofenac ion-exchange materials composites compared with that of simple diclofenac solution with the two diclofenac concentrations of 7.0 and 30.0 mg/ml, respectively. It can be seen that the amount of diclofenac released from the diclofenac-fibers was higher than that released from other ion-exchange materials and the diclofenac simple solution, which suggested that there was an enhancement by ion-exchange fibers in ion-exchange fibers assisted DC iontophoresis across rat skin. Compared to ion-exchange fibers, ion-exchange membranes' effect in promoting the drug's permeation in DC iontophoresis was much smaller. When ion-exchange resins were used it reduced the flux of the drug ions' permeation in DC iontophoresis. The difference in the flux of the drug ions' permeation across rat's skin in DC iontophoresis assisted by different ion-exchange materials was corresponding to their transference numbers. It is because that a high transference number leads to a high iontophoresis efficiency and a high flux of the drug ions' permeation across rat's skin in DC iontophoresis. In DC iontophoresis across rat skin experiments, the ion-exchange fiber's the transference number was the highest; the ion-exchange resin's the transference number was the lowest. Therefore, the rank of the flux of the drug ions' permeation in DC iontophoresis assisted by three ion-exchange materials was fiber > membrane > resin.

From Fig. 6 we can see that the released amount of drug from two concentrations' solutions across the rat skin were similar, this phenomenon can be explained as followed: due to the rat skin's strong inhibition for drug, passive diffusion could not produce a marked effect on drug's transmitting across rat skin. While in DC iontophoresis current play a main role to promote the drug ions transmitting across rat skin. So the drug's concentration in donor compartment had little influence on iontophoretic drug behavior. This result told us that we could directly control the flux of the drug imported into the body by adjusting the current without thinking over the amount of the drug in the donor compartment.

3.4. *In vivo study*

The mean diclofenac concentration–time profiles upon iontophoretic administration at 0.5 mA cm^{-2} with and without ion-exchange materials assisted were shown in Fig. 7. When DC iontophoresis was carried out with ion-exchange fibers assisted, the significant diclofenac plasma concentration levels (10 μg ml^{-1}) was firstly achieved at about 0.5 h, which means that DC iontophoresis with ion-exchange fibers assisted had the fastest input velocity of the diclofenac (Table 2). Furthermore, the diclofenac concentration remained obviously higher than the others DC iontophoresis methods throughout the iontophoretic period. In our experiments regardless of the methods of administration, the iontophoresis behaviors across rat skin in vivo were similar with those in vitro. Comparing the iontophoresis efficiency, the ion-exchange fiber's was the highest, ion-exchange membrane's was second and the last one was ion-exchange resin's. Table 2 shows the estimated pharmacokinetic parameters of the iontophoretic delivery with the

Table 2
Pharmacokinetic parameters for diclofenac in Wistar rats after iontophoretic administration for 14 h at 0.5 mA cm^{-2} (n = 5).

Pharmacokinetics parameter	Diclofenac solution (30.0 mg/ml^{-1})	Diclofenac solution (7.0 mg/ml^{-1})	Diclofenac with ion-exchange membrane	Diclofenac ion-exchange fiber complex	Diclofenac ion-exchange resin complex
k_a (μg h^{-1} cm^{-2})	200.4 ± 56.3	355.2 ± 72.1	379.0 ± 87.9	834.6 ± 209.2	103.6 ± 19.8
K (h^{-1})	0.3581 ± 0.102	0.3570 ± 0.098	0.3494 ± 0.089	0.3581 ± 0.108	0.3574 ± 0.087
$t_{1/2}$ (h)	1.935 ± 0.055	1.941 ± 0.053	1.983 ± 0.048	1.935 ± 0.062	1.939 ± 0.049
c_{ss} (μg ml^{-1})	22.65 ± 8.67	20.25 ± 6.90	32.75 ± 9.14	60.25 ± 17.92	16.00 ± 5.51
AUC (μg h ml^{-1})	318.5 ± 111.8	290.6 ± 140.3	462.3 ± 100.8	840.2 ± 208.9	231.0 ± 85.3

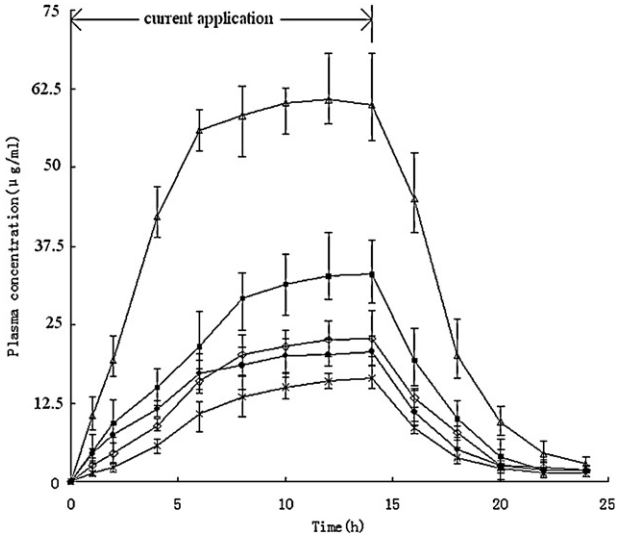

Fig. 7. Diclofenac plasma concentrations in Wistar rats after iontophoretic administration for 14 h at 0.5 mA cm^{-2}. (●) diclofenac solution of 30.0 mg/ml, (◊) diclofenac solution of 7.0 mg/ml, (△) diclofenac-fibers, (■) diclofenac solution with ion-exchange membrane, and (×) diclofenac-resins (n = 5).

different methods. Iontophoretic delivery of diclofenac with ion-exchange fibers assisted resulted in an almost 3-fold increase in diclofenac flux compared to that seen after iontophoretic delivery of the diclofenac sodium solution. This significant effectiveness in promoting drug iontophoresis could be completely attributed to the use of ion-exchange fibers. The enhancement of iontophoretic by ion-exchange membrane and ion-exchange resin was inferior than that by ion-exchange fiber. The reason for this result had been discussed in vitro study results.

In the procedure of the DC iontophoresis of the diclofenac sodium solution across rat skin, there were many small ions such as Na^+, K^+ and H^+. These ions' small volume and fast movement had more contribution to electric conduction. Consequently, in the procedure of the diclofenac sodium solution's DC iontophoresis across rat skin there would be a large amount of small ions moving to the cathode, and few drug ions moving to the anode, resulting in a small transference number and a low efficiency of the drug iontophoresis. This phenomenon was improved in ion-exchange fibers assisted DC iontophoresis. Firstly, when diclofenac was loaded on the ion-exchange fibers a lot of Na^+ were removed from the system. Secondly, in the electric field the drug ion-exchange fiber complexes released drug ions and then became a big multivalence cation, which was in the way of the movement of the counterions to the cathode. Hence, we could see that the contribution to electric conduction by the drug ions was increased.

4. Conclusion

The present study evaluated the ability of ion-exchange fibers used as drug carrier materials to enhance transdermal iontophoretic transport of a model permeant diclofenac. It was observed that when transdermal DC iontophoresis was carried out diclofenac bound to ion-exchange fibers with an ionic bond had a higher transference number than those bound to other ion-exchange materials, and also than those in simple diclofenac solution. The results mean the ion-exchange fiber played a significant role in enhancing transdermal iontophoresis. Compared with the other ion-exchange materials, ion-exchange fiber's enhancement of transdermal DC iontophoresis was more conspicuous, that had been confirmed both in vitro and in vivo experiments. This obvious enhancement offered a great advantage especially on allowing the delivery of the same amount of drug at a lower applied electric current or shorter iontophoresis application time. If this novel method of iontophoresis could be applied to the clinical treatment, it would reduce the suffering of the patients and improve the patient's compliance, and would also reduce the occurrence of electrode reactions and the impact of chemical stability of drugs. Although it is uncertain whether the studied techniques may be applied to human subjects, the present study has demonstrated ion-exchange fiber enhanced transdermal iontophoresis of negatively charged drugs, and proposed a new approach to enhance transdermal iontophoretic transport.

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