Available online at www.sciencedirect.com
SCIENCE DIRECT
International Journal of Pharmaceutics 319 (2006) 107–113
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

The delivery of ketoprofen from a system containing ion-exchange fibers

Limin Yu, Sanming Li *, Yue Yuan, Yi Dai, Hongzhuo Liu

Department of Pharmaceutics, School of Pharmaceutical Science, Shenyang Pharmaceutical University, No. 103, WenhuaRoad, Shenyang 110016, China

Received 26 December 2005; received in revised form 22 March 2006; accepted 28 March 2006
Available online 1 April 2006

Abstract

A postulated model for transdermal delivery using ion-exchange fibers as controlling device was designed, and the main objective of this study was to assess the rationality of the model. The release rates of ketoprofen from the carbopol-based gel vehicles containing ion-exchange fibers to which the ketoprofen had been bound have been determined across 0.22 μm microporous membrane. The fluctuation of the release rate of ketoprofen from the vehicles was much lower compared with that of simple gels, though the cumulative amount of ketoprofen delivery was less. Additional ions could increase the rate and extent of ketoprofen delivery. The iontophoretically assisted transport of ketoprofen across rat skin was also studied and found to be favorable to ketoprofen permeation. According to the tested model, the ion-layer could enhance the ketoprofen delivery and satisfactory results were achieved.

Keywords: Transdermal; Iontophoresis; Gel; Ion-exchange fibers; Ketoprofen

1. Introduction

There has been great interest to develop new transdermal devices in recent years, which can control and sustain the delivery of drugs. When the device controls the transdermal drug flux other than the skin, whose permeability changes with age and anatomical site (Guy and Hadgraft, 1992), the rate of drug permeation into the blood stream is more predictable and reproducible. Ion-exchange materials such as resins or fibers, provide an efficient way to control the rate and extent of drug release and have been studied as vehicles in transdermal drug delivery system recently (Conaghey et al., 1998a,b; Jaskari et al., 2000; Tarja et al., 2000; Kankkunen et al., 2002a,b; Vuorio et al., 2004). Charged drugs are bound into the ion-exchange groups of the fiber until they are released by mobile ions, so that it provides a promising way to achieve controlled drug release and also enhance drug stability (Kankkunen et al., 2002a,b).

However, there had not been any model system designed yet. The purpose of the present investigation was to develop a simplified, ideal transdermal drug delivery system which could be classified as a drug release system employing ion-exchange mechanism (see Fig. 1). The system could be subdivided into (1) the backing layer (2) the ion-offering layer which provides additional ions (3) the drug-containing layer where drug-loaded ion-exchange fibers/resins distributed uniformly in gel matrix structure (4) the skin contact layer (devoid of drug) is separated from the drug reservoir by another drug-free layer. The multilayer structures system should need a iontophoresis power set.

The use of iontophoresis to facilitate underlying deep tissue penetration of drugs (Singh and Roverts, 1993) after topical application will be most beneficial in the treatment of osteoarthritis, soft-tissue rheumatism and other deep rooted local inflammatory conditions associated with sports injuries. Ionthophoresis, a driving force of charged molecules, could drive the additional ions from the ion-offering layer into the drug-containing layer which results in the free ions (e.g. Cl^-) flow into the drug–fibers gel layer, drug could then be released by the ion-exchange process and be carried by the electrical repulsion from the driving electrode to transport across skin. If a constant current density could be maintained, the quantity of free ions drived into drug-layers was equal to that of drug permeation, the aim of controlled delivery could be achieved. Furthermore,

* Corresponding author. Tel.: +86 24 23986258; fax: +86 24 23986258.
E-mail address: li_sanming@sina.com (S. Li).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.03.039

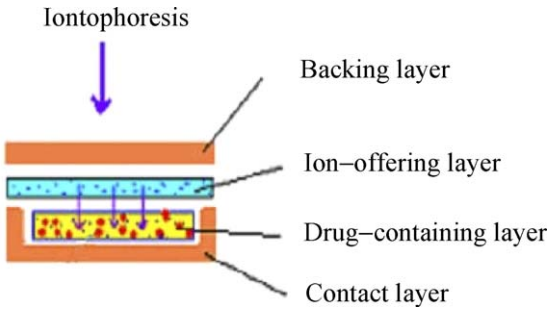

Fig. 1. A postulated model for transdermal delivery using ion-exchange materials as controlling device.

the flow of electric current may increase the permeability of the skin.

Based on the postulated model above, this paper investigated a novel transdermal system that ion-exchange fibers were incorporated into the hydrogel vehicle and the drug ketoprofen was studied as a model drug. Ketoprofen (2-(3-benzoylphenyl)) propionic acid, KP, is a nonsteroidal anti-inflammatory (NSAIDs) with analgesic and antipyretic actions (Peltola, 1976; Zutshi and Mason, 1976; Kantor and Ketofen, 1986). Although KP has a potent anti-inflammatory action, it has undesirable side effects on the stomach gastrointestinal after oral administration like other NSAIDs (Fossgreen, 1976; Chi and Jun, 1991). Among the efforts that have been made, topical administration is one of the best ways to overcome the side effects and to provide higher concentration at the target site (Rolf et al., 1999) which leads to higher efficacy.

The objective of this work were: (1) to determine the in vitro release profiles of KP across 0.22 μm microporous membrane from the complex vehicles (2) to study the additional ions enhancing effect for the release process (3) to investigate the in vitro iontophoretic assisted drug delivery from the system with the aid of additional free ions across rat skin compared to passive transdermal system, so as to assess the rationality of the model.

2. Materials and methods

2.1. Materials

The ion-exchange fibers studied were strong anion-exchanger material of poly(propylene-*g*-vinylbenzyltrimethylammonium-chloride) (ZB-2). The mobile counter-ions initially attached to the trimethylammonium groups were chloride ions. The fibers used were in staple form (170 μm × 3 μm) obtained from Guilin Zhenghan Co. Ltd. (Guangxi, China) with the maximum ion-exchange capacity about 3.0 mmol/g. Ketoprofen was the model drug purchased from the Southwest Synthetic Pharmaceutical Co. Ltd. (China). Carbopol 940 of molecular weight 4,000,000 was supplied by Noveon™ (The Specialty Chemicals Innovator). All the other chemicals were at least analytical grade and were used without further purification. Deionized water with a resistivity of 18 MΩ/cm or greater was used to prepare all the solutions. The pH was adjusted by the addition of chlorhydric acid or sodium hydroxide (1.0 M). The 0.22 μm cellulose acetate microporous membrane was obtained from Sciequip (China). Male rats of about 250 g obtained from Shenyang Pharmaceutical University (China).

The iontophoretic apparatus used to provide a constant direct current was made by Ruoya company (Beijing, China). Sliver and silver chloride (purity >99.99%) were obtained from Green Tree Scientific and Instrument Co. During the experiments, one pair of the drive electrodes, made from a silver plate (anode) and a silver wire coated with silver chloride (cathode), were separated from the donor and receptor chambers by salt bridges.

2.2. Preparation of rat skin

Male 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, then the skins were packed in aluminum foil and stored in refrigerator at −20 °C.

2.3. Preparation of the vehicles

The strong ZB-2 anion-exchanger (100 mg of staple fibers) was bundled up inside a porous membrane. The fiber bundles were hydrated with deionized water for 1 h and were activated in 1 M NaOH solution for 8 h before experiments, then the fibers were washed with deionized water to remove the excess alkali until the pH was about 8. The fibers were immersed in a 2% (w/v) KP solution (50 ml of loading solution/10 mg of the fibers) overnight (8 h). The pH of the KP solution was adjusted to 8 using 1 M NaOH solution, and at this pH point both the KP and the fibers remained in an ionized form. Then the fibers were washed with a known amount of water and squeezed dry at room temperature and subsequently at 313 K in an oven to constant weight. The amount of adsorbed drug in the fibers was determined by HPLC from the different concentration in the collected washing solutions and the initial solution.

Ion change fiber-gel vehicles could be prepared in two ways (Conaghey et al., 1998a). In this paper, the formulations (marked by KP-fibers gel) prepared had been prescribed as follows: carbopol 940 1.0 g, NaOH 0.4 g, ethanol 40 ml, sodium metabisulfide 0.1 g, water qs to 100 ml. Carbopol 940 was dispersed in two-thirds proportion of the water overnight. Ethanol and KP-fibers were added to this solution under stirring for 4 h at room temperature. The NaOH was dissolved in the remaining water and added to the polymer dispersion, and then the mixture was stirred with continual agitation for about 8 h. The pH of the products was about 7. The vehicles prepared without fibers were named as KP simple gel in this paper.

2.4. Release studies

Drug release from gels containing ion-exchange fibers was studied in vertical-typed Franz diffusion cells at 37 °C. The transport of KP from the gel vehicles was studied across the 0.22 μm cellulose acetate microporous membrane which was used as a synthetic barrier and should be hydrated with receiver

medium before experiments. The gels with the concentration of 7.0 or 30.0 mg/ml were placed on the membrane, which were fixed between the two parts of the cell. The surface area of the fiber discs exposed to the PBS receiver medium (0.05 M, pH 7.4) was 0.63 cm^2 and the volume of receptor compartment was 8 ml. Samples were collected at fixed intervals for up to 8 h (1, 2, 3, 4, 6 and 8 h) and replaced with receiver medium. The drug concentrations in the samples were determined by HPLC.

2.5. Permeation studies

Specially designed vertical-type glass diffusion cells with side-arm were used. The available diffusion area was 2.25 cm^2 and the volume of receptor compartment was 13 ml. The rat skin was hydrated for 2 h in PBS (0.05 M, pH 7.4) prior to mounting in the cells with the dermal sides of the skin facing the acceptor compartment. The transport of KP across the rat skin from the vehicles (0.5 g) was studied and samples were withdrawn at 1, 2, 3, 4, 6 and 8 h and replaced with PBS. The other conditions were the same as described above (Section 2.4).

As to the electrically assisted transport, the procedure was similar to passive transport described above with the skin placed between the anodal and the acceptor compartment. The cathodal side was approximately 3 cm below the rat skin in the receptor compartment filled with PBS pH 7.4. The direct current was 1.2 mA and the impulse frequency was 2000 Hz, the voltage was adjusted to maintain a constant current value of 0.5 mA/cm^2 for 4 h, and the passive flux was monitored afterwards.

2.6. Analysis of drugs

Drug concentrations were analyzed by high-performance liquid chromatography (HPLC) (Rodam et al., 2002; Simon et al., 2003; Dvofak et al., 2004). Analyses were performed on a C18 column (5 μm, 250 mm × 4.6 mm, Sigma–Aldrich) with pre-column (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 acetonitrile, 0.02 M KH_2PO_4 adjusted to an apparent pH 3.5 with H_3PO_4 (40:60, v/v). The mobile phase was pumped at a flow-rate of 1.0 ml/min, and the detection wavelength was 254 nm at ambient temperature. The injection volume was 20 μl. Under this condition the retention time of KP was about 6.50 min. The linear calibration range was 0.5–100.0 μg/ml and the LOD was 0.05 μg/ml. Samples collected during the experiments were injected directly into the HPLC system. The concentration of KP was calculated by comparison with the linear regression equation derived from the standard curve. All experiments were carried out at least in triple.

3. Results and discussion

3.1. Drug release studies

The release process could be explained as follows: the PBS receiver medium diffuse into the gels and the $H2PO_4^-$, PO_4^{3-} and also little HPO_4^{2-} in the solution exchange with the KP ions,

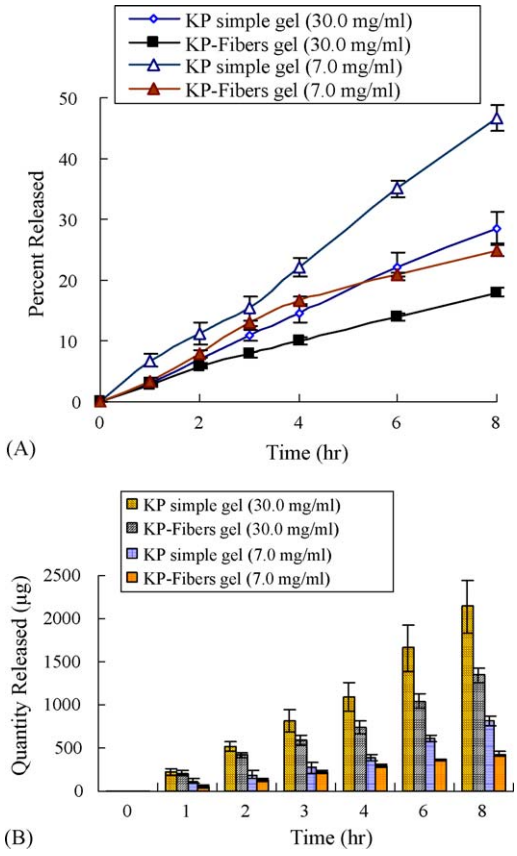

Fig. 2. A comparison of the release profiles of ketoprofen (KP) across 0.22 μm microporous membrane into PBS (pH 7.4), shown both as percentage (A) and weight (B) released, from gel vehicles containing ion-exchange fibers compared with that of simple gels. Average standard deviations ($n = 5$).

drug ions then diffuse through the matrix of the gels and transport across the membrane which was known not present any real barrier to the passage of drugs .The ions from the receiver solution migrated into the vehicles and ion-exchanged with anionic KP which had been bound in fibers, then the released KP diffused into receiver medium, creating an electrical potential difference (Donnan potential) between the fiber phase and the external phase (Helfferich, 1995), so that the flux of the different ions with same charge could be coupled as the result of diffusion potential gradients, and the local electroneutrality condition then being satisfied.

Fig. 2 showed the release profiles of KP-fibers gels compared with that of simple gels with the overall KP concentrations of 7.0 and 30.0 mg/ml, respectively. Though the quantities of KP released from the higher concentration gel (30.0 mg/ml) was much higher than that from the gels of 7.0 mg/ml, the results of percentages released were just inversely which was supported by the results previously reported (Conaghey et al., 1998a). However, the release rate from the KP-fibers gels was lower than that from the KP simple gels, which suggested that there was an interaction between KP and ion-exchange fibers among KP-fibers gels which hindered the release of KP. Furthermore, with the overall concentration of KP in these vehicles decreased from 30.0 to 7.0 mg/ml, the cumulative amount of KP release from the simple gel decreased significantly, while the ion-exchange fibers

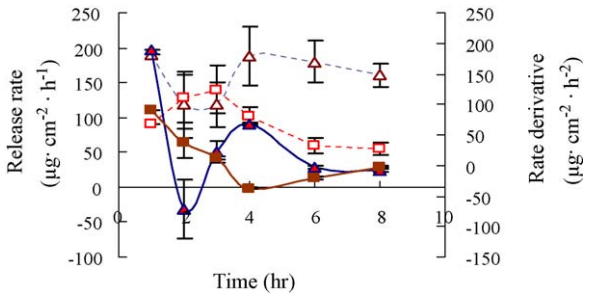

Fig. 3. A comparison of the release rate and the rate derivative of ketoprofen (KP) transport across 0.22 μm microporous membrane into PBS (pH 7.4) from gels containing ion-exchange fibers and the simple gel at the concentration of 7.0 mg/ml. The dash line and solid line connected junctures were representatives of release rate and the rate derivative (rate derivative). (△) KP simple gel; (□) KP-fibers gel; (▲) rate derivative of KP simple gel; (■) rate derivative of KP-fibers gel.

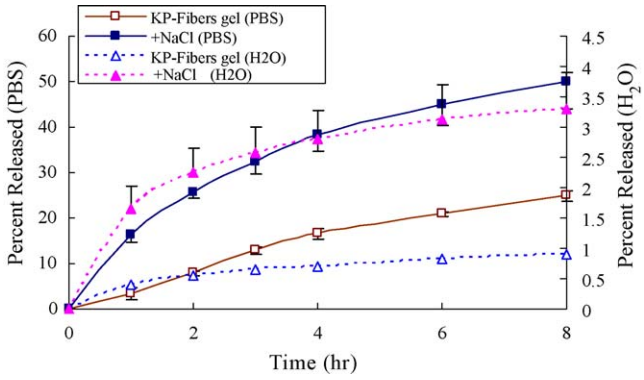

Fig. 4. Enhanced ketoprofen (KP) transport from gel vehicles containing ion-exchange fibers with the aid of ion-layer (2.5% NaCl gel). The dash line and solid line were representatives of release profiles into deionized water and PBS (0.05 M, pH 7.4) receiver medium respectively. In all cases the concentration of the KP in the vehicles was 7.0 mg/ml and the release rates were measured across 0.22 μm microporous membrane.

could lessen the changed profiles when KP concentration was dramatically altered. It could be explained as follows: the pK_a of fibers was about 8 which partly possessed positive electricity on the release condition (pH 7.4), while the KP (pK_a 4.7) was negatively charged at pH 7.4, so the KP ions were tightly held to the fibers with electrostatic interaction. The carbopol 940 consisted of acrylic acid competed with the KP ions to interact with fibers, the interaction between the KP and fibers became stronger at higher concentrations, so the ion-exchange fibers could lessen the changed profiles when KP concentration was dramatically altered.

Fig. 3 showed that the initial release rate from simple gels was decreasing significantly with the fact that KP on the gel surface contacting with receiver medium released fast and interior drugs could not diffuse through gel matrix quickly enough. While the release rates from KP-fibers gels was gradually increased accompanying more and more ions entering into the vehicles, though there was a little drawn down during the later stage. It indicted that it needed a short time for free ions went into gel vehicles, for their exchange with KP ions, for the KP released to diffuse back to receiver medium (Conaghey et al., 1998a).

It was also seen from Fig. 3 that the fluctuation of the release rat from the KP-Fibers gel was much less than the KP simple gel, on the basis of rate derivative (rate derivative) profiles, illustrating the fibers sustained the KP transport and acted as a rate soft-buffer agents in the formulations. The derivative of the release rate is the parameter of the variability of release rate, the larger the value, the more significant change of release rate during the investigated time period. According to Fig. 3, the absolute value of derivative of the drug release rate from gels containing fiber was lower than that from the simple gels during the first 4 h, this phenomenon indicated that during the initial phase of drug release, the fiber had the effect of reducing the fluctuation of release rate compared with that of fiber-free gels. The figures were show in Table 1 in detail. The reason for the narrowing of the rate derivative difference between these two gels after 6 h may due to the decline of total drug concentration in the systems.

3.2. Additional ions effects

The fibers in the formulations were found to decrease its release rate compared with simple gels at the same KP concentration, especially at higher concentration of KP, so other ions were needed to enhance the drug-ion exchange in KP-fiber gels. The ion-layer (Fig. 1) consisted of chitosan gel containing 2.5% NaCl was designed to assess enhancing effects.

The release profiles of KP diffuse passively across 0.22 μm microporous membrane into deionized water were firstly studied to determine the real effects of ion-layer on KP release. The KP solubility was largely increased in PBS as previously reported value of 1100 mg/100 ml at 37 °C (Bramanti et al., 1980), so experiments using PBS (0.05 M, pH 7.4) as the receptor medium were also carried on to overcome the limitation of KP solubility in deionized water. Fig. 4 showed that the percent of KP transport across the microporous membrane from the vehicles containing ion-exchange fibers (7.0 mg/ml) into the deionized water was extremely low, and the cumulative amount release was about 1%, however, with the aid of the ion-layer, the cumulative amount release increased about three-fold though still low. The solid line in Fig. 4 showed that the release of KP from the complex

Table 1
The derivative of the release rate into phosphate buffer (pH 7.4) from the simple gel and the KP-fibers gel at the concentration of 7.0 mg/ml across 0.22 μm microporous membrane

Time (h)	1	2	3	4	6	8
KP simple gel	189.28 ± 48.41	−70.97 ± 18.34	12.40 ± 2.04	18.98 ± 2.65	−13.82 ± 2.61	−19.38 ± 2.69
KP-fibers gel	90.93 ± 24.31	13.29 ± 2.83	8.73 ± 1.60	9.18 ± 1.77	−10.25 ± 2.18	−18.21 ± 1.14

Average standard deviations (n = 4).

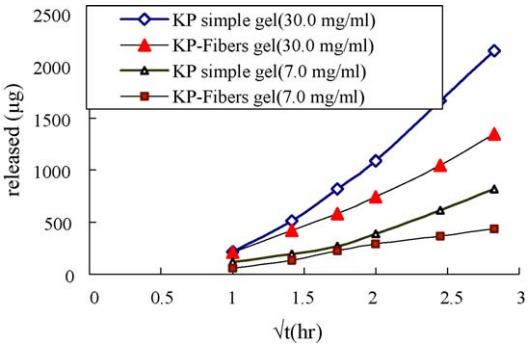

Fig. 5. An illustration of the relationship between the quantity of ketoprofen released and the square root of the time.

vehicles into PBS receptor was found to be considerably faster than that into deionized water, the release rate was about two-fold increased with the enhancing effects of additional ions, so the ion-layer was an effective way to enhance the KP release into either deionized water or PBS, which suggest that the Cl^- used as additional ions in this experiment could diffuse into drug-containing layer and exchange ions with KP to increase and control the rate and extent of KP release.

3.3. Release kinetics

There are several mathematical models of transdermal drug-delivery system. For example, the layer-controlled model was described by Fick's diffusion equation which assuming a linearity between the fraction of the cumulative amount of release (flux) and t, and the matrix diffusion controlled model governed by Higuchi's law of diffusion with a linearity between the flux and $t^{1/2}$. Mathematical analysis of release of KP from different ointment base was carried out by using the Highchi equation for solution type of ointments (Higuchi, 1962). The Higuchi's equation satisfied drug release from the simple gel (Fig. 5) as the release rate was controlled by the gel matrix diffusion (Bannon et al., 1987), and the small intercept reflects the lag time, while drug release from vehicles incorporated with fibers agreed to Fick's equation (Fig. 2).

In order to simplify the parameters for the passive diffusion, the Higuchi equation was adopted. The stead-state flux (J_S) was calculated based on the Higuchi law of diffusion and the real steady-state was achieved after 3 h according to the delivery profiles. For this reason the J_S was calculated from the slope of the plot line between 3 and 8 h. The quantitative parameters of calibration graphs were listed in Table 2. It could be seen that the lag time was short for both simple gel and KP-fibers gel which suggest that KP could transport across skins easily and the ion-exchange action between free ions and drugs loaded in fibers may be a short-time process. There were also some experimental deviation generated during preparation when some KP ions released from the fibers and reached the surface of the gels contacting with the receiver medium, masking the effects of ion-exchange. Compared with ion-exchange resins, the fibers have a non-cross-linked structure (Ekman, 1994) and the enhanced rate of ion exchange in fibers is due to the small shell thickness and larger surface area to unit volume ratio, thus allowing the ions rapidly get access to the ion-exchange groups (Chen et al., 1996). However, the results were similar to that of resins (Conaghey et al., 1998a), which indicated that the drug diffusion through hydrogel matrix was an ultimate controlled process during the release periods.

3.4. Permeation studies

Although ion-exchange materials could be used in gels or other vehicles for transdermal delivery system, it was inapplicable in passive transdermal device across the skin because the hindrance effects caused by ion-exchange mechanism (Conaghey et al., 1998a), however, transdermal systems can be developed with the aid of electric current to control and increase drug delivery (Conaghey et al., 1998b; Tarja et al., 2000; Kankkunen et al., 2002a,b; Vuorio et al., 2004). Furthermore, ion-exchange materials could be considered as concentrated electrolytes with one immobile ionic species (the fixed ionic group) conducing to conduct ability, and could be used as pH buffer materials to sustain constant pH during iontophoretic delivery, thus alleviating the problem of skin irritation (Johnson and Richfield, 1990; Conaghey et al., 1998b).

Transdermal permeation data of ketoprofen across rat skin at pH 7.4 was presented in Fig. 6 both under passive and iontophoretic conditions ($I = 0.5$ mA/cm^2). The electrical assisted transport across rat skin demonstrated an obvious enhancement on releasing process during iontophoretic period and the passive transport afterwards. The increased amount of cumulative delivery was approximately 300 μg/cm^2 for both the simple gel and fiber contained ones. Given the fact that fiber has some hindrance effects during the drug release process, the results indicated that iontophoretic effects can help to overcome the barrier and achieve the similar enhanced response to that of the fiber-free gels and the flux increased significantly with the electrically assisted action. However, the flux of the simple gel was about two-fold increased and the formulation of KP-fibers gel was about four-fold increased. It could be explained that the ion-

Table 2
Parameters obtained when release data were analyzed on the basis of Higuchi's equation

Pattern	Concentration (mg/ml)	Slope × 10^2 (mg/cm^2/$t^{1/2}$)	Lag time (h)	Correlation factor
KP simple gel	7.0	0.797 ± 0.05	1.21	0.999
	30.0	1.938 ± 0.13	1.08	0.999
KP-fibers gel	7.0	0.296 ± 0.01	0.49	0.998
	30.0	1.100 ± 0.06	0.91	0.997

Average standard deviations ($n = 5$).

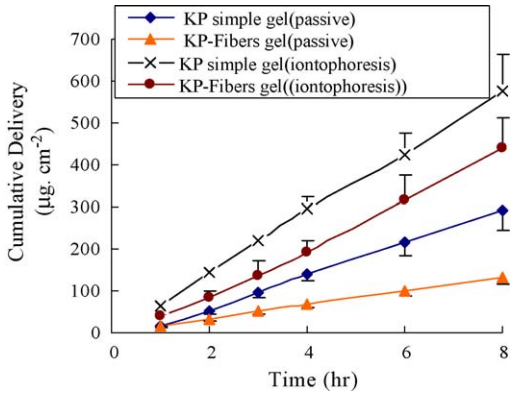

Fig. 6. Passive and iontophoretic assisted ketoprofen (KP) delivery across rat skin into PBS (pH 7.4) in vitro as a function of the fibers compared with the KP simple gels, and the concentrations of ketoprofen in the gels were 7.0 mg/ml. As to the iontophoresis, the current (0.5 mA/cm^2) was on during the first 4 h and off during the last 4 h. Average standard deviations (n = 3–5).

exchange mechanism was not solely responsible for the release of KP, but nonspecific adsorption of free ions also took place on the fibers (Kankkunen et al., 2002a,b). According to the Eq. (1) (Phipps and Gyory, 1992), the higher ion competition for charge, the smaller the chance for the drugs to carry the charge, which decreased the competition between the free ion to the drug ion to carry the current. Furthermore, the fibers in the matrix increase the electro conductivity by the ion-exchange function part.

$$J_d = \frac{t_d I}{F Z_d} \quad (1)$$

In which J_d, t_d and Z_d are the flux, the transport number and the valence of the drug respectively, I the current density and F the Faraday constant.

It is clear that the rate and extent of drug delivery are enhanced with an increasing drug concentration and with an increasing current density until a limiting current value is reached. The maximum strength of current has been suggested to be 0.5 mA/cm^2 which was limited by patient safety considerations (Abramson and Gorin, 1941), and the enhanced transport is nonlinear with the changing electric current (Phipps et al., 1989). Furthermore, 3% (30.0 mg/ml) of KP was the optimum concentration for Carbopol 940 gel (Gurol et al., 1996), so the iontophoresis experiments were operated at 0.5 mA/cm^2 with the KP concentration of 30.0 mg/ml and assisted NaCl ion-layer was at the concentration of 0.6%, 2.5% and 10.0 %, which were investigated to achieve a controlled KP delivery of the maximum transport of drugs.

It was evident from Fig. 7 that the additional ions could promote the permeation rate across rat skin, which was agreed with the results showed above (Section 3.2), and the enhanced J_s were 1.31, 2.17, 3.45 times more than passive transport corresponding with concentration of NaCl 0.6%, 2.5% and 10.0% respectively. At low concentration (0.6%) of NaCl in ion-layer, the release rate could also be increased, which seemed to be contrary to the conclusions gained by Fig. 6. The reason may be that, the increased free ions (Cl^-) dominated the drug delivery over the limited competition with electric current, the combination of the

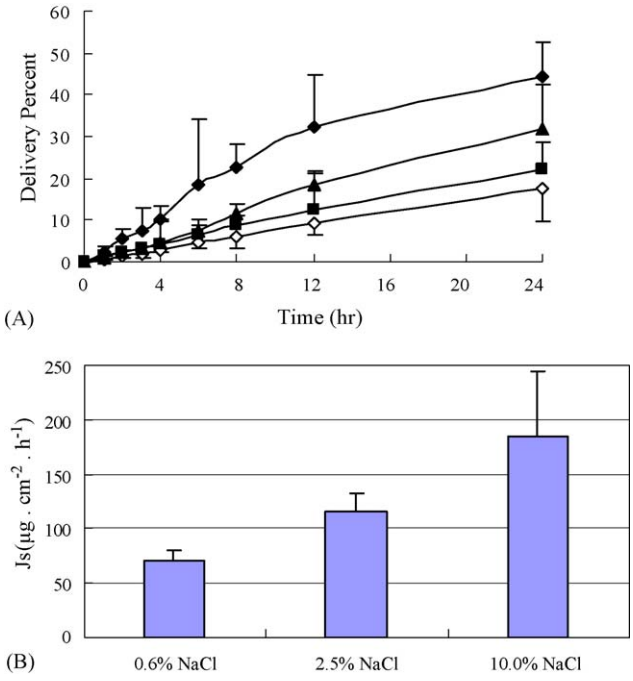

Fig. 7. (A) Iontophosis assisted ketoprofen permeation from gels containing ion-exchange fibers at the concentration of 30.0 mg/ml with the aid of ion-layer cross rat skin into PBS, compared with passive transport. During the iontophoresis the current (0.5 mA/cm^2) was on during the first 4 h and off during the last 20 h. (B) Effect of NaCl concentration on the stead-state flux (J_S). (♦) 0.6% NaCl; (▲) 2.5% NaCl; (■) 10% NaCl; (◊) passive transport. Average ± standard deviation (n = 3–5).

two opposite effects resulted in increased KP transport eventually. However, the initial release with the aid of 2.5% NaCl concentration was slower than that of 0.6% NaCl concentration, demonstrating the correct conclusions gotten from Fig. 6, and as for that of 10.0% NaCl concentration, the factor of the increased quantity of more free ions dominated the drug delivery.

There was an ion-exchange equilibrium between KP ions and counter ions (e.g. Cl^-), and different external conditions, drug properties, and fiber quality contributing to the release kinetics of a drug from ion-exchange systems (Jaskari et al., 2000; Jaskari et al., 2001). The ion-exchange mechanism was described in Eq. (2) and the equilibrium constant K of the reaction was shown in Eq. (3):

$$D^-(\text{fibers}) + Cl^-(w) \leftrightarrow D^-(w) + Cl^-(\text{fibers}) \quad (2)$$

$$K = \frac{C_D(w)\bar{C}_{Cl}}{\bar{C}_D C_{Cl}(w)} = \frac{x^2}{(\bar{n}_D^0)(n_{Cl}^0 - x)} \approx \frac{x^2}{\bar{n}_D^0 n_{Cl}^0} \quad (3)$$

where the top dash denotes the fibers phase, and x is the amount of KP released from the fiber; the latter approximation holds as $x\langle\langle \bar{n}_D^0, n_{Cl}^0$ the initial amounts of KP and NaCl, respectively.

According to the Eq. (3), if the equilibrium constant K was not changed, quadruple the NaCl concentration would increase x and the flux by the factor of $\sqrt{4} = 2$ consequently. However, the ratios of the fluxs were 1:1.7:2.6, in contrast to the expected ratios of 1:2:4. Explanations for the contrasting results may be as follows: the ion-exchange mechanism was not only KP ions but

also other nonspecific ions (Kankkunen et al., 2002a,b); the electric current had an effect on the partition equilibrium between fibers and surrounding ions (Vuorio et al., 2004); though fibers played a important role controlling drug delivery, the presence of the hydrogel surrounding the fibers in these vehicles ultimately controlled the kinetics of release from these vehicles (Conaghey et al., 1998a).

It was found that as the result of high osmosis caused by NaCl in the ion-offering layer, the KP-fibers gel in the donor compartment was diluted by receiver medium gradually as time passed, which could enhance the penetration of NaCl into drug-layer, so the experimental results were deviated from the theoretical results, especially for the 10% NaCl (ion-offering layer) which enabled much higher delivery rate at the beginning but at longer time there was a decrease in the permeation, this phenomenon indicated that the system could not be controlled well with too high concentration of NaCl in ion-offering layer, however, the ion-layer is still an effective way to increase the drug permeation, and with the aid of 2.5% NaCl concentration of the ion-offering layer, a controlled and enhanced delivery under iontophoresis was obtained.

4. Conclusions

The experimental was based on the postulated model and satisfactory results achieved. It was showed that, the ion-exchange fibers could control the rate of drug release and decrease the rate fluctuation caused by concentration variance during drug transportation, which offered great advantage especially for potent drugs with narrow therapeutic windows. With the aid of additional ions at different concentration in ion-offering layer to gain a controlled and enhanced delivery, iontophoresis effects were studied across skins and desired effects were yielded. These studies may provide a semi-quantitative and reasonable means to understand drug delivery from the vehicles containing ion-exchange fibers and across rat skin. However, factors such as nature of the skin (normal or diseased), site of application and the in vivo suitability of the system need to be evaluated and a more perfect transdermal drug delivery system should be developed for practical application.

References

Abramson, H.A., Gorin, M.H., 1941. Skin reactions X. Preseasonal treatment of hay fever by electrophoresis of ragweed pollen extracts into the skin: preliminary report. J. Allergy 12, 169–175.

Bannon, Y.B., Corish, J., Corrigan, O.I., 1987. Iontophoretic transport of model compounds form a gel matrix through a cellophane membrane. Drug Dev. Ind. Pharm. 13, 2617–2630.

Bramanti, G., Pisatura, G., Mazzi, G., Mura, P., Papini, P., 1980. Release of drugs in vitro from different dermatological preparation. Boll Chim. Form. 119, 738–744.

Chen, L., Yang, G., Zhang, J., 1996. A study of the exchange kinetics of ion-exchange fiber. React. Funct. Polym. 29, 139–144.

Chi, S.C., Jun, H.W., 1991. Release rates of ketoprofen from poloxamer gels in a membraneless diffusion cell. J. Pharm. Sci. 80, 280–283.

Conaghey, O.M., Corish, J., Corrgan, O.I., 1998a. The release of nicotine from a hydrogel containing ion exchange resins. Int. J. Pharm. 170, 215–224.

Conaghey, O.M., Corish, J., Corrgan, O.I., 1998b. Iontophoretically assisted in vitro membrane transport of nicotine from a hydrogel containing ion exchange resins. Int. J. Pharm. 170, 225–237.

Dvofak, J., Hajkova, R., Matysova, L., Novakova, L., Koupparis, M.A., Solich, P., 2004. Stimulataneous HPLC determination of ketoprofen and its degradation products in the presence of preservatives in pharmaceuticals. J. Pharm. Biomed. Anal. 36, 625–629.

Ekman K., 1994. Applied radiation processing of polyolefins. PhD Thesis, University of Truku.

Fossgreen, J., 1976. Ketoprofen. A survey of current publications. Scand. J. Rheum. 14, 11–32.

Gurol, Z., Hekimoglu, S., Demirdamar, R., Sumnu, M., 1996. Percutaneous absorption of ketoprofen. I. In vitro release and percutaneous absorption of ketoprofen from different ointment bases. Pharm. Acta. Helvetiae. 71, 205–212.

Guy, R.H., Hadgraft, J., 1992. Rate-control in transdermal drug delivery. Int. J. Pharm. 82, R1–R6.

Helfferich, F., 1995. Ion Exchange. Dover Publications, New York.

Higuchi, W.I., 1962. Analysis of data on medicament release from ointments. J. Pharm. Sci. 51, 802–804.

Jaskari, T., Vuorio, K., Urtti, A., Manzanares, J., 2000. Controlled transdermal iontophoresis by ion-exchange fiber. J. Controlled Release 67, 179–190.

Jaskari, T., Vuorio, M., Kontturi, K., Manzanares, J.A., Hirvonen, J., 2001. Ion-exchange fibers and drugs: an equilibrium study. J. Controlled Release 70, 219–229.

Johnson, M.T.V., Richfield, N.H.L, 1990. pH buffered electrode for medical electrophoresis. US Patent, 4,973,303.

Phipps, J.B., Gyory, J.R., 1992. Transdermal ion migration. Adv. Drug. Deliv. Rev. 9, 137–176.

Kantor, F.G., Ketofen, 1986. A review of its pharmacologic and clinical properties. Pharmacotherpy 6, 93–103.

Kankkunen, T., Huuppouen, I., ahtinen, K.L., Sundell, M., Ekman, K., 2002a. Improved stability and release control of levodopa and metaraminol using ion-exchange fibers and transdermal iontophoresis. Eur. J. Pharm. Sci. 16, 273–280.

Kankkunen, T., Sulkava, R., Vuorio, M., Kontturi, K., Hirvonen, J., 2002b. Transdermal iontophoresis of tacrine in vivo. Pharm. Res. 19, 705–708.

Peltola, P., 1976. Long-term treatment with ketoprofen in rheumatoid arthritis. Scand. J. Pheum. 14, 115–117.

Phipps, J.B., Padmanabhan, R.V., Lattin, G.A., 1989. Iontophoretic delivery of model inorganic and drug ions. J. Pharm. Sci. 78, 365–369.

Rodam, A., Sabatini, L., Mirasoli, M., Baraldini, M., Roda, E., 2002. Bioavailability of a new ketoprofen formulation for once-daily oral administration. Int. J. Pharm. 241, 165–172.

Rolf, C., Engstrom, Beauchard, B.C., Jacobs, L.D., Le Liboux, A., 1999. Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. Rheumatology (Oxford) 38, 564–567.

Simon, J.G., Lionel, T., Charles, M.H., 2003. Ketoprofen: release from, permeation across and rheology of simple gel formulations that simulate increasing dryness. Int. J. Pharm. 268, 37–45.

Singh, P., Roverts, M.S., 1993. Iontophoretic transdermal delivery of salicylic acid and lidocaine to local subcutaneous structures. J. Pharm. Sci. 82, 127–131.

Vuorio, M., Murtomaki, L., Hirvonen, J., Kontturi, K., 2004. Ion-exchange fibers and drugs: a novel device for the screening of iontophoretic systems. J. Controlled Release 97, 485–492.

Tarja, J., Marja, V., Kyosti, K., Arto, U., Jose, A.M., Jouni, H., 2000. J. Controlled Release 67, 179–190.

Zutshi, D., Mason, M., 1976. Ketoprofen in rheumatoid arthritis: its tolerance and therapeutic effect. Scand. J. Rheum. 14, 77–84.