Electrically Modulated Transport of Diclofenac Salts Through Hydrogels of Sodium Alginate, Carbopol, and Their Blend Polymers

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ABSTRACT: The electrically modulated transdermal migration of diclofenac sodium (DS), diclofenac potassium (DP), and diclofenac diethylammonium (DD) drugs from the hydrogels of sodium alginate (NaAlg), carbopol (CP), and blends of NaAlg with CP prepared in 2:1, 2:1.5, and 2:2 ratios was investigated. The release of DS, DP, and DD was investigated through excised rat skin to study the effects of viscosity, pH, and the ionic strength of the receptor medium under the influence of an electrical current in a switch-on and switch-off mode. A pulsatile pattern of transport was observed that depended on the presence or absence of an electrical current. Drug transport was dependent on the electrical current, the ionic nature of drugs, and the ionic strength of the diffusion medium. Drug transport followed the sequence DS > DP > DD. A decrease in viscosity and an increase in the pH of the hydrogel were observed when an electrical current was applied. CP was more responsive to an electrical stimulus, but the rate of transport was higher for NaAlg. Increasing the amount of CP in the blends increased the electrical responsiveness. The blend hydrogel with a high CP content showed the highest enhancement in drug transport, whereas the NaAlg hydrogel showed the least. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 96: 301–311, 2005

Key words: drug delivery systems; stimuli-sensitive polymers; hydrogels; blends

INTRODUCTION

Research on electromodulated drug transport from polymeric hydrogels has been recently reviewed.[1–4] Chemically induced stimuli, such as pH, metabolites, and ionic factors, could alter interactions with polymer chains[5–8] and, thus, modify the drug-release patterns. However, physical stimuli, such as temperature and electrical current, could induce polymer-chain segmental motions due to varying molecular interactions. These interactions are controlled by conformation, swelling, ionic nature, and polymer solubility. Electroresponsive hydrogels that can carry free cations or anions are interesting for the design of electrically modulated drug-delivery systems. Such hydrogels prepared from polyelectrolytes containing relatively high concentrations of ionizable groups along the polymer backbone exhibit electroresponsive and pH-responsive characteristics. From a search of the literature, only a few reports are available on the effect of electrical current versus drug transport across the skin.[9–11] Carbopol (CP), a poly(acrylic acid) (PAA) in anionic form, contains many free hydroxyl groups. Because it can form a gel, it has been used in combination with agarose and xanthan gum for the electrically modulated delivery of hydrocortisone.[11] Yuk et al.[12] prepared calcium alginate/PAA composites and found that increasing the amount of PAA in the composite increased the pH responsivity and electroresponsivity of their hydrogels. Kim and Lee[13] investigated the electrically modulated release of cefazoline (ionic) and theophylline (nonionic) drugs with interpenetrating polymeric networks of poly(vinyl alcohol) and PAA synthesized by ultraviolet irradiation. The amount of drug loading increased significantly with increasing PAA content. The release rate of the ionic cefazoline drug was higher than the nonionic theophylline drug.

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Chitosan, a naturally occurring cationic biopolymer with a low toxicity, has also been used in electrically modulated drug-delivery systems in the form of hydrogels.[14,15] Recently, Agnihotri and Aminabhavi[16] developed a novel method of producing microparticles of chitosan for the controlled release (CR) of clozapine. Kulkarni et al.[17] prepared beads of sodium alginate (NaAlg) with gelatin and egg albumin by crosslinking with glutaraldehyde for the CR of cefadroxil. Similarly, modified guar gum (GG) matrix tablets were developed for the CR of diltiazem hydrochloride.[18] Chemically modified polyacrylamide-*graft*-GG based crosslinked anionic microgels were prepared and characterized as pH-sensitive hydrogels for the CR of nifedipine and diltiazem hydrochloride.[6] NaAlg interpenetrating monolithic membranes were studied for the transdermal delivery of verapamil hydrochloride.[19] The importance of the rheological properties of the dispersions of NaAlg and GG mixtures was shown,[20] wherein it was emphasized that the blending of NaAlg with GG produced hydrogels exhibiting a unique stimuli responsiveness.

As a part of our ongoing studies on the development of novel hydrogel polymers,[16–20] in this study, we have investigated novel polymeric hydrogels that were responsive to electrical stimuli for the transport of diclofenac sodium (DS), diclofenac potassium (DP), and diclofenac diethylammonium (DD) drugs through CP, NaAlg, and NaAlgCP hydrogels in three different compositions. Diclofenac, a nonsteroidal anti-inflammatory drug available in three salt forms, namely, sodium, potassium, and diethylammonium, were incorporated into hydrogel matrices to study their responsiveness to electrical current, pH, and the viscosity of the medium. Diclofenac salts of sodium, potassium, and diethylammonium have poor penetration through the skin,[21] and hence, a pore pathway in the skin constitutes an important route for the penetration of diclofenac salts.[22] However, on the basis of the literature,[23] the permeation of such ionic drugs can be facilitated by the iontophoretic technique. This prompted us to investigate the electrically modulated transport of diclofenac salts across excised rat skin through NaAlg, CP, and their blend hydrogels. The hydrogels were examined for their rheological behavior, pH, and drug-transport characteristics across excised rat skin both in the presence and absence of an electrical direct current (dc); we also studied the effects of the intensity of the applied electrical current and the ionic nature of the drugs.

EXPERIMENTAL

Materials

Gift samples of CP 934P, DD, DS, and DP were provided by Eros Pharma, Ltd. (Bangalore, India). NaAlg (molecular weight ≅ 240,000), triethanolamine (TEA), and sodium chloride were purchased from S. D. Fine Chemicals (Mumbai, India). Double-distilled water was used throughout, and its purity was judged by the measurement of its conductivity at 25°C, which agreed closely with the literature value of 0.043×10^{-6} S/cm. All of the other chemicals were analytical-grade samples and were used as received. Albino rats weighing between 150 and 180 g were procured from the local animal house. Before the experiments, ethical committee clearance was obtained from the center on the submitted protocol.

TABLE I
Preparation and Composition of the Hydrogels Prepared in Water

Hydrogel matrix	NaAlg (g)	CP (g)	Drug (g)
NaAlg	2.0	—	0.5
CP	—	2.0	0.5
NaAlgCP-1	2.0	1.0	0.75
NaAlgCP-2	2.0	1.5	0.875
NaAlgCP-3	2.0	2.0	1.0

Methods

Preparation of the hydrogels

Hydrogels of CP, NaAlg, and their blends (with NaAlg:CP in the ratios 2:1, 2:1.5, and 2:2 and designated as NaAlgCP-1, NaAlgCP-2, and NaAlgCP-3, respectively) were prepared by the dissolution of polymers of known mass (see Table I) in distilled water with a magnetic stirrer for 5 h at 50°C in a water bath to obtain a homogeneous mixture. The drugs (25% w/w of the total polymer concentration), namely, DS, DP, and DD, were uniformly incorporated into polymeric solutions. These solutions were converted to hydrogels by the neutralization of the solution pH with TEA. The drug-loaded NaAlg hydrogel was prepared by the dissolution of 2% (w/v) of NaAlg and the drug in distilled water without neutralization. These prepared hydrogels were stored in a closed container at room temperature for further evaluation.

Measurement of the viscosity

The viscosity of the hydrogels was measured with a Brookfield rheometer (model DV-III; Middleboro, MA). The selection of the spindle was made based on the percentage torque value, which varied from 10 to 90 (the manufacturer's recommended optimum range). T-bar spindles were used for all of the hydrogels except NaAlg. The viscosity of the NaAlg hydrogel was measured with a small volume adopter (SC-21). Two flat electrodes were placed in a beaker (in the opposite direction at a distance of 4 cm) containing the

TABLE II
Percentage Torque, Viscosity, and pH of the Hydrogels Before and After the Application of an Electrical Stimulus

	Before the electrical stimulus			After the electrical stimulus		
Hydrogel	Torque (%)	Viscosity (mPas)	pH	Torque (%)	Viscosity (mPas)	pH
NaAlg	11.7 ± 1.2	975 ± 1.6	7.83 ± 0.02	11.5 ± 1.0	958 ± 1.0	11.29 ± 0.01
CP	36.9 ± 1.4	68500 ± 1.0	8.23 ± 0.04	35.7 ± 1.5	62333 ± 1.4	11.64 ± 0.04
NaAlgCP-1	38.1 ± 0.8	123000 ± 1.2	8.09 ± 0.03	30.8 ± 1.6	102667 ± 0.6	11.05 ± 0.05
NaAlgCP-2	42.8 ± 1.1	127000 ± 0.7	7.99 ± 0.02	35.9 ± 0.9	119000 ± 0.8	10.14 ± 0.04
NaAlgCP-3	41.1 ± 0.9	713333 ± 1.5	7.93 ± 0.01	37.4 ± 0.9	598333 ± 1.1	11.25 ± 0.02

The data presented are the average values of the triplicate measurements. ± Values represent the standard deviations.

hydrogels. The torque and viscosity data were collected with the application of a 10-mA current and without any current. Before the actual readings were taken, the rheometer scale was autozeroed, and data were collected at 37°C. A constant temperature was maintained by placement of the sample chamber in a precision-stirred thermostatic bath (Grant, model GR 150, GP 200, Cambridgeshire, UK). These data are presented in Table II.

Measurement of the pH

The pH values of all of the hydrogels were measured with a pH meter (Jenway, model 4330, Essex, UK) by the dilution of the hydrogels (~100 mg) in 5 mL of double-distilled water at room temperature before and after the application of an electrical current. These results are included in Table II along with their estimated standard deviations.

Electric-current-generating device

The electric-current-generating device[23] was designed and fabricated to meet the following requirements: current range = 0–30 mA; off–on ratios = 1:1 and 1:4; time to charge and discharge = 3-min pulse waveform, square; current type = dc or pulsed dc. The device had manual selector switches for dc and the desired off–on ratio and a knob for current adjustment, which could be read on the ammeter. The device could be operated on an alternating current of 220 V stepped down to 12 V or on two 9-V cells (Scientek Instruments, Bangalore, India).

Electrodes

Two bars of platinum foil were used as electrodes (Scientek Instruments, Bangalore, India). We assumed that the pH of the donor compartment was changed, in which case platinum was used as the electrode.[24] In this study, the pH of the donor compartment was changed before and after the application of the electrical current (the results are shown in Table II). The preliminary experiments indicated that currents of 10, 15, and 20 mA and a potential difference of 10 V were suitable. The duration of each experiment was 2 h. The drug-release study was carried out with switching at intervals of 30 min or without switching. A control study was also carried out without the application of an electrical current (passive).

Preparation of rat skin and *in vitro* excised skin permeation studies

For full-thickness skin, the abdominal skin of the albino rats was thawed before use by immersion in distilled water at room temperature. The hair and underlying subcutaneous dermal fats were scrapped off carefully without damage to the skin, until the skin was about 1 mm thick. The skin was cut into small circular patches, and each skin piece was mounted onto the donor compartment of a Keshary–Chien diffusion cell. We immediately checked the ready-made donor compartment for possible leaks by taking distilled water before the *in vitro* drug-transport study.

In vitro drug-transport experiments were conducted with Keshary–Chien diffusion cells across the excised rat abdominal skin under various conditions: (1) without an electrical stimulus (passive diffusion), (2) with a constant electrical stimulus with 10- and 20-mA currents, (3) with a switching on-and-off electrical stimulus with a 10-mA current, and (4) with normal saline as the receptor medium with ionic strengths of 0.050, 0.100, and 0.155*M*. Vertically assembled Keshary–Chien diffusion cells with a downstream volume of 13 mL were used in these experiments. The excised rat abdominal skin was carefully mounted on the donor compartment containing the hydrogel matrix, facing the stratum corneum toward the donor side and the dermis toward the receptor compartment, which was filled with normal saline. Electrodes of platinum were used. The cathode was placed in the donor compartment, and the anode was placed in the receptor compartment. The electrical stimulus was then applied to the hydrogel with a regulated dc power source, as shown in Figure 1.

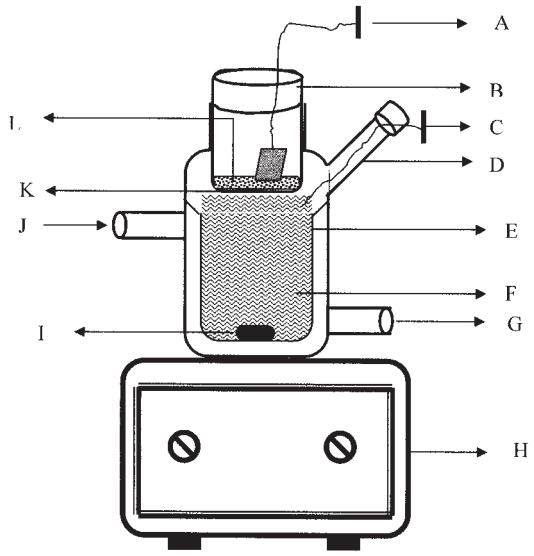

Figure 1 Vertically assembled Keshary–Chien diffusion cell used for electrically modulated drug-release experiments: (A) cathode, (B) donor compartment, (C) anode, (D) sampling port, (E) receptor compartment, (F) diffusion medium, (G) water outlet, (H) magnetic stirrer, (I) Teflon-coated magnetic bead, (J) water inlet, (K) rat skin, and (L) hydrogel matrix.

The receptor solution was constantly stirred at 100 rpm with a magnetic stirrer (Jenway, model 1103), and the entire assembly was maintained at 37°C by circulation of water from the water bath (Grant, model GR 150, GP 200). The concentration of drug transported into the receptor medium was estimated by the withdrawal of 5-mL aliquots at specific time intervals. The withdrawn volume was replenished with an equal volume of fresh normal saline. The samples were analyzed for drug content with an ultraviolet spectrophotometer (Secomam, model Anthelie 2, Domont, France) at a λ_{max} value of 277 nm. There was no interference from the skin contents when we analyzed the drug content.

The cumulative amount of drug permeated per unit of surface area of the skin was plotted versus time, and the slope of the linear portion of the plot was calculated[25] as the steady-state flux (J_{SS}). The permeability coefficient (K_p), was then calculated with the following equation:

$$K_p = \frac{J_{SS}}{C_V} \quad (1)$$

where C_V is the total concentration of the drug in the donor compartment. The enhancement factor (EF) was calculated[26] with the following equation:

$$\text{EF} = \frac{J_{SS}\ (\text{with electric stimulus})}{J_{SS}\ (\text{without electric stimulus})} \quad (2)$$

The computed results are the averages of three independent readings, which are presented in Table III together with the standard deviations.

RESULTS AND DISCUSSION

Hydrogel formation

Electroresponsive hydrogels can be prepared from polyelectrolytes, that is, polymers containing relatively high concentrations of ionizable groups along the backbone and are thus pH responsive and electroresponsive.[27] In this study, we chose CP having carboxylic groups. However, synthetic and natural polymers individually or in combination can be used to form hydrogels because of the formation of H bonds in the network. CP has a pK_a of 6.0, and hence, it forms an acidic solution in water. To convert this solution into a hydrogel, it is necessary to increase the pH to greater than 7.0. This was done by the addition of TEA dropwise and the monitoring of the pH to confirm the end point. The NaAlg hydrogel was formed by the dissolution of 2% (w/v) of NaAlg in distilled water; here, adjustment of the pH was not necessary because NaAlg in water already had a pH of 7.83. The hydrogel formed was transparent and smooth and could conduct an electrical current. The drugs were uni-

TABLE III
Flux, Permeability Coefficient, and Enhancement Factors of Various Hydrogel Formulations with or without an Electrical Stimulus

	Without the electrical stimulus		With the electrical stimulus		
Hydrogel	J_{ss} $(\mu g/cm^{-2}/h)^{-1}$	$K_p \times 10^3$ (cm^2/h)	J_{ss} $(\mu g/cm^{-2}/h)^{-1}$	$K_p \times 10^3$ (cm^2/h)	EF
NaAlg	24.8 ± 0.8	33.7 ± 1.2	115.7 ± 0.5	157.3 ± 1.0	4.6 ± 0.9
CP	17.6 ± 0.6	9.0 ± 0.9	144.0 ± 0.8	73.4 ± 0.7	8.2 ± 0.7
NaAlgCP-1	15.8 ± 1.0	14.4 ± 0.9	96.5 ± 0.8	88.4 ± 0.8	6.1 ± 0.9
NaAlgCP-2	14.4 ± 0.5	11.3 ± 0.7	107.2 ± 0.3	84.6 ± 0.6	7.5 ± 0.6
NaAlgCP-3	12.4 ± 0.9	12.8 ± 0.9	136.6 ± 0.4	142.0 ± 1.1	11.1 ± 1.0

The results are the averages of three observations (n = 3). The ± values represent the standard deviations.

formly dissolved into the hydrogels without the formation of a precipitate when the pH was raised to greater than 7 except for the NaAlg hydrogel.

CP formed stiffer hydrogels than NaAlg at the same concentration (2% w/v). The stiffness of the hydrogel increased with increasing concentration of CP in the blend hydrogel. This resulted in lower transport of the drug from the CP hydrogel than from the NaAlg hydrogel in the absence of an electrical current. To circumvent these problems, we prepared blend hydrogels of CP with NaAlg, and this improved the transport rates without affecting the electrical conductivity. Individual hydrogels of CP or NaAlg were also prepared and studied immediately. However, no hydrogels were stored for more than 7 days after they were prepared. We found that all of the hydrogels were stable up to 30 days without the addition of any preservatives by observing changes in viscosity, phase separation, precipitation of drugs, and microbial growth. Here, the microstructure of the transparent hydrogels formed was responsible for drug transport.

Viscosity of the hydrogels

Viscosity was measured with T-bar spindles to avoid the formation of channels in the hydrogels during the rotation of the spindle. The up-and-down movements of the spindles were achieved by a special helipath stand supplied with the instrument. The viscosity and torque data of NaAlg, CP, and their blends measured with and without an electrical stimulus are presented in Table II. For all of the hydrogels, the torque values were reduced when an electrical current was applied. Also, there was an increase in the torque from the NaAlg hydrogels to the blend hydrogels. However, the torque values in all cases were kept within the manufacturer's recommended range. From a close perusal of the viscosity data of all of the hydrogels with and without an electrical current, we found a considerable decrease in the viscosity when an electrical current was applied. This decrease was considerable, as the amount of CP in the blend hydrogels was increased, thus indicating a collapsed structure of the hydrogel matrix (see the data displayed in Fig. 2).

The reduction in viscosity with increasing speed of the spindle was more prominent in the CP hydrogel than in the NaAlg hydrogel. This was due to the fact that NaAlg formed a highly viscous dispersion, which was rather steady, to withstand the stress. Hydrogen ions generated around the anode might have been responsible for the collapse of the hydrogel network.[12] Thus, negative charges of anionic groups attached to immobile polymer chains built up a negative pressure inside the hydrogel matrix under the influence of the electrical pulse. This pressure varied continuously throughout the gel matrix. When this negative pressure was sufficient to bring about the phase transition, the hydrogel underwent shrinkage.[28] At the cathode, a liquid might have gotten squeezed out of the matrix, and hence, the driving force for liquid separation was electro-osmotic movement from the anode to the cathode.[29]

pH of the hydrogels

The measurement of the pH of hydrogels was done before and after drug-release experiments under the influence of an electrical stimulus. These results are presented in Table II. Before electrification, all of the hydrogels had lower values of pH, ranging from 7.83 to 8.23, but after electrification, the pH values in all of the cases increased dramatically. However, this effect was not as systematic as that observed for the viscosity trends discussed previously. After the electrical stimulus was applied, the following events could have taken place at the donor and receptor compartments.

At the donor compartment (cathode)

$$H_2O \rightarrow OH^- + H^+$$

$$DR \rightarrow D^- + R^+$$

$$2H^+ + 2e^- \rightarrow H_2 \uparrow$$

where D is the drug (diclofenac) and R is Na, K, or N $(C_2H_5)_2$.

At the receptor compartment (anode)

$$NaCl \rightarrow Cl^- + Na^+$$

$$Na^+ + OH^- \text{ or } D^- \rightarrow NaOH \text{ or } NaD$$

$$2Cl \rightarrow Cl_2 + 2e^-$$

During electrification, the electrolysis of water takes place and causes the movement of positively charged ions electrophoretically toward the cathode and negatively charged ions toward the anode. In this process, only small ions such as OH^- and diclofenac can migrate to the donor compartment (anode) throughout the hydrogel matrix, but polymeric ions (polyelectrolytes) cannot pass through. This increases the pH of hydrogel in the donor compartment. The pH gradient acts as a driving force for the enhanced drug transport from the hydrogel in accordance with Tanaka's hypothesis.[28] There are also other reports in the literature[13,15] suggesting that ions could be produced by electrochemical reactions and that these ions will move toward counterelectrodes, which will induce a pH gradient inside the gel matrix under the influence of an electrical current.

In vitro permeation studies

Effect of the electrical current

On the basis of previous studies,[30,31] the permeation of ionic drugs such as diclofenac can be facilitated by the

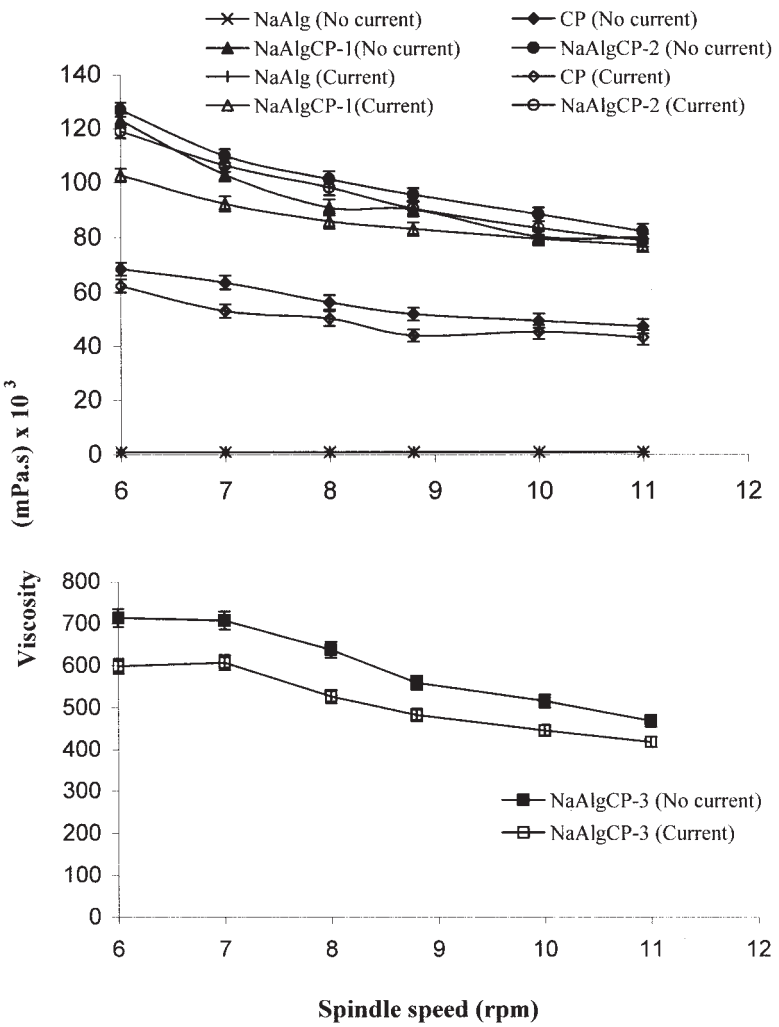

Figure 2 Effect of electrical stimulus and spindle speed on the viscosity of various hydrogels. The closed symbols (■, ▲, ●, ◆, and ×) indicate the viscosity of hydrogels without an electrical stimulus, and the open symbols (△, □, ◇, ○, and +) indicate the viscosity of hydrogels with an electrical stimulus.

application of an electrical potential. However, several variables may influence the transdermal permeation of the drug molecules, including the physicochemical properties of the drug, vehicle composition, electrical factors, and skin barrier properties.[1] In this study, we attempted to investigate the influence of the electrical and chemical properties on the *in vitro* transdermal permeation of the diclofenac salts of sodium, potassium, and diethylammonium to compare their transport characteristics. Electrical and chemical variables, such as current density, drug concentration, and the ionic strength of the medium were studied to optimize the transport rate of these salts.

Electrically responsive polyelectrolyte hydrogels have been studied extensively.[1] In most of these studies, hydrogels were composed of anionic polymers, but in a few cases, cationic hydrogels have also been studied.[15] However, the drug to be transported under the influence of an electrical current may have the same or opposite charge to the polymer network, or it may be neutral. Pulsatile drug release from a hydrogel when an electrical current is switched on and off has been demonstrated, wherein the drug is transported when the current is switched on and drug transport is stopped when the current is switched off.[12] Such an electrically responsive drug transport occurs by a number of different mechanisms. For instance, the charged drug migrates toward the oppositely charged electrode, and thus, drug transport is largely governed by the effect of the electrical current on the hydrogel matrix. Examples of electrically responsive drug transport from hydrogels include the pulsatile patterns of raffinose, pilocarpine hydrochloride, glucose, and insulin.[27] In these studies, the drug was transported after an electrical current was applied, and the rate of drug transport was dependent on the strength of the electrical field.

In this study, we investigated the transport of diclofenac salts as a function of time for hydrogel ma-

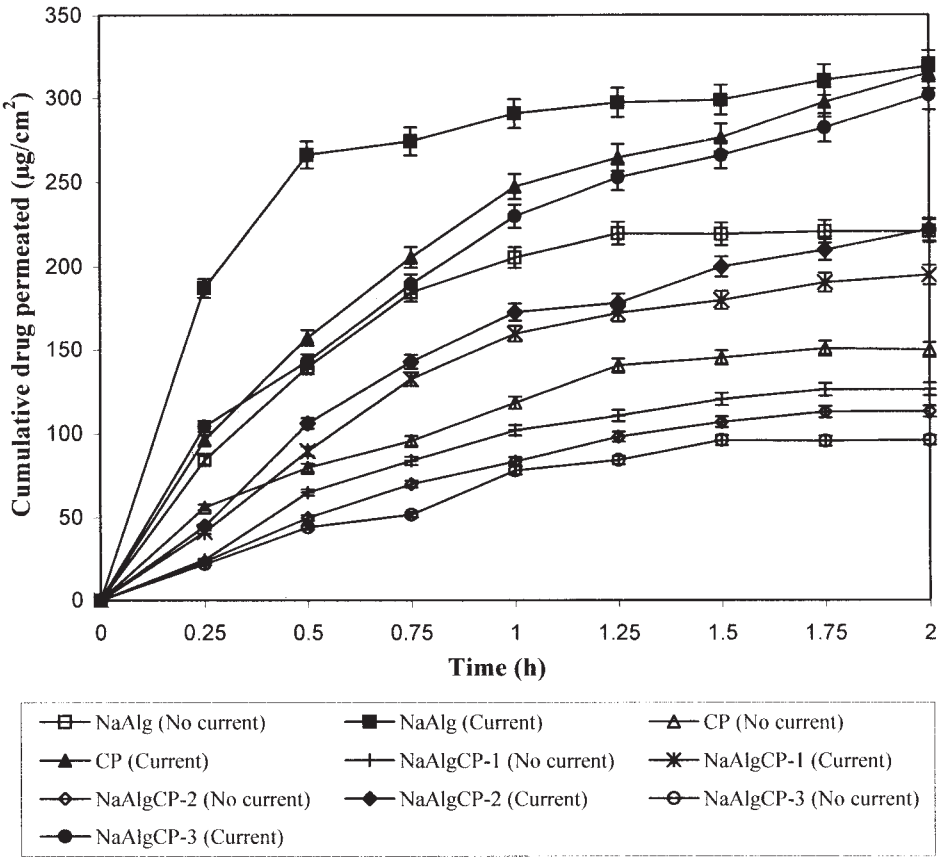

Figure 3 *In vitro* permeation of DD from various hydrogel formulations across the rat abdominal skin with or without an electrical stimulus. The closed symbols (■, ▲, ●, ♦, and ×) indicate the permeation of the drug with an electrical stimulus, and the open symbols (△, □, ◇, ○, and +) indicate the permeation of the drug without an electrical stimulus.

trices developed with and without an electrical stimulus. The J_{SS} and K_p results calculated in the presence and absence of an electrical current are presented in Table III. We observed a considerable increase in J_{SS} and K_p values from no current (passive) to an applied current, indicating that the electrical current exerted a considerable influence on drug transport. EF for the NaAlg hydrogel was lower than that observed for the CP hydrogel, whereas among the blend hydrogels studied, NaAlgCP-3 had the highest EF value (11), but intermediate EF values were observed for other blend hydrogels. A systematic decrease in EF with decreasing CP content in the blend was observed. The response of a hydrogel to an electrical current has been studied earlier[1] with different experimental techniques. However, in this setup, the anode (donor) was placed in the hydrogel matrix, and the cathode was placed in the receptor compartment. On application of the electrical current, certain hydrogels swelled, and others deswelled.

The results of the cumulative drug (typically presented for DD) that permeated across the skin versus time for all of the matrices are displayed in Figure 3, both in the presence and absence of an electrical current. Permeation of DD in the presence of an electrical stimulus was much higher for the pure NaAlg hydrogel than for all of the other matrices. The lowest drug permeation rate was observed for the NaAlgCP-3 hydrogel with no electrical stimulus. The rate of permeation of the drug was always higher when an electrical stimulus was applied in all of the cases compared to when there was no electrical stimulus. Drug transport through the hydrogels under the influence of an electrical stimulus varied as per the sequence NaAlg > CP > NaAlgCP-3 > NaAlgCP-2 > NaAlgCP-1. However, EF was quite large for NaAlgCP-3 (i.e., for the hydrogel matrix containing a higher amount of CP). These data showed a close relationship with the J_{SS} and K_p values of the matrices presented in Table III. For instance, the NaAlg hydrogel with the highest value of J_{SS} and K_p exhibited the highest drug-transport rate compared to the other matrices, both in the presence and absence of an electrical current. The effect of an electrical stimulus on drug transport depends to a large extent on the mechanism by which the hydrogel responds to the stimulus. Particularly, the mechanism via which the hydrogel responds to stimulus and that of drug transport from the hydrogel depends on the interactions between the drug molecules and the hydrogel network.[15]

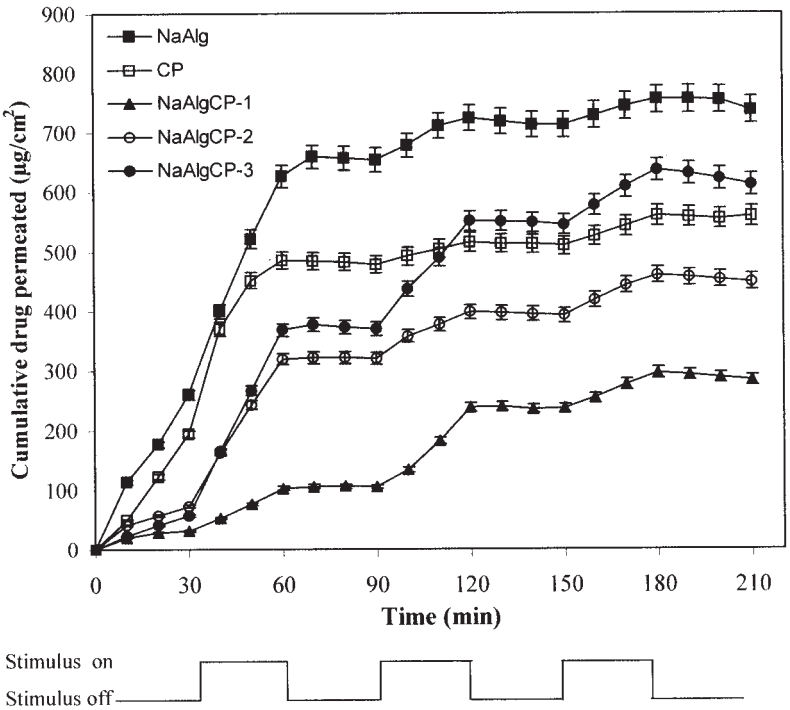

Figure 4 Pulsatile release behavior of various hydrogel matrices in which the electrical stimulus was switched at 30-min time intervals.

The mechanism of drug transport can also be attributed to a forced convection of the drug out of the hydrogel cage along with the syneresed water molecules, the diffusion and electrophoresis of the charged drug molecules, and the liberation of the drug on the erosion of electroerodible hydrogels. In addition to these effects, the pH and viscosity of the hydrogels also play an important role in the transport of drugs through hydrogels. To understand this effect, we measured the pH and viscosity of the hydrogels (see the data presented in Table II). The viscosity of all of the hydrogels decreased on application of the electrical current due to the deswelling of the matrix, but the pH of the medium increased when the electrical stimulus was applied. According to Sawahata et al.,[32] drug transport occurs only if the applied electrical current is sufficiently high to induce dimensional changes in the hydrogel. With increasing CP content in the blend, an increased number of carboxylic acid groups (ionized or un-ionized) induced changes in the local pH, leading to hydrogel deswelling, which in turn, increased the drug-transport rate.

At higher voltages/currents, the slope of the curves decreased (see the data presented in Fig. 4) in the same way that the rate of hydrogel deswelling decreased with increasing voltage. The reduced drug transport may have been due to reduced deswelling and a lower drug concentration in the hydrogel matrix because the latter would have been depleted of the drug. Thus, drug release was stopped when the electrical current was switched off. The results of a pulsatile on-and-off profile of drug transport with switching the electrical current on and off are shown in Figure 4. Sometimes, backflow of the drug from the hydrogel was also observed when the electrical current was switched off. This was due to the swelling of the hydrogel as a result of the absorption of the transported media.[32] Depending on whether the electrical stimulus was turned on or off, drug release was also turned on and off in a pulsatile manner (see Fig. 4) after the electrical current was switched on at 30-min intervals. A possible reason for this type of switching pattern of drug permeation was electrically induced changes in the osmotic pressure of the liquid media within the hydrogel matrix. However, the local pH gradient due to electrolysis of the associated water molecules may have also changed the swelling of hydrogels and the drug-release patterns.

The effect of the electrical current strength on drug transport of DD from the CP hydrogels is displayed in Figure 5. With no electrical stimulus, the drug permeation rate was much lower than that under the influence of an electrical stimulus. With increasing current density from 10 to 20 mA, there was a systematic increase in the drug permeation rate from 15 min to 2 h. Electrically induced anisotropic hydrogel deswelling was first explained by Tanaka et al.,[28] who suggested that electric field strength induces stress on both mobile counterions and immobile charged groups of the hydrogels' network. In addition, electri-

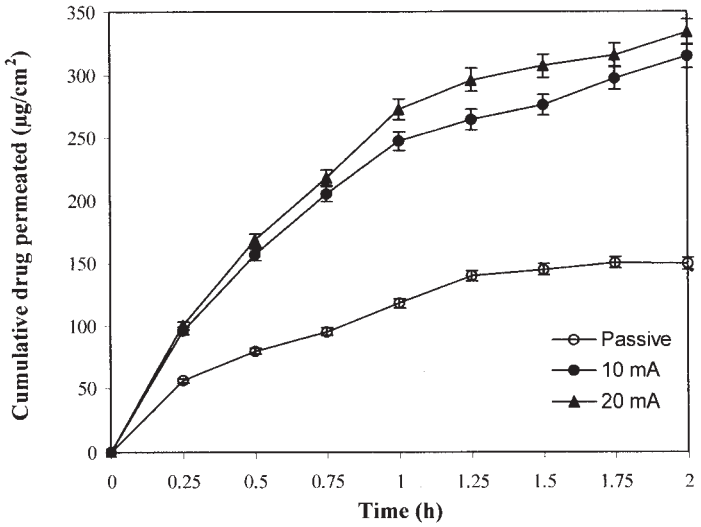

Figure 5 Effect of the electrical current strength on the transport of DD from the CP hydrogels.

cally induced changes in the local pH at the electrodes due to electrolysis of water might also cause anisotropic hydrogel deswelling. The other possibility would be the electro-osmosis of water coupled with electrophoresis. Thus, on the basis of our experimental data, we suggest three possible mechanisms of electroinduced hydrogel deswelling: (1) the establishment of a stress gradient in the hydrogel, (2) changes in the local pH around the electrodes, and (3) electro-osmosis of water coupled with electrophoresis.

Effect of the ionic strength of the diffusion medium

The ionic strength of the diffusion medium exerts an influence on the release rates of drugs. In this study, we investigated the transport of DD through a CP hydrogel matrix in media containing three different ionic strengths, namely, 0.05, 0.1, and 0.155*M*, under a constant applied electrical stimulus of 10 mA. These results are displayed in Figure 6. We found that 16.06% of the drug was released in the medium with an ionic strength of 0.155*M*, whereas 18.33% of the drug was released in the medium with an ionic strength of 0.1*M* compared to no ionic medium. We realized that at higher ionic strengths, the drug-transport rate was lower with time than that observed in the lower ionic strength media. This may have been due to a decrease in the solubility of the drug with increasing ionic strength of the medium.

Effects of the different salt forms of the drugs

A comparison of the drug-transport rates with respect to the salts of diclofenac (DS, DP, and DD) through the hydrogels was also studied in the presence and absence of an electrical stimulus. The data presented in Figure 7 suggest that the transport of diclofenac salts was affected by their counterions. For instance, DS transport across the rat skin was higher than DP transport, which in turn, was higher than DD transport (i.e., the transport followed the order DS > DP > DD). An intercellular lipid pathway may have been responsible for the transport of drug molecules through the skin. In addition, we realized that hair follicles might have created pathways for DD transport compared to DS and DP transport under the same electrical stimulus, as was observed earlier by Fang and coworkers.[30,31]

According to Faraday's law, the number of permeant molecules that can pass through the skin increased with increasing electrical current density. Thus, a higher current density of 20 mA was applied to improve the iontophoretic permeation of the di-

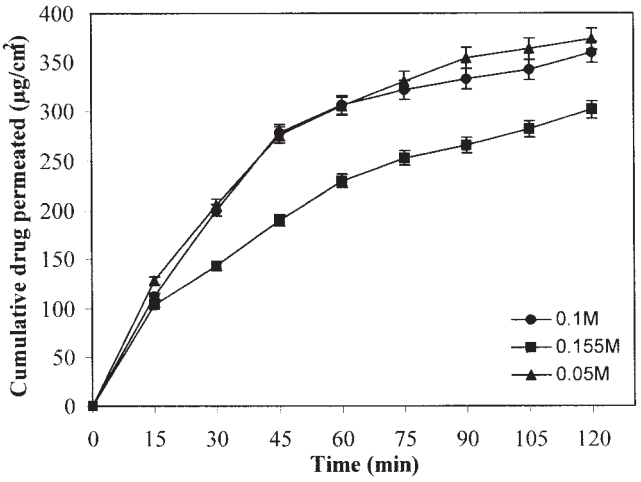

Figure 6 Effect of the ionic strength of the diffusion medium on the permeation rate of DD from the CP hydrogel across the excised rat skin with an electrical stimulus.

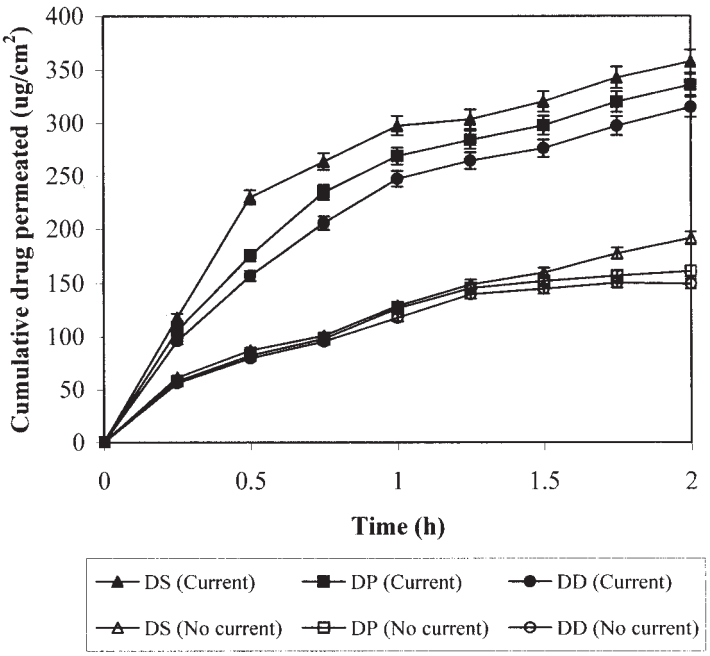

Figure 7 Comparative permeation plot of DS, DP, and DD across the excised rat skin with or without an electrical stimulus. The closed symbols (▲, ■, and ●) indicate permeation with an electrical stimulus, and the open symbols (△, □, and ○) indicate permeation without an electrical stimulus.

clofenac salts. Unlike passive permeation, iontophoretic flux and flux enhancement increased as per the sequence DS > DP > DD. According to Yoshida and Roberts,[33] the free volume model can be used to describe the iontophoretic behavior of the anionic salts of diclofenac. Here, the ion sphere mobility is assumed to be proportional to the fractional volume of the space that is accessible to the ionic sphere. Therefore, the molar volume and solute radius can affect the iontophoretic mobility. In addition to these ion-selective properties, skin also shows size-selective effects in iontophoretic transport.[34] The application of iontophoresis increases the porosity and, thereby, creates pores with the effective radii in the lipid matrix.[35] Even though diclofenac anion was dissociated in the donor compartment during iontophoresis, the radius and mobility of the diclofenac anion was affected by its counterion. Previous studies[36,37] have shown that the radius of diclofenac anions increased with increasing molecular weight and radius of its counterion. The radii of diclofenac showed the trend DD > DP > DS, which was inversely related to the iontophoretic enhancement effect of the diclofenac salts. Thus, the skin was not an inert tissue but presented some resistance to the movement of ions.

CONCLUSIONS

In this study, three diclofenac salts were chosen as model drugs to compare their differences in iontophoretic transport. Parameters such as current density, drug concentration, ionic strength, and iontophoretic application controlled and optimized the delivery of the diclofenac salts. However, the type of ions present in the hydrogel matrix influenced the magnitude of drug iontophoretic permeability. All of the hydrogels in this study were responsive to the electrical stimulus. Drug transport in the absence of the electrical stimulus was attributed to a concentration gradient between the hydrogel matrix and the diffusion medium, whereas in the presence of electrical stimulus, it was due to the local pH gradient, osmotic pressure difference, and electrostatic repulsion of the negatively charged drug molecules at the cathode. Among the three salts of diclofenac studied, the transport rate of DS was higher than those of DP and DD in the presence of an electrical stimulus. Drug transport followed the switch-on and switch-off pattern in a pulsatile manner. Rapid transport of the drugs was observed when the electrical stimulus was present. However, a relatively slow permeation rate was observed in the absence of an electrical stimulus. The hydrogel matrices of this study could be useful as transdermal drug-delivery systems actuated by an electrical current.

References

1. Murdan, S. J Controlled Release 2003, 92, 1.
2. Prausnitz, M. R.; Mitragotri, S.; Langer, R. Nat Rev Drug Discov 2004, 3, 115.
3. Denet, A. R.; Vanbever, R.; Preat, V. Adv Drug Delivery Rev 2004, 56, 659.

4. Thomas, B. J.; Finnin, B. C. Drug Discov Today 2004, 9, 697.
5. Soppimath, K. S.; Aminabhavi, T. M.; Dave, A. M.; Kumbar, S. G.; Rudzinski, W. E. Drug Dev Ind Pharm 2002, 28, 957.
6. Soppimath, K. S.; Kulkarni, A. R.; Aminabhavi, T. M. J Controlled Release 2001, 75, 331.
7. Soppimath, K. S.; Aminabhavi, T. M.; Kulkarni, A. R.; Rudzinski, W. E. J Controlled Release 2001, 70, 1.
8. Suzuki, M. Polymer Gels: Fundamentals and Biomedical Applications; Plenum: New York, 1991; p 221.
9. Conjeevaram, R.; Banga, A. K.; Zhang, L. Pharm Res 2002, 19, 440.
10. Bose, S.; Ravis, W. R.; Lin, Y.-J.; Zhang, L.; Hofmann, G. A.; Banga, A. K. J Controlled Release 2001, 73, 197.
11. Hsu, C. S.; Block, L. H. Pharm Res 1996, 13, 1865.
12. Yuk, S. H.; Cho, S. H.; Lee, H. B. Pharm Res 1992, 9, 955.
13. Kim, S. W.; Lee, Y. M. J Appl Polym Sci 1999, 74, 1752.
14. Banga, A. K.; Chien, Y. W. Pharm Res 1993, 10, 697.
15. Ramanathan, S.; Block, L. H. J Controlled Release 2001, 70, 109.
16. Agnihotri, S. A.; Aminabhavi, T. M. J Controlled Release 2004, 96, 245.
17. Kulkarni, A. R.; Soppimath, K. S.; Aminabhavi, T. M. Eur J Pharm Biopharm 2001, 51, 127.
18. Toti, U. S.; Aminabhavi, T. M. J Controlled Release 2004, 95, 567.
19. Kurkuri, M. D.; Kulkarni, A. R.; Kariduraganavar, M. Y.; Aminabhavi, T. M. Drug Dev Ind Pharm 2001, 27, 1107.
20. Kurkuri, M. D.; Kulkarni, A. R.; Aminabhavi, T. M. Polym Plast Technol Eng 2002, 41, 469.
21. Nishihata, T.; Kotera, K.; Nakano, Y.; Yamazaki, M. Chem Pharm Bull 1987, 35, 3807.
22. Maitini, Y.; Shimada, K.; Nagai, T. Chem Pharm Bull 1996, 44, 403.
23. Varghese, E.; Khar, R. K. J Controlled Release 1996, 38, 21.
24. Ishikawa, O.; Kato, Y.; Onishi, H.; Nagai, T.; Machida, Y. Int J Pharm 2002, 249, 81.
25. Li, G. L.; Geest, R. V.; Chanet, L.; Zanten, E. V.; Danhof, M.; Bouwstra, J. A. J Controlled Release 2002, 84, 49.
26. Shin, S. C.; Lee, H. J. Eur J Pharm Biopharm 2002, 54, 325.
27. Scranton, A. B.; Rangarajan, B.; Klier, J. Adv Polym Sci 1995, 122, 1.
28. Tanaka, T.; Nishio, I.; Sun, S. T.; Ueno-Nishio, S. Science 1982, 218, 467.
29. Pikal, M. J Pharm Res 1990, 7, 118.
30. Fang, J. Y.; Sung, K. C.; Lin, H. H.; Fang, C. L. Int J Pharm 1999, 178, 83.
31. Fang, J. Y.; Wang, R. J.; Huang, Y. B.; Wu, P. C.; Tsai, Y. H. Biol Pharm Bull 2000, 23, 1357.
32. Sawahata, K.; Hara, M.; Yasunaga, H.; Osada, Y. J Controlled Release 1990, 14, 253.
33. Yoshida, N. H.; Roberts, M. S. J Controlled Release 1993, 25, 177.
34. Singh, P.; Anliker, M.; Smith, G. A.; Zavortink, D.; Maibach, H. I. J Pharm Sci 1995, 84, 1342.
35. Inada, H.; Ghanem, A.; Higuchi, W. I. Pharm Res 1994, 11, 687.
36. Kasting, G. B.; Merrit, E. W.; Keister, J. C. J Membr Sci 1988, 35, 137.
37. Maitani, Y.; Kugo, M.; Nakagaki, M.; Nagai, T. J Pharm Sci 1993, 82, 1245.