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RESEARCH PAPER

Topical Permeation Characteristics of Diclofenac Sodium from NaCMC Gels in Comparison with Conventional Gel Formulations

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ABSTRACT

Topical gel formulations of diclofenac sodium were prepared by using sodium carboxymethylcellulose (NaCMC), a low-toxicity cellulose polymer as a gel-forming material that is biocompatible and biodegradable. The influence of various formulation variables, such as initial drug concentrations and NaCMC concentration, and certain skin permeation enhancers on release characteristics of the diclofenac sodium from the prepared gels through a standard cellophane membrane was studied in comparison with four commercially available gel formulations of diclofenac sodium. The cumulative amounts released and the apparent release rates were higher for the prepared gels in comparison with the commercial formulations. Skin permeation studies using abdominal rat skin revealed good improvement of skin permeation characteristics of diclofenac sodium using NaCMC gels as compared to the commercial gels. The cumulative amount permeated at 6 h ($\mu g/cm^2$), steady-state flux J_{ss} ($\mu g/cm^2 h$), lag time t_L (h), permeability coefficient k_p (cm/s), partition coefficient k, and diffusion coefficient D (cm^2/s) were determined for the prepared gels in comparison with the commercial gels. Skin permeation enhancers such as isopropyl alcohol (IPA), Tween 80, and α-tocopherol polyethylene glycol succinate (TPGS) exhibited little or no effect on the permeation characteristics of diclofenac sodium. Infrared (IR) spectrum and differential scanning calorimetry (DSC) studies on the pure diclofenac sodium, NaCMC, and their physical mixture at a 1:1 ratio revealed that there was no positive evidence for the interactions between the drug and NaCMC, indicating the compatibility of the drug and the vehicle.

Based on experimental results, preparation of diclofenac sodium gels using NaCMC vehicle is promising.

INTRODUCTION

In certain cases, transdermal delivery offers several advantages over conventional routes of drug administration (1–3); however, the barrier properties of intact skin limit the permeability of a wide variety of substances, including pharmaceutical active agents (3). Therefore, considerable attention has been directed recently to overcome the low permeability of drugs through the skin (4).

One way of improving low percutaneous absorption is to use skin penetration enhancers such as azone (5–8), pyrrolidone derivatives (9,10), propylene glycol (6,10,11), dimethylformamide (10,12,13), 1-dodecylazacycloheptan-2-one (14), isopropyl alcohol (IPA) (15), isopropyl myristate (16), urea (17), and various vehicles and surfactants (4,18).

Considering the fact that most inflammatory diseases occur locally and near the surface of the body, topical application of nonsteroidal anti-inflammatory drugs (NSAIDs) to the inflamed site can offer the advantage of delivering the drug directly to the diseased site and producing high local concentrations. This bypasses gastric irritation and also reduces adverse systemic effects (3,4,15–32).

Diclofenac sodium or sodium 2-(2,6-dichloro-anilino)-phenylacetate is a potent NSAID advocated for use in painful, inflammatory, and certain non-rheumatic conditions. In 1988, the Food and Drug Administration (FDA) approved marketing of the NSAID diclofenac sodium (Voltaren, Ciba-Geigy) for use in long-term therapy of rheumatic diseases such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis (33,34). Diclofenac sodium also exhibits antipyretic and analgesic activity (33,34).

It has been reported that diclofenac sodium is not easily absorbed by topical application (35). In addition, few studies (15–18,27–29) have yet been recently carried out to investigate the percutaneous transport of diclofenac sodium. However, no report has dealt with the transdermal delivery of the drug from NaCMC gels. Therefore, the purpose of this study was to investigate the usefulness of NaCMC gel as a vehicle for transdermal delivery of diclofenac sodium across excised hairless abdominal rat skin in comparison with the available commercial formulations. The effects of incorporation of certain skin permeation enhancers such as IPA, Tween 80, and α-tocopherol polyethylene glycol succinate (TPGS) on the in vitro release and skin permeation were also investigated. In addition, infrared (IR) spectroscopy and differential scanning calorimetry (DSC) calorimetry studies were performed to investigate interactions between the drug and the vehicle.

EXPERIMENTAL

Materials

The following materials were used: diclofenac sodium (Chemo S.A., Switzerland); NaCMC (C.B.H. Lab Chemicals, Nottingham, U.K.); IPA (Merck, Germany); Tween 80 (Riedel–de Haen, Germany); TPGS (Eastman Chemical Co., USA). All other chemicals were analytical or high-performance liquid chromatography (HPLC) grade and were purchased from Lab-Scan-UK.

Commercial Products Containing 1% w/w Drug

The following commercial products were used: Voltaren Emulgel (Ciba-Geigy, Switzerland, lot B 34 6600); Inflaban gel (Co-L.t.d. Sult-Jordan, lot 329); Diclogesic gel (Dar Al-Dawa, Jordan, lot 2159); Diclofen gel (United Pharm. Co., Jordan, lot 80605). All commercial products contained diclofenac diethylamine 1.16% w/w; the active substance corresponds to 1% w/w diclofenac sodium. The base of Voltaren Emulgel is composed of an oily emulsion in an aqueous gel and contains acrylic acid polymer, cetomacrogol 1000, caprylic/capric acid fatty ester, IPA, propylene glycol, liquid paraffin, perfume, and water. The base of the other commercial products

(Inflaban, Diclogesic, and Diclofen) is composed of an aqueous-alcoholic gel (Carbopol gel) without any fatty substances.

Methods

Preparation of Sodium Carboxymethylcellulose Gels

NaCMC (3% w/w) gels were prepared by dissolving diclofenac sodium in distilled water in a conical flask with the aid of sonication, followed by addition of the required amount of NaCMC under constant stirring with a magnetic stirrer. The prepared gels were then left 3 days to complete dissolution prior to conducting the release and permeation studies. The drug was incorporated into the gel base at three concentrations (1%, 2%, and 3% w/w). In addition, three concentrations of NaCMC (2%, 3%, and 4% w/w) were tested.

Permeation enhancers such as IPA, Tween 80, and TPGS were incorporated into the gel either separately at three concentration levels (5%, 10%, and 15% w/w for IPA and 0.5%, 1%, and 1.5% w/w for both Tween 80 and TPGS) or in combinations (combination I consisted of 5% w/w IPA and 0.5% w/w Tween 80, and combination II consisted of 5% w/w IPA, 0.5% w/w Tween 80, and 0.5% w/w TPGS).

Permeation Studies Across Abdominal Rat Skin

Full-thickness skin was obtained after shaving hair from male rats 7 to 8 weeks old and weighing 200 to 230 g. The rats were sacrificed with 25% urethane. The dermal side of the skin was carefully cleared of adhering blood vessels, fat, or subcutaneous tissue and washed with warm water. The skin samples (1.4 cm × 1.4 cm) were mounted on Franz diffusion cells (1.0 cm i.d., Crown Glass Co., Someervill, USA) with the stratum corneum side up. An infinite dose equivalent to 10 mg drug of each formulation was spread on this side, facing the donor compartment. The dermal side faced downward into the receptor compartment, which consisted of 13 ml buffer maintained at 37°C ± 0.5°C and stirred horizontally at 30 rpm in a thermostatically controlled shaker. The 300-µl samples were withdrawn from the receptor compartment at time intervals (0–6 h) and replaced by equal volumes of fresh buffer at the same temperature. The same procedure was used when a synthetic cellulose membrane (type 30/32, Fisher Scientific Co., London, UK) was used instead of the rat skin. All experiments were carried out on triplicate samples.

Drug Assay

In all skin permeation experiments, the withdrawn samples were filtered using disposable Millipore filters (W-13-2, Tosoh Co., Tokyo, Japan) and analyzed for diclofenac sodium by an improved HPLC assay (15). The mobile phase was acetonitrile:water (50%:50% v/v) adjusted to pH 3.5 with glacial acetic acid. The flow rate was 1 ml/min (SP8810 precision isocratic pump, Spectra Physics, USA). The column was a 25 cm × 4.6 mm C_{18} ODS maintained at room temperature. An ultraviolet (UV) detector (Hitachi L-7400) was set at 280 nm, and signals were recorded on a PM-825 single-pen recorder (Philips, The Netherlands). The quantitation limit of diclofenac sodium was 0.01 µg/ml.

Calculation of the Permeation Parameters of Diclofenac Sodium Through the Cellophane Membrane

The drug release data through the standard cellophane membrane was treated by Eq. 1, described by Higuchi (36):

$$Q = 2C_0\sqrt{D_{\text{app}}t/\pi} \tag{1}$$

where Q is the amount of diclofenac sodium released per unit area at time (t), C_0 is the initial drug concentration in the donor, and D_{app} is the apparent diffusion coefficient. D_{app} is calculated from the slope B of the linear plot of Q versus $(t)^{1/2}$, as shown in Eq. 2:

$$D_{\text{app}} = \frac{B^2\pi}{4C_0^2} \tag{2}$$

Calculation of Permeation Parameters Across Abdominal Rat Skin

The permeation profiles were constructed by plotting the cumulative amount of drug permeated versus time. The apparent steady-state flux, lag time, and permeability coefficients were calculated according to the method of Chow et al. (14):

$$t_L = h^2/6D \tag{3}$$

$$J_{\text{ss}} = KDC_{\text{s}}/h = K_{\text{p}}C_{\text{s}} \tag{4}$$

$$K_p = KD/h \quad (5)$$

where t_L is the lag time, D is the diffusion coefficient within the skin, h is the thickness of the skin (0.1 cm), K is the partition coefficient, J_{ss} is the steady-state flux, K_p is the permeability coefficient through the skin, and C_s is the initial drug concentration in the donor compartment.

Enhancing Factor

The enhancing factor was calculated by dividing the cumulative amount permeated for any formulation by that of the prepared control gel (F2).

Relative Permeation Rate

The relative permeation rate (RPR) was estimated by dividing the steady-state permeation rate of any formulation by that of Voltaren Emulgel (reference gel).

Infrared Absorption Spectroscopy

The IR spectra of diclofenac sodium, NaCMC, and their physical mixture at a 1:1 ratio were examined using a Shimadzu IR-470 spectrophotometer (Japan). The samples were prepared as KBr disks compressed under a pressure of 6 ton/cm^2. The wavenumber selected ranged between 400 and 4000 cm^{-1}.

Differential Scanning Calorimetry

Differential scanning calorimetry by a DSC-50 (Shimadzu, Japan) was performed under the following conditions: sample weight about 12 mg; scanning rate 10°C/min; N_2 purge 30 ml/min. The instrument was calibrated for temperature and energy with pure indium. Thermal analysis data were obtained using a TA 501 PC system with Shimadzu software programs.

RESULTS AND DISCUSSION

In Vitro Release Through Standard Cellophane Membrane

Effect of Sodium Carboxymethylcellulose Concentration

Preliminary experiments were carried out for the selection of the appropriate concentration of NaCMC that produces gels with consistency suitable for topical application. Figure 1 and Table 1

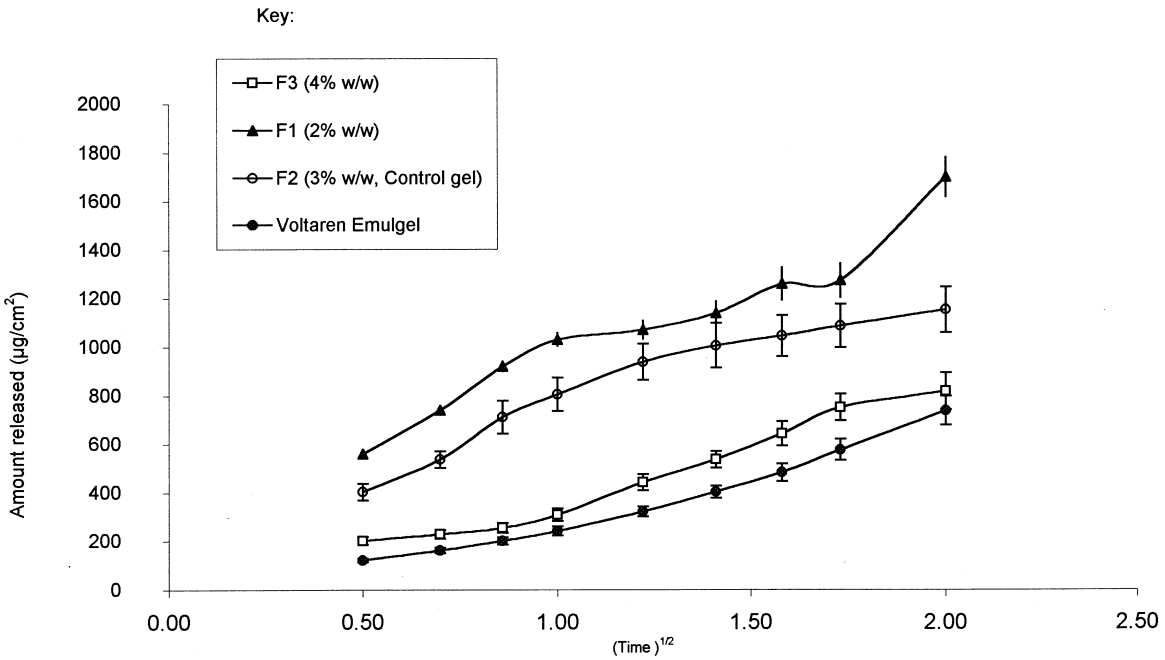

Figure 1. Effect of NaCMC concentration on release of diclofenac sodium from various gel formulations across standard cellophane membrane in comparison with Voltaren emulgel. Control gel composed of 3% w/w NaCMC and 1% w/w drug.

Table 1

Release Characteristics of Diclofenac Sodium from the Prepared Gels with Sodium Carboxymethylcellulose (NaCMC) in Comparison with the Commercial Gels

Formulation Factor	Formulation Code	Amount Released at 4 h ($\mu g/cm^2$)	Apparent Release Rate ($\mu g/cm^2 h$)	r	Diffusion Coefficient (D, $cm^2/s \times 10^{-4}$)	Factor Enhancing[a]	RPR[b]
NaCMC concentration (% w/w)	F1 (2%)	1287.80 ± 111.12	507.27 ± 45.93	0.960	5.61 ± 0.15	1.12	1.23
	F2[c] (3%)	1153.66 ± 90.11	491.94 ± 33.11	0.960	5.27 ± 0.20	[a]	1.20
	F3 (4%)	1126.83 ± 91.50	402.31 ± 22.51	0.991	3.52 ± 0.11	0.97	0.98
Drug concentration (% w/w)	F2 (1%)	1153.66 ± 90.11	491.94 ± 33.11	0.960	5.27 ± 0.20	1.00	1.20
	F4 (2%)	2521.94 ± 207.11	1160.96 ± 81.95	0.972	5.20 ± 0.21	2.18	2.84
	F5 (3%)	2414.63 ± 200.11	999.36 ± 73.11	0.987	1.77 ± 1.70	2.09	2.44
IPA (% w/w)	F6 (5%)	1180.48 ± 97.20	616.03 ± 45.11	0.980	8.27 ± 1.90	1.02	1.50
	F7(10%)	1140.24 ± 90.51	548.36 ± 48.11	0.994	6.56 ± 1.30	0.98	1.34
	F8 (15%)	1032.92 ± 95.31	469.73 ± 41.11	0.988	4.81 ± 0.50	0.89	1.15
Tween 80 (% w/w)	F9 (0.5%)	1314.63 ± 107.91	645.59 ± 55.11	0.983	9.08 ± 1.80	1.13	1.58
	F10 (1%)	1155.66 ± 90.19	576.14 ± 45.50	0.988	7.24 ± 1.20	1.00	1.41
	F11 (1.5%)	1006.10 ± 80.17	532.56 ± 40.50	0.994	6.18 ± 1.11	0.87	1.30
TPGS (% w/w)	F12 (0.5%)	1113.41 ± 97.11	437.94 ± 39.11	0.983	9.18 ± 0.21	0.96	1.07
	F13 (1%)	1019.50 ± 80.11	489.26 ± 37.80	0.986	5.22 ± 0.50	0.88	1.19
	F14 (1.5%)	952.44 ± 80.91	461.70 ± 40.21	0.980	9.64 ± 0.31	0.83	1.13
Combinations	F15 (≠1)	818.29 ± 70.11	461.84 ± 33.11	0.984	4.65 ± 0.11	0.71	1.13
	F16 (≠2)	1649.99 ± 80.11	942.07 ± 70.11	0.984	19.3 ± 2.30	1.43	2.30
Commercial gels	Voltaren[b]	737.90 ± 60.11	408.67 ± 33.11	0.984	3.6 ± 0.15	0.64	[b]
	Inflaban	670.73 ± 54.91	342.20 ± 23.11	0.993	2.55 ± 0.11	0.58	0.83
	Diclogesic	281.71 ± 23.79	182.43 ± 17.90	0.992	0.72 ± 0.01	0.24	0.45
	Diclofen	456.10 ± 44.11	262.80 ± 23.91	0.997	1.5 ± 0.05	0.39	0.64

IPA, isopropyl alcohol; TPGS, α-tocopherol polyethylene glycol succinate.

[a]Enhancing factor was calculated by dividing the cumulative amount of diclofenac sodium released at 4 h by any formulation by that of the control gel (F2).

[b]Relative permeation rate (RPR) was calculated by dividing the apparent release rate of any formulation by that of Voltaren emulgel (reference gel).

[c]Control gel (F2): Prepared with 3% w/w NaCMC and containing 1% w/w diclofenac sodium.

show diclofenac sodium release from gel bases prepared with 2%, 3%, and 4% w/w NaCMC (the drug concentration was kept at 1% w/w in all the prepared gels) in comparison with Voltaren Emulgel (reference gel). The results indicated that the released amount decreased with increasing NaCMC concentration from 2% to 4% w/w. The amounts of drug released at 4 h were 1287.80 ± 111.012, 1153.66 ± 90.11, and 1126.83 ± 91.50 μg/cm^2 for the gels prepared with 2%, 3%, and 4% w/w NaCMC, respectively. This decrease in the release could be attributed to increased microviscosity of the gel by increasing the NaCMC concentration (15,18). A direct relationship existed between the cumulative amount released and the square root of time ($h^{1/2}$) ($r > 0.9$), indicating that the drug was released via Higuchi diffusion mechanism (36).

It was observed that the formulations prepared with 4% w/w NaCMC produced gels with a consistency suitable for topical application, while the other formulations prepared with 2% w/w and 3% w/w NaCMC produced gels with less consistency and high consistency, respectively. Therefore, 3% w/w NaCMC was used to prepare all the gel formulations in this study to investigate the effects of drug concentration and skin permeation enhancers on the permeation of diclofenac sodium. In addition, it was assumed that there were no significant differences between viscosity of gel formulations that contain the same percentage of the polymer (3% w/w).

Effect of Initial Drug Concentration

Figure 2 and Table 1 show the effect of initial drug concentration (1%, 2%, and 3% w/w) on release of diclofenac sodium from 3% w/w NaCMC gels in comparison with Voltaren Emulgel. The cumulative amounts permeated at 4 h were 1153.66 ± 90.11, 2521.94 ± 207.11, and 2414.63 ± 200.11 μg/cm^2 for gels prepared with 1%, 2%, and 3% w/w diclofenac sodium, respectively (Table 1). The results obtained revealed that increasing the drug concentration from 1% to 2% w/w increased the cumulative amount released. However, further increasing the initial drug concentration to 3% w/w diclofenac sodium resulted in decreasing the cumulative amount released (Table 1 and Fig. 2). This could be attributed to the increased microviscosity of the gel at a higher concentration of the added solid drug. These results are in agreement with previous findings on diclofenac and hydrocortisone release rates (37).

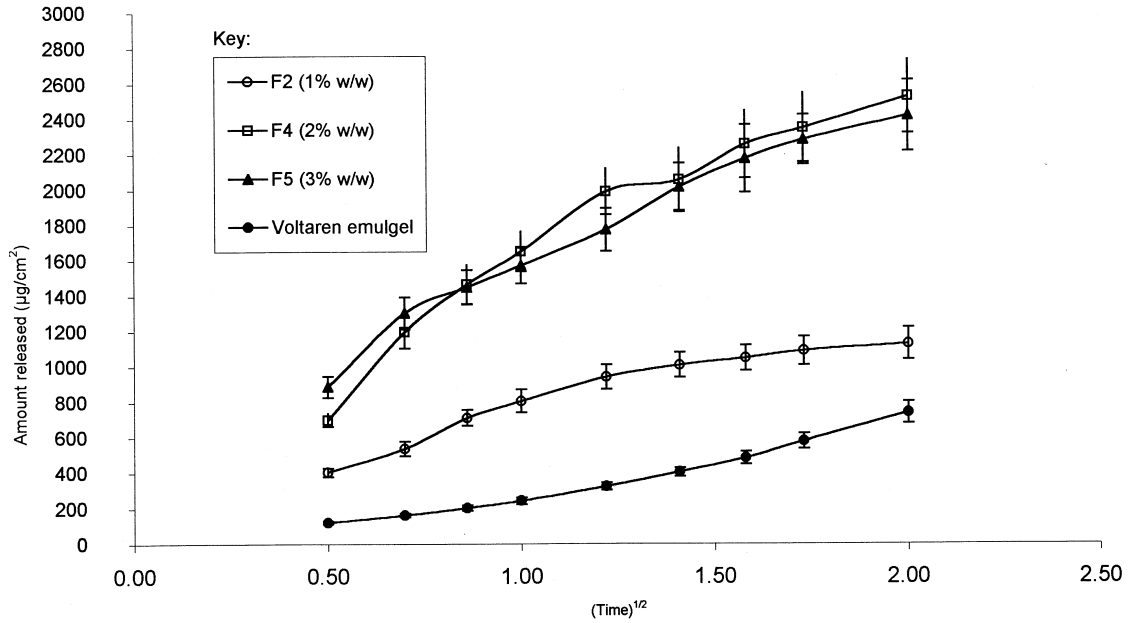

Figure 2. Effect of drug concentration on release of diclofenac sodium from various gel formulations across standard cellophane membrane. All gels were prepared with 3% w/w NaCMC.

Effect of the Added Release Enhancers

Figures 3–5 and Table 1 show the effects of incorporation of different concentrations of IPA (5%, 10%, and 15% w/w) (Fig. 3), Tween 80 (0.5%, 1%, and 1.5% w/w) (Fig. 4), and TPGS (0.5%, 1%, and 1.5% w/w) (Fig. 5) on release of diclofenac sodium from gels prepared with 3% w/w NaCMC in comparison with Voltaren Emulgel (reference gel). For IPA, the cumulative amounts released at 4 h were 1180.48 ± 97.20, 1140.24 ± 90.51, and 1032.92 ± 95.31 μg/cm^2 for 5%, 10%, and 15% w/w IPA, respectively (Table 1 and Fig. 3). Thus, a reduction in the release of the drug was observed on increasing the IPA concentration.

A more pronounced reduction in the release of the drug was observed with Tween 80. The cumulative amounts released at 4 h were 1314.64 ± 107.91, 1155.66 ± 90.19, and 1006.10 ± 80.17 μg/cm^2 for 0.5%, 1%, and 1.5% w/w Tween 80, respectively (Table 1 and Fig. 4).

For TPGS, the cumulative amounts released at 4 h were 1113.41 ± 97.11, 1019.50 ± 80.11, and 952.44 ± 80.91 μg/cm^2 for 0.5%, 1%, and 1.5% w/w TPGS, respectively (Table 1 and Fig. 5).

Thus, unexpectedly, the inclusion of the selected enhancers showed only little or no effect on release of diclofenac sodium as compared to gels prepared without enhancers, the control gel (Table 1). In addition, increasing the concentration of the added enhancers resulted in either a slight increase (low and medium concentration) or even a decreased (at the highest concentration) release of diclofenac sodium.

These results could be attributed in part to an increase of the drug affinity to the vehicle (16) and to a possible decrease in thermodynamic activity as a result of micellar complexation with subsequent increase of the gel viscosity due to formation of emulsion-type gel (18). Maximal enhancement of diclofenac sodium release was obtained with 5% w/w IPA or 0.5% w/w Tween 80 (Table 1). However, the release rates of diclofenac sodium from all the prepared NaCMC gels containing enhancers were higher than that of the reference gel, Voltaren Emulgel (RPR > 1) (Figs. 3–5 and Table 1).

Effect of Combined Enhancers

An attempt was made to investigate the effects of combined release enhancers on the release of

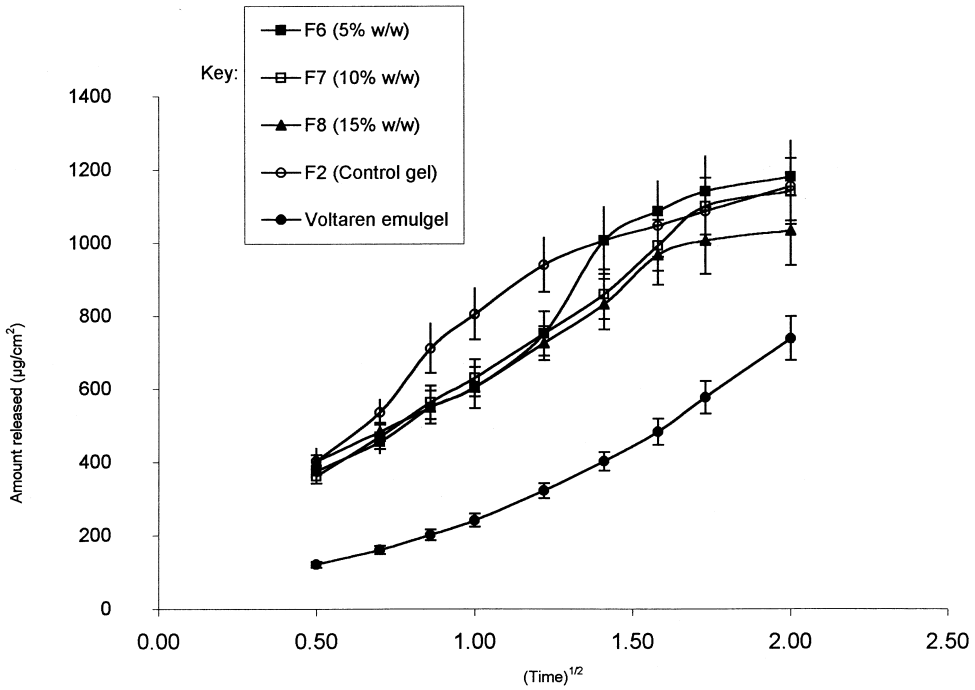

Figure 3. Effect of IPA concentration on release of diclofenac sodium from various gel formulations across standard cellophane membrane. Control gel composed of 3% w/w NaCMC and 1% w/w drug.

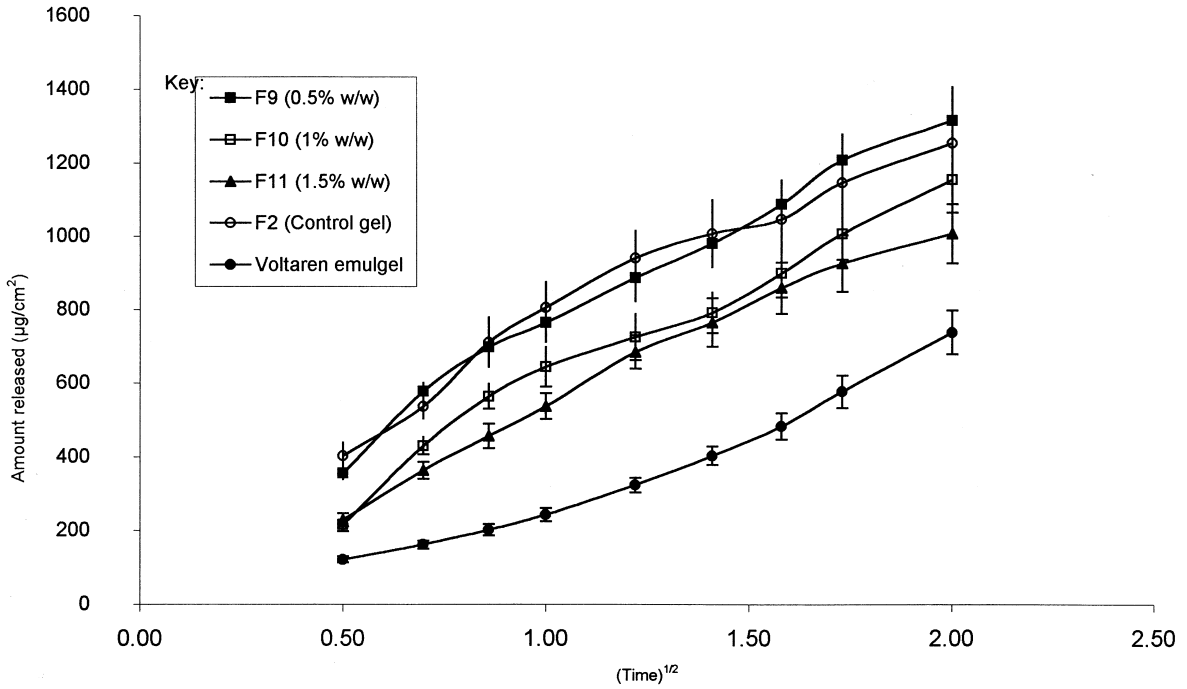

Figure 4. Effect of Tween 80 concentration on release of diclofenac sodium from various gel formulations across standard cellophane membrane. Control gel composed of 3% w/w NaCMC and 1% w/w drug.

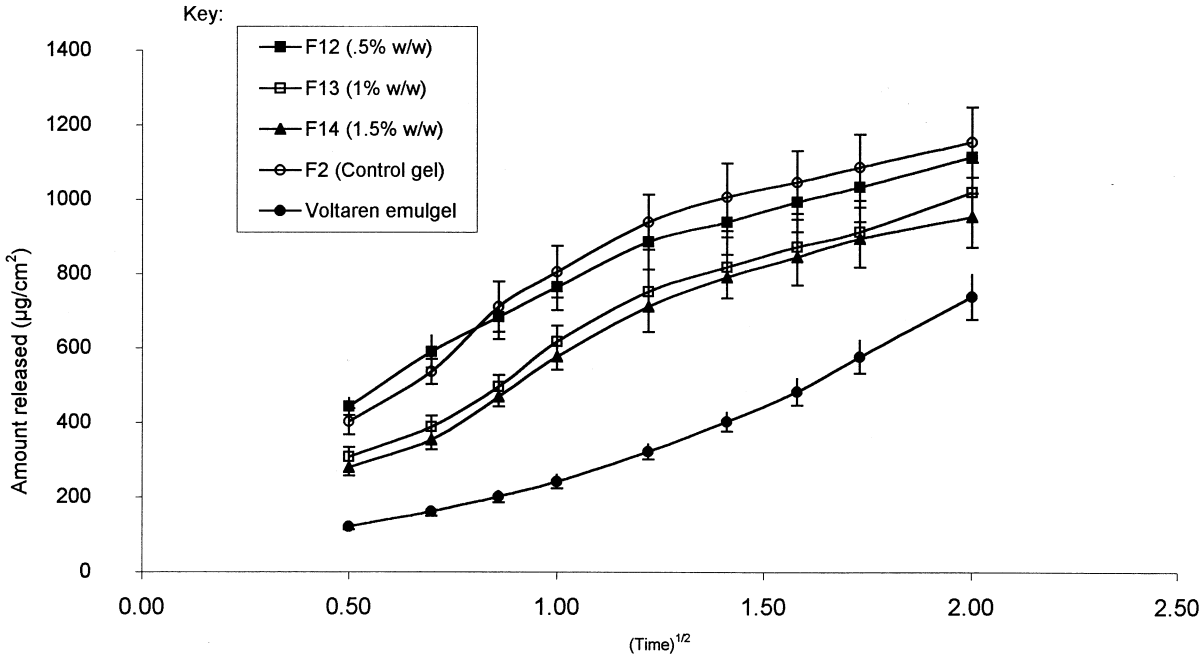

Figure 5. Effect of TPGS concentration on release of diclofenac sodium from various gel formulations across standard cellophane membrane. Control gel composed of 3% w/w NaCMC and 1% w/w drug.

diclofenac from gel formulations prepared with 3% w/w NaCMC and 1% w/w diclofenac sodium. The effects of combined enhancers are shown in Fig. 6 and Table 1.

Combination I (5% w/w IPA and 0.5% w/w Tween 80) did not markedly increase the release of diclofenac sodium. In contrast, combination II (5% IPA, 0.5% Tween 80, and 0.5% TPGS) gave a marked increase in the release of diclofenac sodium. The cumulative amounts released at 4 h were 818.29 ± 70.11 and 1649.99 ± 80.11 $\mu g/cm^2$ for combination I and combination II, respectively (Table 1). The apparent release rates were 461.84 ± 33.11 and 942.07 ± 70.11 $\mu g/cm^2 h$ for combination I and combination II, respectively. The diffusion coefficients were 4.65 ± 0.11 and 19.3 ± 2.30 $cm^2/s \times 10^{-4}$ for combination I and combination II, respectively (table 1). The enhancement of release from combination II as compared with combination I could be attributed to a synergistic enhancement of drug release due to TPGS (0.5% w/w) in the presence of IPA (5% w/w) and Tween 80 (0.5% w/w) (16). Also, there was a possible improvement in the thermodynamic activity of the drug in this formulation (combination II) as a result of increased drug solubility in the base and/or changes in the microviscosity of the vehicle (5–8,15,18). However, both combinations (I and II) improved the release characteristics of diclofenac sodium as compared to those of the reference gel (Voltaren Emulgel) or the control gel (F2) (Fig. 6 and Table 1).

Release of Diclofenac Sodium from the Available Commercial Gels

The release of diclofenac from different commercial gels containing 1% w/w drug is shown in Fig. 7 and Table 1. The cumulative amounts released at 4 h were 737.90 ± 60.11, 670.73 ± 54.91, 281.71 ± 23.79, and 456.10 ± 44.11 $\mu g/cm^2$ for Voltaren Emulgel (reference gel), Inflaban, Diclogesic, and Diclofen, respectively, compared to 1153.66 ± 90.11 $\mu g/cm^2$ for the control gel (3% w/w NaCMC and 1% w/w drug). Among the commercial products, Voltaren Emulgel gave the highest release of the drug, while the lowest release of the drug was observed with Diclogesic gel, which may be attributed to possible interaction of the drug with certain components of this formulation. This finding is manifested by the low diffusion coefficient value (0.72 ± 0.01 $cm^2/s \times 10^{-4}$) for Diclogesic gel (Table 1). The apparent release rates of the drug

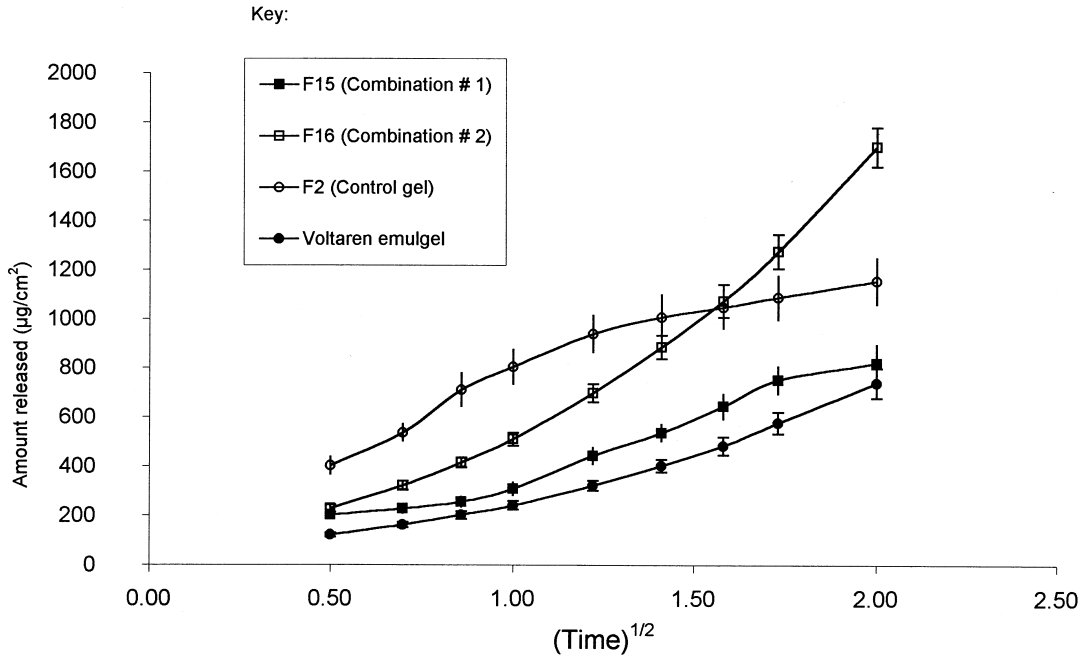

Figure 6. Effect of combined enhancers on release of diclofenac sodium from various gel formulations across standard cellophane membrane. Control gel composed of 3% w/w NaCMC and 1% w/w drug.

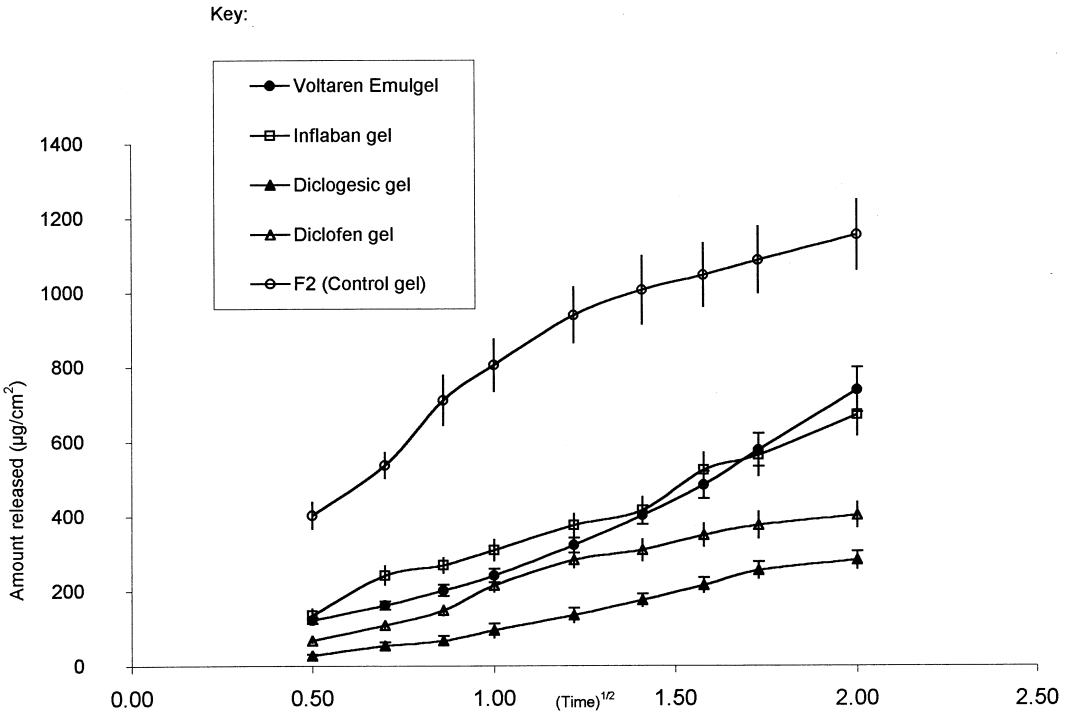

Figure 7. Release of diclofenac sodium from various commercial gel formulations across standard cellophane membrane. Control gel composed of 3% w/w NaCMC and 1% w/w drug.

from the commercial formulations were 407.67 ± 33.11, 342.20 ± 23.11, 262.80 ± 23.91, and 182.43 ± 17.90 μg/cm^{2}h for Voltaren, Inflaban, Diclofen, and Diclogesic gels, respectively. However, the apparent release rate for the control gel F2 (3% w/w NaCMC and 1% w/w drug) was markedly higher (491.94 ± 33.11 μg/cm^{2}h) compared to all the commercial formulations (Table 1).

The slow release of the drug from the commercial products utilized compared with the prepared NaCMC gels could be attributed to three main reasons. First, all the commercial products were formulated by utilizing the diethylamine salt of diclofenac, while the sodium salt was used in the prepared gels. This difference in the salt form of the drug may have resulted in enhancement of the permeation of the drug on using the small molecular form (diclofenac sodium) compared with the larger molecular form (diclofenac diethylamine). Second, Voltaren Emulgel (reference gel) was formulated utilizing a fatty emulsion, which may be the cause of the slow release of the water-soluble drug (diclofenac diethylamine). Inflaban, Diclogesic, and Diclofen gels were prepared with aqueous carbopol gel, and interaction with diclofenac is possible (data not presented). Third, the IR and DSC studies indicated no evidence of interaction between diclofenac sodium and NaCMC (discussed below).

Skin Permeation Studies

The skin permeation profiles and permeation characteristics of diclofenac sodium from the selected gels prepared with 3% w/w NaCMC and 1% w/w drug (control gel, 5% w/w IPA, 0.5% w/w Tween 80, 0.5% w/w TPGS, and combination II) in comparison with the tested commercial gel products are shown in Table 2 and Fig. 8. The cumulative amount permeated at 6 h was higher for all the prepared gels compared to the commercial gels (Table 2). The cumulative amounts permeated at 6 h were 830.55 ± 81.95, 724.38 ± 53.92, 1073.16 ± 72.11, 630.48 ± 33.91, and 918.90 ± 56.11 μg/cm^2 for the control gel, 5% w/w IPA, 0.5% w/w Tween 80, 0.5% w/w TPGS, and combination II, respectively, compared to 657.31 ± 54.41, 536.58 ± 48.11, 509.75 ± 40.11, and 277.68 ± 32.11 μg/cm^2 for Voltaren Emulgel, Inflaban, Diclogesic, and Diclofen gel, respectively (Table 2). The steady-state flux was highest (203.7 ± 17.15 μg/cm^{2}h) for NaCMC gel

Table 2

Percutaneous Penetration Characteristics of Diclofenac Sodium Across Abdominal Rat Skin from the Selected Sodium Carboxymethylcellulose (NaCMC) in Comparison with the Conventional Gels

Formulation	Cumulative Amount at 6 h ($\mu g/cm^2$)	Flux (J_{ss}, $\mu g/cm^2 h$)	r	Lag Time (t_{Lag}, h)	Permeability Coefficient (k_p, $cm/s \times 10^{-6}$)	Partition Coefficient k	Diffusion Coefficient (D, $cm^2/s \times 10^{-7}$)	Enhancing Factor[a]	RPR[b]
F2[c]	830.55 ± 81.95	172.61 ± 12.51	0.999	1.25 ± 0.19	4.83 ± 0.51	1.301 ± 0.20	3.70 ± 0.33	[a]	1.38
F7 (5% IPA)	724.38 ± 53.92	111.34 ± 9.75	0.996	0.25 ± 0.02	3.11 ± 0.25	0.168 ± 0.05	1.85 ± 0.15	0.87	0.89
F10 (0.5% Tween 80)	1073.16 ± 72.11	203.7 ± 17.15	0.995	0.23 ± 0.01	5.70 ± 0.57	0.283 ± 0.15	2.01 ± 0.30	1.29	1.63
F13 (0.5% TPGS)	630.48 ± 33.91	162.27 ± 13.17	0.999	3.5 ± 0.21	4.54 ± 0.35	3.43 ± 0.31	1.32 ± 0.15	0.75	1.30
F17 (combination II)	918.90 ± 56.11	162.98 ± 15.11	0.991	0.74 ± 0.02	4.52 ± 0.75	0.722 ± 0.45	6.25 ± 0.75	1.106	1.31
Voltaren[b]	657.31 ± 54.11	124.5 ± 8.91	0.981	1.50 ± 0.19	3.48 ± 0.25	6.01 ± 0.95	5.11 ± 0.35	0.79	[b]
Inflaban	536.58 ± 48.11	93.23 ± 7.17	0.981	0.95 ± 0.05	2.61 ± 0.22	0.535 ± 0.13	4.87 ± 0.95	0.64	0.75
Diclogesic	509.75 ± 40.11	104.63 ± 9.01	0.995	2 ± 0.15	2.92 ± 0.20	1.263 ± 0.41	2.31 ± 0.75	0.61	0.84
Diclofen	277.68 ± 32.11	92.91 ± 8.15	0.965	4 ± 0.50	2.60 ± 0.56	22.46 ± 3.50	1.15 ± 0.11	0.33	0.75

IPA, isopropyl alcohol; TPGS, α-tocopherol polyethylene glycol succinate.

[a]Enhancing factor was calculated by dividing the cumulative amount of diclofenac sodium released at 4 h by any formulation by that of the control gel (F2).

[b]Relative permeation rate (RPR) was calculated by dividing the steady-state flux (J_{ss}) of any formulation by that of Voltaren emulgel (reference gel).

[c]F2 (control gel) prepared with 3% w/w NaCMC and containing 1% w/w diclofenac sodium.

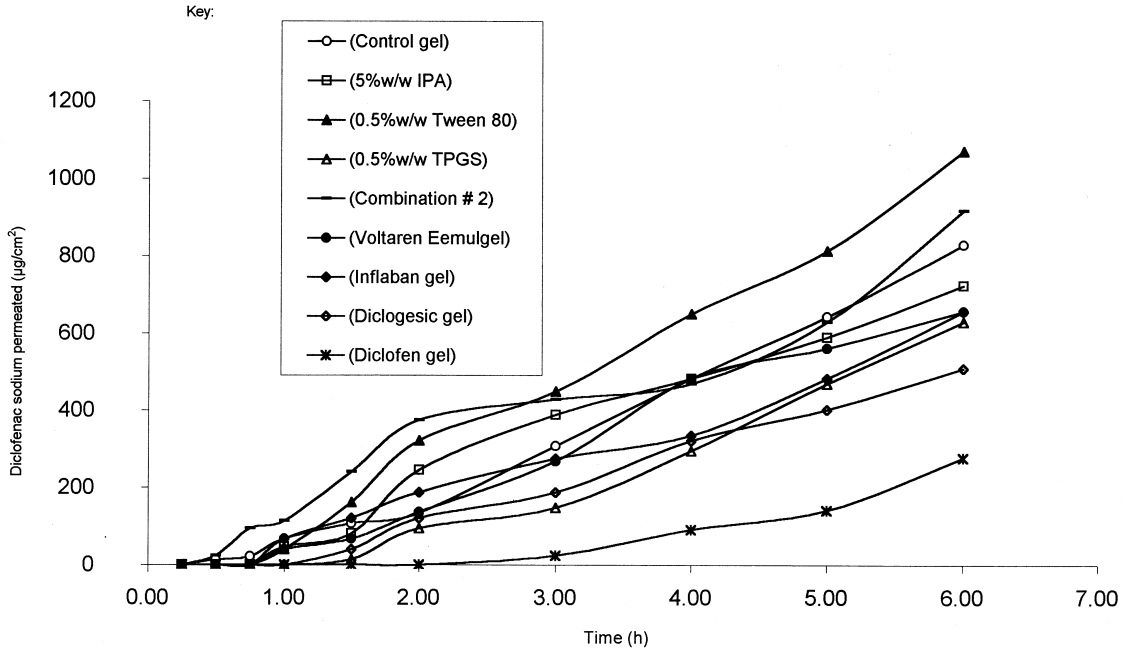

Figure 8. Permeation of diclofenac sodium across abdominal rat skin from the selected gels in comparison with the conventional gel formulations (each point represents the mean of three determinations). Control gel prepared with 3% w/w NaCMC and 1% drug.

containing 0.5% w/w Tween 80 and was lowest with Diclofen gel (92.91 ± 8.15 µg/cm^{2}h). The permeability coefficient was highest (5.70 ± 0.57 cm/s $\times 10^{-6}$) for NaCMC gel containing 1% w/w Tween 80 and lowest for Diclofen gel (2.60 ± 0.5 cm/s $\times 10^{-6}$). In addition, the lag time t_{lag} was 0.23 ± 0.01 h for NaCMC containing 0.5 % w/w Tween 80 compared to 4 ± 0.50, 2.00 ± 0.15, 1.50 ± 0.19, and 0.95 ± 0.05 h for Diclofen gel, Diclogesic gel, Voltaren Emulgel, and Inflaban gel, respectively (Table 2). According to the cumulative amount permeated across rat skin, the tested formulations could be arranged in the following descending order: 0.5% Tween 80 > combination II > control gel > 5% IPA > 5% TPGS > Voltaren Emulgel > Inflaban > Diclogesic > Diclofen gel (Table 2 and Fig. 8).

The lag time for combination II was 0.74 ± 0.02 h. The reduction in the lag time of the prepared gel can be useful for rapid onset of the therapeutic effect (15,16). These data reveal the importance of added enhancers for improving the permeation rate of the drug. In addition, the RPR was greater than 1 for the prepared gels, which indicates the usefulness of NaCMC as a vehicle for diclofenac sodium (Table 2).

Infrared Studies

The IR spectra of diclofenac sodium and NaCMC in pure forms are compared with that of their physical mixture in a 1:1 ratio to obtain some information about any interactions that occurred between the drug and the vehicle . The spectra are presented in Figs. 9a, 9b, and 9c. It is clear from the results obtained that there is no positive evidence for the interactions between the drug and the vehicle other than hydrogen bonding (if any) which may have occurred between donating and accepting groups of both drug and NaCMC, indicating the usefulness of NaCMC as a gelling material for topical application of diclofenac sodium.

Differential Scanning Calorimetry Studies

The DSC studies were performed to confirm the results obtained by IR studies that there is no interaction between diclofenac sodium and NaCMC. DSC thermograms of pure diclofenac sodium and NaCMC were compared with that of their physical mixture in the 1:1 ratio (Fig. 10). The thermograms showing a nonsignificant lowering in the melting

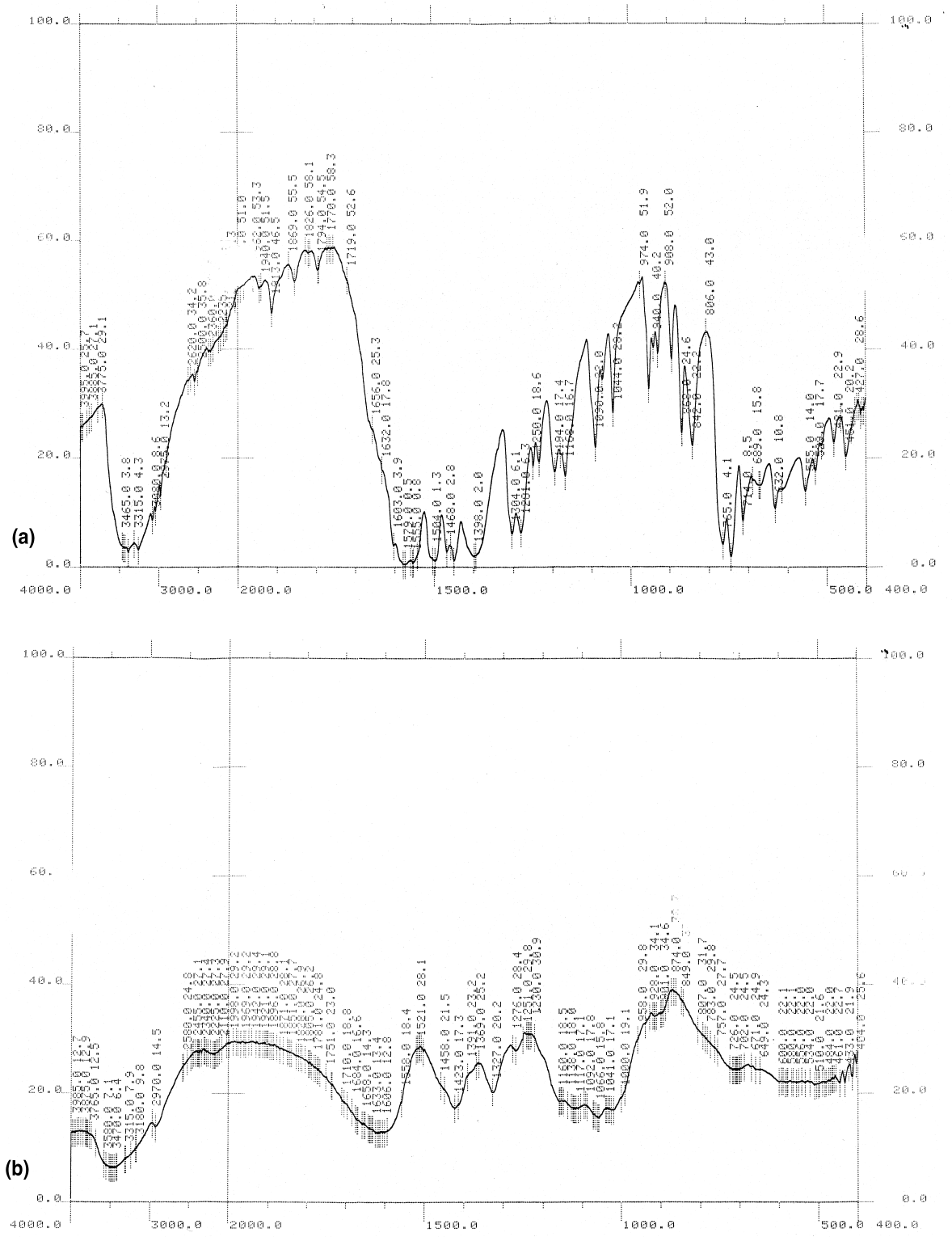

Figure 9. (a) IR spectrum of pure diclofenac sodium; (b) IR spectrum of pure NaCMC; (c) IR spectrum of pure diclofenac sodium: NaCMC physical mixture at a 1:1 ratio.

(continued)

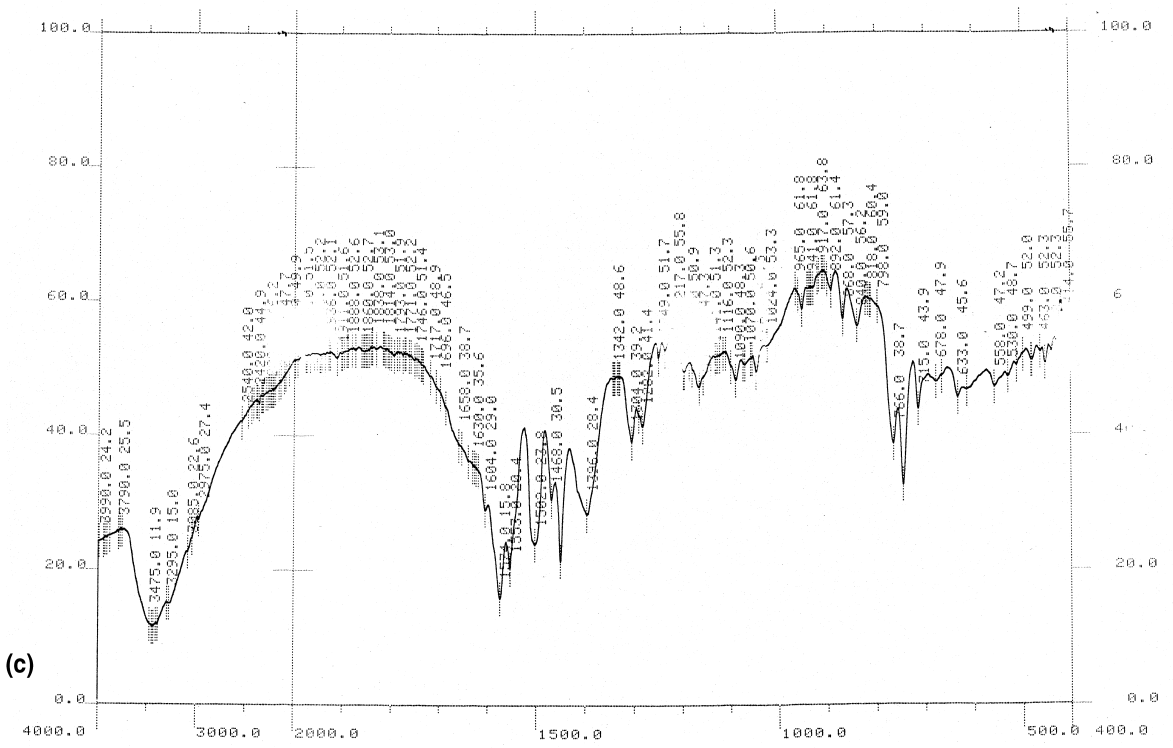

Figure 9. Continued

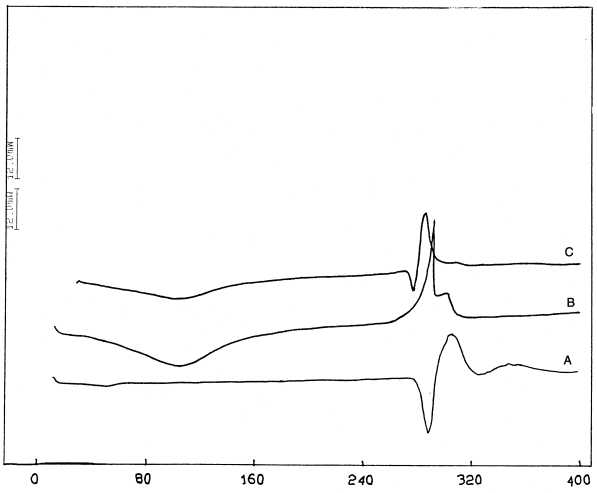

Figure 10. DSC thermograms of (A) pure diclofenac sodium, (B) pure NaCMC, and (C) their physical mixture at a 1:1 ratio.

points of both the drug (decreased from 288°C to 276°C) and NaCMC (decreased from 292°C to 286°C). In addition, there was no change in the thermal behavior of diclofenac sodium in the samples tested (Fig. 10). However, the slight shifting to lower melting points suggests the possibility of formation of an eutectic mixture. Thus, the consistency of the thermograms of the physical mixture with that of the pure drug indicates that no structural changes occurred for diclofenac sodium on incorporation in NaCMC as a vehicle. This investigation confirms the inertness of the vehicle (NaCMC) toward the drug; therefore, the rapid permeation of diclofenac sodium from the prepared gels could be attributed to the absence of interaction between the drug and the vehicle.

CONCLUSION

The higher release rate, steady-state flux, and permeability coefficient, as well as the decreased lag time, of permeation of diclofenac sodium from gels based on NaCMC (3% w/w) compared to conventional gel formulations of diclofenac sodium indicate the usefulness of NaCMC as a vehicle for topical delivery of diclofenac sodium. The faster permeation of the drug as compared to the

commercial products could be attributed to the absence of interaction between diclofenac sodium and NaCMC and to the use of the sodium salt instead of the diethylamine form used in the commercial gel products. Therefore, the use of NaCMC is recommended for topical application of diclofenac sodium.

REFERENCES

1. Ostrenga, J.; Steinmetz, C.; Poulsen, B. J. Pharm. Sci. **1971**, *66*, 1175.
2. Scheuplein, R.J.; Blank, I.H. J. Invest. Dermatol. **1973**, *60*, 86.
3. Comikus, M.; Ncolakis, M.; Kortz, R.; Wilkinson, F.E.; Kaiser, R.; Chlud, K. Arzneim. Forsch. Drug Res. **1996**, *46*, 1138.
4. Goto, S.; Ucika, T.; Lee, C.K.; Yasutake, T.; Zhang, J.B. J. Pharm. Sci. **1993**, *82*, 959.
5. Morimoto, Y.; Sugibayashi, K.; Hosoya, K.; et al. Int. J. Pharm. **1986**, *32*, 31.
6. El-Gindy, N.A. Pharmazie **1993**, *48*, 616.
7. Hadgraft, J.; Watter, K.A.; Watton, P.K. J. Pharm. Pharmacol. **1985**, *37*, 725.
8. Takeushi, Y.; Yasukama, H. Yamaoka. Biol. Pharm. Bull. **1995**, *18*, 304.
9. Bohina, F.P.; Montenegzo, L. Int. J. Pharm. **1994**, *102*, 19.
10. Sasaki, H.; Kojima, M.; Nakamra, J.; et al. J. Pharmacobiol. Pharmacodyn. **1990**, *13*, 200.
11. Imoto, H.; Zhou, Z.; Stinchcomb, A.L.; et al. Biol. Pharm. Bull. **1996**, *19*, 263.
12. Hwang, C.C.; Danti, A.G. J. Pharm. Sci. **1983**, *72*, 857.
13. Single, J.; Tripathi, K.P.; Sakya, T.R. Drug Dev. Ind. Pharm. **1993**, *19*, 1623.
14. Chow, D.S.-L.; Kaka, I.; Wang, T.I. J. Pharm. Sci. **1984**, *73*, 1794.
15. Mohamed, F.A. STP Pharma Sci. **1995**, *5*, 456.
16. Arellano, A.; Santoyo, S.; Martin, C.; Ygartua, P. Eur. J. Pharm. Sci. **1999**, *7*, 129.
17. Priborsky, J.; Takayama, K.; Nagui, T. Acta Univ. Palacki. Olomuc. Fac. Mel. **1998**, *141*, 35.
18. Arellano, A.; Santoyo, S.; Martin, C.; Ygartua, P. Eur. J. Drug Metab. Pharmacokinet. **1998**, *23*, 307.
19. Burnham, R.; Gregg, R.; Healy, P.; Steadward, R. Clin. J. Sport Med. **1998**, *8*, 78.
20. McEwan, L.E.; Smith, J.G. Australas. J. Dermatol. **1997**, *38*, 187.
21. Waikakul, S.; Penkitti, P.; Soparat, K.; Boonsanong, W. J. Med. Assoc. Thai. **1997**, *80*, 593.
22. Rivers, J.K.; McLean, D.I. Arch. Dermatol. **1997**, *133*, 1239.
23. Sandelin, J.; HariLainen, A.; Crone, H.; Hamberg, P.; Forsskahl, B.; Tamelander, G. Scand. J. Rheumatol. **1997**, *26*, 287.
24. Gupta, S.K.; Prakash, J.; Awor, L.; Joshi, S.; Velpandian, T.; Sengupta, S. Inflamm. Res. **1996**, *45*, 590.
25. Patel, R.K.; Leswell, P.F. Clin. Ther. **1996**, *18*, 497.
26. Stei, P.; Kruss, B.; Wiegleb, J.; Tarch, V. Br. J. Rheumatol. **1996**, *35*, 44.
27. Nishihata, T.; Kamada, A.; Saki, K.; Takahashi, K.; et al. Int. J. Pharm. **1988**, *46*, 1.
28. Takahashi, K.; Tamagawa, S.; Katagi, T.; et al. Chem. Pharm. Bull. **1991**, *39*, 509.
29. Obata, Y.; Kakayama, K.; Maintani, Y.; Machida, Y.; Nagi, T. Int. J. Pharm. **1993**, *89*, 191.
30. Rhee, G.J.; Woo, J.S.; Hawang, S.J.; Lee, Y.W.; Lee, C.H. Drug Dev. Ind. Pharm. **1999**, *25*, 717.
31. Stott, P.W.; Williamas, A.C.; Barry, B.W. J. Controlled Release **1998**, *50*, 97.
32. Shin, S.-C.; Cho, C.-W.; Choi, H.-K. Drug Dev. Ind. Pharm. **1999**, *25*, 273.
33. Todd, P.A.; Sorkin, E.M. Drugs **1988**, *35*, 244.
34. Small, R.E. Clin. Pharm. **1989**, *8*, 545.
35. Riess, W. Scand. J. Rheumatol. **1978**, *22*, 17.
36. Higuchi, W.I. J. Pharm. Sci. **1962**, *51*, 802.
37. Tomida, H.; Shinhara, M.; Kuwada, N.; et al. Acta Pharm. Suec. **1987**, *24*, 263.