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Evaluation of Physico-chemical Properties of Acrylic Resin Hydrogel and their Application to Transdermal Delivery System

Uoo Tae Chung, Seung Man Choi, Kee Long Kang, Nak Seo Kim and Youn Bok Chung

College of Pharmacy, Chungbuk National University, Cheongju, Chungbuk 360-763, Korea

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Recently, many attempts have been made to use hydrogels of various polymers as delivery systems of various drugs and bioactive materials to prolong and control their pharmacological activities. In this study, we have evaluated the physico-chemical properties of methacrylic acid-methacrylic acid methyl ester copolymer (Eudispert mv), a acrylic resin hydrogel, and its application to transdermal delivery system. In the dissolution tests, the release rate of salicylic acid (SA) and sodium salicylate (Sod. SA) were faster than lidocain (LD) and lidocain-HCl (LD-HCl). As the concentration of Eudispert mv polymer increased, the extensibility of Eudispert mv hydrogel decreased, whereas the swelling ratio increased. The more NaOH and polymer concentration increased, the more osmotic pressure linearly increased. The skin permeation of Sod. SA, an acidic model drug, was remarkably enhanced by Eudispert mv hydrogel. All fatty acids, except for Sod. glycolate, dramatically increased the skin permeation flux in Eudispert mv hydrogel containing LD-HCl, a basic model drug. Consequently, it is suggested that Eudispert mv hydrogel may be used as potential transdermal delivery vehicle.

Key words : Methacrylic acid-methacrylic acid methyl ester copolymer (Eudispert mv), Salicylic acid, Lidocain, Physico-chemical properties, Skin permeation

INTRODUCTION

During the last decade, transdermal delivery has received increasing attention in the face of growing awareness that drugs administered by conventional means are sometimes excessively toxic and frequently ineffective. Theoretically, the important advantages of transdermal delivery are: (1) reduction of side effects due to optimization of the blood concentration-time profile, (2) extended duration of activity, which allows greater patient compliance owing to elimination of multiple dosing schedules.

Recently, hydrogels have been used as delivery systems for various drugs and bioactive materials to prolong and control their pharmacological activities (Kost and Range, 1986). Hydrogels containing drugs and bioactive materials have attracted special interest as controlled-release preparations that enable administration of drugs by various routes. Hydrogels are defined as infinite three-dimensional polymeric networks (cross-linked structure) containing considerable amounts of water, i.e., more than 20% (Ratner and Hoffman, 1976).

The primary advantages in using hydrogels are : First, due to their high water content, hydrogels possess good biocompatibility (Wichterle, 1971) in general. Second, the swelling kinetics of hydrogels is reproducible and the degree of swelling can be very high, which allows for high permeability to solutes and good prediction of release kinetics. Third, the permeability of a specific drug can be controlled by varying structure and crosslinking density of the hydrogel. In addition to the ability of controlling the release of drug from the device, hydrogels can protect the drug from degradation in the body. Hydrogels have been extensively studied as potential candidates for replacement of soft tissue or for other medical applications (Merril *et al.*, 1987).

Many investigators (Kim *et al.*, 1990; Goto *et al.*, 1991; Kawata *et al.*, 1991; Kim *et al.*, 1992a) have already reported on the preparation and potential suppository use of acrylic resin gels (Eudragit L, Eudragit S, Eudispert hv) that are block copolymers of methacrylic acid and methyl methacrylate. They have reported that, particularly, drug loss caused by first-pass metabolism may be avoided completely by placing Eudispert hv hydrogel and xerogel formulations in the lower part of the rectum for long

Correspondence to: Uoo Tae Chung, College of Pharmacy, Chungbuk National University, Cheongju, Chungbuk 360-763, Korea

periods (Kim *et al.*, 1992b).

The permeation of drugs through the stratum corneum is the rate controlling barrier to transdermal permeation for both lipophilic and hydrophilic drugs. Several investigators have shown that water enhances the permeability of a great number of lipophilic and hydrophilic drugs (Southwell and Barry, 1984).

In these studies, methacrylic acid-methacrylic acid methyl ester copolymer (Eudispert mv), a acrylic resin hydrogel, was evaluated as a novel transdermal delivery system. For this purpose, we have evaluated the physico-chemical properties of acrylic resin hydrogel and their application to transdermal delivery system by measuring in vitro permeation of sodium salicylate, an acidic model drug, and lidocaine-HCl, a basic model drug.

MATERIALS AND METHODS

Materials and animals

Salicylic acid (SA) and sodium salicylate (Sod. SA) were the products of Nakarai Chemical Company (Japan). Lidocaine (LD) and lidocaine-HCl (LD-HCl) were obtained from Sigma Chemical Company. Eudispert mv (Röhm Pharma, 1982) was supplied by R hm Pharma GmbH (Germany). All other reagents were analytical grade.

Hairless female mice (SKH-1 strain) were used for all experiments, and were obtained from Lucky Cosmetic Research Institute, Korea. The mice were maintained at 21-24°C and 50±10% relative humidity, and feed and water were available *ad libitum*. A 12 hour light and dark cycle was maintained, mice were used as the source of *in vitro* skin permeation studies. They were 10-12 weeks old and 27-33 g in body weight.

Preparation of edispert mv hydrogel

SA, Sod. SA, LD, and LD-HCl were dissolved in purified water, and then Eudispert mv polymer was added to 10% (w/w) of the total weight. The mixture was mechanically stirred and allowed to soak and swell for 10-15 min. Then, NaOH (4-7 mEq) was added to the resulting mixture with stirring. Hydrogel preparations (2.0 g) containing 1.25% (w/w) SA, Sod. SA, LD, and LD-HCl were obtained by this procedure.

Dissolution studies

The apparatus was basically the same as the one stipulated in KP VI. The release of the drugs from the Eudispert mv hydrogel was evaluated by the rotating basket method. Each 2.0 g sample of the Eudispert mv hydrogel containing 1.25% (w/w) SA, 1.25% (w/w) Sod. SA, 1.25% (w/w) LD, or 1.25% (w/w) LD-HCl was weighed accurately in a semipermeable cellulose membrane (Visking tube, size 24/32, pore size 24 Å, Viskase Corp., Japan) after preparation and stored for 12 h until the dissolution study was started. The semipermeable cellulose membrane filled with the hydrogel was attached to the rotating basket. Thereafter, the basket was introduced into a beaker containing 500 ml of 0.2 M KH_2PO_4: NaOH buffer (phosphate buffer, pH 7.4) as the dissolution medium.

The dissolution experiments were done at 37°C and at a rotation speed of 100 rpm. At appropriate intervals, 5 ml of the dissolution medium was withdrawn for analysis. An equivalent volume (5 ml) of fresh dissolution medium was added to compensate for sampling.

The dissolved SA and Sod. SA concentrations were determined spectrophotometrically by measuring absorption at 300 nm. The dissolved LD and LD-HCl concentrations were determined by a HPLC method at 210 nm. The results were plotted as dissolved percent of drugs extracted into the dissolution medium from the hydrogel versus time.

Physico-chemical studies

Swelling studies: The apparatus and method were basically the same as the rotating basket method stipulated in the KP VI, except that the hydrogel preparations (2.0 g) were inserted into a cellulose tube (Visking tube as above) Both ends of the tube were ligated to obtain 50 mm of length (weight=W1), and this sample was introduced into the basket. Tests were started immediately in phosphate buffer (500 ml, pH 7.4) at 37℃ and with a rotation speed of 100 rpm. At appropriate time intervals, the weights of the swelled samples were measured (W_2). Swelling ratios were calculated using the following equations.

$$Swelling\ Ratio = \frac{weight(g)\ of\ swollen\ gel\ at\ time\ t}{initial\ weight(g)\ of\ gel}$$

$$= \frac{2.0+(W_2 - W_1)}{2.0}$$

Spreading studies: The spreading of Eudispert mv hydrogels was examined using a spreadmeter (Rigo Company, Japan). A 0.5 g portion of the hydrogels prepared in the same manner was filled uniformly into the spreadmeter and allowed to stand for 1 h at room temperature. The extensibility of the filled hydrogels was measured with the spreadmeter at suitable intervals. The weight of the glass plate used in this experiment was 115 g.

Osmotic pressure studies: The osmotic pressure of the Eudispert mv hydrogel was examined using an os-

mometer (Gonotec, Germany). We examined the osmotic pressure of 1% Eudispert mv hydrogel containing various amount of NaOH (5mEq, 6mEq, 7mEq). We also measured the alteration of the osmotic pressure when different Eudispert mv polymer concentrations were added in Eudispert mv hydrogels containing 5mEq of NaOH.

In vitro permeation studies

The dorsal skin of hairless female mice (SKH-1 strain) was obtained from 10-12 weeks old, 27-33 g animals. The mice were sacrificed by cervical dislocation just before an *in vitro* skin permeation experiment. The full-thickness dorsal skin sections were excised with surgical scissors. Fat on the surface of the skin was carefully removed and the skin was divided into three pieces for the permeation studies.

The above excised skin was inserted into the diffusion cell, and the permeation studies were undertaken essentially the same as described below. We used vertically assembled LOVEDAY type diffusion cells with an effective diffusional area of 0.785 cm^2 and downstream volume of 5 ml. Prior to *in vitro* permeation studies, each cell was individually calibrated with respect to its receiver volume and diffusional surface area.

The receiver compartment was filled with 5 ml of 50 mM phosphate-bufferred saline (PBS, pH 7.4) and the donor comartment was filled with 0.5 ml of PBS containing 1.25% LD-HCl, 1.25% Sod. SA, or 0.5 g of Eudispert mv hydrogels (3%, 5%, 7%, 10%) containing 1.25% LD-HCl or 1.25% Sod. SA. Each cells was immersed in a water bath thermostated at 37°C. The mixture of the receiver compartment was stirred with magnetic stirrer. Aliquots of 0.2 ml were withdrawn from the receiver compartment across the sampling port periodically for 26 h and replaced with an equal volume of fresh PBS maintained at 37°C. The amount permeated for each drug was determined by HPLC. Compensation of drug concentration was also undertaken.

Determination of LD-HCl and SOD. SA: The HPLC system was made by Hitachi Co., Ltd., Japan. The HPLC system consisted of a Model L-6000 pump, L-6000 intelligent pump, L4200 UV/VIS detector and D-2500 chromato-integrator. We used Shim-pack CLC-ODS column made by Shidazu (Japan) and injection volumn was 20 μl. For Lidocaine-HCl, the mobile phase was 0.03 M phosphoric acid : acetonitrile : MeOH (81.3 : 16.7 : 3), the frow rate was 1.5 ml/min, and a wavelength of 210 nm was selected. For Sod. SA, the mobile phase was 0.01 M phosphoric acid : acetonitrile (70 : 30), frow rate was 1.5 ml/min, and the wavelength was 300 nm.

RESULTS AND DISCUSSION

Dissolution studies

Fig. 1 shows the release profiles of salicylic acid (SA), sodium salicylate (Sod. SA), lidocane (LD), and lidocane-HCl (LD-HCl) from 10% Eudispert mv hydrogel with NaOH 5 mEq, containing 1.25% SA, Sod. SA, LD, or LD-HCl. Similar release profiles were obtained for SA and Sod. SA. LD-HCl, from Eudispert mv hydrogel, was released a little faster than LD, with a 10% difference after 8 h. The release rate of SA and Sod. SA from Eudispert mv hydrogel was faster than LD and LD-HCl, suggesting that Sod. SA, an acidic model drug, was released faster than LD-HCl, a basic model drug. Eudispert mv hydrogel, containing 1.25% LD-HCl or 1.25% Sod. SA, gave sustained release in comparison with PBS containing 1.25% LD-HCl or Sod. SA (Fig. 2). The release rate of Sod. SA from Eudispert mv hydrogel at pH 7.4 was faster than at pH 1.2, while the release rate of LD-HCl from Eudispert mv hydrogel was faster at pH 1.2 (Fig. 3).

Physico-chemical Studies

Swelling studies: As the concentration of Eudispert mv polymer was increased, the swelling ratio of Eudispert mv hydrogel increased (Fig. 4). Accordingly,

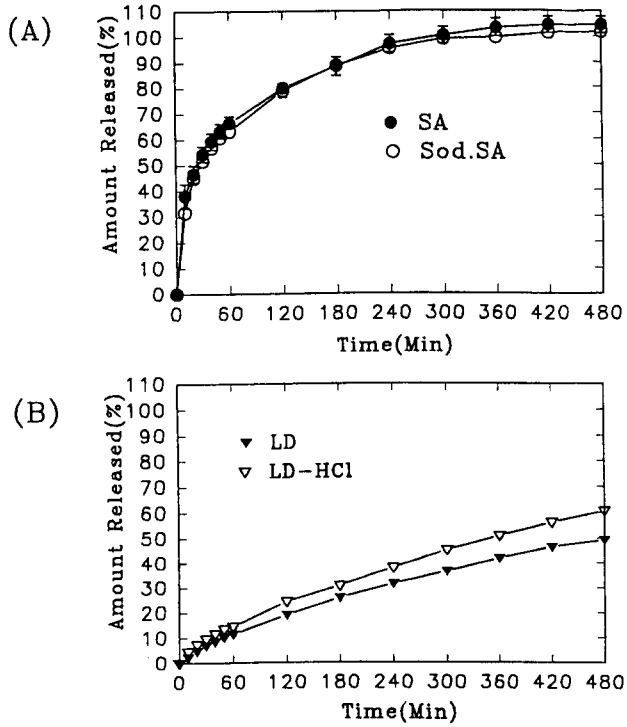

Fig. 1. Release profiles of SA, Sod. SA, LD and LD-HCl from Eudispert mv hydrogel. (A) ●; SA, ○; Sod. SA, (B) ▼; LD, ▽; LD-HCl. Each point represents the mean±S.D. of four different experiments.

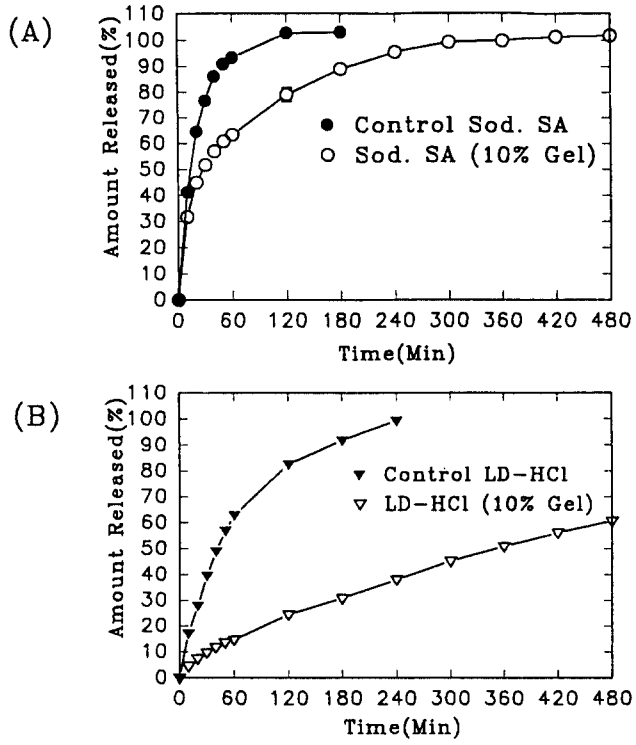

Fig. 2. Release profiles of Sod. SA or LD-HCl from Eudispert mv hydrogel or phosphate buffer (PBS). (A) Sod. SA: (○); Gel, (●); PBS, (B) LD-HCl: (▽); Gel, (▼); PBS. Each point represents the mean±S.D. of four different experiments.

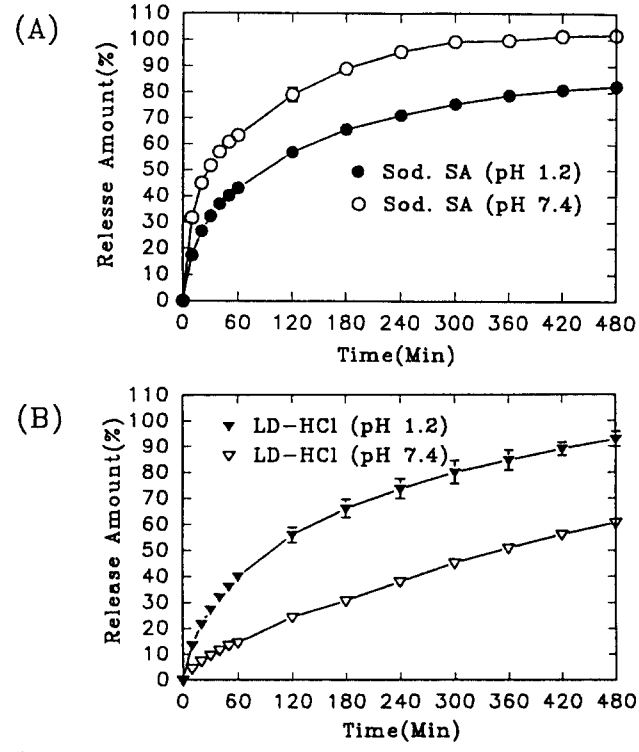

Fig. 3. Release profiles of Sod. SA and LD-HCl at different pH value. (A) Sod. SA: (●); pH 1.2, (○); pH 7.4, (B) LD-HCl: (▼); pH 1.2, (▽); pH 7.4. Each point represents the mean±S.D. of four different experiments.

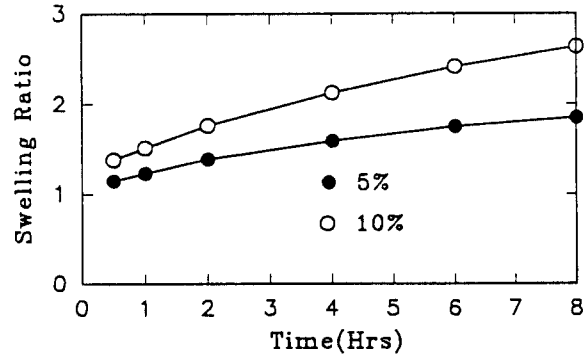

Fig. 4. Time course of swelling for 5% (●) and 10% (○) Eudispert mv hydeogels. Each point represents the mean of three values.

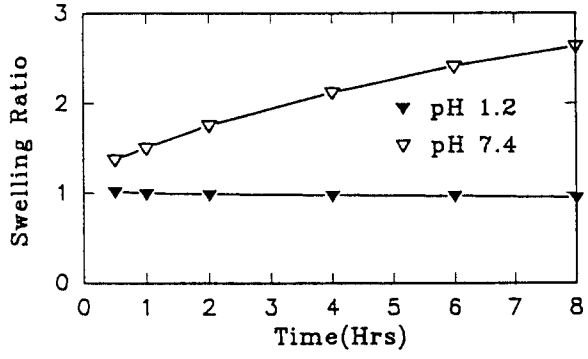

Fig. 5. Effect of different pH (pH 1.2(▼), pH 7.4(▽)) on time course of swelling for 10% Eudispert mv hydrogels. Each point represents the mean of three values.

the swelling ratio of 10% Eudispert mv hydrogel was increased almost 3/2 faster than that of 5% Eudispert mv hydrogel. Possibly due to the degradation of gel in acidic medium, Eudispert mv hydrogel did not swell measurably at pH 1.2 (Fig. 5).

Spreading studies: The extensibility tests of 5%, 10%, and 15% Eudispert mv hydrogel were made 12 h after preparation (Fig. 6). The diameter (ordinate axis) of spread circle of sample gels obtained by giving weight (115 g) of glass plate means the extensibility of Eudispert mv hydrogels, increased linearly with the increasing of logarithm of time (abscissa axis). The intercept on the ordinate axis of each line is closely related to the reciprocal of viscosity of Eudispert mv hydrogel.

Osmotic pressure studies: In the osmotic pressure tests, the effect of various NaOH equivalents (5mEq, 6mEq, 7mEq) on the osmotic pressure of 1% Eudispert mv hydrogels and the effect of different polymer concentrations on the osmotic pressure of Eudispert mv hydrogel containing 5mEq NaOH were shown on Fig. 7. The more NaOH and polymer concentration increased, the more osmotic pressure

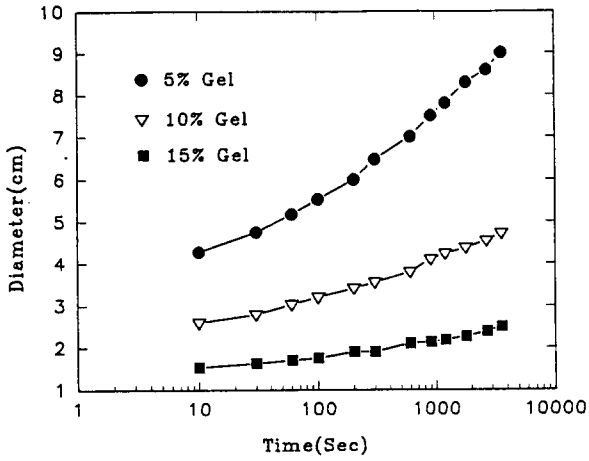

Fig. 6. Time-dependence of diameter measured by spreadmeter for Eudispert mv hydrogels containing the various concentrations (5% (●), 10% (▼), 15% (■)) of Eudispert mv polymer. Each point represents the mean of three values.

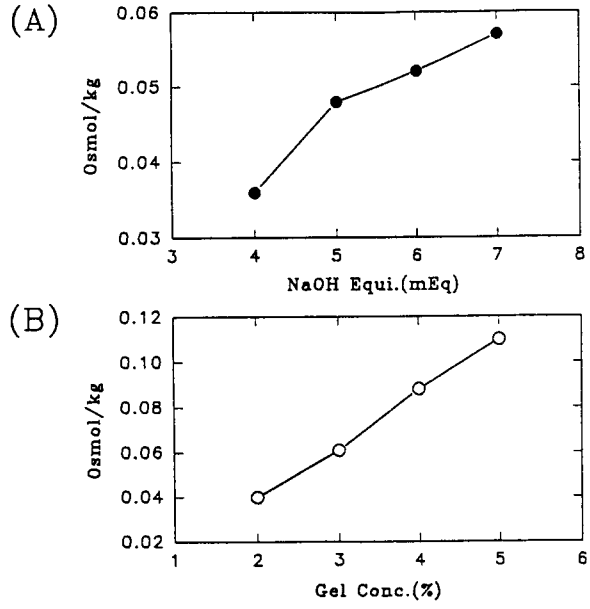

Fig. 7. (A) The effect of various NaOH equivalents on the osmotic pressure of 1% Eudispert mv hydrogel; (B) The effect of various concentrations of Eudispert mv polymer containing 5mEq NaOH on the osmotic pressure. Each point represents the mean of three experiments.

linearly incresed. The increases in osmotic pressure are predicted based on the corresponding increases in ionic strength.

In vitro permeation studies

Fig. 8 represents the permeation profiles of Sod. SA, delivered from PBS or Eudispert mv hydrogels containing different polymer concentrations (3%, 5%, 10%), across the hairless mouse skin. Whereas Sod. SA delivered from PBS did not permeate skin

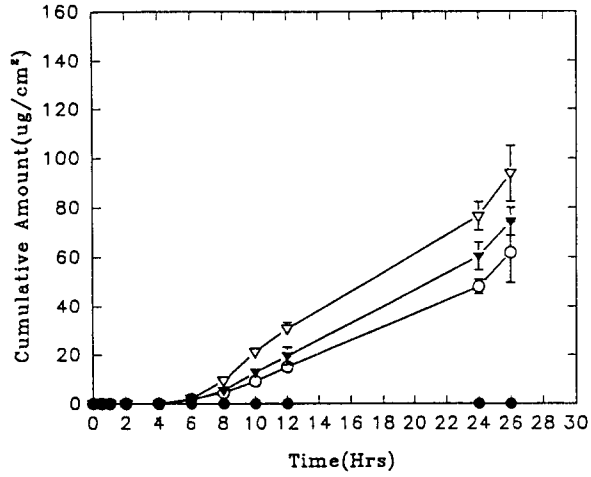

Fig. 8. Permeation profiles of Sod. SA delivered from various vehicles (PBS (●), Eudispert mv hydrogels; 3% (○), 5% (▼), 10% (▽)) containing 1.25% Sod. SA. Each point represents the mean±S.D. of four different experiments.

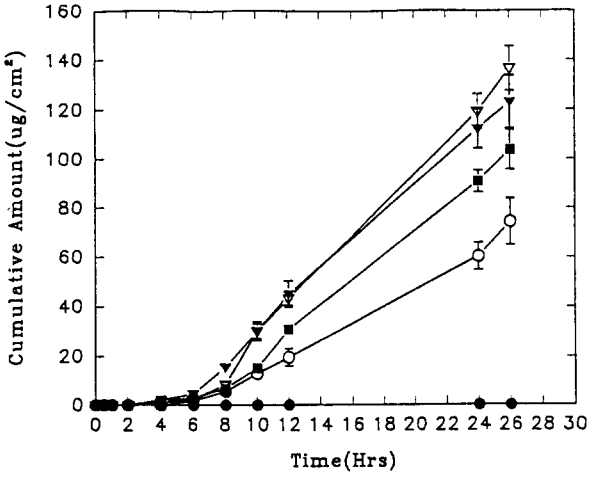

Fig. 9. Permeation profiles of Sod. SA delivered from various vehicles (PBS (●), Eudispert mv hydrogel only (○), 5% Eudispert mv hydrogels containing 3% different fatty acids; Sod. caprylate (▼), Sod. caprate (▽), Sod. laurate (■)) containing 1.25% Sod. SA. Each point represents the mean±S.D. of four different experiments.

completely, the skin permeation of Sod. SA delivered from Eudispert mv hydrogel was significantly enhanced.

We tried to improve the efficiency by the addition of saturated fatty acids (C8~C12) to 5% Eudispert mv hydrogel. The results are shown in Fig. 9. The addition of fatty acids increased the skin permeation amount of Sod. SA in Eudispert mv hydrogels. The corresponding values of lag time, steady-state flux, and permeation percentage by 26 h for each donor composition are listed in Table I. The greatest enhancing effect was observed in Eudispert mv hydrogel containing 3% Sod. caprate. In spite of the notable increase of skin permeability of Sod. SA by the addition

Table I. Permeation parameters of sodium salicylate from various vehicles[a]

Vehicle	Fatty Acid	Lag Time (h)	Flux (μg/cm²)/h	Permeation percent (% of dose at 26h)
PBS	No	not measurable	0	0
3% Gel	No	7.30 (1.80)	1770 (755)[b]	0.99 (0.36)[b]
5% Gel	No	5.87 (1.17)	2110 (314)[b]	1.19 (0.11)[b]
10% Gel	No	6.77 (3.20)	2630 (232)[b]	1.50 (0.22)[b]
5% Gel	Sod. caprylate (C8)	4.30 (0.77)	3310 (565)[b]	1.97 (0.33)[b]
	Sod. caprate (C10)	4.94 (1.58)	3780 (260)[b]	2.18 (0.18)[b]
	Sod. laurate (C12)	5.47 (1.66)	2930 (916)[b]	1.66 (0.55)[b]

[a]Each value represents the mean (SD) of four experiments.
[b]Significantly different from PBS (phosphate-bufferred saline, P<0.01).

of fatty acid, the skin permeation amount of Sod. SA, an acidic model drug, was quite small (about 2% of the total dose in 26 h).

Fig. 10 represents the skin permeation profiles of LD-HCl, delivered from PBS or Eudispert mv hydrogels containing different polymer concentrations (3%, 5%, 10%), across the excised hairless mouse skin. The permeation amount of LD-HCl decreased with increasing polymer concentration. This may be attributed to the lower release rate of LD-HCl from Eudispert mv hydrogels (Fig. 1). Saturated fatty acids (C 8~C12) was added to 5% Eudispert mv hydrogel to improve the permeation of LD-HCl. The results are shown in Fig. 11. Even though the skin permeability of LD-HCl decreased from hydrogels, the skin permeation amount of LD-HCl was enhanced by the ad-

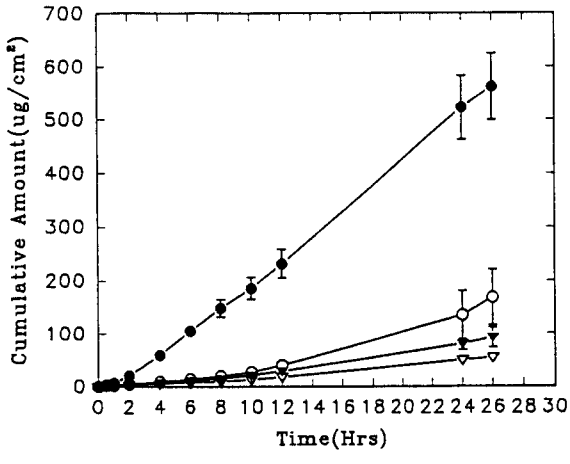

Fig. 10. Permeation profiles of LD-HCl delivered from various vehicles (PBS (●), Eudispert mv hydrogels; 3% (○), 5% (▼), 10% (▽)) containing 1.25% LD-HCl. Each point represents the mean±S.D. of four different experiments.

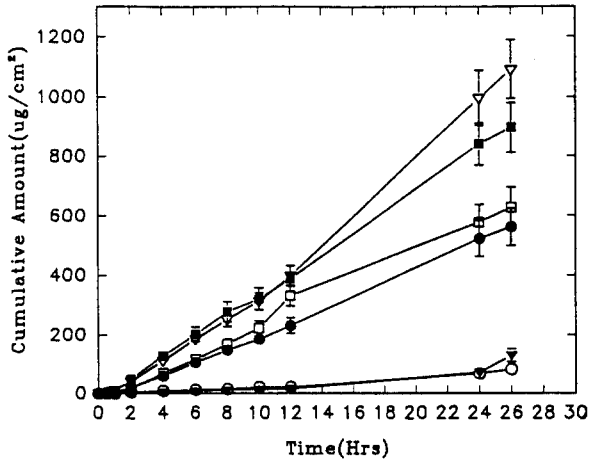

Fig. 11. Permeation profiles of LD-HCl delivered from various vehicles (PBS (●), Eudispert mv hydrogel only (○), 5% Eudispert mv hydrogels containing 3% different fatty acids; Sod. glycolate (▼), Sod. caprylate (▽), Sod. caprate (■), Sod. laurate (□)) containing 1.25% LD-HCl. Each point represents the mean±S.D. of four different experiments.

Table II. Permeation parameters of lidocaine-HCl from various vehicles[a]

Vehicle	Fatty Acid	Lag Time (h)	Flux (μg/cm²)/h	Permeation Percent (% of dose at 26 h)	Enhancing Factor
PBS	No	2.34 (0.08)	27700 (4210)	8.98 (1.57)	1
3% Gel	No	4.44 (0.74)	8820 (2100)	2.69 (1.18)	0.32
5% Gel	No	5.53 (1.92)	5020 (978)	1.48 (0.45)	0.71
10% Gel	No	5.44 (0.96)	2930 (465)	0.87 (0.10)	0.10
5% Gel	Sod. glycolate (C3)	6.45 (0.36)	5460 (1030)	2.07 (0.37)	0.23
	Sod. caprylate (C8)	3.86 (0.38)	39300 (3060)[c]	17.45 (2.21)[b]	1.94
	Sod. caprate (C10)	1.54 (0.63)	29300 (3840)	14.44 (1.53)[b]	1.61
	Sod. laurate (C12)	3.54 (1.17)	24200 (5160)	10.72 (0.78)[c]	1.12

[a]Each value represents the mean (SD) of four experiments.
[b]Significantly diifferent from PBS (phosphate-bufferred saline, P<0.01)
[c]Significantly different than PBs (P<0.05)

dition of fatty acids. The corresponding values of lag time, steady-state flux, and permeation percentage by 26 h for each donor composition are listed in Table II. The greatest enhancing effect was observed in Eudispert mv hydrogel containing 3% Sod. caprylate. All fatty acids, except for 3% Sod. glycolate, dramatically increased the skin permeation flux from Eudispert mv hydrogels (Fig. 11). The skin permeability of LD-HCl increased in the following order: Sod. caprylate (C8)>Sod. caprate (C10)>Sod. laurate (C12)>phosphate-bufferred saline (no fatty acid)>Sod. glycolate=Gel only.

In conclusion, Sod. SA, an acidic model drug, did not easily permeat across the skin. The total increased amount of Sod. SA by the addition of fatty acids was quite small. Whereas fatty acids dramatically increased the skin permeation flux of LD-HCl, a basic model drug, from Eudispert mv hydrogels.

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