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RESEARCH PAPER

Effects of Adhesives and Permeation Enhancers on the Skin Permeation of Captopril

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ABSTRACT

To formulate a transdermal drug delivery system of captopril, monolithic adhesive matrix type patches containing 20% captopril, different pressure-sensitive adhesives, and various permeation enhancers were prepared using a labcoater. The effects of the adhesives and permeation enhancers on skin permeation of captopril from the prepared patches were evaluated using Franz diffusion cells fitted with excised rat skins. The permeation rate of the drug through the excised skin was dependent on the type of polyacrylate copolymers studied. Fatty alcohols resulted in a pronounced enhancing effect on the skin permeation of captopril, while dimethyl sulfoxide, N*-methyl-2-pyrrolidone, oleic acid, Transcutol, and polysorbate 20 showed no significant enhancing effect. The permeation-enhancing effect of the fatty alcohols reached the maximum at the level of 10%. Based on these results, a captopril patch may be developed with further optimization.*

Key Words: *Adhesive; Enhancer; Captopril; Transdermal*

INTRODUCTION

Captopril, a specific competitive inhibitor of angiotensin I–converting enzyme, has been widely used in the treatment of hypertension and congestive heart failure. Its usual daily administered dose is 50–100 mg. The maximum blood drug concentration occurs at about 1 h after oral administration. It has a relatively short elimination half-life of approximately 2 h (1). Since food is known to

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reduce the oral absorption of captopril by about 35%–50% (2,3), it is recommended to be given 1 h before meals.

The food effect and the short elimination half-life make this drug a good candidate for a transdermal drug delivery (TDD) system. A TDD system containing captopril can avoid the reduction of bioavailability by concomitant food or drug intake and provide continuous dosing of the drug with better patient compliance. Captopril also possesses appropriate physicochemical properties as a drug candidate for potential transdermal delivery (4), such as low molecular weight (about 217), low melting point (106°C), suitable partition coefficient ($\log P = 1.9$), and good solubility in both water and organic solvents (5).

In the screening of candidates for an *l*-menthol-ethanol system among several cardiovascular drugs, Kobayashi et al. (6) suggested that captopril is one of the cardiovascular agents that can be used in a TDD system. Wu et al. (7–10) investigated the skin permeation of captopril from hydrophilic cellulose gels containing various permeation enhancers. These investigators suggested that a small-size TDD product may be formulated for captopril based on the permeation rate of the drug from the dosage form. However, they formulated the drug as a solution or gel not as a TDD patch.

TDD systems are classified into the monolithic adhesive matrix type, polymer matrix type, liquid reservoir type, and multilaminate solid-state reservoir type (11). All these systems include a pressure-sensitive adhesive (PSA) layer to hold the system in intimate contact with the skin. There are three different types of PSAs for TDD products: polyisobutylenes, polysiloxanes, and polyacrylate copolymers (12). Among them, polyacrylate copolymers are commonly used in the manufacturing of TDD products due to their relatively cheap price, excellent stability, good adhesive tack, and lack of need for addition of tackifier.

Permeation enhancers are commonly included in the formulation of a TDD system. One or more permeation enhancers are required for a TDD system, except for those containing drugs that pass across the skin barrier actively. The incorporation of a permeation enhancer is indispensable for achieving the desired permeation rate for almost all drugs with limited application size of the TDD system. The type of permeation enhancer employed has a significant impact on the development of the TDD product (13). Appropriate enhancer(s) for a TDD system containing a specific drug can only be selected by trial and error.

In the present study, captopril was formulated as a monolithic adhesive matrix type patch, which is the simplest type among various patches. Captopril patches were prepared using different polyacrylate copolymers, and various permeation enhancers were incorporated in the patch. The effects of different PSAs and permeation enhancers on the skin permeation rate of captopril from prepared TDD patches were evaluated using Franz diffusion cells fitted with excised rat skins.

EXPERIMENTAL

Materials

The following reagents were used as received without further purification: captopril (Sigma Chemical Co., St. Louis, MO); high-performance liquid chromatography (HPLC) grade methanol (Mallinckrodt Chemical Co., USA); lauryl alcohol, *N*-methyl-2-pyrrolidone (NMP), and dimethyl sulfoxide (DMSO; Kanto Chemical Co., Japan); o1ey1 alcohol (Yakuri Pure Chemicals Co., Japan); diethylene glycol monoethyl ether (Transcutol, Gattefosse Co., France); and propylene glycol (PG), oleic acid, and polysorbate 20 (Shinyo Chemical Co., Japan). Duro-Tak polyacrylate copolymers (D-2516, D-2287, D-2510, and D-4098) and Gelva polyacrylate copolymers (G-737 and G-788) were obtained from National Starch Company (USA) and Solutia Company (USA), respectively. Water was deionized and filtered in house. All other chemicals and solvents were analytical reagent grade.

Preparation of Pressure-Sensitive Adhesive Matrix

The PSAs and permeation enhancers used in the preparation of captopril patches are listed in Tables 1 and 2, respectively. For TDD patches containing permeation enhancers, D-2287 was used as the PSA. After a weighed amount of captopril was dissolved in acetone, permeation enhancers and PSA solutions were added to the captopril solution and mixed with a mechanical stirrer (model RW 20 DZM, IKA, Germany) at 200 rpm for 30 min. All these components were miscible under stirring, resulting in formation of a gel. The concentration of each

Table 1

Permeation Parameters of Captopril Through Excised Rat Skins from Patches Containing 20% Captopril Prepared with Various Pressure-Sensitive Adhesives (PSAs)

	Permeation Parameters	
PSA	J_s (μg/cm^2/h)[a]	T_L (h)[a]
D-4098	1.81 ± 0.65	8.8 ± 1.6
D-2516	3.49 ± 0.20	11.6 ± 1.0
D-2510	4.35 ± 0.79	10.5 ± 1.6
D-2287	6.80 ± 1.56	9.2 ± 0.8
G 737	5.68 ± 0.73	11.3 ± 0.6
G 788	4.31 ± 1.50	9.8 ± 1.5

J_s; permeation rate; T_L, lag time.
[a]Mean ±SE, $n = 4$.

Table 2

Permeation Parameters of Captopril Through Excised Rat Skins from Patches Containing 20% Captopril and 5% Different Enhancers

	Permeation Parameters	
Enhancers	J_s (μg/cm^2/h)[a]	T_L (h)[a]
Control	6.80 ± 1.56	9.2 ± 0.8
Dimethyl sulfoxide	7.88 ± 0.67	7.3 ± 0.6[b]
N-Methyl-2-pyrrolidone	9.03 ± 2.38	9.6 ± 1.4
Oleic acid	9.10 ± 2.32	10.6 ± 0.8
Transcutol	6.96 ± 2.27	9.1 ± 1.0
Propylene glycol	11.28 ± 5.62	8.9 ± 1.8
Polysorbate 20	7.30 ± 2.46	11.5 ± 0.7[b]
Oleyl alcohol	21.02 ± 8.33[b]	7.9 ± 1.0
Lauryl alcohol	26.21 ± 6.88[b]	10.5 ± 0.3

J_s, permeation rate; T_L, lag time.
[a]Mean ± S.E., $n = 4$.
[b]Significantly different from the control ($p < .10$).

enhancer was fixed at 5% to the total weight of the final patch except for fatty alcohols. The concentration of oleyl and lauryl alcohols was varied as 5%, 10%, and 20%. Patches were prepared using a labcoater (model LTE-S, Mathis, Switzerland). The mixed PSA solutions were cast at a thickness of 350 μm on a polyester release liner. After drying at 60°C for 10 min without air blowing, the film was further dried at the same temperature for 10 min with air blowing at 1000 rpm. Then, the dried film with a thickness of about 120 μm was laminated with a backing film (3M Scotchpak® polyester multilam film).

Measurement of Skin Permeation Rate of Captopril

Skins were obtained from male Sprague-Dawley rats weighing 230 ± 20 g. After hair was removed carefully with an electric clipper (model 900, TGC, Japan), a 5 cm × 5 cm patch of skin was excised from the dorsal region from each sacrificed rat, and the subcutaneous fat and other extraneous tissue were trimmed. The excised rat skins were stored at −20°C until use. They were used within 1 week after the skin harvest.

The extent and rate of skin permeation of the drug from the captopril patch were measured with Franz diffusion cells fitted with excised rat skins and mounted on a diffusion cell drive console (model FCDS-900A, Fine Scientific Instrument, Korea). The effective diffusion area was 1.77 cm^2. The receptor compartment of the diffusion cell was filled with 11.5 ml of water. The receptor medium was stirred at 600 rpm during the experiment with the temperature maintained at 37°C ± 0.5°C using a thermostatic water pump (model FT-101, Fine Scientific Instrument). After a TDD patch was applied on the epidermal surface of the skin, 0.2 ml of the receptor medium was withdrawn every 4 h up to 24 h and replaced immediately with an equal volume of fresh water at 37°C ± 0.5°C.

High-Performance Liquid Chromatographic Analysis of Captopril

The amount of captopril permeated into the receptor medium was determined with a validated HPLC method. The HPLC system consisted of an isocratic pump (model L-7110, Hitachi, Japan), an autosampler (model L-7200, Hitachi), an ultraviolet/visible detector (model L-7400, Hitachi), and an integrator (model D-7500, Hitachi).

The column used was a C_{18} column (Luna, 4.6 × 250 mm, 5 μm particle size, Phenomenex, USA). The mobile phase was a mixture of water and methanol (1 : 1), with pH adjusted to 3 using 0.1% phosphoric acid. Its flow rate was 1 ml/min, and the detection wavelength was 220 nm. After the receptor medium was mixed with an equal volume of the mobile phase, 200 μl of the mixed sample

was injected onto the column. All operations were carried out at ambient temperature.

Data Analysis

The cumulative amounts of captopril that permeated through excised skins were plotted as a function of time. The slope and intercept of the linear portion of the plot was derived by regression. The permeation rate at steady state (J_s, $\mu g/cm^2/h$) was calculated as the slope divided by the skin surface area. The intercept on the X axis was taken as the lag time (T_L, hours).

Statistics

All the skin permeation experiments were repeated four times, and their mean values with standard error are presented. The Student t test was performed to find any significant difference in the permeation rate between the TDD patches containing permeation enhancers and the control without enhancer.

RESULTS AND DISCUSSION

Effect of Various Pressure-Sensitive Adhesives on Skin Permeation

In the formulation of captopril TDD patches using polyacrylate copolymers, an optimal captopril amount was determined by varying the final drug concentration at 10%, 20%, 30%, and 40%. On preparation of the patch, crystals of captopril appeared on the surface of the TDD patch at concentrations of 30% and higher. Hence, the concentration of captopril in the product was fixed to 20% to prevent crystallization. Crystallization of the drug may decrease the drug concentration in the TDD system and result in a lower permeation rate than expected.

The skin permeation rate of captopril through excised rat skins from TDD patches prepared with different polyacrylate PSAs was determined; the permeation profiles of the drug are shown in Fig. 1. The permeation parameters, permeation rate and lag time, were calculated from the profiles and are presented in Table 1. The permeation rates of captopril from TDD patches through excised rat skins were in the range 2–7 $\mu g/cm^2/h$, which is less than the previously reported values through the same rat skin (9). The reduced permeation rate of captopril

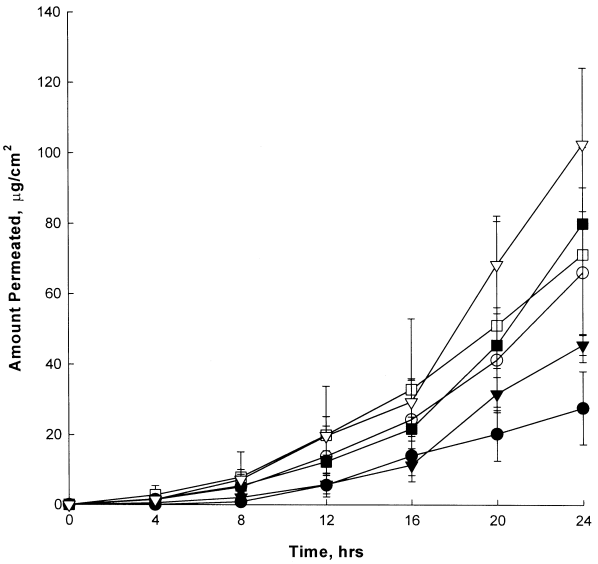

Figure 1. Permeation profiles of captopril through excised rat skins from patches prepared with various PSAs. Each patch contained 20% captopril (mean ± SE, $n = 4$). ●, D-4098; ○, D-2510; ▼, D-2516; ▽, D-2287; ■, G-737; □, G-788.

in this study may be a result of the different dosage forms used in the two studies. The permeation rate of a drug from a patch is usually significantly lower than that from a solution. Among six different PSAs used in this study, D-2287 resulted in the highest skin permeation rate of captopril, while D-4098 showed the lowest permeation rate.

To compare the release property of the adhesives, the release of captopril from the patches using the same diffusion cells fitted with nylon membranes (0.2 μm, Whatman, UK) instead of excised skins. All adhesives, except D-4098, showed similar drug release profiles from the patches (data not shown). However, the amount of drug released from the patch made of D-4098 was less than half of that from the patches made of other adhesives. There was no significant difference in the lag time among the PSAs. Subsequently, D-2287 was used in the development of a monolithic adhesive matrix type patch of captopril.

Effect of Permeation Enhancer on Skin Permeation

The incorporation of permeation enhancers in the TDD patches was essential to increase the permeation rate of captopril from the patches. The effects

of enhancers are specific and dependent on the drug, vehicle used, their concentration, and other factors (14). In this study, various permeation enhancers known to be potent were selected, and their effects on the permeation of captopril through excised rat skins were investigated at a concentration of 5%. The skin permeation profiles of the drug from the prepared patches are shown in Fig. 2. The permeation parameters, calculated from the obtained permeation profiles, are presented in Table 2.

Among the various enhancers employed, fatty alcohols showed the highest enhancing effects. Oleyl alcohol and lauryl alcohol increased the permeation rate of captopril by 3.1 and 3.9 times, respectively, compared to the control containing no enhancer. PG, NMP, and oleic acid increased the skin permeation of captopril moderately. On the other hand, DMSO, Transcutol, and polysorbate 20 showed no significant enhancing effects on the skin permeation of captopril. Although DMSO and polysorbate 20 have been reported as potent enhancers for some compounds (15), they were poor enhancers for other compounds, such as naloxone (14). The nonsignificant effect of DMSO was possibly due to the concentration in the preparation because its effect has been shown at a concentration higher than 50% (16). The addition of permeation enhancers in the patches did not significantly change the lag time of the skin permeation of captopril, except for DMSO and polysorbate 20.

In this study, fatty alcohols showed the most powerful permeation-enhancing effect for captopril. They are known to be safe and have been used to increase the skin permeation of a large number of compounds (15). Their mode of enhancing effect is via disruption of the lipid of the stratum corneum, reducing the resistance of the stratum corneum to the compounds (17).

The enhancing effects of fatty alcohols were further evaluated at different concentrations (10% and 20%) in the patches. The permeation rates at three different concentrations of oleyl alcohol and lauryl alcohol calculated from the permeation profiles are shown in Fig. 3. The addition of both fatty alcohols, from 5% to 20%, in the TDD patches increased the permeation rate of captopril significantly compared to the control containing no permeation enhancer. The permeation rate reached a plateau at the level of 10%, indicating that 10% of oleyl alcohol and lauryl alcohol is the optimum concentration in enhancing the permeation of captopril.

Aungst et al. (14) also found the maximum enhancement of skin permeation of naloxone at a

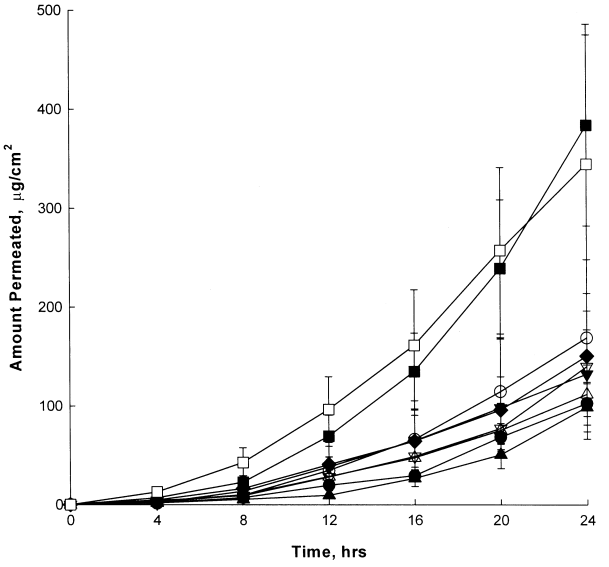

Figure 2. Permeation profiles of captopril through excised rat skins from patches containing different enhancers at the level of 5% (mean ± SE, $n = 4$). ●, control; ○, PG; ▲, polysorbate 20; △, Transcutol; ▼, DMSO; ▽, oleic acid; ◆, NMP; ■, lauryl alcohol; □, oleyl alcohol.

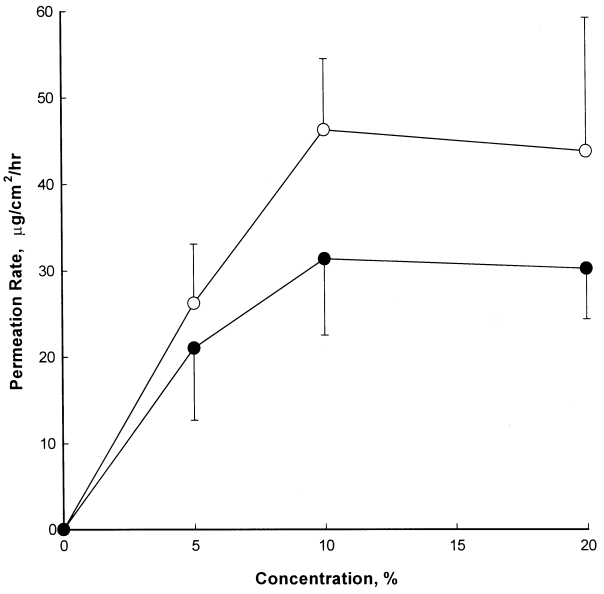

Figure 3. Effects of the concentration of fatty alcohol on the permeation rate of captopril through excised rat skins (mean ± SE, $n = 4$). ○, lauryl alcohol; ●, oleyl alcohol.

certain concentration of lauryl alcohol (20%). They speculated that the skin/vehicle partition coefficient of the drug was reduced at higher concentrations of fatty alcohols, which resulted in the decrease of the permeation rate of the drug.

Although the addition of 20% lauryl alcohol and oleyl alcohol did not further increase the permeation rate of captopril compared to the 10% level, it reduced the lag time significantly compared to the control, while the addition of 10% fatty alcohols did not. The lag times were 6.3 ± 1.2 h for lauryl alcohol and 7.4 ± 0.6 h for oleyl alcohol at the 20% level.

According to a previous study (6), the permeation rate of captopril needed to maintain the minimum effective concentrations is 1,488 μg/h in human skin. Assuming an application area of 30 cm^2, generally acceptable for a TDD product, the permeation rate of captopril should be 49.6 $\mu g/cm^2/h$ or less. Generally, animal skins result in significantly higher permeability for drugs than human skin (18). Furthermore, Wu et al. (9) compared the skin permeation rate of captopril through mouse, rat, rabbit, pig, and human skin, and they found that the permeation rate of captopril through rat skin is approximately 10 times higher than that through human skin. The maximum permeation rate of captopril obtained in this study, 46.26 $\mu g/cm^2/h$, should be further improved to prepare a TDD product containing captopril with an application area of 30 cm^2. For this purpose, the combination of effective permeation enhancers is under evaluation in our laboratory.

CONCLUSIONS

Monolithic adhesive matrix type patches of captopril formulated with various polyacrylate PSAs and permeation enhancers were evaluated for the feasibility of transdermal administration. Among various PSAs, D-2287 resulted in the highest permeation rate of the drug. Fatty alcohols were the permeation enhancers of choice for the percutaneous absorption of captopril. The enhancing effect of fatty alcohols reached a maximum at the level of 10%. These results indicate that a TDD patch containing captopril may be developed with further optimization.

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