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COMMUNICATION

Percutaneous Absorption of Captopril from Hydrophilic Cellulose Derivatives Through Excised Rabbit Skin and Human Skin

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ABSTRACT

The purpose of this investigation was to evaluate the influence of percutaneous absorption of captopril from hydrophilic cellulose derivatives gel bases (carboxymethylcellulose sodium [CMC], hydroxypropylcellulose [HPC] and hydroxylpropylmethylcellulose [HPMC]. The effects of various types and concentrations of penetration enhancers on captopril percutaneous absorption from HPC gel through rabbit skin were evaluated and selected to obtain some optimal formulations for penetration study through human chest skin. Then the required flux (1488 μg/hr) for captopril transdermal drug delivery system to maintain the therapeutic minimum effective concentration through human skin was used to evaluate the development of the optimal formulations. The results indicated that the minimum administered areas for therapeutic minimum effective concentration of captopril (cap) gel containing decanol (dec) were 10.4 cm^2 (5% cap, 7% dec) and 7.6 cm^2 (7% cap, 7% dec). These areas were within acceptable range, so these formulations can possibly be developed for a transdermal drug delivery system.

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INTRODUCTION

The potential advantages associated with transdermal drug delivery are well documented and include avoidance of first-pass gut and hepatic metabolism, potentially decreased side effects, and the relative ease of drug input termination in problematic cases (1).

Captopril is an orally effective angiotensin I converting enzyme inhibitor and is used in treatment of hypertension and congestive heart failure. Captopril has a relatively short elimination half-life in plasma with estimates in man ranging from 1.6 hr to 1.9 hr (2–4). According to the previous research, the oxidation rate of captopril in dermal homogenate is significantly lower than that in intestinal homogenates (5). Consequently, a transdermal drug delivery system (TDDS) may be suitable for captopril as a successful dosage form.

The purpose of this present investigation was to evaluate the abilities of captopril in vitro percutaneous absorption through rabbit skin from various hydrophilic cellulose derivative gel bases such as carboxymethylcellulose sodium (CMC), hydroxypropylcellulose (HPC), and hydroxylpropylmethylcellulose (HPMC). Furthermore, some potent penetration enhancers (such as capric acid, decanol, and undecanoic acid methyl ester) which had significant enhancing effect for captopril (6,7) were used to increase the flux of captopril gel formulations for maintaining the therapeutic minimum effective concentration.

EXPERIMENTAL

Materials

The following reagents were used: captopril (Sigma Chemical Company, St. Louis, MO), capric acid, lauric acid, palmitic acid, myristic acid, decanol, undecanoic acid methyl ester, carboxymethylcellulose sodium (CMC 500; CMC 1050), hydroxypropylcellulose (HPC 150-400 cps; HPC 1000-4000 cps) (TCI, Japan), and hydroxylpropylmethylcellulose (HPMC 90 SH 30000; HPMC 90SH 4000 SR) (Shin Etsu, Japan). All other chemicals and solvents were of analytical reagent grade.

Preparation of Skin Membranes

Male New Zealand rabbits (12–14 weeks old, 2.5–3.0 kg) were used. The hair of the abdominal region was removed with electric hair clippers and skin was excised after careful shaving. The excised full thickness skin samples were stored at -20°C prior to use.

Samples of whole adult human skin (from 24- to 50-year-old patients) were obtained from breast reduction operations and provided by Kaohsiung Medical College. Subcutaneous fat was carefully trimmed and the cadavar skin was rinsed with normal saline. The skin was then sealed in aluminum foil and a plastic bag and stored at -20°C. The thickness of human skin was about 2.68 mm. All the skin samples were allowed to regain room temperature for 1 hr before being used in the experiment.

Preparation of Captopril Gel

Hydrophilic cellulose derivative gel base was taken in a 50-ml beaker and wetted by water for 24 hr. Captopril and enhancers were dissolved in propylene glycol and water mixed solvent. Then the drug solution was added little by little to the wetted gel base and mixed well. The preparation was stored in a tightly sealed container in a wide-mouth bottle.

In Vitro Permeation Studies

The extent and rate of skin permeation of captopril from gel were determined using a Keshary-Chien glass diffusion cell fitted with excised rabbit skins or human skin (8). The skin was mounted on the receptor compartment with the stratum corneum side facing upward into the door compartment and the dermal side facing downward into the receptor compartment. The donor cell was filled with 2 g of gel. The receptor compartment was filled with 20 ml of deoxygenated distilled water and its temperature was maintained at 37 ± 0.5°C by thermostatic water pump during the experiment. The effective diffusion area was 2.54 cm^2. A 0.5-ml aliquot of the receptor medium was withdrawn at determined intervals and replaced immediately with an equal volume of fresh deoxygenated water. This dilution of the receiver content was taken into account when evaluating the penetration data. The sample withdrawn from the receptor compartment was then analyzed by HPLC (9). Each data point represents the average of three determinations.

RESULTS AND DISCUSSION

The Permeation Through Excised Rabbit Skin

The flux of captopril gel formulations containing 5% of various hydrophilic cellulose derivative gel bases through rabbit skin are shown in Fig. 1. The flux of

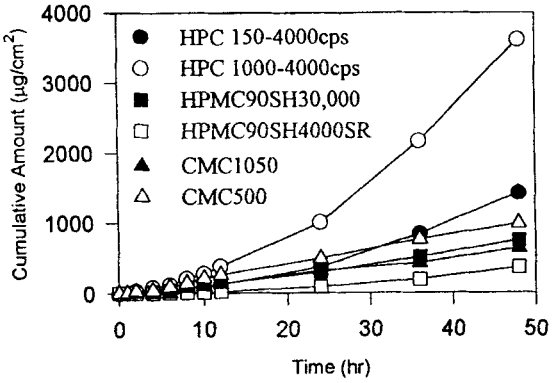

Figure 1. The effect of 5% of various types of hydrophilic cellulose derivative gel bases on captopril penetration through rabbit abdominal skin (n = 3).

these gel formulations increased in the following order: HPMC < CMC < HPC.

To improve the penetration absorption of captopril from HPC gel, some of the most potent penetration enhancers such as capric acid, undecanoic acid, methyl ester, lauric acid, and decanol, which had significant enhancing effect on captopril through rabbit skin, were used to increase the percutaneous capacity (6,7). The penetration flux of captopril was determined using 10% of HPC gel base containing 20% propylene glycol and various type of penetration enhancer at a concentration of 5%. As shown in Table 1, the flux of captopril increased in the following order: palmitic acid < myristic acid < control < undecanoic acid methyl ester < lauric acid < capric acid < decanol. The undecanoic acid methyl ester did not have a significant enhancing effect ($p > 0.05$) in this study, though it possessed excellent enhancement in captopril solution formulation (7). The results might be interpreted that the affinity between polar permanent (captopril) and HPC was lower than that of water, because HPC was less hydrophilic than water.

Table 1

The Permeation Parameters of Captopril HPC Gel with 5% of Penetration Enhancers Through Rabbit Skin (n = 3)

Enhancers	Flux (μg/cm² · hr)
Control	32.20 ± 11.35
Capric acid	98.11 ± 22.84
Lauric acid	65.50 ± 15.34
Myristic acid	18.03 ± 7.97
Palmitic acid	10.62 ± 3.46
Decanol	312.10 ± 18.26
Undecanoic acid methyl ester	38.02 ± 19.56

In saturated fatty acid, the capric acid and lauric acid showed a markedly enhancing effect, and the myristic acid and palmitic acid decreased the flux of captopril in contrast. However, the application of saturated, long-chain fatty acid to the in vitro study showed that a decrease in the number of carbon atoms (Cn) in the fatty acid resulted in an increase in the enhancement of drug permeation. These results are similar to an earlier study (7,10). In addition, the enhancing effect of the different polar groups of penetration enhancer (which have the same carbon number) on the permeation of captopril were compared (Table 1). Decanol showed the most potent enhancing effect, following by capric acid and undecanoic acid methyl ester, in that order. These results are consistent with the study of Yamada and Uda (1987) (11) who have reported the functional group on molsidomine permeation absorption is large, in the following order: alcohol > acid > ester. These compounds (fatty acid, fatty alcohol, and aliphatic ester) may fluidize the stratum corneum lipids and reduce the resistance of the stratum corneum to permanent penetration (10,11).

Decanol shows the most potent enhancing effect on captopril permeation in various types of penetration enhancer from HPC gel through rabbit skin at a concentration of 5% (Table 1). Then the effect of various concentrations of decanol on captopril hydrophilic gel permeation was studied. As shown in Fig. 2, the flux of 5% captopril gel increased with an increase in decanol concentration (from 1% to 10%) and the linear relationship was observed between flux and captopril concentration for rabbit skin (r = 0.9867, $p < 0.01$).

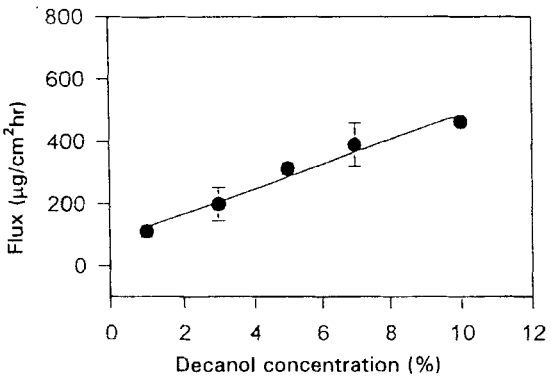

Figure 2. The effect of decanol concentration on captopril penetration through excised rabbit abdominal skin (n = 3).

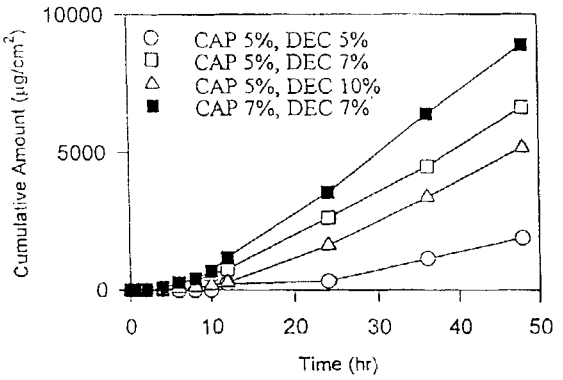

Figure 3. Permeation–time profiles of various concentrations of captopril and decanol from hydroxypropylcellulose (HPC) gel base through excised human chest skin (n = 3).

The Permeation Through Excised Human Skin

The permeation profiles of captopril gels through excised human skin are shown in Fig. 3. The human skin penetration profile of captopril gel exhibited a zero-order permeation at a constant penetration rate. The flux of these formulations containing various concentrations of captopril (cap) and decanol (dec) were 37.5 (5% cap, 5% dec), 143 (5% cap, 7% dec), 115.5 (5% cap, 10% dec), and 196 μg/cm^2 · hr (7% cap, 7% dec). The flux of 5% captopril gel increased with an increase in decanol concentration and the maximum flux of captopril was observed in 7% decanol formulation. According to the previous study (12), the necessary flux of captopril transdermal drug delivery system to maintain the therapeutic minimum effective concentration was 1488 μg/hr through human skin. The required minimum administered area (A_{req}) to attain the therapeutic minimum effective concentration could be calculated by 1488 μg/hr/flux of formulations and used to evaluate the development of formulations. The A_{req} of these formulations were 37.5 cm^2 (5% cap, 5% dec), 10.4 cm^2 (5% cap, 7% dec), and 7.6 cm^2 (7% cap, 7% dec) to attain the therapeutic minimum effective concentration. Therefore, the formulations containing 5% or 7% of captopril with 7% decanol can possibly be developed for transdermal drug delivery systems.

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