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Percutaneous absorption of captorpil from hydrophilic cellulose gel® through excised rabbit skin and human skin

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Abstract

The purpose of this investigation was to design and evaluate the percutaneous absorption of captopril from a hydrophilic cellulose gel base®. The effect of type and concentration of saturated fatty acids, amount of gel base as well as the concentration of drug on percutaneous absorption of captopril gel through rabbit skin were evaluated and selected to obtain some optimal formulations. Then the required flux (1488 μg/h) 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 these formulations containing 3, 5 and 10% captopril with 5% capric acid using 22.89, 6.98 and 4.89 cm^2 of administered area were attained to the therapeutic minimum effective concentration. Therefore these formulations were suitable for possible development of transdermal drug delivery system. Copyright © 1996 Elsevier Science B.V.

Keywords: Captopril; Human skin; Minimum effective concentration; Percutaneous absorption; Required flux; Saturated fatty acid

1. Introduction

The potential advantages associated with transdermal drug delivery have been 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 (Chien, 1992).

Captopril is an orally effective angiotensin I converting enzyme inhibitor and is used in the 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 to 1.9 h (Jarrott et al., 1982; Raia et al., 1990; Levy et al., 1991). According to the previous research, the oxidation rate of captopril in dermal homogenate is significantly lower than that in intestinal homogenates (Zhou and Li

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Wan Po, 1994). Consequently transdermal drug delivery system (TDDS) may be suitable for captopril as a successful dosage form.

The objective of the present study was to design and evaluate the percutaneous absorption of captopril from hydrophilic cellulose gel base® which were influenced by the type and concentration of saturated fatty acids, the amount of hydrophilic gel base as well as the concentration of captopril using rabbit skin as barrier membrane.

Furthermore, the required flux (J_{req}, 1488 μg/h) for captopril transdermal drug delivery system to maintain the therapeutic minimum effective concentration through human skin was used to calculate the required minimum administered area (A_{req}) of captopril fel formulations to attain the therapeutic minimum effective concentration (Kobayashi et al., 1995). Then the required minimum administered area (A_{req}) was used to evaluate the development of gel formulations.

2. Materials and methods

2.1. Materials

The following reagents were used: captopril (Sigma, USA), capric acid, lauric acid and myristic acid (TCI, Japan), hydrophilic cellulose gel base® (Teh Seng Pharmaceutical, Taiwan). All other chemicals and solvents were of analytical reagent grade.

2.2. 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 rabbit skin samples were stored at −20°C prior to use.

Samples of whole adult human skin (24–50 years old) were obtained from breast reduction operations and provided by Kaohsiung Medical College. Subcutaneous fat was carefully trimmed and the 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.

2.3. Preparation of captopril gel

Hydrophilic cellulose base® was taken in a 50 ml beaker and wetted by water for 24 h. 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.

2.4. 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 (Keshary and Chien, 1984) The skin was mounted on the receptor compartment with the stratum corneum side facing upward into the donor compartment and the dermal side facing downwards into the receptor compartment. The donor cell was filled with 2 g of gel. The receptor compartment was filled with 20 ml of deoxygen distilled water and it's temperature was maintained at 37 ± 0.5°C by thermostatic water pump during the experiment. The effective diffusion area was 2.54 cm^2. Approximately 0.5% of the receptor medium was withdrawn at determined intervals and replaced immediately with an equal volume of fresh deoxygen 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 high performance liquid chromatography (HLPC) (Wu et al., 1996). Each data point represents the average of three determinations.

2.5. Data analysis

The total amount of captopril penetration through the unit diffusion surface and into the receptor was calculated and plotted as a function of time. The drug flux, J, is calculated by the slope of the linear portion of the penetration curves and expressed as the mass of drug passing across 1 cm^2 of skin over time. Penetration index is expressed as (Huang et al., 1995):

$$PI = J_{with}/J_{without}$$

Where J_{with} and $J_{without}$ are permeability coefficient of the drug with and without penetration enhancer.

With zero-order delivery, the desired steady state of drug input rate is obtained from the following equation (Kydonieus, 1992; Kobayashi et al., 1995):

drug input rate = target plasma level
× total clearance

Minimum effective concentration (MEC) or the mean plasma concentration after ordinary dosing could be a substitute for the parameter of target plasma level so as to maintain a therapeutic effect. The input rate is defined as required flux (J_{req}). Then the required minimal administered area (A_{req}) to attain minimum effective concentration (MEC) is calculated using the following relationship:

$$A_{req} = J_{req}/J_{target}$$

3. Results and discussion

3.1. The permeation through excised rabbit skin

Saturated fatty acids have been successfully used as penetration enhancers for some drugs, such as naloxone, thiamine disulfide and sodium nonivamide acetate (Aungst et al., 1986; Komata et al., 1992; Fang et al., 1996). In this study, the enhancing effect of various carbon atoms and concentration of saturated fatty acid on the skin permeation of captopril was investigated, capric acid (C10), lauric acid (C12) and myristic acid (C14) were incorporated into captopril hydrophilic cellulose gel® containing 20% propylene glycol and the skin permeation of drug was measured using excised rabbit skin as barrier. The permeation profiles of captopril hydrophilic gel containing 5% of various saturated fatty acid are shown in Fig. 1. The permeation rate of captopril for the control gel base was increased 6.79–61.36 fold with the addition of saturated fatty acids. The capric acid showed the most potent enhancing effect, followed by lauric acid and myristic acid, in that order. The application of saturated, long-chain fatty acid to the in vitro study showed a trend that a decrease in the number of carbon atoms (Cn) in the fatty acid resulted in an increase in the enhancement of captopril permeation. The similar results had been published earlier and indicated that fatty acid disrupts the stratum corneum lipid packing and decrease diffusional resistance to permeants, diffusion of transdermal drug system in the lipid phase is thought to be stimulated depending on the applied concentration of fatty acids (Aungst et al., 1986; Komata et al., 1992; Fang et al., 1996). The effect of various concentration of capric acid on captopril

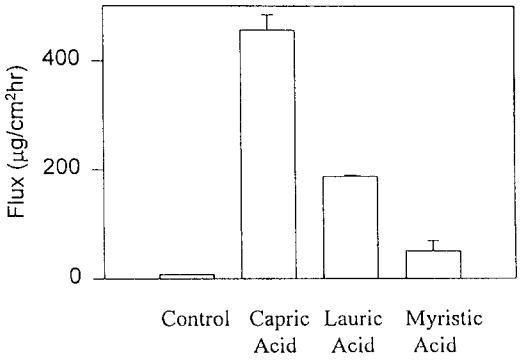

Fig. 1. The effect of 5% of various saturated fatty acids on captopril hydrophilic cellulose gel penetration through rabbit abdominal skin ($n = 3$).

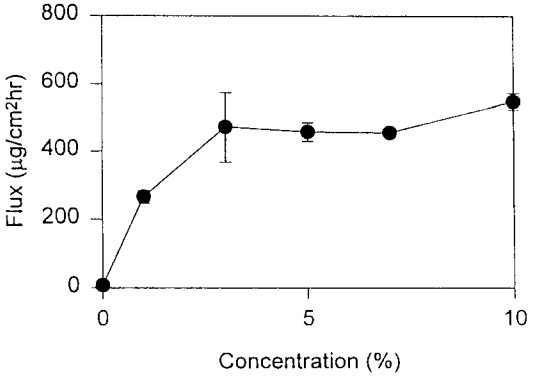

Fig. 2. The effect of capric acid concentration on captopril hydrophilic cellulose gel penetration through excised rabbit abdominal skin ($n = 3$).

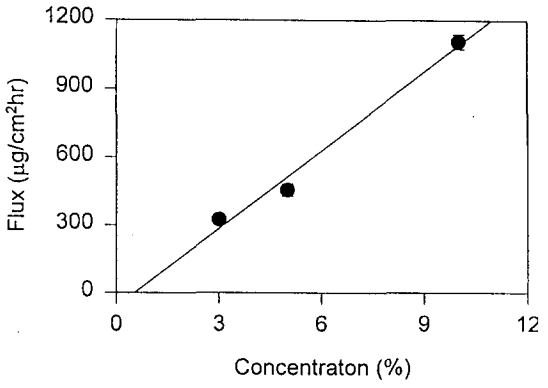

Fig. 3. The effect of amount of hydrophilic cellulose gel base on captopril gel penetration through excised rabbit abdominal skin ($n = 3$).

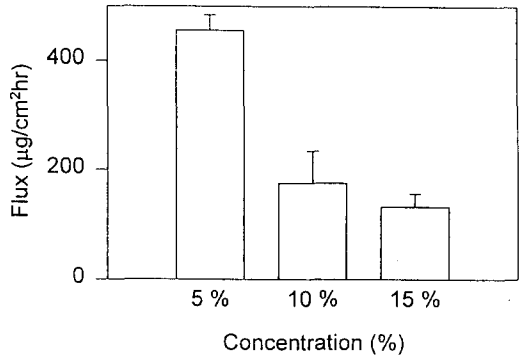

Fig. 4. The effect of captopril concentration on penetration through excised rabbit abdominal skin ($n = 3$).

hydrophilic gel permeation was studied. As shown in Fig. 2, the flux of captopril gel increased with an increase in capric acid concentration and the maximum steady-state flux of captopril was observed in 3% capric acid formulation indicating that this value may be the optimal concentration for captopril to attain the effective penetration capability.

The effect of amount of hydrophilic cellulose gel base® was also investigated. The gel type cannot be form when the amount of hydrophilic cellulose gel base® was lower than 5%. As shown in Fig. 3, the captopril flux is decreased following the increase in the amount of gel base. This was due to the increase in gel base which caused the increase of gel viscosity and resulted in the decrease of captopril flux. To obtain the optimum formulations, the effect of drug concentration to captorpil penetration was also evaluated. Fig. 4 shows the flux of hydrophilic cellulose gel base®incorporated with different concentration of captopril. The flux of captopril was increased linearly when the concentration of captopril increased from 3 up to 10% ($r = 0.9923$). This result was similar with our previous captopril solution study (Wu et al., 1996). However these formulations containing 3, 5 and 10% captopril showed a better penetration capacity through rabbit skin.

3.2. The permeation through excised human skin

According to the previous study (Kobayashi et al., 1995), the flux value of 1488 μg/h through human skin was necessary for the captopril transdermal drug delivery system to maintain the therapeutic minimum effective concentration. The human full thickness skin was used as the transdermal membrane for the formulations which had the better penetration capacity through rabbit skin. Then the required minimum administered area (A_{req}) to attain the therapeutic minimum effective concentration was calculated so as to evaluate the development of formulations.

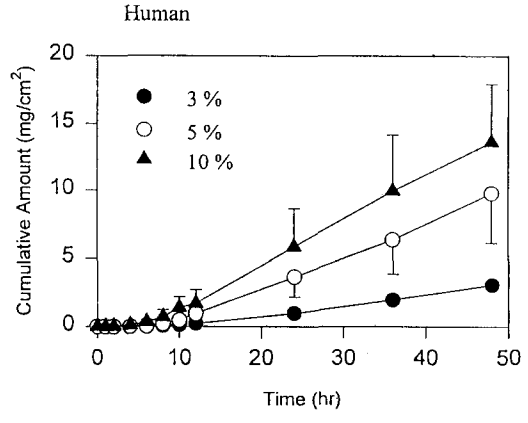

Fig. 5. Permeation-time profiles of various loading dose of captopril hydrophilic gel through excised human abdominal skin ($n = 3$).

Table 1
The permeation parameters of 3, 5 and 10 of captopril gel with 5% capric acid throught rabbit skin and human skins ($n = 3$)

Concentration (%)	Excised rabbit skin		Excised human skin	
	Flux ($\mu g/cm^2/h$)	Increasing ratio	Flux ($\mu g/cm^2/h$)	Increasing ratio
3	325.06 ± 11.15	1.00	65.79 ± 8.85	1.00
5	455.93 ± 28.00	1.40	213.07 ± 107.14	3.23
10	1106.20 ± 32.99	3.40	340.11 ± 106.59	5.16

The permeation profiles of these formulations through excised human skin are shown in Fig. 5. The human skin penetration profile of captopril exhibited a zero-order permeation at a constant penetration rate. The flux of these formulations containing 3, 5 and 10% captopril with 5% capric acid were 65.79, 213.07 and 304.11 $\mu g/cm^2$ per h and the required minimum administered area (A_{req}) were 22.89, 6.98 and 4.89 cm^2 to attain the therapeutic minimum effective concentration, respectively. Moreover, the required minimum administered area (A_{req}) of these formulations were all within the appreciate range of application. Therefore, these formulations were possibly to be developed for the transdermal drug delivery system.

The permeation parameters of 3, 5 and 10% captopril with 5% capric acid gel formulations through excised human and rabbit skin are compared as shown in Table 1. The penetration flux was increased following the increase of captopril concentration both through human and rabbit skin. The flux through rabbit skin was higher than that through human skin. The linear relationship was observed between flux and captopril concentration for rabbit skin ($r = 0.9921$) but not for human skin. Besides, the increasing ratio of flux at various captopril concentration for human skin was higher than that for rabbit skin. The reason of this difference is that the thickness of the stratum corneum varies form species to species and the skin of rodent lacks the sweat glands and abounds in hair an hair follicles which is the important pathway for many drugs penetrated through skin barrier (Chowhan and Pritchard, 1978).

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