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In vitro percutaneous absorption of captopril through excised rabbit skin

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Abstract

The permeation characteristics of captopril through excised rabbit skin at various pH values of McIlvaine buffer solutions were investigated. These results indicated that the pH dependency in skin permeability of zwitterionic drug may reflect the permselective property of the skin dependent on the lipophilicity and/or diffusivity of the ionic species. The surfactants were used as penetration enhancers to increase the percutaneous absorption of captopril. These surfactants all showed significant increase (ANOVA, $P < 0.05$) in the enhancing effect compared with that of the control group. Among the surfactants, sodium lauryl sulfate showed the greastest effect on the penetration which increased the flux approximately 58.8-fold and the enhancement increased following the increase of surfactant concentration.

Keywords: Captopril; Penetration enhancers; Partition coefficient; Surfactant; Sodium lauryl sulfate; Penetration index

The potential advantages associated with transdermal drug delivery were 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 Wan Po, 1994). Consequently the transdermal drug delivery system (TDDS) may be suitable for captopril as a successful dosage form.

The objective of the present study was to investigate the permeation characterics of captopril

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through excised rabbit skin at various pH values. Furthermore, surfactants were used as the penetration enhancers to increase the percutaneous absorption of captopril.

The following reagents were used: captopril and cetylpyridinium chloride (Sigma Chemical, USA), sodium lauryl sulfate, polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan monopalmitate (Tween 40), polyoxyethylene sorbitan monostearate (Tween 60), and polyoxyethylene sorbitan monooleate (Tween 80) (Merck, Germany), benzalkonium chloride (Tokyo Chemical, Japan). All the other chemicals were of analytical reagent grade.

The solubility of captopril in different pH values of McIlvaine buffer solutions at ionic strength of 0.3 was determined by addition of excess amount of the drug to the appropriate solvent at 37 ± 0.5°C. These suspensions were shaken for 48 h and then were filtered through 0.45 μm membrane. The *n*-octanol/water partition coefficients of captopril were also determined at 37 ± 0.5°C. Equal portions of *n*-octanol saturated with buffer and buffer solutions with different pH values were shaken for 48 h. Then the aqueous phase was collected and centrifuged at 3000 rpm for 10 min.

Skin permeation of captopril was measured using a diffusion cell which was similar to the Franz horizontal diffusion assembly (Franz, 1975). The detailed procedure of in vitro permeation studies was reported previously (Fang et al., 1995). The overall yield of captopril was determined by HPLC.

The HPLC analyses were performed on a Waters system consisting of model M-45 pumps, a model 470 UV detector, a SIC chromatocorder 12 integrator. A 125×4 mm i.d. stainless steel column with LichroCART C-18 column (E. Merck) was used. The mobile phase for captopril consisted of 15% acetonitrile and 0.05% triethylamine in water, adjusted to pH 3 with phosphoric acid (30%). The operating temperature was 37 ± 0.5°C, and the flow rate was 1.0 ml/min with UV absorbency monitoring at 220 nm.

Captopril is a zwitterionic drug, with two dissociation constants, pK_{a1} 3.7 and pK_{a2} 9.8, and has an isoelectric point of 6.8 (Windholz et al., 1983). Captopril may be ionized in an aqueous solution so as to affect the capacity of percutaneous absorption. In this study, the permeation characteristics of captopril through excised rabbit skin from aqueous solution at various pH value of McIlvaine buffer solutions were investigated. The solubility, diffusion coefficient and permeability coefficient of captopril through excised rabbit skin at different pH values (3.0–8.0) are shown in Fig. 1. The solubility of captopril was independent on the pH value (Fig. 1). The plot of permeability coefficient against pH showed a V-shaped curve with 12-fold difference between the maximum rate at pH 5.0 and the minimum at around the isoelectric point (pH 7.0).

The profile of partition coefficient at 37°C also showed a V-shaped curve with a minimum at around the isoelectric point (Fig. 1). These results were similar to the previous research (Hatanaka et al., 1995) indicating that the pH dependency in skin permeability of a zwitterionic drug may reflect the permselective property of the skin dependent on the lipophilicity and/or diffusivity of the ionic species.

According to previous reports (Mazzenga et al., 1992; Sznitowska et al., 1993; Hatanaka et al., 1995), zwitterionic compounds show high melting points and low solubility in lipophilic media, and have low permeability through biological membranes. Therefore, the transdermal drug delivery

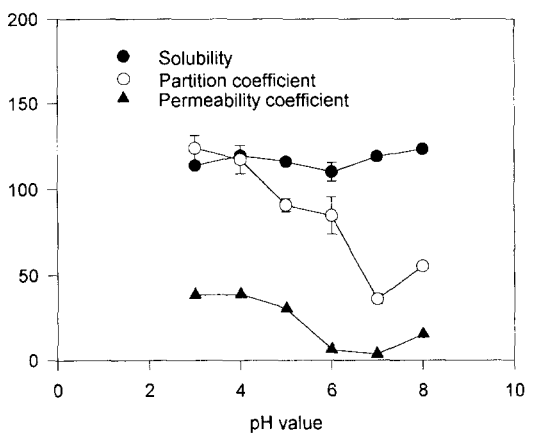

Fig. 1. The solubility (mg/ml), partition coefficient (%) and permeability coefficient ($\times 10^{-6}$ cm/h) of captopril at various pH values. Each value represent the mean ± S.E. of three experiments.

system of these compounds must be with the use of skin penetration enhancers or iontophoretic treatment to achieve optimal permeation rate. Surfactants are extensively used in pharmaceutical, pesticide and cosmetic formulations and have been used as penetration enhancers for many drugs such as methyl nicotinate, theophylline and chlorpheniramine maleate (Ashton et al., 1992; Wells and Parrott, 1992; Kadir et al., 1989). In this present study, the various types of cationic, anionic and nonionic surfactant were used to enhance the permeation rate of captopril through excised rabbit skin.

The cumulative amount of captopril permeated from 1% solution, with or without 5% of the various types of surfactants, is shown in Fig. 2. In addition, the flux data, lag time and accumulated amount (at the 48th hour) of captopril in the presence of surfactants are shown in Table 1. The skin permeation profiles of captopril from aqueous formulations containing surfactant as the enhancer showed zero-order permeation at a constant penetration rate for rabbit skin. From Table 1, anionic surfactant showed the most potent enhancing effect, followed by cationic surfactants and nonionic surfactants, in that order. The presence of 5% sodium lauryl sulfate in the donor solution increased the captopril flux to 313.96 ± 34.33 μg/(cm^2·h). The penetration index (PI) of each enhancer is also shown in Table 1. According to a previous study (Huang et al., 1995), the PI is a ratio of the flux of formulation containing enhancer to the flux of control formulation containing no enhancer. Sodium lauryl sulfate showed the most effective enhancement of captopril penetration, yielding about a 58-fold increase in comparison with the control group. Anionic surfactants were thought to bind strongly with the α-protein of the stratum corneum, thus causing a reversible denaturation and an uncoiling of the filaments. Membrane expansion, likely hole formation, and loss of water binding capacity are consistent with the reversible $\alpha \rightleftarrows \beta$ conversion of keratin, induced by the strong binding of the surfactant with the α-protein (Chowhan and Pritchard, 1978).

In general, the cationic surfactants caused more irritation of the skin and caused greater enhancement than the other surfactants (Stoughton, 1982; Cooper, 1984). In this study, the effects of benzalkonium chloride and cetylpyridinium chloride on

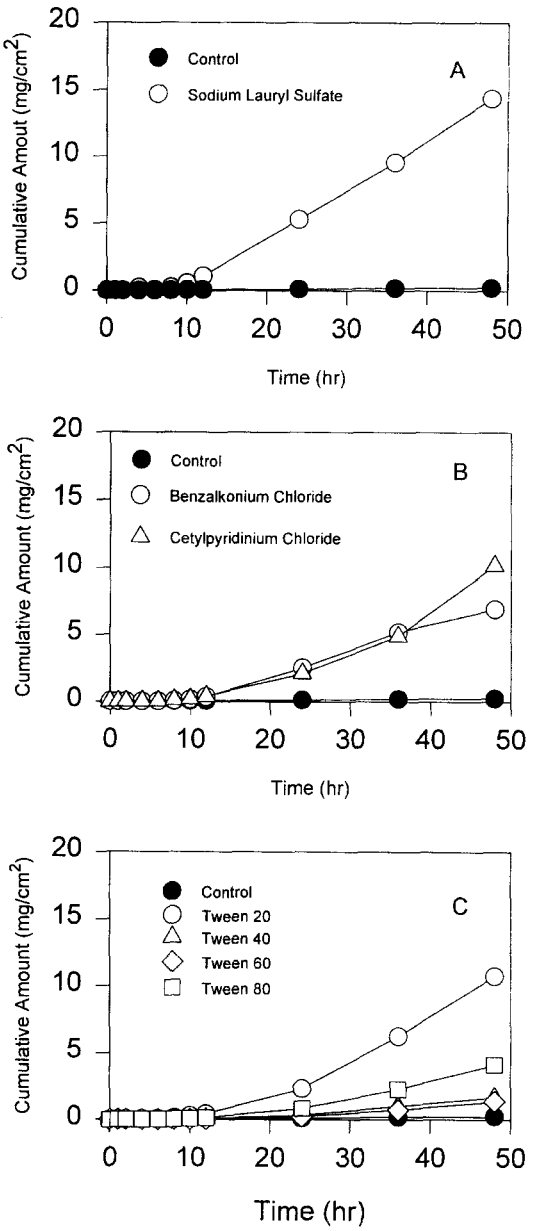

Fig. 2. Permeation–time profiles of captopril through rabbit abdominal skin with various types of surfactants as penetration enhancers. (a) Anionic surfactant; (b) cationic surfactant; (c) nonionic surfactants. Each value represents the mean ± S.E. of three experiments.

Table 1
Flux, cumulative amount (48 h), lag time and penetration index of captopril with various types of enhancers (5%) through rabbit skin ($n = 3$)

Enhancer (5%)	Flux ($\mu g/cm^2h$)	Cumulative amount after 48 h ($\mu g/cm^2$)	Lag time (h)	PI
Control	5.40 ± 1.03	242.61 ± 29.53	2.17 ± 0.12	1.00
Benzalkonium chloride	157.64 ± 85.02	6921.33 ± 3563.86	5.61 ± 0.40	29.19
Cetylpyridinium chloride	200.35 ± 18.73	10179.91 ± 556.74	6.18 ± 0.57	37.10
Sodium lauryl sulfate	313.96 ± 34.33	14347.78 ± 1824.34	5.18 ± 0.43	58.14
Tween 20	221.46 ± 52.81	10755.61 ± 2269.29	6.04 ± 0.35	41.01
Tween 40	34.78 ± 5.38	1692.63 ± 332.48	5.96 ± 0.69	6.44
Tween 60	27.56 ± 8.54	1384.40 ± 361.38	6.47 ± 0.23	5.10
Tween 80	83.81 ± 10.88	4122.96 ± 599.99	6.13 ± 0.09	15.52

Tween 20: polyoxyethylene sorbitan monolaurate (HLB 16.7).
Tween 40: polyoxyethylene sorbitan monopalmitate (HLB 15.6).
Tween 60: polyoxyethylene sorbitan monostearate (HLB 14.9).
Tween 80: Gpolyoxyethylene sorbitan monooleate (HLB 15.0).

the enhancer capacity of captopril were similar but smaller than that of sodium lauryl sulfate (Fig. 2b). The fluxes were increased about 29–37 fold for the penetration of captopril. The results might possibly be due to the formation of a complex between the cationic surfactants and the anionic ion of captopril in aqueous solution (pH 4.5–5.5) to decrease the enhancing effect.

Nonionic surfactants are thought to permeate into the intercellular lipid bilayers thereby reducing the crystallinity of the intercellular lipid bilayers and thus increasing the permeability of these bilayers (Kadir et al., 1987). Among the nonionic surfactants, the polyoxyethylene sorbitan monolaurate had the greatest effect on the flux, followed by polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monopalmitate and polyoxyethylene sorbitan monostearate (Fig. 2c). The effect of enhancement inceased with an increase in the hydrophilicity of surfactant. Moreover, the enhancement of polyoxyethylene sorbitan monooleate was significantly higher (t-test, $P < 0.05$) than that of the polyoxyethylene sorbitan monostearate indicating that the unsaturated fatty acid may possess the higher enhancing effect. Unsaturated fatty acid has been known to have a more pronounced effect than saturated fatty acid (Cooper, 1984; Aungst et al., 1986; Chi et al., 1995). The reason for this phenomenon is that saturated fatty acid, with its linear shape and low solubility, has less ability to disrupt the lipid packing of stratum corneum than kinked unsaturated fatty acid of higher solubility.

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