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Influence of non-ionic surfactants, pH and propylene glycol on percutaneous absorption of piroxicam from cataplasm

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Abstract

The influence of pH in the formulation, ethylene oxide chain length of polyoxyethylene (POE) non-ionic surfactants and addition of propylene glycol (PG) on percutaneous absorption of piroxicam (Px) from cataplasm was investigated in guinea-pig in vivo. The area under the plasma concentration of Px curve until 8 h after the application (AUC_{0-8}) increased with increasing the cataplasm base pH up to 6.5 and then plateaued from pH 6.5 to 7.2. Px solubility in water increased markedly with increasing pH from pH 6 as Px is a weak acid and its pK_a is 5.3. The ionic form of Px in the cataplasm was suspected to contribute to the percutaneous absorption of Px. The percutaneous absorption of Px from the cataplasms containing 5% of POE non-ionic surfactants with various POE lengths were examined. The parabolic relation between the Px absorption and the POE length was observed. POE length from 5 to 15 enhanced percutaneous absorption to a greater extent. An attempt was also made to examine the influence of the addition of PG to the formulation containing POE (9) lauryl ether. The addition of 20% PG to the formulation significantly increased the Px concentration in plasma, compared to 0, 5, 10 and 15% PG. Skin and cutaneous muscle concentrations significantly increased by addition of 20% PG, compared to those by 0% PG but not in deeper muscle.

Keywords: Percutaneous absorption; Polyoxyethylene non-ionic surfactant; pH; Propylene glycol; Topical preparation; Piroxicam

1. Introduction

For regional inflammatory disorders such as muscle pain, low-back pain or osteoarthritis, it is well recognized that the topical application of non-steroidal anti-inflammatory drugs (NSAIDs) is a superior way to avoid the well-known gastrointestinal side-effects or other systemic side-effects induced by NSAIDs. Therefore, topical preparations (gel, cream, plaster or cataplasm) of NSAIDs have been increasingly used to alleviate

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regional inflammation (Wada et al., 1982; Mizushima, 1987; Grahame, 1995). Cataplasm consists of cross linked hydrophilic adhesive polymers, polyhydric alcohols and water as base, and non woven cloth as backing material, known as 'PAP' in Japan. Cataplasm has many advantages compared to other topical dosage forms, i.e. a supporting and cooling effect to treat the inflammatory symptoms in deep tissues beneath the application (Inoki et al., 1985). Piroxicam (Px) is a NSAID prescribed for the treatment of pain and inflammatory disorders as a tablet, suppository or gel ointment (Schiantarelli et al., 1981, 1982). Various studies have been carried out to predict the percutaneous absorption of Px and many chemicals have been challenged as effective absorption enhancers for Px (McNeill et al., 1992; Santoyo et al., 1995). It is well recognized that the drug-vehicle component interaction affects the percutaneous absorption of drugs (Flynn, 1989). A surfactant is one of the possible candidates that enhances drug permeation through skin. Also, it is well recognized that the addition of cosolvents such as propylene glycol (PG) influences the percutaneous absorption of drugs such as glucocorticoids (Bendas et al., 1995). The objective of this study was to investigate the influence of pH in the cataplasm base, ethylene oxide chain length of polyethoxylated non-ionic surfactants and addition of PG on in vivo percutaneous absorption of Px aiming to deliver the drug to local tissues beneath the skin from cataplasm.

2. Materials and methods

2.1. Materials

Px (4-hydroxy-2-methyl-*N*-2-pyridinyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide), USP grade, was purchased from FAR-CA (Milan, Italy). Polyethoxylated non-ionic surfactants were purchased from Nikko Chemicals (Tokyo, Japan). All other additives, pharmacopoeial grade, were purchased from each supplier. Standard and internal standard materials for HPLC analysis were purchased from Sigma-Aldrich Japan (Tokyo, Japan). Other reagents used for analysis were of analytical grade.

2.2. Animals

Male guinea-pigs (Hartley, 250–300 g) were obtained from SLC (Shizuoka, Japan) or Charles River Japan (Yokohama, Japan). They were acclimatized for at least 1 week to our standard environmental conditions (temperature 22–23°C, relative humidity 60–65%, 12 h light/12 h dark).

The guinea-pigs were fasted for 15 h prior to the cataplasm application but had water ad libitum.

2.3. Preparation of piroxicam cataplasm

The composition of the piroxicam cataplasm used in this study is shown in Table 1. Formula-

Table 1
Cataplasm formulation used in this study

	Formulation (% w/w)						
	I	II	III-a	III-b	III-c	III-d	III-e
Piroxicam	0.25	0.25	0.5	0.5	0.5	0.5	0.5
Polyethoxylated non-ionic surfactant	–	5.0	5.0	5.0	5.0	5 0	5.0
Glycerol	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Propylene glycol	–	–	–	5.0	10.0	15.0	20.0
Water-soluble adhesive polymer	8.0	8.0	8.0	8.0	8.0	8.0	8.0
Kaolin	5.0	5.0	5.0	5.0	5.0	5.0	5.0
D-Sorbitol solution (70%)	20.0	20.0	20.0	20.0	20.0	20.0	20.0
pH Regulator and other minor additives	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Add purified water to 100							

tion I was used to examine the influence of pH in the cataplasm on the percutaneous absorption. Various amounts of tartaric acid were added and cataplasms with pH 4.8, 5.2, 5.6, 6.0, 6.5, 7.1 and 7.2 were obtained. Formulation II was used to examine the effect of the polyoxyethylene (POE) chain length of polyethoxylated non-ionic surfactants on percutaneous absorption of Px. The pH of the base was adjusted to 6.5. The surfactants employed were POE (n) lauryl ether ($n = 2$, 9 and 21), POE (n) cetyl ether ($n = 2$, 5.5, 7, 10, 15 and 20), POE (n) oleyl ether ($n = 2$, 10 and 20) and POE (n) stearyl ester ($n = 4$, 10 and 25). The formulations from III-a to III-e whose base pH were adjusted to 6.5, were used to examine the cooperative enhancing effects by polyoxyethylene (9) lauryl ether and PG.

Px was dissolved or dispersed in surfactant, glycerol and/or PG, and mixed with the other additives and swollen polymer in water. The gel was spread onto the non-woven cloth at 0.1 g/cm^2 and was covered by plastic release liner. The content of Px was 0.25 mg/cm^2 for formulations I and II, and 0.5 mg/cm^2 for formulations III-a to III-e to confirm the Px saturation condition. All cataplasms were kept at 25°C after preparation. All cataplasms were certified to be in a Px saturated condition by microscopic observation with polarizing filter before the experiment.

2.4. Solubility and partition coefficient determination at various pH

The solubility of Px in various pH buffer solution (phosphate buffer) was determined. Excess amount of Px was added to each pH buffer and was shaken at 25°C in a water bath for at least 24 h until equilibrium was reached. A partition coefficient of Px between octanol and buffer solution with various pH was determined. The samples were centrifuged at 3000 rpm for 10 min, and the supernatants were filtered by 0.45-μm filter. Aliquots of the filtrates were diluted with acetonitrile and with mobile phase for HPLC, and amount of Px was determined by HPLC.

2.5. Absorption studies

The dorsal hair of guinea-pigs was carefully clipped and shaved 1 day before experiment. The guinea-pig was anesthetized by 50 w/v% ethyl carbamate saline solution (2 ml/kg, i.p.) and a silicone canula (Silastic Tube®, Dow Corning, Michigan, USA) was inserted into jugular vain. The cataplasm (5×6 cm) was applied to the shaved area for 8 h. The experiments on effect of pH in the cataplasm and effect of POE length of non-ionic surfactants were carried out with vapor impermeable polychrol vinyliden film (Saran Wrap®, Asahi Kasei, Tokyo, Japan) covering the cataplasm in order to obtain the occlusive effect to make the differences in the pH or surfactant effects clear. The experiment on effects of PG on the regional absorption of Px were carried out without any covering material equivalent to clinical application.

2.6. Sample preparation

2.6.1. Plasma

Blood samples were collected from the jugular vein into heparinized tubes at pre-determined times (before and 2, 4, 6 and 8 h after cataplasm application). The plasma was separated from whole blood by centrifugation at 3000 rpm for 10 min and transferred into tapered glass tube. Then 200 μl of plasma, 200 μl of methanol, 200 μl of internal standard solution (2.5 μg isoxicam per ml of methanol), 2.5 ml of 0.1 M pH 4.5 acetic acid-sodium acetate buffer and 3 ml of cyclohexan-diethyl ether (1:1) were pipetted into 12-ml glass extraction tube. The stoppered tubes were shaken mechanically for 5 min and centrifuged at 3000 rpm for 5 min. The organic phase was transferred for evaporation under reduced pressure. The resulting residue was immediately reconstituted with 200 μl of 0.1% phosphoric acid-acetonitrile (6:4). A 50-μl volume was then injected into HPLC.

2.6.2. Viable skin, cutaneous muscle, muscle

To investigate the effect of PG on the regional absorption of Px, viable skin, cutaneous muscle and muscle were collected for analysis. At 8 h

post-application, the cataplasm was removed and the application site was wiped with absorbent cotton soaked in warm water. Animals were sacrificed by injection of excess amount of anesthesia (pentobarbital sodium) and the skin with cutaneous muscle at application site and the muscles underneath the application site were collected. The cutaneous muscle was carefully separated from the skin and cut into small pieces for further analysis. The stratum corneum was removed from viable skin by 20 times successive tape stripping with adhesive tape (Celotape®, Nichiban, Tokyo, Japan). The resultant viable skin was cut into small pieces for further analysis. The collected muscle was cut into small pieces and those pieces were thoroughly mixed. A 3-g sample of these pieces was weighed and used for determination of Px concentration in muscle.

The viable skin and cutaneous muscle were weighed. To this, 200 μl of internal standard solution (25 μg isoxicam per ml of methanol) and 15 ml of methanol were added. The tissue was homogenized by Physcotoron (Nichion, Chiba, Japan) under ice cooled condition and the homogenate was made up to 20 ml with methanol. After centrifugation (3000 rpm, 5 min), the organic phase was transferred for evaporation under reduced pressure. The resulting residue was dissolved in 0.1 N sodium hydroxide and washed twice with 5 ml of cyclohexan-diethyl ether (1:1) mixture. Then 150 μl of 1 N hydrochloric acid, 2 ml of 0.1 M pH 4.5 acetic acid-sodium acetate buffer and 3 ml of cyclohexan-diethyl ether (1:1) were added, shaken mechanically for 5 min and then centrifuged at 3000 rpm for 5 min. The organic phase was transferred for evaporation under reduced pressure. The resulting residue was immediately reconstituted with 200 μl of 0.1% phosphoric acid-acetonitrile (6:4). A 50-μl volume was then injected into HPLC.

A 200-μl volume of internal standard solution (2.5 μg isoxicam per ml of methanol) and 15 ml of methanol were added to 3 g of muscle followed by the same procedure as skin or cutaneous muscle.

The influence of pH and surfactants on percutaneous absorption of Px was evaluated by area under the plasma concentration-time curve until 8 h after the application (AUC_{0-8}). The effect of PG on the regional absorption of Px from skin to deeper tissues was evaluated by plasma and other tissue concentration.

2.7. Chromatographic analysis

2.7.1. Solubility determination

HPLC analysis was performed using a system consisting of L-6000 pump, L-4000 UV detector (both Hitachi, Tokyo, Japan), Chromatopac C-R6A integrator (Shimadzu, Kyoto, Japan) and ODS 120T column (5 μm, 150 × 4.6 mm i.d., Tosoh, Tokyo, Japan). The mobile phase consists of an acetonitrile/0.1% acetic acid solution (50:50 v/v) mixture. The operating temperature was 40°C with column oven, and flow rate was 1 ml/min with UV absorbency monitoring at 340 nm. Indomethacin (3 mg/ml in acetonitrile) was used as internal standard solution for HPLC analysis.

2.7.2. In vivo study

HPLC analysis was performed using a system consisting of LC-10A pump, SPD-10A UV detector, Chromatopac C-R4A integrator (all Shimadzu, Kyoto, Japan) and TSK Gel 120T column (5 μm, 250 × 4.3 mm i.d., Tosoh, Tokyo, Japan) with μBondapak® C_{18} guard column. The mobile phase consists of an acetonitrile/0.1% acetic acid solution (40:60 v/v) mixture. The operating temperature was 40°C with column oven, and flow rate was 1 ml/min with UV absorbency monitoring at 365 nm.

2.8. Data treatment

AUC_{0-8} was calculated by trapezoidal rule. Statistical evaluation of data was performed where applicable using Hartley test followed by Bonferroni (one-sided) or using F-test followed by Aspin-Welch t-test.

3. Results and discussion

3.1. Influence of pH

The influence of pH on the cataplasm base was examined in vivo. AUC_{0-8} of various pH cata-

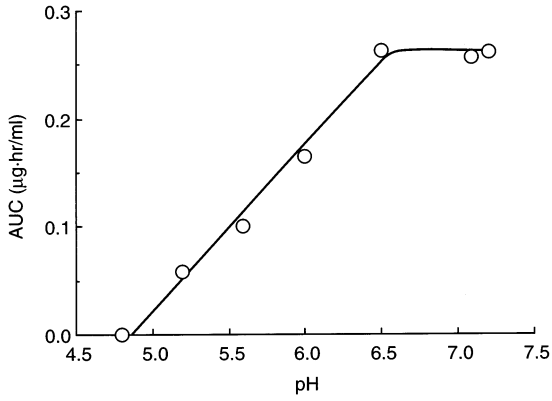

Fig. 1. Influence of pH in cataplasm on percutaneous absorption of Px from cataplasm in vivo. AUC_{0-8}: area under the concentration-time curve until 8 h after application.

plasm increased with increasing the pH up to 6.5 and then plateaued from pH 6.5 to 7.2 (Fig. 1). The relationships between pH and solubility or log octanol/buffer partition coefficient are shown in Fig. 2. It has been reported that the pK_a of Px is 5.3 and the solubility of Px in water increases markedly with increasing pH from 6 (Herzfeldt and Kümel, 1983). It is generally recognized that only the non-ionic form of the drug penetrates through the skin. On the other hand, the fact that NSAIDs permeate through the skin in ionic form has been well documented (Obata et al., 1993). These results suggested the possibility of contribution of ionic species to the percutaneous absorption of Px from cataplasm.

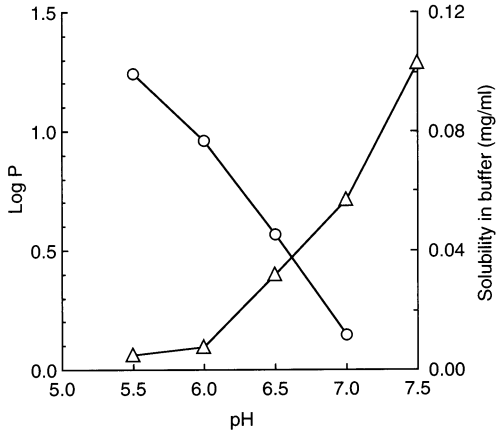

Fig. 2. The relationship between pH and Px solubility in buffer or Log octanol/water partition coefficient (Log P). △, solubility; ○, Log P.

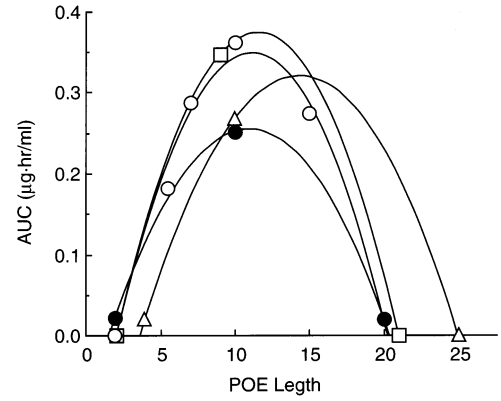

Fig. 3. Influence of POE length of non-ionic surfactants on percutaneous absorption of Px in vivo. AUC_{0-8}: area under the concentration-time curve until 8 h after application. □, POE lauryl ether; ○, POE cetyl ether; ●, POE oleyl ether; △, POE stearyl ester.

3.2. Influence of POE length of polyethoxylated non-ionic surfactants

The influence of POE non-ionic surfactants on the percutaneous absorption of Px was examined. POE lauryl ether, POE cetyl ether, POE oleyl ether or POE stearyl ester with various POE length was added at 5% w/w to the cataplasm whose base pH was 6.5. Each cataplasm was applied to guinea-pig ($n = 3$) and plasma concentrations were determined. AUC_{0-8} after the application of cataplasm containing POE (10) cetyl ether and POE (9) lauryl ether showed the largest followed by POE (7) cetyl ether. The parabolic relation between the POE length and the AUC_{0-8} of Px revealed the existence of optimal length on the percutaneous absorption, as indicated in Fig. 3. Similar phenomena were seen in the other two surfactant groups.

We previously reported that diclofenac delivered from an alcoholic gel ointment showed a higher plasma concentration with shorter POE length (Iwasa et al., 1991). Endo et al. (1996) investigated the effect of 14 types of 5% of non-ionic surfactants including POE oleyl ether on the permeation of tenoxicam through guinea pig skin

from 10% propylene glycol/water lotion in vitro. High skin permeability was obtained by addition of relatively lower hydrophile-lipophile balance (HLB) surfactants. Those results might be explained by the fact that low HLB POE lauryl ether penetrated the skin at a higher rate than more hydrophilic POE lauryl ether with longer POE chain length (Nishiyama et al., 1983). The surfactants with hydrophobic nature can penetrate into the intercellular lipid lamellar domain of stratum corneum rather quickly and alter the barrier function of that region when the surfactant was deposited directly from a volatile solvent or a volatile base onto the skin surface. In the aqueous vehicle, however, optimal enhancement might be observed by the surfactants which have appropriate balance between hydrophilic and hydrophobic nature. To confirm the influence of HLB of surfactant on percutaneous absorption of Px, POE (2) cetyl ether and POE (20) cetyl ether were added in the ratio of 2:3 respectively to cataplasm in order to obtain the same HLB as that of POE (10) cetyl ether. AUC_{0-8} by POE (2) and (20) cetyl ether mixed cataplasm was significantly smaller than that by POE (10) cetyl ether as shown in Table 2. This result suggested that the enhancement effect of POE alkyl ether is dependent on the length of ethylene oxide chain.

In the case of Px cataplasm, the non-ionic surfactants with a POE length from 5 to 15 enhanced percutaneous absorption to a greater extent and parabolic relationship between AUC_{0-8} and POE length was observed. Dalvi and Zatz (1981) examined the influence of POE chain length of POE nonylphenyl ether on penetration of benzocaine through hairless mouse skin from aqueous solution system and found that the maximum flux was obtained by POE (9) followed by POE (12), POE (30) and POE (50). They concluded that percutaneous penetration of benzocaine decreased as POE chain length increased. These results coincide partly with our results although they employed POE nonylphenyl ether only from 9 to 50. Walters and Olejink (1983) showed the in vitro enhancement of methyl nicotinate permeation through hairless mouse skin as a function of POE alkyl ether surfactants and that the maximum enhancement was obtained by POE (10) lauryl ether followed by POE (10) oleyl ether, POE (10) palmitil ether and POE (6) palmitil ether. They found the enhancement effects with ether type of surfactants but our results showed that the ester type surfactants with POE length of 10 also exhibited the enhancing effects.

Table 2
Comparison between the effect of POE length and HLB

Surfactants	AUC_{0-8} (μg h/ml)
POE (10) cetyl ether (5%)	0.28 ± 0.004[a,*]
POE (2) cetyl ether (2%) + POE (20) cetyl ether (3%)	0.06 ± 0.013

[a] Mean ± S.D.
* $P < 0.01$ (Aspin-Welch t-test).

3.3. Effect of addition of PG

The effect of addition of PG to the cataplasm containing POE (9) lauryl ether was investigated. The base pH of those cataplasms were adjusted to 6.5 according to the result of former experiment. The results are shown in Fig. 4. Plasma concentration by 20% PG cataplasm was significantly higher than that of 0, 5, 10 and 15% PG cataplasm ($P < 0.01$). Px concentrations in viable skin and in cutaneous muscle by cataplasm containing 20% PG were significantly higher than those by the cataplasm without PG ($P < 0.05$). But no significant difference of Px concentration in muscle among these five formulations was seen.

Also, ODT effect was clearly shown comparing the AUC_{0-8} by the open application of the cataplasm without PG (in the experiment on influence of PG addition) and by the ODT application of same cataplasm (in the experiment on influence of POE length of polyethoxylated non-ionic surfactants). The AUC_{0-8} by open application and ODT application were 0.11 and 0.35 μg h/ml, respectively.

The presence of a cosolvent in the vehicle may promote conditions that favor surfactant absorption into skin. Sarpotdar and Zatz (1986) investigated the effect of two non-ionic surfactants (polysorbate 20 and 60) on percutaneous absorption of lidocaine in the presence of various con-

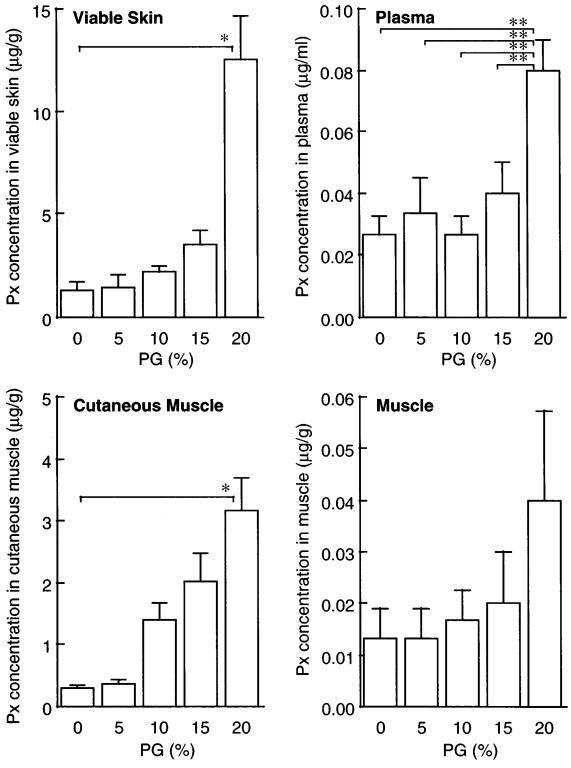

Fig. 4. Influence of PG amount in cataplasm on Px concentration in each tissue. Results are expressed as the mean with a vertical bar showing the S.D. of three experiments. All data were obtained at 8 h after application. $*P < 0.05$; $**P < 0.01$.

centrations (40, 60 and 80%) of PG using hairless mouse skin in vitro. They found that steady-state flux was enhanced by surfactants at high PG concentrations (80%).

Drug applied on the skin surface penetrates through stratum corneum and viable epidermis, and comes across the microvasculature at upper region of dermis. This microcirculation had been thought to act as a perfect sink to the topically applied drugs. However, many reports revealed that a number of chemicals penetrate into the deep tissue beneath the skin (Guy and Maibach, 1983).

The concentration of Px in cutaneous muscles beneath the viable skin was approximately 10–50-fold higher than those in plasma. This may suggest that Px evades the microvasculature capture at upper dermis and directly penetrates into the deeper tissue. Px concentration in deeper muscle by even 20% PG containing cataplasm was lower than that in plasma. This phenomena might be attributed partly to the systemic elimination by blood supply. Because the drug in dermis and subcutaneous tissues is exposed to removal by systemic circulation, higher concentration in dermis and cutaneous muscle might be needed to deliver Px to the deep muscle.

In conclusion, the contribution of ionic form of Px was assumed to be important in the percutaneous absorption from cataplasm. Parabolic relationship between percutaneous enhancement and POE length of polyethoxylated non-ionic surfactants was observed, and 20% PG addition significantly enhanced the Px delivery to skin, plasma and cutaneous muscle. Higher degree of enhancement might be required for the direct enhancement of Px delivery to deeper tissue.

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