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Note

Simultaneous optimization of percutaneous delivery and adhesion for ketoprofen poultice

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Abstract

Topical poultices of ketoprofen were prepared using deionized water, propylene glycol (X_1), and glycerin (X_2) as the vehicle in combination with hydrophilic matrix materials, including gelatin (X_3) and sodium polyacrylate. A mixture design was utilized to evaluate the influence of these constituents (X_1–X_3) on the adhesion of the poultice and the percutaneous penetration of ketoprofen from poultices. The adhesion of the poultice was measured based on the L-Peel test method using a Tensile and Compression Testing Machine. Percutaneous delivery was conducted using nude mouse skin as the barrier. The poultice containing the highest weight fraction of gelatin demonstrated the highest value of peak stress, whereas the poultice containing 0% weight fraction of gelatin showed the smallest value among all formulations. This indicates that gelatin was the main factor determining the adhesion of the poultice. However, the interactive influence of propylene glycol with gelatin on the adhesion of the poultice cannot be ignored. On the contrary, the formulation having the maximal penetration rate was determined to be the vehicle with 0% weight fraction of gelatin and the highest percent weight fraction of glycerin. This indicates that the presence of glycerin in the poultice was able to increase the flux of ketoprofen to some extent. Quantification of individual's effect based on this mixture design resulted in a polynomial equation: Peak stress $= 0.033X_1 + 0.016X_2 + 0.12X_3$, flux $= 1.90X_1 + 4.70X_2 - 6.65X_3$. Finally, an optimized formulation with acceptable adhesion and a flux comparable to two commercial products was developed in this study.

Keywords: Ketoprofen; Penetration; Adhesion; Poultice; Gelatin

Ketoprofen is a non-steroidal anti-rheumatic agent that has a potent inflammatory action but undesirable side effects on the central nervous system. Furthermore, anti-rheumatic drugs of this kind also produce secondary side effects on the stomach (Chi and Jun, 1991). With no doubt, topical administration of therapeutic agents offers many advantages over oral and intravenous administration. Topical applications of ketoprofen allow the attainment of high intra-articular tissue concentration in comparison to oral administration (Rolf et al., 1999). The oleo-hydrogel formulation of ketoprofen has been demonstrated to be more beneficial than K-gel or K-plaster (Rhee et al., 1999). The release characteristics of ketopro-

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fen from swelling-controlled drug delivery copolymer gels have been studied to deduce the transport mechanisms (Negishi et al., 1999).

In an attempt to enhance the efficacy of ketoprofen delivered percutaneously, various formulation bases and enhancers have been examined. The in vivo percutaneous absorption of ketoprofen from different ointment bases at 3% concentration was studied by Gurol et al. (1996). They demonstrated that the rank order of percent edema inhibition was as follows: Carbopol gel $\geq$ hydrophilic ointment $>$ cold cream $>$ white petrolatum. The ability of permeation enhancers such as oleic acid, polyethylene glycol 400, and propylene glycol to provide improved performance of a membrane-controlled transdermal system of ketoprofen containing Carbopol 934P gels has been investigated (Singh et al., 1996). A parabolic relationship between the partition coefficient of thiomenthol derivatives and enhancement factor for ketoprofen delivered in a hydrogel system was noted (Taganashi et al., 1999). The percutaneous permeation studies of a new gel-spray formulation, containing 15% ketoprofen lysine salt, indicate that ketoprofen was delivered to the inflamed area with a very high efficiency using a minimal amount of formulation, even in the absence of permeation enhancers (Porzio et al., 1998).

However, ketoprofen is practically insoluble in water. The use of cosolvents, such as ethanol or glycerol, to increase solubility up to 8556 or 33 times, respectively, has been reported (Singhai et al., 1996). Ketoprofen delivered by hydroalcoholic gel gave persuasive results in the treatment of knee arthrosis stages I and II (Waikakul et al., 1997). A mutual enhancement effect of the ethanol/Panasate 800 (40/60) binary vehicle has been demonstrated to be beneficial due to decreasing the barrier ability of the stratum corneum by ethanol and that of viable skin by Panasate 800 (Goto et al., 1993).

The poultice-form topical delivery system is preferably favored by Chinese. The occlusion effect of such a design might present an enhancing effect on percutaneous delivery of active ingredients. Traditionally, the drug-carrying matrix on the fabric was prepared using an organic solvent as the medium. Obviously, the potential risks of such a process can be eradicated by employing a hydrophilic matrix as the drug carrier with the use of cosolvents to enhance percutaneous delivery (Nakagawa et al., 1986). Gelatin combined with a desirable amount of plasticizer of either glycerin or propylene glycol would expectedly make resulting films hydrophilic and elastic enough for applying on the rough surface of the body. Furthermore, the well-characterized solubilizing and enhancing effects by propylene glycol and glycerin would be beneficial to the formulation development. In this study, topical poultices of ketoprofen were prepared in a cosolvent system, including deionized water, propylene glycol, and glycerin, as the vehicle in combination with the hydrophilic matrix materials, including gelatin and sodium polyacrylate. A mixture design was utilized to evaluate the influence of these factors on the percutaneous penetration of ketoprofen and the adhesion of the poultice.

Table 1
Mixture design of poultice formulations

Set	PG (X_1)	Glycerin (X_2)	Gelatin (X_3)	Peak stress (psi)	Flux (μg/cm^2/h)
1	9.08 [a]	4.52	0.00	0.034 (0.016) [b]	1.888 (0.077) [b]
2	7.80	5.52	0.28	0.040 (0.003)	2.488 (0.087)
3	5.52	7.80	0.28	0.022 (0.001)	2.415 (0.126)
4	7.96	4.52	1.12	0.053 (0.008)	1.668 (0.038)
5	4.52	9.08	0.00	0.020 (0.002)	7.775 (0.198)
6	6.80	6.80	0.00	0.019 (0.004)	1.114 (0.074)
7	6.52	6.52	0.56	0.039 (0.002)	1.044 (0.038)
8	4.52	7.96	1.12	0.043 (0.009)	0.682 (0.027)

[a] Percent weight fraction in each formulation designed.
[b] Mean (SD); $n = 5$.

Table 1 lists the percent weight fraction of these three components (propylene glycol, glycerin, and gelatin) in each formulation designed. The preparation of poultices followed the same procedure: ketoprofen (0.3%) and menthol (3%) were first dissolved in alcohol (4.3%), and then zinc oxide (1.5%) was suspended in this alcohol solution. Water (53.6%), 70% sorbitol solution (12%), propylene glycol, and glycerin were mixed in another container as an aqueous solution. Polyvinyl alcohol (0.8%, MW $\sim$ 60 000), carmellose sodium (2%), and gelatin (type B, MW 15 000–250 000) were subsequently dissolved in this aqueous solution with heating if necessary. After cooling to room temperature, the alcohol suspension was added to this aqueous solution. Finally, sodium polyacrylate (6%, $M_w \sim 2100$) was dispersed in the final mixture with stirring until dissolution. A fixed weight of this viscous paste was then evenly coated onto the fabric to finish the preparation of the poultice.

The adhesion of the poultice was measured based on the L-Peel test method using a Tensile and Compression Testing Machine (MTS, Synergie 200). Generally, a poultice with a surface area of 130 by 25 mm^2 was placed on the glass plate and was then pressed down by rolling over it with a fixed weight load. One side of the poultice in a 1-cm length was clipped and pulled up at a constant rate of 300 mm/min. Both the peak load and percent strains were recorded and the peak stress was calculated. The average results of five replicates are reported.

Percutaneous delivery was conducted using nude mouse skin as the barrier in a Franz-type diffusion cell. A test poultice was placed on the donor side. Phosphate buffer (pH 7.4, 50 mM) containing sodium azide was used as the receptor medium and maintained at 37 °C with a stirring rate of 500 rpm. At predetermined time intervals, 200-μl aliquots were withdrawn from the receptor compartment and replaced with fresh medium of equal volume. Ketoprofen concentration was determined with an HPLC method using a reversed column (HICHROM C_{18}, 150×4.6 mm) and methyl paraben as the internal standard. Measurements were taken at a wavelength of 258 nm (DYNAMAX model UV-C). The mobile phase consisted of acetonitrile and phosphate buffer (pH 7.0, 10 mM) at a ratio of 2:8 and a delivery rate of 1 ml/min.

A mixture design was utilized to examine the effect of propylene glycol, glycerin, and gelatin on the characteristics of adhesion of the resulting poultice products and the in vitro percutaneous delivery of ketoprofen. Poultices were prepared with the same procedure, and percent weight fraction of these three components were varied accordingly keeping the rest of components constant. Table 1 lists the percent weight fraction of these three components in each formulation designed and the respective peak stress (psi).

Poultices of sets 3, 5, and 6 show similar peak stress, which is the smallest among all formulations. Poultice of set 4 demonstrates the highest value of peak stress. The former contained 0% weight fraction of gelatin, whereas the latter contained the highest percent weight fraction. This indicates that gelatin was the main factor determining the adhesion of the poultice.

However, the peak stress for set 8 was smaller than that for set 4, both of which contained the same percent weight fraction of gelatin. Nevertheless, the percent weight fraction of propylene glycol in the former was higher than that in the latter. Therefore, the interactive influence of propylene glycol on the adhesion of the poultice cannot be ignored from the comparison of peak stress for sets 1–5 and 4–8. This means that both propylene glycol and gelatin play an important role in the determination of adhesion.

Quantification of individual's effect of each component on the adhesion of the poultice was examined based on this mixture design. A suitable polynomial equation involving the individual main effects and interaction factors was selected based on the estimation of several statistical parameters such as CV (coefficient of variation), R^2, adjusted R^2, and PRESS, etc. by the software, DESIGN EXPERT (State-Ease Co., USA). The results of model selection for adhesion of the poultice demonstrate that the linear model, which has only main effects, was the most statistically appropriate model for describing the combined effect of three components on the adhesion of the poultice. The mixture design resulted in a polyno-

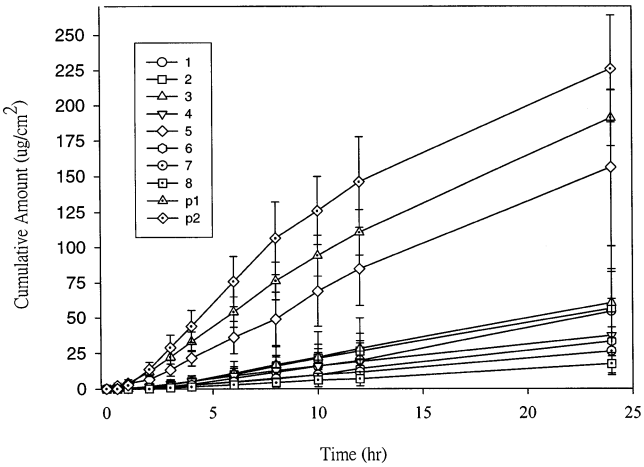

Fig. 1. Penetration profiles of ketoprofen through nude mouse skin from poultices with different formulations ($n = 5$).

mial equation with three terms that quantitatively fits the resulting data:

$$\text{Peak stress} = 0.033X_1 + 0.016X_2 + 0.12X_3$$

(R^2: 0.9035)

where X_1, X_2, and X_3 represent the transformed percentages of the concentrations of propylene glycol, glycerin, and gelatin, respectively. As indicated by the value of coefficient, it can be clearly seen that the greatest extent of improvement in adhesion occurred in the gelatin component. A positive sign of the coefficient indicates that increasing the amount of gelatin increases the adhesion of the poultice. On comparing the coefficients, the influence of gelatin on the adhesion of poultice was more profound than that of the solvent systems examined in this study. It also concludes that gelatin is the most important factor influencing the adhesion of the poultice as described above.

Fig. 1 illustrates the cumulative amount of ketoprofen released versus time for those formulations and two commercial products (p1 and p2). The flux at steady state, expressed as the penetrating amount of ketoprofen per unit time and area, were calculated. The fluxes of ketoprofen from the p1 and p2 poultices were 9.7248 and 13.4450 $\mu g/cm^2/h$, respectively. They show higher flux than the other eight formulations. The fluxes for eight formulations are also listed in Table 1. The fluxes at steady state are compared and showed that percutaneous penetration of ketoprofen from the poultice of set 5 was the fastest among these formulations. Poultices of set 8 demonstrated the smallest value of flux. Poultices of sets 5 and 8 contain the same weight fraction of propylene glycol. However, the former contained 0% weight fraction of gelatin and the highest percent weight fraction of glycerin, whereas the latter contained the highest percent weight fraction of gelatin. This indicates that the presence of glycerin in the poultice was able to increase the flux of ketoprofen to different extent. On the contrary, the higher percent weight fraction of gelatin hindered the penetration of ketoprofen.

Quantification of individual's effect of each component on the flux of ketoprofen from poultice was also evaluated based on this mixture design. The results of model selection for the flux of ketoprofen demonstrate that the linear model, which has only main effects, was the most statistically appropriate model for describing the combined effect of three components on the flux of ketoprofen. The mixture design resulted in a polynomial equation with three terms that quantitatively fits the resulting data:

$$\text{Flux} = 1.90X_1 + 4.70X_2 - 6.65X_3 \quad (R^2: 0.4050)$$

where X_1, X_2, and X_3 represent the transformed percentages of the concentrations of propylene

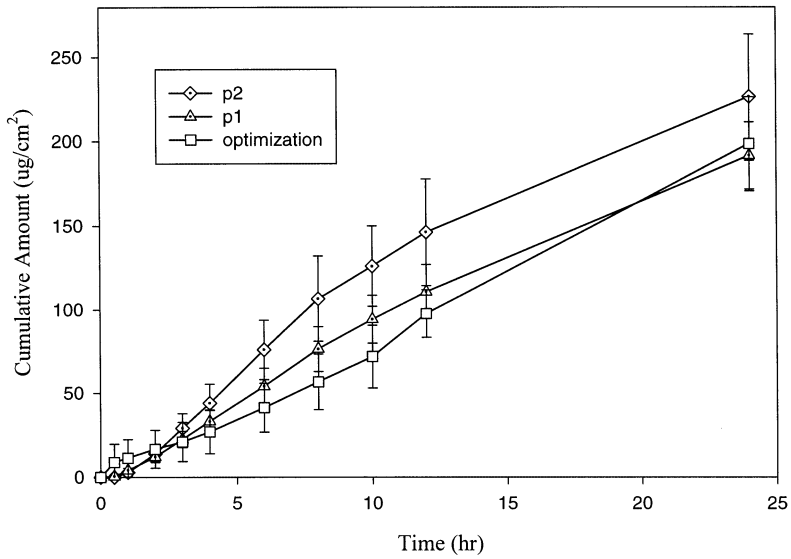

Fig. 2. Penetration profiles of ketoprofen through nude mouse skin from two commercial products (p1 and p2) and an optimized formulation ($n = 5$).

glycol, glycerin, and gelatin, respectively. It can be clearly seen that the greatest extent of improvement in the flux of ketoprofen occurred in the glycerin component. Furthermore, the influence of glycerin on the flux of ketoprofen was more profound than that of propylene glycol. This may be because glycerin might act as a solubilizer of ketoprofen and provide moisturizing effect on the stratum corneum to enhance percutaneous delivery of ketoprofen. Nevertheless, the effect of gelatin on the flux of ketoprofen was shown to have a negative value. A higher viscosity will be expected with an increasing content of gelatin in the formulation resulting in a hindrance of percutaneous diffusion. This clearly reveals that increasing the ratio of gelatin to the solvent system will decrease the flux of ketoprofen.

Overall, it is concluded that the percutaneous penetration of ketoprofen from the poultice of set 5 was the fastest among these formulations. However, the adhesion of this poultice was the worst. There is conflict of simultaneously demanding the penetration rate to be as fast as possible and having excellent adhesion to the skin. After simultaneous optimization, a suitable formulation with a comparable flux and acceptable adhesion was designed. The result of the penetration study is shown in Fig. 2. This indicates that the flux of ketoprofen from the optimized poultice occurs at a level close to that of two commercial products. In addition, the optimized poultice also demonstrates acceptable adhesion.

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