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行政院國家科學委員會補助專題研究計畫成果報告

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Ketoprofen 水性貼布之滲透性和黏著性適宜化研究

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一、中文摘要

本計畫利用水, propylene glycol, 和甘油為溶媒，配合 gelatin 和 sodium polyacrylate 水性基質配製 Ketoprofen 貼布。Mixture Design 用來評估以上組成如何影響Ketoprofen貼布的滲透性和黏著性。Gelatin 為影響 Ketofrofen 貼布黏著性的主要因子。甘油具有某種程度增加 Ketoprofen 滲透性的作用。最後，一個與市售品比較下具有適當滲透性和黏著性的處方被發展。

關鍵詞：滲透性, 黏著性, 貼布

Abstract

Topical poultices of ketoprofen were prepared using deionized water, propylene glycol, and glycerin as the vehicle in combination with hydrophilic matrix materials, including gelatin and sodium polyacrylate. A mixture design utilized to evaluate the influence of these constituents on the percutaneous penetration of ketoprofen and the adhesion of the poultice was evaluated. 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. 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 extents. Finally, an optimized formulation with acceptable adhesion and with a penetration rate comparable to a commercial product was developed in this study.

Keywords: Ketoprofen; Penetration; Adhesion; Poultice

Introduction

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.[1] 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.[2] The oleo-hydrogel formulation of ketoprofen has been demonstrated to be more beneficial than K-gel or K-plaster.[3] The release characteristics of ketoprofen from swelling-controlled drug delivery copolymer gels have been studied to deduce the transport mechanisms.[4]

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.[5] They demonstrated that the rank order of percent edema inhibition was as follows: Carbopol gel ≥ 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.[6] A parabolic relationship between the partition coefficient of thiomenthol derivatives and enhancement factor for ketoprofen delivered in a hydrogel system was noted.[7] 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.[8]

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.[9] Ketoprofen delivered by hydroalcoholic gel gave persuasive results in the treatment of knee arthrosis stages I and II.[10] 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.[11]

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.[12] 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.

RESULTS AND DISCUSSION

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 stresses which are the smallest among all formulations. Poultices of set 4 demonstrate 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. Furthermore, the influence of propylene glycol on the adhesion of the poultice can not be ignored from the comparison of peak

stress for sets 1 to 5 and 4 to 8. This means that both propylene glycol and gelatin play an important role in the determination of adhesion.

Quantification of the effect of each solvent on the adhesion of the poultice was evaluated based on a 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 C.V. (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 solvents on the adhesion of the poultice. The mixture design resulted in a polynomial equation with three terms that quantitatively fits the resulting data:

$$\text{Peak Stress} = 0.033\ X_1 + 0.016\ X_2 + 0.12\ X_3 \qquad (R: 0.9505)$$

where X_1, X_2, and X_3 represent the transformed percentages of the concentrations of propylene glycol, glycerin, and gelatin, respectively. 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. Obviously, the influence of gelatin on the adhesion of poultice was more profound than that of the solvent systems examined in this study. Nevertheless, the effect of glycerin on the adhesion of poultice was shown to be insignificant. As described above, gelatin is the most important factor influencing the adhesion of the poultice.

Figure 1 illustrates the cumulative amount of ketoprofen released versus time for those formulations and two commercial products (p1 and p2). The penetration rates (flux) at steady state, expressed as the penetrating amount of ketoprofen per unit time, were calculated. The penetration rates of ketoprofen from the p1 and p2 poultices were 9.7248 and 13.4450 ug/cm^2/h, respectively. They show higher penetration rates 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 extents. On the contrary, the higher percent weight fraction of gelatin hindered the penetration of ketoprofen.

Quantification of the effect of each solvent on the flux of poultice was also evaluated based on a mixture design. The results of model selection for 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 solvents on the flux of ketoprofen. The mixture design resulted in a polynomial equation with three terms that quantitatively fits the resulting data:

$$\text{Flux} = 1.90\ X_1 + 4.70\ X_2 - 6.65\ X_3 \qquad (R: 0.6364)$$

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

the solvent systems examined in this study. This may be because glycerin might act as a solubilizer of ketoprofen to enhance its percutaneous delivery. 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 penetration rate and acceptable adhesion was designed. The result of the penetration study is shown in Figure 2. This indicates that the penetration rate of ketoprofen from the optimal poultice occurs at a level close to that of two commercial products. In addition, the optimal poultice also demonstrates acceptable adhesion.

CONCLUSIONS

Poultices with a hydrophilic polymer matrix can be processed with no risk of the traditionally used organic solvents. Simultaneous optimization of penetration and adhesion is necessary to obtain a desirable formulation for practical use.

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Table 1. Mixture Design of Poultice Formulations

Set	PG[a]	Glycerin[a]	Gelatin[a]	Peak stress (psi)	Flux (ug/cm^2/h)
1	9.08	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(S.D.); n=5

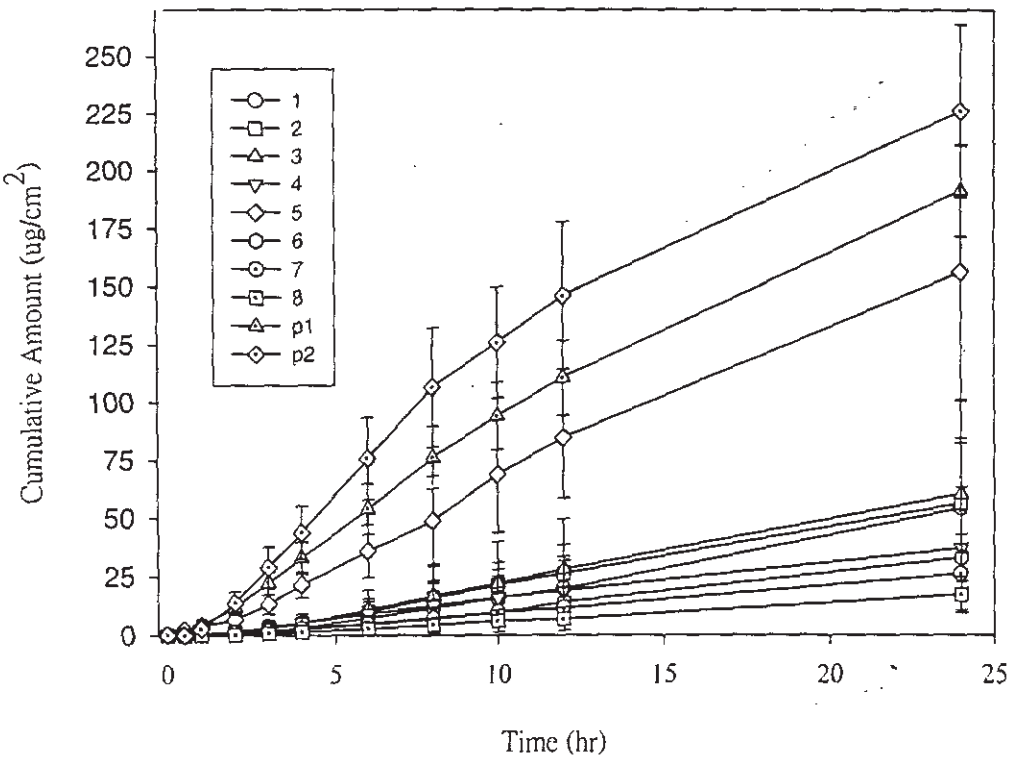

Figure 1. Penetration profiles of ketoprofen through nude mouse skin from poultices with different formulations. (n=5)

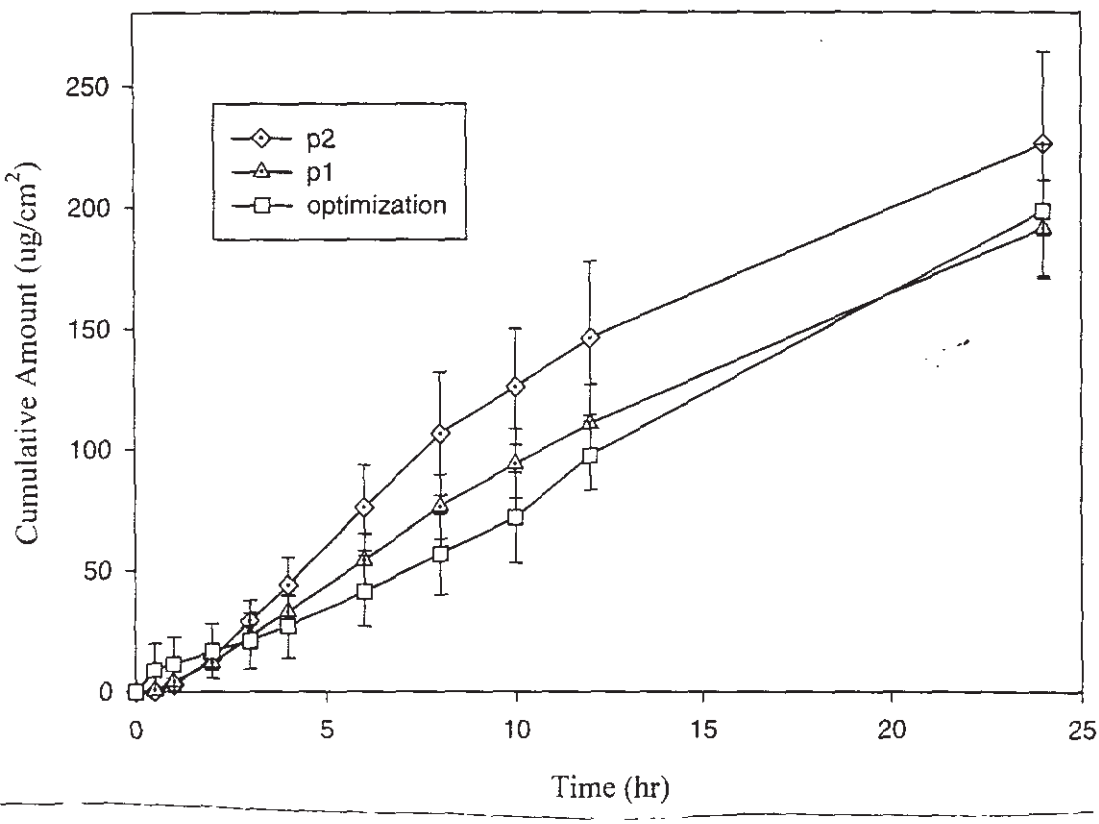

Figure 2. Penetration profiles of ketoprofen through nude mouse skin from two commercial products (p1 and p2) and an optimized formulation. (n=5)