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Effect of additives on the crystallization and the permeation of ketoprofen from adhesive matrix

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Abstract

The crystallization of drug in a matrix may significantly affect the efficacy and quality of the transdermal drug delivery system. Therefore, the control of drug crystallization is of particular interest in the development of efficient transdermal delivery systems. In this study, we investigated the effects of various additives on the crystallization of ketoprofen in polyisobutylene (PIB) adhesive matrix. The effects of various additives on the permeation of ketoprofen from PIB matrix across hairless mouse skin were also examined. Poly(vinyl pyrrolidone) (PVP) K-30 was found to be the most effective crystallization inhibitor. Also, Poloxamer, Tween 80 and Labrasol significantly inhibited the crystallization of ketoprofen in a PIB matrix. In case of Tween 80, Labrasol, and PVP K-30, the flux of ketoprofen decreased as the loading content of the additives increased. However, the addition of Tween 80, Labrasol, or PVP K-30 significantly reduced the decrease in the flux of ketoprofen within the PIB matrix during a storage time of 3 weeks.

Keywords: Crystallization; Ketoprofen; Poly(vinyl pyrrolidone); Polyisobutylene

1. Introduction

Transdermal drug delivery systems (TDDS) have been becoming increasingly popular over the last decade (Lipp and Müller-Fahrnow, 1999). In spite of many advantages of TDDS, only a limited number of drugs have been developed, because of the excellent barrier function of the skin. To overcome this barrier function, both physical and chemical enhancements have been attempted. Physical systems, such as iontophoresis and phonophoresis require complex and expensive delivery devices. Chemical methods involve penetration enhancers or the manipulation of the physico-chemical properties of the formulation. In general, penetration enhancers alter the barrier properties of the stratum corneum: moreover, the long-term effects of such penetration enhancers on the stratum corneum have not been fully elucidated. Therefore, supersaturation provides an attractive alternative (Pellett et al., 1994, 1997). Supersaturation in this context is defined as a state at which the amount of drug solubilized in a vehicle is greater than its equilibrium solubility.

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This has the effect of increasing the thermodynamic activity of a drug, and enhances the flux. However, such systems are thermodynamically unstable and a supersaturated drug solution has a tendency to form crystals. Drug crystallization within a pressure sensitive adhesive matrix may cause a reduction in skin permeation and/or tack of TDDS. Therefore, the control of drug crystallization is of particular interest for the efficiency and quality of TDDS application (Ma et al., 1996).

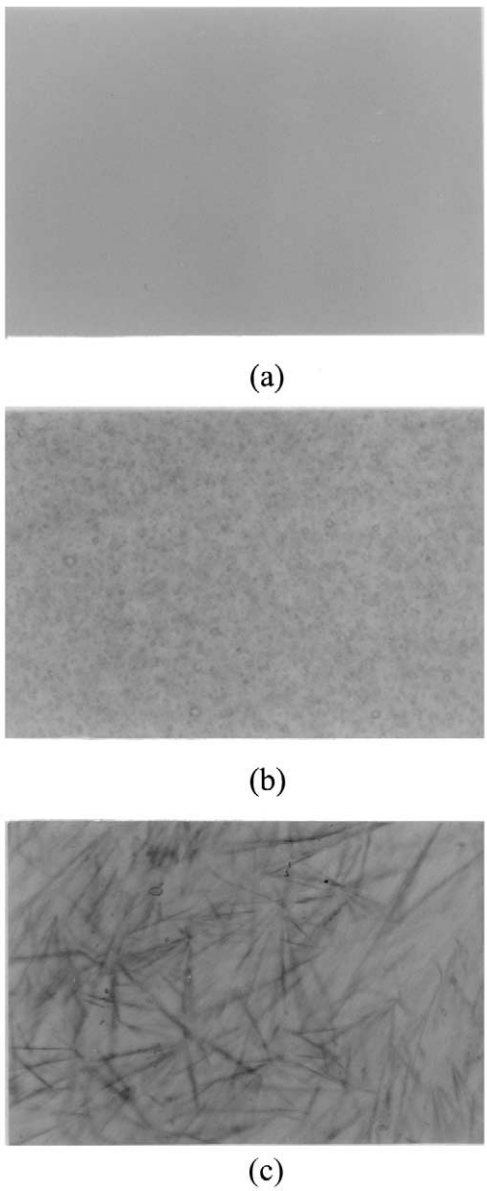

Fig. 1. Microphotographs of different PIB ketoprofen patches: (a) patch without ketoprofen; (b) patch before crystallization containing dispersed ketoprofen; (c) patch after crystallization containing ketoprofen crystal.

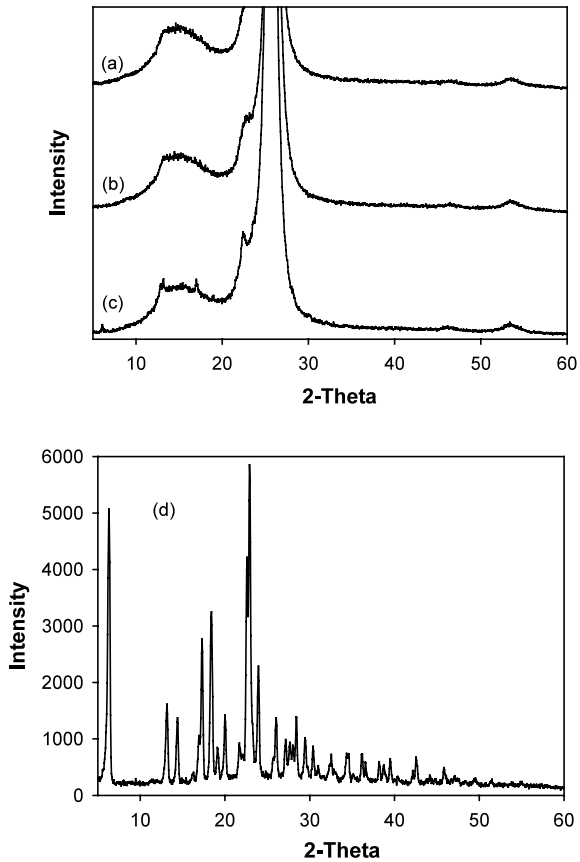

Fig. 2. X-ray diffractograms of different ketoprofen PIB patches: (a) patch without ketoprofen; (b) patch containing ketoprofen before crystallization; (c) patch containing ketoprofen after crystallization; (d) ketoprofen powder.

In this study, we investigated the effects of polymeric additives and solvents on the crystallization of ketoprofen within the adhesive matrix. In addition, the effects of various additives on the permeation rate of ketoprofen across hairless mouse skin and its dependence upon storage time were studied.

Table 1
Induction time (day) of the crystallization of ketoprofen within the PIB matrix versus additives present at different concentrations

Additive	Solubility of ketoprofen (mg/ml)[a]	Concentration of additive (%, w/w)		
		1.8%	2.5%	3.2%
None (control)	–		13	
Solvent				
Transcutol	412 ± 64	15	15	15
Tween 80	280 ± 56	4	9	>120
Labrasol	248 ± 57	40	>120	>120
Labrafil 2609	91 ± 10	0	0	0
Labrafil 1944	53 ± 7	0	0	0
Oleic acid	24 ± 4	0	0	1
Polymeric additive				
PVP K-30	*	>120	>120	>120
Poloxamer 407	*	39	>120	>120

[a] From Cho et al., 1998. Int. J. Pharm. 169, 95–104.

2. Materials and methods

2.1. Materials

Ketoprofen was a gift from Jeil Pharm, Co. (Seoul, Korea). Poly(vinyl pyrrolidone) (PVP) with number average molecular weight (MW) of 30 K was provided by BASF (Ludwigshafen, Germany). Diethylene glycol monoethyl ether (Transcutol®), PEG-8 glyceryl caprylate/caprate (Labrasol®), PEG-6 glyceryl mono oleate (Labrafil® 1944), and PEG-8 glyceryl linoleate (Labrafil® 2609) were obtained from Gatteposse Korea (Seoul, Korea). Mineral oil was purchased from Sigma Chemical Co. (St. Louis, MO). Polyisobutylene (PIB) (Vistanex LM-MH, Vistanex MML-100) were purchased from Exxon Chemical Co. (Houston, TX). All other chemicals were reagent grade or above and were used without further purification.

2.2. Preparation of adhesive matrix

A PIB adhesive matrix containing ketoprofen was prepared by the solvent casting method. The PIB solution containing ketoprofen was prepared by dissolving ketoprofen, PIB (cut into small pieces), and the other components necessary in a chloroform/hexane mixture. When the matrix formulation required PVP, it was dispersed in the mixture. The adhesive matrix was prepared by casting the above solution in polyester release liner using a casting knife. The mixture was set at room temperature for 20 min and subsequently oven-dried at 80 °C for about 15 min to remove residual organic solvents. The dried film was then laminated onto a polyester film. Samples were stored at 25 °C, and examined both visually and

Table 2
Effect of various additives on the flux (μg/cm² h) of ketoprofen from PIB matrix across hairless mouse skin at various concentrations immediately after preparation (storage time: 0 days)

Concentration (%, w/w)	Additive		
	Tween 80	Labrasol	PVP K-30
0		21.9 ± 3.4	
1.8	*	*	7.9 ± 0.4
3.2	11.5 ± 1.8	11.5 ± 0	6.4 ± 0.2
6.3	6.5 ± 0.2	10.2 ± 0.8	6.5 ± 2.7
9.5	4.5 ± 0.8	7.2 ± 1.2	6.5 ± 3.5

*, Not tested

Table 3
Effect of storage time on the flux (μg/cm^2 h) of ketoprofen from the PIB matrix containing various additives at the 3.2% level across hairless mouse skin

Storage time (week)	Additive			
	Control	Tween 80	Labrasol	PVP K-30
0	28.2 ± 1.8	12.1 ± 0.5	12.0 ± 0.2	6.9 ± 0.2
1	14.0 ± 0.5	10.8 ± 0.2	11.1 ± 0.1	9.1 ± 0.3
3	7.0 ± 0.4	8.8 ± 0.2	9.6 ± 0.3	8.2 ± 0.2

This data was obtained from a different set of experiments from Table 2.

microscopically at specified time intervals for the presence of ketoprofen crystals.

2.3. Permeation study

The permeation rate of ketoprofen across hairless mouse skin was investigated using a flow-through diffusion cell system. The flow-through diffusion cell system, the preparation of hairless mouse skins, the procedure used for the penetration studies, and the data reduction methods used in the present study have been described earlier (Kim et al., 2000). The penetration samples were collected every 3 for 21 h or longer, and the collected samples were analyzed by HPLC using a reverse-phase column (Alltima C8, Alltech Ass., IL). The column temperature was maintained at 30 °C by a thin foil temperature controller (CH1445, SYSTEC, MN). The wavelength of UV detector was 250 nm and the mobile phase consisted of methanol/water/phosphoric acid (80:20:0.1). The flow rate was 1 ml/min.

2.4. X-ray diffraction study

X-ray diffraction (XRD) patterns were obtained using an X-ray diffractometer (GMAX-1200, Rigaku Co., Japan). The X-ray copper target tube was operated at 60 kV and 80 mA. The instrument geometry was reflection. The X-ray generator power was 2 kW. The scan time was 5°/min and the step size was 0.05. The X-ray passed through 2° divergence slit. The diffracted radiation from the sample passed through 1° scatter slit and 0.6 mm receiving slit. The matrix sample was attached onto a glass holder.

3. Results and discussion

Ketoprofen crystallization in the patches with additives at various concentrations, including a drug-PIB adhesive matrix without any additives as a control, was observed by microscopy and XRD. Immediately after the preparation of a patch, the patches except one coated with an adhesive matrix containing 3.2% PVP were different degrees of milky-white depending on the additives used and their concentration.

Fig. 1 shows microphotographs of different PIB matrices of ketoprofen. No particles were present in the drug free PIB matrix (Fig. 1a), while ketoprofen particles were observed microscopically within the matrix (Fig. 1b). The X-ray diffractogram of milky-white matrix before crystallization (Fig. 2b) showed no characteristic peaks attributed to ketoprofen crystals (Fig. 2d), indicating that ketoprofen was supersaturated within the PIB matrix with the dispersed amorphous form. The X-ray diffractograms of the patch containing the ketoprofen crystals showed only some of the characteristic peaks of ketoprofen (Fig. 2c), due to interference from the PIB matrix. Fig. 1c shows the ketoprofen crystals formed within the PIB matrix. When the ketoprofen crystals within the matrix were examined visually, it was apparent that the rate and the pattern of crystal growth were dependent on the additive within the patch.

Table 1 shows the effects of various additives on the induction time (day) of ketoprofen crystallization within the PIB matrix. Among the tested solvent additives, Tween 80 and Labrasol significantly inhibited the crystallization of ketoprofen in the PIB matrix. The incorporation of

Labrafil 2609, Labrafil 1944 and oleic acid significantly accelerated the crystallization induction time. Even though the highest solubility of ketoprofen was obtained in Transcutol, its effect on the induction time was minimal. These results suggest that the inhibitory effect of a solvent on the crystallization of a drug may not be predicted simply from the solubility of the drug within the solvent. To elucidate the inhibitory effect a solvent, further studies need to be conducted.

In a matrix containing 7% ketoprofen together with 1.8–3.2% PVP, no drug crystals were observed microscopically up to 120 days of storage. PVP is well known as a drug crystallization inhibitor in pharmaceutical formulations. Many researchers have studied the inhibition mechanism of PVP in aqueous suspension or solid dispersion and suggested that the inhibition of PVP is due to the interaction between the drug and PVP (Ziller and Rupprecht, 1988; Yoshioka et al., 1995; Taylor and Zografi, 1997). Although in the case of TDDS, the solvent for the drug is an adhesive polymer, the possibility that PVP may interact and be adsorbed onto the initial crystals of the drug still remains (Ma et al., 1996).

To investigate the effects of additives on the permeation of ketoprofen across hairless mouse skin from the adhesive matrix, additives showing significant inhibitory effect on the crystallization of the drug were tested. Table 2 shows the effect of Tween 80, Labrasol, and PVP K-30 on the flux of ketoprofen from the PIB matrix across hairless mouse skin at various concentrations immediately after preparation. All additives tested decreased the flux of ketoprofen as the loading content of the additives increased, which may be due to the reduced activity of ketoprofen caused by the surrounding additives.

Table 3 shows the effect of storage time on the flux of ketoprofen across hairless mouse skin from a PIB matrix containing various additives at the 3.2% level. When the permeation of ketoprofen was tested immediately after preparing the patch, the flux from the PIB matrix without enhancer (control) was significantly higher than that of the others. However, as the storage time increased, the flux of ketoprofen from the control decreased. Ketoprofen was initially supersaturated within the PIB matrix, and provided high flux. However, amorphous dispersed ketoprofen particles would be crystallized into drug crystals in time, and this would result in a decreased flux due to the larger particle size. Adding Tween 80, Labrasol, and PVP K-30 prevented this significant decrease in ketoprofen flux within the PIB matrix during a storage time of 3 weeks; however, these additives failed to maintain the initial flux obtained from the matrix without additives. It should be noted that the adhesive force and the flux of ketoprofen from a matrix with no additives may further decrease with time, and that the addition of crystallization inhibitors is still essential in spite of their negative effect on the initial flux. Patches with inhibitors started to show slightly higher flux than control at week 3.

Acknowledgements

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