Adhesive Property, in vitro Release and Permeation Studies of Ketoprofen Transdermal Drug Delivery Systems

Ladda Wongpayapkul[1*], Phuriwat Leesawat[1], Teera Rittirod[2], Kavee Klangtrakul[3] and Yanee Pongpaibul[1]

[1] *Department of Pharmaceutical Sciences, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200, Thailand*

[2] *Department of Pharmacy, Faculty of Pharmacy, Khon Kaen University, Khon Kaen 40002, Thailand*

[3] *Neoplast Co.Ltd., Pathumthani 12150, Thailand*

**Corresponding author. E-mail: laddaw@pharmacy.cmu.ac.th*

ABSTRACT

Transdermal drug delivery system of ketoprofen, a potent non-steroidal anti-inflammatory drug, was prepared using combined acrylate pressure-sensitive adhesives: Eudragit® NE30D and Eudragit® E100. Propylene glycol (PG), butylene glycol (BG) and oleic acid (OA) were the selected additives and added in the ketoprofen transdermal drug delivery systems (KP-TDDSs). The adhesive property of each formulation was determined by rolling ball tack test and peel adhesion 180° test. It was found that all KP-TDDS formulations, except the one containing BG, exhibited the similar tack and peel adhesion values. In vitro release studies of all formulations across cellophane membrane were investigated, using modified Franz® diffusion cells. It was shown that the release rate of KP from the KP-TDDS formulation containing OA or PG was significantly higher than the formulation containing BG. In vitro permeation studies through rat skin were also evaluated. The flux of KP permeating from the formulation containing OA or PG was significantly higher than that from the formulation containing BG or without additives. In summary, both in vitro release and permeation studies revealed that the formulation containing OA or PG was an effective formulation and can be further developed to obtain the high potential transdermal delivery of KP.

Key words: Ketoprofen, Transdermal drug delivery system (TDDS), Adhesive property, *In vitro* release, *In vitro* permeation

INTRODUCTION

Ketoprofen is a potent non-steroidal anti-inflammatory agent, widely used for the symptomatic treatment of inflammatory syndromes such as rheumatoid arthritis, osteoarthritis and acute gouty arthritis (Porzio et al., 1998; Kalia and Guy, 2001; Sweetman, 2002). In order to minimize its gastric irritation after oral administration, various transdermal dosage forms containing ketoprofen have been reported including creams (Itoh et al., 1985; Kyuki et al., 1985), gels (Chi and Jun, 1991; Vincent et al., 1999), ointments (Henmi et al., 1994; Gurol et al.,1996), microemulsion (Rhee et al., 2001) and patches (Yim et al., 1994; Valenta and Almasi-Szabo, 1995; Singh et al., 1996). Although many topical dosage forms of ketoprofen have been investigated, there are only a few reports concerning both adhesive property and *in vitro* drug release and permeation studies of ketoprofen transdermal drug delivery system (KP-TDDS).

Transdermal drug delivery system (TDDS) is one of the novel drug delivery systems. It has many advantages over the other dosage forms such as providing extended therapy with a single application, leading to good patient compliance (Allen et al., 2005). In recent years, all types of TDDS can be described by three basic principles: drug in adhesive, drug in matrix (usually polymeric) and drug in reservoir (Walters, 2002). The most common TDDS is the drug in adhesive system. It is a particularly interesting TDDS due to the ease of fabrication and the lack of dose dumping (Keshery et.al., 1985). It composes of only three layers: backing membrane, the drug with pressure-sensitive adhesive and some additives such as plasticizer, penetration enhancer and the release liner (Tan and Pfister, 1999).

One of the critical considerations in the fabrication of TDDS is adhesion to skin. The adhesive property can be evaluated in terms of "tack" and "peel". Tack is the property that enables an adhesive to form a bond with the surface of another material upon brief contact under light pressure. Peel adhesion is defined as the force required to peel away a strip of tape from a rigid surface (Satas, 1989). There are several tests to evaluate the adhesive property of TDDS: thumb tack test, rolling ball tack test, peel adhesion 180?test, quick stick test and probe tack test (Banakar and Osborne, 1995).

In this study, KP-TDDS was fabricated using two acrylate pressure-sensitive adhesives. Propylene glycol is widely used as a vehicle for penetration enhancers and it has also been used alone as a penetration enhancer. Oleic acid is the most popular penetration enhancer among long-chain fatty acids (Williams and Barry, 2004). Butylene glycol is a common ingredient found in many topical dosage forms. Its chemical structure is similar to propylene glycol. Thus, all of them were selected and added as additives in KP-TDDS formulations. The objectives of the present investigation were to determine the adhesive property of TDDS and KP-TDDS formulations containing various additives, and also to evaluate the *in vitro* release and permeation of KP from all KP-TDDS formulations through cellophane membrane and abdominal rat skin.

MATERIALS AND METHODS

Materials

Ketoprofen was provided by BioLab Co.Ltd. (Thailand) as a generous gift sample. Eudragit® NE30D and Eudragit® E100 were purchased from Rohm GmbH & Co.KG (Germany); Triethyl citrate from Merck (Germany); Propylene glycol from Vidhyasom Co.Ltd. (Thailand); Butylene glycol and Oleic acid from Fluka Chemie AG (Switzerland). All other chemicals and solvents were of analytical grade and were obtained commercially. The backing membrane and the release liner were kindly gifted by the Neoplast Co.Ltd. (Thailand).

Preparation of the Ketoprofen Transdermal Drug Delivery System

In preparing 10 g of the KP-TDDS formulation, first of all, 4.56 g of Eudragit® E100 solution (19%w/w in the mixture of isopropanol and acetone, 3:2 w/w) was mixed with 2.28 g of Eudragit® NE30D, using a magnetic stirrer. Secondly, 0.93 g of triethyl citrate (TEC) and 0.08 g of propylene glycol (PG) or butylene glycol (BG) or oleic acid (OA) was added in the Eudragit(mixture. Finally, 0.30 g of ketoprofen, previously dissolved in 1.85 g of the mixture of isopropanol and acetone, 3:2 w/w, was added into the mixture and well stirred until the homogeneous mixture was obtained. The mixture was degassed to eliminate the entrapped air bubbles. A sheet of backing membrane was placed on a flat glass plate and secured in place with an adhesive. The adhesive mixture was poured carefully onto the backing membrane. The TLC spreader, 1.0 mm. thickness, was then gently passed through the mixture to produce a coating of uniform thickness. The patch was air-dried at room temperature for 15 min. and was then oven-dried at 64°C for 15 min. After complete drying, the KP-

TDDS was covered with a sheet of release liner and kept at room temperature until usage. The initial amount of KP in each KP-TDDS formulation was analyzed by using isopropanol as a solvent. The mixture of KP-TDDS was shaken at room temperature for 3 hr. and filtered through 0.45 μm nylon membrane filter. The absorbance of the appropriate diluted filtrate was measured with UV-visible spectrophotometer (Spectronic 1001, Milton Roy), at λ_{max} 254 nm. Linearity was demonstrated from 2.0 to 16.0 μg/ml ($r^2 > 0.9900$).

Determination of Adhesive Property of Ketoprofen Transdermal Drug Delivery System

Rolling ball tack test (PSTC test no.6) and peel adhesion 180° test (PSTC test no.1) were used in determining the adhesive property of each formulation. Procedures of both tests are briefly described as follow. In rolling ball tack test, a stainless steel ball, 1.1 cm (7/16 in.) in diameter, rolled down an inclined track (21°, 30') to come into contact at the bottom with horizontal, upward-facing adhesive. The distance of the ball traveled out along the adhesive sample is taken as the measure of tack. It was interpreted that the greater the distance, the less tacky is the adhesive. In the peel adhesion 180° test, the adhesive samples were applied to an adherent plate made of stainless steel, smoothed with a 2.0 Kg roller and pulled from the substrate at 180° angle at a rate of 300 mm/min. The force was expressed in Newton per centimeter (N/cm) width of adhesive sample under test (Satas, 1989). Tack and peel adhesion values of each formulation were measured in triplicate.

***In Vitro* Release Studies of Ketoprofen Transdermal Drug Delivery System**

In vitro release studies were carried out by using modified Franz® diffusion cell. The exact surface area of KP-TDDS, 0.951 cm^2, was cut into the circular shape. The cellophane membrane was soaked in the purified water overnight before using in this experiment. All studies were performed at 32±1°C and stirred at 600 rpm. Isotonic phosphate buffer, pH 7.4 was used as the receptor solution. The release liner was removed from the patch and the drug releasing surface was faced on the cellophane membrane which was tightly clamped between the donor and the receptor compartments. The samples were withdrawn, 1.0 ml., at different time intervals for a period of up to 7 h. A fresh equal amount of isotonic phosphate buffer, pH 7.4 was replaced each time. The amount of KP released was then determined using UV-visible spectrophotometer (Spectronic 1001, Milton Roy) at a wavelength of 260 nm. Linearity was demonstrated from 2.0 to 12.0 μg/ml ($r^2 > 0.9900$). Each formulation was carried out in triplicate. The cumulative amount of drug released per square centimeter at each time interval was calculated.

***In Vitro* Permeation Studies of Ketoprofen Transdermal Drug Delivery System**

Preparation of Abdominal Rat Skin

Male Wistar rats (National Laboratory Animal Center, Nakornpathom, Thailand) weighing 180–220 g, were used in this study. On the day before removing the skin from the rat, the hair of the abdominal area of rat was removed with an electric razor. On the next day, the rat was sacrificed by cervical dislocation. The abdominal skin was excised and the adherent fat and subcutaneous tissue were gently removed. The excised skin was rinsed with the normal saline solution and wiped carefully with tissue. The skin was then kept at -40°C until usage.

Skin Permeation studies

The rat skin was thawed at room temperature and cut into small pieces. The release liner was removed from the patch and KP-TDDS was fixed on the stratum corneum surface. The KP-TDDS with the skin was mounted between donor and receptor compartments and both compartments were then clamped together. The receptor compartment volume was 12.0 ml. and the effective surface area available for permeation was 0.951 cm^2. All studies were performed at 32±1°C and stirred at 600 rpm. Isotonic phosphate buffer, pH 7.4 was used as

the receptor solution. The samples were withdrawn, 500 μl, at fixed time intervals and the same volume of fresh receptor medium was replaced periodically up to 24 h. The amount of KP permeated through the abdominal rat skin was filtered through 0.45 μm nylon membrane filter and determined using HPLC (HP 1100, Hewlett Packard). The chromatographic analysis was carried out with a reverse phase Nucleosil 100–5 C_{18} column (5 μm, 250 x 4.6 mm.i.d.) at 40°C and λ_{max} 254 nm. The mobile phase was an acetonitrile/pH 3.5 phosphate buffer mixture (55:45v/v) with a flow rate of 1.0 ml/min. The retention time of KP was 2.73 min. Linearity was demonstrated from 0.6 to 13.0 μg/ml ($r^2 > 0.9900$). The cumulative amount of drug permeated per square centimeter at each time interval was calculated and plotted against time. Each formulation was carried out in triplicate.

Data Analysis

Firstly, the release profiles or permeation profiles of KP between different formulations were statistically analyzed by repeated measurements of general linear model. Secondly, the cumulative amounts of KP released or permeated were plotted as a function of square root time or time. The release or permeation rate of KP was obtained from the slope of the linear portion of the plot. All release rates or permeation rates were subjected to one-way analysis of variance (ANOVA), followed by Tukey's post-test to test the statistical significance of differences among formulations. Data were considered significant at $p<0.05$.

RESULTS AND DISCUSSION

All KP-TDDS formulations were uniform and free of air bubbles. The average drug content was 2,114.91±85.01 μg/cm^2

Adhesive Property of Ketoprofen Transdermal Drug Delivery System

The tack and peel adhesion values of TDDS and KP-TDDS formulations are shown in Table 1. By comparing between the adhesive properties of all plain TDDS formulations, it was found that the highest to the lowest tack value were as follow: formulation no.PBG> PCT>POA>PPG and the highest to the lowest peel adhesion value were as follow: formulation no.PPG>POA>PCT>PBG. Thus, it was concluded that the higher the tack value, the lower the peel adhesion value. When comparing among the KP-TDDS formulations, it was indicated that all formulations, except formulation no. KBG, had the similar tack values (0.37–0.43 cm.) and peel adhesion values (5.67–6.53 N/cm.). Moreover, there were dramatic higher peel adhesion values of all KP-TDDS formulations than those of all plain TDDS formulations. It might be due to the interaction between KP and acrylate polymers. These results corresponded well with the previous report (Kokubo et al., 1994) for the interaction between drugs and pressure-sensitive adhesive containing 2-ethylhexylacrylate and acrylic acid copolymer which strongly interacted with the carboxylic acid KP.

Table 1. Tack values and peel adhesion values of TDDS and KP-TDDS formulations with and without additives.

Formulation No.	Tack (cm.) ±S.D.	Peel Adhesion (N/cm.) ±S.D
PCT	0.93±0.12	0.73±0.12
PPG	0.00±0.00	0.90±0.26
PBG	1.07?±0.12	0.47±0.15
POA	0.67±0.12	0.77±0.21
KCT	0.40±0.17	5.67±0.61
KPG	0.43±0.06	6.13±0.12
KBG	0.07±0.12	3.63±0.47
KOA	0.37±0.06	6.53±0.12

Each value represents the mean±S.D.of three replicates. PCT, TDDS formulation without additives; PPG, TDDS formulation with propylene glycol; PBG, TDDS formulation with butylene glycol; POA, TDDS formulation with oleic acid; KCT, KP-TDDS formulation without additives; KPG, KP-TDDS formulation with propylene glycol; KBG, KP-TDDS formulation with butylene glycol; KOA, KP-TDDS formulation with oleic acid.

In vitro Release Studies of Ketoprofen Transdermal Drug Delivery System

Figure 1 shows the release profiles of KP-TDDS containing various types of additives. These profiles are plotted between the cumulative amounts of drug released as a function of square root time which fits better with the linear regression than the plots between the cumulative amounts of drug released as a function of time (data not shown). From the repeated measurements of statistical analysis, there were significant differences between the release profiles of KP from these formulations. The release rates were calculated from the slopes of the straight lines (coefficient of correlation, r^2 = 0.8823–0.9429) and are shown in Table 2. From the ANOVA statistical analysis followed by Tukey test, it was found that the release rate of KP from formulation no. KOA or KPG was significantly higher than that from formulation no. KBG. Additionally, the release rate of KP from formulation no. KOA was significantly higher than that from formulation no. KCT. In contrast, there was no significant difference among the release rates of KP from formulation no. KPG and KCT. These findings indicate that OA was the most optimal additive in this study. In the case of PG, there was a trend suggesting that PG was also a suitable additive for the KP-TDDS formulation.

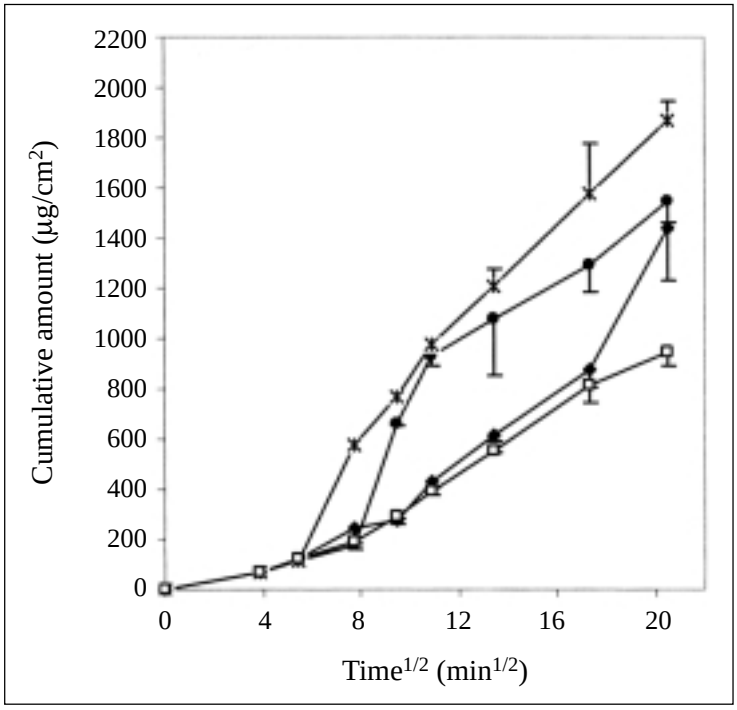

Figure 1. The release profiles of KP from formulation KCT (♦), formulation KPG (●), formulation KBG (□) and formulation KOA(*). Data are reported as mean±S.D.(three replications) of the cumulative amount of KP in the receptor compartment (μg/cm^2) at the sampling time (0, 0.25, 0.5, 1, 2, 3, 5 and 7 hr.).

Table 2. Release rate of KP from KP-TDDS containing different additives.

Formulation No.	Release Rate (μg/cm^2/min$^{1/2}$) ± S.D.
KCT	67.55±18.91
KPG	84.95±9.63
KBG	52.54±7.54
KOA	102.60±8.61

Each value represents the mean±S.D. of three replicates. KCT, KP-TDDS formulation without additives; KPG, KP-TDDS formulation with propylene glycol; KBG, KP-TDDS formulation with butylene glycol; KOA, KP-TDDS formulation with oleic acid.

The correlation between the adhesive property and the release rate of KP was also investigated. It was revealed that the lower adhesive property, the lower release rate of drug. This result was not in agreement with the general concept that the lower adhesion of TDDS, the higher release rate of drug. This might be due to other factors such as the physicochemical properties of the drug which play more important role than the adhesive property.

In vitro Permeation Studies of Ketoprofen Transdermal Drug Delivery System

Figure 2 shows the permeation profiles of KP-TDDS containing various additives. These profiles were plotted between the cumulative amounts of drug permeated as a function of time. From the repeated measurements of statistical analysis, there were significant differences between the permeation profiles of KP from these formulations. Fluxes of KP were calculated from the slopes of the straight line (coefficients of correlation, r^2 = 0.9742–0.9930) and are shown in Table 3. From the ANOVA statistical analysis followed by

Tukey test, the flux of KP permeating from the formulation containing OA or PG (formulation no. KOA or KPG) was significantly higher than the flux of KP permeating from formulation containing BG or without additive (formulation no. KBG or KCT). In contrast, there was no significant difference among the flux of drug permeating from formulations containing OA and PG. Thus, OA and PG acted as permeation enhancers in this study. These results were in accordance with the other reports for the skin permeation enhancing activity of OA or PG (Goodman and Barry, 1989; Morimoto et al., 1996; Gabiga et al., 2000; Viegas et al., 2001; Nair and Panchagnula, 2003). It is also observed in Figure 2 that the cumulative amount of KP permeating through rat skin from formulation containing OA or PG after 24 hr. was still very low. This might be due to the size of KP-TDDS used in this study was only 0.951 cm^2. To improve their potentials, several means will be further investigated: 1) increasing the size of TDDS, 2) increasing the thickness of TDDS, 3) increasing the drug concentration and 4) addition of some chemical permeation enhancers.

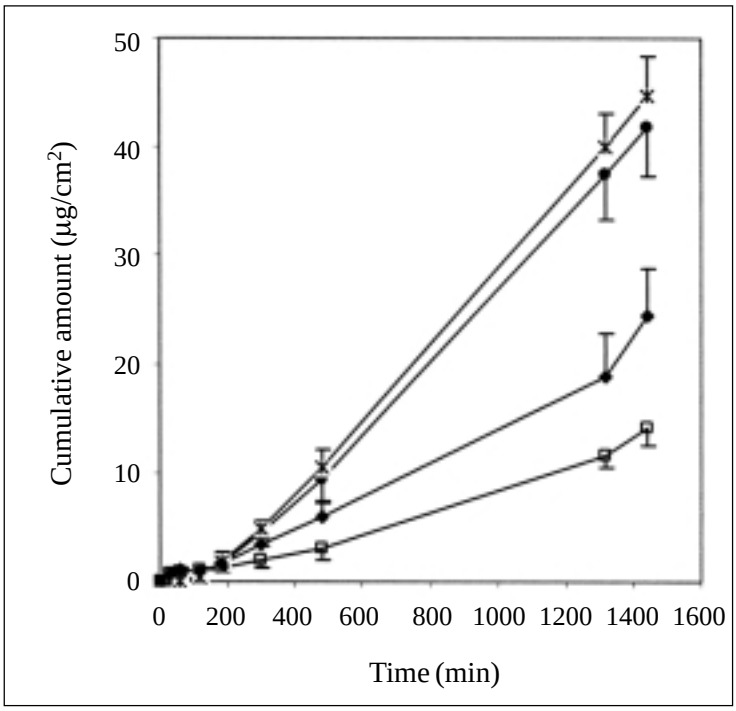

Figure 2. The permeation profiles of KP from formulation KCT (♦), formulation KPG (●), formulation KBG (□) and formulation KOA (*). Data are reported as mean± S.D.(three replications) of the cumulative amount of KP in the receptor compartment (μg/cm^2) at the sampling time (0, 0.5, 1, 2, 3, 5, 8, 22, 24 hr.).

Table 3. Flux of KP permeating from KP-TDDS containing different additives.

Formulation No.	Flux (μg/cm^2/min) ± S.D.
KCT	0.0160±0.01
KPG	0.0306±0.01
KBG	0.0094±0.00
KOA	0.0321±0.01

Each value represents the mean±S.D. of three replicates. KCT,KP-TDDS formulation without additives; KPG, KP-TDDS formulation with propylene glycol; KBG, KP-TDDS formulation with butylene glycol; KOA, KP-TDDS formulation with oleic acid.

The correlation between the release rate and the flux or permeation rate of KP was also studied. Figure 3 shows that there is a good linear correlation (correlation coefficient, r^2 = 0.9182) between the release rate and the flux of all KP-TDDS formulations, although there is a complete difference between the composition of the cellophane membrane and the abdominal rat skin. For this reason, only the release study can be investigated and should represent the permeation study as well. This will be valuable in terms of time- and expense-saving in the further investigations.

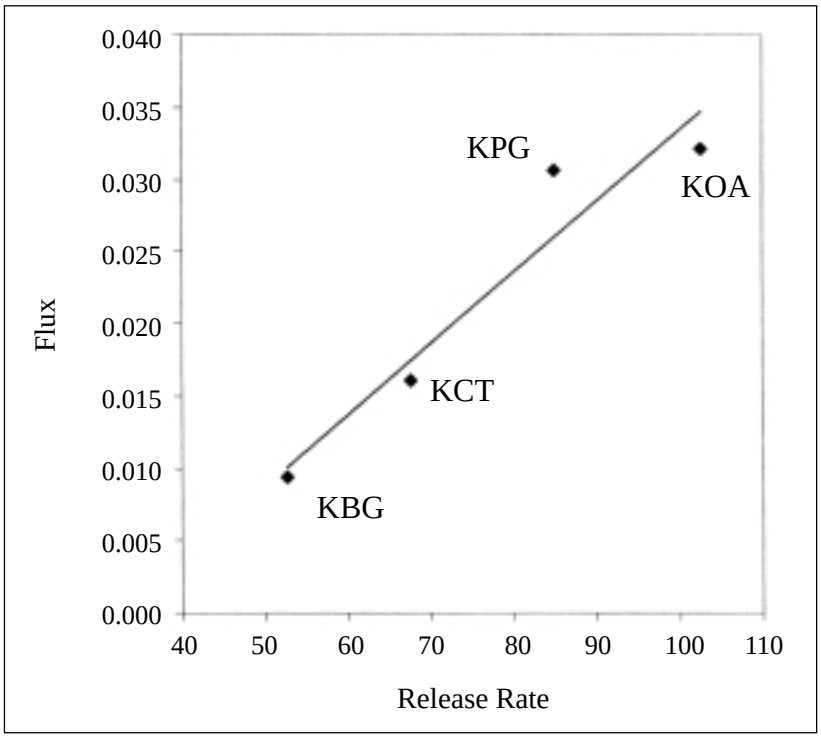

Figure 3. The correlation between the release rate (μg/cm^2/min$^{1/2}$) and the flux (μg/cm^2/min) of all KP-TDDS formulations. KCT, KP-TDDS formulation without additives; KPG, KP-TDDS formulation with propylene glycol; KBG, KP-TDDS formulation with butylene glycol; KOA, KP-TDDS formulation with oleic acid. Each point represents the mean of three determinations.

CONCLUSION

The KP-TDDS formulation containing OA or PG exhibited the higher adhesive property than the formulation containing BG. The release rate and the flux of KP released and permeated from the formulation containing OA or PG was higher than those from the formulation containing BG or the formulation without additives.

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