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In Vitro Skin Permeation of Buprenorphine Transdermal Patch

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ABSTRACT

This study was aimed to develop the new transdermal formulation to improve the permeability of buprenorphine. The apparent partition coefficients of buprenorphine were measured using the buffers at pH 1.2 to 10.0 as aqueous phase. The solubility of buprenorphine was 12.97 μg/mL in the 0.1 M phosphate buffer at pH 6.8. The influences of vehicles at different pH, adhesives, and permeation enhancers on the penetration of buprenorphine through nude mouse skin were investigated using the static Franz diffusion cells. The permeation parameter J_{ss} of buprenorphine increased along with the reduction of the pH of receptor fluid, and the vehicle at pH 6.8 was used in the following skin permeation studies. The pressure sensitive adhesives (PSA) including polyisobutylene (PIB), polystyrene-block-polyisoprene-block-polystyrene (SIS), and acrylic adhesives were evaluated. The permeability of buprenorphine was higher in the PIB or SIS adhesives than that in the acrylic adhesives under the condition without enhancer. When combined the enhancers with propylene glycol (PG) to improve the penetration of buprenorphine, the permeation-enhancing effects of enhancers were in the following order: lauric acid > linolenic acid > menthol > oleic acid > N-methyl-2-pyrrolidone (NMP) > laurocapram > glabridin. Finally, a matrix-type transdermal delivery system for buprenorphine was formulated using acrylic adhesive, PG, and lauric acid. The J_{ss} parameter was 2.68 ± 0.20 μg/cm^2/h and buprenorphine permeated across the nude mouse skin was 31.68%.

Key words: buprenorphine, skin permeation, transdermal patch, adhesive, enhancer

INTRODUCTION

Buprenorphine is a partial agonist at the mu opioid receptor and an antagonist at the kappa receptor in the central nervous system (CNS) and peripheral tissues, where it binds to both receptors with high affinity[(1,2)]. Effects on analgesia appear to occur as a result of mu agonist activity[(3)]. Buprenorphine produces dose-related analgesia and is 25-50 times more potent than an equivalent dose (by weight) of morphine[(4)].

Buprenorphine has been used to control cancer pain via several routes. Parenteral and sublingual preparations have been initially used[(5)]. For example, Buprenex® in the US and Temgesic® in most European countries have been widely prescribed for the treatment of moderate to severe pain[(6)]. A transdermal matrix patch formulation of buprenorphine, Transtec®, has become available in three dosage strengths: the patches contained 20, 30, and 40 mg of buprenorphine and have been designed to release buprenorphine at the controlled rate of 35, 52.5, and 70 μg/h over a period of 72 hours, respectively, each corresponding to a daily dose of 0.8, 1.2, and 1.6 mg. The three dosage strengths are indicated for the treatment of moderate to severe cancer pain and severe pain unresponsive to nonopioid analgesics[(7)]. Transtec® has a significant lag time (12-24 hours) to reach clinically effective concentrations (0.1-0.5 ng/mL)[(7,8)].

The transdermal drug delivery system (TDDS) would avoid the first-pass effect, reduce the side effects, and control the release of drugs over long term. The pressure sensitive adhesives (PSA) used commonly in the transdermal patch are polyisobutylene, polystyrene-block-polyisoprene-block-polystyrene, and acrylic adhesive[(9)]. Because the physicochemical properties of PSA could affect the penetration of a drug in PSA across the skin, the selection of suitable PSA matrix would be important in designing a transdermal patch[(10,11)].

The permeation enhancers are usually incorporated in TDDS to improve the diffusion kinetics of the drug administered and they can overcome the intrinsic resistance of the stratum corneum and enhance the permeation rate of the active pharmaceutical ingredient[(9)]. However, the structure-activity relationship between enhancers and drugs are still indistinct. It is accepted that the effect of

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enhancer is dependent on the physicochemical properties of drugs and the combination with the excipients. A variety of enhancers have been investigated to promote the skin permeability of drugs in the literatures[9,12,13].

The purpose of this study was to develop the new transdermal formulation to improve the permeability of buprenorphine. Because the intrinsic aqueous solubility of neutral buprenorphine base was 12.7 ± 1.2 μg/mL at 23°C, buprenorphine base was practically insoluble[14]. The objectives of this study were firstly to determine the lipophilicity and solubility of buprenorphine. In order to develop an optimal transdermal formulation, the effects of vehicles at different pH, adhesives, and permeation enhancers on the penetration of buprenorphine through the nude mouse skin were also evaluated.

MATERIALS AND METHODS

I. *Materials*

Buprenorphine, 21-cyclopropyl-7α-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine, was purchased from Tasmanian Alkaloid and the purity was 99%. The acrylic adhesives including Acryl-1 (NS-2287®), Acryl-2 (NS-100®), Acryl-3 (NS-200®), and Acryl-4 (NS-300®) were manufactured by National Starch and Chemical Company. Polyisobutylene (PIB), polystyrene-block-polyisoprene-block-polystyrene (SIS), propylene glycol (PG), mineral oil, liquid paraffin, lauric acid, linolenic acid, oleic acid, and menthol were obtained from Sigma-Aldrich. Glabridin and laurocapram were offered by Shanghai Healthwell Chemical. Rosin ester and N-methyl-2-pyrrolidone (NMP) were purchased from Robert Kraemer GmbH and Merck, respectively. The backing sheet SCOTCHPAK® was obtained from 3 M. All other chemicals were of analytical grade.

II. *Determination of Buprenorphine*

The samples of buprenorphine in this study were analyzed by HPLC (Hewlett-Acrylkard 1100) equipped with a UV detector at 230 nm, and an XBridge™ Shield RP18 column (4.6 × 75 mm, 2.5 μm; Waters). The column temperature was 30°C. The mobile phase consisted of acetonitrile / 0.063 M ammonium bicarbonate (pH 9.5) (58:42, v/v) at the flow rate of 1.5 mL/min. The mobile phase was degassed by an ultrasonic bath and filtered by a Millipore vacuum filter system equipped with a 0.22 μm filter prior to use. The injection volume was 40 μL for each analysis. This HPLC analytical system has been validated[15].

III. *Buprenorphine Lipophilicity Studies*

The apparent partition coefficients (P) of buprenorphine were determined using n-octanol as organic phase and 0.1 M phosphate buffers adjusted to pH 4.5, 6.8, or 7.4 as aqueous phase. The pH 1.2 and 10.0 as aqueous phase were also used by titrating with 1.0 M hydrochloric acid and 0.063 M ammonium bicarbonate, respectively. The apparent partition coefficient was determined by adding 20 mg of buprenorphine to 20 mL of aqueous phase and then mixing with 20 mL of n-octanol. After equilibrating for 24 hours in a water bath at 25°C, the aqueous phase was separated by centrifugation (3,000 rpm for 15 min) and assayed for buprenorphine. The above processes were carried out for five times and the partition coefficients were calculated[16,17].

IV. *Buprenorphine Solubility Studies*

The solubility of buprenorphine was determined in 0.1 M phosphate buffers at pH 5.0, 5.5, 6.0, 6.8, and 7.4. Excess amount of buprenorphine were added to known volumes of the phosphate buffers and equilibrated in a water bath at 32°C under continuous stirring at 250 rpm for 24 hours. The samples were filtered through the 0.22 μm filters individually and then analyzed as described. This system was performed three times each[16].

V. *Preparation of Buprenorphine Transdermal Patch*

The PIB-1, PIB-2, SIS-1, Acryl-1, Acryl-2, Acryl-3, or Acryl-4 adhesive solution in organic solvent was mixed with buprenorphine in ethyl acetate with or without permeation enhancers according to the following protocol. The PSA were prepared by coating the above solutions on the polyester release liners, and set in the oven at 50°C for 20 minutes to remove organic solvents. The backing sheets were then placed on the dried adhesive films to make the transdermal patches[10,18,19].

VI. *Buprenorphine in Vitro Permeation Studies*

The skin permeation of buprenorphine was evaluated *in vitro* using the static Franz diffusion cells with dilution area of 1 cm^2. The receptor compartment was filled with 8 mL phosphate buffer as the vehicle. The nude mouse skin (Narl: ICR-Foxn1^{nu}) was cut about 2 × 2 cm^2 and then mounted on the cell and the transdermal patch was applied to the skin. The receptor compartment was stirred at 32°C throughout the experiment. Samples (6 mL) were withdrawn after 3, 6, 9, 21, 33, 45, 57, and 72 hours from the receptor compartment followed by replacement with a fresh vehicle. The samples withdrawn were filtered and analyzed by HPLC for the determination of buprenorphine permeated[20].

(I) *Influence of Vehicles at Different pH*

The Acryl-1 was used as the adhesive and the concentration of buprenorphine was kept at 10% (w/w)

in the formulation. Five 0.1 M phosphate buffers were adjusted to pH 5.0, 5.5, 6.0, 6.8, and 7.4 as the vehicles which were used to evaluate the influence of pH on the skin permeability of buprenorphine[21].

(II) *Influence of Adhesives*

The composition and trade name of seven PSA were employed as follows: PIB-1 (PIB Mw 1.2×10^6: mineral oil: liquid paraffin: rosin ester = 3:1:1:5), PIB-2 (PIB Mw 1.2×10^6: PIB Mw 2.0×10^5: mineral oil: rosin ester = 1:2:1:5), SIS-1 (SIS: rosin ester: liquid paraffin = 4.5: 5.5:1), Acryl-1 (NS-2287®), Acryl-2 (NS-100®), Acryl-3 (NS-200®), and Acryl-4 (NS-300®). Each PSA was used as the adhesive and the concentration of buprenorphine was kept at 10% (w/w) in each formulation. The vehicle used in this study was 0.1 M phosphate buffer at pH 6.8.

(III) *Influence of Permeation Enhancers*

The permeation enhancers used in this study included lauric acid, linolenic acid, oleic acid, menthol, glabridin, laurocapram, and NMP. Acryl-1 was used as the adhesive. The concentrations of buprenorphine, PG, and each enhancer were kept at 10% (w/w) in each formulation. The formulation of control test was of no any enhancer. The vehicle used in this study was 0.1 M phosphate buffer at pH 6.8[21,22].

(IV) *Formulation Optimization*

The skin permeation of buprenorphine was more efficient in PIB-1, PIB-2, SIS-1, and Acryl-2 adhesives than in other acrylic adhesives without any enhancer. Each of the four adhesives was combined with PG/lauric acid or PG/linolenic acid in order to obtain the optimal formulation. The concentrations of buprenorphine, PG, lauric acid, or linolenic acid were kept at 10% (w/w) in each formulation. The vehicle used in this study was 0.1 M phosphate buffer at pH 6.8.

(V) *Data Treatment*

The amount of buprenorphine permeated through the nude mouse skin during a sampling interval was calculated based on the measured concentration and volume of the receptor compartment. Each experiment was replicated at least three to six times. The cumulative amount of buprenorphine permeated per cm^2 of the skin versus time was plotted. The lag time (t_L) and the steady-state flux (J_{ss}, $\mu g/cm^2/h$) were determined from the intercept and the slope of the linear portion of the plot. The percentage of buprenorphine permeated was calculated as the ratio of final cumulative amount of buprenorphine permeated and the amount of buprenorphine loaded. The enhancement ratio (ER) was calculated as the ratio of J_{ss} values in the presence and absence of enhancer. All data were calculated and presented as mean ± SD[16,22-24]. ER = J_{ss} with enhancer / J_{ss} without enhancer

RESULTS AND DISCUSSION

I. *Lipophilicity of Buprenorphine*

The apparent partition coefficients (P) obtained using n-octanol as the organic phase exhibited the pH dependency as predicted by the basic property of buprenorphine with a pKa of 8.24. The obtained P values were 2.11 ± 0.01 for pH 1.2, 25.88 ± 0.10 for pH 4.5, 2098.46 ± 109.89 for pH 6.8, and 65108.75 ± 834.01 for pH 7.4. However, buprenorphine was not detected in the aqueous phase at pH 10.0. The octanol/water partition coefficient of buprenorphine was 1943 ± 50 in the previous literature[25]. The results indicated that buprenorphine was almost insoluble in the vehicle at pH 7.4 in this study. Therefore, it was suggested that the phosphate buffer with lower pH value should be used as the vehicle in our skin permeation studies.

II. *Solubility of Buprenorphine*

The solubilities of buprenorphine in phosphate buffers at different pH were demonstrated in Table 1. The solubility of buprenorphine in 0.1 M phosphate buffer at pH 5.0 was thirty times higher than that at pH 7.4. As the pH value fell, the solubility of buprenorphine increased. Because buprenorphine was an alkaloid with poor water solubility, it would be protonated in low pH phosphate buffers and this enhanced the water solubility of buprenorphine. The intrinsic aqueous solubility of neutral buprenorphine was 12.7 ± 1.2 μg/mL at 23°C[14].

III. *Buprenorphine in Vitro Permeation Studies*

(I) *Influence of Vehicles at Different pH*

The permeation parameters and the corresponding permeation profiles were shown in Table 1 and Figure 1. The relationship of pH and J_{ss} was displayed in Figure 2. As expected, the pH of the vehicle in the Franz cell highly had a impact on the penetration ability of buprenorphine. This could be explained based on the lipophilicity and solubility studies. The aqueous solubility of buprenorphine was higher at low pH (5.0-7.4) conditions. We observed that higher permeability at lower pH for buprenorphine should be attributed to its higher solubility at lower pH, making it partition at a faster rate from the dermal of skin into the vehicle. The J_{ss} of buprenorphine increased along with the reduction of the pH of receptor fluid. The relationship of pH and J_{ss} was linear (r^2 = 0.9901, n =3), as shown in Figure 2. The percentage of buprenorphine permeated was more than 58% in the phosphate buffers at pH 5.0, 5.5, and 6.0.

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Therefore, these pH conditions would not be appropriate to evaluate the effect of the permeation enhancers in this study. For this reason, the phosphate buffer at pH 6.8 would be chosen as the vehicle in the skin permeation studies conducted.

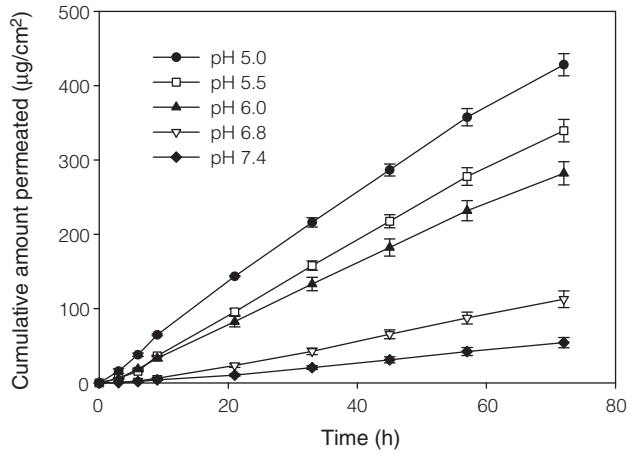

Figure 1. Effect of phosphate buffers at different pH on the cumulative amount of buprenorphine permeated across nude mouse skin (mean ± SD, n = 3).

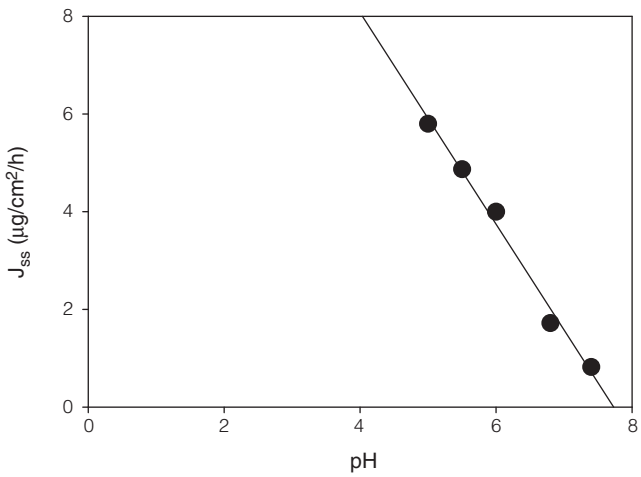

Figure 2. The relationship of pH and J_{ss}.

(II) *Influence of Adhesives*

The objective of this study was to evaluate the effect of various adhesive matrices on the permeation of buprenorphine across the nude mouse skin. Seven adhesive matrices were chosen as the transdermal drug delivery system. The permeation parameters and the corresponding permeation profiles were shown in Table 2 and Figure 3, respectively. It was showed that the permeabilities of buprenorphine were higher in the PIB and SIS adhesives than in the acrylic adhesives. Especially, the permeation of buprenorphine was two-fold higher in the PIB-1 adhesive than in the Acryl-3 adhesive (see Table 2). Same result was observed by Choi *et al*[18]. The permeation of ketoprofen was lower in acrylic adhesive than in PIB adhesive, which may be due to the higher solubility of ketoprofen in acrylic adhesive. The better compatibility of the functional group in the acrylic adhesive with ketoprofen reduced the permeation of ketoprofen in the acrylic adhesive matrix. Similar study has been observed by Choi *et al*[26]. The interaction between the drug and functional group of PSA can influence the permeation of drug. For example, PSA containing acrylic acid (2-ethylhexylacrylate and acrylic acid copolymer, 2EHA/AA) strongly interacted with the amide of lidocaine, and with the tertia-

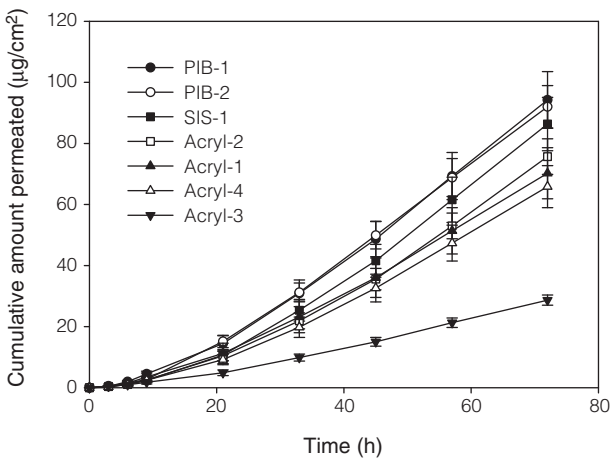

Figure 3. Effect of adhesives on the cumulative amount of buprenorphine permeated across nude mouse skin (mean ± SD, n = 6).

Table 1. Solubility of buprenorphine in 0.1 M phosphate buffers at 32°C and the effect of phosphate buffers at different pH on skin permeation parameters of buprenorphine (mean ± SD, n = 3)

Vehicles (0.1 M Phosphate buffers)	Solubility (μg/mL)	J_{ss} (μg/cm²/h)	t_L (h)	Percentage of buprenorphine permeated (%)
pH 5.0	89.73 ± 0.15	5.80 ± 0.26	3.65 ± 1.13	87.07
pH 5.5	85.35 ± 0.06	4.87 ± 0.22	3.96 ± 1.20	70.64
pH 6.0	57.90 ± 0.03	4.00 ± 0.19	4.83 ± 1.16	58.37
pH 6.8	12.97 ± 0.03	1.62 ± 0.16	10.79 ± 1.20	19.03
pH 7.4	3.03 ± 0.01	0.82 ± 0.10	11.51 ± 1.45	10.48

Table 2. Effect of adhesives on skin permeation parameters of buprenorphine (mean ± SD, n = 6)

Adhesives	J_{ss} (μg/cm^2/h)	t_L (h)	Percentage of buprenorphine permeated (%)
PIB-1	1.57 ± 0.14	12.92 ± 1.31	18.49
PIB-2	1.52 ± 0.11	11.79 ± 1.04	17.52
SIS-1	1.49 ± 0.14	15.41 ± 0.94	16.69
Acryl-1	1.16 ± 0.13	12.66 ± 2.96	13.50
Acryl-2	1.29 ± 0.10	15.04 ± 1.45	15.48
Acryl-3	0.47 ± 0.03	11.59 ± 2.04	5.52
Acryl-4	1.12 ± 0.12	14.44 ± 1.62	12.94

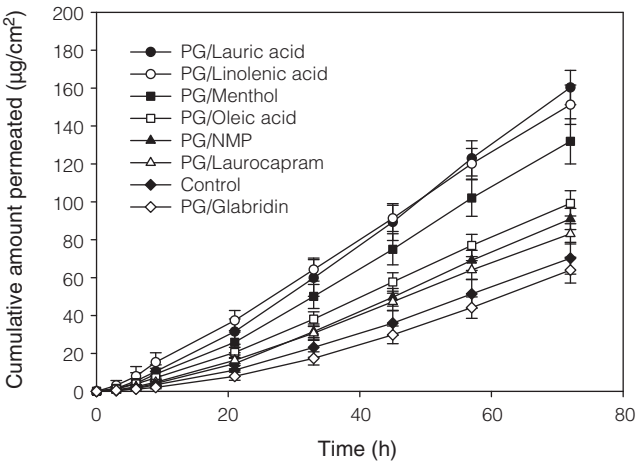

Figure 4. Effect of enhancers on the cumulative amount of buprenorphine permeated across nude mouse skin (mean ± SD, n = 6).

ry amine of aminopyrine, The formulation of Duragesic® (fentanyl transdermal system) contained fentanyl and alcohol which were gelled with hydroxyethyl cellulose and silicone adhesive. No permeation enhancer was used. The amount of fentanyl released from each system per hour was proportional to the surface area (2.5 μg/cm^2/h)[27]. From the product information of Duragesic®, we observed that the appropriate PSA used might efficiently raise the skin permeation of drugs without using enhancers.

(III) *Influence of Permeation Enhancers*

In the absence of a suitable permeation enhancer, the transport of drugs across skin would be limited. Different enhancers including lauric acid, linolenic acid, oleic acid, menthol, glabridin, laurocapram, and NMP were investigated to try to improve the skin permeation of buprenorphine. A synergistic enhancement of drug permeation was usually accomplished by the combination with enhancers and co-solvent PG[28]. The ability of PG to increase transdermal permeability had been attributed to some effects. For example, the primary effect of PG appeared to involve in a solvent-drug effect by partitioning into the stratum corneum itself. When PG improved the solubility of the drugs within the stratum corneum, it led to the enhancement of the partition of the drugs into the skin[29]. However, it was found that PG occupied the hydrogen bonding sites of tissues, leading to decrease the binding ability and increase lipid fluidity and permeation of drugs[30,31]. Therefore, PG was added to each formulation which contained the above enhancers.

As discussed in the influence of adhesives, it was found that better compatibility of the functional group in the acrylic adhesive with the drug would reduce the permeation of the drug in the acrylic adhesive matrix. However, the importance of the hydrogen-bonding ability in permeation enhancers had already been observed[32]. It indicated that the possible mechanism of drug permeation enhancement by enhancers in the acrylic adhesive might be the formation of hydrogen-bonding between the drug and the enhancers. It would decrease the interaction between the drug and the adhesive and then increase the amount of drug permeated across the skin.

The permeation parameters were shown in Table 3 and the corresponding permeation profiles were shown in Figure 4. PG/lauric acid (a saturated fatty acid, C12) and

Table 3. Effect of enhancers on skin permeation parameters of buprenorphine (mean ± SD, n = 6)

Enhancers	J_{ss} (μg/cm^2/h)	t_L (h)	ER	Percentage of buprenorphine permeated (%)
Control	1.16 ± 0.11	12.66 ± 2.96	1.00	13.50
PG/Glabridin	1.11 ± 0.09	16.17 ± 1.67	0.96	12.41
PG/Laurocapram	1.32 ± 0.08	9.07 ± 2.46	1.14	16.12
PG/NMP	1.51 ± 0.10	11.72 ± 2.02	1.30	17.76
PG/Oleic acid	1.56 ± 0.09	8.03 ± 1.45	1.34	19.31
PG/Menthol	2.10 ± 0.22	8.73 ± 3.37	1.81	25.38
PG/Linolenic acid	2.38 ± 0.15	8.46 ± 2.04	1.95	28.71
PG/Lauric acid	2.55 ± 0.18	9.16 ± 3.08	2.20	31.00

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Table 4. Effect of lauric acid or linolenic acid in different adhesives on skin permeation parameters of buprenorphine (mean ± SD, n =6)

Formulations	J_{ss} (μg/cm^2/h)	t_L (h)	Percentage of buprenorphine permeated (%)
Acryl-2/PG/Lauric acid	2.68 ± 0.20	12.08 ± 1.61	31.68
Acryl-2/PG/Linolenic acid	2.34 ± 0.16	12.02 ± 1.33	27.21
SIS-1/PG/Lauric acid	2.26 ± 0.13	14.39 ± 0.69	25.59
SIS-1/PG/Linolenic acid	2.18 ± 0.18	12.25 ± 1.28	24.34
PIB-1/PG/Lauric acid	1.72 ± 0.12	11.99 ± 1.77	20.48
PIB-1/PG/Linolenic acid	1.60 ± 0.10	10.86 ± 1.67	18.70
PIB-2/PG/Lauric acid	1.62 ± 0.10	13.85 ± 1.90	18.13
PIB-2/PG/Linolenic acid	1.55 ± 0.11	11.34 ± 2.01	18.24

PG/linolenic acid (an unsaturated fatty acid with three double bonds, C18) highly increased, while PG/oleic acid (an unsaturated fatty acid with one double bond, C18) slightly increased the permeation of buprenorphine compared with control test. The highest enhancement effect in this study was achieved by PG/lauric acid. PG/oleic acid was not potent in this study although it was reported as an effective skin permeation enhancer for several compounds[33,34]. The results were associated with the carbon chain length of fatty acids and the number of double bonds. The effect of carbon chain length of saturated fatty acids (C7-C18) on the permeation of naloxone across human skin was studied by Aungst. *et al*[35]. When the chain length increased from C7 to C12, there was an increase in the J_{ss} of naloxone. However, further increase in the carbon chain length from C12 to C18 decreased the J_{ss} of naloxone. It had also been proposed that the fatty acid with 12 carbons possessed an optimal balance between partition coefficient and affinity to skin[36]. The unsaturated fatty acids with 18 carbons were more effective enhancers than the corresponding saturated fatty acid in the penetration of naloxone through human skin, as reported by Aungst. *et al*[35]. As the number of double bonds increased from one to three, J_{ss} of naloxone increased.

The J_{ss} of PG/lauric acid or PG/linolenic acid in our study demonstrated that both lauric acid and linolenic acid were effective penetration enhancers. The long-chain fatty acids in combination with PG significantly enhanced the penetration of nicardipine and ketorolac in Rhesus Monkey[37]. The highly lipophilic basic drug, antiestrogen, could be administered transdermally and lauric acid or PG could increase the permeation of it, which was observed by Lipp. *et al*[38]. The mechanisms of the enhancing ability of fatty acids and PG were as follows[39,40]. The mutual permeation enhancement of PG and fatty acids for drugs were firstly due to the enhanced solubility of fatty acids and their penetration into the stratum corneum, both being caused by PG. It was secondly due to enhanced permeability of PG, which was caused by fatty acids insertion between the intercellular lipids of the stratum corneum. Therefore, fatty acids acted as the "co-enhancer" and PG as the "co-solvent" in this enhancer combination[40,41].

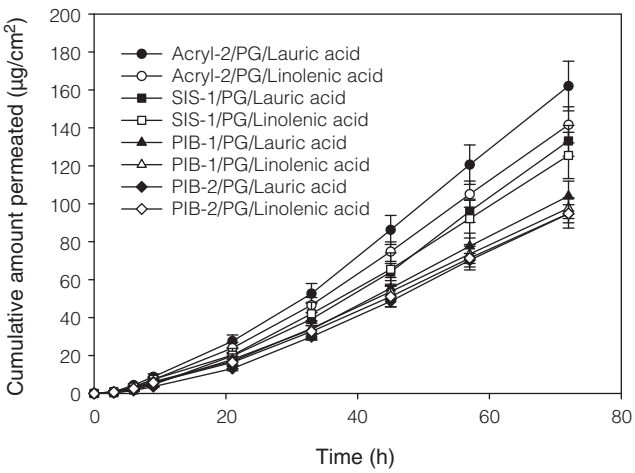

Figure 5. Effect of lauric acid or linolenic acid in different adhesives on the cumulative amount of buprenorphine permeated across nude mouse skin (mean ± SD, n = 6).

The J_{ss} of control test was found to be 1.16 ± 0.11 μg/cm^2/h and the J_{ss} of PG/glabridin was lower than that of control test. The J_{ss} of PG/menthol was found to be 2.10 ± 0.22 μg/cm^2/h and its ER was 1.81. The result suggested that menthol was also a potential enhancer and could be used in the further study.

(IV) *Formulation Optimization*

The permeation parameters were shown in Table 4 and the corresponding permeation profiles were shown in Figure 5. Comparing the J_{ss} in Table 2 and 4, it was shown that the enhancement of buprenorphine permeated was low in the PIB system containing PG/lauric acid or PG/linolenic acid although the permeation of buprenorphine was the highest in the PIB system without

any enhancer. However, the effect of enhancers on the permeation of buprenorphine in the acrylic adhesive was more remarkable than in the PIB adhesive. For example, the J_{ss} of buprenorphine in Acryl-2/PG/lauric acid (2.68 ± 0.20 μg/cm^2/h in Table 4) was higher than in Acryl-2 only (1.29 ± 0.10 μg/cm^2/h in Table 2). Further, the J_{ss} of buprenorphine in Acryl-2/PG/lauric acid was higher than in PIB-2/PG/lauric acid (1.62 ± 0.10 μg/cm^2/h in Table 4). Buprenorphine permeated across the nude mouse skin in Acryl-2/PG/lauric acid was 31.68%. The skin permeability of buprenorphine was limited because buprenorphine was a highly lipophiphic drug with high molecular weight. This led to the development of an acrylic adhesive combined with PG/lauric acid or PG/linolenic acid to deliver buprenorphine across the nude mouse skin in this study. The fatty acids including lauric acid and linolenic acid could indeed improve the skin penetration of some drugs[34-40].

CONCLUSIONS

In this study, the lipophilicity, solubility, different pH vehicles, adhesives, and permeation enhancers have been evaluated to develop the optimal trandermal formulation for buprenorphine. The results have indicated that the appropriate selections of PSA and permeation enhancers are important in the development of TDDS. The interaction between the drug and functional group of PSA should also be considered because it can affect the permeation rate of a drug. It has been demonstrated that the permeabilities of buprenorphine are higher in the PIB and SIS adhesive than in the acrylic adhesive.

Finally, an acrylic adhesive combined with PG and fatty acids as enhancers have been established to penetrate buprenorphine through the nude mouse skin. Among the tested enhancers, it is shown that the enhancement effect of lauric acid and linolenic acid are more effective than other enhancers in our study.

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