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Effect of Enhancers and Pressure Sensitive Adhesives on the Transdermal Delivery of Fentanyl

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ABSTRACT – The purpose of this study was to investigate the feasibility of developing transdermal drug delivery system (TDDS) for fentanyl used for the management of chronic cancer pain. The effect of type of pressure sensitive adhesive on the permeation of fentanyl from polyisobutylene (PIB), silicone and acrylic adhesive was evaluated. Due to the good adhesive force and relatively steady flux for 3 days, both acrylic and PIB adhesives were chosen for further study. The permeation rate of fentanyl was the highest from acrylic adhesive with hydroxyl functional group. Permeation rate increased linearly as the concentration of fentanyl in acrylic adhesive was increased from 2.5% to 10%. In case of PIB adhesive, crystals of fentanyl were developed above 5% drug load. Crovol® A40, Crovol® PK40 and Plurol oleique® provided higher flux of fentanyl.

Key words – Fentanyl, Transdermal, Pressure sensitive adhesive, Enhancer, Permeation

Approximately 60~90% of cancer patients suffer from chronic pain during the treatment period. Current anti-tumor therapies focus on the elimination of tumor proliferation along with the medication for the management of the pain.[1] To improve the quality of life, pain medication has become more necessary than before, especially for the last stage cancer patients. Fentanyl has been used for the relief of acute postoperative and chronic cancer pain.[2] The efficacy of fentanyl is known to be 100 times higher than that of morphine.[3] Despite the high efficacy, fentanyl has a short half-life and high metabolic clearance in humans.[4] To improve the bioavailability and patient compliance, transdermal drug delivery system (TDDS) was developed for fentanyl. The TDDS of fentanyl could reduce frequency of dose and maintain constant drug delivery rate. Moreover, fentanyl could be removed more easily as compared to the oral or injectable dosage form. This could be of great significance to deal with the life threatening respiratory depression observed as the side effect of fentanyl.

TDDS can be classified mainly as matrix and reservoir types. In reservoir system, drug diffuses through the rate controlling membrane. The main advantage of the reservoir system is maintenance of relatively constant delivery rate during the wear of TDDS, but any damage in the rate controlling membrane could result in dose dumping. On the other hand, in matrix system, it is difficult to maintain a constant delivery rate for extended period of time. However, matrix system is preferred to reservoir system due to simpler manufacturing method and the lower cost with greater versatility. Moreover higher patient compliance is reported after switching from reservoir to matrix system for the transdermal delivery of fentanyl.[5] This could be due to higher level of satisfaction, improved skin compatibility and better adhesive property.

The minimum effective plasma concentration for fentanyl to induce analgesia is 1~2 ng/mL, and the systemic clearance of fentanyl in humans is reported to be 50 L/h. Therefore to induce analgesia in human, input rate of 50~100 μg/h would be required.[4] The major factors determining the transdermal efficacy of drug are reported to be mobility of drug in the system, release of drug from the system and permeation of drug into the skin.[6] Based on the selected adhesive and/or enhancer, the penetration rate could be changed as adhesive can control the release of the drug,[7] and enhancer can change the permeation of drug into the skin by disturbing the lipid bilayer of the skin.[8] Moreover, enhancer can also alter the mobility and release of drug[9] by changing the solubility of the drug and property of the adhesive.[10] In this study, the effect of enhancer and adhesive on the transdermal delivery of fentanyl was investigated.

Materials and Methods

Materials

Fentanyl base was obtained from Hana Pharm. Co. (Seoul, South Korea). Polyglyceryl-3 oleate (Plurol oleique® CC497),

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Propylene glycol mono laurate (Lauroglycol®), and Polyoxy glycerate (Labrafil® 1944) were obtained from Gattefosse (Gennevillers, France). PEG sorbitan monooleate (Tween® 80), sorbitan monooleate (Span 80®), oleyl alcohol® and PEG300® were purchased from Junsei Chemicals (Osaka, Japan). PEG-12 palm kernel glycerides (Crovol® PK40) and PEG-20 almond glycerides (Crovol® A40) were obtained from Croda (Parsippany, NJ, USA). Cineole was purchased from Sigma Chemical (St. Louis. MO, USA). Acrylic pressure sensitve adhesive solutions in organic solvents and polyisobutylene were obtained from National Starch and Chemical Company (Bridgewater, NJ, USA). Silicone pressure sensitive adhesive was obtained from Dow Corning (Midland, MI, USA). All other chemicals were reagent grade or above and were used without further purification.

Preparation of adhesive matrices

Drug solution was prepared by dissolving fentanyl in ethanol. An appropriate enhancer and PSA (pressure sensitive adhesive) were added to the drug solution and stirred using teflon-coated magnetic bar. The mixture was then cast on polyester release liner coated with silicone using a casting knife. When silicone adhesive solution was used, it was cast on the release liner coated with fluropolymer. The casted film was left at room temperature for 10 min and was oven-dried at 80°C for 30 min to remove the residual organic solvents. The dried film, thus obtained, was laminated onto a backing film.

***In vitro* permeation study**

A flow-through diffusion cell system, comprising a multi channel peristaltic pump (IPC-24, Ismatec, Switzerland), a fraction collector (Retriever IV, ISCO, NE, USA), a circulating water bath (Jeio-Tech, South Korea) and flow-through diffusion cells, was used. The flow-through diffusion cell consisted of two side arms, which enabled conduction of receiver cell media from a peristaltic pump to a fraction collector. The temperature was maintained at 37°C by circulating water at constant temperature through the outer jacket of the receiver cell. The surface area of the receiver cell opening was 2 cm^2, and the cell volume was 5.5 mL.

The preparation of the hairless mouse skins, the permeability study and the data reduction method adopted has been described previously.[10] The receiver cell was filled with a pH 6.0 phosphate buffer solution and the media were stirred by teflon-coated magnetic bar to keep them well mixed. The samples were collected every 4 h for 36 h or 72 h and assayed by HPLC.

Assay

Fentanyl was analyzed by an HPLC system (Shimadzu Scientific Instruments, MD, USA), consisting of a UV detector (SPD-10A), a pump (LC-10AD) and an automatic injector (SIL-10A). The wavelength of the UV detector was 210 nm and the retention time of fentanyl was 3.1 min. Reversed-phase C8 column was used and the column temperature was maintained at 30°C by a thin foil temperature controller (CH 1445, SYSTEC Inc., MN, USA). The flow rate was 1 mL/min. The mobile phase used consisted of acetonitrile/water/phosphoric acid/triethanolamine (190/310/0.5/0.5).

***In vivo* adhesion test**

In vivo adhesion test was performed by attaching a test patch on the skin of a volunteer for 3 days. The volunteers were allowed to have normal daily activities and adhesion status of the patch was observed daily. The sample patch contained all the components except fentanyl.

Results and Discussion

Effect of adhesive matrix

To investigate the effect of adhesive on the permeation of fentanyl, TDDS was prepared using 2.5% of fentanyl in the silicone, polyisobutylene, or acrylic adhesives that are commonly used in TDDS.[11] The results are shown in Fig. 1. The highest permeation rate was obtained from silicone adhesive followed by PIB and acrylic adhesives. It is well known that the penetration rate increases proportionally with the increase in thermodynamic activity of the drug in the matrix. Maximum penetration rate is expected at saturated concentration as long as specific penetration enhancers are absent.[12] Therefore, high flux in the silicone adhesive at the early stage could be due to high thermodynamic activity of fentanyl based on the low solubility of fentanyl in silicone adhesive. In spite of extremely high initial flux from silicone adhesive, the sharp decrease in flux after 24 hr made it inappropriate to be used as matrix for 3 day system. Based on relatively constant flux of fentanyl and good adhesive force, both acrylic and PIB adhesives were selected for further study.

The acrylic adhesives produced by copolymerization of monomer can be classified by the functional group of the monomer.[11] Fig. 2 shows the effect of functional group of the acrylic adhesives on the permeation rate of fentanyl. Permeation rate of fentanyl from the acrylic adhesive matrix was in following order: acrylic adhesive with hydroxyl functional group>without functional group>with carboxyl functional group. The lowest permeation rate obtained from acrylic adhe-

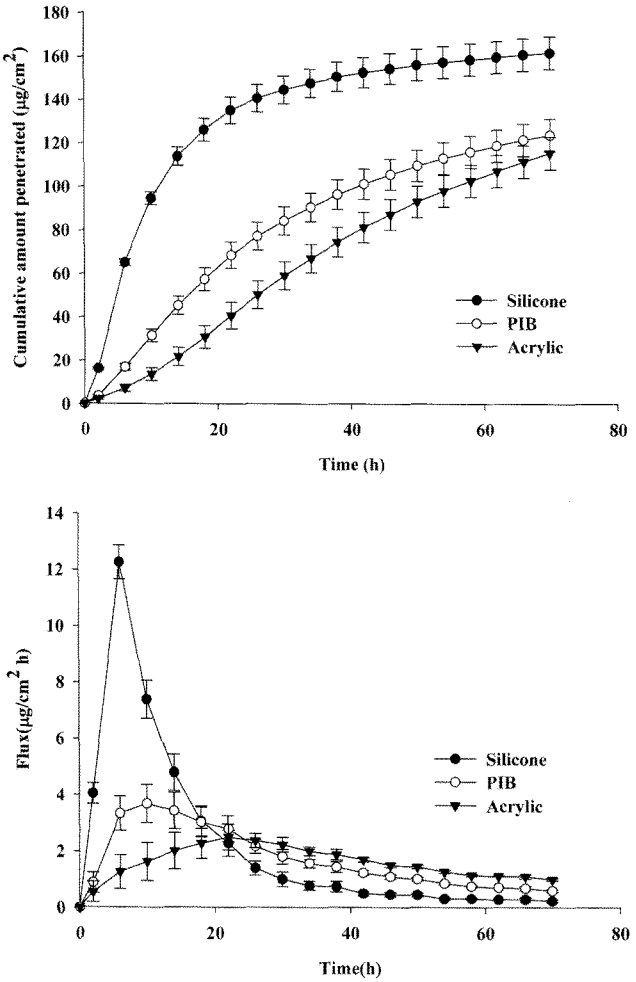

Figure 1—Effect of the type of pressure sensitive adhesive on the permeation of fentanyl with 2.5% drug loading. Each point represents average of three measurements.

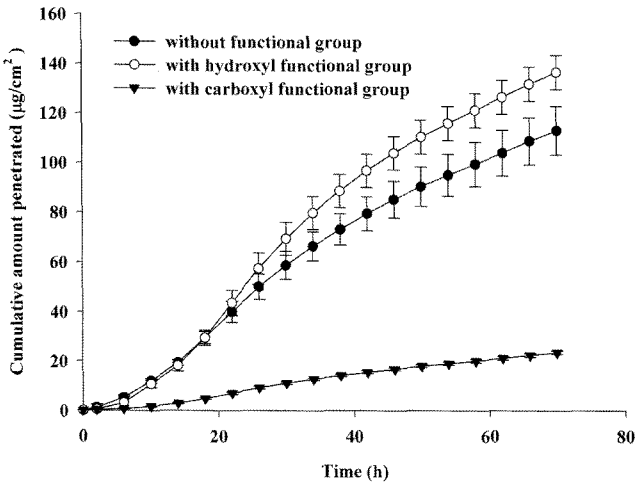

Figure 2—Effect of functional group of the acrylic adhesives (carboxyl, hydroxyl, and no functional group) on the permeation of fentanyl with 2.5% drug loading. Each point represents average of three measurements.

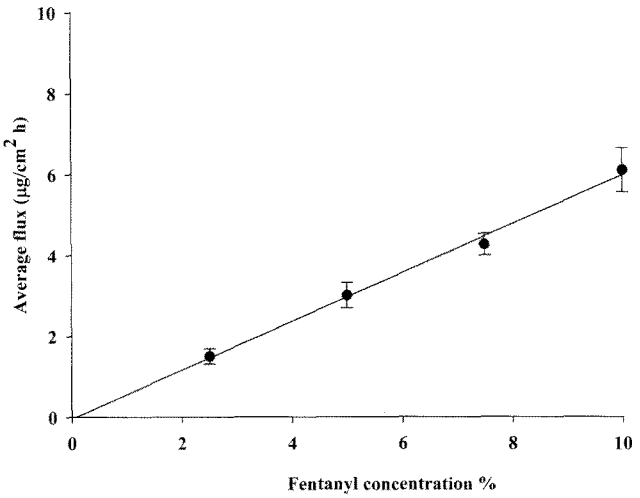

Figure 3—Effect of fentanyl concentration on the permeation of fentanyl across hairless mouse skin from acrylic adhesive matrix with hydroxyl functional group. The thickness of the matrix was fixed at 65 μm. Each point represents average of three measurements.

sive with carboxyl functional group was due to the interaction of carboxyl functional group with the amine group of fentanyl. The lowest permeation rate of tacrine due to the interaction between the amine group of tacrine and carboxyl group of acrylic adhesive has been reported previously.[13]

Effect of drug concentration

The effects of drug concentration in the matrix and the thickness of the matrix on the permeation rate of fentanyl were investigated to optimize the system. Fig. 3 shows the effect of fentanyl concentration in the acrylic adhesive matrix with the fixed matrix thickness of 65 μm on the permeation rate of fentanyl across the hairless mouse skin. The penetration rate of fentanyl increased as the concentration of fentanyl in the matrix increased. Linear correlation was observed between concentration of fentanyl and the average flux across the skin (R^2=0.997). Fig. 4 shows the effect of acrylic adhesive matrix thickness with fixed amount of fentanyl per unit area (365 μg/cm^2) on the permeation rate of fentanyl. The concentration of fentanyl in the matrix will be diluted as the thickness of matrix increased. As can be seen in Fig. 4, the average flux decreased linearly with the increase in the thickness from 40 μm to 160 μm (R^2= 0.993). The results indicated that the average flux could be modulated in a predictable manner by changing drug concentration and/or thickness of the matrix.

TDDS based on PIB adhesive was also formulated with drug concentration ranging from 2.5% to 10%. However, crystals of fentanyl were observed above 5% drug load. Due to the crystallization of fentanyl in the PIB matrix, the effect of drug concentration in the PIB matrix could not be evaluated.

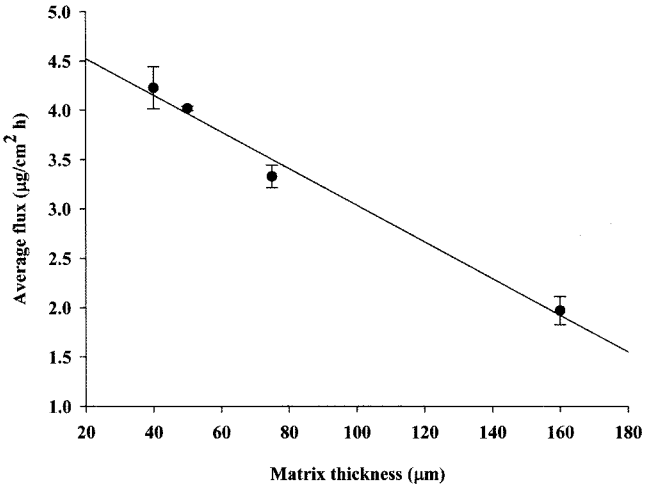

Figure 4–Effect of matrix thickness on the permeation of fentanyl across hairless mouse skin from acrylic adhesive matrix with fixed amount of fentanyl loaded per unit area at 365.5 μg/cm^2. Each point represents average of three measurements.

Effect of enhancer

Different approaches, such as the use of chemical enhancers, iontophoresis, electroporation, ultrasound and chemical modification of a poorly penetrating drug can be applied to improve transdermal drug delivery.[14] Enhancers are known to alter properties of stratum corneum allowing better penetration of drug through the epidermis.[15] To investigate the effect of enhancers on the permeation rate of fentanyl across hairless mouse skin, various enhancers were added into the acrylic adhesive matrix with hydroxyl functional group. Each enhancer was used at 5% with 2.5% of fentanyl loading. The enhancement effects (EE) of tested enhancers are summarized in Table I. The observed order of EE on the permeation of fentanyl was: Plurol oleique® > Crovol® A40 > Crovol® PK40 by 2.25, 1.68 and 1.60 fold, respectively. The other enhancers did

Table I–*Enhancement Effect of Various Enhancers on the Permeation of Fentanyl Across Hairless Mouse Skin from Acrylic Adhesive (n = 3, mean ± S.D.)*

Enhancer	Enhancement effect*
Plurol oleique®	2.25 ± 0.36
Lauroglycol®	1.03 ± 0.31
Labrafil®	1.05 ± 0.28
Crovol® PK40	1.60 ± 0.47
Crovol® A40	1.68 ± 0.50
Oleyl alcohol	1.00 ± 0.12
PEG 300	0.83 ± 0.21
Cineole	0.99 ± 0.28
Span® 80	0.99 ± 0.04
Tween® 80	1.03 ± 0.1

*:Enhancement effect = $\frac{\text{Flux in the presence of enhancer}}{\text{Flux in the absence of enhancer}}$

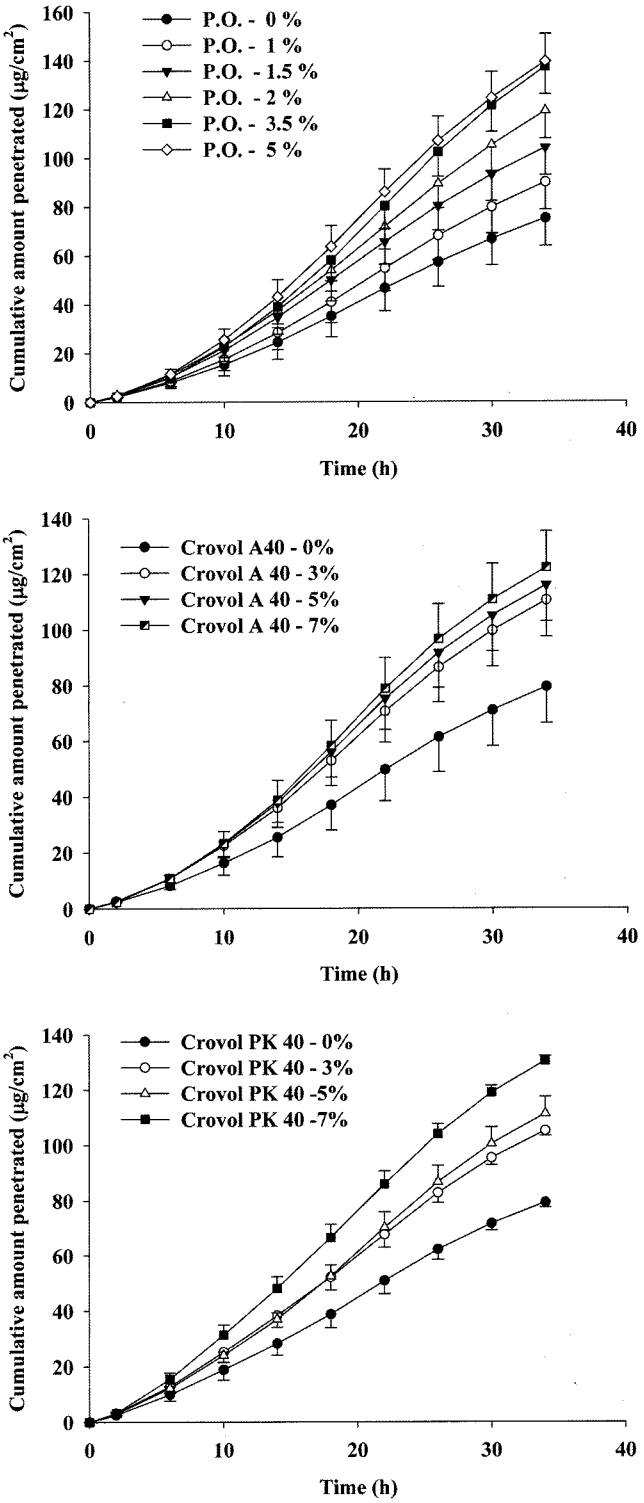

Figure 5–Effect of the enhancer concentration on the permeation of fentanyl (2.5%) across hairless mouse skin from acrylic adhesive. Each point represents average of three measurements.

not show significant EE. The enhancers that show significant enhancing effect were chosen and the effects of their concentration in the matrix on the permeation rate of fentanyl were evaluated. Fig. 5 shows the effect of enhancer concentration on the permeation of fentanyl across hairless mouse skin from acrylic adhesive with hydroxyl functional group. Different concentrations of each enhancer were added to the acrylic adhesive along with 2.5% of fentanyl. In each case, permeation rate was found to be concentration dependent. However, to achieve appropriate adhesion force, the level of enhancer had to be reduced to a certain point depending on the enhancer used. Some of the enhancers may act as a plasticizer of a pressure sensitive adhesive and some may decrease adhesive force. The maximum amount of enhancer that can be used in the matrix should be determined after evaluating adhesive and cohesive force of the pressure sensitive adhesive matrix. Excessive plasticization would cause cold flow during the wear of TDDS and reduced adhesive force would cause peeling off of TDDS from the skin. For instance, Plurol oleique® was restricted to low level due to sharp reduction in adhesion force after incorporating it in the adhesive matrix. Therefore, both the permeation and adhesion force should be considered in the design of TDDS[16]. In vivo adhesion force of 4 cm^2 patch was evaluated with various concentrations of enhancers for 3 days. It was observed that the maximum concentration of Plurol oleique®, Crovol® PK40 and Crovol® A40 in the matrix to withstand application period of 3 days was 2%, 5% and 3%, respectively.

The target delivery rate for transdermal administration of fentanyl, with the patch size of 10 cm^2, is reported to be above 5.0 μg/cm^2/hr.[4] To obtain the required flux, the amount of fentanyl was increased to 10% of the matrix and the effects of Plurol oleique®, Crovol® PK40 and Crovol® A40 at the concentration of 2%, 5% and 3%, respectively, on the permeation rate of fentanyl were evaluated (Fig. 6 and Table II). The results indicate that the systems developed in this study could be used to induce appropriate analgesia. However, in vivo studies are required to evaluate bioavailability of fentanyl in human.

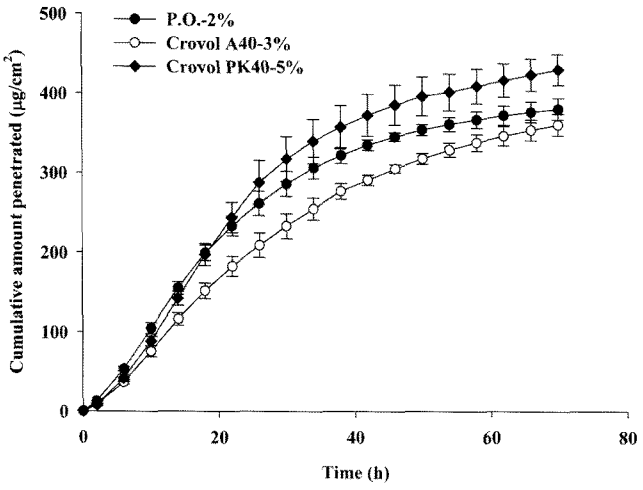

Figure 6–The permeation profile of fentanyl from acrylic adhesive containing 2% Plurol oleique®, 5% Crovol PK40®, or 3% CrovolA40®. The amount of fentanyl loaded was 10% of the weight of pressure sensitive adhesive matrix. Each point represents average of three measurements.

Table II–*The Effect of 2% Plurol Oleique®, 5% Crovol® PK40, and 3% Crovol® A40 on the Flux of Fentanyl (10%) from Acrylic Adhesive (n=3, mean ± S.D.)*

Enhancer	Enhancer concentration	Average flux (μg/cm^2h) 0~72 h
Plurol oleique®	2%	5.41 ± 0.06
Crovol® A40	3%	5.04 ± 0.18
Crovol® PK40	5%	5.77 ± 0.27

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