Effects of pressure sensitive adhesives and chemical permeation enhancers on the permeability of fentanyl through excised rat skin

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Drug-in-adhesive patches (DIAPs) of fentanyl were formulated using various pressure sensitive adhesives (PSAs) and various chemical permeation enhancers (CPEs). The effects of PSAs and CPEs on skin permeation of fentanyl from DIAPs were evaluated using modified jacketed Franz diffusion cells fitted with excised rat abdominal skin. It was demonstrated that the permeation rate or steady state flux ($J_{ss}$) of the drug through the excised rat skin was dependent on the viscosity and type of acrylic PSA as well as the type of CPE. Among different acrylic PSAs, Duro-Tak® 2054 and Duro-Tak® 2516 showed the highest $J_{ss}$ of 1.95 μg cm⁻² h⁻¹ and the lowest $J_{ss}$ of 1.43 μg cm⁻² h⁻¹, respectively. Among the various CPEs used, propylene glycol and polyethylene glycol 400 showed 1.61 and 1.18, the highest and the lowest enhancement ratios (ER) of the skin permeation of fentanyl, respectively. Oleic acid and cetyl alcohol moderately increased the skin permeation of fentanyl. It was also shown that increasing the concentration of CPE led to reduction in the adhesion property of PSA as measured by the 180° peeling strength test. Moreover, it was found that the permeation rate increased as the fentanyl loading increased from 1 to 3%. The skin permeation rate of fentanyl did not increase significantly beyond 3% drug loading. It was concluded that propylene glycol as a CPE and cosolvent in 10% (m/m) with 3% fentanyl loading in Duro-Tak 2054 showed an effective monolithic DIAP for the development of a transdermal therapeutic system for fentanyl.

Keywords: fentanyl, permeation enhancer, transdermal patches, pressure sensitive adhesive, rat skin

Transdermal drug delivery system (TDDS) may offer an attractive alternative for the delivery of drugs because it avoids the problems of gastrointestinal intolerance, reduces the first-pass liver metabolism and eliminates the need for intravenous access (1).

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Transdermal delivery of fentanyl provides the ease of application for patients suffering chronic and post-operative pains. Fentanyl is a narcotic analgesic that predominately interacts with the opioid µ-receptor (2).

The transdermal delivery of drugs depends on their permeability through stratum corneum (3). There are four strengths of fentanyl transdermal patches on the market (Duragesic®). Their average flux is 2.5 µg cm⁻² h⁻¹. Therefore, this minimum flux should be obtained during the development of fentanyl TDDS. Many approaches have been proposed to overcome the low permeability of drugs through the skin. Chemical permeation enhancers (CPEs) are used to promote transdermal delivery of drugs that are insufficiently permeable via skin. Typical CPEs include high-boiling alcohols, diols, fatty acid esters, oleic acid, sulphoxides, terpenes, surfactants, cyclodextrine and water (4, 5). They can modify the skin structure and/or make channels in the skin barrier to facilitate drug transport via skin (6, 7). The CPE type has a significant influence on the development of TDDS. Appropriate type and the proper amount of a CPE for a TDDS containing a specific drug can only be selected by trial and error (8).

All TDDS include a pressure sensitive adhesive (PSA) layer to hold the patch on the skin. PSAs are materials that adhere to a substrate by application of light force and leave no residue when removed. Choosing a suitable PSA for a TDDS is not simple because several requirements should be met. These requirements include no skin irritation or sensitization, no residue when peeled off from skin and easy removal from skin without causing pain. Among the three types of PSAs (polyisobutylene, silicones and acrylic copolymers) acrylic PSAs have several desirable features, such as resistance to oxidation and thermal degradation, permeability for water vapor and oxygen, good tack behavior and moderate cost (9–11). The PSA adhesive properties in a TDDS depend on the CPE type and concentration. Several physical tests measure the adhesive properties of TDDS, e.g., 180° peel strength (12–14).

The present investigation was carried out to study the effects of various acrylic PSAs and CPEs on in vitro permeability of fentanyl across excised rat abdominal skin in order to select suitable drug-in-adhesive patches (DIAP) for use in the development of fentanyl TDDS. Different permeation parameters such as lag time ($T_L$), steady state flux ($J_{ss}$) and enhancement ratio (ER) were calculated to find the highest permeation rate and the lowest lag time of fentanyl penetration through stratum corneum.

**EXPERIMENTAL**

**Materials and methods**

Micronized fentanyl base was purchased from Diosynth (The Netherlands). Oleic acid (OA), cetyl alcohol (CA), propylene glycol (PG), polyethylene glycol 400 (PEG 400) and HPLC grade methanol and acetonitrile were obtained from Merck (Germany). Duro-Tak® (2054, 2051 and 2516) and Acronal® acrylic copolymers were gifts from the National Starch and Chemical (USA) and BASF (Germany), respectively. These PSAs are acrylate-vinylacetate copolymers and non-curing pressure sensitive adhesives supplied in an organic solvent solution. All other chemicals and solvents used in this study were of analytical grade. Cotran™ 9720 (75 µm, polyethylene) backing layer and Scotchpak™ 1022 release liner (also known as peeling or protective liner) were donated by 3M (USA).
**Preparation of DIAPs**

DIAPs were prepared by using a quadruple laboratory film applicator with a lateral guide plate and four thickness choices, 90, 170, 250 and 500 µm with 90 mm gap width (Sandberg & Schneidewind, Germany). The PSAs and CPEs used in the preparation of fentanyl DIAPs are listed in Tables I and II, respectively. The DIAPs were made of a flexible backing, a PSA containing fentanyl and a release liner. The accurate amount of drug was weighed and dissolved in acetone; CPE and PSA solution were added to the fentanyl solution and mixed with a magnetic stirrer (IKA, Germany) for 20 min. The concentration of each CPE was initially set at 5% of the total mass of the patch. The mixture was then poured into the trough of the film applicator and spread on the Scotchpak® 1022 release liner at a constant rate of about 1 mm in–1 at a constant wet thickness of 500 µm. The films were dried in an oven at 60 °C for 15 min and then cut into predetermined sizes. The dried film with a thickness of about 150 µm was laminated with Cotran® backing. Prepared DIAPs were packed in opaque, white heat-sealed pouches (15).

**Table I. Permeation parameters of fentanyl through excised rat skin from drug-in-adhesive patches prepared using various acrylic pressure sensitive adhesives**

<table>
<thead>
<tr>
<th>DIAP</th>
<th>Permeation parametera</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( J_{ss} ) (µg cm(^{-2}) h(^{-1}))</td>
</tr>
<tr>
<td>Duro-Tak® 2054</td>
<td>1.95 ± 0.10</td>
</tr>
<tr>
<td>Acronal® V210</td>
<td>1.71 ± 0.11</td>
</tr>
<tr>
<td>Duro-Tak® 2051</td>
<td>1.60 ± 0.09</td>
</tr>
<tr>
<td>Duro-Tak® 2516</td>
<td>1.43 ± 0.06</td>
</tr>
</tbody>
</table>

\( J_{ss} \) – steady state flux, \( T_L \) – lag time, DIAP – drug-in-adhesive patch, PSA – pressure sensitive adhesive

**Table II. Enhancement ratio values and permeation parameters for four different chemical permeation enhancers and the corresponding ratios of lag times**

<table>
<thead>
<tr>
<th>CPE (5%)</th>
<th>Permeation parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( J_{ss} ) (µg cm(^{-2}) h(^{-1}))a</td>
</tr>
<tr>
<td>PG</td>
<td>2.86 ± 0.15</td>
</tr>
<tr>
<td>OA</td>
<td>2.44 ± 0.19</td>
</tr>
<tr>
<td>CA</td>
<td>2.24 ± 0.12</td>
</tr>
<tr>
<td>PEG</td>
<td>2.32 ± 0.14</td>
</tr>
</tbody>
</table>

a Mean ± SD, \( n \) = 3.

CPE – chemical permeation enhancer, ER – enhancement ratio, \( J_{ss} \), \( T_L \), \( K_p \) and ER denote the steady state flux, lag time, permeation coefficient and enhancement ratio, respectively. \( T_L \) ratio is the quotient of lag time of transdermal patch with CPE to the lag time of the formulation without CPE. PG, OA, CA and PEG denote propylene glycol, oleic acid, cetyl alcohol and polyethylene glycol, respectively.
Measurement of fentanyl skin permeation

**Preparation of rat abdominal skin.** – Male Sprague-Dawley rats (150–200 g) obtained from the animal house of the Faculty of Pharmacy (Tehran, Iran) were sacrificed using diethyl ether asphyxiation. Hair of the abdominal region was carefully removed and a 5 cm × 6 cm full-thickness skin was excised from this region from each sacrificed rat. Subcutaneous fat was carefully removed with a scalpel. Excised rat skins were dipped and soaked in a saline normal solution at ambient temperature and transferred for the *in vitro* skin permeation study within 3–4 hours.

Permission for the experiment was given by the Ethics Committee of the Tehran University of Medical Sciences.

**In vitro permeation studies.** – Permeation investigation was carried out using excised rat abdominal skin in a modified jacketed Franz diffusion cell with a 1.2 cm² effective diffusion area. Receptor compartment of the diffusion cell was completely filled with 5.6 mL of filtered and degassed phosphate buffer solution (PBS), pH 7.2, as receiver medium. Excess water was removed from the surface of the skin by gentle rubbing with lint-free tissue paper. The DIAP was applied to the epidermal side of the rat skin with slight pressure and then mounted over the receptor compartment. The O-ring and donor chamber with a pre-greased flange were placed over the DIAP. Any air bubbles that remained in the receptor compartment and below the skin were carefully removed by gentle tilting of the diffusion cell. The receptor medium was stirred by a magnetic stirrer (IKA, Germany) and the temperature was maintained at 32 ± 0.5 °C using a thermostatic water pump bath (Brookfield, TC-101, USA). To maintain the sink condition throughout the experiments, at predetermined time intervals (2, 4, 8, 12, 24, 32, 48 and 72 h) the receptor medium was completely withdrawn from the receptor compartment and replaced with fresh PBS.

The concentration of fentanyl was determined at each sampling by a fully-validated HPLC method (16) and the cumulative amount of fentanyl was calculated.

**HPLC analysis of fentanyl.** – Quantitative determination of fentanyl was performed by High Performance Liquid Chromatograph (Waters 486, USA). Chromatographic separation was performed on a C₁₈, 250 × 4.6 mm, 5 μm, column (Capital, UK). A similar guard column was used to prevent obstruction by minute particles. The mobile phase consisted of 40 volumes of ammonium acetate solution (1%) and 60 volumes of a mixture of methanol, acetonitril, and glacial acetic acid (400:600:0.6). The mobile phase pH was adjusted to 6.6 ± 0.1 by drop-wise addition of glacial acetic acid. The elute was monitored at 230 nm and the retention time of fentanyl and the mobile phase flow rate were 4.2 minutes and 2 mL min⁻¹, respectively (16).

**Evaluation of adhesive properties.** – The adhesive strength of the DIAPs was determined using an adhesion/release apparatus (Cheminstruments, AR 1000, USA) and by applying the 180° peel test according to the American Standard Test Methods (ASTM). The objective of the 180° peel test is to determine the peel force, in cN per cm, needed to remove the TDDS from the release liner using a 180° peel angle at a constant peel rate of 15.2 cm min⁻¹. DIAP samples were prepared as ribbons of 25 mm width and 305 mm length (12, 14, 17).
Data analysis

Cumulative amounts of fentanyl that permeated through excised rat skin were plotted as a function of time. Steady state flux was expressed as the slope of the linear portion of the resulting permeation profile \( (J_{ss}, \mu g \text{ cm}^{-2} \text{ h}^{-1}) \) by regression analysis. Lag time \( (T_L, \text{ h}) \) was determined by extrapolating the linear portion of the permeation profile to the x-axis \((18, 19)\).

The permeability coefficient \( (K_p) \) was calculated using the following equation \((4)\):

\[
K_p = \frac{J_{ss}}{c_v}
\]

where \(J_{ss}\) is the steady state flux and \(c_v\) is the initial concentration of fentanyl in the donor compartment. The penetration enhancing effect of the CPE was calculated in terms of enhancement ratio \( (ER) \) using the following equation \((20)\):

\[
ER = \frac{K_{p,CPE}}{K_p}
\]

Statistics

All skin permeation experiments were repeated three times, and their mean values are presented with the corresponding standard deviations. Student’s \(t\)-test was performed to find the significant difference, if any, in the permeation rate between the DIAP containing CPE and enhancer-free formulations (control).

RESULTS AND DISCUSSION

Selection of receptor medium

According to our results, the solubility of fentanyl at 32 °C in water and PBS, pH 7.2, was 95 and 731 µg mL\(^{-1}\), respectively. Thus, PBS can be a suitable receptor medium, because the loading of fentanyl in DIAP is 4.5 mg per 10 cm\(^2\), so the amount of fentanyl in the effective area of the diffusion cell (1.2 cm\(^2\)) is less than the amount required to exceed the sink condition. On the other hand, it was found that the solubility of fentanyl in water containing 5% methanol and sodium lauryl sulfate 1% solution in water is much more than the sink condition. It may lead to loss of the discriminative property of dissolution medium \((15)\).

Rat skin permeation parameters

*Influence of various PSAs on skin permeation.* – The skin permeation rate of fentanyl through excised rat abdominal skin from different DIAPs prepared with various acrylic
PSAs was determined. The permeation profiles of fentanyl are shown in Fig. 1a. Permeation parameters, including the permeation rate or steady state flux ($J_{ss}$) and lag time ($T_L$), were calculated from the profiles and are presented in Table I. The permeation rates of fentanyl from DIAPs through rat skin were in the range 1.43–1.95 µg cm$^{-2}$ h$^{-1}$. Among four different PSAs used in this study, Duro-Tak® 2054 resulted in the highest skin permeation rate of fentanyl (1.95 µg cm$^{-2}$ h$^{-1}$), while Duro-Tak® 2516 showed the lowest permeation rate (1.43 µg cm$^{-2}$ h$^{-1}$). These results may be explained by the viscosity and the amount of solid content. According to the manufacturer’s leaflet, the viscosities of Duro-Tak® 2054 and Duro-Tak® 2516 are 2275 and 4350 mPa s, respectively. Also, there were significant differences in the lag time between the PSAs, ranging from 6.7 to 10.2 h ($p < 0.05$). Subsequently, Duro-Tak® 2054 was used in further development of the fentanyl DIAP, because it revealed the highest steady state flux and the shortest lag time, which are essential for getting an appropriate therapeutical effect of fentanyl.

Influence of fentanyl loading in the acrylic PSA on skin permeation. – The permeation rate increased as the drug loading increased from 1 to 3%. From Fig. 2 it is clear that the
skin permeation rate of fentanyl did not increase significantly beyond 3% drug loading. The results suggested that drug loading in the acrylic PSA had reached maximum diffusion of molecules through their matrix and transport of fentanyl through rat skin beyond 3% and it was limited by dissolution of an excess of dispersed drug crystals in the acrylic PSA.

**Influence of CPEs on skin permeation.** – Incorporation of CPEs in the DIAP was essential for increasing the permeation rate of fentanyl from the patches. In this study, two lipophilic and two hydrophilic CPEs were selected and their effects on the permeation of fentanyl from DIAPs prepared with Duro-Tak 2054 (which in our previous study showed the highest permeation rate, data not shown) through excised rat skin were investigated at a preliminary concentration of 5%. The skin permeation profiles of the drug from the DIAPs are shown in Fig. 1b. The permeation parameters calculated from the obtained profiles are presented in Table II.

Among the various CPEs used, PG showed the highest enhancing effect for fentanyl. The mechanism of action of various CPEs may be attributed to their activity on lipophilic matrix and/or hydrophilic protein gel in stratum corneum (18). CPEs act through interaction with intercellular lipids, leading to disruption of their organization and increasing their fluidity. Some of them also interact with intercellular protein, keratin denaturation (e.g., oleic acid), while PG acts by both mechanisms (5). These last enhancement mechanisms are consistent with the findings obtained in our experiments. On the other hand, OA, CA and PEG 400 moderately increased the skin permeation of fentanyl. There are no significant differences between their $J_{ss}$, but their differences are significant compared to PG.

Incorporation of PG into the acrylic PSA matrix significantly enhanced the permeation rate and shortened the $T_L$ of fentanyl. In conclusion, the maximum $I_{ss}$ obtained from DIAP prepared with Duro-Tak 2054 and 5% PG was 2.86 µg cm$^{-2}$ h$^{-1}$. Among these CPEs, the lag time was predominately reduced by two lipophilic enhancers, OA and CA. This phenomenon may be explained by the lipophilic characteristics of both of them. Thus, they can cause more disruption of the lipid matrix of stratum corneum and faster penetration of fentanyl through skin.
The enhancing effects of PG and OA were further evaluated at 10% and 15% concentrations in the DIAPs prepared with Duro-Tak 2054 (Table III). The permeation rates at three concentrations of PG and OA, calculated from the permeation profiles, are shown in Fig. 3. The permeation rate reached a plateau for OA and PG at the level of 5 and 10%, respectively. It showed that the aforementioned concentrations of OA and PG are the optimal concentrations for enhancing the permeation of fentanyl. The steady state flux ($J_{ss}$) obtained from DIAP prepared with Duro-Tak 2054 and 10% PG and 5% OA were 3.16 and 2.48 $\mu$g cm$^{-2}$ h$^{-1}$, respectively.

Although the addition of 15% PG or 10% OA did not further increase the $J_{ss}$ of fentanyl, it reduced the lag time. It should be noted that the excessive or inappropriate usage of CPEs may lead to loss of the PSA’s mechanical properties (10). In Table III, it is shown that the adhesive property as measured by the 180° peeling test was reduced by increasing the CPE concentration. As mentioned, OA significantly decreased the lag time

![Graph](image.png)

**Fig. 3.** Effects of the concentration of propylene glycol and oleic acid on the permeation rate of fentanyl through excised rat skin: ▲ – propylene glycol, ■ – oleic acid. Each value is a mean of three tests with the corresponding SD.

**Table III. Effects of CPE concentration on the lag time and adhesion strength of PSA**

<table>
<thead>
<tr>
<th>CPE concentration (% m/m)</th>
<th>$J_{ss}$ (µg cm$^{-2}$ h$^{-1}$)$^{a}$</th>
<th>Peeling strength (cN cm$^{-1}$)$^{a}$</th>
<th>$T_L$ (h)$^{a}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PG</td>
<td>OA</td>
<td>PG</td>
</tr>
<tr>
<td>0</td>
<td>1.95 ± 0.10</td>
<td>425 ± 27</td>
<td>6.7 ± 0.4</td>
</tr>
<tr>
<td>5</td>
<td>2.86 ± 0.15</td>
<td>2.44 ± 0.19</td>
<td>365 ± 22</td>
</tr>
<tr>
<td>10</td>
<td>3.16 ± 0.28</td>
<td>2.48 ± 0.17</td>
<td>307 ± 31</td>
</tr>
<tr>
<td>15</td>
<td>3.05 ± 0.24</td>
<td>2.39 ± 0.21</td>
<td>253 ± 12</td>
</tr>
</tbody>
</table>

$^{a}$ Mean ± SD, $n$ = 3.

(Table III); another reason for this observation is further loss the adhesion property of PSA by OA. It is noticeable that the peeling strength less than 300 cN cm\(^{-1}\) may lead to poor adhesion (21).

**CONCLUSIONS**

The permeation rate of fentanyl in Duro-Tak\textsuperscript{®} 2054 was the highest among the four PSAs examined. It was clearly demonstrated that PG showed the highest steady state flux among four the chemical permeation enhancers tested. On the other hand, it was found that the skin flux of fentanyl increased as the drug loading in the acrylic PSA increased from 1 to 3\%, and reached a plateau beyond 3\% drug loading.

In summary, the results indicate that the use of PG as CPE and cosolvent (10\%, m/m) with 3\% fentanyl loading in Duro-Tak 2054 is an effective monolithic DIAP for the development of a transdermal therapeutic system for fentanyl. As mentioned, increasing the concentration of PG as CPE led to improvement of \(J_{ss}\) but decreased the adhesion strength. This defect may be explained by excessive plasticizing of PSA resulting in poor adhesion (22). This research work showed that the PSAs that are commonly used in TDDS are not tolerant to enhancers.

The maximum \(J_{ss}\) (3.16 \(\mu g\) cm\(^{-2}\) h\(^{-1}\)) obtained from DIAP prepared with acrylic PSA seemed to be high enough to achieve therapeutic effects. Lag time was decreased to around 3 h by selecting the 10\% PG as CPE and Duro-Tak 2054 as PSA.

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**REFERENCES**


**SAŽETAK**

**Učinci adheziva osjetljivih na tlak i kemijskih promotora na permeaciju fentanila kroz kožu štakora**

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Pripravljeni su transdermalni adhezivni flasteri fentanila (DIAPs) koristeći različite adhezive osjetljivih na tlak (PSAs) i kemijske promotore permeabilnosti (CPEs). Njihovi učinci na permeabilnost fentanila evaluirani su pomoću modificirane Franzove difuzijske čelije s membranom od kože s abdomena štakora. Brzina permeacije ($J_{ss}$) ovisi o viskoznosti i vrsti akrilnih adheziva i o vrsti promotora. Najveća vrijednost $J_{ss} = 1,95 \mu g \, cm^{-2} \, h^{-1}$ postignuta je s Duro-Tak® 2054, a najmanja ($J_{ss} = 1,43 \mu g \, cm^{-2} \, h^{-1}$) s Duro-Tak® 2516. Među različitim promotorima propilen glikol i polietilen glikol 400 pokazali su najveći (1,61) i najmanji (1,18) omjer poboljšanja (ER) permeabilnosti. Oleinska kiselina i cetil alkohol umjereno su povećali permeabilnost fentanila. Za mjerenje adhezivnih svoj-
stava upotrebljena je »metoda ljuštenja«. Povećanje koncentracije CPE smanjilo je adhezivna svojstva PSA. Kada je udio fentanila u flasteru povišen s 1 na 3%, brzina permeacije se povećala, dok daljnine povećanje udjela fentanila nije značajno utjecalo na brzinu. Pripravak s 10% propilena glikola i 3% fentanila u Duro-Tak 2054 pokazao se kao učinkoviti transdermalni terapijski sustav za fentanil.

**Ključne riječi:** fentanil, promotor permeabilnosti, transdermalni flasteri, adhezivi osjetljivi na tlak, koža štakora

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