Formulation and in Vitro Evaluation of Pentazocine Transdermal Delivery System

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The aim of this study was to prepare a pentazocine (PTZ) matrix-type transdermal drug delivery system (TDDS) using acrylic pressure-sensitive adhesives. Among the five Duro-Tak® adhesive polymers tested (87-9301, 87-2677, 87-201A, 87-2196, 87-2852), in vitro dissolution studies demonstrated the highest PTZ release flux from the Duro-Tak® 87-9301 matrix. In addition, the effects of permeation enhancers, isopropyl myristate (IPM) and glyceryl monocaprylate (GEFA-C8), and drug content on PTZ skin permeation from prepared patches were evaluated using Franz diffusion cells fitted with hairless mouse skin. IPM and GEFA-C8 were found to produce effective flux of PTZ at a patch concentration of 10% w/w and 5% w/w, respectively. The PTZ flux increased linearly as the loading dose increased up to 30%, whereas no further increase in flux was observed at loading doses of 40% and 50% due to drug crystallization in the matrix. Thus, the highest skin permeation rate (24.2 μg/cm²/h) was achieved when 30% of PTZ was loaded in Duro-Tak® 87-9301 with 10% IPM and 5% GEFA-C8. These results demonstrate the feasibility of a novel narcotic-antagonist analgesic matrix-type TDDS for PTZ.

Key words pentazocine; isopropyl myristate; glyceryl monocaprylate; transdermal; adhesive

Pentazocine (PTZ), a narcotic-antagonist analgesic, has been widely used in the management of patients with postoperative pain or initial carcinogenic pain. However, PTZ has a number of severe drawbacks, such as a short half-life of 2 to 3 h,1) and low oral bioavailability of about 20% due to an extensive first-pass effect, thus leading to wastage of the dose.2)

A transdermal drug delivery system (TDDS) has many advantages over conventional modes of drug administration, in particular the avoidance of hepatic fast-pass metabolism, a reduction in the frequency of drug administration, and an improvement of patient compliance.3) Thus, transdermal administration is a potential approach to overcoming these problems with PTZ treatment. A TDDS consists of several components, including the active ingredient, a pressure-sensitive adhesive (PSA), a permeation enhancer, backing membrane and so on. A PSA fulfills the adhesion-to-skin function and serves as the formulation foundation. Because the physiochemical properties of PSA significantly affect the permeation rate of a drug across the skin, the selection of an appropriate PSA matrix is of importance in designing a TDDS.4,5) Permeation enhancers can overcome the intrinsic resistance of the stratum corneum, which results in an increase in the flux of the active ingredient.6,7)

We have previously reported the effects of glyceryl monocaprylate (GEFA-C8) as an enhancer of skin permeation of PTZ from isopropyl myristate (IPM) solution across excised hairless mouse skins.8,9) The PTZ flux was about four times greater with a combination of both GEFA-C8 and IPM, than with IPM alone.

In the present study, therefore, we tried to design a monolithic adhesive matrix-type patch, which is the simplest among the various patches used in the present study. PTZ patches were prepared using different polyacrylate copolymers, and both IPM and GEFA-C8 were incorporated in the patch. First, the effect of different PSAs on the release rate of PTZ from TDDS patches was investigated using a shaking method. We also evaluated the effect of IPM and GEFA-C8 on the PTZ flux from TDDS patches using Franz diffusion cells fitted with excised hairless mouse skin.

MATERIALS AND METHODS

Materials PTZ was purchased from Kobayashi Kako Co., Ltd. (Fukuji, Japan). Isopropyl myristate (IPM) was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Glyceryl monocaprylate (GEFA-C8, Sunsoft® 700P-2) was gifted from Taiyo Kagaku Co., Ltd. (Mie, Japan). Acrylic PSA solutions in organic solvents, Duro-Tak® 87-9301, 87-2677, 87-201A, 87-2196 and 87-2852 were kindly gifted from the National Starch and Chemical Company (Bridgewater, NJ, U.S.A.). All other solvents and reagents were commercial products of analytical grade and were used without further purification.

Preparation of Patches Preparation of patches was carried out by a minor modification of the method of Buchi et al.9) Appropriate amounts of the adhesive PTZ and enhancers were mixed and sonicated. The mixed PSA solution was cast at a thickness of 200 μm on the backing membrane (Scotchpak™ 9732, 3M, MN, U.S.A.) with a film applicator (MULTICATOR™ 411, Erichsen GmbH & Co., KG, Hemer, Germany), and kept in an oven at 60°C for 20 min, to remove any residual solvent.10) The dried film was then laminated with a release liner (Scotchpak™ 1022 Release Liner, 3M, MN, U.S.A.) for protection. The resulting three-layered sheets were stored at room temperature for 24 h, and used to die-cut a circular patch of 1.13 cm² (diameter 12 mm) before each experiment.

In Vitro Drug Release Studies Drug release from the patches was characterized by using the shaking flask method. A piece of PTZ, 12 mm in diameter, was then removed from a release liner and stuck on the stainless steel mesh (mesh size #20, 2×2.5 cm²), and then introduced into a 15 ml PBS (pH 7.4) polypropylene tube with a cap. The tube was fixed on the sample holder in a thermostatically regulated water bath (SB-35, Tokyo Rikakiki Co., Ltd., Tokyo, Japan), maintained at 32°C, and shaken at 50 strokes/min. Samples (1 ml) were collected at different time intervals for 120 min. Volumes of fresh PBS (1 ml) were replaced at each sampling point to keep the volume constant. The concentration of PTZ...
in the sample was analyzed by HPLC, as described in Analytical method.

**In Vitro Skin Permeation Studies** All animal experiments were carried out in accordance with the guidelines of the Institutional Animal Care and Use Committee (College of Pharmacy, Nihon University, Chiba, Japan). After sacrifice using ether, the full-thickness dorsal skin of male hairless mice (5—10 weeks) was excised, and adherent fat and other visceral tissue were removed from the undersurface. In vitro permeation studies were carried out with a Franz diffusion cell (Vertical diffusion cell™, Hanson Research Corporation, CA, U.S.A.) at 32 °C. The effective area of diffusion was 1.13 cm², and the receiver cell volume was 7 ml. The receiver cell was filled with PBS (pH 7.4), and stirred at 650 rpm by a magnetic stirrer. The amount of permeated PTZ was quantitated by collecting 0.5 ml samples at designated time intervals. The volume of receptor fluid withdrawn was replaced with PBS.

**Analytical Method** The HPLC system was constructed with a Model PU-2080 plus intelligent HPLC pump, a Model UV-2075 intelligent UV/VIS detector and a Model AS-2055 plus intelligent sampler (all from Jasco Co., Tokyo, Japan). The analytical column, CAPCELL PAK C18, type MG (150 mm×4.6 mm i.d., particle size 5 μm, Shiseido Co., Ltd., Tokyo, Japan) was used at room temperature. The mobile phase consisted of 0.05 M phosphoric acid and acetonitrile (77 : 23, v/v), at a flow rate of 1.0 ml/min. The column elute was monitored at 278 nm ultraviolet wavelength.

**Polarized Microscopy** The circular patches, 12 mm in diameter, were examined for drug crystallization by polarized microscopy, using an Eclipse E600W POL (Nikon Corporation, Tokyo, Japan) was used at room temperature. The field of view consisted of 0.05 m phosphoric acid and acetonitrile (77 : 23, v/v), at a flow rate of 1.0 ml/min. The column eluate was monitored at 278 nm ultraviolet wavelength.

**Results and Discussion**

**Effect of PSAs on the Release of PTZ** Adhesion, chemical stability and compatibility with other components in the system are crucial factors that affect the release and permeation properties of the drug candidate. Therefore, it is important to choose an ideal adhesive when designing a matrix-type adhesive TDDS. The drug dissolution studies from patches are crucial, because to achieve a constant rate of drug permeation, the drug concentration on the surface of the stratum corneum must be consistently maintained. The dissolution studies were performed using a shaking flask method, which is suitable for simultaneous assay of many samples without special equipment. In order to optimize the formulation of PTZ patches, the effect on the release of PTZ of various acrylic PSA matrices containing 5% IPM and 5% GEFAB-C₈ was investigated using the Duro-Tak® series. The cumulative PTZ release profiles from different adhesives are shown in Fig. 1a. The PTZ patch formulated by Duro-Tak® 87-9301 adhesive showed the highest release profile among all the adhesives. The release profiles represent drug release according to a matrix-diffusion kinetics model, where cumulative amounts of drug released per unit of area (Q) was plotted against the square root of time (t) (Fig. 1b). This can be explained by Higuchi’s square-root kinetics equation for release from a matrix-type delivery system:

\[
Q = D(2A - Cs)Cs t^{1/2}
\]  

(1)

where \(D\) is the diffusion coefficient of the drug in the matrix, \(A\) is the concentration of drug in matrix, \(Cs\) is the solubility of the drug in the matrix, and \(t\) is the time. As shown in Fig. 1b, the observed release patterns of PTZ from the adhesive were linear, indicating a strong association (Table 1). In addition, the release flux of PTZ from different adhesives can be obtained from the slope of Higuchi plot. The highest value among the Duro-Tak® adhesives was shown by Duro-Tak® 87-9301. Morimoto et al. reported that the diffusion coeffi-

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cient of drugs in a PSA matrix is affected by the type of functional group of the drug, and drugs with secondary amido and tertiary amine groups interact with the PSA carbonyl group, while those with a carbonyl group or ester group do not interact strongly. It is suggested that there was not interaction between the tertiary amine of PTZ and the Duro-Tak® 87-9301, because this adhesive has no polar functional group (−OH and −COOH) in the adhesive polymer. Consequently, the PTZ released from Duro-Tak® 87-9301 adhesive was better than other Duro-Tak® adhesives. Styrene-isoprene-styrene (SIS) copolymer is widely used for rubber-type PSA, because it does not have a polar functional group. The cumulative amount of PTZ released from the SIS matrix was about 69.6 μg/cm² when SIS copolymer was used (data not shown). The formability of the PTZ patch prepared with SIS was poor, due to heterogeneous dispersion in the adhesive polymer.15) It was observed that a low concentration of IPM as the permeation enhancer did not affect the partition coefficient (adhesive/skin) of PTZ in the TDDS. It disturbs the highly ordered lipid periodicity and increases the diffusion coefficient of the drug through the stratum corneum. As high concentrations of the enhancer solubilize the drug in the polymer matrix, partitioning of the drug in the stratum corneum decreases, causing retardation of the skin permeation rate.17) Moreover, the addition of more than 15% IPM changes the adhesive polymer into a glue-like state, which probably results in a reduction of IPM activity.18) On the other hand, the lag time, which is inversely proportional to the diffusivity, decreased with increases in the concentration of IPM (Rp. 1—4). These results indicate that with increasing concentrations of IPM in the adhesive, both the drug partition from the adhesive to the skin and the drug diffusivity in the skin would increase. Therefore, a concentration of 10% IPM seems to be the optimum value for enhancing the permeation of PTZ.

Effect of IPM on Skin Permeation of PTZ. The enhancing effects of IPM on the skin permeation of PTZ were evaluated at different concentrations (0—15%) in the patches (Table 2, Rp. 1—4). IPM is known to have a potent skin permeation-enhancing effect. This effect appears to affect the stratum corneum, and increases drug diffusivity in the stratum corneum and/or the partition coefficient between the

<table>
<thead>
<tr>
<th>Rp.</th>
<th>PTZ (%)</th>
<th>IPM (%)</th>
<th>GEFA-C₈ (%)</th>
<th>Flux (μg/cm²/h)</th>
<th>Lag time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>—</td>
<td>5</td>
<td>5.7±1.5</td>
<td>5.1±0.4</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>5.5±0.9</td>
<td>3.6±0.8</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>9.9±2.0</td>
<td>3.7±0.6</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>15</td>
<td>5</td>
<td>10.7±0.8</td>
<td>1.9±1.0</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>18.0±1.0</td>
<td>5.2±0.9</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>10</td>
<td>5</td>
<td>24.2±3.9</td>
<td>3.7±1.7</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>10</td>
<td>5</td>
<td>20.3±5.4</td>
<td>2.6±0.4</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>10</td>
<td>5</td>
<td>22.9±1.5</td>
<td>2.3±0.7</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>10</td>
<td>—</td>
<td>16.7±2.6</td>
<td>4.2±1.0</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>10</td>
<td>10</td>
<td>25.8±6.7</td>
<td>3.5±1.7</td>
</tr>
</tbody>
</table>

Each value represents the mean±S.D. (n=4—6).

Figure 2 shows patches with PTZ loads of 30, 40 and 50% captured by polarized microscopy, 24 h after the manufacturing process. Crystallization was not observed in the patch containing 30% PTZ (Fig. 3a) nor in those containing 10% and 20% (data not shown), whereas the patches with 40% and 50% PTZ showed crystal formation in the matrices (Figs. 3b, c), even though no crystals were observed in any of the formulations immediately after the manufacturing process. This result indicates that PTZ may be supersaturated in the patch when 30% loaded. Roy et al. showed a linear in-

![Fig. 2. Effect of IPM (a) and PTZ (b) Concentration on the Flux of PTZ. Each point represents the mean±S.D. (n=4—6).](image-url)
crease in the permeation rate of fentanyl from polyisobutyl-
ene matrices through human cadaver skin for drug loads of up
to the saturation concentration, and a plateau of the curve
with high drug concentrations in the formulation. They
suggested that drug crystals in highly loaded matrices lead to
a reduction of drug thermodynamic activity, and this may re-
duce the drug flux through the stratum corneum as a result.
Furthermore, Inoue et al. reported that the steady-state flux
from amorphous ketotifen-dispersed matrices was about five
times greater than that of crystalline ketotifen-dispersed ma-
trices through excised hairless mouse skin in vitro. This re-

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c

Effect of GEFA-C8 Concentration on the PTZ Flux

The influence of the GEFA-C8 concentration on the flux of
PTZ from Duro-Tak® 87-9301 matrix adhesive is shown in
Table 2. It was reported that the enhancement function of
GEFA-C8 in skin permeation contributes to increased fluidity
of sebaceous lipids and skin-moisturizing capacity. The ad-
dition of 5% GEFA-C8 in the formulation (Rp. 6) effectively
enhanced the flux of PTZ (Rp. 9, p<0.05). However, increas-
ing the concentration of GEFA-C8 from 5 to 10% (Rp. 10)
did not affect the PTZ flux. As well as the results of adding
IPM, we speculated that the skin/vehicle partition coefficient
of the drug was reduced at higher concentrations of GEFA-
C8, which resulted in a decrease in the flux of PTZ. The addi-
tion of more than 10% GEFA-C8 to the formulation did not
enhance the skin permeation of PTZ. The lag time tended to
decrease with increased concentrations of GEFA-C8 (Rp. 6,
9—10). However, the decreasing ratio of the lag time was
very small at 5% and 10% GEFA-C8 concentration, when
compared to the formulation without GEFA-C8 (Rp. 9).
Therefore, the most effective permeation enhancing concen-
tration of GEFA-C8 was estimated to be 5%.

Based on an oral dose of 50 mg and about 20% bioavail-
ability for the clinical use of PTZ in chronic pain, 10 mg
needs to be absorbed transdermally to achieve an analgesic
effect. The highest flux achieved in this study was
24.2 μg/cm²/h (Rp. 6), and the cumulative amount of PTZ
which permeated from the patch (1 cm²) was 576.5 μg at the
final determination at 24 h. Hence, transdermal PTZ patches
with an area of 18 cm² would be sufficient for the manage-
ment of patients with chronic pain. Generally, human skin
shows more resistance for drug permeation when compared
to hairless mouse skin. However, the significance of this
study is that it supports the feasibility of developing a ma-
trix-type TDDS for PTZ that would increase patient compli-
ance.

CONCLUSIONS

This study demonstrated that a novel TDDS patch com-
posed of Duro-Tak® 87-9301 adhesive polymer, 10% IPM
and 5% GEFA-C8 (as skin permeation enhancers, respecti-
vely) could incorporate up to 30% PTZ without crystal for-
mation with the highest flux of 24.2 μg/cm²/h. The PTZ
patch may be a potential formulation for the management of
patients with chronic pain as a long-term release formulation
in the TDDS.

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