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# *In Vitro* Percutaneous Absorption of Ondansetron Hydrochloride from Pressure-sensitive Adhesive Matrices through Hairless Mouse Skin

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To investigate the feasibility of developing a new ondansetron transdermal system, the effects of vehicles and penetration enhancers on the *in vitro* permeation of ondansetron hydrochloride (OS) from a pressure-sensitive adhesive (PSA) matrices across dorsal hairless mouse skin were studied. Vehicles employed in this study consisted of various ratios of propylene glycol monocaprylate (PGMC)-diethylene glycol monoethyl ether (DGME) co-solvents and PGMC-propylene glycol (PG) co-solvents with 3% oleic acid. Duro-Tak® 87-2100 and Duro-Tak® 87-2196 were used as PSAs. The concentration of DGME in PGMC-DGME co-solvent system affected the release rate; as the concentration of DGME increased, the release rate decreased. The cumulative release amount of OS increased as the ratio of PSA to drug solution decreased. The permeation flux was also primarily affected by the amount of PSAs; as the amount decreased, the permeation flux increased. The overall fluxes from matrix formulations were significantly lower when compared to those obtained from solution formulations. The ratio of PG to PGMC did not affect permeation flux, while the lag time decreased significantly from $5.14 \pm 3.31$ to $0.31 \pm 0.12$ h as the PG increased from 40% to 60%.

**Key words:** Ondansetron transdermal system, Vehicles, Pressure-sensitive adhesive matrices, Release, Permeation

## INTRODUCTION

Ondansetron is a serotonin (5-hydroxytryptamine) subtype 3 (5-$HT_3$) receptor antagonist used in the managment of nausea and vomiting (Butcher 1993; McKenzie *et al.*, 1993; Scuderi *et al.*, 1993). 5-$HT_3$ receptors, located centrally in the chemoreceptor trigger zone of the area postrema as well as peripherally on vagal nerve terminals, are key receptors in the nausea and vomiting response (Hesketh and Gandara, 1991). Ondansetron has been used to prevent and control nausea and vomiting after cancer chemotherapy, radiotherapy and surgery (Hesketh and Gandara, 1991; Butcher 1993; McKenzie *et al.*, 1993; Scuderi *et al.*, 1993). Unlike metoclopramide, ondansetron is known not to block dopamine subtype-2 receptors, and therefore not to induce the undesirable side effect such as extrapyramidal reactions. The most commonly reported adverse events with ondansetron are headache, constipation and diarrhea, which are mild to moderate in severity and rarely necessitate treatment withdrawal (Blackwell and Harding, 1989).

Even though ondansetron is thought to be a good candidate for patients receiving highly emetogenic agents, its use has been limited in patients who have difficulty in swallowing after chemotherapy. Also, this drug can be vomited before absorbed in patients who had very high emetogenic agents.

Transdermal delivery has been used as an alternative dosage form for oral delivery (Gwak and Chun, 2002; Gwak *et al.*, 2002; Nokhodchi *et al.*, 2003). We have already reported the effects of vehicles and enhancers on the skin permeation of ondansetron from solution formulaions across excised hairless mouse skins (Gwak *et al.*, 2003a). Based on the results from the previous study, in the present study, the effects of vehicles and penetration enhancers on the permeation of ondansetron from pressure-sensitive adhesive (PSA) matrices across excised hairless mouse skins were evaluated to examine

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the feasibility for developing ondansetron PSA transdermal system.

## MATERIALS AND METHODS

### Materials

Ondansetron hydrochloride (OS) was purchased from Zunan Commerce & Industrial Co., Ltd. (Shenzhen, P.R. China), and used without any further purification. Propylene glycol monocaprylate (PGMC, Capryol® 90) and diethylene glycol monoethyl ether (DGME, Transcutol® P) were obtained from Gattefossé (Gennevilliers Cedex, France). Oleic acid and terazosin hydrochloride were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Acrylic pressure-sensitive adhesive solutions in organic solvents which were Duro-Tak® 87-2196 (copolymer: acrylate-vinylacetate, functional group: -COOH, 45% solution of self-crosslinking acrylic copolymer, 3000 cps, solubility parameter 16) and Duro-Tak® 87-2100 (copolymer: acrylate, functional group: -COOH, 51.5% solution of self-crosslinking acrylic copolymer, 8500 cps, solubility parameter 16) were obtained from National Starch and Chemical Company (Bridgewater, NJ, USA). Acetonitrile and methanol used were of HPLC grade. Other reagents were of analytical grade.

### Animals

Male hairless mice aged 6~8 weeks were purchased from Samtako Bio Korea Co., Ltd. (Osan, Korea).

### Analysis

Ondansetron concentration was determined by high-performance liquid chromatography (HPLC). The HPLC system consisted of a pump (Series 410, Perkin-Elmer, USA) with a detector (Model LC 90 UV, Perkin-Elmer, USA) set at 302 nm and an integrator (Model 4290, Varian, USA). An ODS column (Bondapak C18, 3.9×300 mm, 10 μm, Waters, USA) equipped with a C18 Radial Pak insert was used. The mobile phase was composed of acetonitrile, methanol, water and triethylamine (25:9:66:0.1, v/v), whose pH was adjusted to 4.0 by phosphoric acid, and delivered at a flow rate of 1.2 mL/min. The injection volume was 20 μL. The internal standard used was terazosin hydrochloride (30 μg/mL). A calibration curve was constructed based on peak area measurements.

### Preparation of OS transdermal system

An appropriate amount of OS was dissolved in various pure solvents or co-solvents with/without permeation enhancers, and then mixed with two kinds of acrylic adhesive solutions: Duro-Tak® 87-2196 and Duro-Tak® 87-2100. OS PSA transdermal system was prepared by casting the above solutions on a polyester release liner coated with silicone (Gelroflex ALU-PET 100 μ-2S DR, 3M, USA) using a casting knife. The area of the cast solutions was 10 cm×7 cm. They were set at room temperature for 4 h to evaporate the solvents, and then dried overnight in an oven set at 37°C. The dried film was transferred onto a backing film (Scotchpak 1109, 3 M, USA). Table I shows formulation compositions for the preparation of OS transdermal system.

### Procedure for OS release from OS transdermal system

OS transdermal system was mounted on a side-by-side permeation system (Valia-Chien Permeation System, Crown Bioscientific Inc., NJ, USA); the drug loaded-layer was in contact with the receptor compartment. The area of cell openings was 0.64 $cm^2$. Receptor compartment cells were filled with 0.02 M phosphate buffer (pH 5.0) and the media were stirred by a Teflon-coated magnetic bar to keep them well mixed. The release media were maintained at 32°C. At predetermined time intervals, 100 μL of receptor

**Table I.** Formulation compositions for the preparation of OS transdermal system

| FN | Amount loaded (mg/70cm$^2$) | Vehicles (v/v) | PSA (Duro-Tak®) | Amount of PSA (g) |
|---|---|---|---|---|
| 01 | 7.5 | PGMC:DGME = 8:2 | 87-2196 | 2.0 |
| 02 | 7.5 | PGMC:DGME = 6:4 | 87-2196 | 2.0 |
| 03 | 7.5 | PGMC:DGME = 4:6 | 87-2196 | 2.0 |
| 04 | 7.5 | PGMC:DGME = 2:8 | 87-2196 | 2.0 |
| 05 | 7.5 | PGMC:DGME = 6:4 | 87-2196 | 1.75 |
| 06 | 7.5 | PGMC:DGME = 6:4 | 87-2196 | 1.5 |
| 07 | 7.5 | PGMC:DGME = 6:4 | 87-2196 | 1.25 |
| 08 | 25 | PGMC:PG = 6:4[a)] | 87-2196 | 2.0 |
| 09 | 25 | PGMC:PG = 6:4[a)] | 87-2100 | 2.0 |
| 10 | 25 | PGMC:PG = 6:4[a)] | 87-2196 | 1.75 |
| 11 | 25 | PGMC:PG = 4:6[a)] | 87-2100 | 1.75 |

[a)] Oleic acid (3%) was added as an enhancer. FN : formulation number.

solutions were withdrawn, and mixed with 100 μL of internal standard solution. The amount of OS released from various PSA transdermal system was determined by HPLC.

### Procedure for skin permeation *in vitro*

After sacrificing hairless mouse with ether, the dorsal skin was carefully excised. OS transdermal system of an appropriate size was applied to the epidermal side of the skin, and mounted on a side-by-side permeation system; the dermal side was in contact with the receptor compartment. Receptor compartment cells were filled with 40% PEG 400 in saline and the media were stirred by a Teflon-coated magnetic bar to keep them well mixed. The permeation media were maintained at 32°C. At predetermined time intervals, 100 μL of receptor solutions were withdrawn, and mixed with 100 μL of internal standard solution. The amount of OS permeated was determined by HPLC.

## RESULTS AND DISCUSSION

### Effect of vehicles and PSAs on the OS release from transdermal system

In designing a transdermal drug-in-adhesive system, it is essential to identify an appropriate vehicle which solubilizes a drug, mixes well with PSA, and/or enhances the permeation rate. From our previous study using solution formulations of OS, it was found that, water and ethanol were the most effective vehicles for permeation among pure vehicles used (Gwak *et al.*, 2003a). However, these vehicles are not uniformly mixed with PSAs. Thus, PGMC-DGME cosolvent and PGMC-PG with 3% oleic acid, which showed relatively high permeation fluxes from solution formulation, were used for the fabrication of OS transdermal system in this study, and they appeared reasonable for transdermal system preparations.

Before a drug permeates across the skin, the drug should be appropriately released from matrix; the PSA should allow proper diffusion and release of the drug. Fig. 1 depicts the release profile of OS from PGMC-DGME binary systems. The concentration of DGME in PGMC-DGME co-solvent system affected the release rate; as the concentration of DGME increased, the release rate decreased, probably because the addition of DGME may increase the solubility and decrease the diffusion within the adhesive matrix. The ratio of PG also influenced the OS release; when the ratio of PG increased from 40% to 60%, the cumulative amount released over 24 h decreased from 87.7 to 52.6 μg/cm$^2$.

At the same OS dosing, it was observed that the higher the PSA amount in the transdermal system, the lower the drug release profile. The cumulative release amount of OS at 24 h was calculated to be 42.3, 25.1, 20.4 and 9.9 μg/cm$^2$ when the weight of PSA to the 0.5 mL of drug solution (15 mg/mL in PGMC-DGME (60 : 40) co-solvent) was 1.25, 1.5, 1.75 and 2.0 g, respectively. A matrix-controlled diffusion model ($Q' = k't^{1/2}$, $Q'$ : amount released, $k'$: release rate constant) (Chien and Lambert, 1974) was established for all the PSA amounts studied (Fig. 2); the releases from all test formulations were proportional to the square root of time. The release fluxes, calculated from the slope of the Q vs. $t^{1/2}$ relationship, were 8.37, 5.13, 4.11 and 2.08 μg/cm$^2$/h$^{1/2}$ for the PSA weight of 1.25, 1.5, 1.75 and 2.0 g, respectively. It was speculated that the decreased release by the large amount of PSA was associated with the decreased diffusion

To evaluate the effect of PSA on the OS release from the matrix formulation, PGMC-PG (60:40 v/v) co-solvent with 3% oleic acid was mixed with two kinds of PSAs: Duro-Tak® 87-2196 and Duro-Tak® 87-2100. It was reported that the release rate of a drug from an adhesive matrix is governed by drug solubility and diffusion coefficients in polymer (Roy *et al.*, 1996). These two PSAs have an

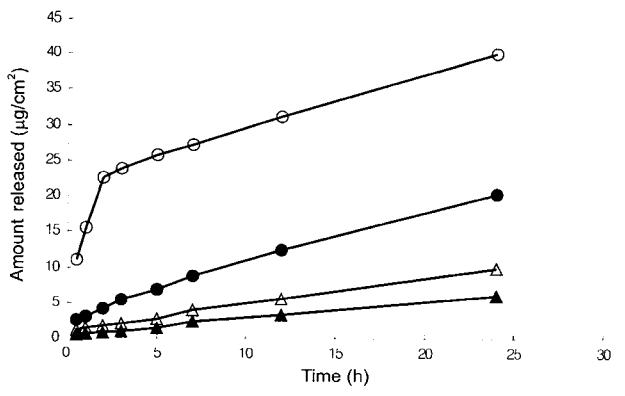


**Fig. 1.** Effect of DGME content (%) in PGMC-DGME co-solvents on the release of OS from PSA transdermal system (n = 3). Key: ○, 20% DGME; ●, 40% DGME; △, 60% DGME; ▲, 80% DGME.

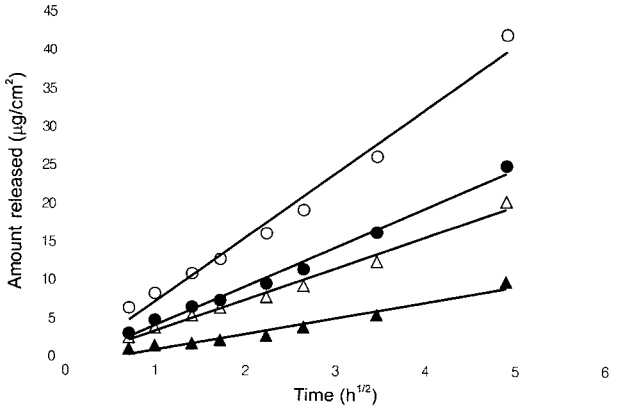


**Fig. 2.** Effect of the amount of PSA mixed with PGMC-DGME (60 : 40) co-solvent on the release of OS from PSA transdermal system (n = 3). Key: ○, 1.25 g; ●, 1.5 g; △, 1.75 g; ▲, 2 g.

identical functional group (-COOH) and solubility parameter (viz, 16). Expectedly, the release rates of OS from the two PSAs were not significantly different from each other; the release fluxes of Duro-Tak® 87-2196 and Duro-Tak® 87-2100 are 8.95 and 9.23 $\mu g/cm^2/h^{1/2}$, respectively.

### Effect of vehicles and PSAs on the OS permeation from transdermal system

The stratum corneum has been found to possess a significant barrier property in percutaneous absorption. To overcome this problem, a number of mechanisms have been proposed; the reduction of skin resistance as a permeability barrier by disruption of tightly packed lipid regions of stratum corneum (Barry, 1987), increased skin/vehicle partitioning of the drug (Green *et al.*, 1988), increased solvent transport into or across the skin (Yamada, *et al.*, 1987), and increased drug solubility in the vehicle (Aungst *et al.*, 1990).

We employed PGMC-DGME and PGMC-PG as cosolvents in the system in the presence of 3% oleic acid (vehicle) and Duro-Tak® 87-2196 (PSA). Different concentrations of OS were loaded based on the solubility; 15 and 50 mg were added to 1 mL of PGMC-DGME and PGMC-PG with 3% oleic acid, respectively. It has been suggested that increasing thermodynamic activity of the drug and/or changing the barrier property of the skin can enhance the permeation of a drug across the skin (Møllgard and Hoelgaard, 1983). Considering thermodynamic activity is proportional to the ratio of drug concentration to its solubility in the vehicle (Cho and Choi, 1998), concentration of drug in a vehicle could be an important factor for the drug permeation. In our earlier study (Gwak *et al.*, 2003a), the solubilities of OS in PGMC-DGME (60:40) and PGMC-PG (60:40) were calculated to be 7.31±0.01 and 68.8±4.71 mg/mL. However, as shown in Fig. 3 and Table II, the ratio did not affect the permeation rate because the amount of vehicle was much less than that of the present formulation. The addition of oleic acid also did not affect the permeation flux of OS from transdermal system even though it was reported to be the most potent penetration enhancer for piroxicam and tenoxicam (Santoyo *et al.*, 1995; Gwak and Chun, 2002).

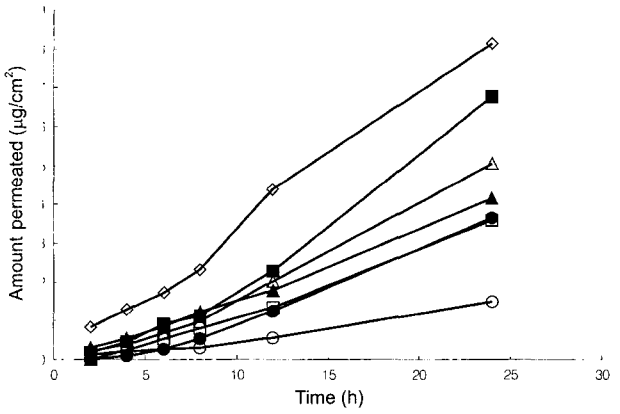


**Fig. 3.** Permeation profiles of OS from PSA transdermal system (n = 3). Key: ○, FN 2; ●, FN 5; △, FN 7; ▲, FN 8; □, FN 9; ■, FN 10; ◇, FN 11

**Table II** Permeation flux and lag time of OS through excised hairless mouse skin from various PSA transdermal system

| FN | $J_s$ ($\mu g/cm^2/h$) | $T_L$ (h) |
|---|---|---|
| 2 | 0.07±0.03 | 4.10±2.10 |
| 5 | 0.20±0.06 | 5.52±2.23 |
| 7 | 0.24±0.08 | 3.13±2.76 |
| 8 | 0.18±0.07 | 1.40±1.20 |
| 9 | 0.18±0.06 | 3.97±2.01 |
| 10 | 0.36±0.10 | 5.14±3.31 |
| 11 | 0.35±0.21 | 0.31±0.12 |

Data were expressed as the mean±S.D. (n = 3). FN: formulation number based on Table I.

The permeation flux was mostly affected by the amount of PSAs; as the amount decreased, the permeation flux increased regardless of the kind of vehicles used. The enhancement factor by using 1.25 g of PSA (FN 7), compared with when using 2.0 g of PSA (FN 2), was more than three. As the amount of PSA mixed with PGMC-PG (60:40) with 3% oleic acid decreased from 2.0 to 1.75 g, the permeation flux increased by two-fold. As suggested in the release study, the decreased amount of PSA resulted in an increase in the diffusion, thereby increasing release and permeation. In addition, PSA itself may affect the drug solubility.

Even though increased PG ratio in the PGMC-PG co-solvent with 3% oleic acid reduced the release rate of OS from PSA matrix formulation, it did not influence the permeation rate. However, the lag time decreased from 5.1 to 0.3 h as the PG concentrations increased from 40 to 60%.

The overall fluxes from matrix formulations were significantly lower when compared to those obtained from solution formulations. In the solution formulations, the OS fluxes from various ratios of PGMC-DGME co-solvents ranged from 1.65 to 15.71 $\mu g/cm^2/h$, and that from PGMC-PG co-solvent (60:40) with 3% oleic acid was 14.91 $\mu g/cm^2/h$ (Gwak *et al.*, 2003b). The low flux from matrix formulations could be induced by decreased fluidity and thermodynamic activity. It was explained that the low flux of ketoprofen from PSA matrix might to be due to its high solubility in the acrylic adhesive matrix resulting in low thermodynamic activity (Cho and Choi, 1998). In the study, the authors demonstrated that the permeation flux increased as the drug loading in the acrylic adhesive matrix increased. Therefore, these results suggest that

OS transdermal delivery system may be feasbility by using appropriate amount of PSA and drug dosing.

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