DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 2, pp. 187–194, 2004

RESEARCH PAPER

Transdermal Delivery of Ondansetron Hydrochloride: Effects of Vehicles and Penetration Enhancers

Hye Sun Gwak,[1] Ik Sang Oh,[2] and In Koo Chun[2,*]

[1]College of Pharmacy, Chosun University, Gwangju, South Korea
[2]College of Pharmacy, Dongduk Women's University, Seoul, South Korea

ABSTRACT

The effects of vehicles and penetration enhancers on the in vitro permeation of ondansetron hydrochloride (OS) across dorsal hairless mouse skins were investigated. Various types of vehicles, including ester, alcohol, and ether and their mixtures were used, and then a series of fatty acids and fatty alcohols were employed as enhancers. Among pure vehicles used, water and ethanol showed high permeation fluxes, which were 48.2 ± 23.7 and 41.9 ± 17.9 $\mu g/cm^2$ per h, respectively. Even though propylene glycol monocaprylate (PGMC) alone did not show a high permeation rate, the skin permeability of OS was increased by the addition of diethylene glycol monoethyl ether (DGME); the highest flux was achieved at 40% of DGME. Also, the combination of PGMC and ethanol (80:20) or PGMC and propylene glycol (PG) (60:40) increased the permeation flux by six- and two-fold, respectively, compared to PGMC alone. The synergistic enhancement was also obtained by using PG-oleyl alcohol (OAl) cosolvent. The greatest flux was attained by the addition of unsaturated fatty acids at 3% concentration to PG. The enhancement factors with the addition of oleic acid or linoleic acid to PG were about 1250 and 450, respectively. But saturated fatty acids failed to show a significant enhancing effect. When the PGMC-DGME (60:40) cosolvent system was used as a vehicle, all fatty acids, including unsaturated fatty acids, failed to show significant enhancing effects. The results indicate that the combinations of oleic acid, linoleic acid, or oleyl alcohol with PG, or PGMC-DGME (60:40) cosolvent could be used for the design of the OS transdermal system.

Key Words: Transdermal delivery; Ondansetron hydrochloride; Vehicles; Penetration enhancers.

*Correspondence: In Koo Chun, College of Pharmacy, Dongduk Women's University, Seoul 136-714, South Korea; Fax: +82-2-941-7652; E-mail: ikchun@dongduk.ac.kr.

DOI: 10.1081/DDC-120028714
0363-9045 (Print); 1520-5762 (Online)

INTRODUCTION

Ondansetron is a serotonin (5-hydroxytryptamine) subtype 3 (5-HT_3) receptor antagonist used in the management of nausea and vomiting.[1–3] 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.[4] Ondansetron has been used to prevent and control nausea and vomiting after cancer chemotherapy, radiotherapy, and surgery.[1–3] Unlike metoclopramide, ondansetron is known not to block dopamine subtype-2 receptors, and therefore not to induce the undesirable side effects 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.[4]

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 paid attention as an alternative dosage form to oral delivery.[5–7] In addition to being appropriate for special populations who may have a problem with swallowing, transdermal delivery can avoid first-pass metabolism and maintain plasma drug concentration constantly. Despite these advantages, only a limited number of drugs can be administered percutaneously, due to low skin permeability of most drugs through the skin. The stratum corneum was recognized as an excellent barrier against skin penetration. To overcome this problem, many penetration enhancers have been examined.[5,6]

The oral bioavailability of ondansetron is about 60% and the volume of distribution is around 140 L. It undergoes extensive hepatic metabolism by the cytochrome P450 enzyme system; the elimination half-life is 3–3.5 h. Less than 5% of an absorbed dose is eliminated unchanged in the urine.[8] Considering that the usual oral dose of OS is 16 mg a day in two divided doses and the oral bioavailability is 60%, for the effective transdermal delivery system, about 10 mg a day should be delivered via the skin into the blood circulation.

In the present study, to examine the feasibility of developing the ondansetron transdermal system, we investigated the effects of pure solvents, cosolvents, and penetration enhancers on the in vitro permeation of ondansetron from solution formulation across dorsal hairless mouse skin.

EXPERIMENTAL

Materials

Ondansetron hydrochloride (OS) was purchased from Zunan Commerce and Industrial Co., Ltd. (Shenzhen, P. R. China), and used without any further purification. Propylene glycol laurate (PGL, Lauroglycol® FCC), propylene glycol monocaprylate (PGMC, Capryol® 90), and diethylene glycol monoethyl ether [DGME, Transcutol® P (Gattefossé, Gennevilliers Cedex, France] were used. Propylene glycol (PG), isopropyl myristate (IPM), and ethanol were of analytical grade. Lauryl alcohol, oleyl alcohol, lauric acid, oleic acid, linoleic acid, capric acid, caprylic acid, and capsaicin, which were used as penetration enhancers, and the internal standard, terazosin hydrochloride, were obtained from Sigma Chemical Co. (St. Louis, MO). Acetonitrile and methanol used were of high-performance liquid chromatography (HPLC) grade. Other reagents were of analytical grade.

Analysis

Samples from solubility and permeation studies were analyzed by high-performance liquid chromatography (HPLC). The HPLC system consisted of a pump (Series 410, Perkin-Elmer, Norwalk, CT) with a detector (Model LC 90, Perkin-Elmer) set at 302 nm and an integrator (Model 4290, Varian, Palo Alto, CA). An octadecylsilane (ODS) column (μBondapak C18, 3.9×300 mm, 10 μm, Waters, Milford, MA) 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.

Methods

Solubility Determination

An excess amount of OS was added to the various pure solvents or cosolvents, and shaken at 32°C for more than 48 h. The solutions were then centrifuged at

Table 1. Permeation parameters of OS through excised hairless mouse skin from various pure vehicles.

Vehicles	J_s (μg/cm^2 per hr)	T_L (h)	P_{app} ($\times 10^7$, cm/s)	Solubility (mg/mL)
Water	48.2±23.7	NA	13.4±6.26	36.1±1.85
Ethanol	41.9±17.9	0.10±0.02	11.6±4.04	20.9±1.81
DGME	4.34±0.07[a,b]	3.23±1.12	1.21±0.02	18.1±3.79
PG	0.08±0.02[a,b]	NA	0.02±0.003	282±3.37
PGMC	4.04±0.31[a,b]	4.32±0.12	11.2±5.73	1.00±0.07
PGL	0.31±0.11[a,b]	NA	2.05±0.63	0.42±0.10
IPM	0.43±0.29[a,b]	NA	149±102	0.008±0.001
PGL-DGME (80:20)	14.2±5.68[a,b]	5.50±1.23	49.3±12.3	0.80±0.14
IPM-DGME (80:20)	1.43±0.29[a,b]	0.77±0.33	36.1±14.8	0.11±0.01
PGMC-ethanol (80:20)	25.9±2.78[a,b]	1.92±0.32	7.19±0.76	21.5±0.84
PGMC-PG (60:40)	8.37±4.29[a,b]	5.68±1.33	2.33±1.25	68.8±4.71

[a]Statistically different from water ($p<0.05$).
[b]Statistically different from ethanol ($p<0.05$).
Note: Data were expressed as the mean±S.D. (n=3). NA, not available.

9000 *g* for 5 min, and the supernatant was assayed by HPLC after appropriate dilution.

Preparation of Donor Solutions

To determine the effects of various vehicles and enhancers on the permeation of OS, appropriate amounts of OS were dissolved in pure solvent or cosolvent. For the preparation of saturated solutions, an excess amount of OS was added to the pure solvent or co-solvent, shaken at 32°C for 24 h, and centrifuged at 9000 g for 5 min.

Procedure for Skin Permeation In Vitro

Male hairless mice aged 6–8 weeks were used. After sacrificing with ether, the dorsal skin of each hairless mouse was excised, and the full skin thickness was measured using dial thickness gauge (Mitutoyo, Kawasaki, Kanakawa-ken, Japan, 0.01–10 mm). Then it was mounted on a side-by-side permeation system; the dermal side was in contact with the receptor compartment. Receptor compartment cells were filled with 3 mL of 40% polyethylene glycol (PEG) 400 in saline and the media were stirred by a Teflon-coated magnetic bar to keep them well mixed. The donor compartment was filled with 3 mL of donor solutions in various pure solvents or cosolvents. The permeated amount of OS was determined by HPLC. The skin permeation studies were performed at 32°C. At predetermined time intervals, 100 μL of receptor solutions were withdrawn and mixed with 100 μL of internal standard solution.

Data Analysis

As described by Barry,[9] the steady-state flux (J_s), lag time (T_L), diffusion coefficient (D), skin/vehicle partition coefficient (K), and apparent permeation coefficient (P_{app}) are defined by Eqs. 1–3.

$$J_s = (dQ/dt)_{ss} \cdot 1/A = DKC/h \quad (1)$$

$$D = h^2/6T_L \quad (2)$$

$$P_{app} = dQ/dt \cdot 1/A \cdot 1/C \quad (3)$$

where A=the effective diffusion area, h=the thickness of skin, C=the constant concentration of the donor solution, and $(dQ/dt)_{ss}$=the steady-state slope.

Statistical Analysis

The mean permeation values calculated for OS were compared by one-way analysis of variance (ANOVA), followed by the Duncan multiple range test.

RESULTS AND DISCUSSION

Effect of Vehicles

Various types of pure vehicles were incorporated into the donor compartment to transport OS into skin, including alcohol, ester, and ether. To the receptor compartment, 3 mL of 40% PEG 400 in saline was filled to maintain sink condition; the solubility of OS in 40%

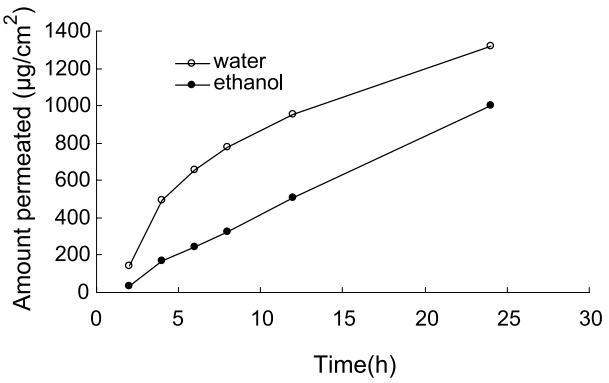

Figure 1. Cumulative amount of OS permeated across hairless mouse skin from 10 mg/mL solution in water or ethanol as a function of time (n=3).

PEG 400 was measured to be 26.8±1.2 mg/mL. It has also been suggested that the addition of 40% PEG 400 to the receptor solution did not measurably alter the barrier properties of the skin.[10] For this reason, this medium has been used as the receptor phase in many studies.[11,12] As described in Eq. 1, permeation flux can be increased by increasing D, K, and/or C. D can be affected by many formulation parameters such as molecular size, shape, and the flexibility of the diffusing molecule as well as the membrane resistance.[13] With a fixed concentration (10 mg/mL) of OS, water and ethanol showed the highest fluxes as listed in Table 1. The solubilities of OS in water and ethanol were relatively high, indicating high C compared to vehicles showing much lower solubilities than 10 mg/mL. Also, water itself has been proved to be a potent enhancer by hydrating the skin. In dry tissue, the intracellular contents will be essentially solid and many hydrogen-bonding groups will be able to interact and hinder drug transport. Therefore, dry cells provide a significant barrier to diffusion. In the hydrated situation, the intracellular regions will be more fluid, and water will compete for drug-binding sites, lowering the diffusional barrier.[14] Ethanol has been known to exert its enhancing effect by increasing the partition coefficient (stratum corneum:vehicle). In this study, the effect of ethanol on the permeation rate of OS, however, was mainly due to the high D; the lag time (0.1±0.02 h) was much shorter than those from other studies.[15,16] Figure 1 represents the permeation profiles of OS across the hairless mouse skin from water and ethanol. Water initially provided a very high permeation rate followed by a gradual decrease. The decrease in the permeation rate with time was explained by the rapid reduction in driving force due to initial high permeation rate.[17]

Even though it is necessary to have vehicles with enough solubility to dissolve the desired dose of OS, vehicles with too high solubility resulted in very low permeation rate because of decreased thermodynamic activity. The other alcohol-type vehicle, PG, produced very low permeation flux, which has very high solubility of OS as described in Table 1.

Because water and ethanol, which showed high permeation fluxes (48.2±23.7 and 41.9±17.9 μg/cm^2/h, respectively), cannot be compatible with acrylic adhesive matrices for developing the transdermal delivery system, ester-type vehicles (PGMC, PGL, and IPM) were investigated. The solubilities of OS in ester type vehicles were very low, less than 1 mg/mL; OS was saturated in these vehicles. As shown in Table 1, the permeation fluxes of OS from these vehicles were very low (less than 5 μg/cm^2/h), even though their permeation coefficients were relatively high. Thus DGME, an ether type vehicle, was added to ester type vehicles to increase the OS solubility.

When DGME was combined with PGL at the ratio of 20:80, the permeation flux of OS increased statistically significantly ($p<0.05$). However, when DGME was mixed with IPM at the same ratio as DGME-PGL, a statistically significant enhancing effect was not observed ($p>0.05$). The higher enhancing effect for PGL-DGME than IPM-DGME was attributed to more increased solubility (0.8 vs. 0.11 mg/mL) and partition coefficient (16.7 vs. 2.0).

Figure 2 shows the cumulative amount of OS permeated from various ratios of PGMC-DGME cosolvents. The highest flux was attained at 40% DGME in cosolvents, even though the solubility of OS in the binary cosolvent system increased as the concentration of DGME increased as follows: 0% DGME

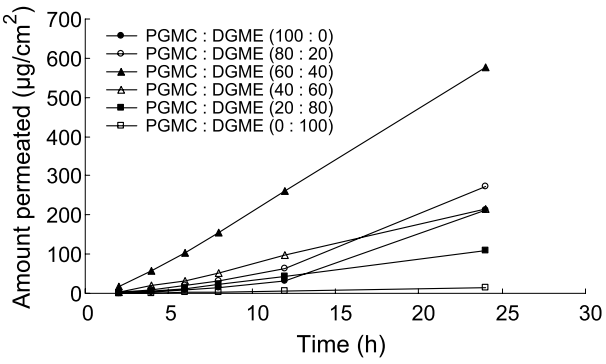

Figure 2. Effect of PGMC-DGME cosolvents on the permeation of OS across hairless mouse skin from 10 mg/mL solution as a function of time (n=3).

Table 2. Permeation parameters of OS through excised hairless mouse skin from DGME/PGMC binary vehicles.

DGME/PGMC ratio	J_s (μg/cm^2 per hr)	T_L (h)	D ($\times 10^5$, cm^2/h)	K
0/100	4.04±0.31[a,b]	4.32±0.12	4.46±0.32	3.08±0.26
20/80	15.67±7.54[a,b]	6.84±0.80	3.16±1.21	12.94±3.49
40/60	25.83±7.23[b]	1.79±0.12	11.41±2.34	1.08±0.52
60/40	9.82±3.26[a,b]	2.28±0.99	11.70±1.70	0.34±0.13
80/20	5.36±2.54[a,b]	3.86±0.25	6.91±2.75	0.31±0.11
100/0	4.34±0.07[a,b]	3.23±1.12	8.26±2.96	0.21±0.13

[a]Statistically different from DGME/PGMC (40/60) ($p<0.05$).
[b]Statistically different between means ($p<0.01$).
Note: Data were expressed as the mean±S.D. (n=3).

(1.00±0.07 mg/mL), 20% DGME (1.38±0.04 mg/mL), 40% DGME (7.31±0.11 mg/mL), 60% DGME (10.6±0.19 mg/mL), 80% DGME (13.8±0.24 mg/mL), and 100% DGME (18.1±3.79 mg/mg). The corresponding parameters are listed in Table 2. Diethylene glycol monoethyl ether has been reported to have an effect on drug penetration by easing the partition through increasing the solubility of the compound in the skin, even though it may not have a profound effect on the structural integrity of the skin.[17] Unexpectedly, as shown in Table 2, the partition coefficient of OS decreased as the volume fraction of DGME in the vehicle increased; the highest value of partition coefficient between the cosolvents was obtained at the 20% DGME. On the other hand, the diffusion coefficient was the greatest at the 60% DGME.

When the hydrophilic vehicle (ethanol) was added to the hydrophobic vehicle (PGMC) at 20% concentration, a significantly enhanced flux (25.9±2.78 μg/cm^2/h) was observed, compared to PGMC alone (4.04±0.31 μg/cm^2/h).

From overall results, it was speculated that permeation flux can be affected by not only the ratio of drug concentration in a vehicle to the solubility but also other factors such as changing barrier properties. Thus, to achieve high penetration rate, vehicles that can greatly change skin barrier property and solubilize the desired amount of drug with a minimal decrease in thermodynamic activity should be employed. To change the skin barrier property, several mechanisms have been suggested: the reduction of skin resistance as a permeability barrier by disruption of tightly packed lipid regions of

Table 3. Permeation parameters of OS through excised hairless mouse skin from PG containing enhancers.

Enhancers	J_s (μg/cm^2 per hr)	T_L (h)	D ($\times 10^5$, cm^2/h)	K	P_{app} ($\times 10^7$, cm/s)	Enhancement factor
No enhancer	0.08±0.02[b,c,d]	NA	NA	NA	0.02±0.003	–
Caprylic acid	0.14±0.12[b,c,d]	1.04±0.82	18.5±12.1	0.003±0.002	0.04±0.03	1.75
Capric acid	0.16±0.08[b,c,d]	4.22±3.01	4.57±1.38	0.012±0.03	0.04±0.01	2.00
Lauric acid	1.50±1.32[b,c,d]	NA	NA	NA	0.42±0.38	18.75
Oleic acid	99.7±0.37[a,c,d]	6.37±0.03	1.91±0.006	14.1±0.07	27.7±0.09	1246.25
Linoleic acid	35.7±3.02[a,b,d]	8.36±3.71	1.79±0.32	5.98±0.07	9.93±0.8	446.25
Oleyl alcohol	28.7±2.93[a,b,c]	8.92±0.92	1.57±0.31	5.29±1.01	7.97±0.82	358.75
Lauryl alcohol	0.15±0.12[b,c,d]	2.33±2.14	9.27±5.2	0.006±0.003	0.04±0.02	1.88
Capsaicin	0.07±0.06[b,c,d]	NA	NA	NA	0.02±0.01	0.88

[a]Statistically different from no enhancer ($p<0.05$).
[b]Statistically different from oleic acid ($p<0.05$).
[c]Statistically different from linoleic acid ($p<0.05$).
[d]Statistically different from oleyl alcohol ($p<0.05$).
Note: Data were expressed as the mean±S.D. ($n=3$). NA, not available. Enhancement Factor=J_s (enhancers)/J_s (no enhancer).

Table 4. Permeation parameters of OS through excised hairless mouse skin from PGMC-DGME (60:40) cosolvent containing enhancers.

Enhancers	J_s (μg/cm^2 per hr)	T_L (h)	D ($\times 10^5$, cm^2/h)	K	P_{app} ($\times 10^7$, cm/s)
No enhancer	25.8±7.23	1.79±0.41	11.4±2.53	1.08±0.79	9.82±2.34
Caprylic acid	20.52±3.81	2.05±1.38	12.4±5.73	0.65±0.58	5.70±1.14
Capric acid	21.26±0.53	0.59±0.64	28.9±22.3	0.24±0.13	5.90±0.15
Lauric acid	19.0±0.81	0.04±0.05	540±210	0.013±0.001	5.28±2.57
Oleic acid	18.44±4.85	0.71±0.68	21.1±19.8	0.26±0.20	5.12±1.60
Linoleic acid	26.87±23.67	1.16±0.64	12.9±10.3	0.62±0.20	7.46±3.61
Oleyl alcohol	28.09±5.89	2.29±1.52	9.96±6.83	1.04±0.56	7.80±1.93
Lauryl alcohol	18.21±7.26	NA	NA	NA	5.06±1.91
Capsaicin	19.30±5.36	2.65±0.23	5.66±1.09	1.02±0.15	5.36±1.73

Note: Data were expressed as the mean±S.D. (n=3). NA, not available.

stratum corneum;[14] and increased skin/vehicle partitioning of the drug;[18] and increased solvent transport into or across the skin.[19]

Effect of Enhancers

In this study, a polar solvent, PG alone failed to show an enhancing effect on the permeation of OS. However, PG has been widely used with lipophilic compounds for transdermal delivery of many drugs.[6,19–22] It has been revealed that there is physical-chemical evidence of separate hydrophilic and lipophilic domains in the barrier area of the stratum corneum.[23] So, penetrants with both hydrophilic and lipophilic properties probably penetrate the stratum corneum most readily.

Fatty acids are known to be enhancers with lipophilic properties, and many studies have shown that the skin permeability enhancing effects of fatty acids are greatest with PG vehicles.[19–22] The binary system was considered to disorganize the multilaminate hydrophilic-lipophilic layers located intercellularly in the stratum corneum, consequently promoting percutaneous absorption of drugs.[24] In this study, five fatty acids at 3% concentration were added to PG: three were saturated fatty acids—C_8 (caprylic acid), C_{10} (capric acid), and C_{12} (lauric acid); and two were unsaturated fatty acids—C_{18} with one double bond (oleic acid) and C_{18} with two double bonds (linoleic acid). Among saturated fatty acids, C_{10}∼C_{12} chain lengths were reported to enhance the permeation of naloxone and tenoxicam the most effectively.[6,22] As summarized in Table 3, compared to other saturated fatty acids, C_{12} showed higher permeation flux, but failed to show a marked enhancing effect. However, the addition of unsaturated fatty acids (oleic acid or linoleic acid) enhanced permeation dramatically; their enhancement factors were 1246 and 446, respectively. The mechanism of oleic acid or linoleic acid as a penetration enhancer in this study was attributed to the increased partition. The parameter K was considerably high when 3% oleic acid or linoleic acid was added to PG.

Fatty alcohols are also known to be enhancers with lipophilic properties. Kitagawa, Endo, and Kametani[25] suggested that fatty alcohols increase fluidization in the stratum corneum by interacting with phospholipids at the boundary lipid layer. It also has been demonstrated that skin permeability increases with increasing chain length because of the increased distribution of fatty alcohols from aqueous vehicles to the skin. We added oleyl alcohol and lauryl alcohol at 3% concentration to PG. Oleyl alcohol increased permeation flux considerably, but the effect of lauryl alcohol was not significant. The enhancing effect of oleyl alcohol was thought to be due to the increased K like unsaturated fatty acids, and they showed long lag time, possibly attributable to their stabilization of the gel structure of the lipid layer.

Capsaicin, which has similar chemical structures with azone, e.g., a ring at one end of a long alkyl chain, was employed at 1% concentration to examine its enhancing effect. It failed to show the enhancing effect of OS, even though it has been demonstrated to enhance the permeation of naproxen through pre-treated human and rabbit skin with azone or capsaicin.[26]

Based on the results using cosolvents, PGMC-DGME (60:40) cosolvent, which showed excellent enhancing effects on the permeation of OS, was mixed with the same penetration enhancers that were used with PG. As listed in Table 4, all enhancers failed to show the significant enhancing effects compared to PGMC-DGME (60:40) cosolvent alone ($p>0.05$). Also,

there were no statistically significant differences between means ($p>0.05$). It was thought that as this binary cosolvent itself showed a maximized flux, the effect of enhancers added was not observed.

As mentioned earlier, for the effective transdermal delivery system, about 10 mg a day should be delivered into the blood circulation via the skin. When it is postulated that 20 cm^2 patch is prepared, the flux of 20.8 $\mu g/cm^2/h$ is required. Among various vehicles and penetration enhancers used in this study, combinations of oleic acid, linoleic acid, or oleyl alcohol with PG, or PGMC-DGME (60:40) cosolvent could be used for the design of the OS transdermal system.

REFERENCES

1. Ye, J.H.; Ponnudurai, R.; Schaefer, R. Ondansetron: a selective 5-HT(3) receptor antagonist and its applications in CNS-related disorders. CNS Drug Rev. **2001**, *7* (2), 199–213.
2. Walton, S.M. Advances in use of the 5-HT3 receptor antagonists. Expert Opin. Pharmacother. **2000**, *1* (2), 207–223.
3. Gregory, R.E.; Ettinger, D.S. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting: a comparison of their pharmacology and clinical efficacy. Drugs **1998**, *55* (2), 173–189.
4. Blackwell, C.P.; Harding, S.M. The clinical pharmacology of ondansetron. Eur. J. Cancer Clin. Oncol. **1989**, *25* (Suppl. 1), S21–S24.
5. Gwak, H.S.; Chun, I.K. Effect of vehicles and penetration enhancers on the in vitro percutaneous absorption of tenoxicam through hairless mouse skin. Int. J. Pharm. **2002**, *236* (1–2), 57–64.
6. Gwak, H.S.; Kim, S.U.; Chun, I.K. Effect of vehicles and enhancers on the in vitro permeation of melatonin through hairless mouse skin. Arch. Pharm. Res. **2002**, *25* (3), 392–396.
7. Nokhodchi, A.; Shokri, J.; Dashbolaghi, A.; Hassan-Zadeh, D.; Ghafourian, T.; Barzegar-Jalali, M. The enhancement effect of surfactants on the penetration of lorazepam through rat skin. Int. J. Pharm. **2003**, *250* (2), 359–369.
8. Culy, C.R.; Bhana, N.; Plosker, G.L. Ondansetron: a review of its use as an antiemetic in children. Paediatr. Drugs **2001**, *3* (6), 441–479.
9. Barry, B.W. Percutaneous absorption. In *Dermatological Formulations*; Barry, B.W., Ed.; Marcel Dekker, Inc.: New York, 1983; 49–94.
10. Friend, D.R.; Heller, J. Simple alkyl esters as skin penetration enhancers. In *Pharmaceutical Skin Penetration Enhancement*; Walters, K.A., Hadgraft, J., Eds.; Marcel Dekker, Inc.: New York, 1993; 31–56.
11. Kim, D.D.; Kim, J.L.; Chien, Y.W. Mutual hairless rat skin permeation-enhancing effect of ethanol/water system and oleic acid. J. Pharm. Sci. **1996**, *85* (11), 1191–1195.
12. Doh, H.J.; Cho, W.J.; Yong, C.S.; Choi, H.G.; Kim, J.S.; Lee, C.H.; Kim, D.D. Synthesis and evaluation of ketorolac ester prodrugs for transdermal delivery. J. Pharm. Sci. **2003**, *92* (5), 1008–1017.
13. Shirley, M.N. Compatibility and synergy of permeation enhancers with solvents, excipients, and drugs. In *Drug Permeation Enhancement*; Dean, S.H., Ed.; Marcel Dekker, Inc.: New York, 1994; 91–105.
14. Barry, B.W. Mode of action of penetration enhancers in human skin. J. Control. Release **1987**, *6*, 85–97.
15. Goto, S.; Uchida, T.; Lee, C.K.; Yasutake, T.; Zhang, J.B. Effect of various vehicles on ketoprofen permeation across excised hairless mouse skin. J. Pharm. Sci. **1993**, *82* (9), 959–963.
16. Oh, H.J.; Oh, Y.K.; Kim, C.K. Effects of vehicles and enhancers on transdermal delivery of melatonin. Int. J. Pharm. **2001**, *212* (1), 63–71.
17. Cho, Y.J.; Choi, H.K. Enhancement of percutaneous absorption of ketoprofen: effect of vehicles and adhesive matrix. Int. J. Pharm. **1998**, *169* (1), 95–104.
18. Green, P.G.; Guy, R.H.; Hadgraft, J. In vitro and in vivo enhancement of skin permeation with oleic acid and lauric acids. Int. J. Pharm. **1988**, *48* (1–3), 103–111.
19. Yamada, M.; Uda, Y.; Tanigawara, Y. Mechanism of enhancement of percutaneous absorption of molsidomine by oleic acid. Chem. Pharm. Bull. **1987**, *35* (8), 3399–3406.
20. Cooper, E.R. Increased skin permeability for lipophilic molecules. J. Pharm. Sci. **1984**, *73* (8), 153–1156.
21. Cooper, E.R.; Merritt, E.W.; Smith, R.L. Effect of fatty acids and alcohols on the penetration of acyclovir across human skin in vitro. J. Pharm. Sci. **1985**, *74* (6), 688–689.
22. Aungst, B.J.; Rogers, N.J.; Shefter, E. Enhancement of naloxone penetration through human skin in vitro using fatty acids, fatty alcohols, surfactants, sulfoxides and amides. Int. J. Pharm. **1986**, *33* (1–3), 225–234.
23. Elias, P.M. Epidermal lipids, barrier function, and

desquamation. J. Invest. Dermatol. **1983**, *80* (1), 44–49.
24. Nomura, H.; Fusao, K.; Sugimoto, Y.; Miyashita, Y.; Dohi, M.; Kato, Y. Percutaneous absorption of indomethacin from mixtures of fatty alcohol and propylene glycol (FAPG bases) through rat skin: effects of oleic acid added to FAPG base. Chem. Pharm. Bull. **1990**, *38* (5), 1421–1424.
25. Kitagawa, S.; Endo, J.; Kametani, F. Effects of long-chain *cis*-unsaturated fatty acids and their alcohol analogues on aggregation of bovine platelets and their relation with membrane fluidity change. Biochem. Biophys. Acta **1985**, *818* (2), 391–397.
26. Degim, I.T.; Uslu, A.; Hadgraft, J.; Atay, T.; Akay, C.; Cevheroglu, S. The effects of Azone and capsaicin on the permeation of naproxen through human skin. Int. J. Pharm. **1999**, *179* (1), 21–25.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016