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Transdermal permeation of selegiline from hydrogel-membrane drug delivery systems

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ABSTRACT

In the present work, we attempted to design a transdermal system for delivering selegiline using a hydrogel-based drug reservoir and a rate-controlling membrane (Solupor polyethylene membranes). The appearances of these preparations were evaluated by scanning electron microscopy (SEM), and the in vitro skin permeation of selegiline across porcine skin was examined. Both the *R*- and *S*-forms of selegiline were examined in this study to elucidate the stereoselectivity of skin to selegiline. Solupor membranes and hydrogels exhibited a cross-linking structure with micropores. *R*-Selegiline revealed a flux of 1.13 $\mu g/cm^2/h$ across porcine skin. Solupor membranes were rate limiting for skin permeation of selegiline. Around a 2-fold reduction in the drug flux was determined after Solupor membrane incorporation. There were no significant differences in drug flux across the four Solupor membranes tested. The flux of *R*-selegiline from cellulose hydrogels approximated that from the aqueous solution (control). Both the membrane and hydrogel greatly reduced the inter-subject variations in skin permeation. According to the results of skin permeation and the partition coefficient between the skin and water ($\log P_{skin/water}$), the *S*-enantiomer may be preferable for permeation into the skin. However, the *R*- and *S*-forms demonstrated equal absorption of the drug fluxed in the presence of the membrane and/or the hydrogel. The results of this study encouraged us to further investigate hydrogel-membrane delivery systems for transdermal selegiline administration.

1. Introduction

Major depressive disorder (MDD) is a highly prevalent and disabling condition. It has a lifetime prevalence of ~16% in the US; worldwide, it is the leading cause of a non-fatal disease burden and the fourth leading cause of total disease burden (Holtzheimer and Nemeroff, 2006; Frampton and Plosker, 2007). Selegiline, an irreversible inhibitor with selectivity for monoamine oxidase type B (MAO-B) at low oral doses, has an established efficacy profile for treating MDD (Pae et al., 2007). Selegiline also shows potential indications for treating Parkinson's disease, Alzheimer's disease, attention deficiency hyperactivity disorder, and cocaine addiction (Elkashef et al., 2006; Thase, 2006; Fernandez and Chen, 2007). The selegiline transdermal system (STS) recently approved for MDD treatment provides greater systemic delivery of selegiline to the brain with relative sparing of the gastrointestinal MAO type A (MAO-A) enzyme (Robinson and Amsterdam, 2008). STS avoids the first-pass effect and achieves antidepressant concentrations of selegiline in neuronal tissues with fewer effects on gastrointestinal MAO-A, the principal enzymatic barrier to the ingestion of tyramine (Small and Dubois, 2007). It is especially feasible for elderly and Parkinsonism patients since they are known to suffer from swallowing difficulties (Pae et al., 2007).

A concern for STS is skin reactions. The most common side effects of the STS patch are mild skin rash, itching, redness, and irritation. The clinical trials have shown a 24–40% of skin reaction occurrence for the patients treated with the STS (Feiger et al., 2006; Howland, 2006; Patkar et al., 2006; Frampton and Plosker, 2007). Hence there is still a need to develop novel systems for skin permeation of selegiline. There are two traditional designs of transdermal patches: matrix-type and membrane systems. The STS is a matrix-type transdermal system consisting of three layers: a backing film, adhesive/drug layer, and release liner. The present study was carried out to develop a transdermal selegiline formulation using a hydrogel-based drug reservoir and a rate-controlling membrane. For this study, a polyethylene microporous membrane (Solupor) was used as the rate-controlling material in this transdermal system. Solupor is a polymeric film composed of a unique combination of randomly oriented fibrils of ultra-high molecular weight (MW) polyethylene of $5–7 \times 10^6$ Da (Ooms et al., 2001). A taurate/porrolidone copolymer and cellulose polymers were selected to form the drug reservoir. The microscopic appear-

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ances of the membranes and hydrogels were examined in this work. The ability of the systems to deliver selegiline was conducted using an in vitro Franz diffusion assembly. Furthermore, an in vitro study was conducted to compare the skin permeation of the *R*- and *S*-enantiomers of selegiline to explore if there is any stereoselectivity with transdermal delivery.

2. Materials and methods

2.1. Materials

R-Selegiline hydrochloride and *S*-deprenyl hydrochloride (the *S*-enantiomer of selegiline) were obtained from Sigma Chemical (St. Louis, MO, USA). The ammonium acryloyldimethyltaurate/vinylporrolidone copolymer (AVC) was supplied by Clariant International (Frankfurt, Germany). Carboxylmethyl cellulose sodium (CMC), hydroxyethyl cellulose (HEC), and hydroxypropyl cellulose (HPC, 1000–4000 cps) were purchased from Wako Chemical (Tokyo, Japan). A series of Solupor membranes was kindly provided by Teijin Solfill (Tokyo, Japan), which was authorized by DSM Solutech (Heerlen, the Netherlands). All other chemicals and solvents were of analytical grade

2.2. Preparation of hydrogels

A polymer (5%, w/v in the final product) and selegiline (0.07%, w/v in the final product) were added to a half-volume of double-distilled water with continuous stirring for 1 h. The other half-volume of double-distilled water was added after 24 h of incubation at room temperature. The total volume of the final product was 10 ml. The hydrogel formulations were used to perform the experiments 24 h after preparation.

2.3. Scanning electron microscopic (SEM) examination

The Solupor membranes and hydrogels were examined by SEM. The hydrogels were frozen at −80 °C and then lyophilized by a freeze-drying method. Samples were fractured in liquid nitrogen and sputter-coated with gold–palladium in an ion coater. The resulting dried samples were examined using a Hitachi S-3000N SEM (Tokyo, Japan). The magnification of the imaging was 500×.

2.4. Atomic force microscopic (AFM) examination

Solupor membranes were further examined by AFM (XE-70, Park Systems, Suwon, Korea). Imaging was carried out using silicon nitrile tip (model ACTA, AppNano, Santa Clara, CA, USA). The non-contact mode was applied to drive the cantilever.

2.5. Preparation of skin membranes

Specific pathogen-free (SPF) pigs (1-week-old) were supplied by the Animal Technology Institute Taiwan (Miaoli, Taiwan). Full-thickness porcine skin was excised from the dorsal region of the pigs. The subcutaneous fat, tissue, blood vessel, and epidermal hairs were carefully removed. To obtain delipidized skin, the stratum corneum (SC) side was pretreated with chloroform–methanol (2:1) for 1 h.

2.6. In vitro skin permeation

Porcine skin was mounted on the receptor compartment of a Franz diffusion assembly with the SC side facing upwards into the donor compartment. Five and a half-milliliters of pH 7.4 buffer were used as the receptor medium. The donor compartment was filled with 0.5 g of vehicle containing selegiline. The available diffusion area between compartments was 0.785 cm^2. The stirring rate and temperature were kept at 600 rpm and 37 °C, respectively. At appropriate intervals, 300-μl aliquots of the receptor medium were withdrawn and immediately replaced with an equal volume of fresh medium. The duration of this experiment was 48 h. Samples were assayed by high-performance liquid chromatography (HPLC).

2.7. HPLC analytical method

The HPLC system for selegiline included a Hitachi (Tokyo, Japan) L-7110 pump, a Hitachi L-7200 sample processor, and a Hitachi L-7400 UV–vis detector. A 25-cm-long, 4-mm inner diameter stainless RP-18 column (Merck, Darmstadt, Germany) was used. The mobile phase was an acetonitrile: pH 7.0 buffer (65:35) at a flow rate of 1.0 ml/min. The UV–vis detector was set to 205 nm.

2.8. Octanol/water partition coefficient ($\log P_{octanol/water}$)

A 1:1 (v/v) ratio of water saturated with octanol and octanol saturated with water was used to partition selegiline of the *R*- and *S*-forms. An appropriate amount of selegiline was added to the water phase in a test tube. The tube was shaken for 24 h at 37 °C at a rate of 200 rpm. Samples from each phase were removed using a syringe. Concentrations of selegiline were determined by HPLC. The $\log P_{octanol/water}$ was calculated by the following equation:

$$\log P_{octanol/water} = \log C_{octanol}/C_{water};$$

where $C_{octanol}$ represents the drug concentration in the octanol phase after 24 h of shaking and C_{water} represents the drug concentration in the water phase.

2.9. Skin/water partition coefficient ($\log P_{skin/water}$)

A piece of porcine skin (0.7 × 0.7 cm) was positioned in the wells of a 24-well culture plate (17-mm inner diameter) with the SC side downward. Double-distilled water (200 μl) with selegiline of the *R*- or *S*-form (0.07%, w/v) was pipetted into the bottom of the well. After a 12-h incubation at 37 °C, the drug medium was withdrawn for analysis by HPLC. The skin/water partition coefficient ($\log P_{skin/water}$) was calculated by the following equation:

$$\log P_{skin/water} = \log (C_{0h} - C_{24h}/C_{24h});$$

where C_{0h} represents the total drug concentration in the medium at 0 h before the experiment and C_{24h} represents the remaining drug concentration in the medium after incubation.

2.10. Statistical analysis

Statistical analysis of differences between different treatments was performed using unpaired Student's *t*-test. A 0.05 level of probability was taken as the level of significance. An analysis of variance (ANOVA) test was also used.

3. Results

3.1. Microscopic examination of Solupor membranes

A series of Solupor membranes was incorporated into a selegiline delivery system for controlling drug permeation across the skin. These included 7P03, 8P07, 10P05, and 16P05 membranes. Solupor membranes are composed of very high MW polyethylene. The polyethylene film has microporous characteristics as shown in

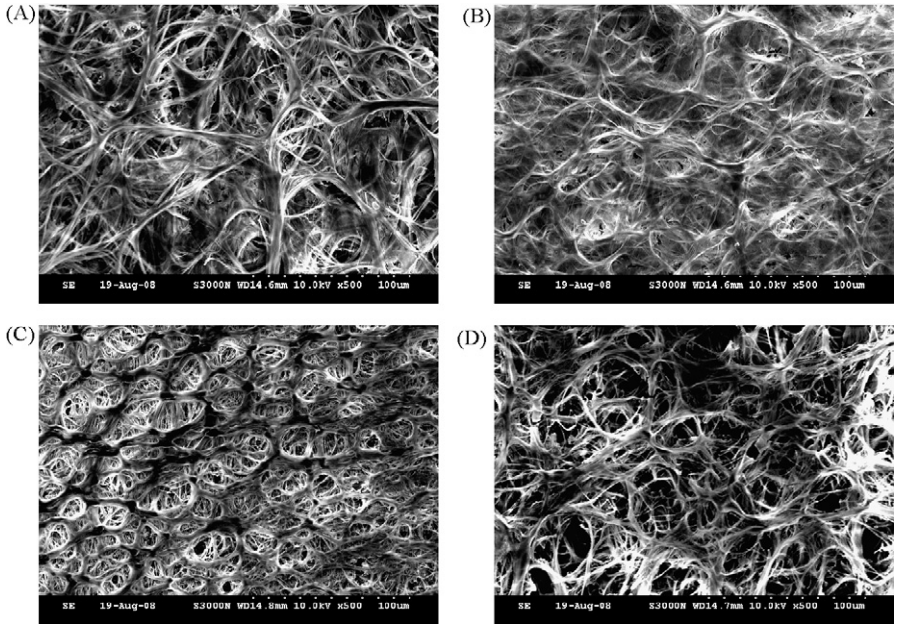


Fig. 1. Scanning electron microscopic (SEM) images (magnification 300×) of Solupor 7P03 (A), 8P07 (B), 10P05 (C), and 16P05 (D).

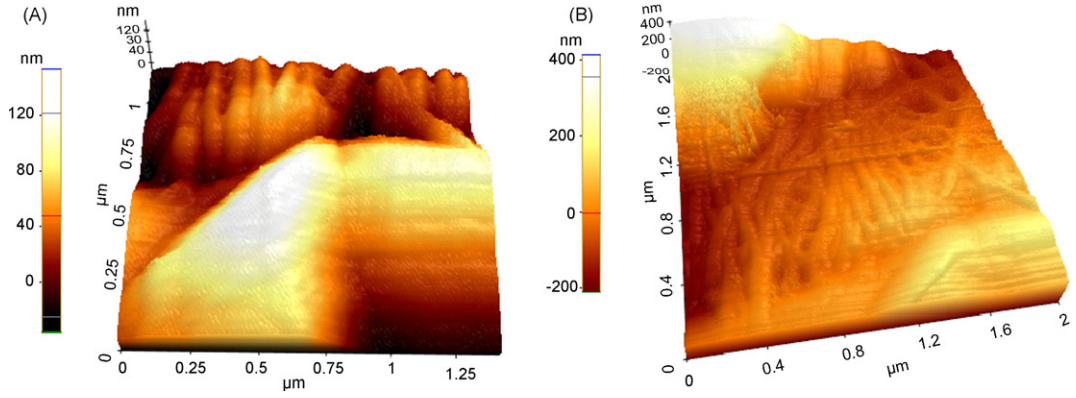


Fig. 2. Images of atomic force microscopy (AFM) of the surface of Solupor 8P07 viewed from different angles (A and B).

Fig. 1. It can be seen that the morphology of Solupor is composed of thick and thin fibrils. In order to confirm the structure of Solupor, AFM was used to examine the microscopic appearance of the membrane surface. Fig. 2A and B shows the Solupor 8P07 surface at different angles of view. The thicker fibrils contributed to the upper surface of the membrane. The diameter of the thick fibrils was approximately 0.75–1.0 μm. The high mechanical properties of the films may be due to the bi-directionally oriented thick fibrils. Table 1 represents the physicochemical characteristics of four Solupor membranes adapted from product information provided by DSM Solutech. Solupor 16P05 had the greatest thickness, followed by 10P05, 8P07, and 7P03. Solupor 8P07 with the largest pore size possessed the lowest Gurley number. A contrary result was observed for Solupor 7P03. The Gurley number (s/50 ml) is proportional to τ^2, where τ is the tortuosity. Tortuosity indicates the effective path length through the pores inside the membrane, while the Gurley number is an indicator of the permeability of a membrane (Ooms et al., 2001). Since Solupor 8P07 had a much lower Gurley number, it therefore had a more open microstructure than the others.

Table 1
Physicochemical characteristics of Solupor membranes.

Characteristics	7P03	8P07	10P05	16P05
Total weight/surface (g/m^2)	7	8	10	16
Thickness (μm)	50	50	60	120
Porosity (%)	85	85	83	87
Mean pore size (μm)	0.3	0.7	0.5	0.5
Gurley number (s/50 ml)	15	2	4	3

Adapted from the product information by DSM Solutech.

3.2. Microscopic examination of hydrogels

Four hydrogel types were formulated to regulate selegiline permeation, including AVC, CMC, HEC, and HPC. The freeze-dried forms of the hydrogels were prepared to examine the SEM appearance. The SEM results showed that the hydrogels were a network with sponge-like structures as shown in Fig. 3. The micrographs show that the spherical pores were well interconnected throughout the scaffold matrix. The white portion is the polymer backbone and the black portion is the space occupied by the water molecules if the polymer had been hydrolyzed with water. It can be observed that the network structure of AVC was more condensed than that of cellulose hydrogels. Among the three cellulose hydrogels, HPC showed the largest pore size (300–400 μm), followed by HEC (100–200 μm) and CMC (50–100 μm).

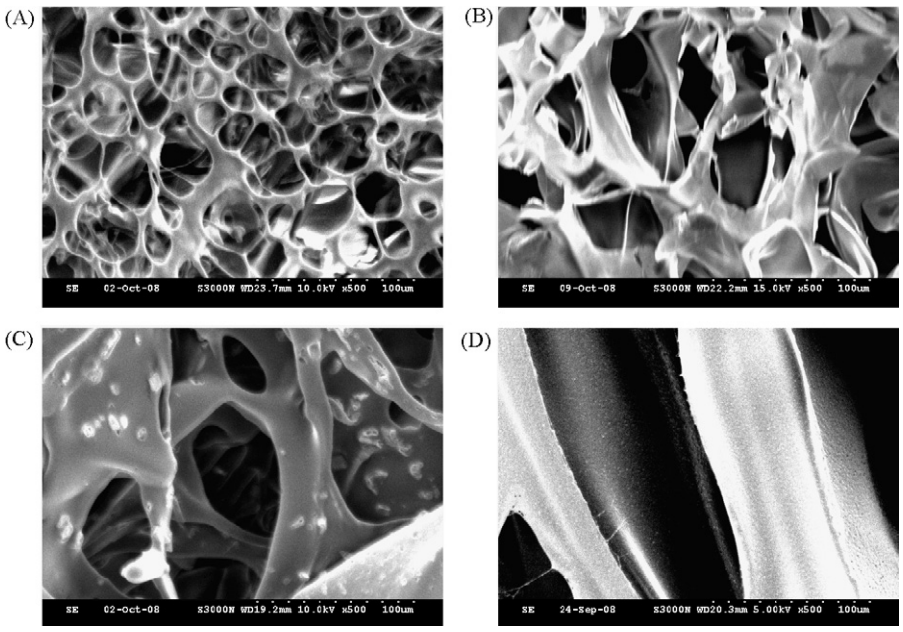


Fig. 3. Scanning electron microscopic (SEM) images (magnification 300×) of the cross-section of the AVC (A), CMC (B), HEC (C), and HPC (D) hydrogels after the freeze-drying process.

3.3. Skin permeation of R-selegiline

A series of Solupor membranes was incorporated on the SC side of the porcine skin to evaluate the effect of these membranes on the transdermal delivery of *R*-selegiline. The cumulative amount–time profiles for various formulations were plotted. The slopes of the resulting linear plots were calculated, and the flux ($\mu g/cm^2/h$) was determined from the slope. A zero-order equation was suitable for use with the curves of all of these formulations. Table 2 summarizes the *R*-selegiline flux from double-distilled water with or without Solupor membranes. Fig. 4 shows an example of a *R*-selegiline permeation profile to illustrate the permeation kinetics during 48 h. Cumulative amount–time profiles demonstrated the attainment of a steady-state flux of *R*-selegiline across the skin. *R*-Selegiline showed a flux of 1.13 $\mu g/cm^2/h$ across porcine skin with no membrane. A wide inter-subject variation was observed (with a coefficient of variance of 143%). This variation can probably be explained by actual biological and morphological differences among skin tissues of different subjects. The permeation of *R*-selegiline across skin with Solupor was slower than its permeation directly across skin without Solupor ($p < 0.05$). A ~2-fold reduction of drug flux was detected after membrane incorporation for all Solupor membranes tested. There was no significant difference ($p > 0.05$) in flux among the four membranes. Another observation was that the coefficient of variance of the flux was substantially reduced to 22–63% after membrane incorporation in the systems.

Table 2
The effect of Solupor membranes on the flux of *R*-selegiline across porcine skin.

Formulation	Flux ($\mu g/cm^2/h$)
Control (no Solupor)	1.13 ± 1.62
7P03	0.65 ± 0.41
8P07	0.49 ± 0.11
10P05	0.54 ± 0.15
16P05	0.61 ± 0.18

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

Hydrogels with various polymers were used as vehicles to examine *R*-selegiline permeation as depicted in Table 3. The drug permeation from hydrogels across the skin followed zero-order kinetics. Among the hydrogels, the formulation with AVC exhibited the lowest flux value. A 2.5-fold decrease in drug permeation was detected for AVC compared to the control (double-distilled water as the drug vehicle). The three cellulose hydrogels showed a negligible resistance to *R*-selegiline delivery. There was no statistically significant difference ($p > 0.05$) between the flux across skin with or without the cellulose polymers. The inter-subject variation was also diminished when using the hydrogels as drug reservoirs. The coefficients of variance ranged 15–29% for drug flux from the hydrogels.

Permeation from the hydrogel matrix of *R*-selegiline through the polyethylene membrane is shown in Table 3. The application of the hydrogel with a membrane decreased the drug flux compared to the hydrogel alone ($p < 0.05$). On the other hand, flux values from the aqueous solution across Solupor were similar ($p > 0.05$) to those

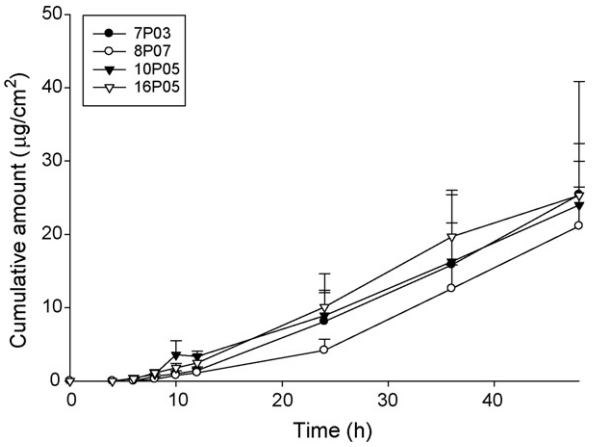


Fig. 4. In vitro cumulative amount versus time profiles of transdermal *R*-selegiline application permeating across pig skin from aqueous buffer with different Solupor membranes. Each value represents the mean ± S.D. ($n = 4$).

Table 3
The effect of hydrogels on the flux of *R*-selegiline across porcine skin in the absence or presence of Solupor membranes.

Formulation	Flux (μg/cm²/h)
AVC[a]	0.45 ± 0.12
CMC[b]	1.03 ± 0.15
HEC[c]	1.09 ± 0.32
HPC[d]	0.93 ± 0.19
CMC/7P03	0.45 ± 0.09
CMC/16P05	0.70 ± 0.11
HEC/7P03	0.67 ± 0.14
HEC/16P05	0.62 ± 0.19

Each value represents the mean ± S.D. ($n = 4$).
[a] Ammonium acryloyldimethyltaurate/vinylporrolidone copolymer.
[b] Carboxylmethyl cellulose sodium.
[c] Hydroxyethyl cellulose.
[d] Hydroxypropyl cellulose.

from a hydrogel across Solupor. The CMC/7P03 system showed a lower flux ($p < 0.05$) compared to the other three combinations.

3.4. Comparison of skin permeation between the R- and S-forms

The enantioselective transfer of selegiline from hydrogels across the polyethylene membrane through porcine skin as a permeation barrier was studied, and the permeation profiles are shown in Fig. 5. Permeation of the *S*-form from the aqueous solution was higher than that of the *R*-form according to the mean flux value. However, there was no significant difference ($p > 0.05$) between the fluxes of the two forms because of the high standard deviation of the two groups. The predominant route for most permeant transport across skin is the intercellular region of the SC. The delipidization process can remove intercellular lipids in the SC (Huang et al., 2008). Although there are similarities in the chemical structure of the enantiomers, the skin permeation across delipidized skin showed a discrepancy. The data of the *R*-form flux across delipidized skin was 1.5-fold higher ($p < 0.05$) than that of the *S*-form. The flux of *R*-selegiline was significantly higher ($p < 0.05$) for delipidized skin than for intact skin. On the other hand, delipidization did not enhance *S*-isomer permeation across porcine skin ($p > 0.05$). The statistical analysis revealed no significant difference ($p > 0.05$) between the flux of *R*- and *S*-enantiomers after the incorporation of Solupor membrane and/or hydrogel in the delivery systems.

The physicochemical characteristics of both isomers were determined as summarized in Table 4. A similar melting point was detected for both enantiomers. Determination of the $\log P_{\text{octanol/water}}$ value is a useful approach to evaluate the lipophilicity of a drug. There was no significant difference ($p > 0.05$) between

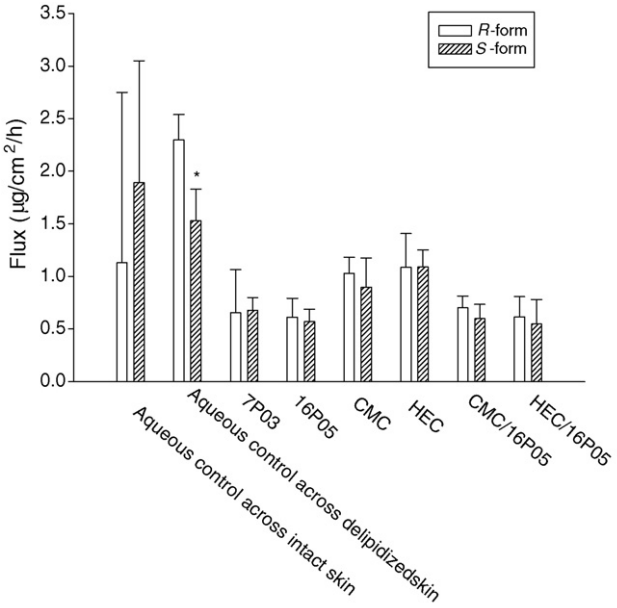


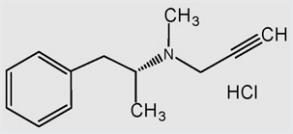
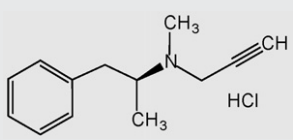
Fig. 5. Comparison of drug flux (μg/cm²/h) between *R*-selegiline and its *S*-enantiomer across intact and delipidized skin from the aqueous control, hydrogels, and Solupor membranes. Each value represents the mean ± S.D. ($n = 4$). * Indicate $p < 0.05$ between the flux of *R*-form and *S*-form.

the $\log P_{\text{octanol/water}}$ values of the enantiomers. The $\log P_{\text{skin/water}}$ value, the partitioning ability of the drug to skin tissue, of the *S*-form was about four times higher compared to that of the *R*-form ($p < 0.05$).

4. Discussion

The commercial transdermal delivery system of selegiline is an acrylic polymer-adhesive matrix skin patch. We have designed a different delivery system for embedding selegiline to evaluate its permeation across the skin. The use of controlled-release membranes is one of the methods to regulate drug release. Solupor membranes are composed of >99.9% polyethylene. They have good chemical resistance, high tortuosity, and favorable biocompatibility and are non-irritating (Ooms et al., 2001; Fang et al., 2005). AVC copolymers and cellulose polymers were used to form the drug reservoir because of their non-toxic nature, swelling property, and ability to control drug release (Doelker, 1987). Hydrogels exhibited porous structures composed of sheets of polymers with interconnecting channels on the basis of the SEM analysis. According to our previous study (Hung et al., 2008), AVC and cellulose polymers exhibited a viscosity of 21–45 Pa s. This indicates a for-

Table 4
Physicochemical parameters of *R*-selegiline and its *S*-enantiomer.

Drug	Structure	Melting point (°C)	$\log P_{\text{octanol/water}}$	$\log P_{\text{skin/water}}$
R-form		142–143	−0.65 ± 0.08	0.21 ± 0.08
S-form		143–144	−0.55 ± 0.12	0.85 ± 0.38

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

mation of semisolid preparations. The three-dimensional structure of the hydrogels is often described as a mesh, with spaces between the polymer chains filled with water. The polymers have the ability to swell in water or aqueous solvent systems. The polymer structure is able to retain the solvents forming a swollen gel phase and in cross-linked systems (Narasimhan and Peppas, 1997; Fang et al., 2006).

A previous study (Rohatagi et al., 1997) also indicated the feasibility of using porcine skin as an animal model of human skin. Hence, the in vitro Franz diffusion cell with porcine skin as the permeation barrier was utilized in this work to examine selegiline delivery. All four Solupor membranes decreased the flux of *R*-selegiline across porcine skin. The much slower penetration indicates that the membranes were rate controlling, and that partitioning and diffusion in the membranes dominated the transfer process (Farinha et al., 2003). Since polyethylene membranes have microporous characteristics, transport of drug through the membranes occurred by diffusion through liquid-filled pore media. The porosity and pore size are indicators of the void volume. These two parameters did not correlate well with *R*-selegiline permeation (Table 1), suggesting that the void volume was not important in controlling drug permeation. It seems that none of the physicochemical characteristics of Solupor predominated drug transport across the skin. The path length and thickness of Solupor membranes were also not important in governing drug permeation.

Transdermal drug therapy is confounded by poor and erratic drug absorption. High inter- and intra-individual absorption rates also limit transdermal therapy to some agents (Lombardi Borgia et al., 2005). Pae et al. (2007) also demonstrated that selegiline absorption largely depends on the condition of a patient's skin. Our results confirm this feature. Although porcine skin is an ideal model for human skin, variations from pig to pig were large. However, this result may reflect the actual conditions which occur in the clinic. The skin is a greatly variable organ, for which species differences are prominent, and also a multitude of possible penetration routes exist (Baert et al., 2007). Solupor successfully reduced the variability of *R*-selegiline permeation among individuals. The low variation in drug flux following transdermal application may have been due to the uniformity and control capability of the membranes, which were effective for all subjects.

The inter-subject variation in flux was also reduced by incorporating hydrogels. Contrary to the polyethylene membranes, cellulose hydrogels did not lower the drug permeation compared to the aqueous control. This indicates the ease of *R*-selegiline diffusion from the hydrogel structure and partitioning from the hydrogel to the skin surface. The AVC hydrogel showed a high resistance to the penetration of *R*-selegiline. This may have been due to the smaller pore size and higher cross-linkage of the AVC hydrogel. The decrease in pore size would increase the tortuosity of the structure. The formation of such channels leads to an increase in the diffusion path length of the drug molecules (Zhan et al., 2006). There was no significant difference between the flux across Solupor in the presence or absence of a hydrogel reservoir. This result suggests that the diffusion of drug through Solupor membranes but not hydrogel was the predominant mechanism controlling the entire permeation process. Transport through membranes occurs via a two-step process: partitioning from the hydrogel into the membrane and diffusion through the membrane. *R*-Selegiline may quickly partition from the hydrogel to the membrane. Although the hydrogels did not provide a rate-limiting step for drug delivery, inter-individual variations of drug permeation across Solupor 7P03 largely decreased after incorporation. The semisolid forms such as hydrogels are also more applicable than a solution as a transdermal delivery system for clinical administration.

The *S*-enantiomer of selegiline is less effective than the *R*-form in treating neural diseases (Löscher and Hönack, 1995). Only the *R*-form can be called selegiline. The *S*-enantiomer transforms in the body to *S*-methamphetamine and via this mechanism possesses a strong central nervous system excitatory effect (Castro-Puyana et al., 2007). Since some drugs are found to be stereoselective when permeating via the skin (Zobrist et al., 2001; Heal and Pierce, 2006; Suedee et al., 2008), the permeation profiles of the *S*-enantiomer was established for comparison with those of *R*-selegiline. The in vitro skin permeation experiments demonstrated that the transdermal delivery of *R*- and *S*-forms was not stereoselective when permeating across intact skin. However, this lack of a difference may have been due to a high inter-subject variation of intact skin. The *S*-isomer flux was 1.7-times higher than that of the *R*-isomer.

Regardless of the different mechanisms implicated in transdermal delivery, the relative impermeability of the SC with its intercellular lipid bilayers provides the principal resistance to skin penetration (Shin et al., 2002). In order to elucidate the permeation of enantiomers, delipidized skin was used as the permeation barrier. The diffusion of the *R*- and *S*-forms through delipidized skin was found to be stereoselective, with the *R*-form showed the higher permeation. The results show that this process appeared to promote the flux of *R*-selegiline by eliminating the rate-limiting SC. This indicates that lipid bilayers in the SC contribute to the barrier function against skin absorption of *R*-selegiline. Permeation of the *S*-isomer did not increase with delipidization, suggesting the ease of *S*-isomer penetration via the intercellular region of the SC. The results suggest evidence of the selective absorption of *R*-form over *S*-form, especially in the intercellular pathways. Heard and Brain (1995) have demonstrated that ceramide monolayers in the intercellular lipids of SC produce qualitative evidence of stereoselective interaction. This chiral interaction can cause the difference in diffusion rates via skin. *S*-form of selegiline may favor this interaction as compared to the *R*-enantiomer. According to the previous works involved in the skin delivery of enantiomers (Roy et al., 1995; Panus et al., 1999), the *S*-form of ketorolac and ketoprofen also exhibits greater skin permeation the *R*-form. Further study is needed to explore the mechanisms about the relationship between drug structure and skin absorption. A reduction in the inter-individual variation of drug permeation after delipidization was also observed. This indicates that intercellular lipids are the main source of variations in selegiline delivery.

The much higher $\log P_{\text{skin/water}}$ values of the *S*-form compared to the *R*-form confirm the preferable entrance of the *S*-enantiomer into the SC, although the lipophilicity of these isomers is the same. The results obtained above suggest that the permeation mechanism of selegiline may predominantly be related to the delivery of specific molecules via facilitated transport pathways through selective channels in the SC. There was no stereoselective permeation of the *R*- and *S*-isomers from formulations containing Solupor and/or the hydrogel. This indicates that Solupor and the hydrogel did not show a stereoselectivity to selegiline diffusion. The control ability of the delivery system was hence further verified.

5. Conclusions

The present work was carried out to develop a Solupor- and hydrogel-moderated transdermal drug delivery system for selegiline. Both the Solupor membrane and hydrogel showed a cross-linking structure with micropores. Pore sizes of the Solupor membranes were smaller than those of the hydrogel. The experimental results suggest that Solupor can be used as a substrate to control the permeation of selegiline. The amount of drug permeating across the skin can be reduced by the membranes. The reductions in *R*-selegiline flux by different membrane types were comparable. The use of cellulose hydrogels as a reservoir for *R*-selegiline did not decrease the drug delivery via the skin. The

inter-subject variation from the skin was greatly reduced by both the Solupor membrane and hydrogel. Drug transfer through Solupor but not the hydrogel was demonstrated to be the rate-limiting step when the membrane and hydrogel were incorporated together as the delivery system. The stereoselective permeation of selegiline across delipidized skin reported in the current study may lead to the relatively higher permeation of the *S*-form than the *R*-form. Nevertheless, the presence of Solupor and/or hydrogel can diminish the stereoselectivity of the skin for isomers. Further study is needed to elucidate the effect of enantiomorphism on selegiline delivery.

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