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Formulation and *In vitro* Evaluation of Transdermal Drug Delivery System for Galantamine

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ABSTRACT – The effects of different formulation variables including pressure sensitive adhesive (PSA), permeation enhancer, thickness of the matrix and loading amount of drug on the transdermal absorption of galantamine were investigated across the hairless mouse skin. The permeation profile of galantamine was different depending on the types of PSA, loading amount of drug, thickness of the matrix and type of enhancer used. Highest flux of galantamine was obtained from acrylic PSA but crystals were formed in the patch within 72 h. Among the PSAs screened, crystal formation was not observed only in the patches formulated in Styrene Butadiene Styrene (SBS) matrix. Permeation rate increased linearly as the concentration of galantamine in SBS matrix increased from 2.5 to 15% w/w. Among the enhancers screened, Brij® 30 provided highest flux of galantamine. Matrix thickness of 80 μm was optimum for maintaining adhesiveness as well as consistently delivering galantamine for longer period of time.

Key words – Galantamine, Transdermal drug delivery, Pressure sensitive adhesive, Permeation enhancement

Alzheimer's disease (AD) is the most common form of dementia. It is a neurological disease characterized by loss of mental ability, severe enough to interfere with normal activities of daily living. AD usually occurs in old age, and is marked by a decline in cognitive functions such as remembering, reasoning, and planning. The median survival time for affected patients is approximately 8 yrs from the onset of symptoms (Coyle and Kershaw, 2001; Heinrich and Teoh, 2004). Galantamine is a tertiary alkaloid and a reversible, competitive acetyl cholinesterase inhibitor (Zarotsky et al., 2001). It is effective and well tolerated for symptomatic treatment of AD. It improves cognition, global function and daily life activities of the patients (Scott and Gao, 2000; Corey Bloom, 2003).

At present, galantamine is available in the market as tablet or oral solution (Raskind et al., 2000; Erkinjuntti, 2002; Migliaccio et al., 2003; Heinrich and Teoh, 2004). Oral administration of galantamine is followed by side effects like abdominal pain (Nordberg and Svensson, 1999), nausea (Fulton and Benfield, 1996; Sramek et al., 2000; Poirer, 2002), and diarrhea (Nordberg and Svensson, 1999; Cummings, 2003). Therefore, an alternative way of galantamine administration could be helpful for the success of therapy.

Transdermal drug delivery system (TDDS) is advantageous to minimize the gastrointestinal side effects such as nausea and vomiting, which are the most common adverse events leading even to discontinuation of treatment (Kays et al., 2007). TDDS offers benefits such as producing sustained and controlled plasma drug concentration, enhancing bioavailability and bypassing first-pass metabolism (Ghosh et al., 1997). Despite these advantages of TDDS, its use is often limited due to the outermost layer of the skin, stratum corneum (SC). Although this layer is only 20-25 μm thick, it provides a potential barrier to the penetration of many compounds and poses a major problem for therapeutic TDDS (Thomas and Finnin, 2004). Various approaches could be utilized to overcome the impermeability of skin. Among these approaches, chemical enhancers are commonly employed in the TDDS to facilitate the penetration of the administered drug (Williams and Barry, 2004). It is well known that the enhancing properties of chemical enhancers depend on the physicochemical properties of drugs and other formulation components (Cho and Choi, 1998). In the matrix based TDDS, especially drug in adhesive (DIA) type, PSA fulfills both the function of adhesion to skin, and serves as formulation foundation (Wilking et al., 1994). Compatibility among drug, PSA and enhancer as well as the adhesive property must be considered before the selection of appropriate PSA.

The objective of this study was to develop DIA type TDDS for galantamine. Different formulation variables like PSA, enhancer and thickness of matrix were evaluated to study their

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effect on the permeation of galantamine through hairless mouse skin.

Materials and Methods

Materials

Galantamine was purchased from Ivax Pharmaceuticals (Opava-Komarot, Czech Republic). PEG-8 glyceryl caprylate/caprate (Labrasol®) was obtained from Gattefosse (Gennevillers, France). PEG-8 glyceryl linoleate (Labrafil® 2609) was purchased from Masung Co. (Seoul, Korea). Oleic acid, propylene glycol and sorbitan monooleate (Span® 80) were purchased from Junsei Chemical (Tokyo, Japan). Isopropyl myristate (IPM) and PEG-20 almond glyceride (Crovol® A40) were obtained from Croda (Parsippany, NJ, USA). Cineole, Lauryl alcohol and Brij® 30 were purchased from Sigma Chemical (St. Louis, MO, USA). Acrylic, poly isobutylene (PIB) and SBS PSA solutions, in organic solvents, were obtained from National Starch and Chemical Company (Bridgewater, NJ, USA). Silicone PSA solution (BioPSA® 7-4302) was obtained from Dow Corning (Midland, MI, USA). All other chemicals were of reagent grade or above and were used without further purification.

Methods

Preparation of adhesive matrix containing galantamine

Drug solution was prepared by dissolving galantamine in chloroform and mixed with enhancer and PSA. The resulting mixture was casted onto the release liner. It was set at room temperature for 10 min, and subsequently dried at 80°C for 20 minutes to remove the residual organic solvents. After removal of the solvents, dried film was laminated with a polyester backing film (ScotchPak® 9728, 3M, USA).

Skin membrane preparation

Full thickness skin was excised from hairless mice aged 6-8 weeks. The mice were sacrificed humanely under anesthetic condition with diethyl ether. Subcutaneous fat, tissue and blood vessel were carefully removed with scissors and scalpel. Only the skin free of holes or any other defects was used. To perform the *in vitro* skin permeation study, the skin was cut into pieces of around 6 cm^2.

In vitro transdermal permeation experiment

The *in vitro* transdermal permeation behavior of galantamine from TDDS across hairless mouse skin was investigated by using modified Franz diffusion cells. Flow-through diffusion cell system was used and the temperature was maintained at 37°C. The surface area of receiver cell opening was 2 cm^2, and its volume 5.5 mL. The receiver cell was filled with phosphate buffer solution (pH 6.0), and the media was stirred by teflon-coated magnetic bar at 500 rpm. The excised skin was mounted onto each receiver cell. O-ring and cell cap were placed on the top of each skin. These components were then clamped. The samples were collected every 4 h for 24 h and assayed by high performance liquid chromatography (HPLC).

Analytical method

Galantamine was analyzed using previously reported method (Ang et al., 2006) with slight modification. HPLC system (Shimadzu Scientific Instruments, MD) consisting of a UV detector (SPD-10A), C18 column (4.6 × 100 mm, 5 μm, Gemini), a pump (LC-10AD), and an automatic injector (SIL-10A) was used. Briefly, the wavelength of the UV detector was 230 nm, the column temperature was maintained at 30°C, the flow rate was 1 mL/min and injection volume was 30 μL. The mobile phase consisted of methanol/water with 0.2% triethylamine adjusted to pH 6.4 by phosphoric acid (35/65).

Data deduction

The permeation data were analyzed by the method developed for flow through diffusion cell system (Choi and Angello, 1994).

Results and Discussion

Effect of pressure sensitive adhesive

Selection of appropriate PSA matrix is important in designing TDDS. It is well known that the physicochemical properties of PSA can significantly affect the flux of drug across the skin (Subedi et al., 2010). The effect of PSA matrix on the permeation of galantamine was investigated using acrylic,

Table I. *Physicochemical information of PSAs used in the study*

Trade name	Chemical Composition	Functional group
Durotak® 87-2510	Acrylate	OH
Durotak® 87-504 A	Acrylate rubber hybrid	OH
Durotak® 87-2979	Acrylate vinyl acetate	OH/COOH
Durotak® 87-9301	Acrylate copolymer	Non functional
SBS 6174	Thermoplastic rubber block copolymer	Non functional
BIO-PSA® 7-4302	Siloxane	Non functional
PIB 10711-62	Polyisobutylene	Non functional

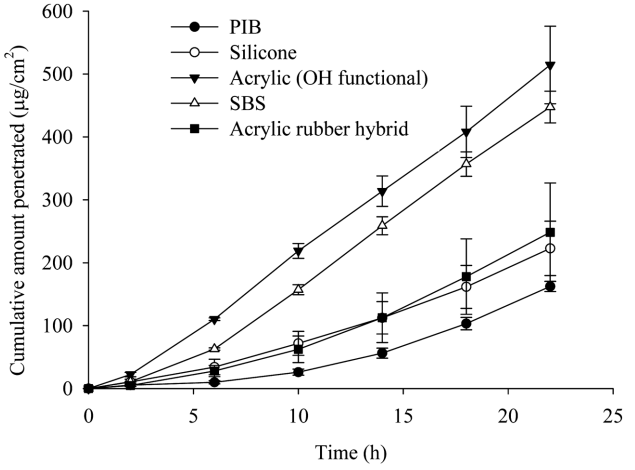

Figure 1. Effect of types of pressure sensitive adhesive on the permeation of galantamine across the hairless mouse skin at 15% w/w of drug load. Values are expressed as mean ± standard deviation. (n=3)

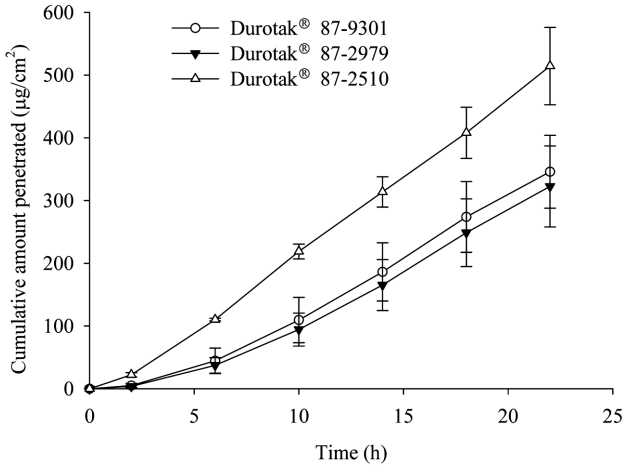

Figure 2. Effect of functional group in acrylic pressure sensitive adhesive on the permeation of galantamine at 15% w/w of drug load. Values are expressed as mean ± standard deviation. (n=3)

acrylic rubber hybrid, SBS, silicone and PIB matrices. The physicochemical properties of PSAs screened are given in the Table I. Initially, patches containing acrylic, acrylic rubber hybrid, SBS, silicone and PIB matrices were screened at 15% w/w drug load. The permeation rate of galantamine was highest from acrylic PSA followed by SBS, acrylic rubber hybrid, silicone and PIB (Fig. 1). The effect of different functional groups in acrylic PSA on the permeation of galantamine was also studied (Fig. 2). The highest permeation of galantamine was observed from the matrix containing acrylic adhesive with a hydroxyl functional group (Duro-Tak® 87-2510). The lowest permeation of galantamine was observed from acrylic PSA containing carboxyl functional group (Duro-Tak® 87-2979). This could be due to the interaction of tertiary amine group in

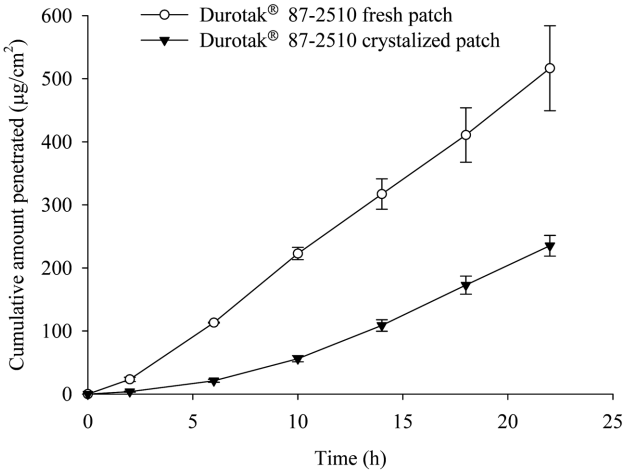

Figure 3. Comparison between fresh and crystallized patch prepared using acrylic pressure sensitive adhesive with hydroxyl functional group (Duro-Tak® 87-2510) at 15% w/w of drug load. Values are expressed as mean ± standard deviation. (n=3)

galantamine with the -COOH group in Duro-Tak® 87-2979. The possibility of this type of drug polymer interaction is widely reported (Kim et al., 2000; Morimoto et al., 1992; Subedi et al., 2010).

Observation of the patches stored at room temperature revealed that crystals developed in all the matrices, except SBS, within a week. Although highest flux was obtained from fresh samples prepared in acrylic matrix with hydroxyl functional group, the crystallization of the drug in the patch caused significant reduction in flux of the drug (Fig. 3). Other studies have also reported that the crystallization of drug in PSA matrix reduces the permeation rate of the drug across the skin and changes the adhesive properties of the matrix (Imani et al., 2010; Inoue et al., 2005; Kim and Choi, 2002). Considering drug loading capacity, appropriate permeation rate, and good adhesive properties, SBS matrix was selected for further study.

Effect of galantamine concentration on skin permeation

Fig. 4 shows the effect of drug loading in SBS matrix on the permeation of galantamine across the hairless mouse skin. When drug loading was increased from 2.5 to 15% w/w of polymer weight, permeation rate also increased proportionally. The correlation coefficient obtained between galantamine concentration in the patch and the average cumulative flux was $R^2 = 0.998$. At drug loading of 20% w/w, crystals were observed in the matrix within 72 h. Galantamine might have been supersaturated in the SBS matrix at concentrations above 15% w/w, which led to recrystallization of the drug in the matrix (Inoue et al., 2005; Kim and Choi, 2002). Roy et al. showed a linear increase in the permeation rate of fentanyl

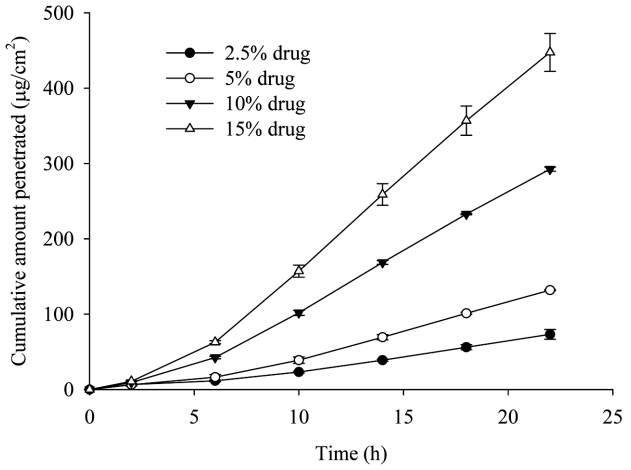

Figure 4. Effect of drug loading in SBS matrix on the permeation of galantamine across hairless mouse skin at dried matrix thickness of 80 μm. Values are expressed as mean ± standard deviation. (n=3)

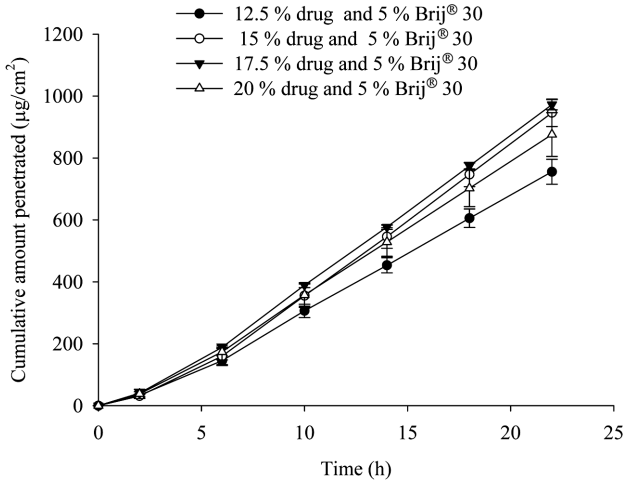

Figure 5. Effect of drug loading in the presence of enhancer on the permeation of galantamine in SBS matrix. Values are expressed as mean ± standard deviation. (n=3)

from PIB matrix for drug load up to saturation concentration (Roy et al., 1996). Further increase in the drug load did not lead to significant increase in permeation. To have a better insight and to optimize drug loading, the effect of drug loading on the flux of galantamine was also studied in the presence of an enhancer. Fig. 5 shows the effect of drug loading from 12.5 to 20% w/w, in the presence of 5% v/w Brij® 30. The permeation of galantamine increased significantly up to 15% w/w of drug load. However, beyond 15% w/w of drug load, flux remained almost constant, and it even decreased at 20% w/w of drug load. This decrease in flux could be due to the crystallization of galantamine in the matrix. In an earlier study, it was observed that the development of drug crystals in the matrix lead to reduction of thermodynamic activity and the

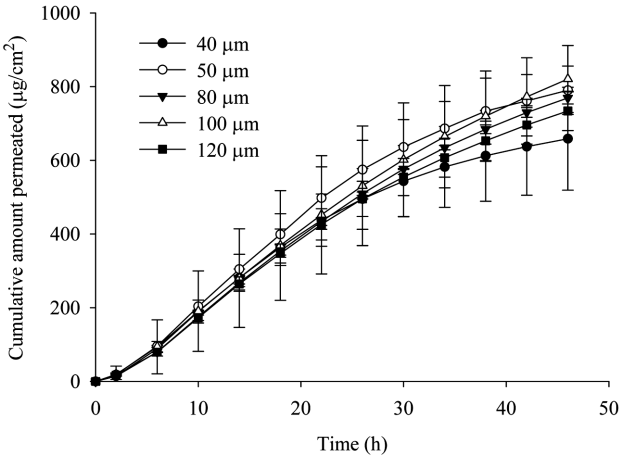

Figure 6. Effect of dried thickness of SBS matrix on the permeation of galantamine at 15% drug load for 48 h. Values are expressed as mean ± standard deviation. (n=3)

flux (Kim and Choi, 2002). Therefore, drug loading was fixed at 15% w/w for further study.

Effect of matrix thickness

The thickness of the matrix layer is one of the important parameters in the development of matrix-based TDDS. Thicker matrix is able to deliver higher amount of drug to the skin over relatively longer application time (Furuishi et al., 2008). It is due to higher amount of drug available for permeation from the patch. However, thicker matrix also has higher tendency to cause cold flow (Wokovich et al., 2006). Therefore, effect of thickness was studied in the galantamine loaded patches to evaluate the permeation as well as adhesion characteristics. During 24 h study, it was not possible to distinguish the permeation characteristics from matrices with various thicknesses. Prolonging the study up to 48 h, thicker adhesive matrices showed better and consistent profile (Fig. 6). Especially in the later part of study period, thinner matrices (40 and 50 μm) showed a declining permeation profile. One of the critical considerations in the fabrication of TDDS is adhesion to the skin (Banakar and Osborne, 1995). The adhesive properties of the prepared patches were manually evaluated by thumb tack test. It was found that matrix thickness above 50 μm possessed sufficient adhesive force. Beyond matrix thickness of 80 μm, flux did not increase significantly and the profile obtained was almost similar. Thicker matrix may not be desirable since it could result in cold flow upon applying on the skin (Wokovich et al., 2006). Therefore, considering the adhesiveness and potential cold flow, matrix thickness of 80 μm was selected for further study.

Table II. *Enhancement ratio of galantamine flux from the patches containing 15% w/w drug load and 5% v/w enhancer (with respect to dry polymer weight) in SBS matrix. Values are expressed as mean ± standard deviation. (n=3)*

Enhancer	Enhancement ratio*
Control	1.00 ± 0.00
Lauryl alcohol	1.28 ± 0.10
Labrafil® 2609	1.28 ± 0.03
Labrasol®	1.16 ± 0.07
Propylene glycol	0.76 ± 0.06
Span® 80	1.09 ± 0.07
Crovol® A40	0.98 ± 0.02
IPM	1.26 ± 0.14
PEG 400	0.92 ± 0.01
Brij® 30	1.68 ± 0.08
Cineole	1.12 ± 0.03
Triacetin	1.19 ± 0.01
Glycerin	0.86 ± 0.01
Lauroglycol® FCC	1.59 ± 0.04
Transcutol®	0.80 ± 0.02

*Enhancement ratio = Flux with enhancer / Flux without enhancer

Effect of enhancer

Incorporation of permeation enhancer is a widely used approach that reversibly reduces the permeability barrier of the SC (Williams and Barry, 2004). Enhancers can also act as a plasticizer, increasing the mobility of the drug in the matrix. Table II shows the effect of enhancers (5% v/w) in SBS matrix with 15% w/w drug load. Among the enhancers screened, Crovol® A40, propylene glycol, polyethylene glycol (PEG) 400, Transcutol® and glycerin did not enhance the permeation of galantamine. Whereas Lauroglycol® FCC, lauryl alcohol, triacetin, Isopropyl myristate (IPM), cineole, Brij® 30 and Labrafil® 2609 significantly enhanced the permeation of galantamine. Among them, Brij® 30 and Lauroglycol® FCC showed comparatively higher enhancement ratio for galantamine. It has been reported in the literature that Lauroglycol® FCC was used to enhance the permeation of drug by efficiently disrupting the skin barrier (Choi and Yong, 2002; Kikwai et al., 2002). Brij® 30 belongs to the chemical class of polyoxyethylene alkyl ether with HLB value of 9.7, ethylene oxide chain length of 4, and alkyl chain length of C-12. This structure imparts both lipophilic and hydrophilic characteristics to the enhancer, thus allowing it to enhance the penetration of a drug via both the lipophilic and the hydrophilic molecular mechanisms (Breuer, 1979; Walters et al., 1987). Although significant enhancement of galantamine flux was obtained from both Brij® 30 and Lauroglycol® FCC, Brij® 30 was selected for further study based on the highest enhancement ratio (Table II).

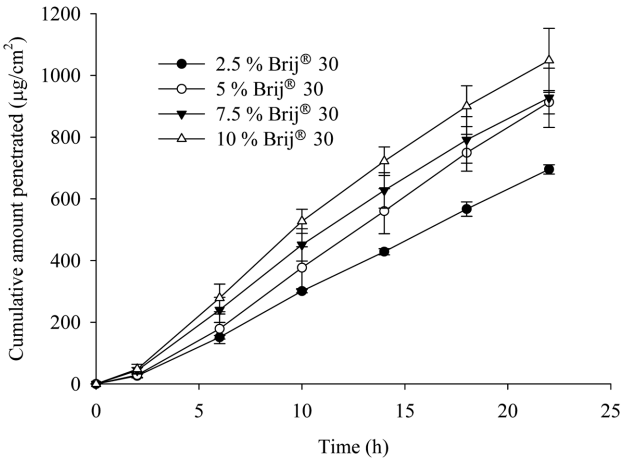

Figure 7. Effect of Brij® 30 concentration in SBS matrix on the permeation of galantamine across the hairless mouse skin at 15% w/w of drug load and dried matrix thickness of 80 μm. Values are expressed as mean ± standard deviation. (n=3)

The enhancing effect of Brij® 30 on the skin permeation of galantamine was evaluated at different concentrations (2.5-10% v/w of polymer weight), with 15% w/w of drug load. An increasing trend in the permeation of galantamine was observed with an increase in the enhancer concentration (Fig. 7). Significant increase in permeation profile was observed when the level of Brij® 30 increased from 2.5 to 5 % v/w. However, the increase in permeation was not much pronounced beyond 5% v/w of Brij® 30 concentration. Furthermore, in the patches containing more than 5% v/w of Brij® 30, significant decrease in adhesiveness was observed. Hence, considering the permeation and adhesive properties, the optimum level of Brij® 30 in the patch seemed to be 5% v/w.

Conclusions

The present study has indicated that the appropriate selection of PSA, permeation enhancers, enhancer concentration, drug concentration and matrix thickness are important factors in the development of TDDS. Based on the obtained flux of 38 μg/cm^2/h from the optimized formulation, a reasonable patch size (smaller than 9 cm^2) could deliver 8 mg of galantamine per day. Thus, the present study indicates that matrix type TDDS for galantamine is feasible. However, permeation rate of drug from hairless mouse skin may be different from human skin. Therefore, the actual size of the system must be determined after evaluating the permeation rate of galantamine across the human skin.

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