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Investigation of formulation factors affecting *in vitro* and *in vivo* characteristics of a galantamine transdermal system

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ABSTRACT

Because of low treatment compliance with the Alzheimer disease patients, there have been clinical needs for the alternative administration route to effective and well-tolerated approaches of galantamine (Small and Dubois, 2007). In this study, drug-in-adhesive transdermal patches with galantamine were prepared and evaluated *in vitro* and *in vivo*. The *in vitro* permeation studies indicated that DT-2510 was the most suitable pressure-sensitive-adhesive and oleic acid was the most promising enhancer for galantamine drug-in-adhesive patch. The optimized galantamine drug-in-adhesive patch could be physicochemically stable for 28 days at 40 °C/75% RH. The *in vivo* studies of the optimized galantamine drug-in-adhesive patch showed high absolute bioavailability of around 80% and sustained effect on the drug plasma levels for 24 h. The *in vitro* and *in vivo* studies of galantamine drug-in-adhesive patches with different pressure-sensitive-adhesive functional groups showed a strong correlation between the skin permeation rate and the area under the curve. The results suggest that the transdermal application of galantamine drug-in-adhesive patches might be the alternative dosage form to have good efficacy and tolerability for the treatment of Alzheimer disease.

1. Introduction

Galantamine {(4aS, 6R, 8aS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol} (GLT; Fig. 1) is a slightly lipophilic tertiary amine with a pK_a of 8.32 (Heinrich and Lee Teoh, 2004; Prvulovic et al., 2010; Sramek et al., 2000). GLT is the first-line pharmacological agent for the treatment of Alzheimer disease (AD) (Tariot, 2001). It has a dual mechanism of action on the cholinergic system that inhibits acetylcholinesterase and allosterically modulates nicotinic acetylcholine receptors (Lilienfeld, 2002). The therapeutic use of GLT confers several benefits in AD treatment, such as improving cognition and global functioning, maintaining the ability to perform instrumental and basic activities of daily living, postponing the emergence of behavioral symptoms, and apparently reduces caregiver burden (Prvulovic et al., 2010; Scott and Goa, 2000; Sramek et al., 2000; Tariot, 2001).

Although various routes of administration, such as intravenous (IV), subcutaneous (SC), and intranasal (Heinrich and Lee Teoh, 2004), have been experimentally studied, only oral administration is presently approved for clinical use (Prvulovic et al., 2010). As with other cholinesterase inhibitor agents, the most frequent adverse event of GLT is due to discontinuation of oral administration, resulting in cholinergically mediated gastrointestinal effects, such as nausea, vomiting, diarrhea, and anorexia (Heinrich and Lee Teoh, 2004; Raskind et al., 2000; Sramek et al., 2000; Turiiski et al., 2004). Furthermore, because of low treatment compliance with the AD patients, there have been clinical needs for the alternative administration route to effective and well-tolerated approaches of GLT (Small and Dubois, 2007). With the intention to overcome these problems, drug-in-adhesive (DIA) transdermal patches of GLT were developed. The objective of this study was to formulate DIA patches containing GLT using pressure-sensitive-adhesive (PSA). The effects of the formulation factors (*i.e.*, including PSAs, enhancers, and the loading concentration of the drug) on the skin permeation rate of GLT through excised rat skin were evaluated. For *in vivo* studies, the pharmacokinetic characteristics of the optimal patch were evaluated and compared with the IV and oral administration routes in rabbits. The pharmacokinetic parameters

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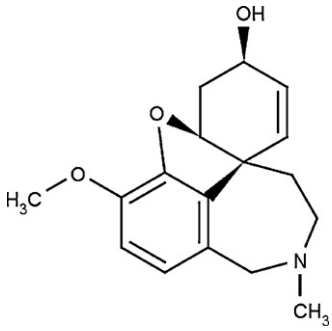

Fig. 1. Chemical structure of galantamine.

of patches with different PSAs were also evaluated in rabbits to establish the correlationship between *in vitro* skin permeation rates and *in vivo* pharmacokinetic parameters.

2. Materials and methods

2.1. Materials

The galantamine hydrobromide was a gift from Hyundai Pharm. Co., Ltd. (Seoul, Korea). The DURO-TAK® series were provided by National Starch and Chemical Co. (Bridgewater, NJ, USA). Oleic acid was supplied by Sigma-Aldrich (St. Louis, MO, USA). The backing film (ScotchPak® 9732 Polyester Film Laminate) and the release liner (ScotchPak® 1022 Release Liner) were gifts from 3 M Co. (St. Paul, MN, USA). HPLC grade acetonitrile, toluene, methanol, and ethanol were purchased from J.T. Baker Co. (Valley, PA, USA). All the other chemicals were reagent grade or higher. Water was purified by reverse osmosis and filtered in-house.

2.2. Preparation of GLT from GLT hydrobromide

GLT hydrobromide was transformed into freebase GLT by following a modified method (Hille et al., 1999, 2003a,b; Janssen et al., 2002). In brief, GLT hydrobromide suspension prepared in water (0.3 g/mL) was titrated with concentrated aqueous ammonia solution to pH 9; the aqueous phase was subsequently extracted 3 times with diethyl ether. The organic layer was washed twice with brine (26.3% NaCl in water-saturated solution; the ratio of the extracted solution and the brine was 3:1, v/v). The washed ether fractions were collected and dried with the addition of anhydrous sodium sulfate. The ether was filtered and evaporated using a rotary evaporator (R-205, Büchi Labortechnik AG, Flawii, Switzerland) at 40 °C. The white crystal residue was transferred to an amber glass container and kept in a vacuum evaporator until there was no weight loss. The final product, GLT, was identified using Fourier transform infrared (FT-IR) spectroscopy, differential scanning calorimetry (DSC), and HPLC.

2.3. Preparation of DIA patches containing GLT

The DIA patches containing GLT were prepared using various PSAs and enhancers. The list of acrylic polymers used in this study is summarized in Table 1. The concentration of GLT in the patch ranged from 1 to 10% (w/w). A laboratory coating unit (Labcoater LTE-S, Mathis AG, Oberhasli, Switzerland) was used to prepare the DIA patches. An appropriate amount of GLT was dissolved in a suitable amount of ethanol, added to the PSA solution, and mixed homogenously with a mechanical stirrer. The obtained drug-PSA solution was coated onto a fluoropolymer-treated polyester released liner (ScotchPak® 1022) at a thickness of 400 μm. After the solvent was removed, it was laminated with a polyester backing film (ScotchPak® 9732). The final thickness of the DIA layer was approximately 100 μm.

2.4. In vitro skin permeation studies across excised rat skin

2.4.1. Rat skin preparation

Rat skin was prepared from male Sprague-Dawley rats weighing 220–250 g (Samtako, Osan, Korea). The rats were sacrificed by diethyl ether in a desiccator. The hairs in the abdomen regions were carefully shaved with an electric shaver after using clippers. Full-thickness skin (the epidermis with the stratum corneum and the dermis) was excised from the shaved abdominal site in 3 cm × 3 cm portions. The subcutaneous fat and connective tissue were carefully removed using operating scissors. The blood from the tissue under skin was wiped away with soft paper. The integrity of the skin (upper and under skin faces) was carefully checked by microscopic observation; when observed skin had no uniformity, it was rejected. The obtained skin was stored at −20 °C and used within 1 week after the skin harvest.

2.4.2. In vitro skin permeation test

The skin permeation rates of GLT were evaluated by Franz diffusion cells fitted with excised rat skins; the volume of the Franz diffusion cell was 11.5 mL, and the effective diffusion area was 1.77 cm^2. Ethanol (5%) in phosphate-buffered saline (pH 6.5) was used as the receptor medium (Hsu et al., 2002), which was maintained at 37 ± 0.5 °C using a thermostatic water pump (WBC 1520, Jeio Tech Co., Seoul, Korea) and stirred at a constant rate of 600 rpm during the experiment. At 2, 4, 6, 8, 10, 12, and 24 h after the transdermal application of the patch or the solution containing GLT on the skin, 200 μL of the receptor medium was withdrawn and replaced with an equal volume of freshly prepared receptor medium. The amounts of GLT that permeated through the skin into the receptor medium were determined using a validated HPLC method.

2.4.3. GLT analysis in the non-biological samples

The concentrations of GLT in the solution or the receptor medium were determined using a validated HPLC method with a slight modification (Tian et al., 2003). The HPLC system consisted of an isocratic pump (L-7100, Hitachi, Tokyo, Japan), a fluorescence detector (L-2480, Hitachi), an automatic injector (L-7200, Hitachi), and an integrator (L-7000, Hitachi) connected to a PC. The column was a Zorbax Eclipse XDB C8 column (4.6 mm × 150 mm, 5 μm; Agilent Technologies, Santa Clara, CA, USA). The mobile phase was 0.2% triethylamine in an acetonitrile–water mixture (10:90, v/v) adjusted to pH 5.9 for the skin permeation study. The flow rate was maintained at 0.8 mL/min. The fluorescence detector was read at excitation and emission wavelengths of 290 and 320 nm, respectively. The samples were diluted with the mobile phase, and 100 μL was injected into the column.

2.5. In vivo pharmacokinetic studies in rabbits

2.5.1. In vivo studies in rabbits

GLT hydrobromide solutions for the IV and PO administrative routes were prepared for pharmacokinetic study of the drug. Appropriate amounts of the drug were dissolved in water to give concentrations of 18 mg/mL (as GLT base) for IV administration and 9 mg/mL (as a GLT base) for oral administration. GLT hydrobromide solution was filtered through a 0.2 μm filter membrane (Dsismic®-25AS, Advantec®, Tokyo, Japan). Each solution was prepared immediately before performing the study.

The pharmacokinetics of DIA patches containing GLT were evaluated after their application to New Zealand white rabbits weighing 1.8–2 kg. The 3 cm × 3 cm DIA patches (equivalent to 5 mg/kg GLT