Poloxamer/Cyclodextrin/Chitosan-Based Thermoreversible Gel for Intranasal Delivery of Fexofenadine Hydrochloride

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ABSTRACT: To enhance permeation and solubility of an intranasal delivery system of fexofenadine hydrochloride (FXD HCl), a new formulation using poloxamer 407 (P407)/hydroxypropyl-β-cyclodextrin (HP-β-CD)-based thermoreversible gels with chitosan, was developed. Prepared gels were characterized by gelation temperature, viscosity, viscoelasticity, and drug release profile. The *in vitro* permeation study was performed in primary human nasal epithelial cell monolayers cultured by air–liquid interface method. The addition of chitosan caused the slight elevation of gelation temperature and viscosity-enhancing effect. Viscosity enhancement by the incorporation of chitosan caused the retardation of drug release from P407 gels in *in vitro* release test. The *in vitro* permeation profile showed that the increase in chitosan content (0.1% and 0.3%, w/v) significantly enhanced the permeation of FXD HCl. After intranasal administration of P407/HP-β-CD–based thermoreversible gels containing 0.1% and 0.3% of chitosan in rabbits at 0.5 mg/kg dose, plasma concentrations of FXD HCl were significantly higher than those of nasal solutions ($p < 0.05$). In particular, the bioavailability of the optimized thermoreversible gel containing 0.3% chitosan was about 18-fold higher than that of the solution type. These results suggested the feasibility that thermosensitive gels could be used as an effective dosage form to enhance the nasal absorption of FXD HCl. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:681–691, 2011

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INTRODUCTION

Fexofenadine hydrochloride (FXD HCl) is a nonsedating, nonanticholinergic H1-receptor antagonist that does not penetrate the blood–brain barrier. It has been extensively used in the treatment of allergic rhinitis symptoms.[1] FXD HCl has interesting characteristics including a low human intestinal permeability (BCS class III), a minor degree of metabolism, and a number of drug–drug interactions.[2,3] It has been reported that the apparent permeability coefficients (P_{app}) of FXD in the apical-to-basolateral (A to B) direction was low in Caco-2 cell transport study due to the involvement of P-glycoprotein (P-gp).[3] It was also reported that the pharmacokinetics of FXD was influenced by a few organic anion–transporting peptide family.[4,5] FXD tablet formulation (Allegra®) for oral administration has been mainly available in the market. However, its oral bioavailability in human was not reported but that in rat was reported to be about 4.2%.[6] Thus, development of new approaches is required for enhancing bioavailability of FXD.

Intranasal delivery has frequently been considered as the most attractive and feasible alternative route for local and systemic drug delivery. This is due to the high permeability of the highly vascularized nasal epithelium, allowing a higher molecular mass cutoff at approximately 1000 Da, and the rapid drug absorption rate with plasma drug profiles sometimes almost identical to those from intravenous injections.[7,8] Despite the advantages of nasal drug delivery, this route of drug administration has several limitations. The

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limited surface of the nasal cavity restricts the total amount of the formulation that can be administered. Consequently, only drugs with low-dose or high aqueous solubility can be given intranasally so as not to adversely influence the normal physiological functions of the nasal cavity, especially with respect to olfaction and conditioning inspired air. Moreover, mucociliary clearance system that clears the drug rapidly from human nasal cavity with a clearance half-life of approximately 21 min and irritation of nasal mucosa by drug and its formulation components have also been considered as major barriers for nasal drug delivery.[9]

Numerous studies have been reported that the permeability and bioavailability of aqueous drug solution in the nasal delivery were quite low, probably due to low permeability and/or fast mucociliary clearance.[7] Thus, several systems have been investigated for the formulation of nasal delivery, including mucoadhesive polymers,[10,11] absorption enhancers,[12,13] surfactants,[14] and lipid emulsions,[15] to prolong the contact time of drug molecules with the nasal mucosa and to enhance its absorption into the nasal mucosa. Among those formulations now adopted in nasal drug delivery, thermoreversible gel is a relatively new formulation. Compared with liquid formulations or powder dosage forms, bioadhesive gel has high viscosity, so it can not only prolong the contact time between the drug and the absorptive sites in the nasal cavity but also release drug slowly and continuously.

Poloxamer, a nontoxic poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide) (PEO–PPO–PEO) triblock copolymers, is an important *in-situ* gelling system. Accompanying with a sol–gel transition, the aqueous solution of poloxamer (15%–20%) at a lower temperature becomes hydrogel at a higher temperature.[16] The temperature-induced gelation of poloxamer 407 (P407) has been explained on the basis that, as the temperature is increased, polymer desolvation and subsequently micellization occur forming more closely packed viscous gel. The driving forces for the micellization and the accompanied expulsion of the hydrating water from the core of the micelles are the conformational changes in the orientation of the methyl groups in the (PPO) side chains of the polymer.[16] P407 has been shown to provoke neither skin irritation nor sensitivity, thus confirming its good tolerability, and has thus far been found to be useful in topical, rectal, and ocular formulations.[16]

Thus, the objective of this study was to develop a thermoreversible gel formulation of FXD HCl for intranasal delivery using P407 as a thermoreversible polymer. The addition of HP-β-CD (10%, w/v) attained 10 mg/mL of FXD HCl concentration in the gel formulation in our preliminary study. Considering the administered volume (150 μL) for human subjects,[8] this concentration is thought to be sufficient for intranasal administration of FXD (1–5 mg per nostril).[17] Although the P407/HP-β-CD system[18,19] and P407/chitosan system[20,21] were independently reported, to the best of our knowledge, this is the first report on the P407/HP-β-CD/chitosan system for intranasal drug delivery of FXD HCl. Moreover, the P407/chitosan system seemed unsuitable for a nasal delivery system because it revealed a lack in drug solubility for clinical dose in the nose; the *in vitro* and *in vivo* performance of this system was not evaluated.[21] On the other hand, the P407/HP-β-CD system could reach the desired solubility better, but studies were limited to ophthalmic delivery systems.[18,19] Therefore, in the current study, a formulation that could make use of the advantage of chitosan as a permeation enhancer and HP-β-CD as a solubilizer was attempted for nasal delivery of FXD HCl. This system was designed to have high permeability and high solubility to achieve a clinical dose in the nose, which would eventually lead to an increase in bioavailability. The thermoreversible nasal gels were characterized by gelation temperature, viscoelasticity, and *in vitro* release characteristics. They were also evaluated by *in vitro* permeation study in primary human nasal epithelial (HNE) cell monolayers and *in vivo* pharmacokinetic study in rabbits.

MATERIALS AND METHODS

Materials

FXD HCl was kindly provided by Handok pharmaceuticals Corp. (Seoul, Korea). Propranolol hydrochloride, HP-β-CD, and chitosan (medium molecular weight) were purchased from Sigma (St. Louis, Missouri). Poloxamer 407 (Lutrol® F-127) was donated by BASF (Ludwigshafen, Germany). BEGM bullet kit was purchased from Cambrex Bio Science Inc. (Walkersville, Maryland), and other cell culture reagents and supplies were obtained from Invitrogen (Grand Island, NY). Transwell® (0.4-μm pore size, 12-mm diameter, polyester) was obtained from Costar (Cambridge, MA). All other chemicals and reagents were of analytical grade purchased from commercial sources and used without further purification.

Preparation of P407-Based Thermoreversible Gel

The poloxamer gels were prepared by the cold method.[22] Briefly, P407 (17%, w/v) was dissolved in deionized distilled water containing HP-β-CD (10%, w/v) and drug (10 mg/mL) at room temperature, and the solution was cooled down to 4°C. The container was left overnight in a refrigerator to ensure complete dissolution. Chitosan (0.1% or 0.3%, w/v) solubilized in 1% acetic acid solution was then slowly added to the poloxamer solution with continuous stirring at 4°C. The poloxamer gels were kept at 4°C minimum for 24 h before use.