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RESEARCH ARTICLE

Development of the loratadine gel for enhanced transdermal delivery

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Abstract

Background: The oral administration of loratadine, an antihistamine, can have a variety of adverse side effects, such as headache, fatigue, and nausea, because of the transient high blood concentration. To avoid these effects, loratadine can be administered using a transdermal drug delivery system. *Method*: This study examined the effects of the drug concentration on drug release from prepared hydroxypropyl methylcellulose gels using a synthetic cellulose membrane at 37°C. The drug concentrations tested were 0.1%, 0.2%, 0.3%, 0.4%, and 0.5% (w/w). The effect of temperature on drug release from the 0.3% loratadine gels was evaluated at 27°C, 32°C, 37°C, and 42°C. Various types of penetration enhancers, such as glycols, glycerides, propylene glycol derivatives, nonionic surfactants, and fatty acids, were incorporated in the gel formulation to increase the level of drug permeation. *Results*: The rate of drug release increased with increasing drug concentration or temperature. The activation energy for the release of the drug was 5.714 kcal/mol for 0.3% loratadine gel. Among all the enhancers used in this study, polyoxyethylene 2-stearyl ether showed the best enhancing effect. The enhancement factor of the loratadine gel containing the polyoxyethylene 2-stearyl ether was 2.03 compared with that of the loratadine system containing no enhancer. *Conclusions*: These results suggest that the topical gel formulation of loratadine containing a penetration enhancer could be developed to enhance the penetration of loratadine.

Key words: *Diffusion; enhancer; gels; loratadine; penetration; transdermal*

Introduction

Loratadine is a tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonist activity that is used to relieve the symptoms of seasonal allergies and skin rash. After oral administration, loratadine is absorbed rapidly and reaches a peak concentration at 1.3 hours[1]. However, when administered orally, loratadine can cause side effects, such as headache, fatigue, and nausea, owing to the transient high blood concentration[2]. On the other hand, loratadine can be administered using a transdermal drug delivery (TDD) system in order to avoid such adverse effects and obtain a constant plasma drug concentration.

Transdermal drug delivery is convenient for the delivery of therapeutic agents and can be a valuable alternative to oral administration by avoiding gastrointestinal disturbances. The percutaneous administration of bioadhesive gels has good accessibility, and can be applied and removed easily. Self-placement of a dosage form is possible because of its excellent accessibility, and the dosage form can be removed at any time. Because of its natural function, the skin is less sensitive to irritation and damage than the other administration routes[3]. In recent years, the use of hydrophilic polymers, particularly cellulose derivatives, has attracted considerable attention for the development of controlled release technology in the formulation of pharmaceutical products on account of their ability to form gels in an aqueous medium[4].

Percutaneous delivery of loratadine has advantages of avoiding the hepatic first pass effect, increased compliance, controlled plasma levels, and a decrease in the overall dose[5]. In addition, it can allow the delivery of a drug at a sustained level for an extended period of time.

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However, it is very difficult for a drug to penetrate the skin owing to the intrinsic barrier function of the skin.

To improve the skin permeation of loratadine, various penetration enhancers such as the fatty acids, the PGs, the glycols, the nonionic surfactants, and the glycerides were incorporated in the gels, and the permeation study through the rat skin was performed at 37°C for choosing the best enhancer. To optimize the loratadine gel formulation, the effects of drug concentration, temperature, and addition of an enhancer on drug permeation were evaluated.

The present study was carried out to evaluate the enhanced permeation of loratadine by using the penetration enhancer and examine the in vitro release characteristics and further develop a new gel formulation for the enhanced percutaneous delivery of loratadine.

Materials and methods

Materials

Loratadine was supplied from Aju Pharm. Co., Ltd. (Seoul, Korea). Hydroxypropyl methylcellulose (HPMC) was obtained from Dow Chemical Co. Ltd. (Midland, MI, USA). Poloxamer 407 was purchased from BASF Co. (Ludwigshafen, Germany). Lauric acid, oleic acid, and caprylic acid were acquired from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). Polyoxyethylene-23-lauryl ether (Brij 35), polyoxyethylene-2-oleyl ether (Brij 92), polyoxyethylene-23-lauryl ether (Brij 72), tetraethylene glycol (TEG), and diethylene glycol (DEG) were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Oleyl macrogol-6 glyceride, caprylocaproyl macrogol-8 glyceride, propylene glycol monocaprylate, propylene glycol laurate, and propylene glycol monolaurate were gifts from Gattefose (St. Priest, France). Anhydrous ethyl alcohol and acetonitrile was of high-performance liquid chromatography (HPLC) grade from Merck Co. (Darmstadt, Germany). All other chemicals were of regent grade and used without further purification.

Instruments

An ultraviolet/visible (UV/vis) spectrophotometer (Hewlett Packard 84542A, Palo Alto, CA, USA) and HPLC (Waters, Milford, MA, USA) were used. A two-chamber diffusion cell (Hana Seoul, Co., Korea), Keshary-Chien diffusion cell (Hana Co., Korea), and circulating water bath (Jeio Tech Co., Ltd., Seoul, Korea) were used.

Preparation of HPMC-poloxamer gels containing loratadine

Five hundred milligrams of HPMC was dissolved in hot water to make a 20 g solution. Twenty grams of poloxamer 407 was dissolved in 5°C water to make a 40 g solution. The solution was left to stand overnight in a refrigerator to allow complete dissolution. Three hundred milligrams of loratadine and water was added with vigorous stirring to the above two combined polymer solutions to make a 100 g solution.

Permeation of loratadine from the HPMC-poloxamer gels

The flux of loratadine from the HPMC-poloxamer gels was determined at various polyethylene glycol (PEG) concentrations (0%–50%, v/v) as a receptor. The synthetic cellulose membrane was mounted on the receptor compartment of the diffusion cell. Two grams of prepared loratadine gel was placed in intimate contact with the cellulose membrane, and the donor cap was covered with a parafilm and clamped. The sampling port was sealed with parafilm to prevent evaporation of the receptor medium. A 40% PEG solution was used as the receptor solution. The receptor solution was maintained at 37°C using a circulating water bath and stirred with a magnetic stirring bar. The donor compartment was maintained at 37°C. The effect of the drug concentration on its release from the gels was examined using different drug concentrations of 2%, 3%, 4%, and 5% (w/w), and the effects of temperature on drug release was investigated at 27°C, 32°C, 37°C, and 42°C using a circulating water bath. The total samples from the receptor compartment were withdrawn at predetermined intervals and replaced immediately with the same amount of fresh 40% PEG solution in order to maintain a sink condition.

HPLC determination of loratadine

Loratadine was assayed using a HPLC method. The mobile phase was a mixture (80:20, v/v) of acetonitrile and 0.025 M sodium dihydrogen phosphate buffer, adjusted to pH 3.7 with H_3PO_4. A flow rate of 1.0 mL/min yielded an operating pressure of ~1000 psi. The UV detector was operated at a wavelength of 248 nm. Under these conditions, the loratadine peak appeared at a retention time of 5.9 minutes[6].

In vitro skin permeation study

Skin preparation

A male rat (Spragul Dawley rat strain) was sacrificed by snapping the spinal cord at the neck. The hair of the abdominal area was carefully removed with electric clippers. A square section of the abdominal skin was excised. After the incision, the adhering fats and other visceral debris in the skin were removed carefully

from the undersurface with tweezers [7]. The excised skin was used immediately.

Permeation of loratadine from the HPMC-poloxamer gels containing various enhancers

The 0.3% loratadine gels containing the 5% (w/v) enhancer were prepared. Different types of enhancers were used to compare the effects. The enhancers used were fatty acids, PGs, nonionic surfactants, and glycerides. A freshly excised full-thickness skin sample was mounted on the receptor site of the diffusion cell with the stratum corneum side facing upward into the donor compartment, and the dermal side facing downward into the receptor compartment. An appropriate amount of gel was placed on the stratum corneum side, covered with a round glass plate and clamped[4]. The receptor medium was a 40% PEG 400 solution to achieve a sink condition, and it was maintained at 37°C using a circulating water bath. The total samples were withdrawn at predetermined times and replaced immediately with an equal volume of fresh medium. The permeation quantities of loratadine were analyzed using HPLC at 248 nm.

Calculation

The cumulative amount of the permeated drug (from the mucosal side to the serosal side) was plotted as a function of time, and the flux was calculated from the steady state part of the curve. A linear profile was observed for a 12-hour period, and the slope of the linear portion of the curve was obtained by linear regression. The effectiveness of the penetration enhancer was determined by comparing the flux of loratadine in the presence or absence of the enhancer and was defined as the enhancement factor (EF). The EF was calculated using the following equation:

EF = (flux of loratadine gel containing an enhancer)/(flux of loratadine gel not containing enhancer)

Results and discussion

Solubility of loratadine

Loratadine has an extremely low aqueous solubility, which can be improved by adding a water-miscible hydrophilic polymer, such as PEG 400, into the aqueous solution as a solubilizer. PEG 400 was reported to be an excellent solubilizer for many steroids[8]. In this study (Table 1), the solubility of loratadine increased with increasing volume fraction of PEG 400 with the highest solubility being observed at 40% PEG 400.

Table 1. Effects of the PEG volume fraction in water on the flux of loratadine from HPMC-poloxamer gels containing loratadine through a synthetic cellulose membrane.

PEG 400 %	Equilibrium solubility (μg/mL)	Rate of permeation (μg/cm^2/h)	Permeability coefficient (cm/h) × 10^3
0	5.36	0.15 ± 0.07	27.98
10	19.48	0.26 ± 0.10	13.34
20	43.09	0.28 ± 0.15	6.50
30	58.78	0.33 ± 0.11	5.61
40	68.92	0.47 ± 0.19	6.82
50	60.29	0.37 ± 0.10	6.14

Permeation of loratadine from the HPMC-poloxamer gels

The cumulative amount of drug permeating through a unit surface area (Q) can be expressed mathematically using the following relationship:

$$J = P \cdot (C_D - C_R) \quad (1)$$

where P is the permeability coefficient, and C_D and C_R are the drug concentrations in the donor (D) and receptor (R) solutions, respectively.

When the drug concentration in the donor solution (C_D) is maintained at a level greater than the equilibrium solubility (C_e) (i.e., $C_D > C_e$), and the drug concentration in the receptor solution (C_R) is maintained below the sink condition (i.e., $C_R << C_e$), Equation (1) can be simplified as follows:

$$Q = P \cdot C_e \cdot t \quad (2)$$

and a constant permeation profile should be yielded. The rate of permeation can then be defined as follows:

$$\frac{Q}{t} = P \cdot C_e \quad (3)$$

As expected from Equation (2), a constant permeation profile was achieved when the loratadine concentration in the donor solution was maintained at a level greater than its equilibrium solubility (Figure 1). The rate of permeation (Q_t/t), which was measured from the slope of the Q versus t plots (Equation (2)), increased with the addition of PEG 400. The effect of PEG 400 on the permeability coefficient (P) of loratadine across the HPMC-poloxamer gel can be determined using the following equation:

$$P = \frac{Q/t}{C_e} \quad (4)$$

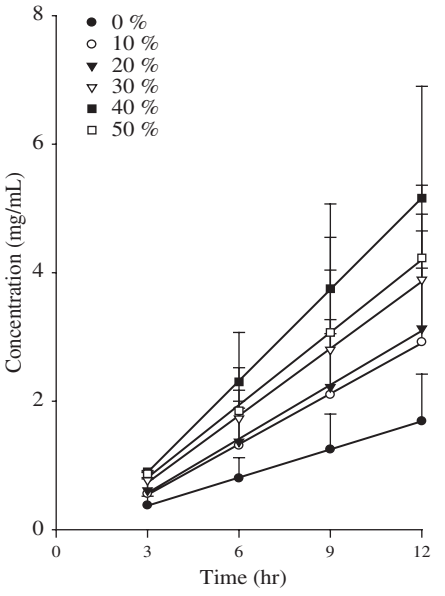

Figure 1. Effects of the PEG 400 volume fraction in water (vol/vol %) on drug release through the cellulose membrane from the loratadine gels.

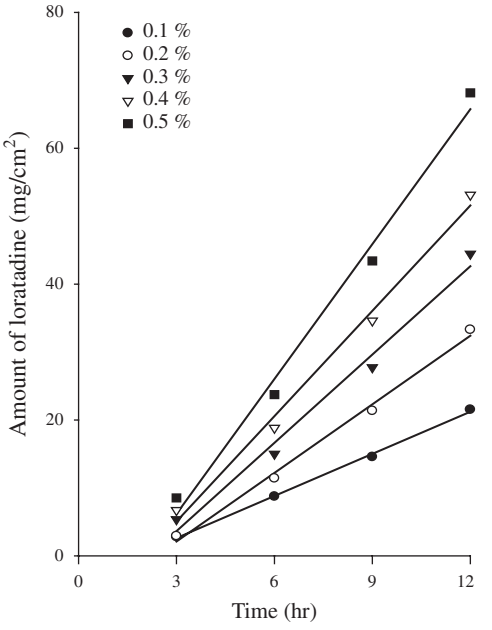

Figure 2. Effects of the loratadine concentration on drug release through the cellulose membrane from the loratadine gels.

As expected from Equation (3), the increase in the permeation rate (Q/t) is dependent on the equilibrium solubility (C_e) of loratadine in the PEG 400 solutions. These results showed that the permeability coefficient (P) decreased with increasing volume fraction of PEG 400 in the saline solution (Table 1).

Effect of loratadine concentration on drug release

The effect of the loratadine concentration on drug release across a synthetic cellulose membrane was examined at 37°C. The concentrations tested were 0.1%, 0.2%, 0.3%, 0.4%, and 0.5%, respectively (Figure 2). The rate of drug release increased with increasing concentration of loratadine from the gels.

Two mathematical equations were proposed by Higuchi to describe the kinetics of drug release based on the state of the drug in the vehicle: release from solutions and release from suspensions. In this study, the drug release rates were evaluated using the following simplified Higuchi diffusion equation, which depicts the drug release from one side of a semisolid layer in which the drug is dissolved.

$$q = 2C_0(D_t/\pi)^{1/2} \tag{5}$$

where q is the amount of drug released into the receptor medium per unit area of exposure, C_0 is the initial drug concentration in the vehicle, D is the apparent diffusion coefficient of the drug, and t is the time elapsed since the start of drug release.

In the case of passive diffusion, the steady-state flux through unit area of a membrane is given by Fick's law,

$$J = P \cdot (C_D - C_R) \tag{6}$$

where J is the flux per unit area, P represents the permeability coefficient, and C_D, C_R are the concentrations in the donor and receptor solutions, respectively. (C_D – C_R) is replaced by C_D when sink conditions are maintained on the receptor side.

$$J = P \cdot C_D \tag{7}$$

The permeability coefficient, P, is constant for a given drug under the same experimental conditions. There should be a linear relationship between the flux and donor concentration.

Effect of temperature on drug release

The effect of temperature on the release of loratadine from the gel formulations was evaluated at 27°C, 32°C, 37°C, and 42°C. Figure 3 shows the temperature dependency of drug release as a function of time. The apparent diffusion coefficient increased with increasing temperature.

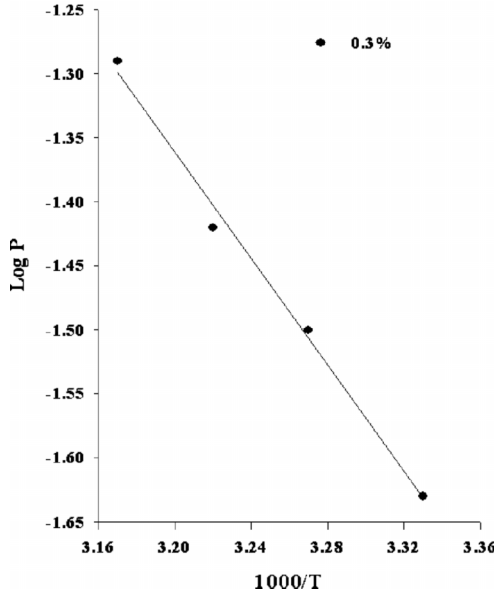

Figure 3. Effect of temperature on drug release from the loratadine gels containing a 0.3% loading dose.

However, for the practical use, 37°C was chosen to reflect the temperature of the stratum corneum[9]. The relationship between the diffusion coefficient and temperature is as follows:

$$D = D_0 \cdot e^{-E_a/RT} \tag{8}$$

A linear relationship was observed between the natural logarithm of the apparent diffusivity (D) and the reciprocal of temperature (T) as shown in Figure 3. The slope was used to calculate the activation energy (E_a) for drug diffusion. The intercept was used to calculate the pre-exponential term.

The permeability coefficient is then defined by

$$P = \frac{\text{Flux}}{\text{Solubility}} \tag{9}$$

$$P = P_0 \cdot e^{-E_a/RT} \tag{10}$$

$$\text{Log}\, P = \text{Log}\, P_0 - \frac{E_a}{R \times 2.303 \times 1000} \times 1000 \tag{11}$$

$$\text{Slope} = -\frac{E_a}{R \times 2.303} \times \frac{1}{1000} \tag{12}$$

$$\begin{aligned} E_a &= -\text{Slope} \times R \times 2.303 \times 1000 \text{ cal} \\ &= -\text{Slope} \times 1.987 \times 2.303 \text{ kcal} \end{aligned} \tag{13}$$

As expected from Equation (11), a plot of log P versus $1000/T$ yielded a straight line (Figure 3). The E_a (activation energy), which was measured from the slope of log P versus $1000/T$ plots (Equation (12)), was 5.714 kcal/mol for 0.3% loratadine gels.

Effect of enhancers on the permeation of loratadine across rat skin

The transdermal route for systemic drug delivery has attracted considerable attention in recent years[10–13]. Penetration enhancers, accelerants, or promoters are believed to interact with some components of the skin, causing increased fluidity in the intercellular lipid lamellae and the SC to swell and/or leach out some of the structural components, and increase the level of drug penetration through the barrier membrane[14,15]. These substances may also reduce the capacity for the drug to bind to the skin, thereby improving drug transport. Consequently, a penetration enhancer is a more prevalent and growing trend in TDD.

We investigated the enhancing effects on drug permeation into skins using some kinds of enhancers such as the glycols, the glycerides, PG derivatives, the non-ionic surfactants, and the fatty acids (Table 2).

Fatty acids are currently receiving much attention as penetration enhancers[16,17]. This class of enhancers presents the advantage of being an endogenous component of human skin. Fatty acids are capable of inserting between the hydrophobic tails of stratum corneum lipid bilayer, disturbing their packing, increasing their fluidity, and, subsequently, decreasing the diffusional resistance to permeants[18–22]. Fatty acids have been

Table 2. Enhancement factor according to the various enhancers.

Enhancer	Flux (μg/cm^2/h)	EF
Control	3.88 ± 0.19	1
Polyoxyethylene 23-lauryl ether	5.22 ± 0.20	1.34
Polyoxyethylene 2-stearyl ether	7.88 ± 0.25	2.03
Polyoxyethylene 2-oleyl ether	7.74 ± 0.35	1.99
Oleic acid	4.00 ± 0.22	1.03
Octanoic acid	4.53 ± 0.23	1.16
Tetraethylene glycol	4.45 ± 0.23	1.14
Diethylene glycol	3.92 ± 0.19	1.01
Oleoyl macrogol-6 glyceride	6.50 ± 0.31	1.67
Caprylocaproyl macrogol-8 glyceride	5.82 ± 0.28	1.50
Propylene glycol mono caprylate	4.01 ± 0.21	1.03
Propylene glycol laurate	3.30 ± 0.15	0.85
Propylene glycol monolaurate	4.14 ± 0.22	1.06

shown, by way of interactions with intercellular lipid domains, to promote the skin permeation of drugs with a wide range of polarities[23,24]. Among the fatty acids used, octanoic acid showed increased permeation rate of loratadine from HPMC-poloxamer gels.

Surfactants have been reported to enhance the permeability of drugs[25–29]. They have effects on the permeability characteristics of several biological membranes, including skin[27], and for this reason they can enhance the skin penetration of other compounds present in the formulation. Therefore, in recent years, they have been employed to enhance the permeation rates of several drugs[30,31]. Shin et al.[28] reported the mechanism of the effect of nonionic surfactants as permeation enhancers. The skin pretreated with the nonionic surfactant showed that the SC was loosely layered and that intercellular spaces were wide. Table 2 shows the permeation aspect of loratadine gels containing nonionic surfactants. With other experiments carried out in our laboratory, Brij 35 (polyoxyethylene 2-stearyl ether) showed a higher enhancing effect than Brij 92 (polyoxyethylene 2-oleyl ether) or Brij 72 (polyoxyethylene 23-lauryl ether) (Figure 4).

Caprylocaproyl macrogolglyceride (Labrasol) was found to increase the passive transport of drug molecules. In addition, it shows high tolerance and low toxicity. It is included as a pharmaceutical excipient in European Pharmacopoeia in 1998. Oleoyl macrogol-6 glyceride (Labrafil) is a PEG derivative, used as a cosurfactant in pharmaceutical systems such as microemulsions. This substance is biocompatible and biodegradable[32]. Among the glycerides, oleoyl macrogol-6 glyceride showed increased permeation rate of loratadine (Table 2).

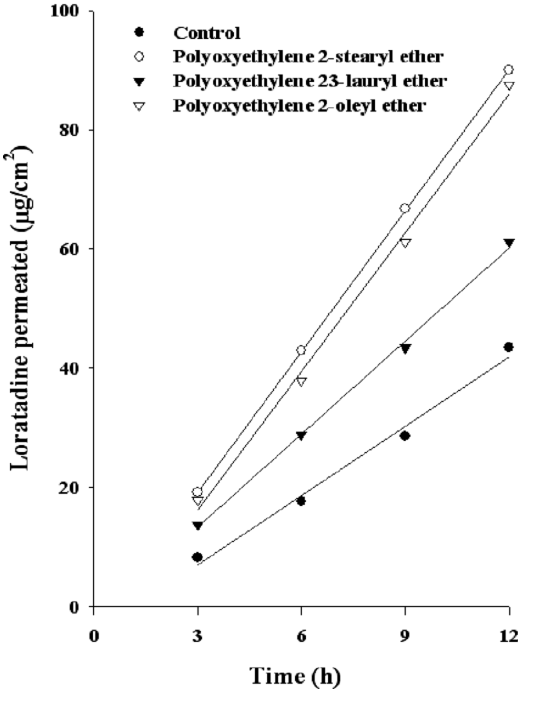

Figure 4. Effects of nonionic surfactants on drug permeation from the loratadine gels through rat skin.

Propylene glycol is widely used as a vehicle for penetration enhancers and permeates well through human stratum corneum. PG readily permeates the skin and in doing so may carry the drug molecules across[33]. The permeation of PG through the tissue could alter thermodynamic activity of the drug in the vehicle, which would in turn modify the driving force for diffusion. PG may penetrate into the tissue, facilitating uptake of the drug into skin, and there may be some minor disturbance to intercellular lipid packing within the stratum corneum bilayers[34]. PG monolaurate showed a little increased permeation rate of loratadine (Table 2).

Among all the enhancers used in this test, polyoxyethylene 2-stearyl ether showed the best enhancing effects. The enhancement factor of the gels containing polyoxyethylene 2-stearyl ether was 2.03 compared with that of the loratadine gels containing no enhancer (Table 2).

Conclusion

The rate of drug release increased with increasing drug concentration or temperature. The activation energy for the release of the drug was 5.714 kcal/mol for 0.3% loratadine gel. Among all the enhancers used in this test, polyoxyethylene 2-stearyl ether showed the best enhancing effects, with the enhancement factor ratio of 2.03. These results suggest that a topical gel formulation of loratadine containing a penetration enhancer could be developed to enhance the penetration of loratadine.

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