Effect of Charge Carrier Lipid on Skin Penetration, Retention, and Hair Growth of Topically Applied Finasteride-Containing Liposomes

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Abstract

The aim of this study was to investigate the effect of charge carrier lipid on the skin penetration, retention, and hair growth of topically applied finasteride-containing liposomes. Finasteride-containing liposomes were prepared by traditional thin film hydration method using Phospholipon® 85 G and cholesterol with or without charge carrier lipid (1,2 dimyristoyl-sn-glycero-3-phosphate or 1,2-dioleoyl-trimethylammonium-propane for anionic and cationic charge, respectively). Freshly prepared finasteride-containing liposome suspension was applied on the hairless mouse skin, and skin penetration and retention were measured using Keshary-Chien diffusion cell. Non-liposomal formulation (ethanol 10% solution containing 0.5 mg/ml of FNS) was also used as a control. The amount of finasteride in the diffusion cell and mouse skin was measured by HPLC. The hair growth was evaluated using depilated male C57BL/6N mice. Mean particle size of all finasteride-containing liposomes was less than a micron, and polydispersity index revealed size homogeneity. Skin penetration and retention studies showed that significantly less amount of finasteride was penetrated when applied as anionic liposome while more amount of the drug was retained. Specifically, in liposome prepared with 10% anionic charge carrier lipid, penetration was 12.99 μg/cm² while retention was 79.23 μg/cm² after 24 h of application. In hair growth study, finasteride-containing anionic liposomes showed moderate efficacy, but the efficacy was not found when applied as cationic liposomes. In conclusion, topical application of finasteride using anionic lipid formulation appears to be useful option for the treatment of androgenetic alopecia to avoid systemic side effects of the drug.

Key Words: Finasteride, Liposomes, Skin penetration, Skin retention, Hair growth, Androgenetic alopecia

INTRODUCTION

Androgenetic alopecia, also referred to as male-pattern hair loss or common baldness in men, affects at least 50% of men by the age of 50 and up to 70% of all men in later life (Norwood, 1975). Although there is no treatment to completely reverse androgenetic alopecia in advanced stage, treatment with minoxidil or finasteride (or combination of both) can slow down and partly reverse the progression in the majority of patients who have mild to moderate stage (Otberg et al., 2007). The US Food and Drug Administration approved topical solution of minoxidil and low-dose finasteride (FNS) for the treatments of the hair loss and androgenetic alopecia.

FNS (Fig. 1) is a synthetic antiandrogen which acts as specific inhibitor towards type II 5α-reductase, an intracellular enzyme that converts testosterone into 5α-dihydrotestosterone which is believed to cause androgenetic alopecia. There are two distinct isozymes of the enzyme, i.e., type I and type II. In humans, type I 5α-reductase is predominantly expressed in the sebaceous glands of most regions of skin. In contrast, type II 5α-reductase is predominantly found in hair follicles where hair growth begins as well as prostate, seminal vesicles, and epididymis. Therefore, FNS is widely used for the treatment of androgenetic alopecia and benign prostate hyperplasia. Although FNS is effective in the treatment of androgenetic alopecia, oral use of this drug is largely limited due to various side effects such as erectile dysfunction and impotence. Another serious adverse effect includes gynecomastia, develop-
ment of abnormally large mammary gland in males resulting in breast enlargement.

There have been several studies which showed that topical application of the drug might be better option to avoid the unwanted side effects encountered when orally administered (Tabbakhian et al., 2006; Kumar et al., 2007). Specifically, since the target tissue of FNS for the treatment of androgenetic alopecia is hair follicles in the scalp, various topical formulations of the drug was pursued using liposomes, ethosomes, niosomes, solid lipid nanoparticles, and nanostructured lipid carriers (Biruss and Valenta, 2006; Biruss et al., 2007; Rao et al., 2008; Balakrishnan et al., 2010).

In present study, we prepared charged liposome formulations of FNS in an attempt to enhance delivery of the drug to the target tissue (hair follicle) using phosphatidylcholine, cholesterol, and charge carrier lipids, 1,2-Dimyristoyl-sn-glycero-3-phosphate monosodium salt (DMPA, negative charge) or 1,2-dioleoyl-trimethylammonium-propane chloride salt (DOTAP), positively charged, respectively. Liposome without charge carrier lipid was also prepared for comparison by the same procedure. We performed hair growth study of FNS-containing liposome suspension was diluted with distilled water before the measurement to adjust the temperature. FNS-containing liposome suspension was diluted with distilled water for 2 h at 60°C with gentle agitation. The lipid solution obtained was allowed to anneal overnight at 4°C and sonicated for 10 min in bath sonicator (42 KHz) for size reduction. The resultant dispersion was transferred to nitrogen purged vials and stored at 4°C until further studies.

**Physical properties of liposomes**

Particle size and zeta potential of FNS-containing liposomes were measured by electrophoretic light scattering spectrometer (ELS-8000, OTSUKA Electronics Co. Ltd., Japan) at room temperature. FNS-containing liposome suspension was diluted with distilled water before the measurement to adjust the intensity. The system was used in the auto-measuring mode at 80 mV. Polydispersity index was also determined as a measurement of particle size homogeneity of the prepared liposomes. A small value of polydispersity index (<0.3) indicates homogeneous liposome population.

**HPLC assay**

FNS was determined using HPLC system (Shimadzu, Japan) equipped with Class VP computer software, LC 10 AD VP pump, and SPD 10A UV-VIS detector at 210 nm. Column used was Inertsil ODS-3 (4.6×150 mm, GL Science Inc, Japan) and the mobile phase consisted of acetonitrile and distilled water (60:40) adjusted to pH 2.8 with phosphoric acid. Ibuprofen was used as internal standard for the assay. Flow

**Materials and methods**

**Materials**

Phospholipon® 85G (PL) was generously provided by the Phospholipid GmbH (Nattermannalée, Germany). Cholesterol (CH) was obtained from Wako Pure Chemical Industries (Osaka, Japan). FNS was kindly gifted from Dong-A Pharmaceutical Co., Ltd. South Korea, and ibuprofen was obtained from Sigma Chemical Co., (St. Louis, USA). Dialysis bag (Spectra/Por no. 2, MWCO: 12,000-14,000 g/mole) was purchased from Spectrum Laboratories Inc. (Rancho Dominguez, USA). 1,2-Dimyristoyl-sn-glycero-3-phosphate monosodium salt (DMPA) and 1, 2-dioleoyl-trimethylammonium-propane chloride salt (DOTAP) were purchased from Avanti Polar Lipids (Alabaster, AL). All other chemicals were of analytical grade and used without further purification.

**Preparation of FNS-containing liposomes**

FNS-containing liposomes were prepared by traditional thin film hydration method. Composition of FNS-containing liposomes is listed in Table 1. Accurately weighed amount of each constituent was transferred to a 100-ml round bottom flask and dissolved in a mixture of chloroform and methanol (2:1, v/v). The organic solvent was removed under vacuum by rotary evaporator at 35°C for 15 min to form a thin film on the wall of the flask. Subsequently, the residual organic solvent was suctioned for 2 h to ensure complete removal. The dried lipid film was hydrated with 20 ml of distilled water for 2 h at 60°C with gentle agitation. The lipid solution thus obtained was allowed to anneal overnight at 4°C and sonicated for 10 min in bath sonicator (42 KHz) for size reduction. The resultant dispersion was transferred to nitrogen purged vials and stored at 4°C until further studies.

**Table 1. Composition of liposomes containing finasteride**

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<tr>
<th>Code</th>
<th>PL (mg)</th>
<th>CH (mg)</th>
<th>DMPA (mg)</th>
<th>DOTAP (mg)</th>
<th>Finasteride (mg)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>100</td>
<td>50</td>
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<td>-</td>
<td>10</td>
</tr>
<tr>
<td>AL-1</td>
<td>100</td>
<td>50</td>
<td>1.5</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>AL-5</td>
<td>100</td>
<td>50</td>
<td>7.5</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>AL-10</td>
<td>100</td>
<td>50</td>
<td>15</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>CL-1</td>
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<td>-</td>
<td>1.5</td>
<td>10</td>
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<tr>
<td>CL-5</td>
<td>100</td>
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<td>-</td>
<td>7.5</td>
<td>10</td>
</tr>
<tr>
<td>CL-10</td>
<td>100</td>
<td>50</td>
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**Fig. 1. Chemical structure of finasteride: N-(1,1-dimethylethyl)-3-oxo-(5α, 17β)-4-azaandrostan-1-ene-17-carboxamide.**
rate was 1 ml/min and the injection volume of the sample was 20 ml. Validation of the HPLC assay was performed by repeating five times a day for five consecutive days under the same ambient condition in the range of 0.05-50 μg/ml concentration. Linearity of calibration curve for determination of FNS was $r^2=0.9997$. The regression equation was as follows: $y=0.817x+0.0138$.

**Skin penetration and retention studies**

Animal care and procedures were conducted according to the guidelines for animal use in toxicology (Society of Toxicology USP 1989) and the study protocol was approved by the Animal Care and Use Committee, College of Pharmacy, Yeungnam University. Seven-week-old male hairless mice (weighing 35 ± 3.0 g) were obtained from Orient Bio (Seoul, Korea) and housed in groups not exceeding six per cage and maintained under standard conditions. The acclimation period was two weeks before the experimental procedure with a dark/light cycle of 12 h/12 h at the temperature of 23 ± 2°C. Food and tap water were available ad libitum during the acclimation period. Mice were sacrificed and full-thickness skin was taken, followed by removal of subcutaneous fat adhering to dermis with a scalpel. Approximately 3×3 cm of the trimmed skin was placed into Keshary-Chien diffusion cell with 2.1 cm² diffusion area.

Freshly prepared FNS-containing liposome suspension (0.5 ml) was applied on the skin and allowed to spread over the skin. The donor compartment (epidermal layer of the skin) and the sampling port were covered by parafilm to avoid evaporation during the study, and the receptor compartment (dermal layer of the skin) was perfused with distilled water maintaining temperature at 37°C. Preliminary experiments confirmed the maintenance of the sink conditions by this procedure. At predetermined time intervals for 24 h (1, 3, 6, 9, 12 and 24 h), aliquots of 0.5 ml were withdrawn, and were replaced with equal volume of receptor medium to maintain the receptor volume at a constant level. Samples were diluted appropriately and measured by HPLC. Non-liposomal formulation (ethanol 10% solution containing 0.5 mg/ml of FNS) was also used in this study as a control.

Followed by skin penetration experiments, skin retention study was performed with the effective penetration part (2.1 cm²) of the skin. The skin was washed with distilled water ten times and blotted with tissue paper to remove any adhering formulation from the surface. The skin was homogenized with distilled water under ice bath followed by centrifugation at 12,000 g for 5 min. The supernatant was collected and mixed with same volume of absolute ethanol and subjected to vortex for 30 sec and centrifugation at 16,000 g for 5 min. The supernatant was used for skin retention study by using HPLC assay described above.

**Hair growth study**

The detailed procedure of hair growth study was described elsewhere (Shanmugam et al., 2009). Briefly, The hair on the back of seven-week-old male mice (weighing 32 ± 2.5 g) was removed by electric clipper and depilated using thioglycolic acid 80% cream one day before applying the samples. Freshly prepared FNS-containing liposome suspension (0.2 ml) was applied onto the depilated back of the mice (n=5) and allowed to dry. The sample application was done once a day for twenty days. Saline solution (0.9%) and Minoxil® (minoxidil 5% solution) were also used as negative and positive control, respectively. The hair growth was evaluated every five days using quantification scale reported by Chen and his colleagues (0: initial state, 1: grey to black coloration, 2: short visible hair, 3: sparse long hair, 4: dense long hair, 5: complete hair growth) (Fig. 2) (Chen et al., 2005).

**Data analysis**

All the data obtained were analyzed by a one-way analysis of variance (ANOVA) using SPSS 12.0 for windows program and significance level of $p<0.05$ were used to indicate the statistically significant difference between data sets.

**RESULTS**

Mean particle size of FNS-containing liposome prepared without charge carrier lipid was 360.2 nm. Liposomes prepared with anionic (DMPA) or cationic (DOTAP) charge carrier lipid showed slightly smaller size than that of liposome prepared without charge (Table 2). The size decreased in proportion to the amount of charge carrier lipid added in both anionic and cationic liposomes. Polydispersity index of the FNS-containing liposomes was less than 0.3 in all liposomes, indicating homogeneity of the particle size. Zeta potentials for the FNS-containing anionic liposomes were −28.4, −31.2, and −34.8 mV in AL-1, AL-5, AL-10, respectively. Zeta potentials for the FNS-containing cationic liposomes were +26.5, +32.4,

![Image](308x283 to 539x407)

**Fig. 2.** Hair growth quantification scale. 0: initial state, 1: grey to black coloration, 2: short visible hair, 3: sparse long hair, 4: dense long hair, 5: complete hair growth.

<table>
<thead>
<tr>
<th>Code</th>
<th>Size (nm)</th>
<th>PI</th>
<th>Zeta potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL</td>
<td>360.2 ± 12.6</td>
<td>0.24</td>
<td>-</td>
</tr>
<tr>
<td>AL-1</td>
<td>354.2 ± 13.5</td>
<td>0.25</td>
<td>−28.4 ± 2.3</td>
</tr>
<tr>
<td>AL-5</td>
<td>304.8 ± 12.6</td>
<td>0.25</td>
<td>−31.2 ± 3.2</td>
</tr>
<tr>
<td>AL-10</td>
<td>285.6 ± 15.9</td>
<td>0.24</td>
<td>−34.8 ± 3.7</td>
</tr>
<tr>
<td>CL-1</td>
<td>336.8 ± 12.6</td>
<td>0.16</td>
<td>26.5 ± 2.7</td>
</tr>
<tr>
<td>CL-5</td>
<td>287.6 ± 19.8</td>
<td>0.18</td>
<td>32.4 ± 3.1</td>
</tr>
<tr>
<td>CL-10</td>
<td>279.6 ± 15.7</td>
<td>0.23</td>
<td>38.1 ± 2.6</td>
</tr>
</tbody>
</table>

Table 2. Physical properties of liposome containing finasteride
and +38.1 mV in CL-1, CL-5, CL-10, respectively.

The FNS-containing liposomes were investigated for their ability to deliver FNS through the hairless mouse skin for 24 h using Keshary-Chien diffusion cell in vitro. The skin penetration study showed that penetration of the drug remarkably increased in cationic liposomes compared to both neutral liposome and non-liposomal formulation (ethanol 10% solution containing 0.5 mg/ml of FNS) (Fig. 3). Cumulative amount of FNS penetrated through the skin for 24 h was 22.35, 33.31, and 37.50 μg/cm² in CL-1, CL-5, and CL-10, respectively, while it was 7.03 μg/cm² in neutral liposome and 4.78 μg/cm² in non-liposomal formulation. This amount represents 3-5 times and 5-8 times increase of skin penetration compared to neutral liposome and non-liposomal formulation, respectively.

Cumulative amount of FNS penetrated through the skin for 24 h was 8.84, 10.53, and 12.99 μg/cm² in AL-1, AL-5, and AL-10, respectively.

The FNS-containing liposomes were also investigated for the amount of FNS retained in the skin after 24 h. The skin retention study showed that retention of the drug was 65.80, 62.81, and 51.26 μg/cm² in CL-1, CL-5, and CL-10, and it was 84.59, 87.08, and 79.23 μg/cm² in AL-1, AL-5, and AL-10, respectively (Fig. 4). The amount of FNS retained in neutral liposome and non-liposomal formulation was only 42.47 and 17.81 μg/cm², respectively. This result represents that, when FNS was applied as anionic liposome, the amount of the drug retained in the skin was about two times compared to application as neutral liposome. When compared to non-liposomal formulation of the drug, it was about four times increase.

The effect of FNS-containing liposomes on the hair growth was investigated and depicted in Fig. 5. The degree of hair growth was evaluated by visual scoring of hair growth quan-
tification scale as described in the hair growth study section and Fig. 2. Neutral and cationic liposomes of the drug did not show significant difference from negative control in terms of hair growth quantification score (Fig. 5A). In contrast, anionic liposomes of the drug showed moderate increase compared to both neutral liposome and negative control (Fig. 5B). Particularly, AL-5 (FNS-containing liposome prepared with 5% anionic charge carrier lipid) showed statistically significant hair growth improvement compared to neutral liposome (p<0.05). The hair growth quantification score was 4.36 ± 0.34 after 20 days of treatment with AL-5 while it was 3.53 ± 0.21 and 3.13 ± 0.35 for treatment with NL and negative control, respectively. However, the efficacy was not comparable to minoxidil 5% solution which is widely used topical formulation for the treatment of alopecia.

DISCUSSION

FNS is drug of choice for the treatment of androgenetic alopecia since it was approved by US Food and Drug Administration in 1997. However, the use of the drug has been implicated in problematic side effects such as sexual disturbance and gynecomastia (Mella et al., 2010). Furthermore, the drug is associated with incidence of high-grade prostate cancer (Thompson et al., 2003; Thompson et al., 2008; Lebdai et al., 2010). Therefore, topical formulation of the drug has been anticipated as an alternative route for the drug application. In the present work, therefore, we prepared liposome formulation of the drug using soybean lecithin (Phospholipon® 85 G, a lecithin enriched with phosphatidylcholine) and cholesterol. The extent of penetration and retention of the drug depends on the physicochemical properties of the drug itself combined with the influence of the composition of the liposomes. Lipid layer in the stratum corneum of skin contains high ratio of negatively charged lipids. Therefore, surface charge on the liposome may play a role in penetration and retention behavior of the drug by electrostatic interaction during permeation process through the skin (Rojanasakul et al., 1992; Piemi et al., 1999).

We prepared neutral, anionic, and cationic liposome formulations of FNS using Phospholipon® 85 G and cholesterol (molar ratio of 1:1) with addition of charge carrier lipid, i.e., DMPA and DOTAP. Cholesterol was added to protect phosphatidylcholine from oxidation and to provide rigidity to the liposome vesicles (Allen et al., 1991; Grit et al., 1993). Weight percentage of the charge carrier lipid was varied from 1-10% to see the effect on physical properties and hair growth of the liposomal formulations. Particle size of all liposome formulations containing FNS was less than a micron, and polydispersity index revealed size homogeneity of the prepared liposomes. Smaller size in the charged liposomes appears to be due to electrostatic repulsion between the vesicles.

Skin penetration study was performed with 0.5 ml of FNS-containing liposome suspension (equivalent to 0.25 mg of FNS) or same volume of ethanol 10% solution containing 0.5 mg/ml FNS. In terms of cumulative amount of FNS penetrated through hairless mouse skin, it was significantly higher when applied as cationic liposome, compared to anionic liposome (p<0.01). Specifically, CL-10 showed highest amount reaching 37.5 μg/cm², representing 31.5% of total drug applied on the skin. In contrast, it was only 8.84 μg/cm² in AL-1 which accounts for only 7.43% of total drug applied. It is not clear why the drug loaded into cationic liposomes resulted in greater penetration over anionic liposomes. But it appears that cationic charge on the surface of liposome played a role because epidermis layer contains negatively charged lipids (Burnette and Ongpipattanakul, 1987; Kirjavainen et al., 1996). This speculation is further supported by the fact that the higher percentage of DOTAP shows the greater penetration.

Interestingly, however, the amount of FNS retained after 24 h penetration study was not in consistent with penetration study result. In fact, the amount of the drug retention was generally greater when applied as anionic liposomes compared to cationic liposomes. Specifically, it was 79.23 μg/cm² in AL-10 while it was 51.26 μg/cm² in CL-10 (p<0.05). It appears that the drug loaded into negatively charged liposome remained in the skin layer due to electrostatic repulsion between the liposome and epidermis layer. However, it is not clear why the amount of the drug retained is greater when applied as anionic liposome compared to cationic liposomes. Further research is warranted to elucidate the mechanistic difference between the negatively and positively charged liposomes of the drug.

Since the final outcome of our FNS-containing formulation is hair growth, we performed hair growth study for 20 days using depilated C57BL/6N mice. In the present study, the drug loaded into anionic liposomes showed moderate enhancement of the hair growth, but the enhancement was not found when the drug was applied as cationic liposomes. The reason why FNS-containing anionic liposomes were more effective than cationic liposomes might be associated with greater retention in the skin (Fig. 4). Although anionic liposomes showed generally better enhancement compared to cationic liposomes, both liposomes were not as effective as minoxidil 5% solution.

FNS exerts its efficacy of alopecia treatment by inhibition of type II 5α-reductase in the systemic level, reducing both serum and tissue concentration of 5α-dihydrotestosterone (Rittmaster et al., 1992; Peters and Sorkin, 1993). This is why FNS causes problematic side effects such as sexual disturbance, gynecomastia, and high-grade prostate cancer. Considering that conversion from testosterone to 5α-dihydrotestosterone also takes place in hair follicles (Fazekas and Sandler, 1972; Takayasu et al., 1980; Hoffmann and Happle, 2000), topical application of the drug may be a reasonable option. Although hair growth enhancement in our study was not comparable to currently available topical preparation (minoxidil 5% solution), future study with different lipid composition along with various charge carrier lipids may lead to comparable or even better formulations for the treatment of androgenetic alopecia. Such topical formulation would be advantageous for patients with androgenetic alopecia who need finasteride without the risk of side effects associated with oral use of the drug.

In the present study, finasteride-containing liposomes with anionic surface charge showed moderate enhancement of the hair growth, but the enhancement was not found when the drug was applied as liposomes with cationic surface charge. Therefore, topical application of finasteride using anionic liposome formulation appears to be useful option for the treatment of androgenetic alopecia to avoid systemic side effects of the drug.

ACKNOWLEDGMENTS

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REFERENCES


