Feasibility of Transdermal Delivery of Fluoxetine

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ABSTRACT

Feasibility of developing a transdermal drug delivery of fluoxetine has been investigated. Permeation studies of fluoxetine across human cadaver skin were carried out using Franz diffusion cells. The receptor phase consisted of pH 7.4 phosphate buffer maintained at 37°C. Permeation enhancement of fluoxetine, either in the salt or base form, was achieved using various enhancers like azone, SR-38, and ethanol. Various O/W microemulsion systems of fluoxetine were developed to study their effect on the skin permeation of fluoxetine. The results indicated that ethanol at 65% vol/vol was able to increase the permeation of fluoxetine the most, while microemulsion systems showed decrease in the permeation of fluoxetine. The permeation of fluoxetine obtained using a 65% vol/vol ethanolic solution was found to be sufficient to deliver the required dose (20–80 mg) from a patch of feasible size. The results seem promising for developing a transdermal drug delivery system of fluoxetine.

KEYWORDS: transdermal, fluoxetine, microemulsion, enhancer, ethanol

INTRODUCTION

A number of drug molecules have been or are being developed in the transdermal drug delivery system (TDDS). Some of the potential advantages of TDDS include: avoidance of first-pass metabolism, elimination of gastrointestinal irritation resulting from some drugs, reduced dosing frequency, and rapid termination of drug action.

Nevertheless, the barrier property of the skin and lack of inherent permeability exhibited by most of the drugs limit the development of TDDS for most of the drugs. Therefore, the major challenge for TDDS is to provide enhanced drug permeation through the skin, without inducing significant irreversible alterations to the skin barrier function. Various approaches have been taken for permeation enhancement, including changing the properties of the drug, the vehicle, or the skin. Recently, various studies have suggested that microemulsions have a potential of increasing cutaneous drug delivery compared with conventional vehicles.[1,2] A microemulsion is defined as a system of water, oil, and surfactants that is a transparent, single optically isotropic, and thermodynamic stable liquid solution.[3]

Fluoxetine (Fx), a novel antidepressant, is widely used to treat various types of psychiatric disorders, such as major depression, bipolar depression, and obsessive compulsive disorders, as well as a range of other clinical conditions, such as eating disorders, obesity, attention deficit hyperactivity disorder, and panic attacks.[4-7] Fx is a selective serotonin reuptake inhibitor and possesses weak affinity for muscaranic receptors and, therefore, exhibits lesser anticholinergic side effects than that caused by other traditional antidepressants such as tricyclic antidepressants and monoamine oxidase inhibitors. The dose of Fx ranges from 20 to 80 mg administered as 1 to 4 capsules a day. This dose and frequency may cause enhanced drug-related side effects and may pose compliance problems.[8] It has also been reported that fluoxetine undergoes hepatic first-pass metabolism.[9,10] A transdermal delivery system of fluoxetine may help to avoid the above problems and make it useful over the oral drug delivery in terms of both dose and frequency. The objective of this research was to evaluate the feasibility of TDDS of fluoxetine using different vehicles and permeation enhancers.

MATERIALS AND METHODS

Materials

Fluoxetine HCl was obtained as a gift sample from the Lilly Research Laboratory (Greenfield, IN). Fluoxetine free base was prepared from Fluoxetine HCl using standard alkaline precipitation of base followed by solvent extraction. Infrared spectroscopy was used to confirm the formation of free base, whereas purity of the free base was confirmed using high-performance liquid chromatography (HPLC). Human cadaver skin was obtained from Ohio Valley Tissue and Skin Center (Cincinnati, Ohio). Labrasol, transcutol, and lauroglycol were kindly provided by Gattefosse France (Gennevilliers, France). Propylene glycol was purchased from Spectrum Chemicals

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(Gardena, CA). Azone (1-dodecyl-hexahydro-2*H*-azepin-2-one) was obtained from Discovery Therapeutics (Richmond, VA). SR-38 (4-decyloxazolidin-2-one) was obtained from Pharmetrix (Menlo Park, CA). All other chemicals were HPLC-grade and obtained from Fisher Scientific (Fairlawn, NJ).

Analytical Method

Fluoxetine was analyzed using an HPLC system (HP 1100 liquid chromatography) equipped with a manual injector, HP 1100 UV detector, and HP 3395 integrator (Hewlett Packard, Mountain View, CA). A Zorbax column (Rx-C_{18} 4.6 × 150 mm; 5 μm) was used as an analytical column, and the injection volume was 50 μL. The mobile phase was composed of 25 mmol/L phosphate buffer, acetonitrile (65:35) with 0.1% 0-phosphoric acid, and 0.2% triethylamine. Flow rate of mobile phase was 1 mL/min, the wavelength of detection was 225 nm, and fluoxetine eluted at 5.6 minutes.

Sample Preparation

Permeation of drug was studied using vehicle systems, such as microemulsion and solution with or without permeation enhancers like Azone (1-dodecyl-hexahydro-2*H*-azepin-2-one) and SR-38 (4-decyloxazolidin-2-one). Fx was used at a level of 15 mg/mL or 15 mg/g.

Preparation of Microemulsion

The solubility results of Fx in lauroglycol (oil phase) indicated that 75 mg of lauroglycol was required to dissolve the targeted drug loading of 15 mg of Fx per gram of formulation. Therefore, various microemulsion (ME) formulations were tried by keeping the oil phase at the same level while varying the total amount of surfactant (labrasol) and cosurfactant (transcutol) and also varying the ratios of surfactant to cosurfactant (K_m). Formulations were prepared by first dissolving Fx and butylated hydroxytoluene (BHT; antioxidant) in the oil phase. Surfactant, cosurfactant, and permeation enhancers, if present, were added to the oil phase. The oil phase was stirred until a clear solution was obtained. Sodium metabisulfite (antioxidant) and sodium benzoate (preservative) were dissolved in aqueous phase. The aqueous phase (water or hydroalcoholic solution) was added to the oil phase, and the resulting mixture was stirred and observed for clarity.

Preparation of Solution

To study the effect of Azone and SR-38 on permeation of Fx.HCl, the drug and enhancer solutions were prepared in 50:50 propylene glycol to water. To compare the permeation characteristics of fluoxetine free base and salt, the solutions of both Fx.HCl and Fx were prepared in propylene glycol. Also, the solution of Fx was prepared in various hydroalcoholic solutions to study permeation enhancement effect of alcohol.

Skin Permeation Studies

Full-thickness dermatomed human cadaver skin specimens (taken from the back region of male subjects) were obtained from Ohio Valley Tissue and Skin Center. The skin was frozen in a 10% glycerol solution to −70°C; when received, the skin was placed at −65°C until further use.

For permeation studies, properly thawed dermatomed human cadaver skin was mounted on a Franz diffusion cell with the stratum corneum side facing the donor compartment and the dermal side facing the receptor compartment. The diameter and the volume of the Franz diffusion cells were 9 mm and 3 mL, respectively. The donor solution consisted of 500 μL of drug solution, which was in the form of a simple solution or microemulsion. The donor compartment was covered with a cover slip to create an occlusive environment. The receptor solution (phosphate buffer; pH 7.4, 37°C) was introduced into the stirred receptor compartment, which was maintained at 37°C by a circulating water bath (Hanson Research, Chatsworth, CA). At predetermined time intervals, 300 μL of the samples was withdrawn from the receptor compartment and replaced by an equal volume of fresh buffer solution maintained at 37°C. Samples were then analyzed by HPLC.

Data Analysis

The cumulative amount of Fx permeated versus time was plotted. The slope of the steady-state portion of the plot represents the flux (J; micrograms per squared centimeter per hour), whereas the x-intercept represents the lag time (t_L; hour).

Statistical Analysis

The flux values obtained from the various systems were tested for significant differences using a one-way analysis of variance (ANOVA) or unpaired t test. If the significant differences exist when ANOVA was used, the pairwise comparison of different systems (post hoc analysis) was done to find out statistical significant difference in flux values using a Tukey's test. When the normality test failed, Kruskal-Wallis one-way ANOVA was used to find out if the significant differences exist between different systems. The statistical analysis was conducted using SigmaStat software version 2.0 (Systat Software, Inc, Point Richmond, CA).

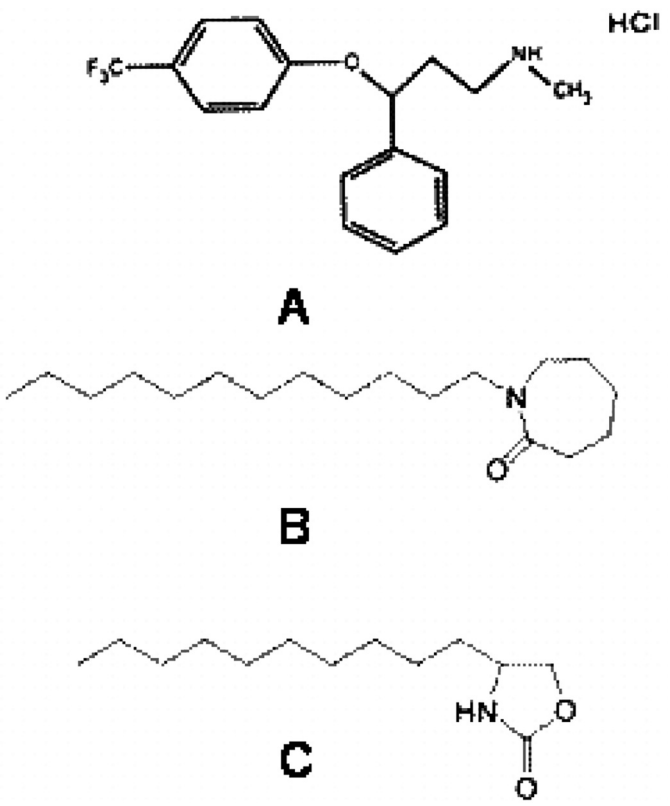

Figure 1. Structures of fluoxetine HCl (A), Azone (B), and SR-38 (C).

RESULTS AND DISCUSSION

Effect of Azone and SR-38 on the Skin Permeation of Fluoxetine HCl

Azone (1-dodecyl-hexahydro-2*H*-azepin-2-one) has been widely used as a permeation enhancer[11,12] and is reported to be nonirritant and nonallergenic.[13] Azone increases the skin permeability of compounds by disordering the lipid bilayers, causing lipid solubilization, and increasing fluidization of structured lipids.[14] SR-38 (4-decyloxazolidin-2-one) has been recently studied as permeation enhancer and is reported to be nontoxic and free from dermal irritation. SR-38 is a new and proprietary oxazolidinone class of permeation enhancers and has been reported to cause fluidization of the bilayer lipids in skin, thereby resulting in enhanced permeation of various compounds.[15] Structures of fluoxetine, Azone, and SR-38 are shown in Figure 1.

Flux values obtained using different concentration of Azone and SR-38 are summarized in Table 1. As evident from Table 1, permeation of Fx.HCl increased by 6 times when 2% Azone was used and by about 8 times when 5% wt/vol SR-38 was used. Further increase in the concentration of Azone and SR-38 showed a decrease in skin permeation. Similar results have been reported for permeation enhancement of indomethacin and urea using Azone as enhancer. The permeation rate was shown to decrease with an increase in the concentration of Azone from 3% to 5%.[12] A parabolic relationship between the concentration of Azone and its permeation enhancement effect may exist, with the optimum concentration varying from drug to drug.[13] On the other hand, SR-38 has a tendency to form micelles at concentrations of about 10%, which may result in the entrapment of drug.[15]

The increase in the concentration of Azone and SR-38 beyond 2% and 5%, respectively, may have increased the solubilization of the fluoxetine in the vehicle resulting in an increased affinity of fluoxetine for the vehicle. This would result in decreased partitioning of fluoxetine between vehicle and skin. The result of the permeation studies using Azone and SR-38 indicates that the highest permeation of Fx.HCl was obtained with 5% wt/vol SR-38. The permeation obtained using 5% wt/vol SR-38 was statistically significantly higher than that obtained using control. However, the flux values obtained were not sufficient to deliver the required dose of the drug (20-80 mg) from a reasonable patch size consisting of fluoxetine hydrochloride. Therefore, evaluation of the fluoxetine free base was conducted to study the feasibility of transdermal delivery of fluoxetine.

Comparison of the Permeation Profile of Fx.HCl and Fx Base

Usually the base form of drug, because of its higher lipid solubility, shows better permeation compared with the more water-soluble salt form. However, because Fx.HCl is official in the United States Pharmacopeia, earlier permeation studies were carried out to evaluate the feasibility of formulating TDDS with Fx.HCl. The permeation profiles of Fx and Fx.HCl are shown in Figure 2. As expected, permeation of Fx was found to be significantly higher ($P < .05$); therefore, further studies were conducted using free base.

Table 1. Effect of Azone and SR-38 on the Permeation of Fluoxetine HCl

Enhancer (% wt/vol)	Flux (J) (μg/(cm^2•h) Mean ± SD*	
	Azone	SR-38
Control	2.263 ± 2.285	2.263 ± 2.285
2%	13.153 ± 6.606	15.337 ± 5.328
5%	8.51 ± 1.993	17.977 ± 9.552
10%	8.425 ± 2.765†	5.21 ± 1.207

*Mean ± SD of 3 determinations.
†Mean ± SD of 2 determinations.

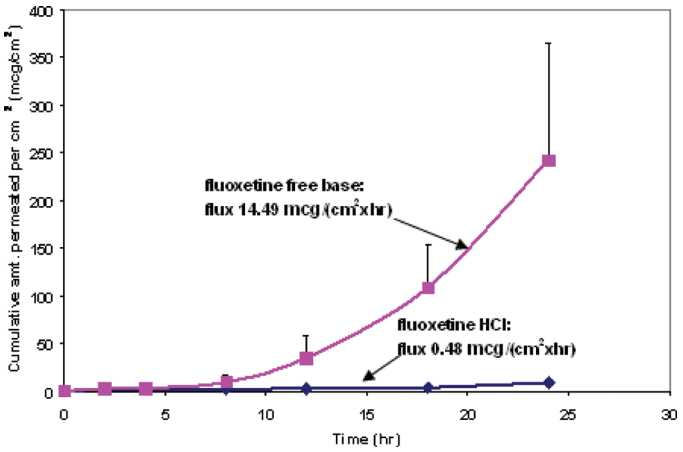

Figure 2. The comparative permeation of salt and the base form of fluoxetine.

Table 2. Effect of Hydroalcoholic Solutions and Microemulsions on the Permeation of Fluoxetine Free Base

System	Flux (J) (μg/(cm^2•h)) Mean ± SD
65% vol/vol ethanolic solution	79.71 ± 10.804*
80% vol/vol ethanolic solution	25.31 ± 21.013†
95% vol/vol ethanolic solution	10.825 ± 10.13‡
Formulation A	9.85† (0.646)
Formulation B	5.813† (0.588)
Formulation C	2.663† (1.691)

*Mean ± SD of 6 determinations.
†Mean ± SD of 3 determinations.
‡Mean ± SD of 4 determinations.

Effect of Ethanol on Permeation of Fluoxetine Base

Ethanol is a commonly used vehicle for transdermal drug delivery. It possesses the dual function of acting as a solvent and a permeation enhancer. Ethanol has been reported to increase the flux of ibuprofen, flurbiprofen, indomethacin, isosorbide dinitrate, cyclobarbital, zalcitabine, didanosine, and zidovudine.[16,17]

Various mechanisms are reported for the skin permeation enhancement effect of ethanol. Hatanaka et al reported that ethanol may enhance diffusion of drugs through the lipid pathway of the skin.[16] Some researchers have reported that ethanol may cause the reduction of lipid polar head interactions or may disorder liquid-crystalline phases within the membrane, thereby resulting in increased skin permeation.[18] Megrab et al[19] have reported that ethanol may increase drug-skin permeability by increasing drug solubility in the stratum corneum.

The effect of the percentage of ethanol (v_e; vol/vol) on the permeation of Fx is shown in Table 2. As evident from Table 2, the flux values for Fx decreased as the v_e increased from 65% to 95% vol/vol. Megrab et al[19] have reported similar results in which the flux of estradiol decreased with increases in v_e above 60%vol/vol.

At higher v_e, the solubility of Fx in the vehicle would be increased, resulting in decreased activity of the drug. This will result in decreased partitioning of Fx into the skin, which is evident by the skin partition data, thereby decreasing the permeation of Fx. Moreover, Berner et al[17] reported that when the v_e increases beyond 80%, the outer layer of the stratum corneum is substantially dehydrated, and this dehydrated layer could add to barrier properties of the skin. ANOVA showed that the flux values obtained for Fx with 65% vol/vol ethanol were significantly higher ($P < .05$) than that obtained using 80% and 95% vol/vol ethanol.

Table 3. Formulations of Various Microemulsion Systems

Ingredient	Function	Formulation A (% wt/wt)	Formulation B (% wt/wt)	Formulation C (% wt/wt)
Lauroglycol	Oil phase	7.50	7.50	7.50
Fluoxetine	Drug	1.50	1.50	1.50
Water	Aqueous phase	58.26	51.76	45.82‡
Labrasol	Surfactant	32.50*	39.00*,†	45.00§
Transcutol	Cosurfactant			
SR-38 (2% wt/wt)	Permeation enhancer	0.00		0.00
BHT	Antioxidant	0.02	0.02	0.02
Na-Metabisulfite	Antioxidant	0.10	0.10	0.05
Na2-EDTA	Chelating agent	0.02	0.02	0.01
Na-Benzoate	Preservative	0.10	0.10	0.10

*K_m (surfactant / cosurfactant) = 2.
†2% wt/wt of SR-38 replaces equal amount of transcutol.
‡65% vol/vol ethanolic solution in water used as the aqueous phase instead of water.
§K_m = 5.

Effect of Microemulsion on the Permeation of Fx

Skin permeation studies were conducted using ME to examine if these systems can further improve the permeation of Fx. Various ME formulations, with and without the permeation enhancer SR-38, and also formulations in which the aqueous phase was replaced by the optimum v_e (65% vol/vol ethanol) were tried. During the formulation of microemulsions, the systems consisting of 5% SR-38 required very high levels of surfactant and cosurfactants to form microemulsions. The amounts of surfactants and cosurfactants needed to formulate microemulsion was reduced when 2% SR-38 was used. The formulations that formed microemulsion with minimum amount of total surfactant and cosurfactant were selected for permeation studies.

Components of microemulsion formulations A (without SR-38), B (with SR-38), and C (aqueous phase replaced with 65% vol/vol ethanol) are listed in Table 3. The effect of ME on the permeation of Fx is shown in Table 2.

As illustrated in Table 2, permeation of Fx was found to be significantly lower in all the microemulsion formulation compared with drug solution in a 65% vol/vol ethanol solution. Gallarate et al[14] also reported a decrease in the permeation of levobunolol from ME across hairless mouse skin. These researchers have proposed that the dispersed oil phase may act as a drug reservoir. Similar effect may be expected in this study. Dispersed oil phase of ME may act as a drug reservoir decreasing the partitioning of drug into the skin, thereby decreasing the permeation.

Calculation for Patch Size

It has been reported that following oral administration of an average fluoxetine dosage of 32 mg daily for 3 to 6 weeks to patients suffering major depression, the mean steady-state plasma concentration (Cp_{ss}) was 145 ng/mL (range, 47-469 ng/mL).[20] The apparent volume of distribution (V_d) of fluoxetine is reported to be 20 to 45 L/kg and does not change substantially following multiple dosing.[20] Following a single oral dose of fluoxetine, the average half-life is reported to be 2 to 3 days. The half-life of fluoxetine is prolonged (approximately 4-5 days) after administration of multiple doses.[20] Using the reported values of mean steady-state plasma concentration (145 ng/mL), a volume of distribution of 30 L/kg and an average half-life of 3 days in a healthy 70 kg individual, the required input rate was calculated[21] to be about 2931 μg/h, using the following equation: Input rate = $Cp_{ss} \times V_d \times k_{el}$.

With a flux of 80 μg/(cm^2·h) obtained from a vehicle system consisting of 65% vol/vol ethanol, it can be estimated (input rate/maximum flux) that a transdermal patch of about 35 cm^2 consisting of 65% vol/vol ethanol should be able to attain and maintain 145 ng/mL fluoxetine over a period of 1 day. Patch size may be varied should higher or lower levels be desired.

SUMMARY AND CONCLUSIONS

Permeation of fluoxetine free base was significantly enhanced from a vehicle system consisting of 65% vol/vol ethanol, whereas microemulsion systems showed a decrease in the permeation of fluoxetine. These initial studies demonstrate the feasibility of developing a transdermal drug delivery system for fluoxetine.

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