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FORMULATION AND DEVELOPMENT OF FLUOXETINE TRANSDERMAL PATCHES: IN VITRO AND IN VIVO EVALUATION

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ABSTRACT

The objective of the present study was to develop matrix type transdermal patches of fluoxetine using a polymeric combination of ethyl cellulose (EC) and polyvinylpyrrolidone (PVP) by solvent evaporation method. All the formulations were evaluated for *in vitro* drug release studies and *in vitro* permeation studies through excised rat skin. The physiochemical compatibility between drug and polymers was determined by Fourier Transform Infrared Spectroscopy (FTIR). The results of *in vitro* permeation studies showed that the formulation FT1, containing EC/PVP in the ratio of 3:2 with 2% tween-80 as a permeation enhancer exhibited the greatest cumulative amount of drug permeated with a flux 43.91 µg/cm^2/h. The formulation was taken up for further evaluation of *in vivo* pharmacological and skin irritation potential. The antidepressant efficacy of transdermal patches (FT1) was comparable to oral formulation during forced swim and tail suspension test in Wistar rats with no skin irritation. The results of FTIR study indicated that the combination of drug and polymers is suitable for formulation of transdermal patches of fluoxetine. On the basis of results it was concluded that the fluoxetine matrix-type transdermal therapeutic system could be prepared with the required flux to improve the patient compliance and provide maintenance therapy to patient in depression.

Keywords: Transdermal patches, fluoxetine, ethyl cellulose, polyvinylpyrrolidone, *in vitro* drug release and antidepressant.

INTRODUCTION

Fluoxetine is a selective serotonin reuptake inhibitor which act by blocking the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane and thereby enhancing the actions of serotonin on $5HT_{1A}$ autoreceptors. Fluoxetine is used to treat depression, bulimia nervosa, panic disorder, post-traumatic stress and premenstrual dysphoric disorder. It is commercially available in the form of conventional tablets and capsules. The oral dose of fluoxetine hydrochloride salt is ranges from 20 to 80 mg administered as 1 to 4 times a day.[1] But usefulness of fluoxetine is limited due to its dose and frequency.

Fluoxetine produces various gastrointestinal related side effects like abdominal pain, dyspepsia, nausea, vomiting, constipation and diarrhoea are more common side effects with oral administration. A transdermal delivery system of fluoxetine may help to avoid the above problems and make it beneficial over the oral drug delivery system in terms of both frequency and dose.[2-3]

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MATERIALS AND METHODS

Materials

Fluoxetine was purchased from Yarrow Chem Pvt. Ltd., Mumbai, India. Ethyl cellulose, polyvinylpyrrolidone, chloroform, dibutyl phthalate and tween-80 were procured from S.D. Fine Chem. Ltd., Mumbai. Dimethyl sulphoxide (DMSO) was supplied from Central Drug House, New Delhi. All other chemicals and reagents used were of analytical grade and procured from an authorized dealer. The study protocols were

approved by the Institutional Animal Ethical Committee.

Table 1. Composition of fluoxetine transdermal patches

F. Code	Fluoxetine (% w/w)	EC:PVP	Permeation Enhancers (% w/w)
F1	20	4.5 : 0.5	-
F2	20	4 : 1	-
F3	20	2 : 1	-
F4	20	3:2	-
F5	20	2:3	-
FD1	20	3:2	DMSO 2%
FD2	20	3:2	DMSO 5%
FD3	20	3:2	DMSO 10%
FT1	20	3:2	Tween-80 2%
FT2	20	3:2	Tween-80 5%
FT3	20	3:2	Tween-80 10%

Note: 30% w/w dibutyl phthalate to the total polymer weight, incorporated as plasticizer.

Drug-Excipients Interaction Study

FTIR spectra of pure drug (fluoxetine), EC, PVP and physical mixtures of fluoxetine with EC and PVP were recorded. A pellet of pure drug and physical mixture of drug and polymers (1:1) were prepared by compressing with IR grade potassium bromide in a 100:1 ratio by applying 5.5 metric ton of pressure in hydraulic press. The pellet was mounted in IR compartment and scanned between wave number 4000-450 cm^{1} using FTIR spectrophotometer (Model-8400S, Shimadzu, Japan).[4]

Development Of Transdermal Systems

The matrix type transdermal patches of fluoxetine were prepared by solvent evaporation technique using different proportion of EC and PVP with 30% w/w of dibutyl phthalate as a plasticizer to the total dry weight of polymers. The polymers were mixed in different ratios (Table-1) and they were dissolved in chloroform by magnetic stirrer. The drug 20 % w/w of polymer weight was added slowly to the polymers solution and mixed thoroughly by continuous stirring for 30 min to obtain a homogenous solution. On the basis of preliminary studies, the optimized EC/PVP ratio (3:2) were mixed with the permeation enhancers (like DMSO and tween-80) added in three different concentrations *i.e.* 2%, 5% and 10% w/w of total polymers weight for each. The resulting drug-polymers solution was poured in petridish on which aluminium foil was spread previously as backing membrane. The rate of evaporation was controlled by inverting a funnel over the petridish and the solvent was allowed to evaporate for 24 h at room temperature. After 24 h, the films were collected and a wax paper was applied on the other side of the film as a release liner to complete the formulation.[5-6]

EVALUATION OF TRANSDERMAL PATCHES

In Vitro Release Studies

The dissolution studies were performed by using dissolution rate test apparatus (USP-II) for the assessment of the release of the drug from the transdermal patches. The commercially available water-impermeable adhesive backing membrane was placed over the patch and it was further fixed on a glass slide (2.3x2.3 cm) using cyanoacrylate adhesive. Then the transdermal patch was covered with a dialysis membrane and placed at the bottom of dissolution vessels with the release surface facing upward. The apparatus was equilibrated to 32 ± 0.5^{0}C and the dissolution medium was 20% methanol in PBS pH 7.4 solution. The paddle speed was kept 50 rpm. The samples were withdrawn at different time intervals up to 24 h and analyzed spectrophotometrically for its drug contents.[7]

In Vitro Permeation Studies

In vitro permeation studies across excised rat skin were carried out in vertical assembled Franz-type diffusion cell having a capacity of 11ml and the effective surface area for permeation was 2 cm^{2}. The rat skin was mounted between the donor and receptor cell with the epidermis facing upward into the donor compartment. The prepared patch was placed on the skin. The receptor fluid was kept same as dissolution media and continuously stirred throughout the experiment by using magnetic bead at 32 ± 0.5^{0}C. 1ml samples were withdrawn at different time intervals and replaced with equal amount of fresh dissolution media. The samples were analyzed by UV spectrophotometer for its drug contents. The cumulative amount of drug permeated per sq. cm of patch was calculated and plotted against time. The flux was calculated as the amount of drug permeated per sq. cm per hour. The effectiveness of permeation enhancers

was determined by comparing drug flux in the presence and absence of each permeation enhancer and obtained ratio was known as the enhancement factor. [8-9]

Scanning Electron Microscopy

The surface morphology of the transdermal patches was studied before and after *in vitro* permeation study using scanning electron microscopy. The patch samples were splutter coated with gold before scanning.

Skin Irritation Studies

Transdermal patch was applied onto the dorsal skin of Wistar rats (150 – 250g) which was shaved on the previous day of the study. The animals were applied with new patch/formalin solution (0.8%) each day upto 7 days and skin irritation (erythema and edema) was evaluated by visual scoring. The scores were given for erythema from 0 to 4 depending on the degree of erythema as follows: no erythema 0, slight erythema (barely perceptible- light pink) 1, moderate erythema (dark pink) 2, moderate to severe erythema (light red) 3, severe erythema (extreme redness) 4. The edema scale was: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, severe.[11]

Pharmacological Studies

Wistar rats (220 - 250 gm of weight) were used in present study. They were maintained on standard temperature (25 ± 1^{0}C) and were fed with standard pellet diet and water ad labitum**.** The animals groups (n=5) were treated as follows:

Group-I: Blank patches

Group-II: Fluoxetine patches (FT1)

Group-III: Fluoxetine 10 mg/kg body weight per oral in 0.5% of suspension of carboxy methylcellulose.

The patches and oral dose administered to rats for 7 successive days and immobility period was observed after 24 h and 7 days of drug administration.

Forced swim test: In forced swim test, the rats were placed individually in plastic jar (height 60 cm, diameter 20 cm), containing 30 cm of water at 25 ± 1^{0}C. After 15 min they were removed and dried before returning to their home cage. The animals were replaced in the jar 24 h later after drug administration and immobility period was recorded. The total duration of immobility was recorded in 5 minutes duration of the test. Following swimming session, rats were towel dried and returned to their housing conditions. Water in the chamber was changed after subjecting each animal.[12-13]

Tail suspension test: In this test, the animals were allowed to adopt laboratory condition for 2 hour before the test. The each rat was individually suspended on the edge of a shelf 50 cm above a table top by adhesive tape, placed approximately 1 cm from the tip of the tail. In such a position the rat cannot escape or hold on to nearby surfaces.

Each animal under test was both acoustically and visually isolated from other animals during the test. The total period of immobility was recorded in 5 minutes duration test and then subsequently analyzed. The animal was considered immobile when it did not show any movement of the body except for those required for respiration and hanged passively. The test was conducted in a dim lighted room.[14]

Stability Studies

Stability studies of formulation FT1 was conducted according to ICH guidelines by storing at 40 ^{0}C and 75 % RH for 3 months. The samples were withdrawn at 30, 60 and 90 days and evaluated for physical appearance and drug contents. The *in vitro* permeation study was performed after 90 days and compared with fresh batch.[15]

Statistical Analysis

The formulation parameters were statistical evaluated by Graph pad prism 5 using one-way analysis of variance (ANOVA), followed by Dunnett test multiple comparison tests and unpaired t-test. A difference below the probability level of 0.05 was considered statistical significant. The obtained results were expressed as the mean ± standard deviation.

RESULTS AND DISCUSSION

Drug-Excipients Interaction Study

The IR spectra of fluoxetine alone and its physical mixtures with EC and PVP are shown in Figure-1. The peaks corresponding to various functional groups indicating purity of the drug sample and with no or slight shift in their positions in physical mixture indicated absence of interaction. However some additional peaks were also observed with the physical mixture, possible because of the presence of polymers.

In Vitro Release Studies

The cumulative % of drug release from patches without permeation enhancer was found 40.70 to 59.66% (Figure-2). It was observed that increased in the addition of hydrophilic polymer (PVP), the rate of drug release increased. Similar results were also reported by others.[6] But in case of formulation F5, increased in concentration of hydrophilic polymer, the rate of drug release was deceased. This may be attributed to the previous finding that higher concentration of PVP K-30 may

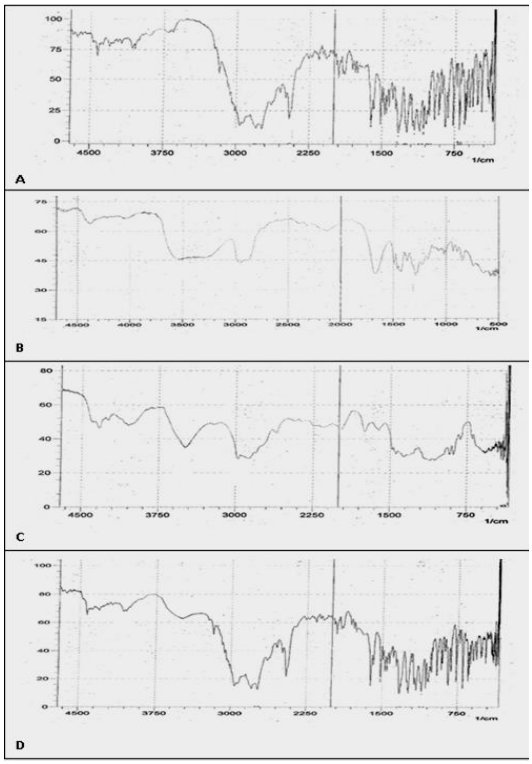

Fig.1. I.R. spectra of fluoxetine (A), ethyl cellulose (B), polyvinylpyrrolidone (C) and physical mixture of fluoxetine with EC and PVP K-30 (D)

decrease the crystalline drug in patch and thus decease drug release.[16] The greatest % of drug release (59.66%) was observed from formulation F4 (EC/PVP, 3:2) in 24 h. Therefore, formulation F4 was selected for incorporation of permeation enhancers in a concentration of 2%, 5%, and 10%. It was observed that the formulations containing DMSO as permeation enhancer, release rate was found to be directly proportional to the concentration of the DMSO (64.58, 70.49 and 78.29% for 2, 5 and 10% respectively in 24 h) in transdermal patches (Figure-3). It has been reported that DMSO is relatively polar in nature having small and compact structure which could lead to higher release rate.[17]

In case of batch FT, *i.e.* formulation containing tween-80 as a permeation enhancer, the highest % of drug release (88.72%) was observed with 2% of tween-80 (FT1). This may be due to the solubilisation effect of tween-80. But further increase in the concentration of tween-80 from 5 (FT2) to 10% (FT3), there was a decreased in the percentage of drug release from 77.32 to 70.38% respectively (Figure-4). Tween contribute to achieving critical micelle concentration (CMC). The concentration of surfactants above CMC could probably make micelles of drug which could be difficult to diffuse out from the patch.[18]

Interpretation Of Release Mechanism

Model fitting of fluoxetine release profile from transdermal patches of best formulations (F4, FD3 and FT1) of every batch is presented in Table-2. The data of control group (F4), formulations containing DMSO (FD3) and tween-80 (FT1) revealed that the release pattern of formulations are best fitted for Higuchi kinetic equation as the predominates over zero-order and first-order release kinetics. This indicates drug release mechanism by diffusion, *i.e.* a slow and sustained release of drug from matrix, as proposed by Higuchi. On the basis of Korsmeyer-Peppas model, the value of release exponent (n) of formulations F4 and FT1 was higher than 1 (n>1), indicating super case II. It is well known that when the chain relaxation process is very slow compared with diffusion, the case II transport occurs, which again confirms that the drug release is controlled mainly by diffusion.[19]

In Vitro Permeation Studies

On the basis of *in vitro* dissolution studies, the best formulations F4, FD3 and FT1 was selected for *in vitro* permeation studies. The results of *in vitro* skin permeation studies of fluoxetine from transdermal patches were shown in Figure-5. It was observed that the permeation of fluoxetine across rat excised skin was significantly *(p<0.05)* enhanced by the addition of permeation enhancers than the control formulation (without enhancer) 217.19 ± 14.33 µg/cm^2 with flux of 10.06 ± 0.86.

Table 2- Model fitting of fluoxetine release profile

	Zero order		First order		Higuchi Model		Korsmeyer-Peppas Model
F. Code	r^2	K^0	r^2	K^1	r^2	K^H	**(n)**
F4	0.935	2.669	0.976	0.017	0.980	16.31	1.289
FD3	0.844	3.227	0.955	0.027	0.958	18.94	0.756

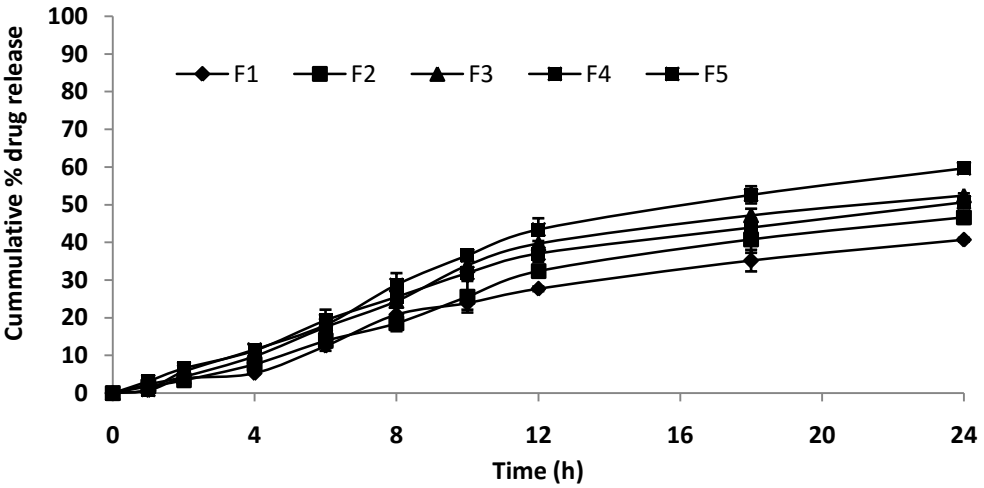

Fig. 2. *In vitro* dissolution profile of fluoxetine from transdermal patches containing EC/PVP in different proportion 4.5:0.5 (F1), 4:1 (F2), 2:1 (F3), 3:2 (F4) and 2:3 (F5)

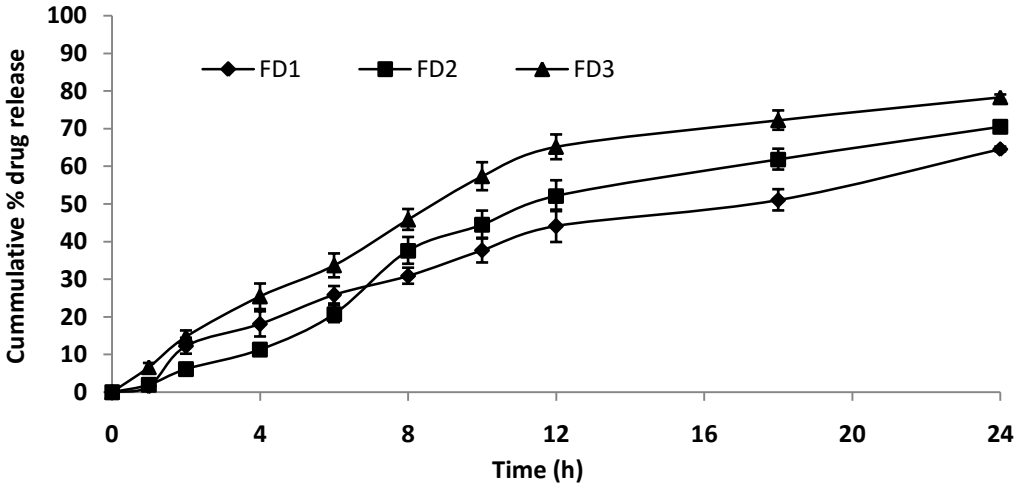

Fig.3. *In vitro* dissolution profile of fluoxetine from transdermal patches containing EC/PVP (3:2) and different proportion of DMSO 2% (FD1), 5% (FD2) and 10% (FD3)

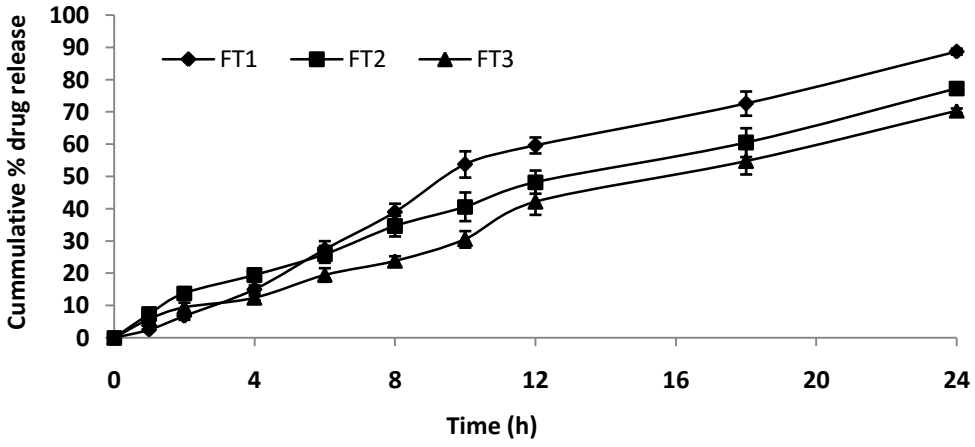

Fig.4. *In vitro* dissolution profile of fluoxetine from transdermal patches containing EC/PVP (3:2) and different proportion of tween-80 2% (FT1), 5% (FT2) and 10% (FT3)

The DMSO demonstrated a cumulative amount of drug permeated was 637.78 ± 31.63 µg/cm^2 with flux of 27.39 ± 1.76 µg/cm^2/h. There was an enhancement of 2.72 times. DMSO is an effective penetration enhancer that promotes penetration via reducing skin resistance to drug molecules or by inducing of drug partitioning from the dosage form.[20]

The transdermal patches containing tween-80 as permeation enhancer showed highest cumulative amount of drug permeated 1020.29 ± 40.88 µg/cm^2 with flux 43.91 ± 1.29 µg/cm^2/h and enhancement of 4.36 times. Tween-80 is a nonionic surfactant; it enhanced the rate of transport by two possible mechanisms. Firstly the surfactants may penetrate into the intercellular regions of stratum corneum, increase fluidity and eventually solubilise and extract lipid components. Secondly, penetration of the surfactant into the intercellular matrix followed by interaction and binding with keratin proteins filaments may result in a disruption within the corneocyte. Tween-80 may be enhancing the penetration of fluoxetine via both lipophilic and hydrophilic molecular mechanisms and to disrupt the lipid arrangements in the stratum corneum and to increase the proteins water content in the barrier.[21] On the basis of *in vitro* permeation studies, the formulation FT1 containing tween-80 (2%) facilitates the flux of fluoxetine to a greater extent than the formulation FD3 containing DMSO (10%).

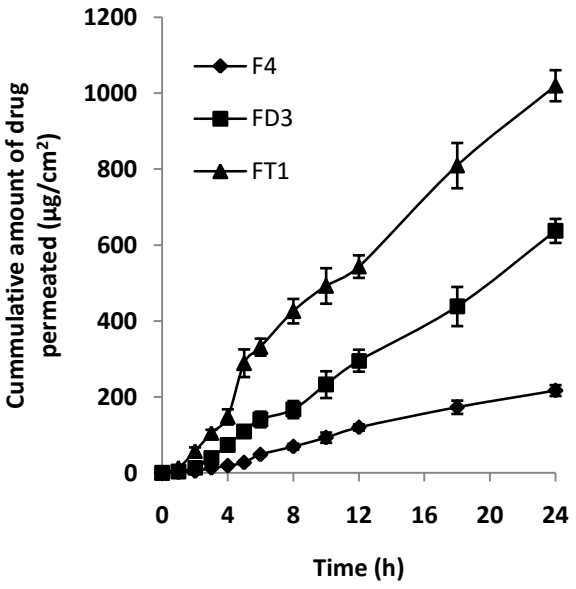

Fig.5. *In vitro* permeation studies of fluoxetine from transdermal patches of FD4 (without enhancer), FD3 (DMSO 10%) and FT1 (tween-80 2%)

Scanning Electron Microscope

The surface morphology of the transdermal patches before and after *in vitro* permeation study was scanned using a scanning electron microscope**.** The result shown in Figure-6, indicated that the drug is uniformly distributed in prepared transdermal patch and after permeation study; it was observed that the drug is released from the patch onto the skin which can be then permeated through skin into the systemic circulation.

Skin Irritation Studies

The *in vivo* skin irritation test of fluoxetine transdermal patch FT1 was performed on dorsal skin of Wistar rats in comparison with USP adhesive tape and standard irritant formalin (0.8%). The skin irritation score (erythema and edema) was less than 2, according to Draize et al compound producing score of less than 2 are considered negative. Hence the prepared transdermal patches of fluoxetine were free of skin irritation result given in Table 3.

Pharmacological Studies

The antidepressant efficacy of optimized transdermal patch of fluoxetine (FT1) was performed by forced swim (FST, Figure-7) and tail suspension test (TST, Figure-8). After 24 h studies, it was observed that significantly (*p>0.05*) reduction in immobility period in both fluoxetine patches treated group (156.40 and 145.60 sec) and oral treated group (147.80 and 132.80 sec) as compared to control group (190.80 and 176.60 sec) in FST and TST respectively.

Table: 3- Skin irritation test results

Formulation	Visual Observation	
	Erythema	Edema
Control	0.00 ± 0.0	0.00 ± 0.0
Adhesive Tape (USP)	1.16 ± 0.40*	1.00 ± 0.63*
Blank Patch	1.33 ± 0.51*	0.66 ± 0.51*
Formulation FT1	1.16 ± 0.75*	0.83 ± 0.40*
Formalin (0.8%)	3.16 ± 0.40	3.50 ± 0.54

*Visual observations are expressed as mean ± standard deviation, n = 6. FT1, Formulation containing tween-80 (2%). *Significant compared with formalin (p < 0.05)*

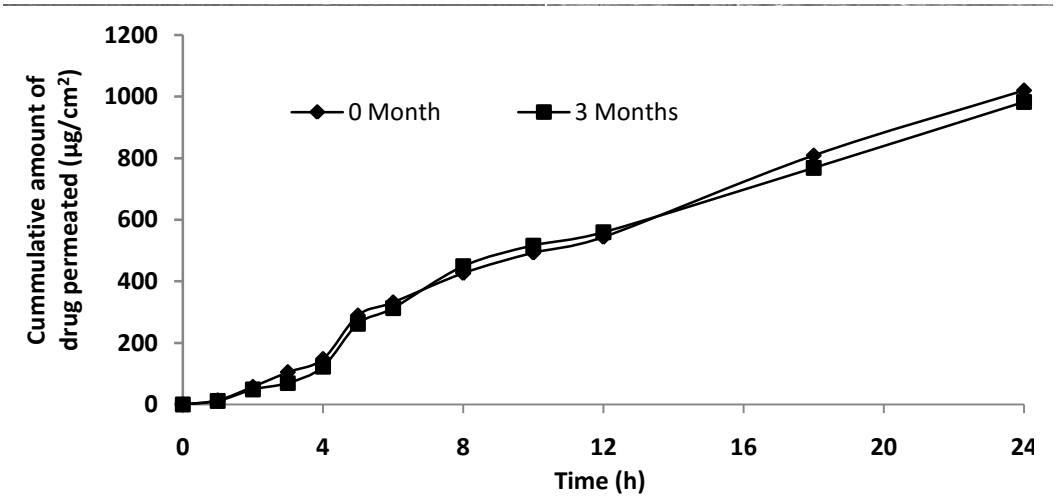

Fig.9. *In vitro* drug permeation study of fresh and 3 month old transdermal patches of optimized formulation (FT1)

Similar results were observed after 7 days studies with significant immobility reduction of transdermal patches treated group (95.60 and 61.80 sec) and orally treated group (73.80 and 77.60 sec) as compare to control group (197.40 and 166.80 sec) in FST and TST respectively. On the basis of results it was observed that, the fluoxetine transdermal patch could be a promising alternative route to oral administration.

Stability Studies

The stability study of optimized formulation (FT1) was conducted according to ICH guidelines the formulation was stored at 40 ^{0}C and 75 % relative humidity for 3 months. The result indicated that no change in physical appearance was observed after 90 days. The drug content of the patch was found 97.11, 96.91 and 96.84% after 30, 60 and 90 days respectively, indicated that no significant *(p>0.05)* change after 3 months. The results of *in vitro* permeation studies of fresh batch and 3 month old batch are shown in Figure-9, also confirm that no significant change in drug release after 3 months. So on the basis of results, the optimized fluoxetine transdermal patch (FT1) was found stable enough.

CONCLUSION

From the present work it can be concluded that fluoxetine can be administered via matrix-type transdermal drug delivery system, which provides controlled release and reduces the frequency of drug administration. Hence this non-invasive, compatible patch with ease of application and removal may improve patient compliance. Present work may require further studies involving pharmacodynamic and pharmacokinetic studies in animal and human models.

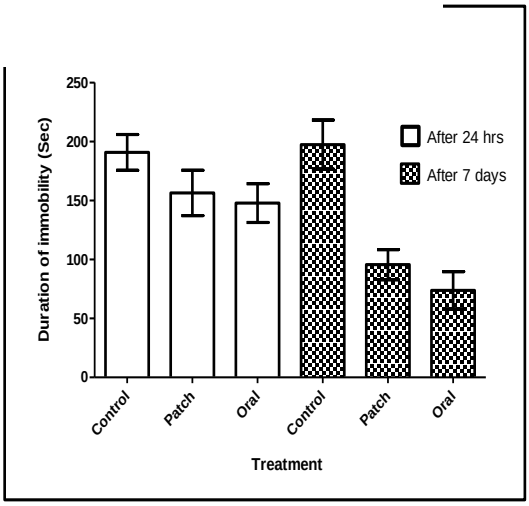

Fig.7. Effect of fluoxetine transdermal patch (FT1) and oral fluoxetine on immobility period in forced swim test

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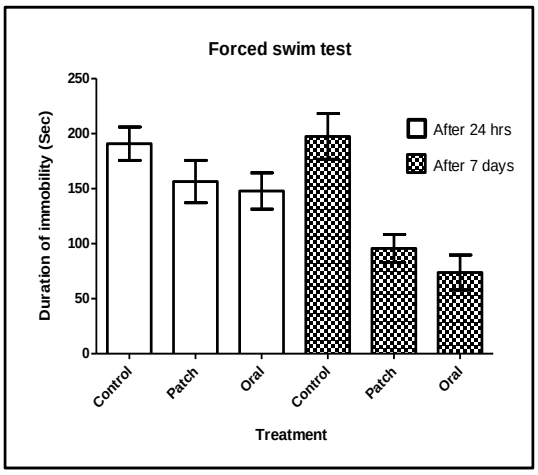

Fig.8. Effect of fluoxetine transdermal patch (FT1) and oral fluoxetine on immobility period in tail suspension test

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