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FORMULATION AND EVALUATION OF TRANSDERMAL FILMS OF ANTI-DEPRESSANT DRUG SERTRALINE USING EUDRAGIT E100, HPMC

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Abstract

Transdermal drug delivery system (TDDS) was designed to sustain the release and improve the bioavailability of drug and patient compliance. The matrix type transdermal film of Sertraline was prepared by solvent evaporation method using two different polymers Eudragit E 100 & hydroxy propyl methyl cellulose (HPMC) in different ratios. Dibutyl phthalate was used as a plasticizer. The films were evaluated for physical properties such as thickness, percentage moisture absorption, percentage moisture loss, drug content, folding endurance and flatness. The in-vitro release studies were performed using USP dissolution apparatus. The optimized film was further evaluated for skin permeation, stability and skin irritation studies. The data obtained shows that the transdermal film F5 (Eudragit E 100 & HPMC at ratio of 2:1) had produced a highest drug release of 98 ±1.02% up to 24 hrs. When the release study was conducted for F5 on an animal skin there was a drastic decrease (61.56 ± 0.14%) in the percentage of drug release. The kinetics of drug release followed higuchi model with diffusion controlled mechanism. Skin irritation studies showed no sign of edema and erythema. There was no interaction found between the drug and polymer as proved by FTIR studies. The prepared film of Sertraline is found to provide a controlled release and permeation which is suitable for transdermal delivery.

Key words: Transdermal Delivery, Sertraline, Hydroxy Propyl Methyl Cellulose, Eudragit E 100, In-vitro Evaluation, Skin Permeation.

1. Introduction

Transdermal drug delivery is the non-invasive delivery of medications from the surface of the skin. The transdermal film comprises a polymer to control the rate of delivery of the drug that can pass through the skin into the bloodstream over a period of several hours to days. A skin patch uses a special membrane to control the rate at which the drug contained within the patch can pass through the skin and into the bloodstream. In the modern era, depression is one of a major disease affecting human kind and is treated pharmacologically using antidepressant. One such agent is Sertraline is an antidepressant that belongs to a group of drugs called selective serotonin reuptake inhibitors (SSRIs). It is used to treat major depressive disorder, obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder (SAD), and post-traumatic stress disorder (PTSD). The drug upon oral administration produces adverse effects of nausea, dry mouth, diarrhea, constipation, insomnia, anxiety, restlessness, decreased sex drive, dizziness, weight gain, tremors, sweating, sleepiness or fatigue and headaches. These effects are mainly due to the dose and fluctuation in plasma drug concentration. The side effects could be reduced by controlled administration of drug using transdermal films so as to improve the treatment efficacy. The main objective of this work was to prepare transdermal films of Sertraline using two different polymers Eudragit

E 100 and hydroxy propyl methyl cellulose and to evaluate the film for physicochemical characteristics, in vitro drug release and skin permeation behavior. The chosen polymer combination has been used successfully for the transdermal administration of several therapeutic a gents.

2. Materials and Methods

A.Materials

Eudragit E 100 received as a gift sample from evonik industries (Mumbai, India). Hydroxy propyl methyl cellulose was procured from Loba Chemie pvt. Ltd. (Mumbai, India). Dibutyl phthalate, dichloro methane, anhydrous calcium chloride and hydrochloric acid were purchased from Loba Chemie pvt. Ltd, (Mumbai, India). Potassium chloride, potassium dihydrogen phosphate and sodium hydroxide were purchased from Qualigens Fine Chemicals (Mumbai, India).

B.Methods

1. Compatibility Study

The infrared spectra of drug and physical mixture of drug and polymer were studied by potassium bromide disc method using FTIR (Perkin Elmer Spectrum RXI) (Jamakandi VG et al. 2009) to identify any possible physical, chemical interaction.

2. Preparation of Transdermal Film

Sertraline films were prepared by solvent evaporation .Weighed quantity of eudragit E100 was added to 5 ml ethanol and dissolved completely using mechanical stirrer (Remi, Mumbai). To the above solution, drug (10mg), PVP, HPMC were added and mixed thoroughly followed by plasticizer (dibutyl phthalate) addition and mixed. The solution was poured on the thick aluminum foil (five cm2 area) and covered by a funnel for 24 hrs for the solvent to evaporate. Total 12 formulations were prepared and stored for evaluation.

Table 1
Composition of transdermal films containing Sertraline

S.no	Formulation	Drug polymer ratio		Drug (mg)	Film Formation
		Eudragit RL 100	HPMC		
1	F1	1	-	10mg	Film formed
2	F2	1	1	10mg	Film not formed
3	F3	1	2	10mg	Film not formed
4	F4	1	3	10mg	Film not formed
5	F5	2	1	10mg	Film formed
6	F6	3	1	10mg	Film formed
7	F7	1	4	10mg	Film not formed
8	F8	4	1	10mg	Film formed
9	F9	2	3	10mg	Film not formed
10	F10	3	2	10mg	Film formed
11	F11	1	5	10mg	Film not formed
12	F12	5	1	10mg	Film formed

4. Evaluation Parameters

4. 1. Thickness of the patch:

The thickness of the drug loaded patch is measured in different points by using a digital micrometer(Mitutoyo co;Japan) and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

4.2. Percentage moisture absorption:

The films were weighed accurately and placed in the desiccators containing 100 mL of saturated solution of potassium chloride, which maintains 79.50% RH. After 3 days, the films were taken out and weighed. The study was performed at room temperature. The percentage moisture absorption was calculated using the formula:

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

4.3. Percentage moisture loss:

The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula:

$$\% \text{ moisture loss} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

4.4. Moisture Content:

The prepared films were marked, then weighed individually and kept in a desiccators containing activated silica at room temperature for 24 h. The films were weighed again and again individually until it showed a constant weight. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight

$$\%\text{moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

4.5. Folding endurance:

This was determined by repeatedly folding the film at the same place until it broke. The maximum number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance

4.6. Flatness test:

Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness

$$\% \text{ constriction} = \frac{I_1 - I_2}{I_1} \times 100$$

I_2 = Final length of each strip

I_1 = Initial length of each strip

4.7. Weight uniformity:

The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

4.8. Drug content:

A film was cut into 4 quadrants and put in a 100 mL buffer (pH 6.8).This was then shaken in a mechanical shaker for 24 h to get a homogeneous solution and filtered. The drug content was determined spectroscopically at 240 nm after suitable dilution

4.9. Uniformity of dosage unit test:

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the

supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2m membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

4.10. *In vitro* drug release studies:

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

4.11. *In vitro* skin permeation studies:

An *in vitro* permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm^{-2}) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm^{-2}).

4.12. Skin Irritation test:

Skin irritation studies are performed on healthy rabbits. The dorsal surface of the rabbits are cleaned, and the hairs are removed by shaving. The skin is cleansed with rectified spirit. Treated skin areas are then evaluated according to a modified Draize scoring method and the irritation index is evaluated. The first or "Primary Irritation Index" (P.I.I.) is studied which is an average value reflecting irritation both immediately after dressing removal.

The rabbits are divided into two groups (n = 6). Group I receiving prepared transdermal patch and Group II receiving 0.8% v/v aqueous solution of formalin as a standard irritant. At 24 and 72 h after test article application, the test sites are examined for dermal reactions in accordance with the Draize scoring criteria.

3. Result and Discussion

A. Compatibility Study

The existence of principal peaks of the drug in the spectra of the mixture of drug and polymer (spectra not shown) showed no physical and chemical interaction between them at the concentration used in the film.

B. Evaluation of Transdermal Film

The percentage moisture absorption (%MA) and percentage moisture loss (% ML) was found to be increased with increasing in HPMC concentration, which might be attributed to the hydrophyllic nature of the HPMC. The thickness of the patches varied from 0.16 to 0.22mm. Folding endurance measures the ability of patch to withstand rupture. When the folding endurance high it was found to be high in patches containing higher amount of the Eudragit E 100. Flatness studies were performed to judge the same. The results of the flatness study showed that formulation strip lengths before and after their cuts indicating good uniformity of the polymers throughout the transdermal films. It indicates 100% flatness observed in the formulated patches.

Table 2
Physiochemical Properties of Sertraline Transdermal Patch

Formulation	%MA±SD[a]	%ML ±SD[a]	Thickness±SD (mm)[a]	Folding endurance[a] (No of folds)	Flatness	Weight (mg)
F1	1.62±0.02	1.12±0.03	0.16±0.01	40	100	430±0.57
F5	5.94±0.01	3.95±0.01	0.21±0.02	30	100	413±0.36
F6	4.36±0.04	2.77±0.02	0.22 ±0.01	40	100	411±0.44
F8	3.17±0.02	2.64±0.04	0.15±0.01	40	100	412±0.41
F10	6.54±0.05	4.88±0.02	0.17±0.02	30	100	416±0.36
F12	1.66±0.03	1.63±0.01	0.21±0.01	60	100	415±0.42

Values are expressed as mean ± SD(n=3)

C. Drug Content Determination

The drug content in patches was observed using UV spectrophotometer with phosphate buffer as a solvent system for Amitriptyline hydrochloride and the concentration was calculated using the standard graph.

Table 3
Drug content of Sertraline transdermal patch

S.NO	FORMULATION	DRUG CONTENT (mg)
1	F1	9.752±0.098
2	F2	9.624±0.142
3	F3	9.810±0.089
4	F4	9.010±0.132
5	F5	9.543±0.198
6	F6	9.685±0.088

Values are expressed as mean ± SD(n=3)

D. In vitro drug release

The results of the in vitro release are shown in figure 1. The film F5 has released a maximum of 98 ± 1.03% of Sertraline release up to 24 hrs. The cumulative percentage of drug released from film formulation F5 was significantly high when compared with other film formulations. The addition of hydroxy propyl methyl cellulose with the Eudragit E 100 resulted in more drug release than the Eudragit E 100 alone i.e. in case of film F1. It was revealed from the release results that an increase in concentration of Eudragit E100 in the film tends to decrease the Sertraline release, a burst release followed by a slow release was observed for all the formulations. This burst release might be due to the presence of water soluble polymer HPMC which gets dissolved rapidly when exposed to the dissolution medium. The water permeable polymer Eudragit E 100 may be responsible for the slow and constant release of drug in the later stages. This may be due to the polymeric network which restricts the diffusion of the drug molecules out of the film.

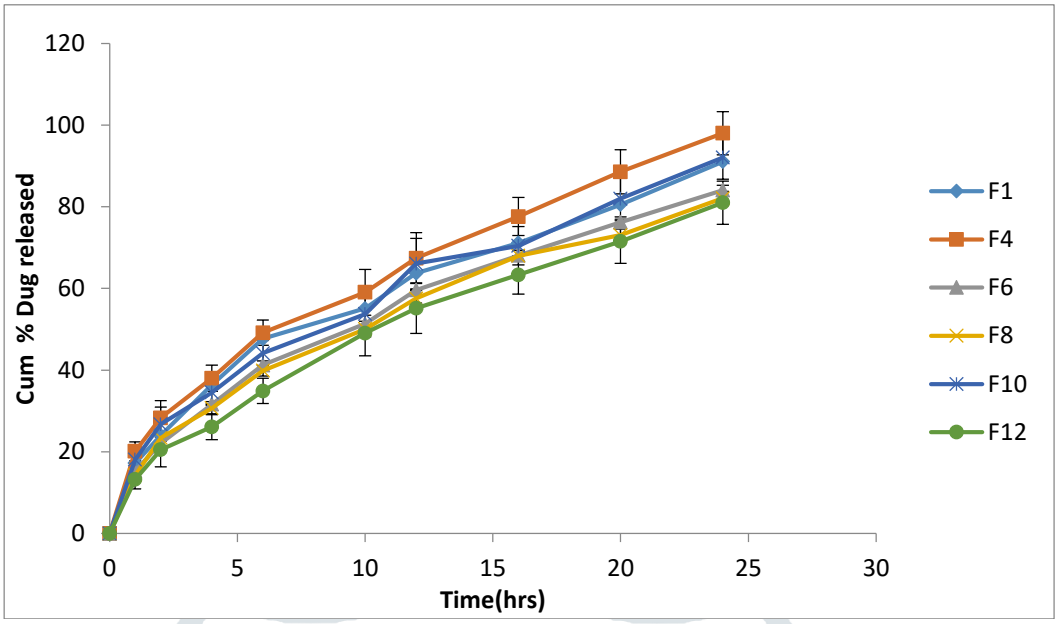

Figure 1
***In vitro* release of Sertraline from Transdermal patch**

E. In vitro Skin permeation

The film F5 was selected for the skin permeation study based on the higher drug release obtained in the in vitro release data. The skin permeation of Sertraline film F5 was 61.56 ± 0.14% over a period of 24 hrs. The drastic decrease in the amount of drug release was due to the barrier nature of skin for the transport of small molecules. A result of the skin permeation study is given in figure 2. A lag time of 30min was observed. The permeation was slow and sustained and the transdermal flux of 26µg/cm2 /hr was obtained for the film without the addition of any penetration enhancer.

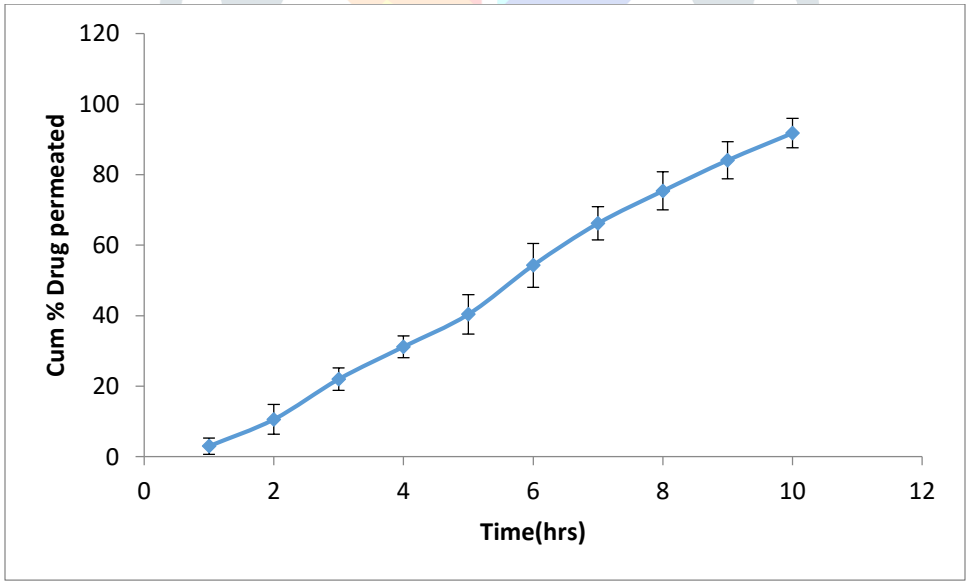

Figure 2
***In vitro* skin permeation of Sertraline drug solution**

F. Release Kinetics

The data obtained from the release kinetic study of film F5 is shown in table 4. The n value obtained from the korsmeyer peppas equation was 0.4938. The R2 values of the kinetic models are given in table 4. The release process can be represented by a fickian mechanism (0.45<n< 0.85). (Harris Shoaib M et al. 2006). It can be concluded that the drug release from the matrix films followed higuchi model and the mechanism of the drug release was diffusion mediated.

Table 4
The R2 Value for the Various Kinetic Models for the Transdermal Film F5

KINETIC MODEL	R 2 VALUE
Zero order	0.936
First Order	0.8847
Higuchi Model	0.998
Hixon-Crowell	0.9696
Korsmeyer-Peppas	0.9977

G .Skin Irritation Study:

Skin irritation studies carried out on rabbits revealed that the formulation F5 of Sertraline showed no erythema and edema. The photographs taken are shown in figure 3, 4, 5 & 6. Figure 3 show the rabbit skin treated with standard irritant. The score assigned to the skin reactions at various time points are given in table 5. There was no irritation produced by the film formulation as found from the primary dermal irritation index value of 0.25. The results showed that the prepared film is suitable for application on skin.

Table 5
Skin irritation test of Sertraline Transdermal patch for F5

Animal No	Sex	1hr	24hrs	48hrs	72hrs
1	Male	0/0	0/0	0/0	0/0
2	Male	0/0	1/0	0/0	0/0
3	Male	0/0	0/0	0/0	0/0

Erythema scale: 0-none, 1-slight, 2-well defined, 3-moderate and 4-scar formation Edema scale: 0-none, 1-slight, 2-well defined, 3-moderate and 4-severe

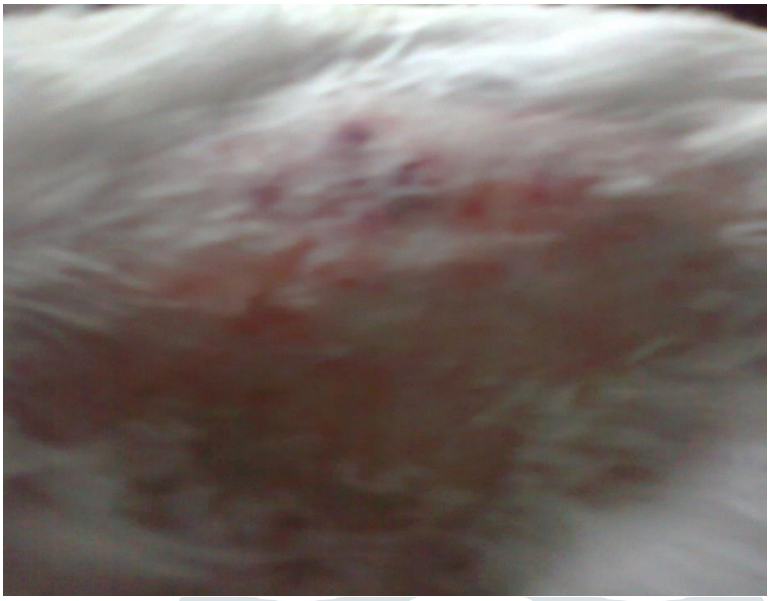

Figure 3
Rabbit treated with standard irritant

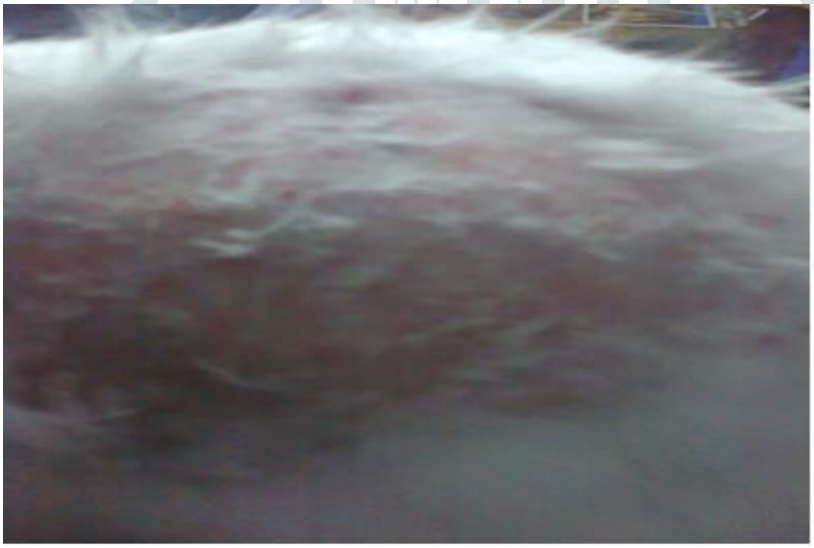

Figure 4
Rabbit skin after shaving the hair

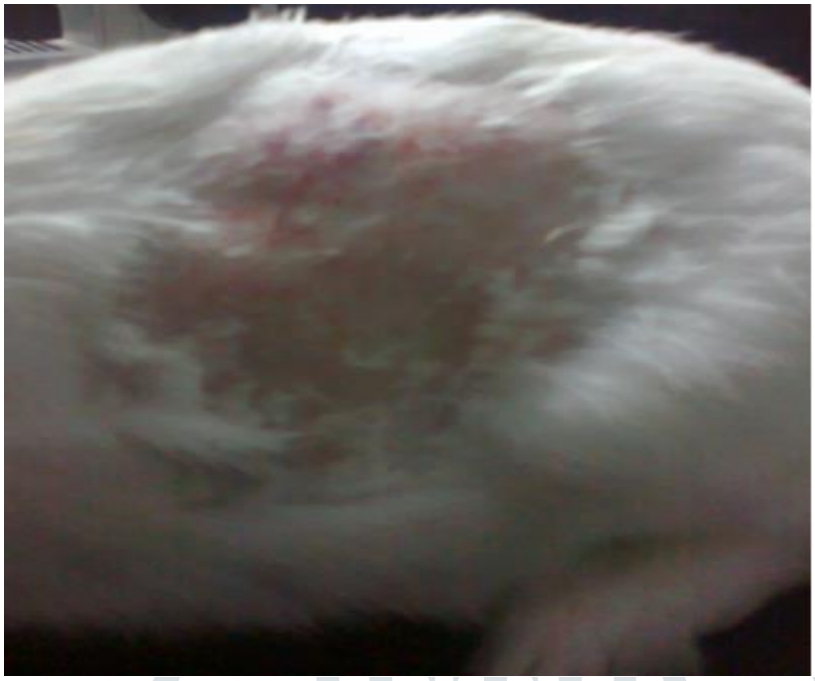

Figure 5
Rabbit skin after 24hrs the removal of transdermal patch

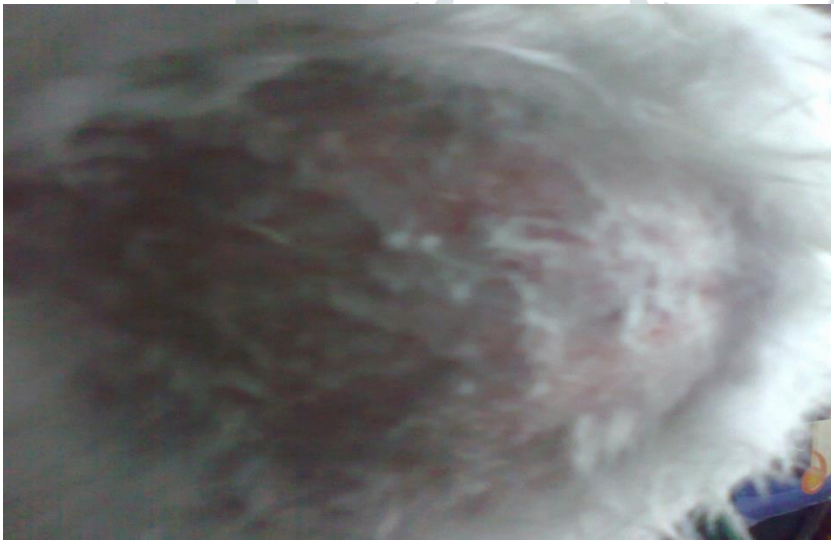

Figure 5
Rabbit skin after 72hrs the removal of transdermal patch

4. Conclusion

It can be concluded that the composition of the polymer influences the film formation and the addition of HPMC had influenced the drug release from the film. The film F4 (Eudragit E100 and HPMC at a ratio of 2:1) revealed a 98% of Sertraline release up to 24 hrs. Both the release and permeation were exhibited a controlled release of drug from the film. The drug release was found to follow higuchi model and the mechanism of the drug release was diffusion mediated. There was no interaction found between the drug and polymer as proved by FTIR studies. Skin irritation study on rabbits proved no erythema and edema formation. The prepared film of Sertraline is suitable for the transdermal route of delivery in the treatment of depression. However the in vivo studies need to be conducted in future to confirm the therapeutic efficacy of the developed film.

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