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Original Article

Design and development of hydroxypropyl methycellulose (HPMC) based polymeric films of sertraline hydrochloride: Physicochemical, *in vitro* and *in vivo* evaluation

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Abstract

Transdermal patches of sertraline hydrochloride were prepared using different ratios of hydroxypropylmethylcellulose (HPMC) K4M, K15M and K100M by solvent evaporation technique. The possible drug and polymer interaction was studied by Fourier transmission infrared spectroscopy. The effect of the polymers on the technological properties, i.e., drug release, water vapor transmission rate, and percentage moisture loss, percentage moisture absorption, folding endurance and thickness was investigated. *In vitro* release studies showed zero-order release of the drug from all the patches, and the mechanism of release was diffusion mediated. Moreover, the release of the drug was sustained and it extended over a period of 24 hr in all formulations. Further, release and permeation of the drug from the most satisfactory formulation (K15MD) was evaluated through biological barrier (albino mice).The effect of permeation enhancer's i.e. oleic acid, span 80 and limonene was also investigated. However, the formulations containing oleic acid depicted the higher flux, higher diffusion coefficient and permeability coefficient. The skin irritation test of the transdermal formulation showed a skin irritation score of 0. The antidepressant activity and sustaining action of the drug loaded matrix patches were evaluated by performing forced swim test and tail suspension test. The results indicated that sertraline hydrochloride elevated struggling behavior of the albino mice. However, the floating behavior was decreased .The immobility behavior is seen increased during tail suspension test, in case of transdermal patch as compared to oral administration. It can therefore be concluded that the patch containing HPMC K15M in the ratio 1:1.5 has achieved the objectives of transdermal drug delivery system, such as avoidance of first pass effect, extended release, and reduced frequency of administration.

Keywords: Transdermal; antidepressant; sertraline hydrochloride; permeation enhancers; forced swim test; tail suspension test.

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1. Introduction

The transdermal therapeutic system is a discrete dosage form which, when applied to the intact skin, delivers the drug through the skin at a controlled rate to the systemic circulation. The systemic treatment of the disease via transdermal route is not a recent innovation .But, in the last two decades; transdermal drug delivery has gained increasing interest. So, transdermal controlled drug delivery systems have been investigated or developed in order either to avoid hepatic first pass effect improving drugs bioavailability or to decrease the dosing frequency required for oral treatment. However, at present, marketed transdermal drug delivery patches are available only for a few drugs.

Sertraline hydrochloride is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Sertraline is primarily used to treat clinical depression in adult outpatients as well as obsessive-compulsive, panic and social anxiety disorders in both adults and children. Sertraline shares the common side effects and contraindications with other members of SSRI class; however, it does not cause weight gain. In 2006 it was the most prescribed antidepressant on the U.S. retail market with 28,060,000 prescriptions [1).

Sertraline is primarily a serotonin reuptake inhibitor (SRI). Therapeutic doses of sertraline (50-200 mg/day) taken by patients for four weeks resulted in 80-90% inhibition of serotonin transporter (SERT) in striatum as measured by positron emission tomography. Sertraline is also a dopamine reuptake inhibitor with 1% of its SRI potency and sigma-1 receptor agonist with 5% of its SRI potency [2). Sertraline weakly blocks α1-adrenoreceptors with 1-10% of its SRI potency [3,4].

Sertraline is absorbed slowly after oral administration with peak plasma concentrations being reached within 4.5 to 8.4 h. Steady state levels are achieved after one week of daily dosing. 98.5% of sertraline in the blood is bound to the plasma proteins. Its half-life in the body is 13-45 hours and is about 1.5 times longer in women (32 hours) than in men (22 hours), resulting in the proportionally 1.5 higher exposure of women and its bioavailability is 44% [5]. In order to improve the bioavailabilty of sertraline hydrochloride and reduce its frequency of administration, it was proposed to make transdermal patches of the drug. It is suitable for transdermal administration owing to its low molecular weight (342.7) and low melting point (160-240 °C).

The aim of the present study was to develop different transdermal matrix patches with varied ratios of hydroxy propyl methyl cellulose (HPMC) and, containing the drug sertraline hydrochloride and to perform the physicochemical, *in vitro*, and *in vivo* evaluation of the prepared patches. The purpose was to provide the delivery of the drug at a controlled rate across intact skin to achieve a therapeutically effective drug level for a longer period of time from transdermal patches. An attempt was made to establish the best possible combination of polymeric ratio of formulated transdermal patches with maximum controlled and sustained drug release capability as well as physical stability.

2. Experimental section

2.1 Materials

HPMC (K4M, K15M, K100M) were gifts from Colorcon Ltd, UK. A gift sample of sertraline hydrochloride was received from Unichem Laboratories, Baddi, India. Glycerin, dichloromethane, chloroform and ethanol were purchased from Central Drug House (P) Ltd., Mumbai, India. All the chemicals purchased or received were of high purity.

2.2 Development of the Patch

Matrix-type transdermal patches containing sertraline hydrochloride were prepared using different ratios (Table 1) of HPMC by solvent evaporation technique in cylindrical both sides open glass moulds. As depicted in Table 1, casting solutions were prepared by dissolving appropriate polymers, plasticizer in suitable vehicle using magnetic stirrer. The drug was added slowly to the solution and dissolved by continuous stirring for 30 minutes. For the formulation of films, mercury was used as the backing membrane. Mercury was spread uniformly on glass petridish. The mould was kept on a table with smooth horizontal surface. About 5 ml of the solution was poured on the mercury (10.74 cm^2). The rate of evaporation was controlled by inverting the funnel over the mould. After 2 hours, the dried patches were cut into 2.5 cm diameter, wrapped in aluminium foil and stored over fused calcium chloride in a desiccator at room temperature for further use.

2.3 Solubility Studies

The solubility studies were performed in phosphate buffer solution, pH 7.4 by adding excess amount of drug in each case and keeping the excess drug containing phosphate buffer flasks on a water bath shaker NSW-133 (REMI Equipment, Mumbai, India) for 24 h at 32 °C. After 24 h, solutions were analyzed spectrophotometrically at 273 nm, and drug concentrations were calculated.

2.4 Determination of Partition Coefficient of the Drug

The partition coefficient of sertraline hydrochloride was determined in n-octanol: phosphate buffer pH 7.4 system. 10 mg of the drug was accurately weighed and added to 10ml of n-octanol: phosphate buffer pH 7.4 (1:1), in a separating funnel. The mixture was shaken until equilibrium was attained. Phases were separated in a separating funnel and aqueous phase was filtered through 0.2 µ filter, suitably diluted and amount of sertraline hydrochloride solubilized in aqueous phase was determined by measuring the absorbance at 273 nm using UV spectrophotometer.

The partition coefficient of sertraline hydrochloride was calculated from the ratio between the concentration of sertraline hydrochloride in organic and aqueous phase using following equation.

$$P_{o/w} = (C_{oil}/C_{phosphate\ buffer})\ \text{equilibrium}$$

2.5 Drug–Excipient Interaction Study

For formulating transdermal patch, it is imperative to give consideration to the compatibility of drug and polymer used within the system. It was therefore necessary to confirm that drug is not interacting with the polymer under experimental conditions and shelf life.

The drug-excipient interaction studies were confirmed by FTIR spectra. The infrared absorption spectra of physical mixture of polymer and drug were run for drug excipients compatibility studies between 400 cm^{-1}- 4000 cm^{-1}. The FTIR spectrum of pure drug is shown in figure 1 respectively.

2.6 Physicochemical evaluation of polymeric films

2.6.1 Weight variation

Uniformity of weight was determined by weighing three matrices of each formulation. After each film unit was weighed individually on a digital balance, the average weight of film was taken as the weight of the film. [6]

2.6.2 Percentage Moisture Absorption

The films were weighed accurately and placed in the desicccator containing 100 ml of saturated solution of aluminum chloride, which maintains 79.50% RH. After 3 days, the

films were taken out and weighed. [6] The percentage moisture absorption was calculated using the formula

Percentage moisture absorption:

$$\frac{\text{Finalweight-Initial weight}}{\text{Initial weight}} \times 100$$

2.6.3 Percentage Moisture Loss

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

Percentage moisture loss:

$$\frac{\text{Final weight-Initial weight}}{\text{Initial weight}} \times 100$$

2.6.4 Water Vapor Transmission Rate

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1 g anhydrous calcium chloride was placed in the cells and the respective polymer film was fixed over the brim. The cells were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 6, 12, 24, 36, 48, and, 72 h of storage. The amount of water vapor transmitted was found using the formula.

Water vapor transmission rate:

$$\frac{\text{Final weight-Initial weight}}{\text{Time} \times \text{Area}} \times 100$$

2.6.5 Thickness

The thickness of the patch was measured at five different points using a screw guage and average thickness was recorded.

2.6.6 Folding Endurance

The folding endurance is expressed as the number of folds or number of times the film is folded at the same place either to break the film or to develop visible cracks. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness.

Folding endurance of the film was determined repeatedly by folding a small strip (2 cm × 2 cm) at the same place till it breaks. The number of times the film can be folded at the same place without breaking gives the value of folding endurance.

2.6.7 Flatness

Longitudinal strips were cut out from each film, one from the center and two from either side. The length of each strip was measured and the variation in the length because of non uniformity in flatness was measured by determining percent constriction, considering 0% constriction is equivalent to 100% flatness

$$\% \text{ Constriction} = \frac{l_1 - l_2}{l_2} \times 100$$

Where l_1= initial length of each strip.

l_2= final length of each strip.

2.6.8 Content Uniformity

The uniformity of drug content of the transdermal patches was determined, based on the dry weight of drug and polymers used by means of a UV spectrophotometric method. The formulations were dissolved in 10 ml methanol and stirred for 30 minutes. The resulting solutions were quantitatively transferred to volumetric flasks, and appropriate dilutions were made with pH 7.4 Phosphate buffer. The resulting solutions were filtered and analyzed for Sertraline hydrochloride content at 273 nm in UV spectrophotometer. The average reading of three patches was taken as the content of drug in one patch.

2.6.9 *In Vitro* Permeation Studies

The permeation studies were performed in a modified Keshary-Chien cell (cell capacity 25 ml, cross-sectional area 2.906 cm^2).The permeation studies were performed using mice skin. Animal was sacrificed using chloroform anesthesia. Freshly excised mice abdominal skin was used for the studies. After excision, the skin was thoroughly washed to remove the adhering tissue and fat, trimmed to the required size, and used as permeation barrier. The holder containing the skin and formulation was then placed on the receiver compartment of the modified diffusion cell, containing phosphate buffer pH 7.4. The donor and receiver compartment were kept in an intimate contact by wrapping parafilm at the junction. The temperature of the diffusion cell was maintained at 32 °C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and solution in the receiver compartment was constantly and continuously stirred during the whole experiment using magnetic bead.

The samples were withdrawn (1 ml each time) at different time intervals and an equal amount of phosphate buffer, pH 7.4, was replaced each time. Absorbance's of the samples were read spectrophotometrically at 273 nm taking phosphate buffer solution, pH 7.4, as blank. The amount of drug permeated per square centimeter at each time interval was calculated and plotted against time. Release-rate constants for different formulations were also determined.

2.7 Selection of formulations for further studies

Based on the physiochemical characterization, the formulations containing HPMC K15M showed the best results. Therefore further investigations were carried out with HPMC K15M to study the effect of penetration enhancers.

Modification of formulations was effected by casting the films using permeation enhancer viz., oleic acid, span 80 and limonene. They were designated K15MA, K15MB, K15MC, K15MD, K15ME, K15MF, K15MG, K15MH, K15MI.

2.8 Scanning Electron Microscopy

The external morphology the transdermal patches before the application were analyzed using scanning electron microscopy.

2.9 *In vitro* Studies

Depression is characterized by lack of "motivation" rather than a lack of "physical space" to move around [9]. The present study was performed to investigate the selective involvement of 5HT receptor in the mechanism of action of sertraline hydrochloride, a SSRI used as antidepressant and anti-OCD drug [10,11]. The evaluation of antidepressant action of sertraline hydrochloride was based on modified forced swim test [12,13] and tail suspension test [14].

Animal study:

Swiss albino mice of either sex weighing between 20-35 gm were used for the present study. The mice were given free access to water and food, which were supplied by Sanjay Biological Museum, Amritsar. They were housed in groups of eight in individual polypropylene cages with husk as bedding. They were maintained on standard temperature (25 ± 10^oC) and were fed with standard pellet diet and water ad labium. Animals were kept for quarantine in 2 weeks, before being used for experimentation. The backsides of the mice were shaved before starting the experiments. The study fully conformed to the guidelines outlined in CPCSEA and was approved by Institutional Animal Ethical Committee.

2.9.1 Modified Forced Swim Test

Mice were placed individually in plexi glass cylinders (height 40 cm, diameter 18 cm), containing 20 cm of water at 25°C. After 15 min they were removed and dried before returning to their home cage. [12] The water was changed between each animal. The animals were replaced in the cylinders 24 h later, and the procedure was repeated but on this occasion, the duration(s) for which mice remained immobile during, a 5 min observation period was

recorded. Immobility was defined as the absence of active escape oriented behaviors such as swimming, diving, rearing and sniffing. The antidepressant patch was affixed on the shaved dorsal surface 15 min after removal of mice from the water. The number of mice in each group was six.

2.9.2 Tail Suspension Test

The "Tail Suspension Test" is a facile means of evaluating potential antidepressants. [14] The immobility displayed by rodents when subjected to an unavoidable and inescapable stress has been hypothesized to reflect behavioral despair which in turn may reflect depressive disorders in humans.

In this test the mice were suspended on the edge of a shelf 58 cm above a table top by adhesive tape placed approximately 1 cm from the tip of the tail. The duration of immobility was recorded for a period of 5 min. Mice is considered immobile when they hang passively and completely motionless for at least 1 min.

2.9.3 Statistics

Immobility scores in the FST and TST were analyzed by one-way analysis of variance (ANOVA).

2.10 Skin Irritation Studies

Skin irritation studies were carried out on six healthy mice weighing 25-35 gms. The dorsal surface of the mice was cleared and the hair was removed by shaving. The skin was cleared with rectified spirit. The patches (K15MD) were placed over the skin with the help of adhesive tape. They were removed after 24 hr and the skin was examined for any untoward reaction. No signs of erythema, edema, or ulceration were observed.

2.11 Stability Studies

Accelerated stability testing was conducted for 60 days at different temperatures: 4, 45, and 60 °C. At specific intervals, patches were analyzed for their drug content, appearance, and texture (15,16]

3 Results and Discussion

Sertraline hydrochloride is a well-established antidepressant drug, which undergoes substantial hepatic first-pass metabolism, and thus only about 44% of the administered drug reaches the circulation. Therefore, there is a need to search for an alternative route of administration, which may bypass the hepatic first pass metabolism. The transdermal patch delivery system may be an attractive choice of an alternative route of administration of this drug because the drug also possesses characteristics such as low molecular weight and a smaller dose range (25–50 mg). Moreover, the logarithmic value of the partition coefficient of the drug in octanol-phosphate buffer, pH 7.4 showed the value of 5.19. The result obtained in the present study demonstrated that the drug possesses sufficient lipophilicity, which fulfills the requirement of formulating it into a transdermal patch. Drug-excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR technique was used to study the physical and chemical interactions between drug and excipients employed in the present study and the results obtained from the FTIR study indicates no chemical interaction between drug (sertraline hydrochloride) and the polymers used. No significant shifts in the peak corresponding to the drug or the polymer were observed. Hence, the drug and the polymers can be successfully incorporated in the formulation of transdermal patch.

The transdermal matrix type patches containing sertraline hydrochloride of variable ratios of HPMC were prepared. It was desired to design a polymer matrix that allows one to control the release of sertraline hydrochloride via the most appropriate choice of polymeric ratios among the formulations studied, using the different diffusion pathways of the individual

polymeric composition to produce the desired overall prolonged/sustained drug release.

The prepared transdermal patches were evaluated for various physicochemical parameters. The physicochemical properties of the patches are recorded in Table 2. The thickness of the patches varied from 0.40 to 0.61 mm. Low standard deviation values in the film thickness measurements ensure uniformity of the patches prepared by solvent casting technique. The drug content analysis of the prepared formulations has shown that the process employed to prepare films in this study was capable of giving films with uniform drug content and minimum batch variability.

The percent moisture absorption and percent moisture loss studies indicated that the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture absorption and moisture loss of the patches. The moisture loss of the prepared formulations was low, which could help the formulations to remain stable and from being a completely dried and brittle film during long term storage. The prepared formulations also demonstrated low moisture absorption, which may protect the formulations from microbial contamination and bulkiness of the patches.

The smooth surface of the formulated patches which should not constrict with time indicates the formulation of an ideal patch. This contention is further supported by the fact that, in the present study, flatness studies were performed to assess the smooth surface of the patches formed. The results obtained in the flatness study showed that none of the formulations had the differences in the strip lengths before and after their cuts. It indicates 100% flatness in the formulated patches. Thus, no amount of constriction was observed in the film of any formulation which further indicates smooth flat surface of the patches.

An *in vitro* skin permeation study is predictive of *in vivo* performance of a drug. *In vitro* skin permeation experiments are known for their value for studying the rate and mechanism of percutaneous absorption of drugs. The formulated transdermal patches were subjected to *in vitro* study across semipermable membrane using modified Keshary Chien permeation cell having a volume of 20 ml and effective surface area of 2.9 cm^2.The results of *in vitro* drug permeation from formulations HPMC K15M are depicted in Figure 2.

The in vitro diffusion studies (Table 3) showed that all the formulations have zero-order release and mechanism of release was diffusion mediated [7]. Regression analysis of the in vitro permeation curves was carried out. The slope of the straight line obtained after plotting the mean cumulative amount released per patch vs. time was taken as the experimental flux for sertraline. The flux obtained for all the formulations was in the range of 11–16 mg/hr, but formulation K4MD showed not only the maximum flux, i.e., 16.716 mg/hr, but it also exhibited sustained release up to 24 hr. Although the other formulations also exhibited release for 24 hr, the flux obtained was lesser than that of K4MD (Table 4). The diffusion coefficient was calculated according to the modified Higuchi's equation [8]. The results of in vitro diffusion studies indicated the effect of polymers, their combinations, and concentrations on the technological properties Facilitated transfer of drug across a lipoidal membrane by oleic acid increases the permeation of drug by increasing partition to lipid phase. Oleic acid acts upon the lipids of stratum and therefore easily partition into the stratum corneum. Furthermore, it also increases the permeation of drug by formation of polar channels by solvents such as ethanol and exists as pools within the lipid domains. On the other hand, span 80, partitions into the intercellular lipid phases of the stratum corneum. This results in the increased fluidity in the region, which presumably reduces diffusional resistance. The decrease in drug permeation from formulations containing limonene as penetration enhancer as compared to other enhancers is attributed to the presence of naturally occurring hydrocarbon constituents. These hydrocarbons increase the

drug permeation by affecting the highly ordered structure of stratum corneum lipids. Span 80 and limonene, both penetration enhancers also have suitable molecular orientation for alignment with the lipid bilayer. However, the formulations containing oleic acid depicted the higher flux, higher diffusion coefficient and permeability coefficient when compared to formulations containing span 80 and limonene.

Therefore, in the present study, when the physicochemical observations and release rate kinetics were observed, the formulation K15MD gave the best results.

The surface morphology of the transdermal patches of K4MA and K4MD was predicted by using a scanning electron microscope (Fig 3), which shows uniform distribution of drug in the polymer matrix for formulation K15MD.

The antidepressant activity and sustaining action of the drug loaded matrix patches were evaluated by performing forced swim test and tail suspension test. The objective of these experiments was to determine whether the administration of sertraline hydrochloride via the transdermal route, which bypasses hepatic metabolism, was effective as an antidepressant as assessed by the forced swim test and tail suspension test. This contention is further supported by the fact that, in the present study, the results demonstrate that (a) Sertraline hydrochloride is effective as an antidepressant in the forced swim test and tail suspension test after both oral (B) and transdermal delivery (C); (b) the transdermal delivery of Sertraline hydrochloride is 10–20 times more potent (on a mg/kg basis) than oral sertraline hydrochloride in producing its antidepressant effect.

The effects of oral and transdermal sertraline hydrochloride administration on struggling and floating behavior in the forced swim test are presented in Fig 4 and 5. Regarding vehicle treated animals (A), these animals showed the usual pattern of activity shown by albino mice-considerable time spent floating (i.e., approximately 700 of the 900 s of the test were spent floating) and very little struggling behavior. The results indicated that sertraline hydrochloride elevated struggling behavior of the albino mice. However, the floating behavior was decreased. The oral administration of 30 mg/kg/day significantly (p<0.05) decreased immobility. In contrast, the administration of sertraline hydrochloride through the transdermal patch K15MD significantly increased the swimming behavior. The immobility behavior is seen increased during tail suspension test, in case of transdermal patch as compared to oral administration. This clearly indicates that the transdermal patches release the drug gradually over a period of time, which results in prolonged control of depression.

Table 1: Transdermal films: polymers and composition

S. No.	Formulation	Code	Composition (drug: polymer)	Plasticizer Glycerin (% w/w)*	Casting solvent (2:2:1)
1	HPMCK4M	A	1:1	150	Chloroform: Dichloromethane: Ethanol
2	HPMCK4M	B	1:1.5	150	Chloroform: Dichloromethane: Ethanol
3	HPMCK15M	C	1:1	150	Chloroform: Dichloromethane: Ethanol
4	HPMCK15M	D	1:1.5	150	Chloroform: Dichloromethane: Ethanol
5	HPMCK15M	E	1:2	150	Chloroform: Dichloromethane: Ethanol
6	HPMCK100M	F	1:1	150	Chloroform: Dichloromethane: Ethanol

- %w/w of the polymer.

Table 2: Physicochemical Properties of transdermal films

S.No	F.C.	Weight Variation* (mg) ±SD	%MA*±SD	%ML*±SD	WVTR* ($g/cm^2/hr$) ±SD	Thickness (mm)** ±SD	Drug Content* (mg) ±SD	Folding Endurance (No. of folds)
1	K15MA	87±0.001	5.55±1.9662	4.87±0.6326	2.81×10^{-3}±0.0005	0.61±0.05	21.57±0.037	1326
2	K15MB	85±0.001	5.75±0.7518	4.85±0.1603	2.84×10^{-3}±0.0003	0.6±0.02	21.38±0.058	1334
3	K15MC	87±0.0005	5.68±1.521	4.80±1.4206	2.81×10^{-3}±0.0001	0.61±0.052	21.22±0.073	1330
4	K15MD	125±0.004	11.75±1.354	6.98±0.9832	3.74×10^{-3}±0.0002	0.40±0.026	21.62±0.42	1505
5	K15ME	123±0.0005	11.64±0.7239	4.77±0.4156	3.33×10^{-3}±0.0004	0.40±0.02	20.69±1.06	1514
6	K15MF	124±0.001	11.78±2.257	4.75±1.2336	3.76×10^{-3}±0.0003	0.40±0.03	21.34±0.03	1506
7	K15MG	139±0.002	6.62±1.5601	7.98±0.7247	5.94×10^{-3}±0.0002	0.54±0.04	20.87±0.37	1725
8	K15MH	136±0.002	6.69±1.5468	8.06±0.0072	5.75×10^{-3}±0.0004	0.54±0.061	21.28±0.014	1714
9	K15MI	138±0.004	7.41±1.9651	7.96±1.3108	5.78×10^{-3}±0.0002	0.52±0.05	21.61±0.065	1422

* Indicates values are average of three observations.

** Indicates values are average of five observations. (Mean± SD)

Table 3: Kinetics of *In Vitro* Sertraline Hydrochloride Permeation from Transdermal Patches K4MA-K100MC

F.C.	Zero Order		Higuchi Equation		First Order		Korsmeyer-Peppas	
	k_0(mg h^{-1})	R^2	k	R^2	$k_1(h^{-1})$	R^2	n	R^2
K15MA	3.178	0.9842	14.755	0.7974	-0.0587	0.9246	1.049	0.9807
K15MB	3.059	0.9967	14.789	0.8759	-0.0552	0.964	0.8468	0.9684
K15MC	2.680	0.9873	12.588	0.8188	-0.042	0.9525	1.033	0.9865
K15MD	3.551	0.9965	17.419	0.9015	-0.083	0.9377	0.8631	0.9965
K15ME	2.936	0.9878	13.694	0.8079	-0.050	0.9343	0.9562	0.9713
K15MF	2.461	0.9942	11.62	0.8333	-0.036	0.9628	1.068	0.9958
K15ME	3.176	0.9947	15.051	0.8397	-0.059	0.94	0.9836	0.9886
K15MG	2.897	0.9888	13.744	0.8367	-0.051	0.9372	0.9562	0.9595
K15MH	2.445	0.9978	11.753	0.8671	-0.0518	0.9831	0.7709	0.9713
K15MI	2.129	0.9969	10.336	0.8824	-0.029	0.9925	1.0609	0.9958

Table 4: Release Kinetics of Sertraline Hydrochloride Diffusion from Transdermal Patches K4MA-K4100MC

F.C	Kinetics of Drug Release	Drug Transport Mechanism	Diffusion Coefficient (cm2/h) ± SD	Flux (mg/cm2/hr) ± SD	Permeability Rate(cm/h) ± SD
K15MA	Zero order	Super Case II	0.16803±0.0003	15.877±0.023	9.68497±0.172
K15MB	Zero order	Anomalous	0.15732±0.0001	15.636±0.255	9.3816±0.041
K15MC	Zero order	Super Case II	0.13979±0.0001	12.852±0.347	7.83972±0.005
K15MD	Zero order	Anomalous	0.10768±0.00069	16.716±0.036	6.6864±0.106
K15ME	Zero order	Anomalous	0.09615±0.0002	13.900±0.107	5.5600±0.244
K15MF	Zero order	Super Case II	0.08581±0.0001	12.090±0.122	4.836±0.0632
K15ME	Zero order	Anomalous	0.14280±0.0003	15.744±0.59	8.50176±0.001
K15MG	Zero order	Anomalous	0.13081±0.0001	14.253±0.11	7.69662±0.106
K15MH	Zero order	Anomalous	0.10412±0.005	11.326±0.366	5.88952±0.011

Table 5: stability profile of formulation k15md at different temperatures

Time in days	Refrigerated (4°C/75%RH)		Real Time (30°C/75%RH)		Accelerated (40°C/75%RH)	
	R.D.C*	P.A.	R.D.C	P.A.	R.D.C	P.A.
0	21.87±0.0.307	+	21.87±0.307	+	21.87±0.307	+
7	21.80±0.128	+	21.77±0.211	+	21.51±0.197	+
14	21.68±0.076	+	21.60±0.76	+	21.42±0.096	+
21	21.59±0.106	+	21.52±0.069	+	21.31±0.122	+
28	21.51±0.189	+	21.47±0.102	+	20.80±0.115	+
35	21.32±0.080	+	21.33±0.067	+	20.67±0.053	+
42	21.21±0.067	+	21.20±0.056	+	20.52±0.06	+
49	20.85±0.043	+	20.70±0.112	+	20.41±0.103	+
60	20.73±0.107	+	20.66±0.118	+	20.09±0.04	+

Abbreviations: R.D.C.: Remaining Drug Content.

P.A.: Physical Appearance; +: Good; -: Hard; #: Rigid, Brittle

*: ± S.D. of three determinations.

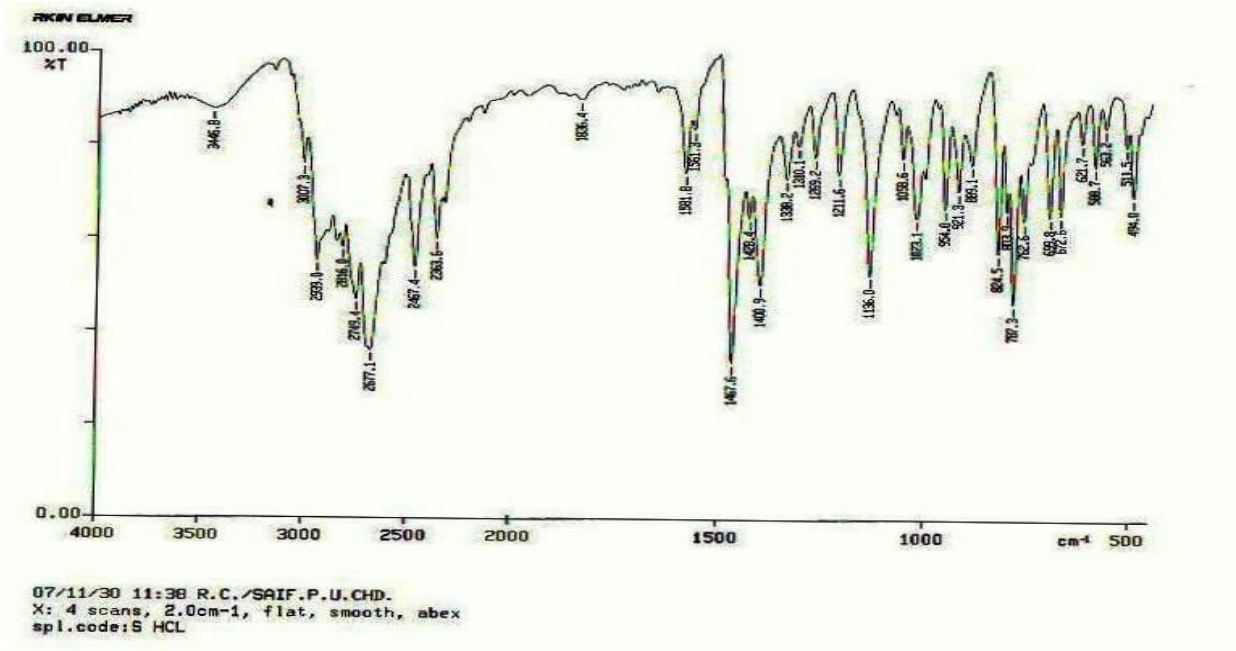

Figure 1: FTIR Spectra of Sertraline Hydrochloride Test Sample

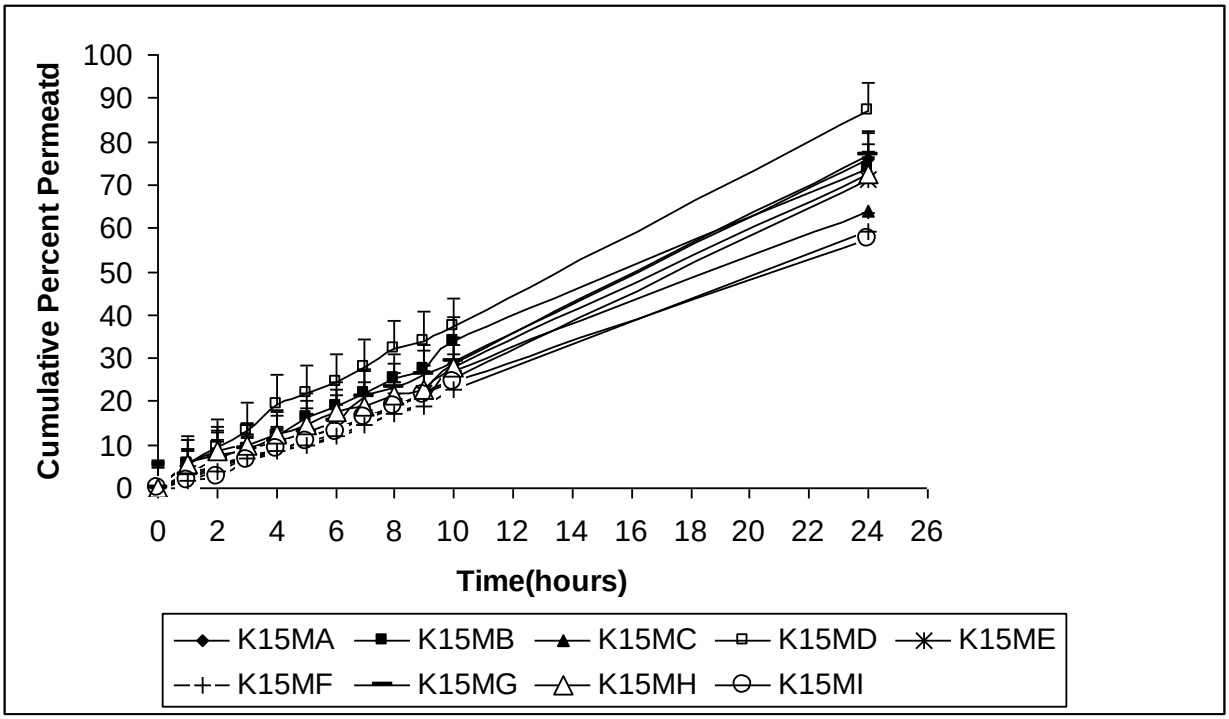

Figure 1: Plot of Cumulative Percent Permeated Versus Time for Various Formulations

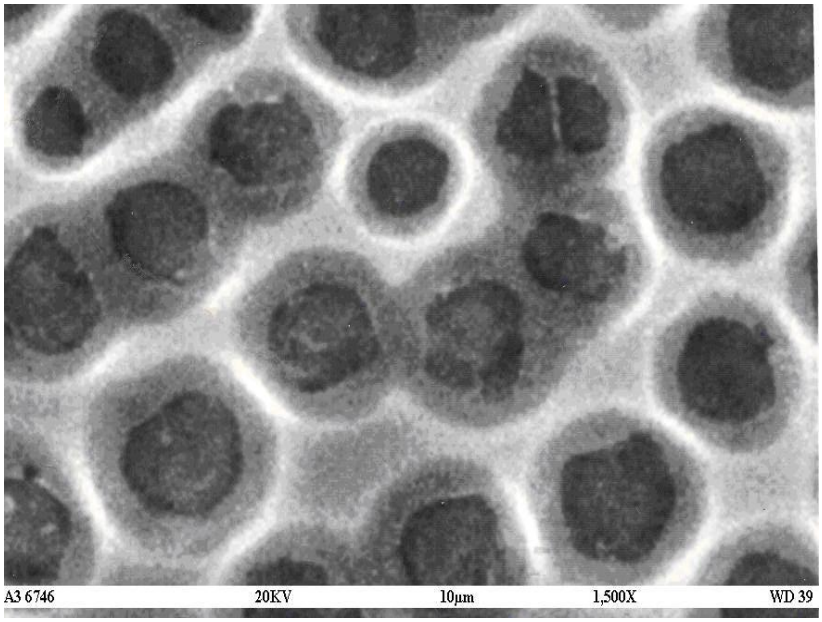

Figure 2: SEM Photograph of Transdermal Patch of HPMC K15MD Showing Homogenous Dispersion of Drug in the Patch

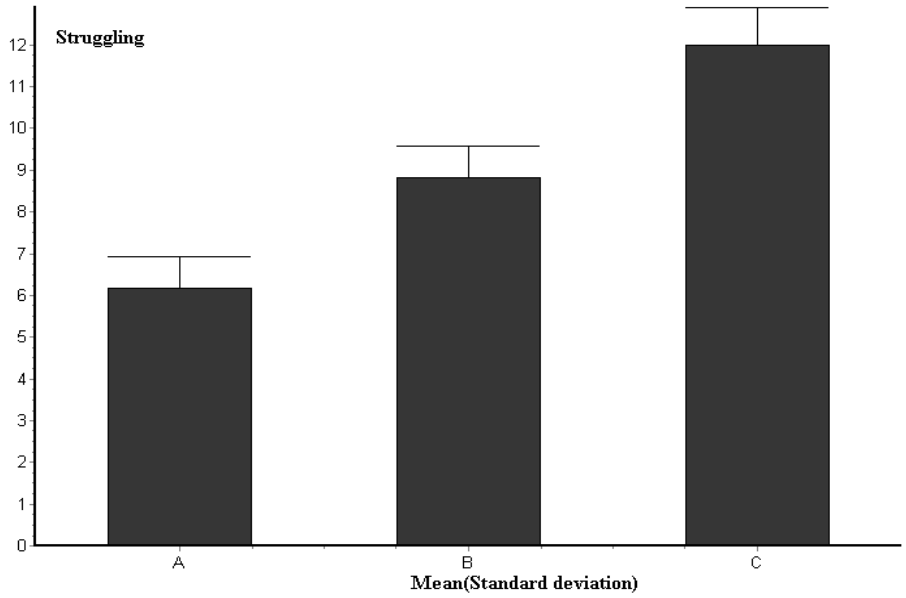

Figure 4: Mean (and Standard Error) Time Spent Struggling (in minutes) during Forced Swim Test

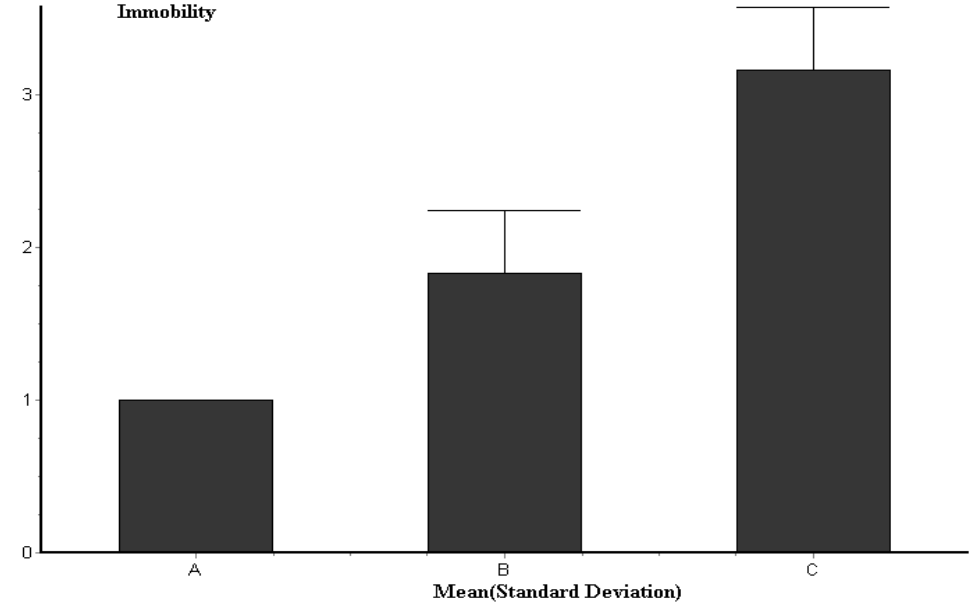

Figure 5: Mean (and Standard error) of Immobility Behaviour (in minutes) in Tail Suspension Test

In the skin irritation test, compounds producing scores of 2 or less are considered negative demonstrating no skin irritation. [14] Thus, in the present study, the skin irritation test was carried out using the transdermal formulation, which showed a skin irritation score (erythema and edema) of 0. Hence, the developed transdermal formulations are free of skin irritation.

Stability studies of the selected patches were performed at Refrigerated (4°C/75%RH), Real Time storage (30°C/75% RH), and Accelerated (40 ° C/75% RH) conditions. The test results of the study for the formulation K15MD are presented in the Table 5. The physical stability of sertraline hydrochloride transdermal patch proved to be unchanged after storage up to 2 months at 4°C/75% RH, 45°C/75% RH and after months under accelerated conditions at 60°C/75% RH.

The result obtained for the test item's "appearance" was not changed significantly at all the three temperatures. Significant changes in physical and chemical stabilities were not observed. Since the accelerated data show little or no change over time and little variability, a statistical analysis was considered unnecessary.

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