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Preparation, *in vitro* Characterization of Transdermal Patch Containing Atenolol and Hydrochlorothiazide: A Combinational Approach

Akelesh Thyagarajan*, J. Sam Johnson Udaya Chander, C. Senthil Kumar, Vidya Sreenivasan, R. Venkata Narayanan

RVS College of Pharmaceutical Sciences, Coimbatore, Tamil Nadu, India.

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ABSTRACT

Background: In the present days, the prevalence of hypertension is potentially increasing. To overcome the effects of this disease, a complex therapeutic regimen is often introduced, but the patient compliance is always questionable. **Methodology**: To improve patient compliance, a novel approach has to be implemented. Hence, the present study was designed to develop a transdermal patch containing Atenolol and hydrochlorothiazide in combination using blends of different polymeric combinations such as hydroxypropyl methyl cellulose, sodium alginate, and polyethylene glycol. The patches were subjected to physicochemical tests and *in-vitro* drug release study. **Results**: Good results were obtained in all the evaluated parameters. The drug release of all formulation followed zero order kinetics. The medicated films also went through primary skin irritation test and the results showed that the films were non-irritant. **Conclusion**: The developed transdermal delivery system containing Atenolol & hydrochlorothiazide might be a milestone in the combinational therapy of hypertension.

INTRODUCTION

During the past few years, the ordinary dosage forms are rapidly being replaced by the new and novel drug delivering systems. Amongst these, the controlled release dosage forms have become extremely popular in modern therapeutics because of their advantages over conventional dosage forms. With the advent of new era of pharmaceutical dosage forms, the conventional dosage forms can be duplicated without its harmful effects by using skin as the port of entry of drugs into the body. This is known as transdermal administration and the drug delivery systems are known as transdermal drug delivery system (TDDS) or popularly transdermal patches. This has been established as an integral part of novel drug releasing systems (Singh, 2000). TDDS is a system where medicaments are administered topically as either gels or patches that can deliver drugs for the systemic effects at a predetermined and controlled rate (Brahmankar and Jaiswal, 2009; Vyas and Khar, 2002; Chopda, 2006; Patel *et al.*, 2006; Aulton, 2004; Chein, 1983). The TDDS shows certain benefits like increasing bioavailability, increasing therapeutic efficacy, bypassing first pass metabolism, decreasing side effects, and controlled release of drugs thereby increasing the frequency of dosing, which improves patient compliance (Cho and Shin, 2004). Patients with hypertension often take multiple medications. Some studies have suggested that patients fail to adhere to the medication regimen because of the number of medicines required and duration (Kruse *et al.*, 1991; Eisen, 1990; Taggart, 1981; Greenberg, 1984; Farmer *et al.*, 1994). The more medications prescribed, the fewer patients adhere to the full treatment regimen. In contrast, the total number of medications taken per day could be reduced if both the combinations were given in a single formulation. Though Joint National Commission 7 (JNC-7) guidelines state a preference for a thiazide diuretics as the initial step for all the patients with uncomplicated hypertension, this is not universally followed, as there are other guidelines which suggest preference for more patient-specific approach (Houston, 2004; Scott and Stowasser, 2003; Sica, 2005). This combinatorial concept was built on the assumption that when two antihypertensive drugs are to be given in a hypertensive patient, then two drugs having different BP-regulating pathways should be combined and, since JNC-7 state a preference for a thiazide

* *Corresponding Author*
Email: tmakelesh@gmail.com

diuretics, one of the combining drugs should be a thiazide diuretic. Hence, the present study aims to prepare transdermal films that are loaded with both atenolol and hydrochlorothiazide to treat hypertension and to improve patient compliance. Atenolol (A) is a β-blocker and is prescribed widely in diverse cardiovascular diseases such as hypertension, angina pectoris, arrhythmias, and myocardial infarction. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting in either manifestation of side effects or reduction in drug concentration at the receptor site (Young-Chang, 2010; Modamio, 2000). Hydrochlorothiazide is a Thiazide diuretic drug which is mainly used in treatment of hypertension and edema associated with heart failure and renal and hepatic disorders. It blocks the reabsorption of sodium and chloride ions thereby increasing the quantity of sodium in the distal tubule and the volume of water excreted (The United States Pharmacopeia, 2007). In the present study, a novel strategy was attempted to develop and evaluate transdermal membranes incorporated with both atenolol and hydrochlorothiazide with varied ratios of non-irritating and pharmaceutically acceptable polymers such as Soidum Alginate (SA) and hydroxypropyl methyl cellulose (HPMC) in combination with permeation enhancer PEG because PEG is considered as a good permeation enhancing agent, as it increases the fluidity of stratum corneum lipid by increasing the formation of capillary channels (Inayat and Setty, 2009). The purpose was to provide the delivery of drug at a controlled rate across intact skin to achieve a therapeutically effective drug level for a longer duration of time from transdermal patches (Chien, 1987).

MATERIALS AND METHODS

Materials

Hydrochlorothiazide, atenolol, sodium alginate, polyethylene glycol, electronic digital balance, digital pH meter, vernier caliper, digital melting point apparatus, magnetic stirrer, mechanical stirrer, UV spectrophotometer, Franz diffusion cells, and synthetic cell membrane. Drug-Excipient Interaction Study (Shivakumar *et al.*, 2009; Ubaidulla *et al.*, 2007; Patel, 2009): The drugs Atenolol and Hydrochlorothiazide along with polymers were subjected to infrared (IR) studies using an FTIR spectrophotometer by the KBr pellet method and the spectra were recorded in the wavelength region of 4000 and 400 cm^{-1}. The procedure consisted of dispersing the sample in KBr in the ratio of 100:1 and compressed into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the way of light and the spectrum was obtained with principle peaks. The peaks obtained by IR spectroscopy of Atenolol and Hydrochlorothiazide were compared with the standard.

Preparation of Drug Free Patches

Polymers of single or in combination are accurately weighed and dissolved in respective solvent and then casted on a glass surface containing ring with inner radius of 4.425 cm. The films were allowed to dry overnight at room temperature. Then, the films were separated and noticed for film formations.

Preparation of Drug-Loaded Transdermal Membranes

Transdermal membrane was prepared with the polymer polyvinyl alcohol as backing membrane and HPMC-50CPS as dispersion polymer. Atenolol 25 mg and hydrochlorothiazide 12.5 mg was used invariably in all formulations. The composition of the transdermal formulations can be seen in Table 1.

Table 1: Composition of Transdermal Patches.

Formulation Code	Composition of Transdermal Patch				Solvent Used
	PVA%w/v	HPMC-50 CPS%w/v	PEG-400% of polymer weight	Drug % of polymer weight	
F1	4	7	10	5	Water
F2	4	6	10	5	Water
F3	4	5	10	5	Water
F4	4	4	10	5	Water
F5	4	4	10	5	EtOH
F6	4	5	10	5	EtOH
F7	4	6	10	5	EtOH
F8	4	7	10	5	EtOH

The matrix-type patches were prepared by first preparing the backing membrane of Polyvinyl Alcohol and dispersing HPMC–50CPS in different proportion in water and ethanol. The backing membrane was prepared and dried for overnight at room temperature. Weighed quantity of atenolol, hydrochlorothiazide, and HPMC with suitable solvent was continuously stirred for one hour. Then, polyethylene glycol (PEG) was added as plasticizer and continuous stirring was continued for another one hour. Then the 5 ml of dispersion containing atenolol/hydrochlorothiazide was withdrawn by a pipette and poured slowly over the previously prepared backing of PVA. By placing an inverted funnel over the glass plate, the solvent was allowed to evaporate at a controlled rate. After drying at room temperature, the membranes were retrieved and evaluated.

Evaluation of Transdermal Patches of Atenolol and Hydrochlorothiazide

Initial drug content

The total content of transdermal patch was placed in a 100 ml volumetric flask and dissolved in water. The solution was filtered through a Whatman filter membrane (0.45µm). The absorbance of the solution was measured against the corresponding blank solution at 225 nm for atenolol and 275 nm for hydrochlorothiazide using UV spectrophotometer (Shimadzu, model UV-1601 PC, Japan).

Patch Weight and Thickness

With the help of vernier caliper, the thickness of patches was measured at different points and the average thickness was noted.

Weight Uniformity

The prepared patches were dried at 60 C for four hours before testing. A specified area of patch was cut in different parts of the patch and weighed on digital balance. The average weight and standard deviation values were calculated from the individual weights.

Percentage Flatness

Transdermal patches (1 x 1 cm^2) were tested for % flatness and the results were recorded. Lesser standard deviation values indicate that the patches have uniform % flatness.

Folding Endurance

The folding endurance of the patches was determined manually by folding the film repeatedly at the same place until it broke.

Content Uniformity

Presence of Salbutamol in all formulations was analyzed spectrophotometrically at 225 nm and the data are recorded.

Percentage Moisture Content

The prepared membranes were weighed individually and kept in desiccators containing fused calcium chloride at room temperature for 24 hours. After 24 hours, the films were re-weighed and percentage moisture content was determined.

Water Vapor Transmission Rate

Glass vials of equal diameter were used as transmission cell (Kulkurni, 2000). These transmission cells were washed thoroughly and dried completely. About 1 g of fused calcium chloride was taken in cells and the polymeric patches measuring 1 cm^2 area were fixed over the brim with the help of an adhesive.

The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccator containing saturated solution of potassium chloride to maintain 80-90% RH. The cells were taken out and weighed after 24 hrs. The amount and rate of water vapor transmitted was calculated by the difference in weight using the formula W V T = WL/S where, W is water vapor transmitted in mg, L is thickness of the film in mm, S is exposed surface area in cm2. Water vapor transmission rate is usually expressed as the number of grams of moisture gained/hr/cm^2.

In Vitro Dissolution Studies

The in-vitro release was carried out with the egg membrane using Franz diffusion cell. The cell consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at room temperature and receptor compartment was provided with sampling port. The diffusion medium used was Phosphate Buffered Saline (PBS) (pH 7.4). The drug containing film with a support of backing membrane was kept in the donor compartment and was separated from the receptor compartment by egg membrane. The egg membrane was previously soaked for 24 hours in PBS. The donor and receptor compartments were held together using a clamp. The receptor compartment with 15 ml of PBS was maintained at room temperature and stirred with magnetic stirrer, to prevent the formation of concentrated drug solution layer below the dialysis membrane (Vlassios *et al.*, 1995; Weiyong *et al.*, 2005; Narasimha Murthy *et al.*, 2001). Samples of 3 ml were collected at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by UV spectrophotometer at 225 nm and 275 nm for atenolol and hydrochlorothiazide respectively.

Primary Skin Irritation Study (Bureau of Indian Standards, 1997)

The primary skin irritation test was performed for prepared transdermal films after approval of the protocol by the Institutional Animal Ethics Committee (IAEC) and animal care was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India (Registration No. 1012/c/06/CPCSEA). Skin irritation test was performed since skin is a vital organ through which drug is transported. Skin irritation studies were performed on healthy Albino rats of average weight of 150 mg to 200 mg. The dorsal surface (3 cm^2) of the rat was cleaned, and the hair was removed by shaving. The skin was cleansed with rectified spirit. The best formulation (F_7) was placed over the skin with the use of adhesive tape and was removed after 24 hrs. The resulting skin reaction was evaluated and compared with control group which was placed with a placebo film.

RESULTS AND DISCUSSION

The physicochemical compatibility of the drugs and the polymer was established through FTIR studies. In the physical mixture of hydrochlorothiazide and atenolol with HPMC, sodium alginate, and polyethylene glycol, the chief absorption bands of the drugs indicate that there is an absence of physical and chemical interactions among both active component and the excipients, which is shown in table 2.

Partition coefficient determination study of Atenolol and hydrochlorothiazide was carried out with n-octanol and pH 7.4 phosphate buffer. The partition coefficient [log P(octanol] of atenolol was found to be 0.230 and hydrochlorothiazide was found to be 0.855. The partition coefficient value indicates that the drug has required lipophilicity.

The placebo films were studied for flexibility, clarity, elasticity, and ease of removal of films from melds. The study showed that polyvinyl alcohol and HPMC along with PEG-400 10% w/v polymer weight were suitable for good flexibility and elasticity. The drug content analysis of the prepared formulations showed that the process employed to prepare patches in this study was capable of providing films with a uniform drug content and minimum batch variability.

Table 2: Drug Excipient Compatibility Results.

	Atenolol	Atenolol with excipients	Hydrochlorothiazide	Hydrochlorothiazide with excipients
O-H	3336.62	3336.62	-	-
H-N	3336.62	3336.62	3360.73	3361.69
C-C	3148.58	3148.58	-	-
C-H	2917.13	2917.13	-	-
C=O	1635.52	1635.52	-	-
Conjugated C=C	1612.38	1612.38	1601.77	1604.00
C-O	1179.39	1179.39	-	-
C-N	1035.70	1035.70	-	-
O=S=O			3382.00	3388.00

Table 3: Drug content, physical characterization, %flatness of salbutamol transdermal patches.

Formula Code	Drug content Aten (%±SD)	Drug content HTZ (%±SD)	Uniformity of weight (gm) (Mean±SD)	Uniformity of thickness (mm) (Mean±SD)	Percentage Flatness (Mean±SD)
F1	99.68±0.21	99.36 ±0.18	0.0426±0.0067	0.2100±0.0067	100±0.00
F2	96.72± 0.31	98.88 ±0.21	0.0336±0.0022	0.2100±0.0067	100±0.00
F3	95.7±60.12	98.56 ±0.19	0.0313±0.0045	0.1900 ±0.0133	100±0.00
F4	97.72± 0.22	98.32 ±0.26	0.0333±0.0000	0.2000 ±0.0045	99.82±.18
F5	94.84±0.24	95.12 ±0.22	0.0336±0.0003	0.1800±0.0155	99.64±0.00
F6	96.72 ±0.17	98.08 ±0.18	0.0330±0.0003	0.2066±0.0111	99.46±0.18
F7	99.76 ±0.14	99.68 ±0.16	0.0336±0.0003	0.1900±0.0022	100±0.00
F8	93.84 ±0.18	98.72±0.28	0.0330±0.0013	0.1866±0.0056	100±0.00

Table 4: Folding endurance, %moisture absorption and loss, and water vapor transmission rate.

Formula Code	Folding Endurance (Mean±SD)	%Moisture Absorption Mean ± S.D	%Moisture Loss Mean ± S.D	Water Vapour Transmission Rate (mg/cm2/hr) ± SD
F1	267.33±2.78	1.56 ±0.00	1.01± 0.01	0.0013±0.0000
F2	276.50±5.89	1.56 ±0.00	1.02± 0.00	0.0014±0.0001
F3	267.33±3.78	1.56 ± 0.00	1.02± 0.00	0.0012 ±0.0001
F4	270.00±3.22	1.57 ± 0.01	0.80± 0.03	0.0018 ±0.0000
F5	265.00±1.78	1.60 ± 0.01	0.76± 0.01	0.0018± 0.0000
F6	265.33±1.45	1.59 ± 0.01	0.76± 0.01	0.0019 ±0.0001
F7	271.33±3.00	1.58 ± 0.01	0.78± 0.02	0.0011 ± 0.0001
F8	267.33±1.00	1.59±0.00	0.76± 0.00	0.0012 ±0.0000

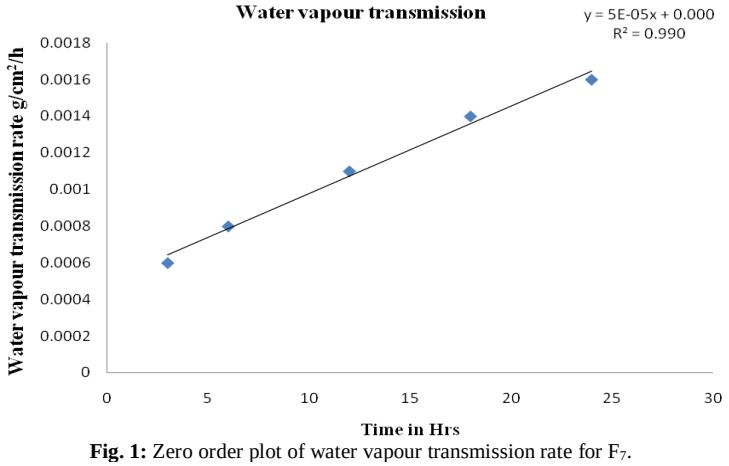

Fig. 1: Zero order plot of water vapour transmission rate for F_7.

All the prepared patches compiled with pharmacopoeial limits for content uniformity. The prepared patches had thickness ranging from 0.1800 mm to 0.2100 and their weight was uniform, varying from 0.0313 g/patch to 0.0426 g/patch. These ranges are suitable for application to the skin as reported earlier. Almost all patches prepared has >99.5% flatness. The optimized patch F7 contained 99.76±0.14% of Atenolol and 99.68±0.16% of Hydrochlorothiazide. These are all depicted in Table 3.

The folding endurance values of matrix films were found within 277 number of folds, indicating good strength and elasticity. Within these films, the optimized patch F7 exhibited the optimal folding endurance 271.33±3.00. The percentage moisture uptake was found in formulation F9 with high rate of moisture absorption (1.60± 0.01). The formulations F2 and F3 show higher value of moisture loss 1.02± 0.00. The formulation F6 has shown maximum water vapor transmission of 0.0019 ±0.0001 and formulation F7 shows less water vapor transmission of 0.0011 ± 0.0001. These are all indicated in Table 4.

The optimized patch has the water vapour transmission rate of 0.0011±0.0001 with r^2=0.990, which is shown in Figure 1.

Table 5 indicates the cumulative percentage drug release of various formulations. The cumulative percentage of drug released in 12 hours was high for formulation F7, which has shown the drug release of 82.879% and 73.007% respectively for atenolol and hydrochlorothiazide.

Table 5: Data for *in vitro* drug release of all formulation.

Formula Code	Time (h)	Cumulative %release of drug (%)	
		A	H
F1	11	96.403	94.416
F2	11	95.561	93.413
F3	11	96.652	94.066
F4	11	94.452	95.716
F5	11	94.093	93.642
F6	10	94.562	96.356
F7	12	82.879	73.007
F8	12	79.623	71.980

The cumulative percentage drug release profile of various formulations is shown in Figure 2 and Figure 3.

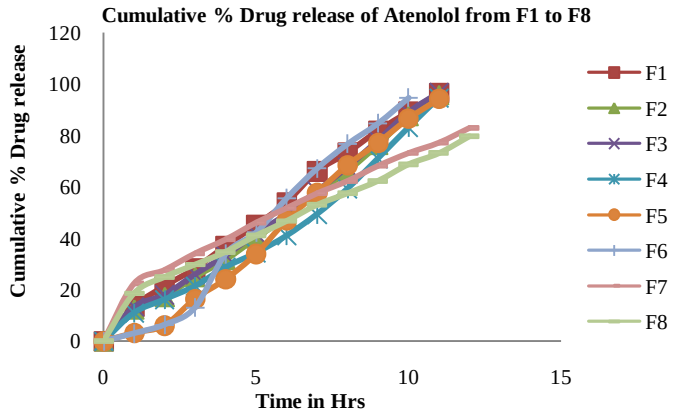

Fig. 2: Cumulative % of drug release of Atenolol from F1 to F8.

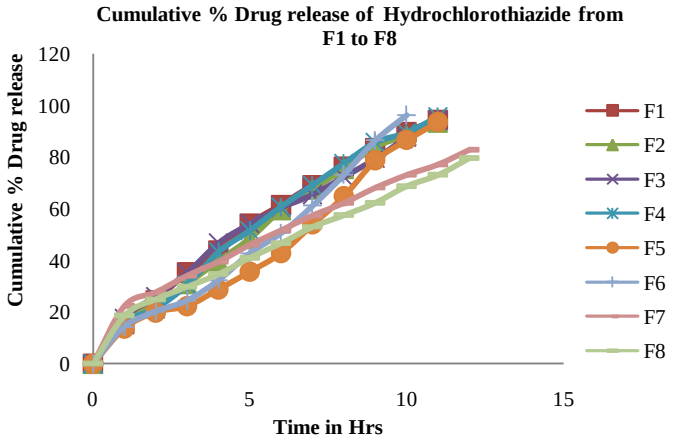

Fig. 3: Cumulative % of drug release of Hydrochlorothiazide from F1 to F8.

The kinetics of atenolol and hydrochlorothiazide diffusion profiles was found out by plotting different graphical models. This can be explained as:

1. Korsemeyer and Peppas model indicates the mechanism of drug release from the formulation is by diffusion.
2. The release kinetics from optimized formulation F_7 followed zero order release kinetic (r^2=0.987) and (r^2=0.995) for Atenolol and Hydrochlorothiazide respectively. The 'n' value of Peppas equation was found to be 0.472 for Atenolol and 0.338 for Hydrochlorothiazide, which shows that the release from optimized formulation F_7 follows Fickian transport. This can be shown in Table 5.

FTIR studies of formulation F7 was done and it was concluded that there was no interference in the functional group of the atenolol and hydrochlorothiazide in formulation F_7 and was compatible both physically & chemically. This is depicted in Figure 4 and Table 6.

Table 6: IR compatibility Results for formulation F_7.

FREQUENCY BAND (cm-1)	GROUP RESPONSIBLE
3404	O=S=O
3365	O-H
3360	H-N
3168	C-C
2916	C-H
1665	C=O
1606	Conjugated C=C (aromatic)
1180	C-O
1018	C-N

Stability study of the optimized formulation F7 was carried out for three months as per ICH guidelines. The transdermal system was analyzed for its physical parameters and drug content.

From the results, it is observed that the compatibility studies do not show any interaction with the physical appearance and there was no change in the drug content and the *in vitro* drug release results were reproducible. It can be concluded that F_7 formulation was stable under room temperature and provides satisfactory results after 90 days time period. This is depicted in Table 7.

The primary skin irritation studies revealed that neither the adhesive nor the drug caused any noticeable irritation on the rat's skin throughout the study. The results are depicted in Table 8.

Table 8: Score of skin irritation studies.

TEST	SKIN REACTIONS	SCORE
ERYTHEMA	Very slight erythema	0
	Well defined erythema	0
	Moderate to severe erythema	0
	Severe erythema	0
Total possible erythema score		0
EDEMA	Very slight edema	0
	Well defined edema	0
	Moderate to severe edema	0
	Severe edema	0
Total possible edema score		0
Total score for primary skin irritation		0

The figures 5 and 6 show the status of rat's skin before application and after removal of salbutamol transdermal patch.

Table 7: Stability study data of the optimized formulation F_7.

Sl. No.	Parameter		Stability studies					
			Initial		30thday		90thday	
			25°±2°C and 60±5% RH	40°±2°Cand 60±5% RH	25°±2°C and 60±5% RH	40°±2°Cand 60±5% RH	25°±2°C and 60±5% RH	40°±2°Cand 60±5% RH
1	Weight uniformity (mg)		0.033	0.034	0.033	0.034	0.033	0.033
2	Thickness (mm)		0.19	0.19	0.18	0.19	0.18	0.18
4	% Moisture loss		0.78%	0.79%	0.78%	0.78%	0.78%	0.78%
5	Drug content(%)	ATEN	24.94%	24.94%	24.93%	24.93%	24.93%	24.92%
		HCTZ	12.46%	12.47%	12.45%	12.46%	12.45%	12.45%
6	Diffusion studies	ATEN	81.656%	81.342%	80.121%	79.987%	79.643%	79.531%
		HCTZ	72.007%	71.956%	71.834%	71.443%	71.121%	70.952%
7	IR Studies		Compatible		Compatible		Compatible	

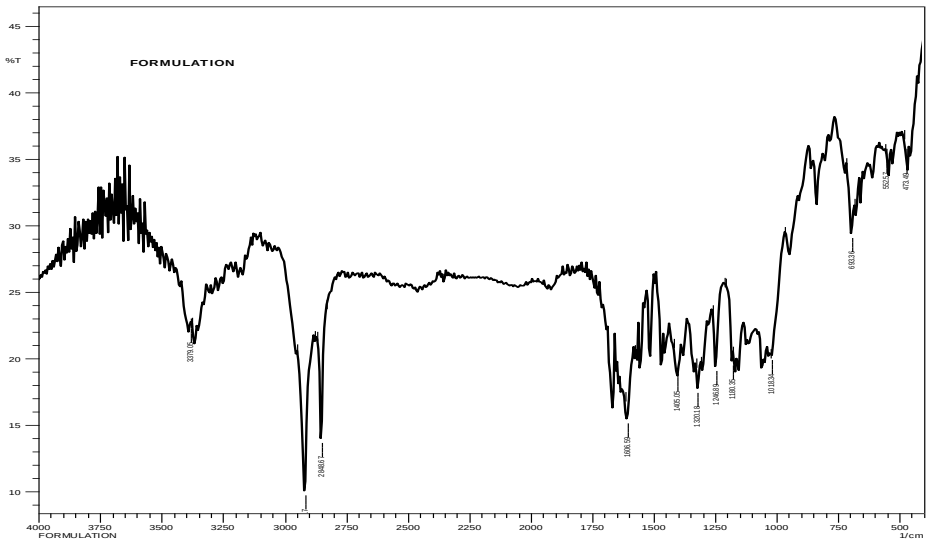

Fig. 4: FTIR Spectra of formulation F7.

Fig. 5: Skin irritation test before application of Transdermal patch.

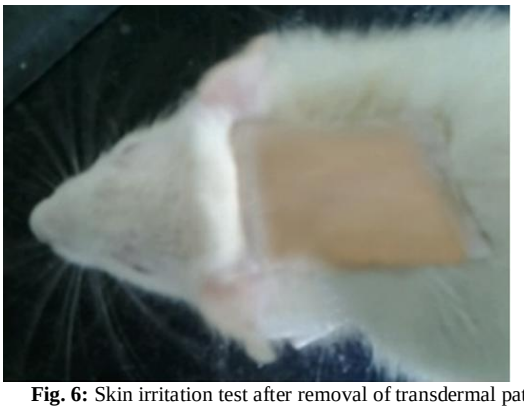

Fig. 6: Skin irritation test after removal of transdermal patch.

DISCUSSION

Transdermal drug delivery system is an alternative route of administration of systematically acting drugs since this route of administration has the advantage of avoiding the first pass metabolism, minimizing the side effects, and improving the physiological and pharmacological response of the drugs and most importantly it gives patient compliance.

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