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Der Pharmacia Lettre, 2014, 6 (1):120-127
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Effect of dimethylsulfoxide on transdermal patches of azelnidipine

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ABSTRACT

In the present study, is to development of Azelnidipine (AZP) transdermal patches and to study the effect of Dimethyl sulfoxide (DMSO) on drug permeation through across the rat abdominal skin. The transdermal patches were prepared by solvent casting method using different amounts and combination of hydroxyl propyl methyl cellulose (HPMC E15), Ethyl cellulose (EC) and Eudragit RS100 (ERS). The drug and excipients compatibility studied by Fourier transform infrared spectroscopy (FTIR). In-vitro drug release studies were studied using dialysis membrane and Ex-vivo skin permeation studies were performed on rat abdominal skin using Franz diffusion cell. Diffused drug was quantified by Uv-Spectrophotometer. The prepared patches were subjected to physicochemical studies such as drug content, weight variation, thickness, moisture absorption, moisture loss, water vapor transmission rate (WVTR) and folding endurance. The prepared films were smooth, flexible, uniform thickness, and content of drug. The FTIR studies indicated that there was no interaction between drug and excipients. Ex-vivo studies showed that as an increasing DMSO concentration to an increased cumulative amount of drug released.

Key words: Dibutylpthalate, Dimethyl sulfoxide, Transdermal patch, Skin permeation,

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INTRODUCTION

Now-a-days attention is been given to develop Transdermal Drug Delivery System which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time. The worldwide transdermal patch market approaches £ 2 billion, based on only ten drugs including scopolamine, nitroglycerine, clonidine, estrogen, testosterone, fentanyl, and nicotine, with a lidocaine patch soon to be marketed[1]. Transdermal delivery of drugs promises many advantages over oral or intravenous administration, such as a better control of blood levels, a reduced incidence of systemic toxicity, an absence of hepatic first-pass metabolism, etc [2]. Chemical enhancers partition into and interact with the SC constituents to induce a temporary, reversible increase in skin permeability where as physical enhancers induce the skin permeability by using physical forces such as magnetic field, electric current, vibration etc [3]. Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells.

Azelnidipine is a new dihydropyridine calcium channel antagonist with selectivity for L-type calcium channels that has recently been approved in Japan for the treatment of patients with hypertension. Compared with other drugs, it is a long-lasting drug and does not induce the reflux increase of heart rate, Improve the contractile dysfunction in myocardium and Antiatherosclerotic. Its trend name is calblock. Azelnidipine has two enantiomers. The pharmacological action of azelnidipine resides in the (R)-enantiomer. This is in marked contrast to other calcium channel blocker (CCB) in which the (S)-enantiomer is responsible for the biological activity [4]. Azelnidipine low dose, low molecular weight and $t^{1/2}$ are ideal characteristics for choosing as model drug for preparing transdermal patches.

The objective of the present work was to develop and characterize the nitrendipine monolithic transdermal therapeutic systems for *in -vitro* release, *ex-vivo* permeation and mechanical properties.

MATERIALS AND METHODS

Materials:
Azelnidipine was received as gift sample from Themis Medicare (India) Ltd, Eudragit RS100 (RS100) received from Evonik Roehm Pharma polymers, Mumbai. Hydroxy propyl methyl cellulose (HPMC E15) and Ethyl cellulose (EC) received from Fenaso Pharma, Hyderabad and all chemicals purchased were of high purity.

Drug-polymer compatibility studies:
The drug–polymer compatibility studies were carried out by using FTIR Shimadzu, Japan. The FTIR analysis to verify the possibility of interaction between drug and polymer. Pure drug and physical mixture of drug & polymers were used for FTIR studies [5, 6]. The samples were scanned in the spectral region between 4000 cm^{-1} – 400 cm^{-1}.

Preparation of Transdermal Patches:
The transdermal patch was prepared by solvent evaporation technique using glass petriplate diameter is 67 cm^2. The polymers composition in the transdermal film is shown in Table 1. Polymeric solutions were prepared using dichloromethane (DCM) and methanol in 1:1 ratio (20 ml) and 100 mg of Azelnidipine and dibutylpthalate (plasticizer) were added and stirred well to get a homogenous solution. The solutions was poured on glass petriplate and allowed to dry, the rate of solvent evaporation was controlled by inverting a glass funnel over the petriplate. After 24 h 2 cm diameter (3.14 cm^2) patch were cut and placed in desiccators [7].

Preparation of Transdermal Patches with penetration enhancer:
These transdermal patch was prepared by solvent evaporation technique using glass petriplate diameter is 67 cm^2. The composition of transdermal films were given in Table 2. Polymeric solutions were prepared by dissolving HPMC E15 and RS100 in 20 ml of DCM and methanol (1:1) and incorporated Azelnidipine, dibutylpthalate (plasticizer) allowed for mixing to get a homogenous solution, after that added DMSO in different amounts, again it was mixed to get homogeneous drug contained solution. Then the solutions was poured on glass petriplate and allowed to dry, the rate of solvent evaporation was controlled by inverting a glass funnel over the petriplate. After 24 h 2 cm diameter patch were cut and placed in desiccator.

EVALUATION OF TRANSDERMAL PATCHES:
Determination of drug content:
The prepared patches of specified surface area (3.14 cm^2) was cut and dissolved in 100 ml of sorenson buffer pH 7.4 containing 0.5% SLS. And it sonicated for 15 min, centrifuged at 5000 rpm for 30 min. The solution filtered through 0.45µm pore diameter of whatman filter paper, the drug content determined by using Uv-Spectrophotometer with respected placebo patch was taken as a blank solution [8].

Weight variation:
Each formulated films were prepared in triplicate and then cut 3.14 cm^2 diameter surface areas. Their weight was measured using Sartorius digital balance [9].

Thickness variation:
The thickness of each formulation was measured at different points of the film by digital screw gauge (Mitutoyo, Japan) [10].

Moisture absorption:
The prepared all formulations were subjected for moisture absorption studies. The specific area of each film was accurately weighed and placed in desiccators, it containing saturated solution of potassium bromide (80% RH). After three days, the film was taken out and reweighed accurately. The percentage of moisture absorbed was calculated using following equation [11].

% Moisture absorbed = {Final wt – Initial wt/Initial wt} X100

Moisture loss:
The prepared all formulations were subjected for moisture absorption studies. Each film specific area was accurately weighed and placed in desiccators, it containing 1g of calcium chloride at 40^oC for 24 hr. The final weight was noted when there was no further change in the weight of individual films. The percentage of moisture loss was calculated using following equation [12].

% Moisture Loss = {Initial wt – Final wt/ Final wt} X100

Water vapor transmission rate (WVTR):
Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in oven at 100^{o}C for some time. About 1g of anhydrous calcium chloride was placed in the cells and respective formulation film was fixed over brim. The cell was accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain 84% RH. The cells were taken out and weighed after 24 h storage. The rate water vapor transmitted was calculated using following formula. It is expressed as the number of grams of moisture gained per hr per cm^2 area [13].

WVTR = {Final Wt –Initial Wt/ Time} X Area

Folding endurance:
The folding endurance was measured manually for the prepared films. A strip of film (4x3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times of film could be folded at the same place without breaking gave the exact value of folding endurance [14, 15].

Flatness:
Three longitudinal strips were cut out from each film: one from the center, one from the left side, and one from the right side. The length of each strip was measured and the variation in length because of nonuniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness [16].

Constriction (%) = {Final length of strip- Initial length of strip/ Final length of strip} X100

***In-vitro* drug release studies through dialysis membrane:**
Franz diffusion cell was used for these studies. It consisting of donor and receptor compartment. Donor compartment for placing of drug or formulation and receptor compartment for collecting drug samples. The receptor compartment was filled with sorenson buffer pH 7.4. And it was stirred magnetically by placing small magnetic bead. Dialysis membrane was placed over it and prepared film was placed in center position of dialysis membrane. The donor cell was fixed using clips. The setup placed on magnetic stirrer and temperature maintained at 32 ± 1^{o}c. Samples were withdrawn at different time intervals over the 24 h and analyzed for drug content. Receptor phase was replaced with an equal volume of sorenson buffer at each time interval [17].

***Ex-vivo* drug permeation studies through rat skin:**
Franz diffusion cell was used for these studies. The full thickness of rat abdominal skin was mounted onto a receptor cell in such a way that stratum corneum side of skin continuously remained in an intimate contact with transdermal film in the donor compartment and the dermis side was in constant contact with receptor solution. The receptor compartment was filled with sorenson buffer pH 7.4 at 32 ± 1^{o}c. The receptor medium was stirred magnetically. 3ml samples were withdrawn at predetermined time intervals over the 24 h and analyzed for drug content using Uv-Spectrophotometer at 254nm. Receptor compartment medium maintained constant by replaced with an equal volume of fresh sorenson buffer for each time interval [18].

RESULTS AND DISCUSSION

The transdermal films were found to be smooth, flexible and uniform thickness. The FTIR spectrum of AZP and its formulations using HPMC E15, EC and HPMC E15, ERS100 are shown in Fig. 1, 2 and 3 respectively. The characteristic peaks of drug found at 825 cm^{-1} C-Cl stretching, 1122 cm^{-1} C-N stretching, 1288 cm^{-1} C-O stretching, 1348 cm^{-1} N-O symmetric stretching, 1631 cm^{-1} N-H bending, 1675 cm^{-1} C=O stretching. The spectrum results were shown no change in characteristic peaks of drug. So that indicated compatibility of drug and polymer.

Thickness of the transdermal films was almost uniform and it was found to varying from 168 ± 0.15 to 180 ± 0.15 µm. The weights of transdermal films were found to be uniform and it was found to in the range of 75.00 ± 0.12 to 81.67 ± 0.15. The amount of drug estimated in each formulation was found to be varying from 95.01±0.61 to 98.39±0.46. The lowest standard deviation values indicate more uniformity of the transdermal films. The results are shown in Table 3. The above results proved that the solvent evaporation technique to produces uniform thickness, weight and drug content of transdermal patches.

The Fig. 4 showed that the moisture absorption found to be 4.72±0.45 to 6.45±0.52 and moisture loss found to be 4.14±0.28 to 5.66±0.73. The results indicate that the moisture absorption and moisture loss values were increases with increasing concentration of HPMC E15 (hydrophilic polymer). This may be due to high affinity of water for the

hydrophilic polymer than the EC and RS100 (hydrophobic polymer). The low percentages of moisture loss help them to remain stable and free from completely drying and brittle. The low moisture absorption, which could protect the formulation from microbial contamination and reduce the bulkiness.

Table 4 shown wvtr found 0.01±0.30 to 0.03±0.42, The increase in weight was indicative of water transmission across the patch and Folding endurance found in the range > 200 times.

The flatness of all prepared films was found to 0% constriction equivalent to 100% flatness. The Fig.5 shows *In-vitro* cumulative amount drug release profile of azp through dialysis membrane, F1,F2,F3,F4,F5 and F6 exhibited 2.42, 2.13,1.87,1.53,1.20,0.75mg per 24h respectively. These studies concludes that an increasing EC (F1-3) and RS100 (F4-6) concentration to decreasing amount of drug release.

The Fig.6 shows *Ex-vivo* cumulative amount drug release profile of azp through rat abdominal skin, F1,F2,F3 F4,F5 and F6 exhibited 3.26,2.68, 2.18, 2.01, 1.65 and 1.16 mg per 24h respectively. Comparatively the *ex-vivo* studies were given better cumulative amount of drug release over 24 h. due to the nature of barrier is biological membrane. The F6 was selected for studying effect of DMSO, since it was showed low permeation; the Fig.7 shows as an increasing proportion of DMSO in 2, 3, 4, 5% v/v to an increased cumulative amount of drug release. The F10 exhibited 3.18 mg per 24h. Thus formulation F1 and F10 selected as best transdermal patches of azp. The ex-vivo studies results indicate that azp released from patches and penetrated through rat skin, hence it could possibly permeate through human skin.

The description of ex-vivo studies by a model function has been attempted using different kinetics (zero order, first order, Higuchi square root model, Korsmeyer's Peppas model.

All the formulations (Table 5) followed zero order release kinetics. The correlation coefficients (R^2) were found to be in the range of 0.948-0.998. Further to find out whether diffusion was involved in the drug release, the data was subjected to Higuchi. The line obtained were comparatively linear (R^2 = 0.914-0.957) suggesting that the diffusion might be of drug release. To confirm further release mechanism of drug, the data was subjected to Korsmeyer's Peppas equation. The release exponent 'n' value (0.5 < n < 1) of Korsmeyer's peppas model indicated that release of drug from all the patches followed non fickian (anomalous transport).

Table 1. Composition of Transdermal Patches of Azelnidipine

Formulation code	HPMC (mg)	EC (mg)	RS-100 (mg)	AZP (mg)	DBP (ml)	DMC:M (1:1) (ml)
F1	800	200	-	100	0.4	20
F2	600	400	-	100	0.4	20
F3	400	600	-	100	0.4	20
F4	800	-	200	100	0.4	20
F5	600	-	400	100	0.4	20
F6	400	-	600	100	0.4	20

Table 2. Composition of Transdermal Patches of Azelnidipine with DMSO

Formulation code	HPMC (mg)	RS-100 (mg)	AZP (mg)	DBP (ml)	DMC:M (1:1) (ml)	DMSO (ml)
F7	400	600	100	0.4	20	0.4
F8	400	600	100	0.4	20	0.6
F9	400	600	100	0.4	20	0.8
F10	400	600	100	0.4	20	1.0

Table 3. Weight variation, thickness, percentage of drug of transdermal films of Azelnidipine

Formulation	Mean Weight (mg)±SD	Mean Thickness (µm)±SD	% Drug content ±SD
F1	80.00±0.20	172.00±0.18	97.46±0.49
F2	78.67±0.58	170.00±0.15	95.01±0.61
F3	75.00±0.12	168.00±0.15	96.72±0.38
F4	80.00±0.15	170.00±0.26	95.62±0.31
F5	76.00±0.32	168.00±0.21	96.85±0.26
F6	77.00±0.53	168.00±0.18	95.13±0.54
F7	79.00±0.42	170.00±0.25	96.85±0.35
F8	80.00±0.34	176.00±0.16	97.22±0.34
F9	80.67±0.53	178.00±0.31	98.39±0.46
F10	81.67±0.58	180.00±0.15	97.34±0.63

Table 4. Water vapor transmission rate and folding endurance of transdermal patches of Azelnidipine

Formulation	WVTR (g/h/cm^2)±SD	Folding endurance
F1	0.03±0.001	>200
F2	0.02±0.006	>200
F3	0.03±0.003	>200
F4	0.03±0.014	>200
F5	0.03±0.004	>200
F6	0.01±0.005	>200
F7	0.01±0.001	>200
F8	0.01±0.003	>200
F9	0.01±0.002	>200
F10	0.01±0.001	>200

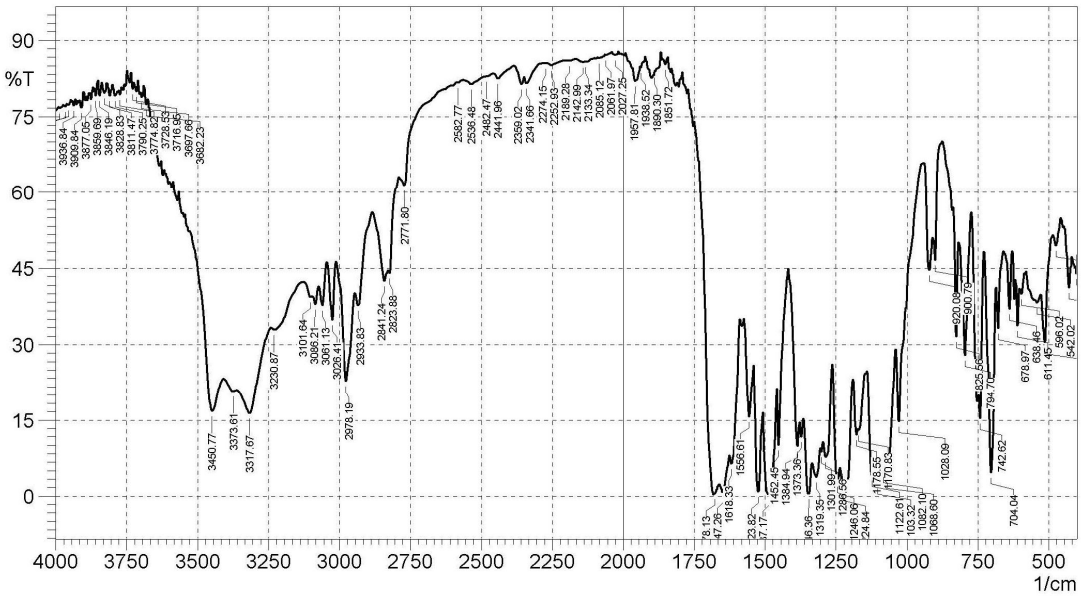

Fig.1. FTIR spectrum of Azelnidipine

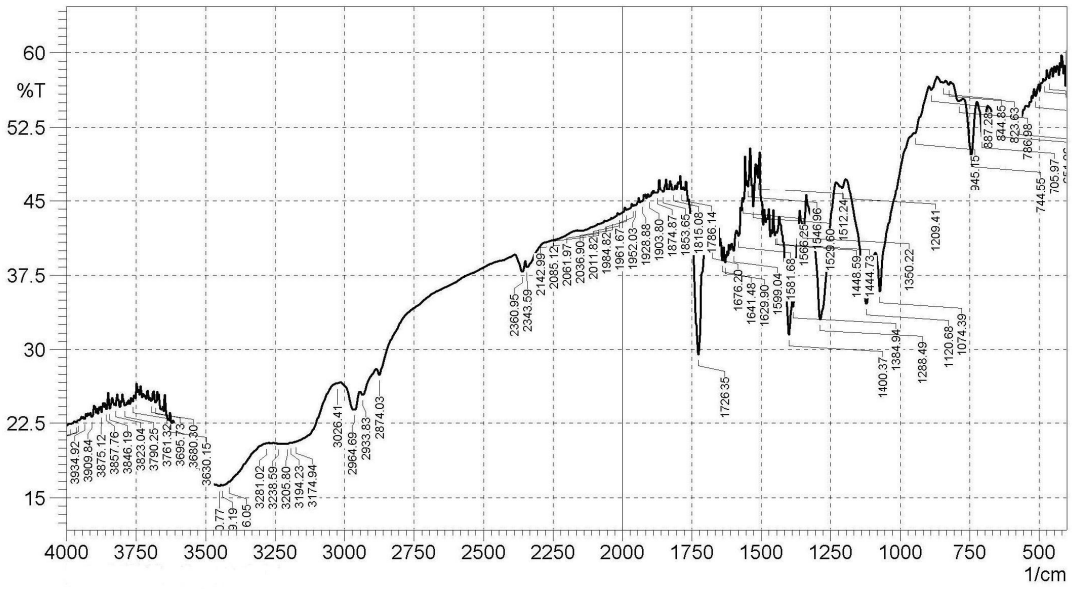

Fig. 2. FTIR spectrum of formulation F1 (HPMC, EC and AZP)

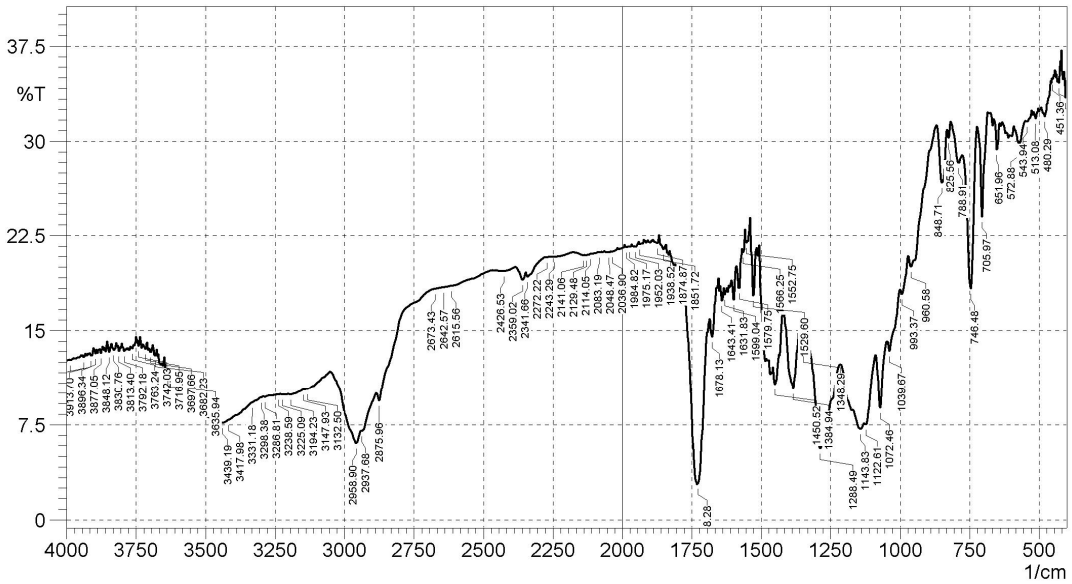

Fig. 3. FTIR spectrum of formulation F6 (HPMC, RS100 and AZP)

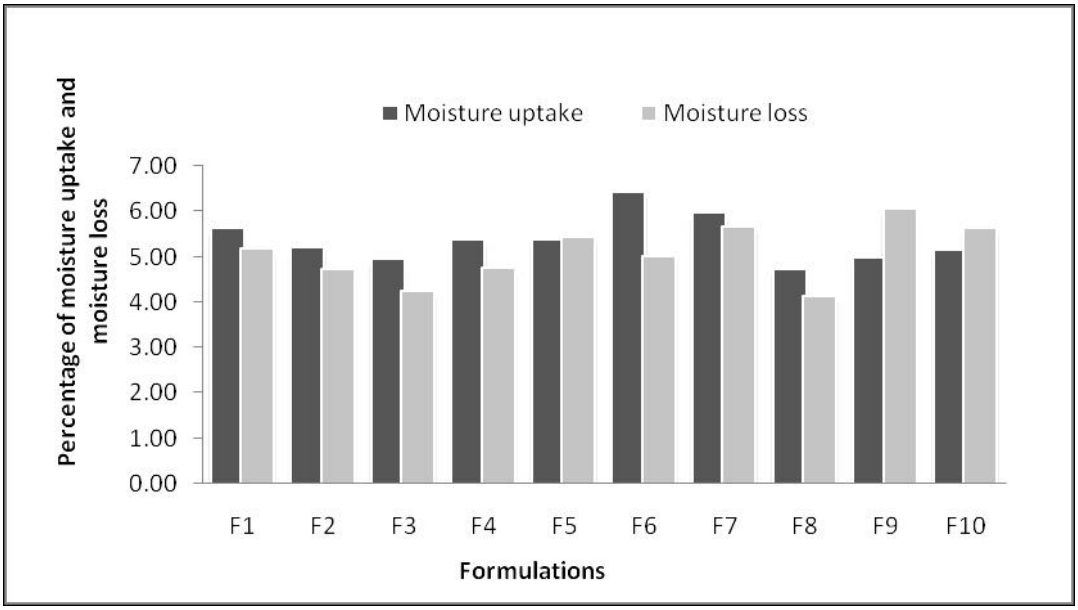

Fig. 4. Moisture absorption and moisture loss of transdermal films of Azelnidipine

Table 5. R^2 value of model fitting of transdermal patches

Formulation	Zero	First	Highuchi	Korsmeyer-Peppas	n
F1	0.996	0.973	0.927	0.997	0.841
F2	0.996	0.987	0.925	0.990	0.822
F3	0.998	0.991	0.918	0.986	0.879
F4	0.992	0.997	0.914	0.997	0.818
F5	0.998	0.995	0.919	0.993	0.887
F6	0.991	0.994	0.929	0.975	0.813
F7	0.967	0.991	0.950	0.976	0.643
F8	0.948	0.990	0.957	0.972	0.596
F9	0.953	0.990	0.959	0.975	0.614
F10	0.964	0.981	0.951	0.973	0.629

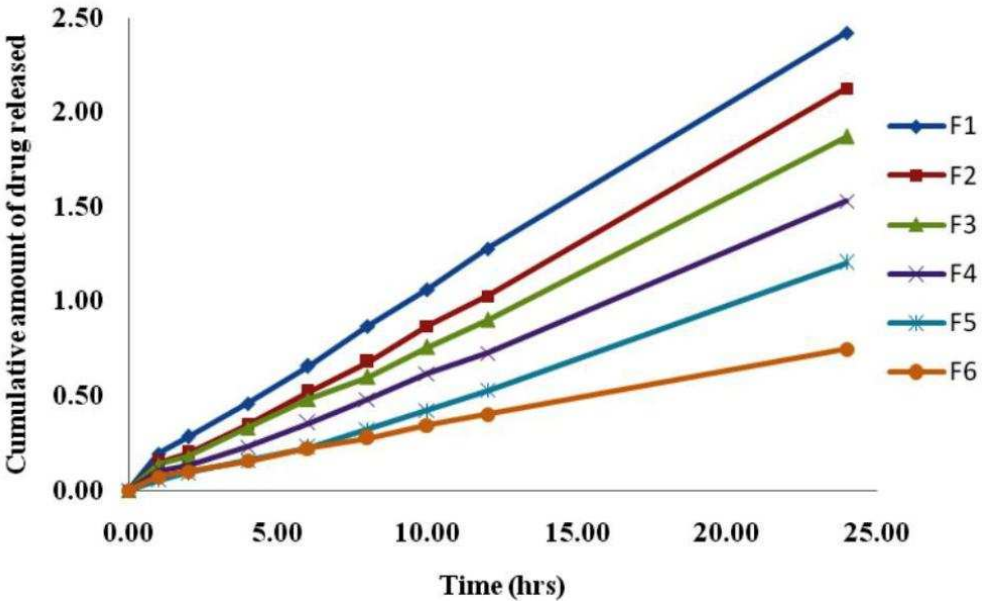

Fig. 5. *In-vitro* drug diffusion through dialysis membrane

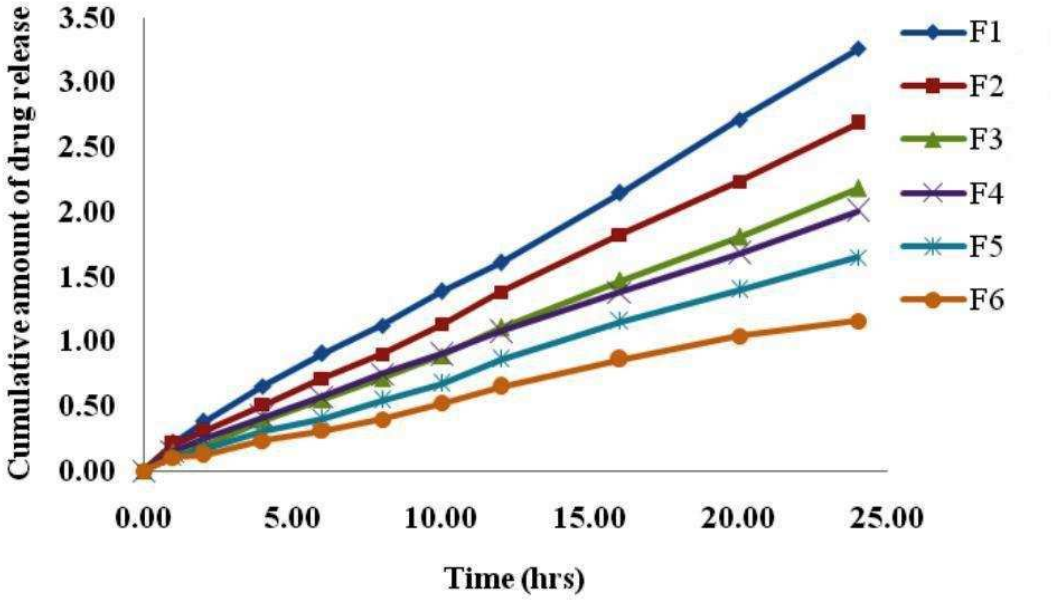

Fig. 6. *Ex-vivo* drug permeation through rat abdominal skin

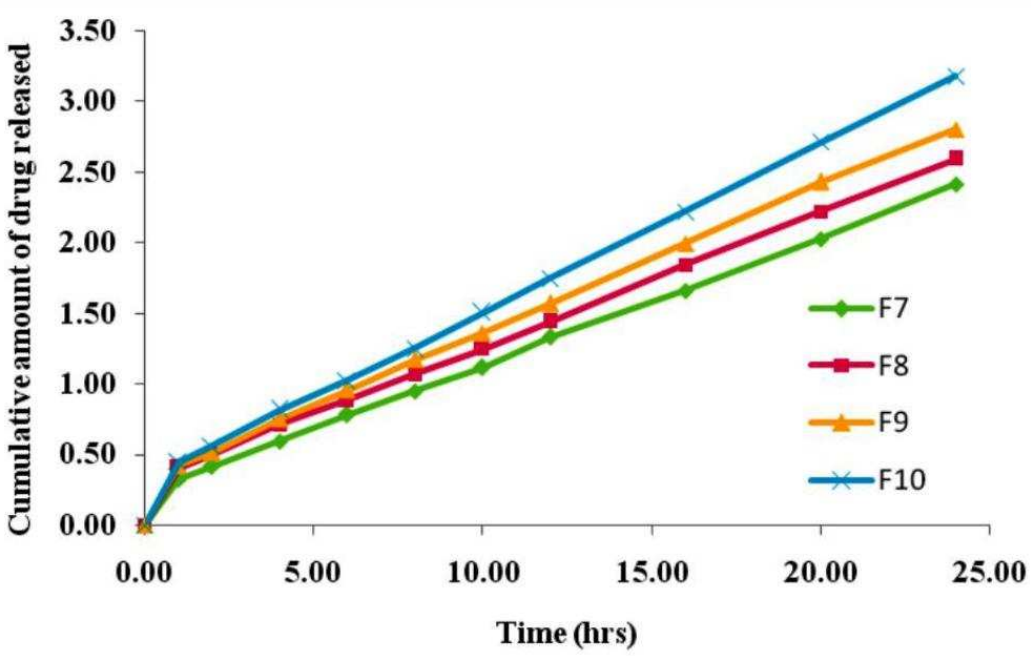

Fig. 7. *Ex-vivo* drug permeation through rat abdominal skin with penetration enhancer

CONCLUSION

The transdermal films were smooth, flexible, uniform thickness, and content of drug. The FTIR studies indicated that there was no interaction between drug and excipients.

Research in this area has proved the usefulness of chemical penetration enhancers for low permeability of formulations. The F10 showed better cumulative drug release through rat skin.

Acknowledgements
The authors are thankful to Dr. Mlv Setti, Themis Medicare (India) Ltd, and Evonik Roehm Pharma polymers, Mumbai and Fenaso Pharma, Hyderabad for gift samples of Azelnidipine, Eudragits and HPMC respectively.

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