

DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCHES OF AZELNIDIPINE

PRABHAKAR.D^{1*}, SREEKANTH.J², JAYAVEERA.K.N³Department of Pharmaceutics, Trinity College of Pharmaceutical Sciences, Karimnagar¹, MSN Laboratories Ltd, Hyderabad², Jawaharlal Nehru Technological University, Anantapur-Dist³ (A.P) India. Email: Prabhakardontha@gmail.com

Received: 02 July 2013, Revised and Accepted: 01 Aug 2013

ABSTRACT

Objective: Azelnidipine, a long-acting dihydropyridine based calcium channel blocker, on oral administration, the drug undergoes extensive first pass metabolism. Delivery of azelnidipine (AZP) via transdermal route would minimize some of the deficiencies associated with the oral delivery and increase the bioavailability of the drug. In the present study, is to investigate the development and evaluation transdermal patches of azelnidipine for controlled release medication and to increase bioavailability by avoiding hepatic first-pass metabolism and degradation of drug in GIT fluids.

Methods: The drug and excipients compatibility studied by FTIR. The transdermal patches were prepared by solvent casting method using different amounts and combination of hydroxyl propyl methyl cellulose (HPMC E15), Eudragit RL100 (ERL) and Eudragit RS100 (ERS). Ex-vivo skin permeation studies were performed on rat abdominal skin using Franz diffusion cell. Diffused drug was quantified by Uv-Spectrophotometer at 281nm.

Results: The patches were found to be smooth in appearance, uniform in thickness, The Formulations were shown subjected to physicochemical studies such as drug content, weight variation, thickness, moisture absorption, moisture loss, water vapor transmission rate (WVTR) and folding endurance.

Conclusions: Azelnidipine is a new DHP basis calcium channel blocker; transdermal route is very safe and convenient for patients who are unable to take oral administration of tablet. And its combination of HPMC, Eudragit RL100 and RS 100 shown better compatibility and controlled release for 24hrs.

Keywords: Sorenson buffer, Drug content, Skin permeation, Dibutylphthalate.

INTRODUCTION

Drugs administered in the conventional dosage forms usually produce large range fluctuations in plasma drug concentrations leading to undesirable toxicity or poor effectiveness. This factor as well as other factors such as repetitive dosing and unpredictable absorption, led to the concept of the controlled drug delivery system or therapeutic system. A dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ is a controlled drug delivery system [1].

Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation [2]. The primary objective of controlled drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing [3].

Azelnidipine, a long-acting dihydropyridine (DHP) based calcium channel blocker (CCB), has been recently approved and used for treating ischemic heart disease and cardiac remodeling after myocardial infarction. And reduce blood pressure without increasing the heart rate in patients with hypertension [4]. Azelnidipine low dose, low molecular weight and t_{1/2} are ideal characteristics for choosing as model drug for preparation of transdermal patches.

MATERIALS AND METHODS

Materials

Azelnidipine was received as gift sample from Themis Medicare (India) Ltd, Eudragit RL100 and RS100 received from Evonik Roehm

Pharma polymers, Mumbai. Hydroxy propyl methyl cellulose (HPMC E15) received from Fenaso Pharma, Hyderabad and all chemicals purchased were of high purity.

Preformulation studies

Solubility study

The saturation solubility studies were conducted in 20 ml of Sorensen's buffer pH 7.4 and including surfactant in different concentrations. These different solutions were taken in test tubes and added an excess amount of AZP up to supersaturate solution obtained. And it allowed for shaking 24 hr. Then supernatant solution used to prepared sufficient dilution of solution with respected same buffers and drug quantity detected using Uv-visible spectrophotometer at 281nm [5,6].

Partition coefficient

The partition coefficient determined by using shake-flask method. The partition coefficient of the drugs was determined by taking equal volumes of chloroform and Sorensen's buffer pH 7.4 in a separating funnel. Known amount of AZP was added and shaken for 10 min. and allowed it to stand for 1 h. Then these two phases were separated and filtered through a whatman filter paper. The amount of drug dissolved in two phases determined using UV-spectrophotometer to get partition coefficient. Triplicate readings were taken and average was calculated [7].

Drug and excipients compatibility study

The compatibility between drug and polymer was detected by FTIR (Shimadzu, Japan). The spectrum carried out on pure form of AZP and their physical mixture of polymer using KBr pellet method [8].

Table 1: Composition of Azelnidipine Transdermal patches.

Excipients(mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Azelnidipine	100	100	100	100	100	100
HPMC E15	800	600	400	800	600	400
Eudragit RL100	200	400	600	---	---	---
Eudragit RS100	---	---	---	200	400	600
DBP(ml)	0.4	0.4	0.4	0.4	0.4	0.4

Preparation of patches

AZP matrix type transdermal patches were prepared by using (Table 1) by solvent evaporation technique in a glass plate. The polymeric solution was prepared by dissolving the polymers in 20 ml of dichloromethane and methanol mixture. Then required quantity of dibutylphthalate (DBP) and drug was added and vortexed for 10 min. Further, it is set-a side for some time to exclude any entrapped air and is then poured in a cleaned anumbra petriplate. The rate of solvent evaporation was controlled by inverting a glass funnel over the petriplate. After over night, the dried films were taken out and stored in desiccators [9].

Evaluation of transdermal patches

Drug content

The prepared patches of specified surface area (3.14 cm²) was cut and dissolved in 100 ml of Sorenson buffer pH 7.4 containing 0.5% SLS and vigorously shaken and then sonicated for 15min, centrifuged at 5000 rpm for 30 min. Filtered through no.42 whatman filter paper, using spectrophotometer to determined drug content at λ 281.0 nm with respected placebo patch was taken as a blank solution [10, 11].

Weight variation

Each formulated films were prepared in triplicate and then cut 3.14 cm² diameter surface areas from each film. Their weight was measured using Sartorius digital balance. The mean weight, \pm SD values were calculated [12].

Thickness variation

The thickness of the films was measured at six different points of the patch by digital screw gauge (Mitutoyo, Japan) [13]. The mean thickness, \pm SD values were calculated.

Moisture absorption

The prepared films were weighed accurately and placed in a desiccator containing saturated solution of Potassium bromide (80% RH). After three days, the films were taken out and weighed [14]. The percentage of moisture absorbed was calculated as

$$\% \text{ Moisture absorbed} = \frac{\text{Final wt} - \text{Initial wt} \times 100}{\text{Initial wt}}$$

Moisture loss

The patches were weighed accurately and placed in a desiccator containing calcium chloride at 40°C for 24 hr. Then the final weight was noted when there was no further change in the weight of individual patch [15]. The percentage of moisture loss was calculated as

$$\% \text{ Moisture Loss} = \frac{\text{Initial wt} - \text{Final wt} \times 100}{\text{Final wt}}$$

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°C for some time. About 1gm anhydrous calcium chloride was placed in the cells and respective polymer film was fixed over brim. The cell were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a relative humidity of 84%. The cells were taken out and weighed after 24 hr storage. The amount of water vapor transmitted was found using following formula [16]. It is expressed as the number of grams of moisture gained/hr/cm².

$$\text{WVTR} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Time} \times \text{Area}}$$

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 the film could be folded at the same place without breaking gave the exact value of folding endurance [17, 18].

Preparation of rat skin

The study was conducted with the prior approval of Institutional Animal Ethical Committee. The Wistar rat with a weight range of 120-200 gm was decapitated. The abdominal skin of excised hairless rat skin was separated along the epidermal junction and it was kept in water bath, which was maintained at 60°C for 50s. The heat-treated skin was cleared of its subcutaneous fatty substances and immediately kept in normal saline solution for flattening and smoothing [19].

Ex-vivo rat abdominal skin permeation

Franz diffusion cell was used for these studies. Above prepared full thickness of rat abdominal epidermis was mounted onto a franz-diffusion 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 \pm 1°C. The receptor medium was stirred magnetically. 3ml samples were withdrawn at different time intervals and analyzed for drug content. Receptor phase was replaced with an equal volume of sorenson buffer at each time interval [20-23].

Flux calculation

The flux of AZP was calculated from the slope of the plot of the cumulative amount of drug permeated per cm² of skin at steady state against the time using linear regression analysis [24].

RESULTS AND DISCUSSION

The prepared transdermal patches were transparent, smooth, uniform and flexible. AZP solubility in water has been reported as < 1mg/ml. The results of saturation solubility of AZP (Fig.1).

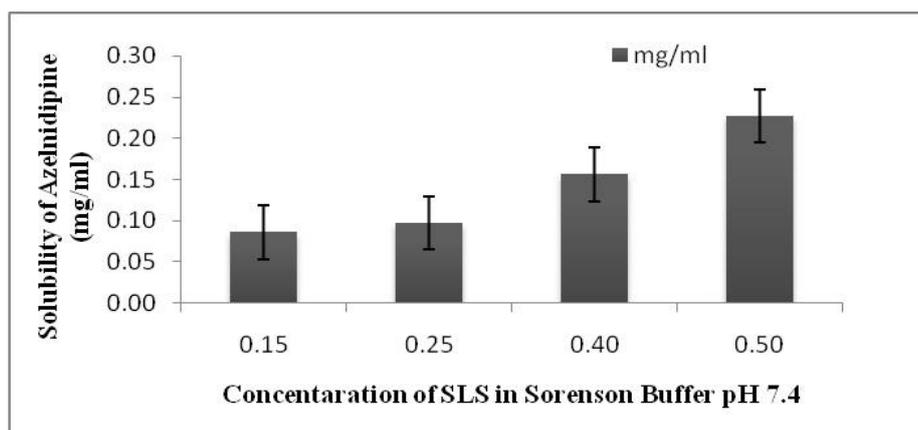


Fig. 1: Solubility of Azelnidipine in Different Concentrations of SLS in Sorenson Buffer PH 7.4.

Indicated that there was increased solubility in sorenson buffer pH 7.4 due to addition of surfactant as cosolvent. Based on results 0.5% SLS sorenson buffer pH 7.4 selected as diffusion medium for better sink condition maintenance over the diffusion studies. Partition coefficient in the octanol/sorenson buffer pH 7.4 systems was found to be 7.0.

The FTIR study to assess any interaction between drug and polymer used in transdermal patch. The spectrum of AZP and its physical mixture of HPMC E15, ERL and HPMC E15, ERS are shown in Fig. 2, 3 and 4 respectively. The characteristic peaks of drug found at 3439 cm^{-1} O-H stretching, 2978 cm^{-1} C-H stretching, 1728 cm^{-1} C=O

stretching, 1618 cm^{-1} N-H bending, 1122 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.

The result showed (Table 2) that the weight of the AZP transdermal patches was ranges from 80.00 ± 0.68 to 76.00 ± 0.54 mg/3.14 cm^2 . The thickness of patches was varied from 172.0 ± 0.46 to $164 \pm 0.36 \mu\text{m}$. Low standard deviation values in the film thickness measurement ensure the uniformity of patches prepared by solvent evaporation technique. The drug content was found to be ranged from 96% to 98%.

SHIMADZU

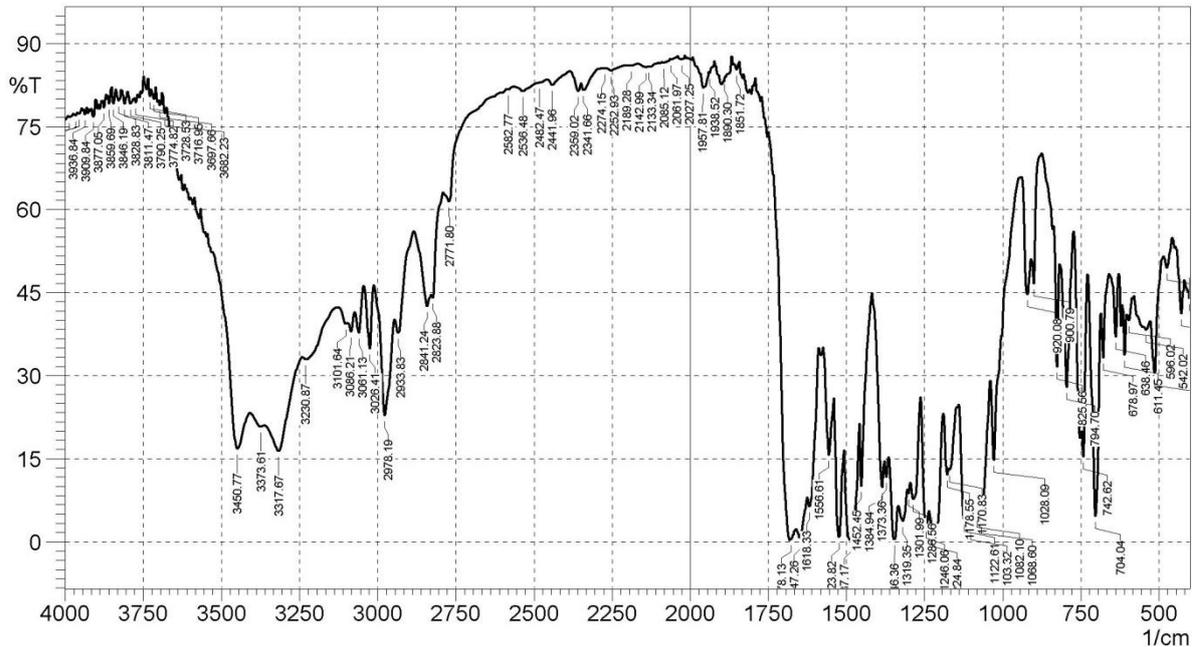


Fig. 2: FTIR of pure Azelnidipine.

SHIMADZU

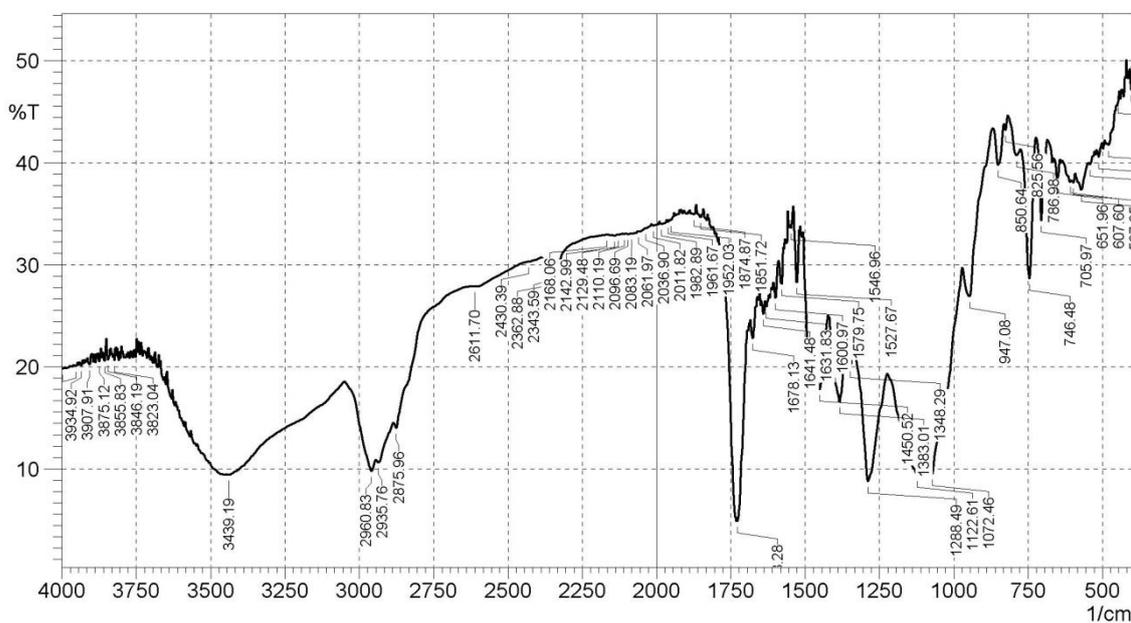


Fig. 3: FTIR of formulation F2.

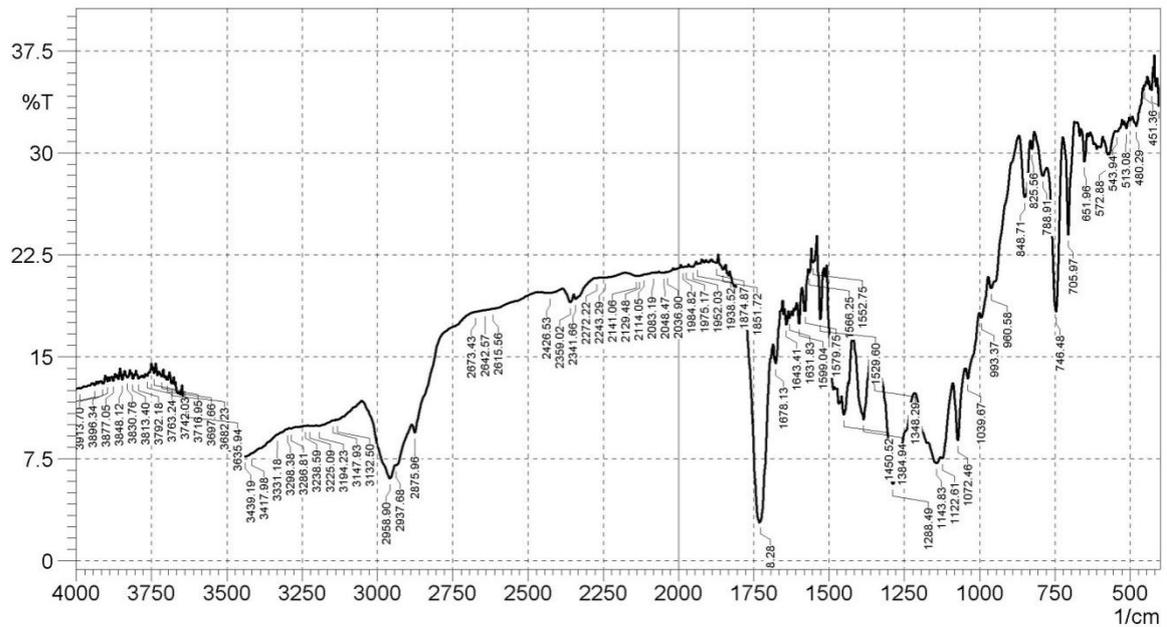


Fig. 4: FTIR of formulation F6.

Table 2: Mean Weight, Thickness and Drug content of Azelnidipine Transdermal patches.

Formulation code	Mean of Weight (mg)		Mean of Thickness (µm)		Drug Content (%)	
	Mean	±SD	Mean	±SD	Mean	±SD
F1	80.00	0.68	171.0	0.44	98.0	0.54
F2	76.83	0.32	170.0	0.44	97.0	0.84
F3	76.67	0.65	168.0	0.54	98.0	0.56
F4	80.00	0.77	172.0	0.46	97.0	0.64
F5	76.00	0.54	168.0	0.32	96.0	0.32
F6	77.00	0.81	164.0	0.36	98.0	0.43

The results of moisture absorption and moisture loss studies were shown in Fig. 5. The % of moisture absorption in the patches is ranged from 12.69 to 6.32 and the % of moisture loss is ranged from 3.35 to 1.92. The results revealed that the moisture absorption and

moisture loss was found to increase with increasing concentration of hydrophilic polymer (HPMC). The low moisture absorption protects the material from microbial contamination and bulkiness of the patches.

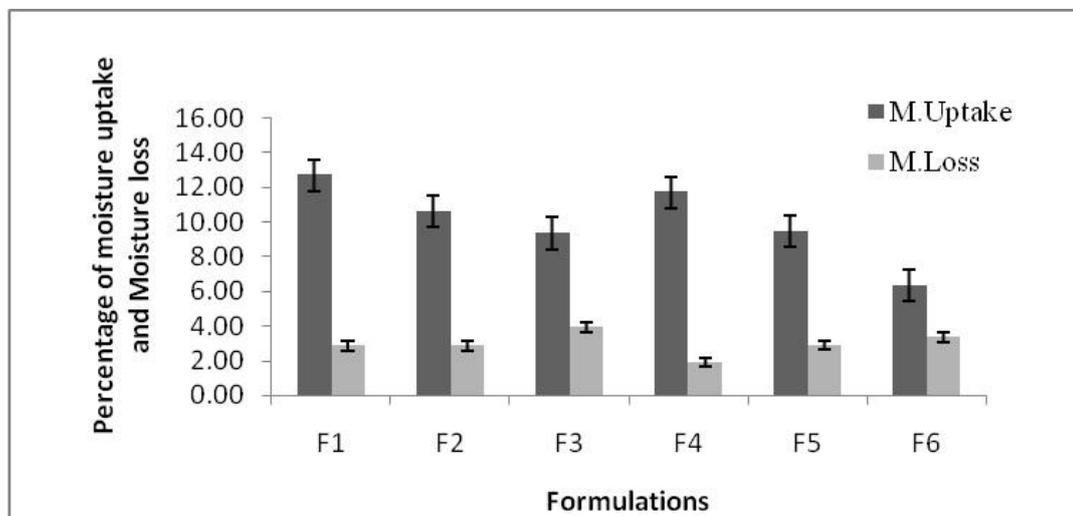


Fig. 5: Moisture absorption, Moisture loss from Transdermal patches.

The formulation F1 has shown (Table 3) maximum water vapor transmission among all the patches this may be due to the presence of more amounts of HPMC and ERL. All formulations were permeable to water vapor. Folding endurance test results indicated that the patches would maintain the integrity with general skin folding when applied.

The prepared transdermal patches were subjected for *ex-vivo* drug permeation studies by using rat abdominal skin. The obtained results were shown in Fig. 6.

The cumulative % of drug permeation in 24 h was found to be in order of F1>F2>F3>F4>F5>F6. The F1, F2 and F3 showed greater % of drug permeation may due to higher proportion of

hydrophilic polymer HPMC and the higher proportion of quaternary ammonium groups in ERL resulted in rapid hydration and drug release, where as F4, F5 and F6 shown comparatively low % of drug permeation is observed, because of the lower proportion of ammonium groups in ERS is responsible for slow release of AZP.

The flux was calculated by plotting a graph cumulative % of drug permeation verses time, values are shown Table 3.

The drug release kinetics was calculated (Table 4), the zero-order plots of F1, F2 and F3 were found to be fairly linear, as indicated by their high regression values (R^2). Hence from these formulations could follow either near zero or zero-order kinetics.

Table 3: WVTR, Flux and folding endurance of Azelnidipine Transdermal patches.

Formulation	WVTR (gm/hr/cm ²)	\pm SD	Folding Endurance	Flux (μ g/hr/cm ²)
F1	9.02X 10 ³	0.014	>200	13.59
F2	8.14X10 ³	0.004	>200	11.76
F3	6.60 X10 ³	0.005	>200	10.14
F4	5.79 X10 ³	0.002	>200	09.53
F5	6.01 X10 ³	0.001	>200	07.71
F6	5.57 X10 ³	0.001	>200	06.49

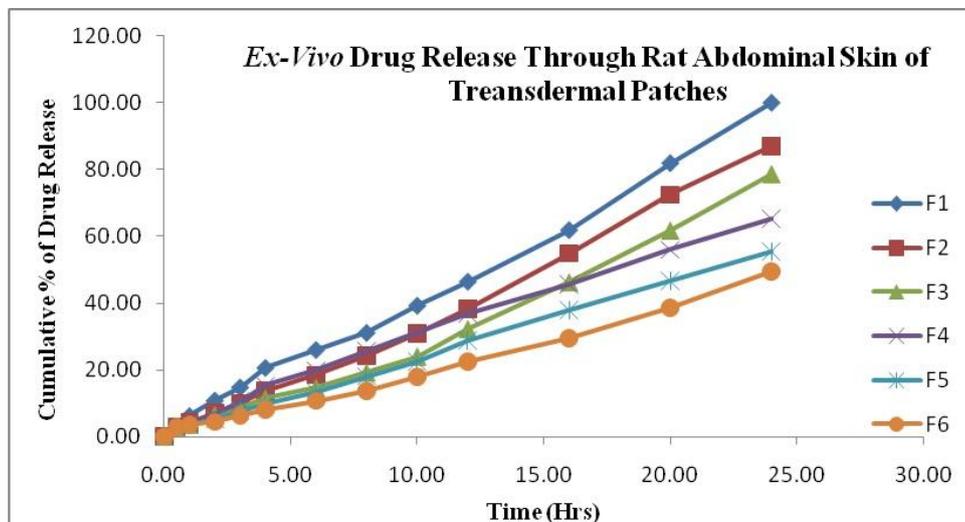


Fig. 6: *Ex-vivo* Drug Permeation Through Rat Abdominal Skin From Transdermal patches.

Table 4: Kinetic Modeling of Drug Release.

Formulation	Zero order R ²	First order R ²	Higuchi R ²	Korsmeyer-Peppas n	R ²
F1	0.994	0.614	0.852	1.182	0.940
F2	0.992	0.897	0.808	1.209	0.903
F3	0.980	0.900	0.778	1.135	0.900
F4	0.988	0.991	0.899	1.241	0.937
F5	0.998	0.985	0.853	1.177	0.900
F6	0.991	0.966	0.821	1.018	0.878

The zero order and first order plots of F4, F5 and F6 were found to be linear, as indicated by their high regression values (R^2). Hence these formulations could follow mixed order kinetics. The korsmeyer-peppas model is a simple empirical equation to describe the general solute release behavior from controlled release polymer matrices. In the present study, the Korsmeyer-Peppas equation R^2 values were found to be $n > 1.0$ suggest that the drug permeation from transdermal patches (F1 and F4) followed the super case II transport mechanism, may due to chain disentanglement and swelling of hydrophilic polymers.

CONCLUSION

Based on the results of above studies, it may be concluded that polymers selected were better suited for the development of TDDS of azelnidipine and the formulation F1 and F2 may used for further studies in animals or humans.

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.

REFERENCES

- Kale Tukaram, Santhi K, Sajeeth C.I. and Naveen Kumar CH: Design and Characterization of Diltiazem Hydrochloride Sustained Release Matrix Tablets. *Int J Res Pharm Biomed Sci* 2011; 2 (2): 714-721.
- Panner Selvam P, Anoop Kumar Singh and Sivakumar T: Transdermal Drug Delivery Systems for Antihypertensive Drugs -A Review. *Int J Pharm Biomed Res* 2010; 1:1-8.
- Sridevi S, Chary G.M, Krishna D.R, Prakash V Diwan: Pharmacodynamic Evaluation of Transdermal Drug Delivery System of Glibenclamide in Rats. *Indian J Pharmacology*. 2000; 32: 309-312.
- Vasundhara Kain, Sandeep Kumar, Amrutesh S Puranik and Sandhya L Sitasawad: Azelnidipine protects myocardium in hyperglycemia-induced cardiac damage. *Cardiovascular Diabetology* 2010; 9(82):2-9.
- Damodharan N, Gopa Roy and Biswajit Mukherjee: Skin Permeation of Rosiglitazone from Transdermal Matrix Patches. *Pharm Tech* 2010; 34(5): 56-72.
- Modamio P, Lastra C.F and Marin E: A comparative *in-vitro* study of Percutaneous Penetration of β -blockers in human skin. *Int J Pharm* 2000; 194: 249-259.
- Priyanka A and Biswajit Mukherjee: Design, Development, Physicochemical and *in-vitro* and *in-vivo* Evaluation of Transdermal Patches containing Diclofenac Diethylammonium Salt. *J Pharm Sci* 2002; 91: 2077-2089.
- Ramesh Gannu, Vamshi Vishnu Y, Kishan V and Madhusudan Rao Y: Development of Nitrendipine Transdermal Patches: *In-Vitro* and *Ex-Vivo* Characterization. *Curr Drug Deliv* 2007; 4: 69-76.
- Pravin G, Gaikwad A, Radhika P.R and Sivakumar T: Design and Development of Hydroxypropyl Methylcellulose based polymeric film of Enalapril Maleate. *Int J Pharm Tech Res* 2010; 2(1): 274-282.
- Shankar M.S, Suresh V, Kulkarni and Sandeep: Development and Evaluation of Aceclofenac Transdermal Patches using Hydrophilic and Hydrophobic Polymers. *J Global Pharm Tech* 2010; 2(4):102-109.
- Uendra Kulkarni and Siddarth S: Design and Development of Felodipine buccal mucoadhesive patches. *Int J Curr Pharm Res* 2010; 2(3):71-75.
- Mohamed EL-Nabarawi, Aliaa Nabil Elmeshad, Mohamed Yousif Moutasim: Assessment of Bioavailability of Sumatriptan Transdermal Delivery Systems in Rabbits. *Int J Pharm Sci* 2013; 5(2): 225-240.
- Shalu Rani, Kamal Sarohaa and Navneet Syanb: Transdermal Patches A Successful Tool In Transdermal Drug Delivery System: An Overview. *Der Pharmacia Sinica* 2011; 2 (5):17-29.
- Prabhu Prabhakara, Marina Koland and Vijaynarayana K: Preparation and Evaluation of Transdermal Patches of Papaverine Hydrochloride. *Int J Res Pharm Sci* 2010; 1(3):259-266.
- Shankar V, Velrajan G, Palaniappan R and Rajasekar S: Design and Evaluation of Nifedipine Transdermal Patches. *Indian J Pharm Sci* 2003; 65(5):510-515.
- Kavitha K and Mangesh M. Rajendra: Design and Evaluation of Transdermal films of Lornoxicam. *Int J Pharm Bio Sci* 2011; 2(2):54-62.
- Noha Adel Nafee and Nabila Ahmed Boraie: Design and Characterization of Mucoadhesive buccal patches containing Cetylpyridinium Chloride. *Acta Pharm* 2003; 53:199-212.
- Sonia Dhiman, Thakur Gurjeet Singh and Ashish Kumar Rehni: Transdermal Patches: A Recent Approach to New Drug Delivery System. *Int J Pharmacy and Pharmaceutical Sci* 2011; 3(5):26-34.
- Sanjay Dey, Ananya Malgope: Preparation of Carvedilol Transdermal Patch and the effect of Propylene Glycol on Permeation. *Int J Pharmacy Pharm Sci* 2010; 2(1):137-143
- Sridevi U, Prakash Vaman Rao Diwan: Optimized Transdermal Delivery of Ketoprofen using pH and Hydroxypropyl- β -Cyclodextrin as Co-Enhancers, *Eur J Pharm Biopharm* 2002; 54: 151-154.
- Kosuke Kusamori, Hidemasa Katsumi and Mari Abe: Development of a Novel Transdermal Patch of Alendronate, a Nitrogen-Containing Bisphosphonate, for the Treatment of Osteoporosis. *J Bone Mineral Res* 2010; 25(12): 2582-259.
- Dandigi M Panchaxari, Sowjanya Pampana, Tapas Pal: Design and Characterization of Diclofenac Diethylamine Transdermal Patch using Silicone and Acrylic Adhesives Combination. *DARU J Pharmaceutical Sci* 2013; 21(6): 2-14.
- Ravindra Bhana, Ajay Verma, Sanjay Jain: Development and characterization of Ethosomes bearing Losartan Potassium for Transdermal Drug Delivery. *Int J Pharmacy and Pharmaceutical Sci* 2013; 5(1): 35-40.
- Rakesh P Patel and Grishma Patel Ashok Baria: Formulation and Evaluation of Transdermal Patch of Aceclofenac. *Int J Drug Deliv* 2009; 1: 41-51.