DESIGN AND EVALUATION OF TRANSDERMAL PATCHES OF AZELNIDIPINE

Dr. A.V. Badarinath *[1], Pabbu Pravalika[1], Tamarapalli Bhavya Naga lakshmi [1], Punna Navyasri[1], Anthati Srivarshini [1], Dr SA Srinivas[2]

****[1] Department of Pharmaceutics, Sree Dattha Institute of Pharmacy, Sheriguda, Ibrahimpatnam, Ranga Reddy, 501510.***

[2]Department of Pharmacognosy, Sree Dattha Institute of Pharmacy, Sheriguda, Ibrahimpatnam, Ranga Reddy, 501510.

ABSTRACT : The objective of present study was to develop matrix type transdermal therapeutic systems of Azelnidipine using various such as Eudragit and Ethyl cellulose polymers as matrix formers. Results revealed that prepared patches showed good physical characteristics and no drug-polymer interaction was observed. The in vitro release study revealed that F2 formulation showed maximum release in 12 hrs. Formulation F2 was subjected for accelerated stability studies. The F2 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus, conclusion can be made that stable transdermal patch of Azelnidipine has been developed. F2 formulation showed highest cumulative percentage drug release of 98.50% were obtained during in vitro drug release studies after 12 hrs. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F2 formulation was concluded as optimized formulation.

Key words: Azelnidipine, Eudragit and Ethyl cellulose, solvent casting technique, in vitro drug release studies.

I.INTRODUCTION

During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent. [1] Transdermal Drug Delivery System (TDDS) are defined as self-contained, discrete dosage forms which are also known as "patches" ' when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation[2]. TDDS are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin.[3] A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.[4] Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation into the skin through skin at predetermined rate with minimal inter and intra patient variation.[5] Currently transdermal delivery is one of the most promising methods for drug application. It reduces the load that the oral route commonly places on the digestive tract and liver.[6] It enhances patient compliances and minimizes harmful side effects of a drug caused from temporary over dose and is convenience in transdermal delivered drugs that require only once weakly application.[7]That will improves bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms.[8] To develop and characterize the Azelnidipine. transdermal patches by using solvent casting method and by using different polymers. Azelnidipine is used in the treatment of Hypertension (high blood pressure). Azelnidipine is a calcium channel blocker. It regulates the blood pressure by relaxing the blood vessels and reducing the pressure on them, thereby making it easier for the heart to pump more blood throughout the body[9,10].

II. MATERIALS AND METHOD

2.1 MATERIALS

Azelnidipine was collected as a gift sample from Aurobindo ltd,Hyd, polymers and other excipients were

purchased from AR Chemicals,Hyd.

2.2 METHODODOLOGY

Compatibility studies:

The drug-polymer compatibility was ascertained by subjecting the drug and homogenates of drug and polymer to Infrared spectrophotometric study.

Fourier Transform Infrared Spectroscopy (FTIR)[11,12]

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a dosage form. The use of FTIR technique allows pointing out the implication of the different functional groups of drug and excipients by analysing the significant changes in the shape and position of the absorbance bands. In this method individual samples as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a mortar and compressed into disc by applying pressure of 5 tons for 5 mins in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm-1 in FTIR spectrophotometer. Then the characteristics peaks were obtained of all sample as well as mixtures.

Formulation design

Preparation of transdermal patches:

Transdermal patches containing Azelnidipine were prepared by the solvent casting evaporation technique. The drug Azelnidipine was dissolved in suitable solvent. Polymers Ethyl cellulose, Eudragit were taken in a boiling tube, to this add Azelnidipine drug which was previously dissolved in methanol. PEG was taken as a plasticizer, and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned petri plate ($40cm^2$), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation[13].

Table-: 1 Formulation Design of Azelnidipine Transdermal Patches

S. No	Formulation code	Ingredients (gms)		
		Drug (mg)	Eudragit	Ethyl cellulose
1	F1	10	20	-
2	F2	10	40	-
3	F3	10	-	20
4	F4	10	-	40

Evaluation of transdermal formulation:

Physico- chemical evaluation:

Physical appearance:

All the prepared transdermal films were observed for color, clarity, flexibility, and smoothness.

Folding endurance:

Folding endurance of the patches was determined by repeatedly folding at the same place till it broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches for three times and the mean values plus standard deviation was calculated[14].

Thickness of the film:

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film[15].

Weight uniformity:

The prepared patches are to be dried at 60^0C for 4hrs before testing. A specified area of 4.52 cm^2 of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weight[16].

Drug content:

The formulated transdermal films were assayed for drug content in each case. Three patches from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one film from each was taken and assayed for content of drug[17].

Moisture absorption studies:

The films were weighed accurately and placed in a desiccator containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.[18]

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

Moisture loss studies:

Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^0C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.[19]

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

***in-vitro* Drug release studies:**

The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz type glass diffusion cell. The modified cell having higher capacity is (10 ml) is used to maintain sink condition. The samples were analysed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal[20].
Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug in the patch
Da = The amount of drug released

Stability studies:

Optimized medicated films were subjected to short term stability testing. The transdermal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 1 month as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week[21].

III. RESULTS & DISCUSSION

FT-IR Spectrum of Azelnidipine

FT-IR Spectra of Azelnidipine and polymers were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Azelnidipine and polymers. It also confirmed that the stability of drug during process.

Evaluation of Transdermal formulation

Physical appearance:

The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance:

The folding endurance numbers of all the Azelnidipine patches are 180 – 292. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high

mechanical property. The folding endurance number was increased with increasing the Eudragit content. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

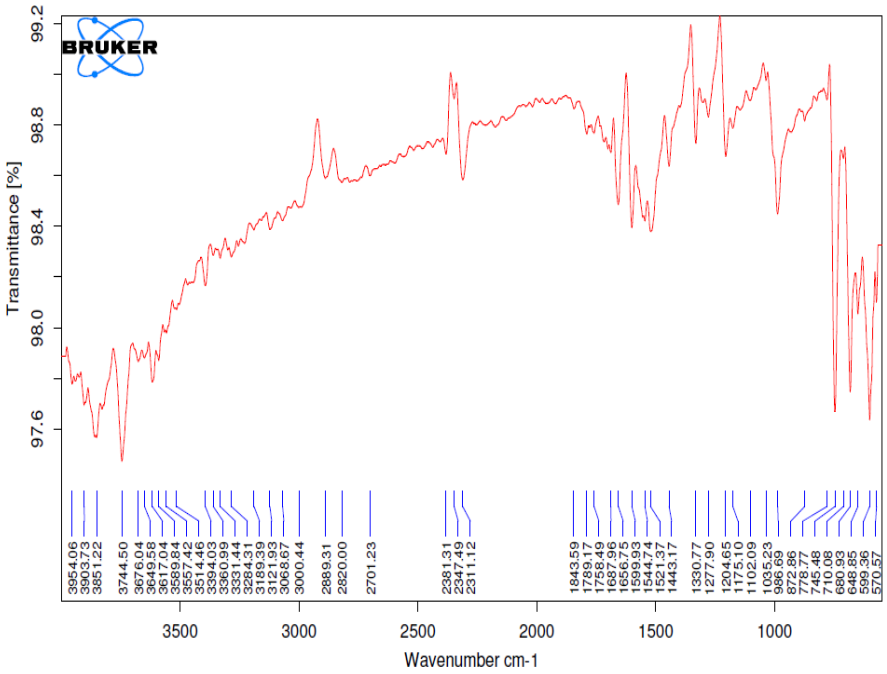

Fig.1. FTIR Studies of Azelnidipine

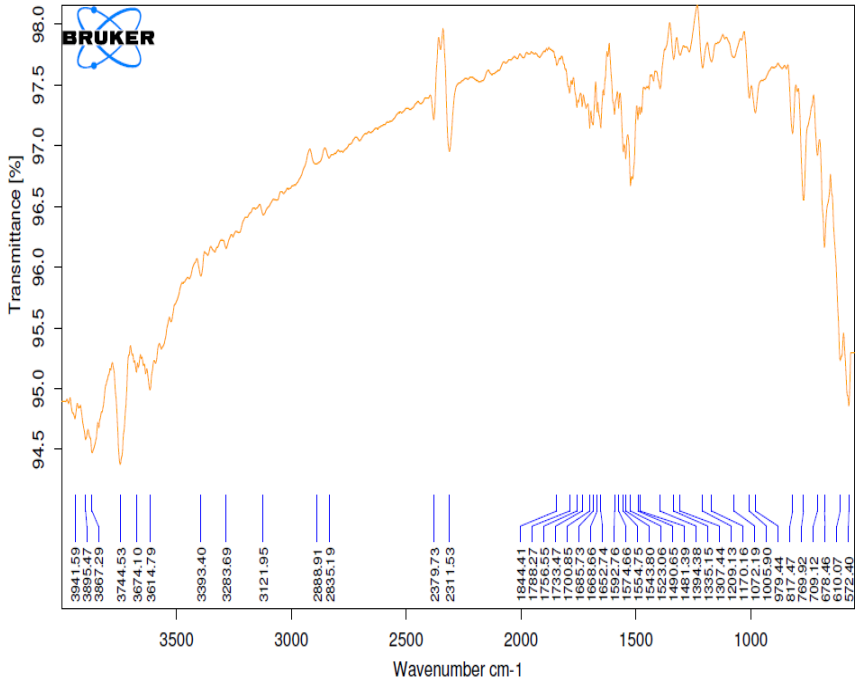

Fig.2. FTIR Studies of Physical mixture of drug and excipients

Thickness of the film:

Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carry uniform thickness..

Weight uniformity:

The mean weights of all the prepared patches are shown in table . The weights are in the range of 230-286.

The F2 formulation patches showed maximum weight.

Drug content:

The drug content analysis of the prepared formulations have shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the patches were found to have drug content in the range of 90 – 101%. So the method employed i.e. solvent evaporation method is satisfactory for the preparation of Azelnidipine transdermal patches.

Table:2 Physicochemical evaluation of Azelnidipine patches

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% moisture loss	% moisture absorption
F1	245.9	0.90	192	96.62	6.85	9.95
F2	265.4	0.96	190	99.89	9.20	10.20
F3	286.2	0.91	189	99.65	10.85	10.95
F4	274.7	0.95	191	98.42	9.85	11.85

***In vitro* release study:**

Phosphate buffer pH 7.4 containing 0.5% SLS was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.999. The drug release profiles of Azelnidipine patches containing different ratios of polymers Eudragit, Ethyl cellulose. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content.

Table : 3 *In vitro* drug release profiles of Azelnidipine transdermal patch (F1-F4)

Time	F1	F2	F3	F4
0	0	0	0	0
0.5	14.56	15.68	13.48	11.80
1	23.72	25.25	26.50	24.67
2	34.94	37.52	31.71	36.627
3	41.16	49.28	44.36	40.18
4	51.88	53.63	50.25	56.71
5	65.33	67.46	61.07	69.20
6	73.46	78.60	75.53	73.76
8	82.87	83.35	82.15	80.92
10	89.01	93.61	90.71	89.08
12	95.93	98.50	93.30	96.48

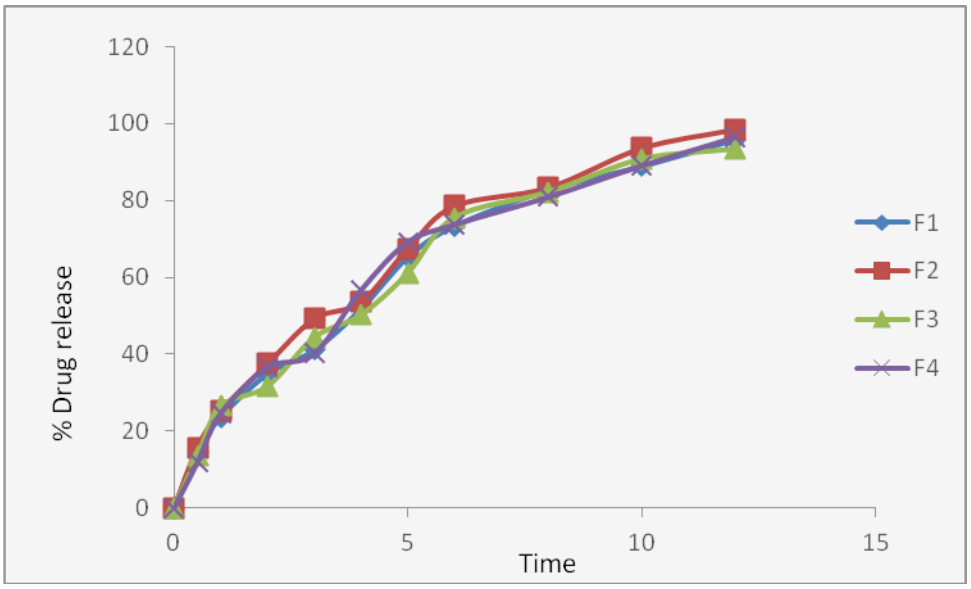

Fig.3. Drug release for all formulations

Stability studies:

Optimized formulations F2 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table : 4 Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	99.89	190	No change in color	98.50
90	99.70	190	Slight yellowish color	97.98

IV. CONCLUSION

From the obtained results, it can be concluded that; Transdermal patches of Azelnidipine were formulated by solvent casting technique. The I.R spectra let out that, there was no interaction between polymers and drug. All the polymers used were compatible with the drug. Characterization parameters like thickness, tensile strength, folding endurance, percentage moisture loss indicates that films were mechanically stable. Percentage weight variation and content uniformity were found to be uniform in all the films. In-vitro drug release showed an abrupt release in the first day. There after the release profile was controlled and extended till the end of static release study, and the concentration was found to be above the minimum inhibitory concentration, which is an encouraging observation. Among the four formulations, the formulated patch F_2 showed 98.50% of release. Throughout the *in-vitro* release studies, the films remained intact without any disintegration. All the patches were found to be stable over the storage period and conditions tested. Overall study suggests that among the films prepared F_2 was found to show the best results. Hence it was considered as optimized formulation.

REFERENCES

1. Jalwal P, Jangra A, Dhaiya L, Sangwan Y, Saroha R. A review on transdermal patches. Pharm Res. J. 2010; 3:139-149.
2. Bhowmik D, Chiranjib, Chandira M, Jayakar B, Sampath KP. Recent advances in transdermal drug delivery system. Int. J Pharm Tech Res. 2010; 2(1):68-77.
3. Kumar A, Pullankandam N, Prabhu SL, Gopal V. Transdermal drug delivery system: an overview. Int. J Pharm Sci. Review Res. 2010;3(2):49-54.
4. Divya A, Rao MK, Gnanprakash K, Sowjanya A, Vidyasagar N, Gobinath M. A review on current scenario of transdermal drug delivery system. Int. J Res. Pharm Sci. 2012;3(4):494-502.
5. Jain NK, Controlled and novel drug delivery. 1st, CBS Publisher and Distributors, New Delhi. 2001:100-129.
6. Rani S, Saroha K, Syan N, Mathur P. Transdermal patches a successful tool in transdermal drug delivery system. Plegia Res. Lib. 2011;2(5):17-29.
7. Dhawan S, Aggarwal G. Development, fabrication and evaluation of transdermal drug delivery system- a review. Pharm info.net. 2009:1-25.
8. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. The Pharm Innovation. 2012;1(4):66-75.
9. https://pubchem.ncbi.nlm.nih.gov/compound/Azelnidipine.
10. https://en.wikipedia.org/wiki/Azelnidipine.
11. https://en.wikipedia.org/wiki/Fourier-transform_infrared_spectroscopy
12. https://www.mee-inc.com/hamm/fourier-transform-infrared-spectroscopy-ftir.
13. hankarM.S, SureshV, Kulkarni and Sandeep: Development and Evaluation of Aceclofenac Transdermal Patches using Hydrophilic and Hydrophobic Polymers.J Global Pharm Tech 2010; 2(4):102-109.
14. Upendra Kulkarni and Siddarth S: Design and Development of Felodipine buccal mucoadhesive patches.Int J Curr Pharm Res 2010; 2(3):71-75.
15. .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
16. .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.
17. 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.
18. 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.
19. KavithaK and MangeshM. Rajendra: Design and Evaluation of Transdermal films of Lornoxicam. Int J Pharm Bio Sci 2011; 2(2):54-62.
20. Noha Adel Nafee and Nabila Ahmed Boraie: Design and Characterization of Mucoadhesive buccal patches containing Cetylpyridinium Chloride.Acta Pharm 2003; 53:199–212.
21. 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.