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FORMULATION DEVELOPMENT, OPTIMIZATION AND CHARACTERIZATION OF TRANSDERMAL PATCHES OF DIHYDROPYRIDINE BASED CALCIUM CHANNEL BLOCKER

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ABSTRACT

The reason of this research was to develop a matrix-type transdermal therapeutic system containing drug azelnidipine with different ratios of of polyvinylpyrrolidone (PVP) and ethylcellulose by solvent evaporation technique using 10%w/w of dibutyl phthalate incorporated as plasticizer. Azelnidipine, a long-acting dihydropyridine based calcium channel blocker, on oral administration, the drug undergoes extensive first pass metabolism. Delivery of azelnidipine via transdermal route would minimize some of the deficiencies associated with the oral delivery and increase the bioavailability of the drug. The drug matrix film of polyvinylpyrrolidone and ethyl cellulose was casted on a polyvinylalcohol backing membrane that was previously dried at 60˚C for 6 hrs. 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. The physicochemical compatibility of the drug and the polymers studied by differential scanning calorimetry and infrared spectroscopy suggested absence of any incompatibility. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance, percentage of moisture content and water vapour transmission rate. All prepared formulations indicated good physical stability. Ex-vivo skin permeation studies were performed on rat abdominal skin using Franz diffusion cell. Diffused drug was quantified by UV-Spectrophotometer at 281nm.

INTRODUCTION

The aspiration of controlled release dosage form is to ascertain relatively constant plasma drug concentrations, avoiding the peak and valleys associated with conventional dosage forms. Controlled delivery of drugs by the transdermal route provides inimitable opportunity in order to uphold constant plasma levels of drug. The skin is the most magnanimous and readily accessible organ of the human body. It has been used as an administration site of drugs with local action on it and on muscle beneath, and it is now recognized that other drugs with systemic action can also be introduced through the skin.[1, 2, 3]

The frequent method to develop drug permeation through the skin is to bring into play penetration enhancers. Penetration enhancers can transform the structure of skin lipids and alter the skin barrier function. These compounds, even if they augment the transdermal flux of several drugs. The incidence of systemic side-effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. [4, 5, 6]

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. Azelnidipine low dose, low molecular weight and t1/2 are ideal characteristics for choosing as model drug for preparation of transdermal patches.[7]

The objective of the current study were to prepare transdermal patches of azelnidipines using hydrophilic and hydrophobic polymer, optimization of transdermal patch formulation using 32 full factorial design and study the *in-vitro* diffusion behavior of prepared transdermal patch formulations in the charisma and nonappearance of penetration enhancer. The rationale was to endow with the delivery of the drug at a controlled rate across intact skin.

MATERIALS AND METHODS

Azelnidipine was received as a gift samples from Themis medicare, India. Hydroxyl propyl cellulose and ethyl cellulose were generous gift from S.D Fine chemicals Pvt. Ltd Mumbai, India. Oleic acid and di-n-butyl-phthalat were procured from Sigma Chemicals Ltd. (Ahmedabad, India). Other materials used in the study (chloroform, methanol, dichloromethane, glycerol, potassium dihydrogen phosphate, etc.) were of analytical grade.

PREFORMULATION STUDIES

1. Solubility study:

The saturation solubility studies were conducted in 20 ml of Sorensen's buffer pH 7.4 and including surfactant in dissimilar concentrations. These diverse solutions were engaged in test

tubes and added a surfeit amount of azelnidipine up to supersaturate solution obtained. And it allowed for quivering 24 hr. Then supernatant solution used to prepared ample dilution of solution with esteemed same buffers and drug quantity detected using Uv-visible spectrophotometer at 281nm.[8, 9]

2. Partition coefficient:

The partition coefficient unwavered by using shake-flask method. The partition coefficient of the drugs was determined by taking alike volumes of chloroform and Sorensen's buffer pH 7.4 in a separating funnel. Known quantity of azelnidipine 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 quantity of drug dissolved in two phases resolute by UV-spectrophotometer to get partition coefficient. Triplicate readings were taken and average was calculated. [10]

3. Compatibility studies between active pharmaceutically ingredient and excipients:

The physicochemical compatibility between azelnidipine and polymers used in the films was studied by using differential scanning calorimetry (DSC- Shimadzu 60 with TDA trend line software, Shimadzu Co., Kyoto, Japan) and fourier transform infrared (FTIR- 8300, Shimadzu Co., Kyoto, Japan) spectroscopy.[11]

Fabrication of transdermal patches of azelnidipine:

Transdermal patches containing azelnidipine were prepared by the solvent evaporation technique in cylindrical glass molds with both sides opens. The backing membrane was cast by pouring a 3 % (*m*/*V*) polyvinyl alcohol solution followed by drying at 60 °C for 6 h. The drug reservoir was equipped by dissolving hydroxyl propyl cellulose or ethyl cellulose in Chloroform: Methanol 1:1 mixture. Dibutyl phthalate 20 % (*w/w* of dry polymer composition) was used as a plasticizer. The active pharmaceutical ingredient 100 mg (in 5 mL solvent mixture Chloroform: Methanol) was added into the homogeneous dispersion under slow stirring with a magnetic stirrer. The uniform dispersion was cast on a PVA backing membrane and dried at room temperature. (Table 1) Further, it is set-a side for some time to leave out 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.[12, 13]

Table1: Composition of transdermal patches of azelnidipine

S.No	Ingredients	Formulation Code					
		TDF1	TDF2	TDF3	TDF4	TDF5	TDF6
1	Active pharmaceutical ingredient(mg)	100	100	100	100	100	100
2	PVP	150	125	100	75	50	25
3	EC	25	50	75	100	125	150
4	Dibutyl phthalate* (%)	10	10	10	10	10	10
5	Oleic acid (ml)	2.0	2.0	2.0	2.0	2.0	2.0
6	Chloroform (ml)	3.5	3.5	3.5	3.5	3.5	3.5

Note: 20 % w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer

Characterization of transdermal patches of azelnidipine:

Drug content:

The prepared patches of specified surface area was cut and dissolved in 100 ml of Sorenson buffer pH 7.4 containing 0.25% SLS and vigorously shaken and then sonicated for 15min, centrifuged at 5000 rpm for 20 min. Filtered through no.42 whatman filter paper, using spectrophotometer to determined drug content at 281 nm with respected placebo patch was taken as a blank solution.[14]

Weight variation:

Each formulated patches were prepared in triplicate and then cut 1 cm^2 diameter surface areas from each film. Their weight was measured using Sartorius digital balance. The mean weight, ±SD values were calculated. [15]

Thickness variation:

The thickness of the films was measured at six different points of the patch by digital screw gauge. The mean thickness,±SD values were calculated.[16]

Flatness:

Three longitudinal strips were cut out from each film: 1 from the center, 1 from the left side, and 1 from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness. [12]

Folding Endurance

This was determined by repeatedly folding one patch at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance. [19]

Tensile strength:

In order to determine the elongation as a tensile strength, the polymeric patch was pulled by means of a pulley system; weights were step by step added to the pan to enhance the pulling force till the patch was broken. The elongation i.e. the distance travelled by the pointer before break of the patch was noted with the help of magnifying glass on the graph paper, the tensile strength was calculated as kg cm^{-2}.

Percentage of Moisture Absorbed:

The patches were weighed individually and set aside in a desiccators containing activated silica at room temperature for 24 hours. Individual patch were weighed repeatedly until they showed a unvarying weight. The percentage of moisture content was premeditated as the difference between initial and final weight with respect to final weight.[20]

% Moisture absorbed = Final wt – Initial wt/ Initial wt X 100

Water vapour transmission rate (WVTR):

WVTR is defined as the quantity of moisture transmitted through unit area of film in unit time. Glass cells were filled with 2 g of anhydrous calcium chloride and a film of specified area was affixed onto the cell rim. The assembly was accurately weighed and placed in a humidity chamber (80 ± 5% RH) at 27 ± 2 °C for 24 hours. Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in oven at 100oC for some time. 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. It is expressed as the number of grams of moisture gained/hr/cm^2. [21, 22]

WVTR = Final Weight –Initial Weight/Time X Area

Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log (Q_o-Q) v/s t], Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_o-Q) is the cumulative percentage of drug remaining after time t.[23]

Stability study of optimized formulation:

Stability study was carried out for optimized patch formulation at 40°C temperature in a humidity chamber having 75 % RH for 3 months. After 3 months samples were withdrawn and characterized for physicochemical properties and *in-vitro* diffusion study.[23]

RESULT AND DISCUSSION

The formulated transdermal patches were visible, downy, unvarying and bendable. Azelnidipine solubility in water has been reported as < 2mg/ml. Indicated that there was increased solubility in sorenson buffer pH 7.4 due to addition of surfactant as cosolvent.

Investigation of Physicochemical Compatibility of Drug and Polymer:

The FTIR study to consider any interaction between drug and polymer used in transdermal patch. Infrared absorption spectroscopy (IR) of ACF showed sharp band at 3319, 3278 and 1770 cm-1 due to stretching vibration bands of OH, N-H and C=O, respectively

The spectrum of azelnidipine and its physical mixture of HPC and EC results were shown no change in characteristic peaks of drug. So that indicated compatibility of drug and polymer.

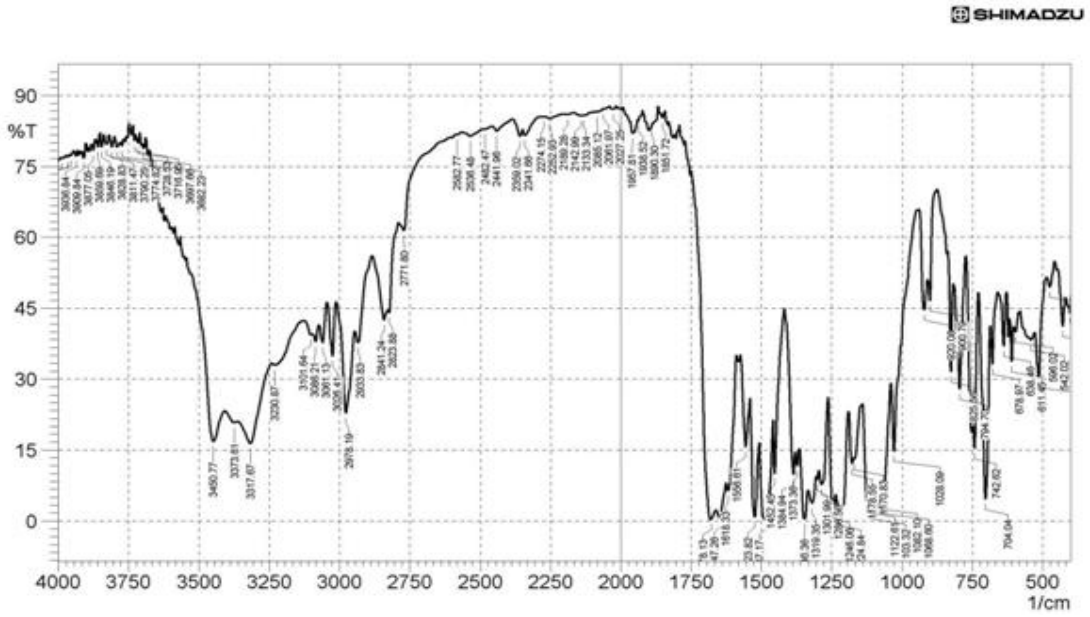

Figure 1: FTIR Spectra of active pharmaceutical ingredient (Azelnidipine)

Physicochemical characterization of films:

The outcome of the physicochemical evaluation of the patches are shown in Table 2. The thickness ranged between 0.16 ± 0.05 to 0.24 ± 0.01 mm, which indicates that they are unvarying in thickness. The weights ranged between 198 ± 2.1 mg to 210 ± 2.11 mg, which indicates that dissimilar batches patch weights, were reasonably analogous. Excellent uniformity of drug content among the various batches were seen, with all formulations and ranged from 97.8 ± 0.42 % to 99.7 ± 0.1 %. The results indicate that the process employed to formulate patches in this aim was capable of producing patches with uniform drug content and negligible patch variability. The flatness study showed that all the formulations had the identical strip length before and after their cuts, indicating 100% flatness.

Table 2: Characterization of transdermal patches of azelnidipine

Parameters	TDF1	TDF2	TDF3	TDF4	TDF5	TDF6
Weight variation	198 ± 2.1	203 ± 3.8	200 ± 2.01	209 ± 3.6	206.6 ± 1.23	210.3 ± 2.11
Drug content	98.7 ± 0.15	97.9 ± 0.12	97.8 ± 0.42	98.9 ± 0.62	96.1 ± 0.3	99.7 ± 0.19
Thickness	0.23 ± 0.01	0.22 ± 0.0	0.16 ± 0.05	0.24 ± 0.01	0.19 ± 0.005	0.18± 0.01
Tensile strength	12.14 ± 2.21	15.55 ± 1.98	14.87 ± 2.35	15.08 ± 1.89	16.22 ± 2.32	15.14 ± 2.21
WVTR	3.348±0.558	4.748± 0.527	4.344 ±0.512	4.792 ±0.539	4.452± 0.512	3.898±0.558
Moisture content	4.565 ± 0.06	3.783 ± 0.11	3.904 ± 0.08	3.878 ± 0.07	3.786 ± 0.03	4.675 ± 0.06
Folding endurance	178.3 ± 5.27	196 ± 7.13	223.6 ± 3.55	255.6 ± 8.7	246.3 ± 3.51	228.3 ± 5.23

Thus, no amount of constriction was observed; all patches had a smooth, flat surface; and that smooth surface could be maintained when the patch was applied to the skin. Folding endurance test results indicated that the patches would not fracture and would sustain their veracity with general skin folding when applied. Moisture content and moisture uptake studies indicated that the augment in the concentration of hydrophilic polymer was directly proportional to the raise in moisture content and moisture uptake of the patches. The moisture content of the equipped formulations was stumpy, which could facilitate the formulations remain unwavering and diminish brittleness during long term storage. The moisture uptake of the formulations was also low, (Figure 1) which could defend the formulations from microbial contamination and reduces bulkiness.

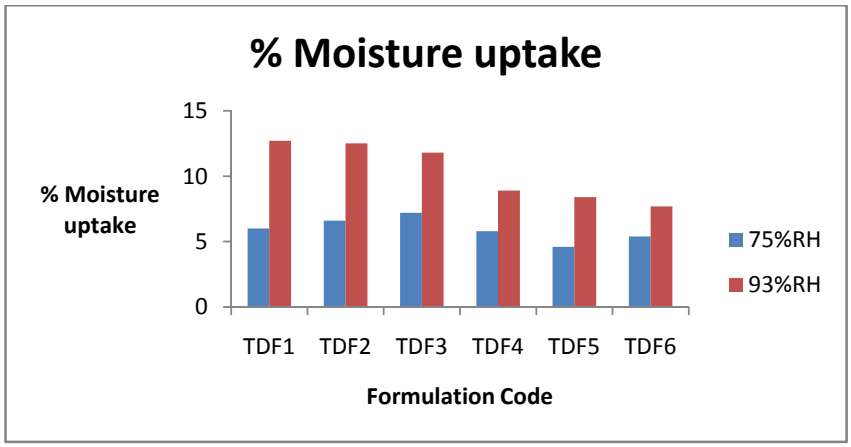

Figure 1: Determination of moisture uptake of different formulation

***In-vitro* drug release:**

The cumulative amount of drug released from formulations containing more amount of hydrophilic polymer and less Hydrophilic polymer in the same formulation, release drug at quicker rate than supplementary amount of hydrophobic polymer and less hydrophilic. The cumulative amount of drug released from formulations TDF5 and TDF6 is much higher than

formulation TDF1, TDF2,TDF3 and TDF4. The drug release from the patch is ordered as TDF6 > TDF5 > TDF4 > TDF3 > TDF2> TDF1. Unlike the formulations TDF2, TDF3, TDF4, and TDF5 and, the formulations TDF6 achieved a high cumulative amount of drug permeation at the end of 14 hours. Based on physiochemical and *in-vitro* release experiments, TDF6 was chosen for further pharmacodynamic studies.

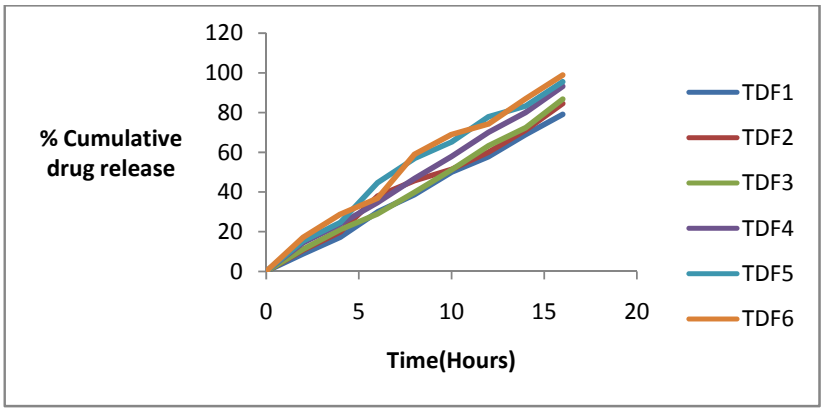

Figure 2: **Release profile of azelnidipine from patches containing different concentration of PVP and EC**

Kinetic modeling of drug release:

Table 3: Kinetic modeling of drug release

Formulation Code	Zero-order	First order	Higuchi	Korsmeyer peppas
TDF1	0.973	0.976	0.988	0.943
TDF2	0.988	0.989	0.989	0.989
TDF3	0.989	0.967	0.990	0.997
TDF4	0.989	0.998	0.967	0.980
TDF5	0.998	0.949	0.978	0.990
TDF6	0.978	0.987	0.994	0.998

Stability study:

Stability study was carried out for optimized patch (F1) formulation at 40 ^{o}C temperature in a humidity chamber having 75 % RH for 3 months. After 3 months samples were withdrawn and evaluated for physicochemical properties and *in-vitro* diffusion study, which shows no change. (Figure 3).

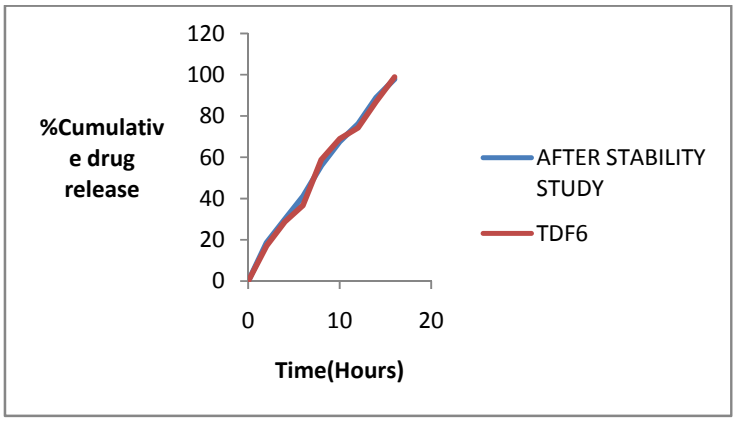

Figure 3: Drug release profile of azelnidipine before and after stability study of formulation TDF6.

CONCLUSION

Based on the results of above studies, it may be concluded that polymers selected were better suited for the development of transdermal delivery system of azelnidipine. The method of preparation of transdermal patches of azelinidipine accessible in this research work is simple. All formulation also exhibit good physicochemical properties like thickness, weight variation, drug content, flatness, folding endurance, moisture content and moisture uptake. The *in-vitro* release data reveal that drug release from the patch formulation have been affected by types of polymer and concentration of polymer. Upshot of penetration enhancer like oleic acid has been checked on *in-vitro* permeation of drug and was found to be effective. The verdict of this result exposed that the problems of azelnidipine on oral administration like dissolution rate limited absorption and gastric side effects can be overcome by applying azelnidipine topically in the form of transdermal patch.

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