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Formulation and Evaluation of Transdermal patch of Antihypertensive Drug

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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 HPMC E5 and Eudragit RL100 by solvent evaporation technique using 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. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, tensile strength, and folding endurance, percentage of moisture content, surface pH and water vapour transmission rate. The thickness ranged between 0.17 ± 0.02 to 0.23 ± 0.01 mm, Excellent uniformity of drug content among the various batches were seen, with all formulations and ranged from 96.3 ± 0.2 % to 98.9 ± 0.4 %. In-vitro drug release studies were performed by using Franz diffusion cell. Among all formulations, the maximum in vitro drug release (70.56 mg) over a period of 10 h was observed in the case of formulation no. F6, The cumulative % of drug permeation in 10 h was found to be in order of F6>F5>F4>F3>F2>F1.***

Keywords: Azelnidipine, Eudragit RL100, Dibutyl phthalate, Transdermal patch

1. Introduction

Transdermal drug delivery systems are devices containing drug of defined surface area that delivers a pre-determined amount of drug to the surface of skin at a pre-defined rate. This system overcomes the disadvantages associated with oral products like first pass hepatic metabolism, reduced bioavailability, dose dumping, drug degradation in gastrointestinal tract due to enzymes, pH etc. In this transdermal delivery system medicated adhesive patches are prepared which deliver therapeutically effective amount of drug across the skin when it placed on skin. Transdermal patches are of different sizes, having more than one ingredient. Once they apply on skin they deliver active ingredients into systemic circulation passing via skin barriers. A patch containing high dose of drug inside which is retained on the skin for prolonged period of time, which get enters into blood flow via diffusion process. Drug can penetrate through skin via three pathways-through hair follicals,through sebaceousglands, through sweat duct.

Azelnidipine, a long-acting dihydropyridine based calcium channel blocker, it is an L-typed calcium channel blocker. Has been recently approved and used for treating ischemic heart disease and cardiac remodelling after myocardial infarction. And reduce blood pressure without increasing the heart rate in patients with hypertension.Azelnidipine, on oral administration, the drug undergoes in 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.

2. Material Method

Material

Azelnidipine was obtained as a gift sample from Glenmark Pharmaceutical Ltd., Sinner, Nashik. Eudragit RL100 (Research lab fine chem industries, Mumbai), HPMC E5 (Research lab fine chem industries, Mumbai),Dibutyl phthalate (Research lab fine chem industries, Mumbai), Propylene Glycol (Research lab fine chem industries, Mumbai), Polyvinyl Alcohol (Research lab fine chem industries, Mumbai), were procured for above study. All other chemicals used were of analytical grade.

Method:

Backing membrane was prepared by casting 5% aqueous solution of PVA followed by drying at 60° C for 6 h. Transdermal patches of Azelnidipine were prepared by using solvent casting method. Polymers were accurately weighed and dissolved in 30 ml of dichloromethane: methanol (3:2) solution and kept aside to form clear solution. Drug was dissolved in the above solution and sonicated in bath sonicator for 15 min. to obtained clear solution. Add 30% w/w propylene glycol as a permeation enhancer &dibutyl phthalatethen stir this solution. The resulted uniform solution was casted on the backing membrane as a plain surface and dried at room temperature for 24 h. An inverted funnel was placed over the petri-dish to prevent fast evaporation of the solvent. The films were cut into small patches (1 cm^2). After 24 h the dried patches were taken out and stored in desiccators for further studies.

Table 1: Composition of Azelnidipine transdermal patch

Ingredient (mg)	Batches						
	F1	F2	F3	F4	F5	F6	F7
API	100	100	100	100	100	100	100
HPMC E5	100	200	300	400	500	600	700
Eudragit RL 100	50	75	100	100	100	100	100
Dibutyl phthalate	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Propylene glycol	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Solvent (ml) Dichloromethane: methanol	(3:2)						

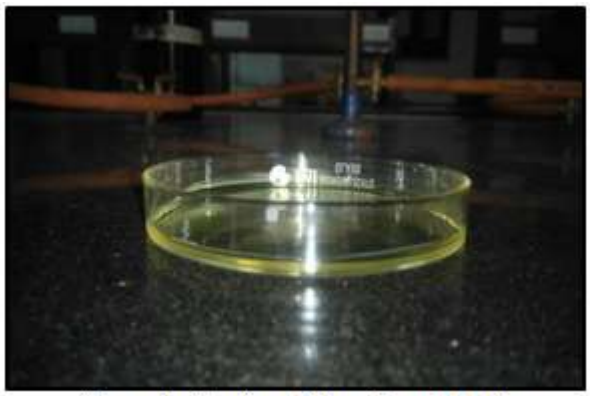

Figure 1: Casting of Transdermal Patch

Figure 2: Transdermal patch of Azelnidipine

2.2 Evaluation Parameter

Weight Uniformity:
A specified area (1 cm^2) of dried patch was cut in different parts of the patch and weighed on digital balance.

Folding Endurance:
A patch of specific area (1 cm^2) was cut accurately and repeatedly folded at the same place till it was broken. The number of times the patch folded at the same place without breaking gave the value of the folding endurance.

Tensile Strength:
The tensile strength of the patch was evaluated by using the tensilometer. It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips were fixed between these cell grips and force was gradually applied till the film broken. The tensile strength was taken from the dial reading in kg/cm.

Thickness:
Patch thickness was measured using digital micrometer screw gauge at three different places and the mean value was calculated.

Surface pH:
Transdermal patches were left to swell for 1 h on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and then poured the solution into the petridish allowed to stand till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen film.

Drug Content:
A specified area of patch (1 cm^2) was mixed with 100 ml phosphate buffer pH 7.4 containing 30% PEG and shaken for 12 h, on magnetic stirrer. Then it was filtered and absorbance of the solution was measured at 255 nm.

Percentage Moisture Content:
The patch was weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the patch was reweighed and the percentage moisture content was determined using below mentioned formula.

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100

Water Vapour Transmission (WVT):
WVT 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 h. The cell was reweighed and the water vapour transmission was determined using below mentioned formula.

$$WVT = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Time X Area}}$$

In-vitro Drug Release Study:
The *in-vitro* diffusion study is carried out using Franz Diffusion Cell. Egg membrane is taken as semi permeable membrane for diffusion. The Franz diffusion cell has receptor compartment with an effective volume approximately 60 ml and effective surface area of permeation 3.14 sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A weighed amount of transdermal patch is placed on one side of membrane. The receptor medium is PBS (pH 7.4). The receptor compartment is surrounded by water jacket to maintain the temperature at 37 ± 0.5˚C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell. During each sampling interval, samples were withdrawn and replaced by equal volumes of fresh receptor fluid on each occasion. The sample withdrawn was analysedspectrophotometrically at 255 nm.

3. Result and Discussion

The prepared transdermal patches were transparent, smooth, uniform and flexible. The prepared Patches were evaluated results obtained are given in table 2.

Table 2: Evaluations Parameters of Different Batches of Transdermal Patch

Parameters	F1	F2	F3	F4	F5	F6	F7
Weight uniformity	194±2.1	198±3.8	203±2.1	208±3.6	211±1.2	213±2.1	216±3.4
Thickness	0.26±0.01	0.25±0.03	0.23±0.05	0.21±0.01	0.20±0.05	0.18±0.01	0.17±0.02
Tensile strength	13.17±2.21	15.55±1.98	14.87±2.35	15.08±1.89	16.22±2.32	15.14±2.21	15.43±2.37
WVTR	3.29±0.55	3.74±0.52	4.34±0.51	4.79±0.53	4.45±0.51	3.89±0.55	3.67±0.48
Moisture content	3.47±0.06	3.78±0.11	3.90±0.08	3.87±0.07	3.78±0.03	4.67±0.06	4.74±0.03
Folding endurance	159.3±5.27	196±7.13	223.6±3.55	255.6±8.7	246.3±3.51	228.3±5.23	238.2±5.64
Surface pH	5.03	5.22	5.47	5.53	5.79	5.84	5.92

The thickness ranged between 0.17±0.02 to 0.23±0.01 mm, which indicates that they are unvarying in thickness. The weights ranged between 194±2.1mg to 216±3.4 mg, which indicates that dissimilar batches patch weights, were reasonably analogous. Folding endurance test results indicated that the patches would not fracture and would sustain their veracity with general skin folding when applied. Tensile strength of the patch range in 13.17±2.21to 15.43±2.37. 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, which could defend the formulations from microbial contamination and reduces bulkiness. All formulations were permeable to water vapor. Surface pH of the formulation was found in ranged between 5.03 to 5.92.

Drug Content:

Excellent uniformity of drug content among the various batches were seen, with all formulations and ranged from 96.3 ± 0.2 % to 98.9 ± 0.4 %. 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.

Table 3: Result of Drug Content of Azelnidipine patch

Batch code	Drug content (%)
F_1	96.3±0.2
F_2	96.5±0.4
F3	97.8±0.5
F4	98.1±0.1
F5	98.0±0.6
F6	98.9±0.4
F7	98.5±0.8

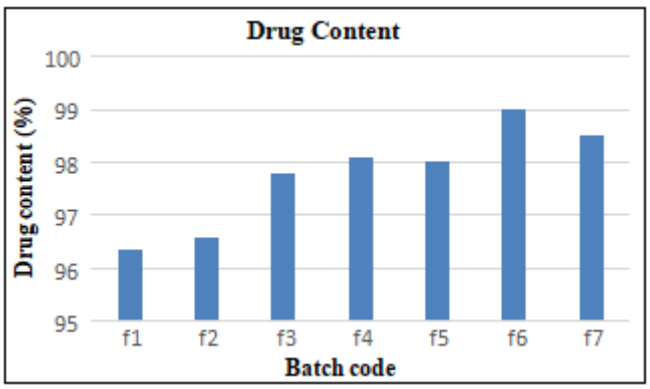

Figure 3: Drug Content of Azelnidipine patch

***In-vitro* Drug Release Study:**

All of these patches slowly released the drug, incorporated and sustained over a period of 10 h. The drug release from patches varied with respect to the polymer composition and nature. An increase in drug release from the patches was found with increasing concentration of polymers that are more hydrophilic in nature.

Table no. 4: *In-Vitro* diffusion studies of various Azelnidipine transdermal patches

Sr. no.	Time (h)	F1	F2	F3	F4	F5	F6	F7
1	0	0	0	0	0	0	0	0
2	0.5	4.58	5.55	6.78	7.98	8.14	4.45	8.65
3	1	6.26	7.56	8.22	9.55	10.45	6.03	15.80
4	2	12.22	14.26	16.25	16.34	17.41	10.06	29.65
5	3	17.56	19.45	21.40	22.14	24.51	18.09	41.23
6	4	22.26	25.16	27.48	29.42	31.26	22.18	54.61
7	5	28.26	30.20	32.55	33.27	35.85	28.37	--
8	6	34.56	36.08	39.21	41.12	43.56	32.60	--
9	7	40.22	43.57	46.79	48.06	50.21	46.90	--
10	8	45.65	49.25	48.24	53.11	55.22	59.28	--
11	9	48.95	49.26	50.21	56.54	58.42	61.72	--
12	10	52.39	54.46	55.98	57.68	64.49	70.56	--

Among all formulations, the maximum in vitro drug release (70.56 mg) over a period of 10 h was observed in the case of formulation F6, on further increase in concentration of HPMC E5 in batch F7 (700 mg) the release of drug occurs rapidly and disintegration of film take place within 6 h. hence, it is concluded that the optimized concentration of polymer is 600 mg that is batch F6. The cumulative % of drug permeation in 10 h was found to be in order of F6>F5>F4>F3>F2>F1. The F4, F5 and F6 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, whereas F1, F2 and F3 shown comparatively low % of drug permeation is observed, because of the lower proportion of ammonium groups in is responsible for slow release of AZP. The increase in proportion of hydrophilic polymer shows more diffusion of drug.

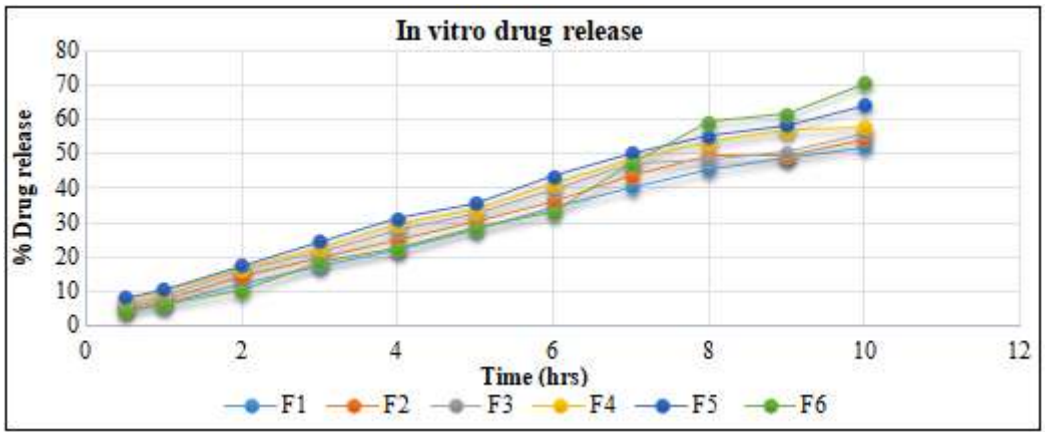

Figure 4: *In vitro* drug release of different formulation

4. Summary and Conclusion

This study was thus, a step towards the goal of preparing the transdermal patch of Azelnidipineby solvent casting method. The drug is antihypertensive which goes under to the hepatic first pass metabolism. To avoid this drawback prepared transdermal dosage form in which drug release directly in to the systemic circulation and give onset of action.

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 azelnidipine accessible in this research work is simple. All formulation also exhibits good physicochemical properties like thickness, weight variation, drug content, folding endurance, surface pH, moisture content and moisture uptake. *In-vitro* drug release studies were performed by using Franz diffusion cell. Diffused drug was quantified by UV-Spectrophotometer at 255nm.

Among all formulations, the maximum in vitro drug release (70.56 mg) over a period of 10 h was observed in the case of formulation no. F6. further increase in concentration of HPMC E5 in batch F7 (700 mg) the release of drug occurs rapidly and disintegration of film take place within 6 h. hence, it is concluded that the optimized concentration of polymer is 600 mg that is batch F6. The cumulative % of drug permeation in 10 h was found to be in order of F6>F5>F4>F3>F2>F1. 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 DBP has been checked on *in-vitro* permeation of drug and was found to be effective.

The all 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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