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FORMULATION AND EVALUATION OF MATRIX TYPE TRANSDERMAL PATCHES OF DILTIAZEM HYDROCHLORIDE

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ABSTRACT

The aim of the present work was to formulate and evaluation matrix type of transdermal patches containing Diltiazem hydrochloride by solvent evaporation method by using tree different polymer ratio. Aluminium foil cup technique was used as a substrate. Dimethyl sulfoxide (DMSO) was used as penetration enhancer and polyethylene glycol (PEG) was used as plasticizer. The physicochemical parameter like thickness, weight variation, % moisture loss, % moisture uptake, folding endurance, flatness, drug content were evaluated. *In vitro* drug release study was carried out by using Franz diffusion cell. Cumulative drug released in 24 hrs from the six formulations were 79.54, 70.81, 68.46, 78.10, 75.89 and 66.45% respectively. On the basis of *in vitro* drug release performance, formulation P1 was fond to be better than other formulations and it was selected as the optimized formulation.

KEYWORDS

Diltiazem hydrochloride, Matrix type of transdermal drug delivery system, Physical evaluation and *In vitro* drug release.

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INTRODUCTON

Recently, oral route of drugs delivery is the most common form. However this system has its oven notable advantage of easy administration, it also has major drawbacks; specifically poor bioavailability due to first pass effect and the tendency to produce rapid both low and high blood level, leading to a need for high and/or frequent dosing, which can be both inconvenient and high-priced. Transdermal drug delivery has advantage over oral route which is first-pass effect[1]. Transdermal system is defined as self-contained, distinct dosage forms which, when applied to the intact skin, delivers the drugs,

through the skin, at a controlled rate to the systemic circulation[2]. The main aim in the development of new transdermal drug delivery devices is to achieve a controlled, expectable, and reproducible release of the drug into the blood stream of the patient[3]. Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically active amount of drug across a patient's skin. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product[4].

Diltiazem is a non-DHP member of the group of drugs known as benzothiazepines, which are coming under the class of calcium channel blockers, used in the treatment of angina pectoris, hypertension, and some types of arrhythmia[5]. It is also an real preventive medication for migraine. It is a class 3 anti-anginal drug, and a class IV antiarrhythmic. Diltiazem acts as an inhibitor of the CYP3A4 enzyme[6]. The biological half-life of Diltiazem is 3-4.5 h make it a suitable candidate for administration by transdermal route[7].

In the present study six formulation were formulated using hydroxy propyl methyl cellulose LV-15, Polyvinylpyrrolidone K-30 and Eudragit L-100 polymer by solvent evaporation method employing aluminium foil as substrate polyethylene glycol 400 (PEG-400) was fused at concentration of 36% W/W of polymer as plasticizer and Dimethylsulfoxide (DMSO) was fused at the concentration of 12% W/W of polymer as penetration enhancer.

MATERIAL AND METHODS
Diltiazem hydrochloride gift sample obtained from Strides shasun Ltd. The other chemical were obtained from authenticated manufactures i.e HPMC LV-15 (Shreeji chemicals, Mumbai), PVP K-30(Loba chemical Ltd., Mumbai), Eudragit L-100 (Rhomghbh and co, India), DMSO (Shreeji chemicals, Mumbai), PEG (Shreeji chemicals, Mumbai).

Preparation of Teransdermal patches
Transdermal patches containing different ratio of HPMC LV-15, PVP K-30, Eudragit L-100, with diltiazem hydrochloride (Table No.1) were prepared by solvent evaporation method in a glass ring. The bottom of the ring was wrapped with aluminium foil by adhesive and placed in a petridish of area 23.75 cm^2. A fixed volume (5ml) of polymeric solution with drug and permeation enhancer, plasticizer was poured on the petridish and an inverted funnel was placed on the petridish to facilitate the evaporation of solvent at a controlled rate over the drying period of 24 h at room temperature. The dried films were removed and cut into 2.009 cm^2 area and kept in a desiccator until used.

EVALUATION OF TRANSDERMAL FILMS
The physical parameters such as thickness, weight variation, % moisture uptake, % moisture loss, folding endurance, flatness, drug content, *in-vitro* drug release were determined.

Thickness
Patch thickness was measured using digital micrometer screw gauge at three different places and the mean value was calculated[8].

Weight Variation
Six films from each batch were weighed individually and the average weight was calculated[9].

Percentage moisture uptake
The films were weighed accurately and placed in the desiccator containing 100ml of the saturated solution of aluminium chloride, which maintains 79.50% RH. After three days the films were taken out and weighed[10].

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

Percentage moisture loss
The film were weighed first and kept in the desiccator having anhydrous calcium chloride, after 3 days, the films were weighed and taken out[11].

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

Folding Endurance
Folding endurance was determined by continually folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking was the folding endurance value[12].

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 every strip was measured and the difference in length because of nonuniformity in flatness was measured by

determining percent constriction, with 0% constriction equivalent to 100% flatness[13,14].

Constriction (%) = $(I_1-I_2)/I_2 \times 100$

Where, I_1 is the initial length of strip and I_2 is the final length of strip.

Drug content uniformity

The patches were tested for the content uniformity. The patches of size 1 cm^2 was cut and placed in a 100 ml volumetric flask. The contents were stirred continuously using a magnetic bead for 24 hrs to dissolve the patches. Consequent dilutions were made with phosphate buffer (pH 7.4). The absorbance of the obtained solution was measured against the corresponding blank solution at 236 nm using UV-visible spectrophotometer. The experiment was repeated three more time to validate the result[15].

***In vitro* drug release studies**

Franz - diffusion cell was used in our studies for *in vitro* drug release. The cell contains of two chambers, the donor and the receptor. The donor compartment is open at the top and is showing to the atmosphere. The receptor compartment is surround contain a water jacket for maintaining the temperature at 37°C ± 2 and is provided with a sampling port. The diffusion medium was pH7.4 buffer, which was stirred with magnetic beads used a magnetic stirrer. A semi-permeable cellophane membrane earlier soaked overnight in 0. 1N HCl was placed between the two chambers. The diffusion media was stirred continuously to prevent the formation of concentrated drug solution just below the membrane. Samples from the receptor compartment were taken at different intervals of time over a period of 24 hours and the concentration of the drug was determined by UV Spectrophotometric method using the standard curve. Amount of drug diffused at several time intervals was calculated and plotted against time[15].

RESULTS AND DISCUSSION

Transdermal patches of Diltiazem hydrochloride were developed by solvent evaporation technique using aluminium foil as a substrate. Different formulation of HPMC LV-15/PVP K-30 and HPMC LV-15/E L-100 were developed containing Diltiazem hydrochloride to prefer the optimum drug release through the most suitable choice of polymer blend of HPMC LV-15/PVP K-30 and HPMC LV-15/E L-100 between the formulation studies.

The prepared transdermal patches were uniform, transparent, smooth and flexible. The thickness of the patches was varied from 0.053±0.0036mm to 0.034±0.0032mm. Low standard deviation values in the film thickness measurement ensured uniformity of the patches developed by solvent evaporation technique. The films developed by HPMC LV-15/PVP K-30 were relatively more transparent and flexible than HPMC LV-15/E L-100. The weights of the patches were between 51.5±1.11mg to 50.2±0.97mg. % moisture uptake found to be between 7.213±0.008 to 4.556±0.006, % moisture uptake found to be between 4.456±0.009 to 2.787±0.005. The result revealed that the moisture uptake/moisture loss was found to increasing with increasing concentration of hydrophilic polymer. The slight moisture uptake protects the material from microbial contamination and bulkiness of the patches. The lesser moisture loss in the formulation helps the films to remain stable, brittle and free from complete drying. Folding endurance was found to be >200. Flatness of the patches was between 100.02±0.003 to 99.98±0.003. The drug content was found to be 99.35±0.45 to96.15±0.23. The percentage cumulative drug release in 24 hrs was found to be the highest (79.54±0.61) from formulation P1 carrying HPMC LV 15 and PVP K-30 in ratio 9:1 (Table No.1, Figure No.1) and minimum (66.45±0.59) from formulation E3 carrying HPMC LV 15 and EL-100 in ratio 7:3 (Figure No.1). The drug release was found to increase on increasing in concentration of hydrophilic polymers in the polymer matrix (Figure No.1). This is due to the fact that dissolution of aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to decrease the mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate.

Table No.1: Composition of transdermal patches

S.No	Formulation code	Polymer ratio			PEG-400 (% 0f polymer wt)	Drug (% 0f polymer wt)	DMSO (% 0f polymer wt)	Solvent
		HPMC LV 15	PVP K-30	EL-100				
1	P1	9	1	---	36%	20%	12%	chloroform: methanol(1:1)
2	P2	8	2	---	36%	20%	12%	chloroform: methanol(1:1)
3	P3	7	3	---	36%	20%	12%	chloroform: methanol(1:1)
4	E1	9	---	1	36%	20%	12%	chloroform: methanol(1:1)
5	E2	8	---	2	36%	20%	12%	chloroform: methanol(1:1)
6	E3	7	---	3	36%	20%	12%	chloroform: methanol(1:1)

Area of the patch =23.75cm2
Amount of drug incorporated =50mg
Weight of polymer =250mg

Table No.2: Physical characterization of transdermal patches

S.No	Formulation code	Thickness (mm)±SD	Weight variation(mg) ±SD	%moisture uptake ±SD	%moisture loss ±SD
1	P1	0.053±0.0036	50.2±0.97	7.151±0.005	4.456±0.009
2	P2	0.042±0.0025	50.8±0.96	7.213±0.008	3.968±0.006
3	P3	0.037±0.0031	51.3±0.75	6.145±0.007	3.772±0.001
4	E1	0.048±0.0035	51.1±0.99	5.872±0.004	3.778±0.008
5	E2	0.034±0.0032	50.8±1.06	4.556±0.006	3.685±0.003
6	E3	0.039±0.0022	51.5±1.11	4.989±0.006	2.787±0.005

Table No.3: Physical characterization of transdermal patches

S.No	Formulation code	Folding endurance	Flatness (%)±SD	Drug content mg ±SD	%CDR
1	P1	>200	100.00±0.001	99.35±0.45	79.54±0.61
2	P2	>200	100.02±0.003	98.89±0.55	70.81±0.68
3	P3	>200	99.99±0.001	96.15±0.23	68.46±0.74
4	E1	>200	100.01±0.002	99.04±0.44	78.10±0.85
5	E2	>200	99.98±0.003	97.88±0.36	75.89±0.66
6	E3	>200	100.00±0.001	96.25±0.33	66.45±0.59

Table No.4: Kinetic model for in vitro drug release

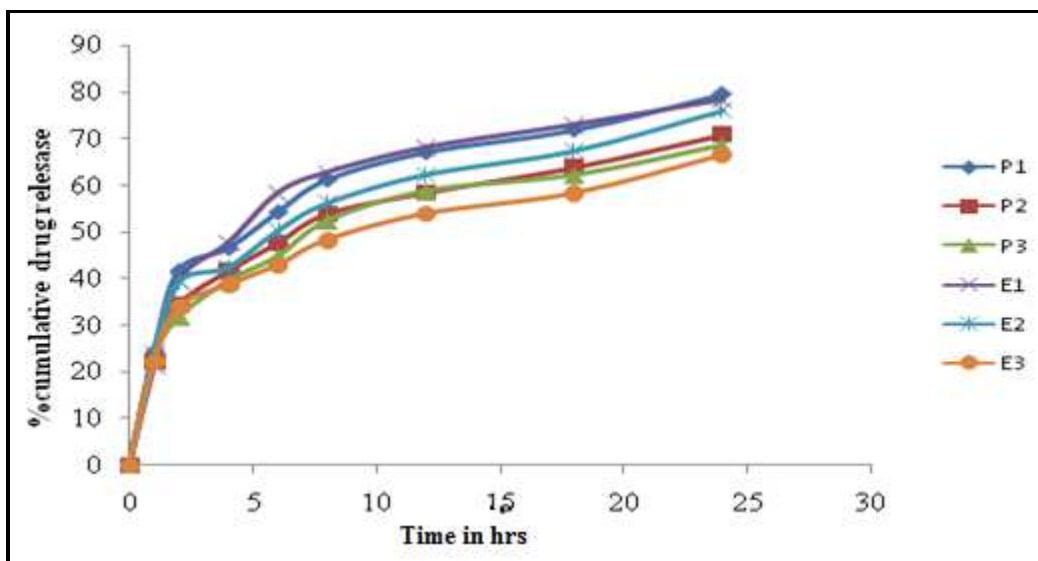| S.No	Formulation code	Zero order	First order	Higuchi matrix	Peppas plot	'n' value	Best fit model
1	P1	0.7183	0.8979	0.9256	0.5046	0.8226	HIGUCHI
2	P2	0.8550	0.8802	0.9382	0.5157	0.8058	HIGUCHI
3	P3	0.7632	0.8955	0.9519	0.5199	0.8036	HIGUCHI
4	E1	0.7142	0.796	0.8945	0.5366	0.8597	HIGUCHI
5	E2	0.7406	0.8996	0.9365	0.5047	0.8079	HIGUCHI
6	E3	0.753	0.8739	0.9357	0.5002	0.7766	HIGUCHI

Figure No.1: Cumulative drug release profile

CONCLUSION

Matrix type transdermal patch of Diltiazem hydrochloride was successfully formulated using solvent evaporation method. The transdermal films were uniform thickness, smooth, flexible and content of drug. It can be concluded from the above study that formulation P1 was found to be better as compared to other formulation on the basis of evaluation and *in vitro* release profile. It shows that Diltiazem hydrochloride could be administered transdermally.

ACKWOLEDGEMENT

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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