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Formulation Design and Evaluation of Transdermal Film of Losartan Potassium Using Hydrophilic and Hydrophobic Polymers

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ABSTRACT

The purpose of this research work was to develop and evaluate matrix-type transdermal therapeutic system containing Losartan potassium (LP) with different ratios of hydrophilic and hydrophobic polymeric combinations. Formulations were prepared by using solvent evaporation technique. Matrix type transdermal film of Losartan Potassium, antihypertensive drug were prepared using different polymers like Ethyl Cellulose, Hydroxy Propyl Methyl Cellulose and Eudragit RL100 in varied ratios. The present study aims to formulate and evaluate Transdermal film for sustained release of Losartan potassium. The results suggested no physicochemical incompatibility between the drug and the polymers. All formulations carried dimethyl sulfoxide as penetration enhancer and propylene glycol as plasticizer in chloroform and ethanol as solvent system. The diffusion studies were performed by using modified Franz diffusion cells. The formulation, F1 with combination of polymers (4:1) emerging to be ideal formulations for Losartan potassium. The developed transdermal films increase the efficacy of for the therapy of hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. Physicochemical parameters were characterized. The permeability study indicates that the drug is suitable for Transdermal drug delivery. The film were evaluated for various parameters like Thickness, Water-Vapour permeability, Tensile Strength, moisture loss, moisture uptake, film folding endurance, Drug Content, flatness, surface pH, swellability, % elongation, skin irritation and Diffusion studies. The films were further evaluated by DSC to ensure uniform distribution of the drug and compatibility of drug with polymer. The Optimized formulation containing HPMC: Eudragit RL100 (4:1), with enhancer DMSO showed 87.13% drug release after 24 hours.

Keywords: Ethyl cellulose; Eudragit RL100, HPMC; Losartan potassium

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INTRODUCTION

Losartan potassium (2-butyl-4 chloro-1 (2-(1H tetrazol-5yl) (1, 1' biphenyl- 4 yl) methyl)-1H-imidazole-5-methanol) ¹ is the first angiotensin receptor antagonist which is extensively used for treatment of hypertension². However, the drug is subjected to high degree of hepatic metabolism, and meal has also effects on its absorption. Transdermal patches provide an alternate route of drug delivery avoiding the hepatic first pass effect ³. It also improves patient compliance and confirms the safety and efficacy of the drug ⁴. Losartan potassium (LP) is the drug of choice for sustained release formulation since it has a low terminal elimination half life of about 1.5 to 2 h, which requires frequent dosing necessary to maintain the therapeutic blood level for long term treatment. LP shows considerable first pass metabolism in the liver and thereby has poor bioavailability (25-35%) when administered orally. Molecular weight (422.91) of LP again indicates its suitability for administration by the transdermal route. LP containing transdermal films were prepared using two combinations of the three polymers namely Ethyl cellulose (EC) with Eudragit RL 100 and ethyl cellulose with hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl methyl cellulose (HPMC) and Eudragit RL 100 in different proportions by solvent evaporation technique. Propylene glycol (30% w/w) was added as plasticizer. The physicochemical parameters like moisture content, moisture uptake, thickness, film folding endurance, tensile strength, skin irritation and surface morphology were studied. For all the formulations, skin permeation of the drug through cellophane membrane was studied using Keshary Chien (KC) diffusion cell ⁵. Transdermal drug delivery systems are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a tissue. In response to these advances, several Transdermal drug delivery systems have been developed to achieve the objective of systemic medication through application on the intact skin surface. The advantage of Transdermal drug delivery system is that they can provide sustained drug delivery and enhance constant drug concentrations in plasma over a prolonged period of time. Thus it is anticipated that Transdermal drug delivery systems can be designed to deliver drugs at appropriate rates to maintain suitable plasma–drug levels for therapeutic efficiency, without the periodic into plasma concentration that would accompany toxicity or lack of efficiency. Ultimately the success of all Transdermal systems depends on the ability of the drug to permeate skin in sufficient quantities to achieve its desirable therapeutic effects ⁶.

MATERIAL AND METHODS

Losartan potassium was obtained as a gift from the Macloed pharmaceuticals, Mumbai, INDIA. Eudragit (Eu) RL100, Ethyl cellulose and Hydroxy propyl methyl cellulose were from Glenmark Pharmaceutical Ltd, Nashik. Rat used were from Animal house of Amrutvahini College of pharmacy, sangamner, India and used as per the institutional guidelines. All other reagents were HPLC grades.

Drug partition coefficient ⁷:

The partition coefficient studies were performed using n-octanol as the non aqueous phase and water as the aqueous phase. The two phases were mixed in equal quantities and kept for saturation with each other on a water bath at 37°C for 24 hours with occasional shaking. The saturated phases were separated by centrifugation at 2500 RPM. The standard curves of the drug were plotted from both water and n-octanol. Equal volume (10ml) of two phases was placed in six conical flasks, and 100 mg of drug was added to each flask. The flasks were shaken at 37°C for 5 hours to achieve complete partitioning at 100 RPM. The two phases were separated by centrifugation at 1000 RPM for 5 minutes and the solution was passed through membrane filter and the filtrate was analyzed for drug content using spectrophotometrically λ_{max} of Losartan 204 nm.

Drug –excipient compatibility studies ⁸:

In the preparation of film formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug –polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between losartan and the selected polymer. The pure drug and drug with excipients were scanned separately .potassium bromide was mixed with drug and polymer and the spectra were taken. FT-IR spectrum of LP was compared with FT-IR spectra of LP with polymer .Disappearance of losartan peaks or shifting of peak in any of the spectra was studied .

Preparation of model patches

Solvent evaporation technique was followed for preparation of film. A 5% w/v solution of polymer Eudragit RL100, HPMC, Ethyl cellulose was prepared in the different ratio using ethanol as solvent. Propylene glycol (30% w/w) was incorporated as plasticizer. The drug was dissolved in solvent. DMSO (15 % w/v) was separately dissolved in ethanol and added gradually to the mixture of drug and polymer with constant stirring and the resulting mixture was

used as treatment formulation. Respective solutions were then poured into Petri plate. The formulation was shown in **Table 1**.

Table 1 Composition of transdermal films containing Losartan (dose decide as per the literature review area of plate is 61.44 cm²)

Formu. code	Drug (mg)	Polymer(%w/w)			Ethanol + chloroform (ml)	Plasticizer (%)	Penetration Enhancer (%)
		HPMC	Eudragit RL 100	EC			
F1	30	0.4	0.1	-	15	30	15
F2	30	0.1	0.4	-	"	"	"
F3	30	0.4	-	0.1	"	"	"
F4	30	0.1	-	0.4	"	"	"
F5	30	-	0.4	0.1	"	"	"
F6	30	-	0.1	0.4	"	"	"

Evaluation

Physical appearance ⁹:

All the prepared films were visually inspected for colour, clarity, flexibility and smoothness.

Thickness¹⁰

The thickness of the films was determined by measuring the thickness at random sites on the formulated films using micrometer screw gauge and the average thickness was determined.

Folding endurance ¹⁰:

Folding endurance of the film was determined by repeatedly folding a small strip of film (2cm x 2cm) at the same place till it broke. The number of times, the film could be folded at the same place without breaking, gave the value of folding endurance.

Tensile strength ¹⁰:

A small film strip (40 x 15 mm) was used. One end of the strip was fixed between adhesive tapes to give support to the film when placed in the film holder. Another end of the film was fixed between the adhesive tapes with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hook was inserted. A thread was tied to this hook, passed over the pulley and a small pin attached to the other end to hold the weights. A small pointer was attached to the thread, which travels over the graph paper affixed on the base plate. To determine the tensile strength; the film was pulled by means of a pulley system.

Percentage moisture absorption ¹¹:

The films were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of potassium chloride, which maintains 80-90% RH. The final weight was noted when

there was no change in the weight of individual patch. The study was performed at room temperature. The percentage moisture absorption was calculated using the formula .

$$\text{Percentage moisture absorption} = \frac{(\text{Final weight} - \text{initial weight}) \times 100}{\text{Initial weight}}$$

Percentage moisture loss¹¹:

The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. The final weight was noted when there was no change in the weight of individual patch. The moisture loss was calculated using the formula.

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

Water vapour transmission rate¹²:

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride was taken in the vials and the polymer films of 1 cm were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 hrs. The vials were removed and weighed at 24 hrs time intervals to note down the weight gain.

Swellability¹³:

The film of 3.14 cm² was weighed and put in a petridish containing 10ml of double distilled water and were allowed to imbibe. Increase in weight of the film was determined at preset time intervals; until a constant weight was observed. The degree of swelling (% S) was calculated using the formula

$$S (\%) = \frac{W_t - W_o}{W_o} \times 100$$

Where S is percent swelling, W_t is the weight of patch at time **t** and W_o is the weight of patch at time zero.

Surface pH¹³:

Surface pH of the film was determined by the method described by Bottenberg et al. The films were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1 hour in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the film and allowing it to equilibrate for 1 minute.

Flatness¹⁴:

Three longitudinal strips were cut out from each film: 1 from the centre, 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.

Drug content¹⁵:

A 5-cm² film was cut into small pieces, put into a 100-ml buffer (pH 7.4), and shaken continuously for 24 hours. The whole solution was ultrasonicated for 15 minutes. After filtration, the drug was estimated spectrofluorometrically at wavelength of 248 nm.

In-vitro permeation studies^{16,17}:

Films of 3 sq. cm were subjected to an in vitro permeation studies by using Franz diffusion cell containing cellophane membrane. The film was placed in a donor compartment over the membrane. The temperature of the receptor compartment was maintained at 37 ±2°C throughout the experiment. The compartment was in contact with the ambient environment. The amount the drug permeated through membrane was determined by withdrawing 1ml of sample at predetermined time interval and replacing them with an equal volume of buffer. The withdrawal samples filtered by membrane and the samples were analyzed spectrophotometrically

Skin irritation study^{18,19}

The films were tested for their potential to cause skin irritation in rats. The rats were shaved carefully avoiding peripheral damage and the films were applied onto the nude skin using an adhesive. The rats were divided into five groups. On the previous day of the experiment, the hair on the back side area of rat was removed. The animals of group I was served as normal without any treatment. One group of animals (Group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8 % v/v aqueous solution of formalin was applied as a standard irritant (Group V). (Figure 1)

Table 2 Draize scoring method

Sr.no.	Skin Reaction		Score Assigned
	Erythema and Eschar Formation	Edema formation	
1	No erythema	No erythema	0
2	Very slight erythema	Very slight erythema	1
3	Well defined erythema	Slight edema	2
4	Moderate to severe erythema	Moderate edema	3
5	Severe erythema	Severe edema	4

The animals were applied with new film/formalin solution each day upto 7 days and finally the application sites were graded according to a scoring scale always by the same investigator (Table 2). Ethical clearance for the handling of experimental animals was obtained from the institutional animal Ethical committee (IAEC) formed for this purpose.

Stability studies ²⁰

Optimized medicated film was subjected to short term stability testing. Films were placed in a glass beaker lined with aluminium foil and kept in humidity chamber maintained at $40\pm 2^{\circ}\text{C}$ and $75\pm 5\%$ RH for 1 month as per ICH guideline. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week. The data presented were the mean of three determinations.

RESULTS AND DISCUSSION

n-Octanol and in vitro study fluid (here phosphate buffer, pH 7.4) are considered to be the standard system for determining the drug partition coefficient between skin and in vitro fluid. The logarithmic value of the partition coefficient ($\log P$) was found to be 4.02. The results obtained indicate that the drug possesses sufficient lipophilicity, which meets the requirements of formulating it into a transdermal patch. In the present study, transdermal patches of Losartan were formulated using the hydrophilic polymer matrix of hydroxyl propyl methyl cellulose and the effect of Eudragit RL100 and Ethyl cellulose as rate-controlling membrane was studied. The prepared patches were characterized for physicochemical properties, in vitro permeation profile and skin irritation studies in rats. (Figure 1)



a) Application of standard irritant formalin



b) Application of films containing drug



c) After removal of transdermal film.

Figure 1: Photographs of skin irritation test

Skin Irritation Scores Following Transdermal film Administration was shown in **Table 3** The physicochemical properties of Losartan transdermal patches are presented in **Table 4 and 5** The thickness of patches varied from 0.09 ± 0.01 to 0.18 ± 0.0 mm. folding endurance measures the ability of patch to withstand rupture; folding endurance was in the range of 180 ± 7.4 to 270 ± 2.3 ; patch T-1 representing the least value. The patch formulated with HPMC alone showed maximum WVT of 6.88 gm/ cm which can be attributed to the hydrophilic nature of the polymer. The casting of the HPMC-drug reservoir with the rate-controlling membrane of Eudragit RL100 decreased the values of the water vapour transmission rate. Drug content was between 93.12-99.20% per patch. The drug content analysis of the prepared formulations has shown that the process employed to prepare patches in this study was capable of giving films with a uniform drug content and minimum batch variability. Release of the drug from transdermal patches is controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane. In vitro permeation studies are predictive of in vivo performance of a drug% cumulative drug permeation profile. Was shown in **Figure 2**: In this study, different formulations released variable amounts of LP through cellophane membrane. The drug content after stability study of formulation F3 (**Table 6**) was 95.82%

Table . 3. Skin Irritation Scores Following Transdermal film Administration

Rat No	Control		F3		F6		Formalin	
	Erythema*	Edema	Erythema*	Edema	Erythema*	Edema	Erythema*	Edema
1	0	0	0	1	2	0	2	2
2	0	0	1	0	0	0	3	1
3	0	0	1	0	1	1	3	2
4	0	0	2	1	1	0	2	3
5	0	0	1	0	2	1	3	3
6	0	0	2	0	2	2	3	2
Ave.	0	0	± 0.3073	$\ddagger 0.2108$	$\ddagger 0.3333$	$\ddagger 0.3333$	$\ddagger 0.2108$	± 0.3073

Erythema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, scar formation.

†Edema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, severe.

‡Significant compared with formalin.

Table.4 Physicochemical parameters of transdermal films of Losartan

Formulati on code	Thickness (mm)	Tensile strength (kg/ mm ²)	Folding Endurance	Surface pH	Swellability (%)
F1	0.18 ± 0.012	0.473 ± 0.0036	272 ± 4.34	5.5 ± 0.14	38.59 ± 0.61
F2	0.17 ± 0.011	0.463 ± 0.0045	265 ± 3.11	5.6 ± 0.12	34.59 ± 0.61
F3	0.16 ± 0.014	0.449 ± 0.0057	259 ± 5.23	5.7 ± 0.13	32.87 ± 0.46
F4	0.15 ± 0.012	0.435 ± 0.0069	248 ± 3.88	5.8 ± 0.10	30.13 ± 0.55
F5	0.12 ± 0.014	0.386 ± 0.0055	198 ± 2.88	5.5 ± 0.14	18.32 ± 0.39
F6	0.11 ± 0.012	0.377 ± 0.0072	191 ± 3.74	5.2 ± 0.11	16.97 ± 0.43

Table 5 Physicochemical parameter of transdermal films of Losartan (not optimized only trials taken in this f3 shows best result)

Formulation code	Water vapour transmission (gm /cm ² / 24h)	Flatness (%)	Drug Content (%)	Moisture uptake (%)	Moisture Loss (%)	%CDR
F1	6.88*10 ⁻⁴	100	98.92	14.69	2.79	87.13
F2	6.53*10 ⁻⁴	100	96.90	13.45	2.71	77.32
F3	6.36*10 ⁻⁴	100	95.82	12.20	2.65	74.12
F4	6.25*10 ⁻⁴	100	99.32	11.55	2.54	72.52
F5	5.19*10 ⁻⁴	100	97.71	11.98	2.18	70.58
F6	4.93*10 ⁻⁴	100	96.62	10.88	2.16	68.12

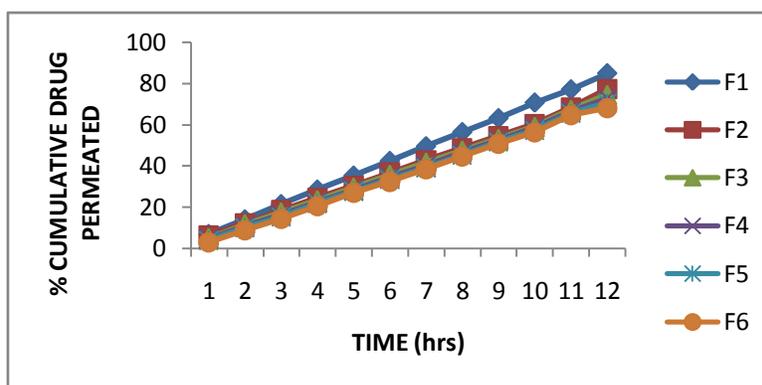


Figure 2: % cumulative drug permeation profile

Table 6: Result of stability study of formulation F3

Formulation code	Physical appearance	Drug content
F3	Flexible ,homogenous	95.82%

CONCLUSION

The prepared transdermal drug delivery system of Losartan potassium using different ratios of polymers such as EC and PVP had shown good promising results for all the evaluated parameters. Based on the *In vitro* drug release and drug content result, formulation F1 was concluded as an optimized formulation, which shows its higher percentage of drug release.

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