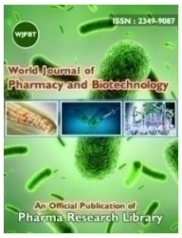

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Formulation and Characterization of Transdermal Drug Delivery System of Losartan Potassium

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A b s t r a c t
The aim of present work is to fabricate and characterize the transdermal patches of Losartan potassium by using HPMC K 100, Carbopol 934 and Eudragit RL 100 as a polymers with following objectives such as design and evaluated results of present investigation revealed that, Suitable analytical method based on UV-Visible spectrophotometer was developed for Losartan Potassium λ_{max} of 205 nm was identified in phosphate buffer, pH 7.4. All the excipients used did not interfere with the estimation of Losartan Potassium at analytical wavelength 205 nm respectively. Transdermal patches of Losartan Potassium were successfully prepared using HPMC K100, Eudragit RL100 and Carbopol 934 as polymers by Solvent casting Technique. The formulation L8 (2% HPMC, 1% CP) has shown optimum and high percentage of drug release (99.21%) in concentration independent manner. Hence, transdermal patch of Losartan Potassium could be promising drug delivery as they minimize the dose, overcome the side effects, simplify treatment regimen and improve patient compliance. The present investigation is worthy of further research, especially in terms of performance in pharmacokinetics**,** *In-vivo* studies on higher animals and controlled clinical studies on human beings.

Keywords: Transdermal patches, HPMC K 100, Carbopol 934, Eudragit RL 100.

A r t i c l e I n f o

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C o n t e n t s

1. Introduction

Transdermal drug delivery system is defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation.[1] Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth. Patients often forget to take their medicine, and even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day.[2] Some of the oral medications have an adverse effect on the gastrointestinal system; some make the patient feel drowsy, nauseated, and dizzy. The solution to get over all the side effects might not be available, but there are surely ways and means to reduce them. One way is use of transdermal drug delivery patches that target only the area that needs to be treated. [3] Oral Losartan potassium has a short elimination half-life (1.5-2 hrs), low bioavailability (35%) under goes high first pass metabolism and frequent high doses (100 mg two divided doses for 24hrs) are required to maintain the therapeutic level as a result, dose development toxic side effects are

frequently observed. To avoid serious toxic effects resulting from oral administration, the use of transdermal approach for Losartan potassium delivery has been proposed. [4] The aim of present work is to fabricate and characterize the transdermal patches of Losartan potassium by using HPMC K 100, Carbopol 934 and Eudragit RL 100 as polymers.

2. Material and Methods

Materials

Losartan potassium, Eudragit RL100 (Hetero Drugs Ltd.), HPMC k 100, Propylene glycol, Glycerine, Ethanol (Drugs India, Hyderabad), Carbopol S 930 (Hi media laboratories Pvt. Ltd, Mumbai).

Fabrication of Losartan potassium incorporated TDDS patch:

TDDS composed of different polymers containing Losartan potassium were prepared by Solvent Casting technique. Firstly, drugs were dissolved in water. Base materials were added into the solution and swelled in ambient temperature. Permeation enhancers and plasticizer were added to the solution, and then agitated in a sonicator. The homogenous semisolid mixture was casted on a glass surface; it was covered by funnel for controlled evaporation of solvent and allowed to dry at room temperature overnight. After being dried, the single-layer patch was obtained. The films were separated and the backing membrane used was aluminum foil. The formulations were stored in desiccators until used for further study. [5] The Composition of transdermal patches using Losartan potassium used in present work was given in Table 1.

Drug – polymer compatibiltiy studies:

One of the requirements for the selection of suitable excipient (or) carrier for pharmaceutical formulations is its compatibility. Therefore in the present work, a study was carried out using FTIR to confirm the absence of any possible chemical interaction between the Drug (Losartan potassium) and Polymer namely hydroxy propyl methyl cellulose K100, Eudragit Rl 100 and Carbopol 930. The pure drug Losartan potassium and a mixture of it with the polymers, Eudragit, CP and HPMC were mixed separately with IR grade KBr in the ratio of 100:1 and corresponding pellets were prepared by applying 5.5 metric ton of pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000–400 cm^{-1}. The resultant spectra were then compared with Original Spectra and observe for any type of deviation from the original spectra.[6] IR Spectra for Pure Losartan potassium, and combination of polymers and Drug were represented in Fig No.1 and 2.

Evaluation of Transdermal Patches

The physicochemical evaluation of Transdermal patch of Losartan potassium was done by using the following evaluation methods.

Thickness, Weight Variation and Drug Content

The thickness of the patch at three different points was determined using thickness gauge and the patches were then weighed individually using digital balance to determine the weight of each patch taken out from the casted film. The patches were subjected to weight variation by individually weighing ten randomly selected patches. Such determinations were carried out for each formulation. Films of specified area were cut and weighed accurately. Pieces were taken into a 100 ml volumetric flask containing phosphate buffer (pH 7.4), and the flask was sonicated for 8 h. A blank was prepared in the same manner using a drug-free placebo patch of same dimensions. The solution was then filtered using a 0.45-µm filter and the concentration is found in respective nm. [7] The values of Thickness, Weight Variation and Drug Content of all Formulations were given in Table 2.

Folding endurance test

Folding endurance test was carried out by folding the patch at the same point a number of times till it broke. The test was carried out to check the efficiency of the plasticizer and the strength of the film prepared using varying ratios of the polymers. The test was carried out in triplicate. [8] The values of folding endurance of all Formulations were given in Table 2.

Percentage Moisture Uptake

Accurately weighed films of each formulation were kept in a desiccator which is maintained at 79.5% relative humidity (saturated solution of aluminium chloride) at room temperature and weighed after 3 days. The test was carried out in triplicate. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. The Values of Percentage Moisture Uptake of all Formulations were given in Table 2.

Percentage Moisture Loss

Accurately weighed films of each formulation were kept in a desiccator and exposed to an atmosphere of 98% relative humidity (containing anhydrous calcium chloride) at room temperature and weighed after 3 days. The test was carried out in triplicate. The percentage of moisture loss was calculated as the difference between initial and final weight with respect to initial weight. [9] The Values of % Moisture losses of all Formulations were given in Table 2.

In-Vitro Drug Release Studies

Freshly treated commercial semi permeable membrane was employed in this study. The membranes used were transparent and regenerated cellulose type, which were permeable to low molecular weight substances. The semi permeable membrane was tied to the open end cylinder which acted as donor compartment. The entire surface of the membrane was in contact with the receptor compartment containing 100 ml of pH 7.4 buffer. The content of the receptor compartment was agitated by a magnetic stirrer at 45 rpm. A transdermal patch of 5 cm in diameter was placed over the membrane which in turn placed over the donor compartment. Samples of 1ml were withdrawn from receptor compartment for every hour and replaced by equal volumes of fresh receptor medium. The concentration of Losartan potassium permeated was determined spectrophotometrically at 205nm after suitable dilution against blank of Phosphate buffer pH 7.4 by U.V spectrophotometer. The release profiles for all Formulations (L1-L9) were given in Fig. 4 and diffusion release data for all formulations are given Table 3. [10]

Stability Studies

Prepared patches were kept in refrigerator, stability chamber and incubator for maintaining the temperature of 4 ^{0}C, 40 ^{0}C and 60 ^{0}C respectively. Accelerated stability

testing of formulation L8 (HPMC 2% and 1% carbopol) was conducted for 30 days at different temperature condition like 4 ^{0}C, 40 ^{0}C and 60 ^{0}C. At specific interval of time 0, 10, 20, 30 day the patches were taken out to assay their drug content, Physical appearance and texture. The Values of stability studies drug release of the Formulation L8 was given Table 4. [11]

Table 1: Composition of Transdermal Patches using Losartan potassium

Formulation Code	Losartan potassium(mg)	HPMC K100 (%)	EUDRAGIT RL 100(%)	CARBOPOL 930(%)	Propylene glycol (ml)
L1	50	1	1	-	0.5
L2	50	-	1	1	0.5
L3	50	1	-	1	0.5
L4	50	2	1	-	0.5
L5	50	1	2	-	0.5
L6	50	-	2	1	0.5
L7	50	-	1	2	0.5
L8	50	2	-	1	0.5
L9	50	1	-	2	0.5

3. Results and Discussion

Drug – Polymer Compatibility Studies

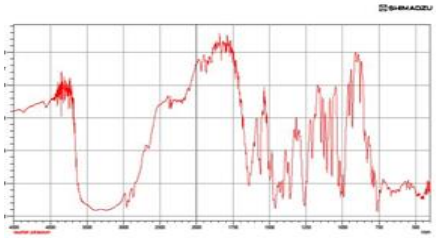

Fig No.1: FTIR Spectra of Losartan potassium

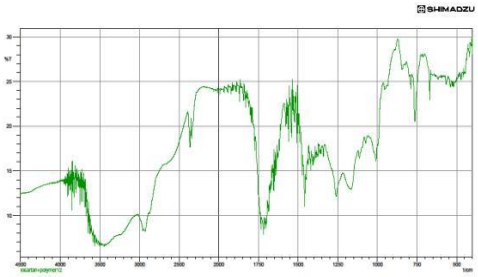

Fig No.2: FTIR spectra of Losartan potassium with polymers like HPMC 100, CP 934 and EUDRAGIT RL 100

The physicochemical compatibility of the drugs and the polymer was established through FTIR studies. IR spectral analysis of Losartan potassium showed the peaks at wave numbers of 2950 cm^{-1}(Carboxylic OH group –OH-stretching), 2830 cm^{-1}(Alkane CH stretching), 1650 cm^{-1}(C=C stretching in Aromatic ring), 1450 cm^{-1}(Aromatic C-C stretching), 1250 cm^{-1} (C-C stretching, alkyl halide), 1000 cm^{-1} (May be C-O stretching), 750 cm^{-1} (C-H bending in Aromatic ring), 900 (NH bending in amines)confirming the purity of drug with standard respectively.

In the physical mixture of Losartan potassium with Hydroxy propyl methyl cellulose, Carbopol and Eudragit were 3500 cm^{-1}(O-H stretching), 2900 cm^{-1}(May be CH stretching, C-H stretching), 1700cm^{-1} (C=C stretching in Aromatic ring), 1400 cm^{-1}(Aromatic C-C stretching), 1260 cm^{-1}(CH bending in Alkyl halide), 750 cm^{-1}(CH bending in Aromatic ring) wave numbers. However additional peaks were absorbed in physical mixtures which could be due to presence of polymers and indicated that there was no chemical interaction between Losartan potassium and other excipients.

Standard Curve

Losartan potassium was scanned in the UV wavelength region of 200-400nm, for maximum absorption. The λ_{max} was found to be 205nm respectively. A linear relationship was observed within the concentration values in the range of 2-20 µg/ml.

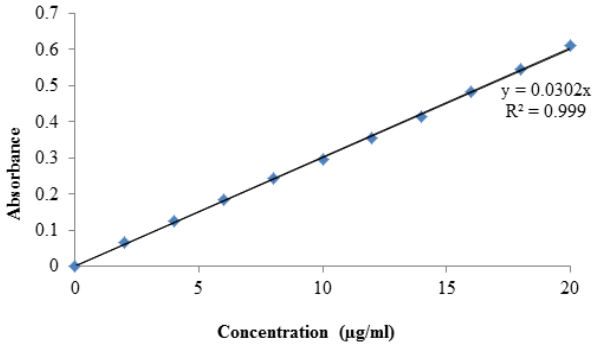

Fig No.3: Standard Curve of Losartan Potassium

Table 2: Physico Chemical Evaluation of Transdermal Films containing Losartan potassium

Formulation Code	Thickness (mm) ± SD	Folding endurance ± SD	%Moisture uptake ±SD	%Moisture loss ±SD	% Drug content	Weight variation± SD
L1	0.30 ±0.01	251± 1.0	6.4±0.012	6.5±0.013	99.22	228± 0.68
L2	0.35± 0.04	230 ±2.0	5.3±0.015	7.1±0.01	98.52	235± 0.53
L3	0.32 ±0.02	253± 2.0	7.2±0.024	5.3±0.018	99.12	242± 0.42
L4	0.42± 0.04	286± 2.0	11.2± 0.01	5.8±0.021	98.65	321± 0.52

L5	0.45 ±0.03	270 ±1.0	8.1±0.035	7.2±0.03	97.85	285± 0.12
L6	0.47 ±0.01	220 ±1.0	6.5±0.013	7.8±0.05	99.52	316± 0.38
L7	0.44 ±0.04	246 ±1.0	10.4± 0.01	6.4±0.016	98.64	328± 0.28
L8	0.41 ±0.02	272± 2.0	12.2± 0.02	5.1±0.014	99.35	332± 0.18
L9	0.43± 0.03	262± 1.0	11.6± 0.05	4.6±0.016	99.46	326± 0.36

n=3

The thickness of the patches varied from 0.30 ± 0.01 to 0.47 ± 0.01. The drug content analysis and the weight uniformity of the prepared formulation have shown that the process adopted for casting the films in this investigation is capable of giving films with uniform drug content and with minimum intra batch variability. Folding endurance values of matrix films was found within 230±2.0 to 286±2.0 no of folds, indicating good strength and elasticity. Folding endurance test results indicated that the patches would maintain the integrity with general skin folding when applied. The percentage Moisture uptake in the formulation L8 (2% HPMC, 1% CP) has shown the highest value of moisture absorption 12.2±0.02. This may be due to the presence of high hydrophilicity of HPMC and CP. The formulation L6 (2%eudragit RL 100, 1% CP) shows higher value of Moisture loss 7.8±0.05which is due to presence of higher concentration of EUDRAGIT RL 100 and formulation L9 (1% HPMC, 2% CP) shows low value of 4.6 ± 0.016.

***In-vitro* Drug Release studies:**

In-vitro Drug Release studies were carried out in phosphate buffer (pH 7.4) for 24 hours. In order to find out the order of release and the mechanism, which were predominately influences, the drug release from the membrane.

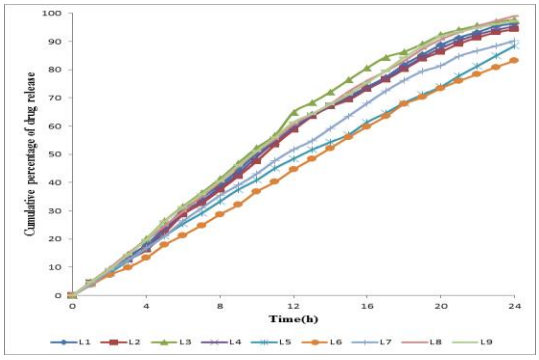

Fig 4: *In-vitro* Drug Release for all Formulations L1-L9

The formulation L1 formulated with 1 % HPMC, 1% EUDRAGIT has shown release 95.3%of drug release at 24th hour. The formulation L2 formulated with 1% EUDRAGIT, 1%CP has shown release 94.3% of drug release at 24th hour. The formulation L3 (1% HPMC, 1%CP) has shown the drug release of 97.7% of drug release at 24th hour. The formulation L4 (2%HPMC, 1%EUDRAGIT) has shown the drug release of 96.3%of drug release at 24th hour (Table no.19). The formulation L5 (2%HPMC, 1%EUDRAGIT RL 100), has shown the drug release of 88.4% of drug release at 24th hour. The formulation L6 (2%EUDRAGIT RL 100, 1%CP), has shown the drug release of 83.1%of drug release at 24th hour The decrease in drug release L6 compared to L1, L5, L7and L8 is due to the nature of the polymer. Hydroxy propyl methyl cellulose and Carbopol has better control release of drug when compared with Eudragit RL 100. The formulation L7 (1%EUDRAGIT RL 100, 2%CP), has shown the drug release of 90.2% of drug release at 24th hour. The formulation L8 (2%HPMC, 1%CP), has shown the drug release of 99.21% of drug release at 24th hour. The formulation L9 (1%HPMC, 2%CP), has shown the drug release of 97.2 % of drug release at 24th hour. Based on the drug release the L8 (2% HPMC, 1% CP) was selected as optimized formulation.

Table 3: Diffusion characteristics for all formulations L1-L9

Batch code	Regression for in-vitro plot (r^2)	Regression for higuchi's plot (r^2)	Slope for peppa's plot (n)
L1	0.992	0.981	0.849
L2	0.992	0.978	0.816
L3	0.987	0.981	0.807
L4	0.992	0.980	0.869
L5	0.998	0.977	0.817
L6	0.998	0.970	0.874
L7	0.996	0.977	0.869
L8	0.993	0.981	0.861
L9	0.992	0.982	0.871

The *in-vitro* drug release plot has shown that the drug release followed zero order kinetics, which was evinced from the regression value ($r^2$0.992) of the above mentioned plot. The Higuchi's plot has shown the regression value of 0.981 respectively, which indicated that diffusion mechanism influencing the drug release. In order to confirm this fact, Peppa's plot was drawn which has shown slope value of 0.849 respectively, which confirms that the diffusion mechanism involved in the drug release was of non-fickian type.

Stability studies

The results of stability studies obtained were given in table 4. The analysis of the parameters studied namely drug content and physical appearance after storage at 4°C, 40^0 C and 60°C for one month showed no significant change.

Table 4: Stability Studies Data for L8 (2% HPMC, 1% CP)

Time in days	4^0C		40^0C		60^0C	
	R.D.C	P.A	R.D.C	P.A	R.D.C	P.A
0	99.35	+	99.35	+	99.35	+
10	99.29	+	99.32	+	99.28	+
15	99.21	+	99.29	+	99.19	+
30	99.19	+	99.26	+	99.12	_

n=3

R.D.C = Remaining Drug Content

P.A = Physical Appearance

+ = Good, Translucent
- = Hard

4. Conclusion

The design and evaluated results of present investigation revealed that, Suitable analytical method based on UV-Visible spectrophotometer was developed for Losartan Potassium λ_{max} of 205 nm was identified in phosphate buffer, pH 7.4. All the excipients used did not interfere with the estimation of Losartan Potassium at analytical wavelength 205 nm respectively. Transdermal patches of Losartan Potassium were successfully prepared using HPMC K100, Eudragit RL100 and Carbopol 934 as polymers by Solvent casting Technique. The prepared Transdermal patches were evaluated for Physico chemical evaluation which shows clear, smooth, uniform, flexible and desired thickness film. All the formulations which undergone for *in-vitro* drug release studies follows zero order kinetic of drug release. Higuchi's plot for the formulation revealed that the predominant mechanism of drug release is diffusion. Peppa's plot for the formulation revealed that the predominant mechanism of drug release is non fickan type. The formulation L8 (2% HPMC, 1% CP) has shown optimum and high percentage of drug release (99.21%) in concentration independent manner. Hence, transdermal patch of Losartan Potassium could be promising drug delivery as they minimize the dose, overcome the side effects, simplify treatment regimen and improve patient compliance. The present investigation is worthy of further research, especially in terms of performance in pharmacokinetics**,** *In-vivo* studies on higher animals and controlled clinical studies on human beings.

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