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Original Article

Formulation and characterization of anti hypertensive transdermal delivery system

Aparna Pisipati [a,*], *S. Chavali Venkata Satya* [b]

[a] *Department of Pharmaceutics, Gokaraju Rangaraju College of Pharmacy, Jawaharlal Nehru Technological University, Hyderabad, Andhra Pradesh, India*

[b] *Gokaraju Rangaraju College of Pharmacy, Osmania University, Hyderabad, Andhra Pradesh, India*

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ABSTRACT

Background and aim: Losartan, an anti hypertensive agent, is required to be administered for a long period and it is AT-1 receptor antagonist. Aim of present work was to develop the controlled release formulation, transdermal delivery of losartan because of poor oral bioavailability (33%) due to extensive first pass metabolism.

Methods: Matrix type TDDS was designed using polymers, polymethylmethacrylate (PMMA) and ethyl cellulose (EC), dimethyl sulfoxide (DMSO) a penetration enhancer and PEG-400 as plasticizer.

Results: Non-sticky, tough patches were obtained. Physical characteristics like moisture content, folding endurance and drug content were satisfactory with high drug content (97%), and uniform weights. Thirteen formulations were prepared and tested for integrity and *in vitro* drug release studies were carried out on Franz diffusion cell using dialysis membrane.

Conclusions: Among 13 formulations, LP-11 was better with *in vitro* cumulative drug release-76.5% in 24 h. The order of release was found to be first order and the mechanism of drug release was found to be Higuchi diffusion mediated.

1. Introduction

Transdermal systems (TDS) are aimed to achieve the objective of delivering systemic medication through topical application to the intact skin surface.[1] Recently a lot of development is seen in controlled drug delivery systems (CDDS) worldwide and one of them is transdermal delivery system. These delivery systems use skin as either a rate controlling barrier to drug absorption or as a reservoir for drug.[2] This technology was successfully utilised for developing various drugs like, nitroglycerine, oestradiol, clonidine, nicotine and testosterone patches. This route maximises bio-availability, thereby optimising the therapeutic efficacy and minimises the side effects.[3]

Present work was aimed at developing a matrix drug delivery system using a model anti hypertensive agent, losartan potassium (LP), an angiotensin II receptor (type AT_1) antagonist. Rationality of selecting losartan was based on various physicochemical, pharmacokinetic and pharmacodynamic parameters.[4] Physicochemical parameters include molecular weight (461.0), pka (4.9) and melting point – 183.5 °C to

* *Corresponding author.*
E-mail address: aparna_16p@hotmail.com (A. Pisipati).

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Table 1 – Composition of the TDDS formulation containing losartan potassium.

Formulation code	Ingredients					
	Losartan (mg)	PMMA (mg)	EC (mg)	PEG-400 % (v/v)	DMSO % (v/v)	Chloroform (ml)
LP-5	20	100	–	20	–	10
LP-6	20	95	5	20	–	10
LP-7	20	90	10	20	–	10
LP-8	20	80	20	20	–	10
LP-9	20	90	10	20	10	10
LP-10	20	90	10	20	20	10
LP-11	20	90	10	20	30	10
LP-12	20	95	5	20	20	10
LP-13	20	95	5	20	10	10

Note: – indicates the ingredient was absent.

184.5 °C Pharmacokinetic and pharmacodynamic parameters include plasma elimination half life 1.5–2.5 h, bioavailability 33%. Usage of polymethylmethacrylate is widely seen as a component in eudragit mixtures.[5] Ethyl cellulose, a hydrophobic polymer finds its usage in TD delivery.[6]

In the present study hydrophobic polymers were selected to prepare patches of losartan potassium which is a hydrophilic drug. Release profile was observed by altering the concentrations of these two polymers. DMSO, sulfoxides class of enhancers, was used.[3,7–9] and PEG-400, as plasticizer were used.[10] The prepared patches were tested for various physicochemical parameters and *in vitro* drug release using dialysis membrane.[11]

2. Materials and methods

2.1. Materials

Losartan was purchased from SL Drugs, Hyderabad. PMMA was purchased from Himedia laboratories, Mumbai. All other chemicals of pharmaceutical grade, are purchased from SD Fine Chemicals, Mumbai.

2.2. Methods

2.2.1. Transdermal patches design – casting method

The films were prepared as given in the Table 1 and solvent casting technique was used to prepare the films. A dispersion of polymers was prepared by dissolving PMMA and then EC to form a matrix in chloroform. Then losartan was separately dissolved in chloroform, containing 5% v/v methanol and was added to the polymer dispersion and mixed thoroughly to facilitate distribution of drug in the polymer matrix. To the formed dispersion required amount of PEG-400 and DMSO were added one after the other and mixed. Resultant dispersion was checked for any air entrapment and was poured in a glass petri plate of known area 70 cm^2 and allowed to dry overnight at room temperature by inverting a funnel to ensure uniform evaporation of the solvent. Dried patches were removed from petri plate and stored in a dessicator with aluminium foil wrapping for further evaluation.

2.3. Estimation of losartan potassium

UV spectrophotometric method based on the measurement of absorbance at 254 nm in phosphate buffer of pH 7.4 was used to estimate the drug content in the prepared transdermal patches. The method obeyed Beer's law in the concentration range of 5–40 μg/ml and was validated for linearity, accuracy and precision. No interference with excipients was observed.

2.4. Characterization of transdermal patches

Prepared patches were evaluated for various physicochemical parameters viz., thickness, weight variation, folding endurance, loss of moisture, moisture uptake and drug content.[13] The results were given in Table 2.

Table 2 – Physical evaluation of losartan potassium transdermal patches.

Formulation	Weight variation (AM ± SD)[a]	Thickness (μm) (AM ± SD)[a]	Folding endurance (AM ± SD)[a]	% Moisture content (AM ± SD)[a]	% Drug content (AM ± SD)[a]
LP-5	17.5 ± 0.072	30	56 ± 1.000	6.6	97.79 ± 0.002
LP-6	16.0 ± 0.057	30	57 ± 2.000	6.1	97.51 ± 0.002
LP-7	15.8 ± 0.057	15	58 ± 2.081	5.0	97.63 ± 0.004
LP-8	15.6 ± 0.052	10	59 ± 1.000	5.0	93.05 ± 0.002
LP-9	17.8 ± 0.152	20	59 ± 1.527	4.9	97.79 ± 0.001
LP-10	17.2 ± 0.152	20	52 ± 1.460	4.5	97.94 ± 0.002
LP-11	16.6 ± 0.100	20	53 ± 1.091	5.0	98.41 ± 0.002
LP-12	18.0 ± 0.072	30	56 ± 1.527	6.6	98.18 ± 0.001
LP-13	17.8 ± 0.152	30	55 ± 1.987	6.1	97.73 ± 0.055

a Data presented as mean ± SD $n = 3$.