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Der Pharmacia Lettre, 2016, 8 (5):12-16
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ISSN 0975-5071
USA CODEN: DPLEB4

Formulation and Evaluation of Captopril Transdermal patches for the treatment of hypertension

Pravin Uttekar*, Akshata Kulkarni, Pravin Chaudhari, Manoj Dhage and Vishal Dhangarmali

P. E. S. Modern College of Pharmacy, Sector-21, Yamunanagar, Nigdi, Pune-44

ABSTRACT

The absorption of drugs via transdermal route improves the bioavailability of drugs that could have might otherwise been metabolized by first-pass way (pre-systemic drug elimination) by gastrointestinal tract. Drug absorption is mainly through passive diffusion through the lipoidal membrane. Thus TDDS have attracted the attention worldwide for optimizing the drug delivery. The aim of the present research is to formulate matrix type TDDS which contains the drug captopril using hydroxy propyl methyl cellulose E-15(HPMC E-15), Eudragit RS 100 as a release controlling polymers. The formulated patches were characterized by diffusion studies. The work was aimed to develop the TDDS which controls the release of captopril up to max time period.

Keywords: Captopril, HPMC E-15, Eudragit RS 100, ACE inhibitor

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INTRODUCTION

Transdermal drug delivery system (TDDS) provides sustain drug release and reduce the intensity of action and thus decreases the side effects associated with its oral therapy.[1]The main objective of transdermal drug transport is to deliver drug across skin to achieve systemic effect over a prolonged period of time.[2]Skin of an person body covers a surface of approximately $2m^2$ and receives about $1/3^{rd}$ of blood.[3] Over the past few years, controlled drug delivery has become an important part in the pharmaceutical industry.Astandard dosage form would be maintaining the drug concentration in the blood at a constant level nearly coinciding with the minimum effective concentration (MEC) of drug throughout the treatment period. This leads to the controlled drug delivery.[4]The primary objective of controlled drug delivery is to ensure safety and efficacy as well as patients compatibility. TDDS is one of the systems lying under the sustain drug delivery, in which the objective is to deliver the drug through epidermis in a predetermined and controlled rate.[5]

Transdermal systems are ideally suited for ailments that demands for the treatment of hypertension, etc[6]. Angiotensin converting enzyme (ACE) inhibitors are becoming major choice of drugs for long term therapy. [7]Regardless of their good tolerability, ACE inhibitors are known for their activity. A more steady action could be achievable if ACE inhibitors are given in the form of their pro-drugs or their active forms systemically through skin.[8]Captopril is active in unmodified form. Captopril gets rapidly absorbed through GIT but its bioavailability decreases by 30-40% in presence of food. The half life of captopril is less than 3 hrs. Blood levels correlate poorly with clinical response.[9] According to a previous research, the oxidation rate of captopril in dermal homogenateis significantly lower than the intestinal homogenate because the oxidative product of captopril, a captopril disulfide shows poor absorption from the intestine. [10]

MATERIALS AND METHODS

Materials:
Chemicals purchased were Captopril (Aurochem pharmaceuticals) HPMC E15 (Colorcon Asia,Ptd), Eudragit RS100 (Evonil Ptd), Dibutyl phthalate (Loba chemicals).

Method:
Transdermal patches of captopril were formulated by solvent evaporation technique shown in Table 1. Solutions of HPMC E-15 and eudragit RS 100 were prepared separately in the methanol and ethanol. The two polymeric solutions were mixed to which weighed amount of captopril was added slowly. To the mixture, 30% Propylene glycol and 30% Dibutyl phatalate was added. The drug-polymer solution was casted in aluminium mould of 25cm^2 which was wrapped by aluminium foil. The mould was kept aside for drying at room temperature for 24 hrs. Inverted funnel was placed over the mould to prevent the current of air. After drying, the patches were peeled from mould.[11, 12]

Evaluation Of Transdermal Patch :
Physical appearance of Formulation
The prepared patches were physically examined for colour, clarity and surface texture. [12]

Thickness uniformity
The thickness of patches was measured by using electronic calliper, with a least count of 0.01mm. Thickness was measured at three different points on the film and average readings were taken. [12]

Uniformity of weight
The patch of size 1x1 cm2 was cut and weight of each patch was taken individually, the average weight of the patch was calculated. [12]

Tensile strength
Tensile strength of the patches was determined with Universal Strength Testing Machine (Hounsfield, Slinfold, Horsham, U.K.). The sensitivity of the machine was 1 gram. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 × 1 cm2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength is expressed as follow. [12]

$$\text{Tensile stregth} = \frac{\text{Tesille load at a break}}{\text{Cross section area}}$$

Folding endurance
The folding endurance was measured manually for the prepared patches. A strip of patch (2 x 2 cm2) was cut and repeatedly folded 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.[12]

Percentage moisture loss
The patches were weighed individually and kept in a desiccators containing calcium chloride. The final weight was noted when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight. [12]

Percentage moisture uptake
The patches were weighed accurately and placed in adesiccators where a humidity condition of 80-90% RH was maintained by using saturated solution of potassium chloride. The patches were kept until uniform weight is obtained, then taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. [12]

Drug content uniformity
The patches were tested for the content uniformity. The patches of size 1 cm2 was cut and placed in a 100 ml volumetric flask. The contents were stirred using a magnetic bead for 24 hrs to dissolve the patches. Subsequent dilutions were made with phosphate buffer (pH 7.4). The absorbance of the solution was measured against the corresponding blank solution at 209 nm using UV-visible spectrophotometer. The experiment was repeated three more time to validate the result. [12]

In vitro release studies

The fabricated patch were cut into 1 cm2 and placed on the commercial semi permeable membrane(regenerated cellulose which was permeable to low molecular weight substances) and attached to the diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37±10C. The elution medium was stirred magnetically. The aliquots (1ml) was withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analysed for drug content using UV spectrophotometer at 209nm. [12]

Differential scanning calorimetric (DSC)

The DSC thermo gram was recorded using differential scanning calorimeter (TA-60 WS thermal analyzer, Schimadzu, Japan). Approximately 2-5 mg of drug sample was heated in an aluminium pan (Al-Crucibles, 40 Al) from 300C to 3000C at a heating rate of 100C/min under a stream of nitrogen at flow rate of 50ml/min. [12]

RESULTS AND DISCUSSION

Result of Characterisation of patches is shown in Table 2. It was found to be 9.1 hours for most optimized formulation F-9 as shown in Fig.1. Skin irritation studies show no sign of erythma or any other skin irritation reaction, so it can be concluded that neither the drug nor any polymer or excipient was found to cause adverse effects on skin, hence, patch was found. Result of all evaluation parameters was found to be satisfactory within permissible limits as shown in Fig.3 and Fig4.

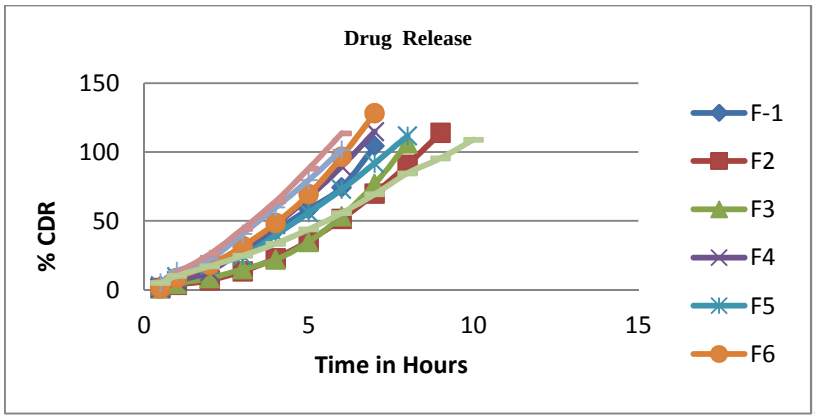

Fig.1: % CDR v/s Time (Hrs)

DSC study

DSC analysis of Captopril showed the endothermic peak at its melting point i.e. at 109°C (*H* = -135.08 J/g) (Fig.11.2) Enthalpy of peak is 39.52 mW Thus it can be proved that the endothermic peak obtained is melting peak which is sharp and it indicates purity of drug.

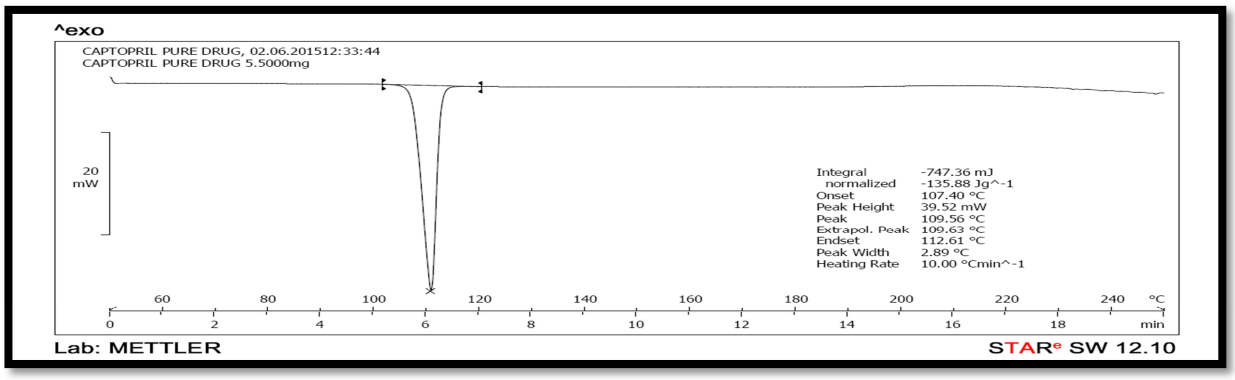

Fig.2: DSC of Captopril pure drug

DSC thermo grams of pure drug and formulation revealed that there is no considerable change observed in melting endotherm of captopril pure drug (110.6 0C) and drug in optimized formulation (122 0C) which are shown in

Fig:11.3 & . It indicates that there is no interaction takes place between pure drug and excipients used in the formulation.

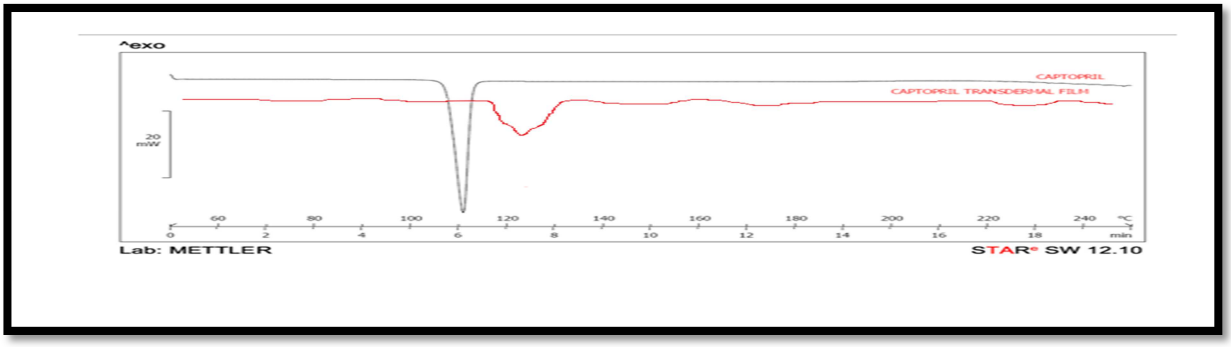

Fig.3: DSC of Pure Drug and Optimize Formulation (Transdermal patch)

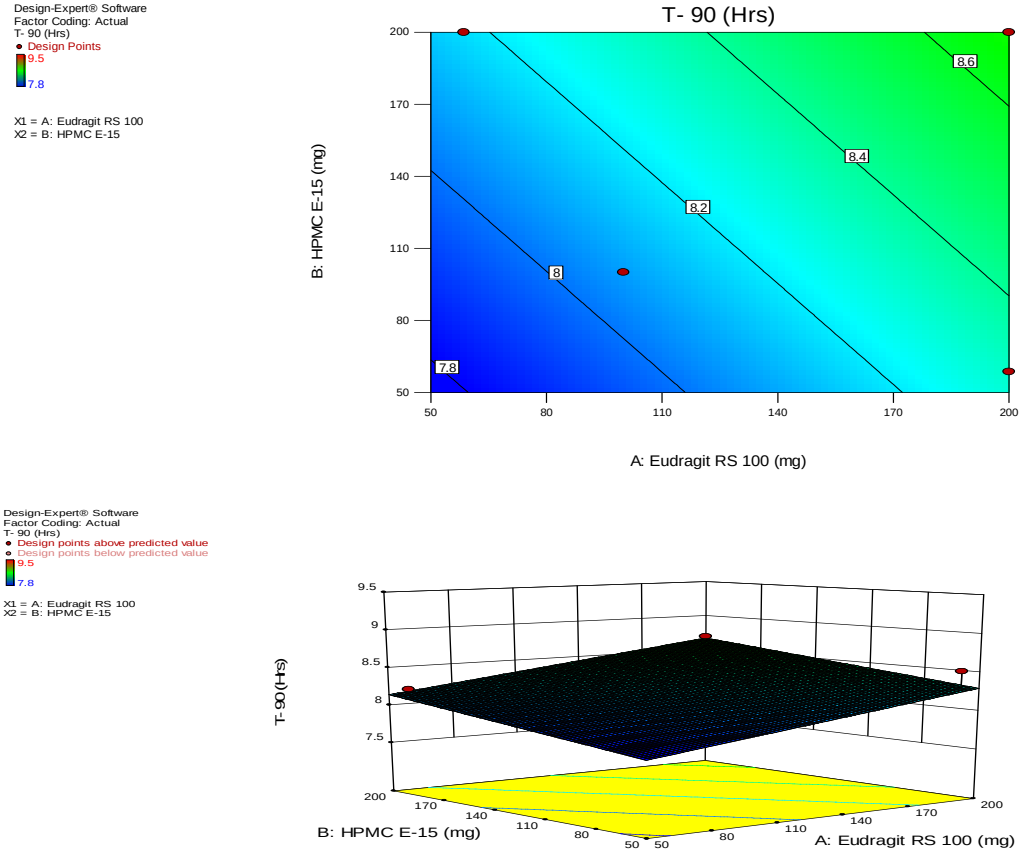

Fig.4: (A) Contour and (B) Response surface plots for effect of HPMC E15 and Eudragit RS 100 on% Drug Release at T-90

Table 1: Composition of different formulation containing captopril

F- code	Eudragit RS-100 (mg)	HPMC E-15 (mg)	Dibutyl phthalate (% w/w)	Propylene Glycol (%w/w)
F-1	200	341.42	30	30
F-2	200	58.58	30	30
F-3	100	100	30	30
F-4	200	200	30	30
F-5	58.58	200	30	30
F-6	300	100	30	30
F-7	100	300	30	30
F-8	300	300	30	30
F-9	341.42	200	30	30

Table 2: characterisation of evaluation parameters

Code	Thickness mm	Folding endurance	Weight variation	Percentage elongation	Drug content	T90	Tensile strength
F1	0.256±0.005	214±1.154	0.053±0.005	20.25±0.032	89.40±0.517	8.133±0.05	0.5459±0.0126
F2	0.246±0.005	106.6±1.527	0.05±0.01	21.21±0.012	85.45±0.160	8.566±0.057	0.3710±0.031
F3	0.27±0.01	113.3±1.527	0.073±0.020	26.32±0.052	88.50±0.471	7.73±0.057	0.2650±0.033
F4	0.236±0.015	145±1	0.05±0.01	22.35±0.532	90.53±0.223	5.96±0.057	0.3796±0.020
F5	0.253±0.005	150±2	0.013±0.005	26.56±0.052	91.63±0.437	5.13±0.057	0.3549±0.032
F6	0.246±0.005	177.3±0.577	0.073±0.005	23.98±0.012	90.16±0.144	5.733±0.057	0.2213±0.006
F7	0.27±0.01	190.3±0.577	0.056±0.011	23.51±0.032	87.79±0.665	5.53±0.057	0.4739±0.011
F8	0.236±0.015	187.6±0.577	0.05±0.01	23.51±0.012	92.34±0.506	5.266±0.057	0.4532±0.011
F9	0.253±0.005	142.6±1.15	0.056±0.011	26.51±0.052	93.93±0.348	9.1±0.1	0.3205±0.005

CONCLUSION

Transdermal antihypertensive drug patch of captopril were successfully formulated using solvent casting method. The process variables that could affect the film qualities were systematically investigated. Additionally, application of experimental design resulted into selection of significant factors that could affect the disintegration, dissolution and ultimate bioavailability of drug from film formulation. A film containing HPMC E15 (film forming polymer) and Eudragit RS100 (rate controlling polymer) at specific amount is desirable for prolong the drug release and specific amount of penetration enhancer with them help to diffusion of captopril. The results of this study indicate that captopril containing transdermal patch is a promising approach therapy to maximum bioavailability and prolong release of the drug.

Acknowledgement
I am thankful to Modern College of Pharmacy, Nigdi, Pune for providing all the facilities for completion of this research work. I would like to acknowledge the support of Dr. P. D. Chaudhari and Mr. Samarth Kaluskar (University Of Toronto) for their help throughout the study.

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