

Research Article

**FORMULATION AND EVALUATION OF TRANSDERMAL DELIVERY SYSTEM
COMPRISING CAPTOPRIL AS ANTIHYPERTENSIVE DRUG**

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ABSTRACT

Captopril was the first ACE inhibitor used for the treatment of hypertension. The present study was aimed to design and evaluate a matrix-type transdermal formulation containing captopril with different ratios of hydrophilic (Hydroxy propyl methyl cellulose E-15) and hydrophobic polymeric (Eudragit RS100) combinations plasticized with glycerin by the solvent evaporation technique. Effect of permeation enhancers such as oleic acid, dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) were studied. The interference of the polymers was ruled out by FT-IR studies. The prepared patches were tested for their physicochemical characteristics such as physical appearance, weight variation, thickness, folding endurance, percentage moisture absorption, percentage moisture loss, water vapour transmission, tensile strength and drug content. In vitro release studies of captopril loaded patches in phosphate buffer (pH, 7.4) exhibited drug release for 24 hours in the following order F3 < F6 < F5 < F4. Data of in vitro release from patches were fit in to different equations and kinetic models to explain release kinetics. The models used were zero and first-order equations, Higuchi and Korsmeyer-Peppas models. Based on physicochemical properties and in vitro release studies, patch containing hydroxyl propyl methyl cellulose E-15 and Eudragit RS 100(1:1) with oleic acid as permeation enhancer, emerges as a best formulation. Skin irritation studies for the transdermal patches were assessed and were found to be free of irritation.

Key words: Captopril, hypertension, transdermal formulation, kinetic models.

INTRODUCTION

Transdermal drug delivery offers many important advantages. For instance, it is easy and painless, it protects the active compound from gastric enzymes, and it avoids the hepatic first-pass effect, controls absorption rate, variations in delivery rates, interference due to the presence of food, increases patient compliance, suitable for unconscious patients and enables fast termination of drug delivery, if needed. But skin is a natural barrier,

which are mainly composed of lipids & proteins and only a few drugs can penetrate the skin easily and in sufficient quantities to be effective [1]. Recently it is evident that the benefits of intravenous drug infusion can be duplicated, without its hazards, by using the skin as the port of drug administration to provide continuous transdermal drug infusion in to the systemic circulation. The penetration across epithelial borders is a slow process due to the effect of the barrier properties. The skin, in particular the stratum corneum, possesses a barrier to drug penetration due to its high density (1.4 g/cm² in dry state), its low hydration of 15 to 20%. The barrier function is further facilitated by the continuous replacement of stratum corneum, thereby limiting the topical & transdermal bioavailability. Therefore, in recent years, numerous studies have been conducted in the area of penetration enhancement [2]. Limitations include slow penetration rates, lack of dosage flexibility and a restricted to

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relatively low dosage drugs [3]. The fundamental components of transdermal include the following

- a) Polymer matrix
- b) The drug substance
- c) Penetration enhancer
- d) Backing membrane
- e) Adhesives

On oral administration of therapeutic doses of captopril, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent. So, the present study deals with the research work to formulate and evaluate transdermal patches of Captopril by solvent evaporation technique and also to characterize the transdermal patches for various parameters and calculate the release kinetics for optimized formulation.

MATERIALS & METHODS

Captopril was obtained from Strides acro labs, Bangalore. Hydroxypropyl methylcellulose and Eudragit RS 100 obtained from Shreeji chemicals, Mumbai. Dimethyl formamide from Loba Chemie, Mumbai and all other chemicals used are obtained from S.D. Fine Chem. Ltd., Mumbai.

The preformulation studies like determination of melting point, solubility, pH and partition coefficient were performed for captopril and polymers.

Compatibility studies:

FT-IR Spectroscopy:

IR spectroscopy can be used to investigate and predict any physicochemical interactions between different components in a formulation and therefore it can be applied to the selection of suitable chemically compatible excipients [4].

One part of the sample and three parts of potassium bromide were taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet maker and was compressed at 10kg/cm² using hydraulic press. The pellet was kept on to the sample holder and scanned from 4000cm⁻¹ to 400cm⁻¹ in Bruker IR spectrophotometer. Then it was compared with original spectra.

Preparation of transdermal patches of captopril:

Transdermal patches of captopril were prepared by solvent evaporation technique for the formulations shown in Table 1. Solutions of HPMC E-15 and eudragit RS 100

were prepared separately in dichloromethane: methanol (1:1) mixture. The two polymeric solutions were mixed to which weighed amount of captopril was added slowly. To the mixture, 4 drops of glycerin (0.25 ml), and permeation enhancer (oleic acid / DMSO/DMF) were added and mixed. The drug-polymer solution was casted in aluminum mould of 25cm² which is wrapped by aluminum 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, wrapped in aluminum foil, and preserved in desiccator for further studies.

Table 1: Composition of different formulations containing captopril

Formulations	F1	F2	F3	F4	F5	F6
Captopril, mg	50	50	50	50	50	50
HPMC E-15(15cps), mg	30 0	20 0	15 0	15 0	15 0	15 0
Eudragit RS 100, mg		10 0	15 0	15 0	15 0	15 0
Glycerin (4 drop), ml	0.2 5	0.2 5	0.2 5	0.2 5	0.2 5	0.2 5
Dichloromethane:Methanol 1:1	7	7	7	7	7	7
Oleic acid, ml				0.2 5		
DMSO, ml					0.2 5	
DMF, ml						0.2 5

Evaluation of transdermal patches of captopril:

Physical appearance [5]: The prepared patches were physically examined for colour, clarity and surface texture.

Thickness uniformity [7]: The thickness of patches was measured by using electronic caliper, with a least count of 0.01mm. Thickness was measured at three different points on the film and average readings were taken.

Uniformity of weight [6]: The patch of size 1x1 cm² was cut and weight of each patch was taken individually, the average weight of the patch was calculated.

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.

Folding endurance [6-8]: 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.

Percentage moisture loss:

The patches were weighed individually and kept in a desiccator 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.

Percentage moisture uptake [9]: The patches were weighed accurately and placed in a desiccator 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.

Water vapor transmission (WVT) rate:

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1 g of fused calcium chloride was taken in cells and the polymeric patches measuring 1 cm² area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccator containing saturated solution of potassium chloride to maintain 80-90% RH. The cells were taken out and weighed after 24 hrs. The amount and rate of water vapor transmitted was calculated by the difference in weight using the formula.

Water vapour transmission rate is usually expressed as the number of grams of moisture gained/hr/cm².

Drug content uniformity [5, 11]:

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.

In vitro release studies [9, 10]:

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 analyzed for drug content using UV spectrophotometer at 209nm.

RESULTS & DISCUSSION

The preformulation studies like determination of melting point, solubility, pH and partition coefficient were performed for captopril.

FT-IR Spectroscopy: FTIR spectra obtained for Captopril, polymer and physical mixture presented in the fig. 1 & 2. The characteristics peaks found in Captopril, physical mixture and formulations, hence it appears there was no chemical interaction between Captopril and polymer and it can be concluded that the characteristics bands of Captopril were not affected after successful load formulation of transdermal patches.

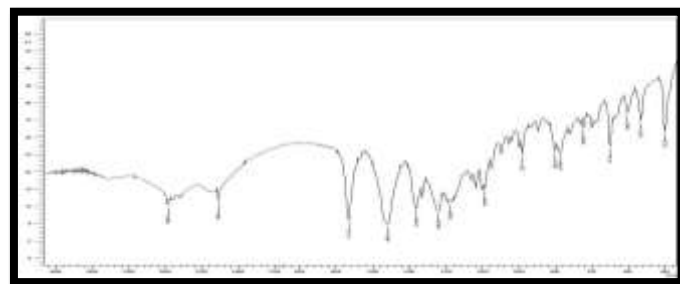


Fig 1: IR spectrum of captopril pure

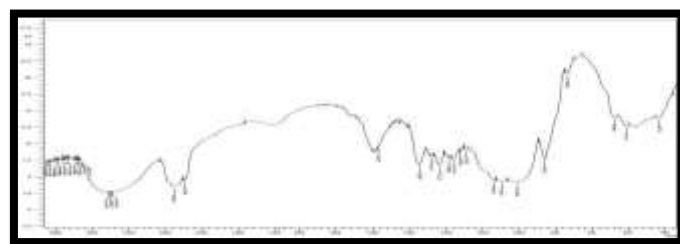


Fig 2: IR spectrum of HPMC E-15 pure

DISCUSSION:

Captopril, an antihypertensive agent which selected for the preparation of transdermal delivery system as it complies with physicochemical properties required to permeate through skin. The preformulation studies involving description, solubility, melting point, partition

coefficient of the drug were found to be comparable with the standard.

The patches were prepared by solvent evaporation method. The patches were subjected for following evaluation parameters such as physical appearance, weight variation, thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss, water vapour transmission rate, tensile strength, diffusion studies and skin irritation studies. All the parameters shows were within the limits.

Based on all these results, the transdermal drug delivery system F1 which is containing HPMC E-15 alone showed better drug release, but lasts for only 7 hrs. Formulation F2 containing HPMC E-15: eudragit RS 100 (2:1) shows comparable release with F1 but it lasts for 12 hrs. The formulation F3 containing HPMC E-15: eudragit RS 100 (1:1) shows extended release up to 24 hrs when compared to formulations F1 and F2 but the drug is not completely released at the end of 24 hrs. The patches F4 to F6 were prepared by incorporating permeation enhancers, which showed promising result. The patches containing oleic acid shows near complete release followed by DMSO and DMF.

From the above studies, it is revealed that the present work was a satisfactory preliminary study of improving bioavailability of captopril by transdermal patches using HPMC E-15 and eudragit RS 100.

Further detailed investigations and elaborate in vivo studies need to be carried out and an in vitro – in vivo correlation need to be established to guarantee the efficiency and bioavailability of the formulation. Further studies on improving bioavailability have to be carried out with different polymers.

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