DEVELOPMENT OF TRANSDERMAL MATRIX SYSTEM OF CAPTOPRIL BASED ON CELLULOSE DERIVATIVE

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Summary

The transdermal delivery system of Captopril employing different ratios of polymers, ethylcellulose (EC) and hydroxypropylmethylcellulose (HPMC) as (3:1) and (2:2) were developed. The matrix diffusion type of system was developed. The potential for drug delivery was evaluated by *in vitro* dissolution studies and *in vitro* skin permeation studies using depilated freshly excised abdominal rat skin. The *in vitro* dissolution study was performed using paddle over disk method and *in vitro* skin permeation of drug was studied using modified Franz diffusion cell . Also the transdermal matrix of Captopril with EC : HPMC ratio 2:2 were subjected to *in vivo* release of drug for 24 hrs. through rabbit abdominal skin, skin irritation studies, SEM studies and accelerated stability study.*In vitro* dissolution data suggested that the systems followed Higuchi kinetics i.e. cumulative amount of drug was proportional to the square root of time. The *in vitro* skin permeation and *in vitro* dissolution studies showed that Captopril release was more in matrices containing ratio EC : HPMC as 2:2 compared to 3:1. Captopril from matrix containing EC : HPMC ratio 2:2 was able to penetrate through rabbit abdominal skin. The prepared matrices were free from any irritating effect and stable for 3 months. The SEM photographs supported the results of *in vivo* studies.

KeyWords: Ethylcellulose,hydroxypropylmethylcellulose, transdermal matrix, *in vitro* studies and *in vivo* studies

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Introduction

Cardiovascular diseases account for a large proportion of all deaths and disability worldwide .Global Burden of Disease (GBD) Study reported that in 1990 there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries (1&2). Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension(3). Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. Pooling of Indian epidemiological studies shows that hypertension is present in 25% urban and 10% rural subjects. Therefore cost effective approaches to optimally control blood pressure among Indians are very much needed. Although novel controlled-release drug-delivery systems have been used in other areas of medicine, their application in the treatment of hypertension has been relatively recent**.** Angiotensin converting enzyme (ACE) inhibitors are becoming first choice of drugs for long term therapy of hypertension (4). Together with their good tolerability, ACE inhibitors are known for their reliable activity. The plasma levels of ACE inhibitors are subject to a high variation. The high variation in the blood levels of ACE inhibitors or their active forms leads however to uncertain courses of action. In order to make the action of ACE inhibitors independent of the metabolic condition of the patients, a pharmaceutical form which makes possible a reliable reproducible systemic supply of the active compounds would be desirable. A more reliable steady action could be achievable if ACE inhibitors are given in the form of their prodrugs or their active forms systemically available transdermally (5). The first substance of the ACE inhibitor, Captopril is active in unmodified form. Captopril is 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 (6).

Material and Methods

The matrix – diffusion type transdermal films (matrices) were prepared for Captopril using the mercury substrate method (7) .The drug load was kept 5 mg / cm^2. The polymers EC : HPMC were used in ratio of 3:1 and 2:2 . Thickness of matrices was measured at 5 different places and their mean value ± SEM were calculated. Six patches of 1 cm^2 area were weighed for

each matrices and their average ± SEM were calculated.The matrices were evaluated for their uniformity of drug content. The matrices for each drug were tested for their water absorption capacities (8). The percentages of water absorbed by different matrices were calculated. The release of drug from matrices was observed using Dissolution apparatus of USP 27 (Paddle over disk method) (9). The cumulative amount of Captopril release was determined with an interval of 1 hr. in each sampling. The cumulative release of drug was plotted against square root of time and the release flux value was calculated. The *in vitro* skin permeation studies were performed on rat abdominal skin and the cumulative release of drug from matrices were estimated(10). The cumulative release was plotted against time and the permeation flux values were calculated from linear portion of the plot. The matrices which had shown better release flux and permeation flux values were considered for *in vivo* studies on male albino rabbits(11). The concentration of drugs in blood samples after application of matrices on rabbit abdominal skin were estimated. The matrices used for *in vivo* studies were also tested for their skin irritation potential. Matrices were applied to the intact skin of rabbits occluded for 24 hrs and then removed for screening of irritancy, erythema or oedema (12). The surface morphologies of the drug dispersed films before and after *in vivo* studies for Captopril were examined by scanning electron microscopy. Accelerated stability study of matrices was performed for 3 months (13).

Results

The matrices of the Captopril were prepared using the ratio of polymer selected EC: HPMC as 3:1 and 2:2 .These matrices were evaluated for various parameters.

All matrices were opaque, moderately fine, smooth, dry, flexible and non sticky. The matrices had shown thickness to be uniform. The SEM value for thickness at 5 different places was not significant indicating the matrices were uniform throughout. Six matrices of each were weighed (1 cm^2) and their mean values were calculated. The results had shown very less variation from their mean values indicating the uniformity of weight in prepared matrices. Three samples for each matrix were tested for drug content. The samples were cut from different places of film formed on moulds. The drug was uniformly distributed in the matrices (Table I).

TABLE I :PHYSICAL PROPERTIES OF MATRICES

CODE	THICKNESS (n=5) (μm)	WEIGHT (n=6) (mg/cm^2)	DRUG CONTENT (n=3) (%)
C_1	169.8 ± 0.20	12.85 ± 0.003	97.12 ± 0.45
C_2	156.2 ± 0.37	12.63 ± 0.02	97.08 ± 0.40

When the formulations were stored at different humidity at 20^{o}C, increase in weight was observed at 76% RH and 84% RH while negligible change in formulation weight was observed at 52% and 58% RH (Table II).

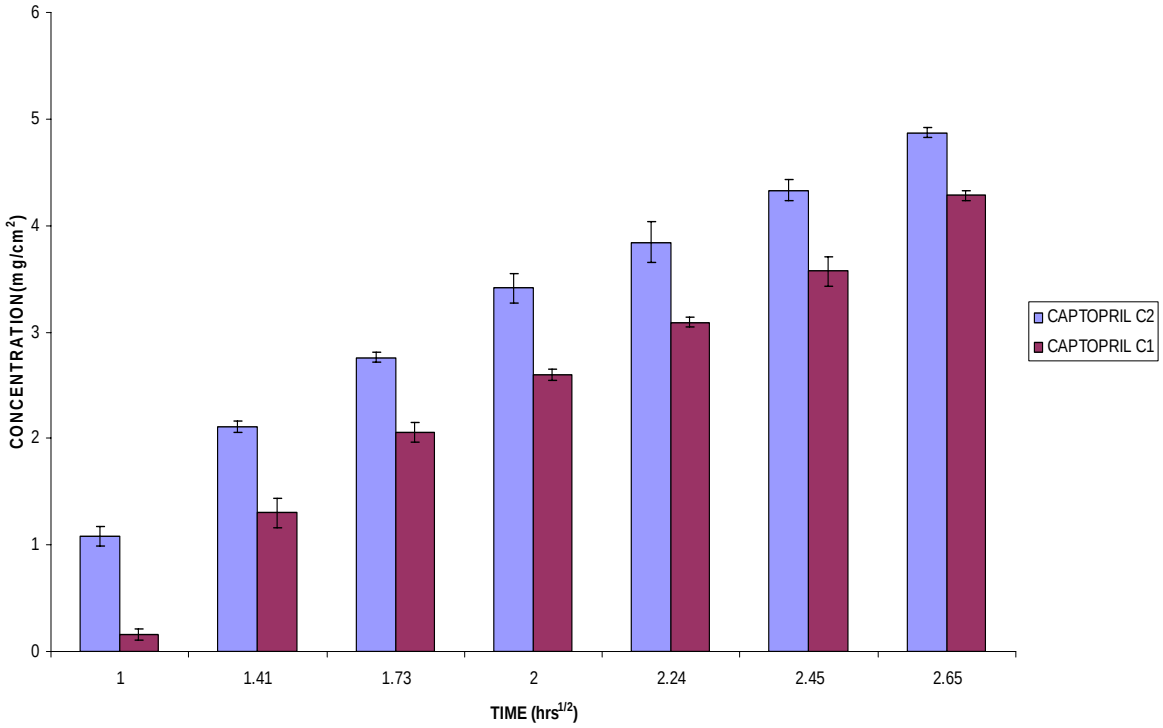
TABLE II : WATER ABSORPTION CAPACITY (%) OF MATRICES

CODE	52% RH	58% RH	76% RH	84% RH
C_1	0.91 ± 0.07	1.79 ± 0.09	5.48 ± 0.11	8.74 ± 0.08
C_2	1.29 ± 0.03	2.59 ± 0.22	9.55 ± 0.16	11.58 ±0.38

n=3
MEAN ± S.E.M.
RH RELATIVE HUMIDITY

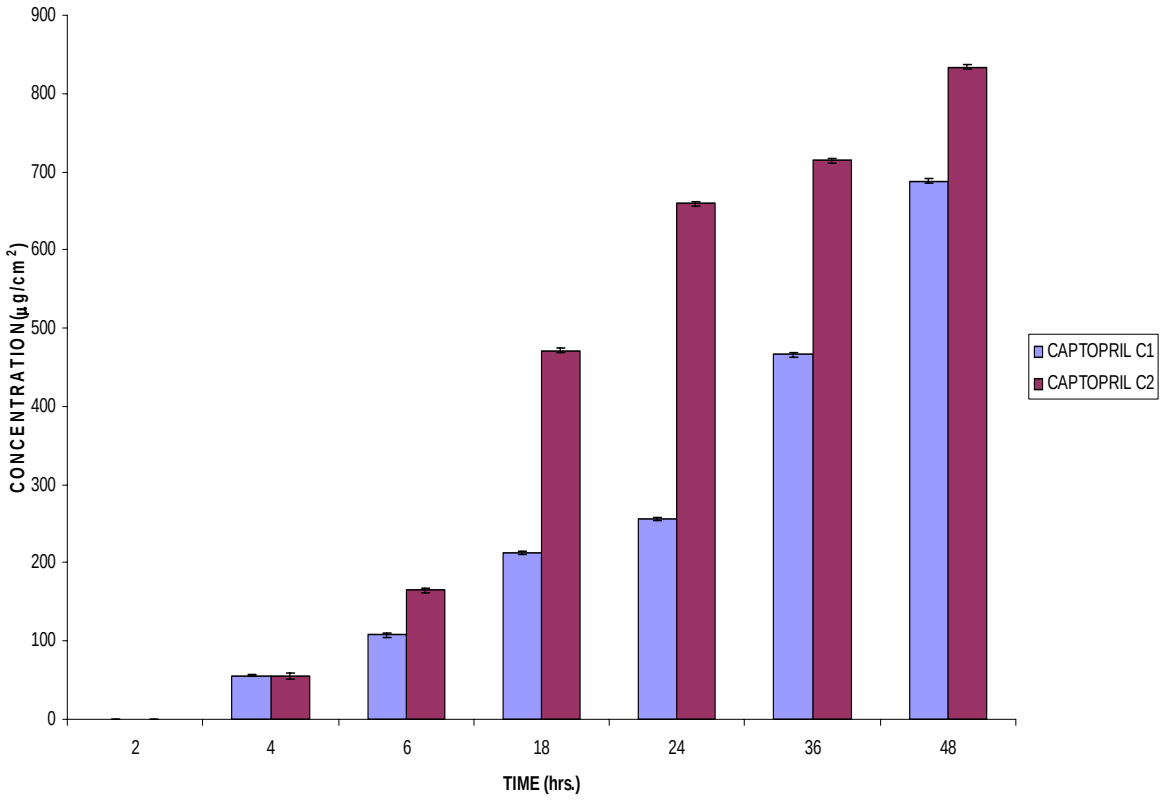
Dissolution study indicated that Captropril was released approximately 3.2%, 26%, 41.2%, 52%, 61.8%, 71.4% and 96.4% from matrices C_1 after 1, 2, 3, 4, 5, 6 and 7 hrs of study whereas C_2 matrices had shown release as 21.6%, 42.2%, 55.2%, 68.2%, 76.8%, 86.6% and 97.4% respectively. The release flux for matrices C_1 was 1.6989 $mg/cm^2 . hr^{½}$ and matrices C_2 was 1.8874 $mg/cm^2\ hr^{½}$ (Fig.1).

Fig.1:COMPARATIVE *IN VITRO* RELEASE OF CAPTOPRILFROM MATRICES



No Captopril release from matrices C_1 was observed after 2 hrs. of in *vitro* skin permeation study. Only 1.10% release was observed after 4th hr. and released in 3.29%, 9.4%, 13.18%, 14.29% and 16.67% cumulative amount after 6, 18, 24, 36 and 48 hrs. of study. Captopril matrices C_2 had shown better release than C_1. It was 0.94%, 2.92%, 4.87%, 10.56%, 15.28%, 16.79% and 19.20% after 2, 4, 6, 18, 24, 36 and 48 hrs. The permeation flux for C_1 matrices was found to be 13.71 μg /cm^2. hr and for C_2 matrices 18.965 μg/cm^2. hr through skin membrane (Fig.2).

Fig.2:COMPARATIVE *IN VITRO* SKIN PERMEATION OF CAPTOPRIL FROM MATRICES



Captopril was permeated through skin of male rabbits and had shown permeation of 302.25 ng/cm^2 from C_2 matrices after 24 hrs. of matrices application (Table III).

TABLE III : IN VIVO DRUG RELEASE STUDY FROM MATRICES

TIME (hrs)	C_2 (ng/cm^2)
0	0
2	42.13 ± 0.36
4	51.63 ± 1.58
6	67.01 ± 0.26
18	274.64 ± 0.40
24	302.25 ± 0.43

n=3; MEAN ± S.E.M

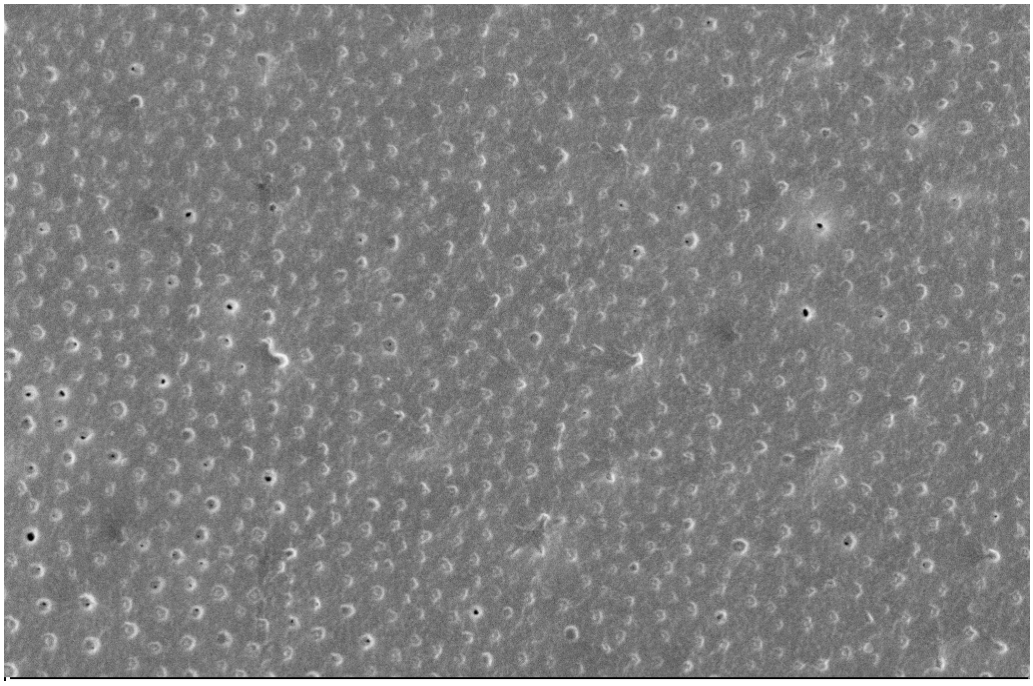


Fig. 3: The surface morphology of C_2 matrix in SEM photograph is visible as smooth and uniform before application on abdominal skin of rabbit

It was observed that all were free from skin irritant effect. None of the matrices had shown any sign of erythema after 24 hrs. application on abdominal skin of rabbits. The SEM photographs obtained for matrices clearly indicated that the matrices were uniform in their structure. The matrices were also observed after *in vivo* studies. The matrices for Captopril was clearly showing large holes which indicated a large amount of drug was released from that particular place (Fig.3 & 4).

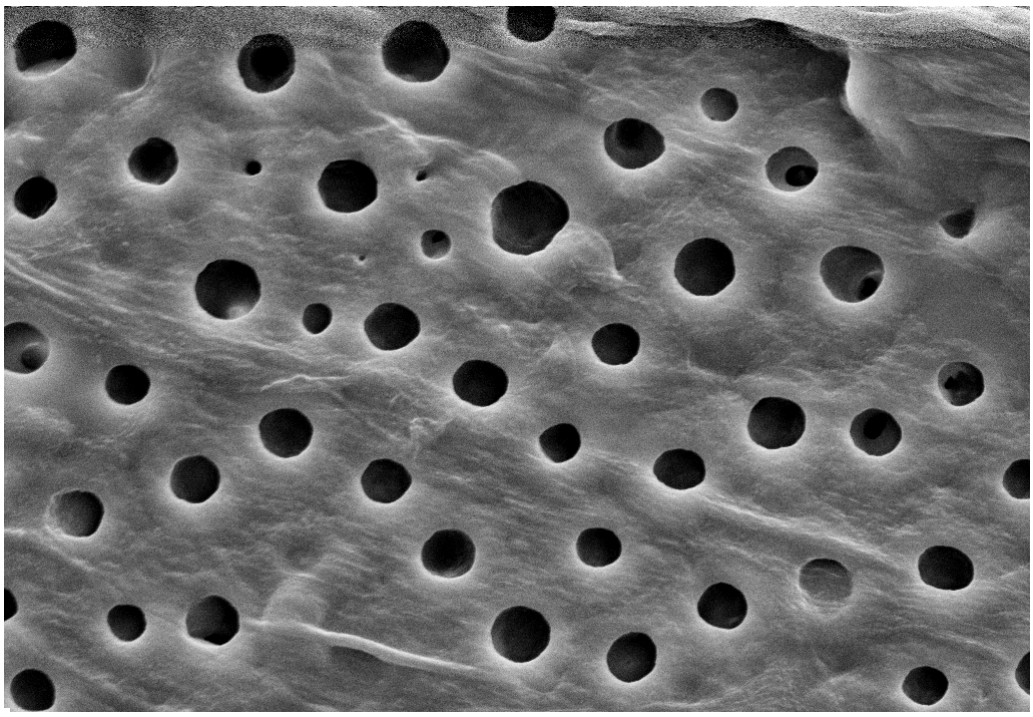


Fig. 4 : The SEM photograph of matrix C_2 after *in vivo* study is showing large holes indicating the release of Captopril from that site into the blood stream of rabbit through skin.

The matrices used for in vivo studies (C_2) were also evaluated for their stability as per ICH Guidelines, 2003 (Table IV). The results obtained after 3 months of study revealed that there was no change in thickness as compared to initial thickness. There was very less increase in weight .The drug content of matrices had changed to little extent than the initial ones for matrices but they were all in the acceptable limits. All the matrices were found uniform in thickness, weight and drug content and hence stable for 3 months.

TABLE IV : ACCELERATED STABILITY STUDY OF MATRICES

CODE	PHYSICAL APPEARANCE		DRUG CONTENT(%)		THICKNESS (μm)		WEIGHT (mg/cm^2)	
	INITIAL	FiINAL	INITIAL	FiINAL	INITIAL	FiINAL	INITIAL	FiINAL
C_2	*	*	97.12 ± 0.45	96.67 ± 0.26	156.8 ± 0.13	156.8 ± 0.20	12.62 ± 0.01	12.70 ± 0.00

n=3; MEAN ± S.E.M. *OPAQUAE, MODERATELY FINE, SMOOTH, DRY, FLEXIBLE, NON STICKY

Discussion

Water absorption studies revealed that moisture uptake was more in matrices with polymer ratio of EC : HPMC as 2 : 2 as compared to 3 : 1. The results were in parallel to the work of Mosquera, et al. who had shown that there were significant changes in properties like reduced crushing strength, increased total porosity and increased pore diameter in hydrophilic polymer containing matrices due to moisture uptake(14). In our study, it was found that Captopril was permeated well and was more when the concentration of HPMC was more (EC : HPMC 2: 2). The *in vitro* skin permeation study of Captopril yielded a plateau curve because of saturation of the drug thermodynamic activity. A constant activity dosage form may not exhibit a steady state process from the initial time of release. It was observed that the curve of cumulative release of drugs through skin is convex to the time axis in the early stage and then became linear. The early stage is the non steady – state condition. At later times the rate of diffusion was constant, the curves were linear and the systems were at steady state.

The TDDS for Captopril was prepared by various researchers (15-20).Matrix type patches were developed by using pressure sensitive adhesives (16) and aqueous based polymers viz eudragit RL-100 and polyvinyl pyrrolidone (PVP) (17). They had shown that the permeation flux through excise skin was dependent on type of polymer (16) and temperature at which they were formulated (17).

In our study, it was found that Captopril was permeated well in parallel to above studies and it was more when the concentration of HPMC was more (EC : HPMC 2: 2). HPMC was used by Wu et al(16) for preparing Captopril experimental gel. The use of EC is not reported in any study of Captopril TDDS. EC may have its impact on controlling the rate of release as it was slow and steady when EC is high (EC : HPMC 3 : 1 as compared to 2 : 2). The release flux and permeation flux were more for C_2 as compared to C_1 hence C_2formulation was considered better than C_1 *in vivo* studies.

The data revealed that Captopril was found in blood after each sampling. This may be due to the route they follow for penetration (15). As reported earlier Captopril being hydrophilic in nature may have followed transcellular pathway. The matrices selected for *in vivo* studies were subjected to skin irritation studies. The matrices were proved to be safe after 24 hrs. of its application on rabbit abdominal skin. The SEM photographs were justifying the results of *in vitro* and *in vivo* studies. Further it was observed that the matrices C_2 were stable at 40° ± 2°C/ 75% RH ± 5% RH. The matrices were found uniform in thickness, weight and drug content after 3 months.

Conclusion

Hydroxypropyl methylcellulose content had significant impact on release flux as well as permeation flux values. The release flux and permeation flux were more when HPMC content is more. The prepared matrices were opaque moderately fine, smooth, dry and flexible , they were also uniform in thickness and weight. Drugs were homogenously dispersed in the matrices as evidenced by SEM study also. Water absorption studies revealed that maximum water was absorbed in matrices having more HPMC content. Also there was negligible absorption of water at 52 - 58% RH. Hence they can be stored at room temperature and stable for 3 months. It is concluded that EC : HPMC ratio 2:2 is suitable for the formulating matrix system of Captopril.

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