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DESIGN, DEVELOPMENT AND EVALUATION OF TRANSDERMAL DRUG DELIVERY OF CAPTOPRIL, AN ANTIHYPERTENSIVE DRUG

Md. Khaja *, Muneer Syed, D. Srinivasa Rao
Department of Pharmaceutics, K.C Reddy Institute of Pharmaceutical Sciences, Guntur

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 $F_3 < F_6 < F_5 < F_4$. 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.*

Address for Correspondence:
K. C. Reddy Institute of Pharmaceutical Sciences,
Guntur, Andhra Pradesh.
E-mail: *muneerkcrp@gmail.com*

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/cm^2 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 relatively low dosage drugs. [3]

The fundamental components of transdermal include the following

- Polymer matrix
- The drug substance
- Penetration enhancer
- Backing membrane
- 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/cm^2 using hydraulic press. The pellet was kept on to the sample holder and scanned from 4000cm^{-1} to400cm^{-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 25cm^2 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	F_1	F_2	F_3	F_4	F_5	F_6
Captopril, mg	50	50	50	50	50	50
HPMC E-15(15cps), mg	300	200	150	150	150	150
Eudragit RS 100, mg		100	150	150	150	150
Glycerin (4 drop), ml	0.25	0.25	0.25	0.25	0.25	0.25
Dichloromethane:Methanol 1:1	7	7	7	7	7	7
Oleic acid, ml				0.25		
DMSO, ml					0.25	
DMF, ml						0.25

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 and presented in **Table-3**.

Uniformity of weight [6]

The patch of size 1x1 cm^2 was cut and weight of each patch was taken individually, the average weight of the patch was calculated, the results were represented in **Table-4.**

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 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. The readings which are observer are in **Table-5.** The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength is expressed as follows;

$$\text{tensile strength} = \frac{\text{(load at break)}}{\text{(original width)(original thickn}}$$

Folding endurance [6,7,8]

The folding endurance was measured manually for the prepared patches. A strip of patch (2 x 2 cm^2) 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. The results are in **Table-6.**

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. The results were presented in **Table-8.**

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. The results were presented in **Table-7.**

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 cm^2 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

$$\text{WVT rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} * \text{Area}}$$

expressed as the number of grams of moisture gained/hr/cm^2. The results are in **Table-9.**

Drug content uniformity [5, 11]

The patches were tested for the content uniformity. The patches of size 1 cm^2 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. The observed results were placed in **Table-10.**

In vitro release studies [9,10]

The fabricated patch were cut into 1 cm^2 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±1^{0}C. 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 and results were placed in **Table-11** and graph in **Fig .5** and also kinetic studies results shown in **Fig. 6-9 and Table 12.**

RESULTS & DISCUSSION

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

Table 2: Melting point, solubility, partition coefficient and pH of captopril

Melting Point	**105 ± 1.15^{0}c**
Solubility	23.41mg/ml
Partition coefficient	3.27
pH	3.46

FT-IR Spectroscopy:

FTIR spectra obtained for Captopril, polymer and physical mixture presented in the **fig. 1-4**.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.

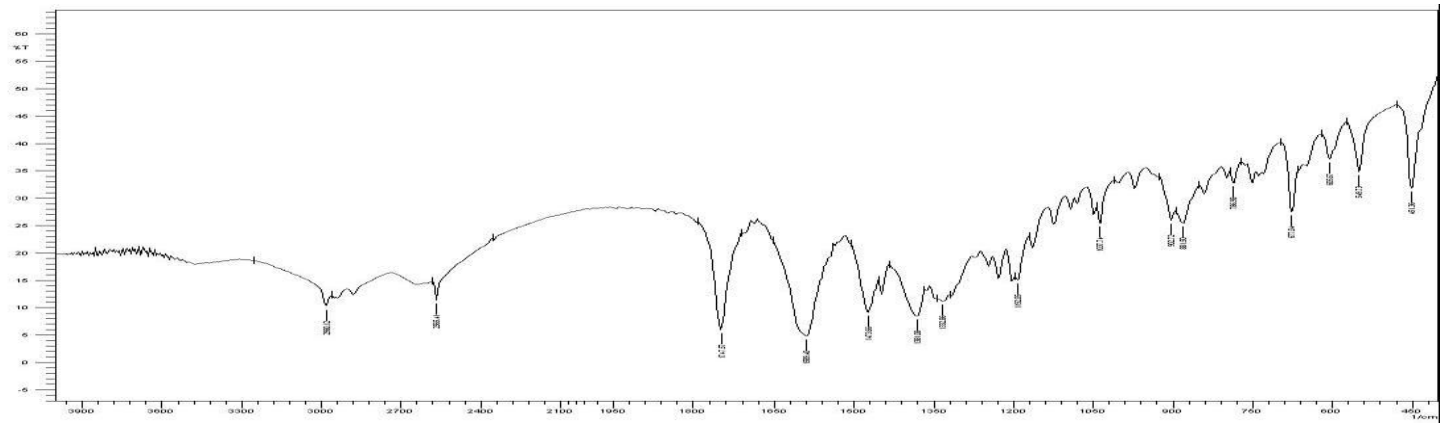

Figure 1: IR spectrum of captopril pure

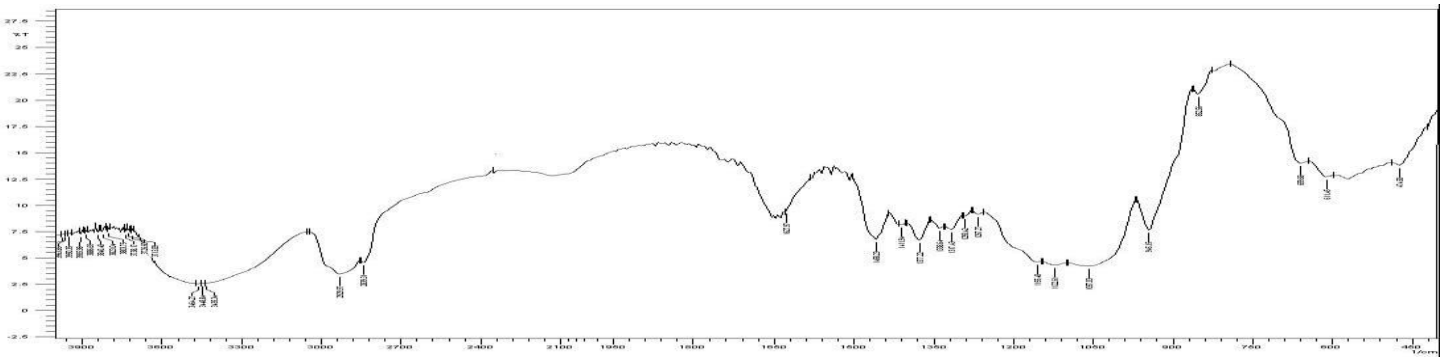

Figure 2: IR spectrum of HPMC E-15 pure

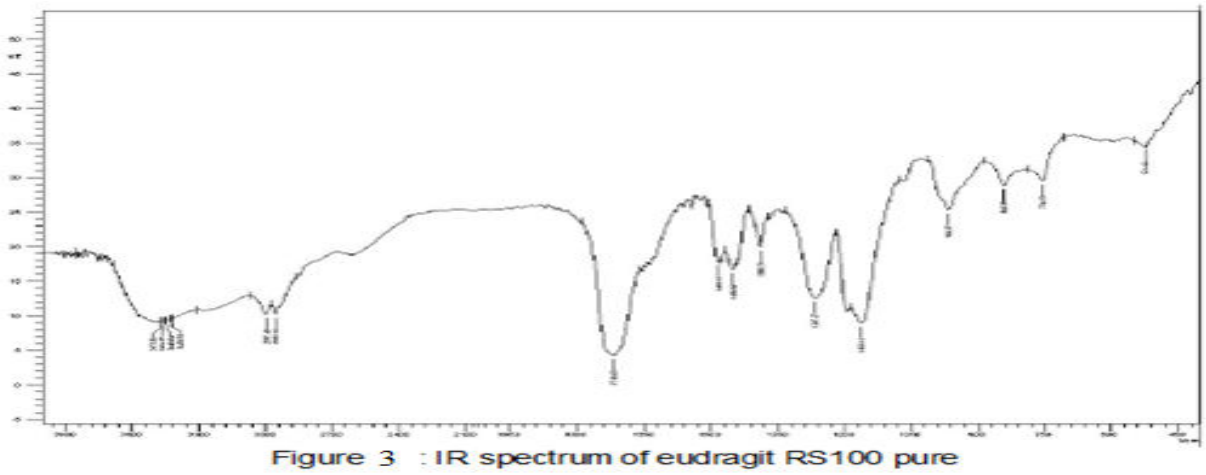

Figure 3: IR spectrum of EugragitRS-100 pure

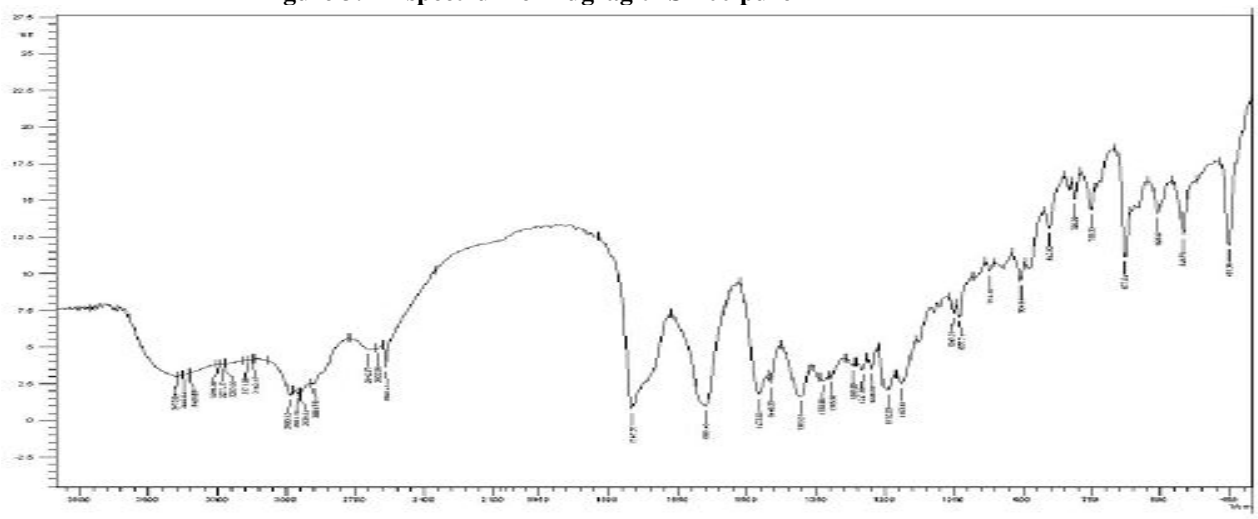

Figure 4: IR spectrum of captopril, HPMC E-15 and eudragit RS100 mixture

Thickness

Table 3: Thickness uniformity data of F_1 to F_6 formulations

Formulation Code	Trial 1(mm)	Trial 2(mm)	Trial 3(mm)	Mean ± S.D.*
F_1	0.22	0.2	0.21	0.21±0.001
F_2	0.19	0.19	0.19	0.19±0.000
F_3	0.18	0.19	0.18	0.1833±0.0057
F_4	0.18	0.18	0.18	0.18±0.000
F_5	0.19	0.18	0.19	0.1866±0.005
F_6	0.17	0.18	0.17	0.1733±0.005

S.D*: Standard deviation of three determinations

Weight uniformity

Table 4: Weight uniformity data of F_1 to F_6 formulations

Formulation	Trial 1	Trial 2	Trial 3	Mean ± S.D.*
F_1	0.042	0.044	0.042	0.0426±.0016
F_2	0.035	0.033	0.033	0.0336±0.0016
F_3	0.033	0.030	0.031	0.0313±0.0015
F_4	0.034	0.034	0.032	0.0333±0.0016
F_5	0.035	0.032	0.034	0.0336±0.0015
F6	0.033	0.033	0.034	0.0335±0.0015

S.D*: Standard deviation of three determinations

Tensile strength

Table 5: Tensile strength data of F_1 to F_6 formulations

Formulation	Trial 1	Trial 2	Trial 3	Tensile strength(Kg ± S.D.)
F_1	2.842	2.831	2.850	2.841±0.009
F2	2.224	2.229	2.223	2.225±0.003
F_3	1.692	1.699	1.702	1.697±0.005
F4	1.846	1.842	1.848	1.845±0.003
F_5	1.823	1.827	1.821	1.823±0.003
F_6	1.870	1.868	1.865	1.867±0.002

S.D*: Standard deviation of three determinations

Folding endurance

Table 6: Folding endurance data of $F_1$to F_6 formulations

Formulation	Trial 1	Trial 2	Trial 3	Mean ± S.D.*
F_1	150	165	158	157.66±7.505
F_2	113	129	125	122.33±8.326
F_3	82	76	88	82±6
F_4	104	92	97	98±6.027
F_5	75	76	67	72.66±4.932
F_6	86	89	93	89.33±3.511

S.D*: Standard deviation of three determinations

Percentage moisture absorption

Table 7: Percentage moisture absorption data of $F_1$to F_6 formulations

Formulation	Trial 1 %	Trial 2 %	Trial 3 %	Mean ± S.D* %
F_1	6.976	6.976	9.302	7.751±1.342
F_2	2.857	8.571	8.571	6.666±3.298
F3	8.823	5.882	8.823	7.842±1.697
F_4	12.121	15.151	9.09	12.12±3.03
F_5	9.09	9.09	9.09	9.09±0.00
F_6	9.375	12.5	9.375	10.416±1.815

S.D*: Standard deviation of three determinations

Percentage moisture loss

Table 8: Percentage moisture loss data of $F_1$to F_6 formulations

Formulation	Trial 1 %	Trial 2 %	Trial 3 %	Mean ± S.D.* %
F_1	42.857	39.285	42.857	41.666±2.062
F_2	11.111	11.111	14.814	12.345±2.137
F_3	13.793	13.793	10.344	12.643±1.991
F_4	9.677	6.451	9.677	8.6016±1.862
F_5	15.625	12.5	12.5	13.541±1.804
F_6	18.75	12.5	12.5	14.583±3.608

S.D*: Standard deviation of three determinations

Water vapour transmission rate (WVTR)

Table 9: Water vapour transmission rate data of $F_1$to F_6 formulations

Formulation	Trial 1	Trial 2	Trial 3	Mean ± S.D.*
F1	0.066	0.0063	0.0066	0.0065±0.0001
F_2	0.0072	0.0083	0.0063	0.0072±0.001
F3	0.0063	0.0046	0.0072	0.006±0.001
F_4	0.0063	0.0075	0.0075	0.0071±0.0006
F_5	0.0057	0.0075	0.008	0.007±0.0012
F_6	0.0049	0.0077	0.0083	0.0069±0.0018

S.D*: Standard deviation of three determinations

Drug content uniformity

Table 10: Drug content uniformity data of $F_1$to F_6 formulations

Formulation	Trial 1 (mg)	Trial 2(mg)	Trial 3(mg)	Mean ± S.D.* (mg)
F_1	1.97	1.96	1.98	1.97±0.001
F_2	1.95	1.94	1.93	1.94±.01
F_3	1.8	1.81	1.8	1.8±.005
F_4	1.91	1.91	1.92	1.91±.005
F_5	1.88	1.92	1.86	1.88±0.03
F_6	1.93	1.9	1.88	1.9±0.025

S.D*: Standard deviation of three determinations

In vitro release studies

Table 11: Compilation of in vitro release of captopril at 24 hrs

S. No	Formulation code	% cumulative release
1	F_1	97.093±1.71*
2	F_2	97.37±1.33**
3	F_3	85.53±2.403
4	F_4	97.626±1.142
5	F_5	96.37±1.117
6	F_6	94.573±0.534

*7 hrs and ** 12 hrs

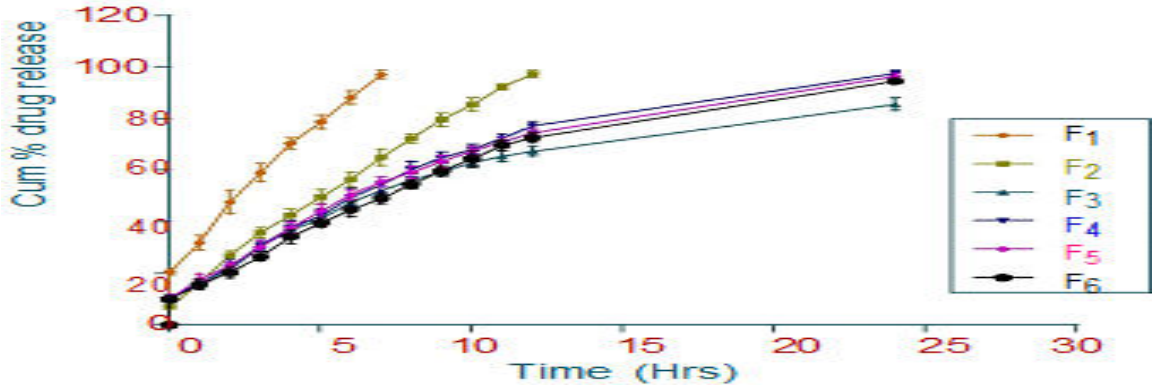

Figure 5: Cumulative % drug release from transdermal patches

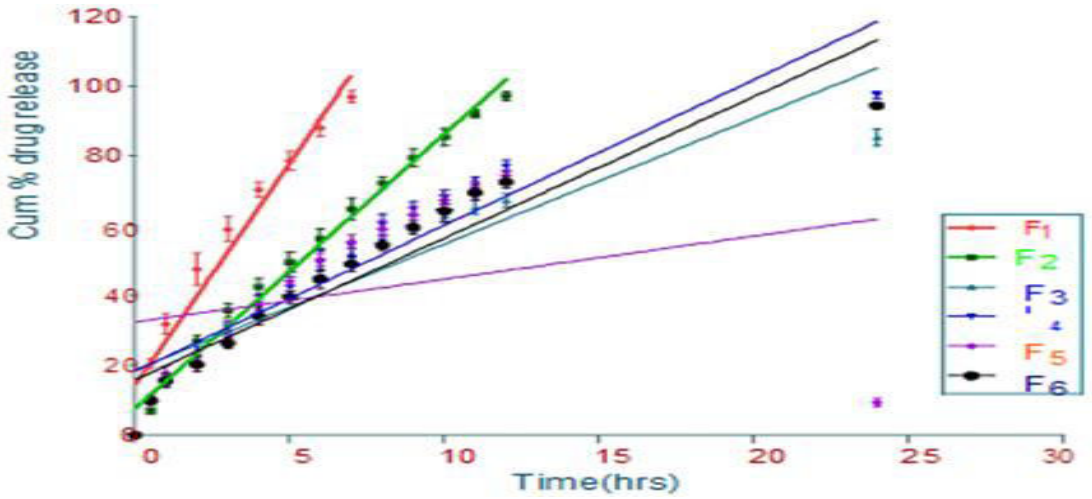

Figure 6: Zero order release kinetic profile of captopril TDDS

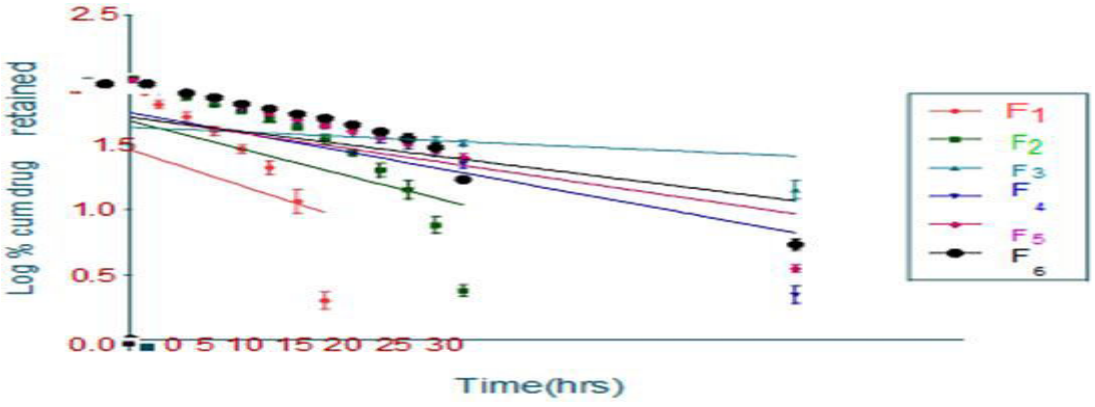

Figure 7: First order release kinetic profile of captopril TDDS

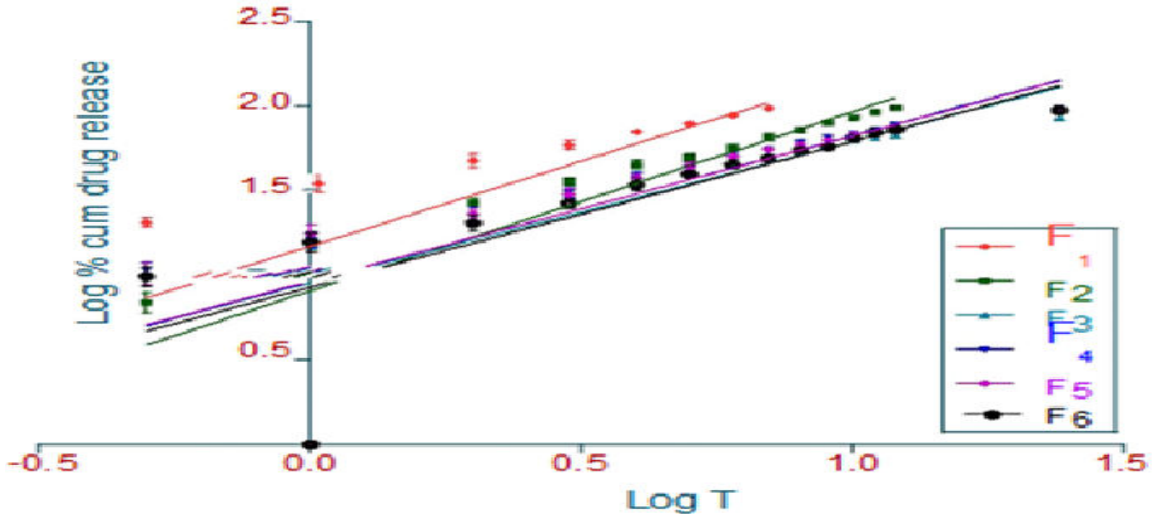

Figure 8: Peppas release kinetic profile of captopril TDDS

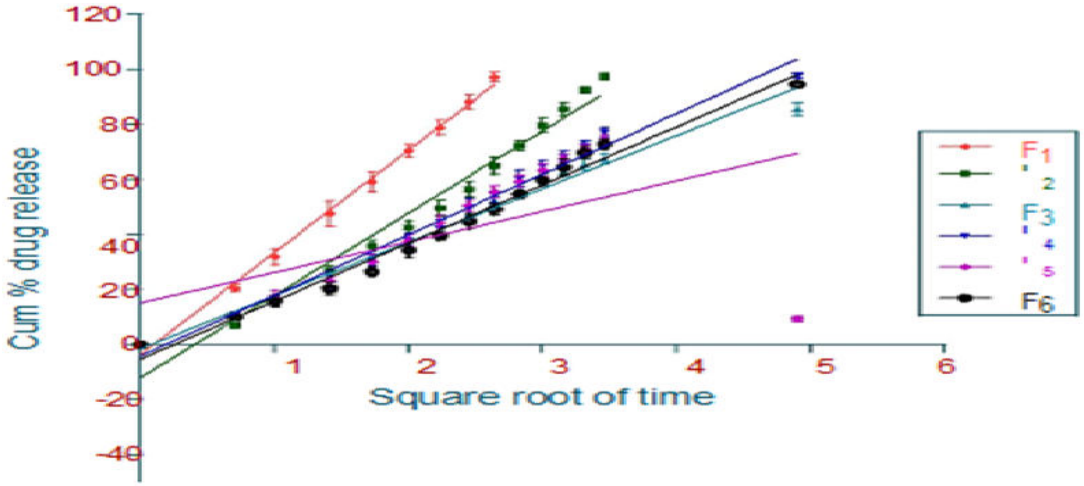

Figure 9: Higuchi release kinetic profile of captopril TDDS

Table 12: Results of model fitting of captopril TDDS

Formulation	Zero order	First order	Higuchi	Peppas	' n'values for Peppas
F1	0.9779±0.013	0.8432±0.027	0.9959±0.002	0.9883±0.010	0.5679±0.006
F2	0.9903±0.004	0.8573±0.027	0.9896±0.005	0.9894±0.007	0.7872±0.030
F3	0.8483±0.004	0.9870±0.004	0.9767±0.001	0.9873±0.002	0.5855±0.003
F4	0.8789±0.124	0.9657±0.013	0.9830±0.002	0.9920±0.001	0.6105±0.029
F5	0.9002±0.011	0.9793±0.007	0.9859±0.001	0.9908±0.0008	0.6039±0.038
F6	0.8787±0.005	0.9864±0.002	0.9840±0.002	0.9904±0.001	0.6184±0.035

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 F_1 which is containing HPMC E-15 alone showed better drug release, but lasts for only 7 hrs. Formulation F_2 containing HPMC E-15: eudragit RS 100 (2:1) shows comparable release with F_1 but it lasts for 12 hrs. The formulation F_3 containing HPMC E-15: eudragit RS 100 (1:1) shows extended release up to 24 hrs when compared to formulations F_1 and F_2 but the drug is not completely released at the end of 24 hrs. The patches F_4 to F_6 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.

REFERENCES

1. Singh P, Maibach HI. Iontophoresis in drug delivery: basic principles and applications. Crit Rev Ther Drug Carrier Syst 1994; 11:161-213.

2. Joseph R, Robinson, Vincent HL. Controlled drug delivery fundamentals and applications. Revised and Expanded: Lee. Marcel Dekker, Inc; 2005. p.524.

3. Moser K. Passive skin penetration enhancement and its quantification in-vitro. Eur J Pharm Biopharm 2001; 52:103-112.

4. Hussein I. El-Subbagh, Abdullah A.Al-Badr, Profiles of drug substances, Excipients and Related Methadology, Elsevier Inc, 2009; 34: 38-110.

5. Sanap GS, Dama GY, Hande AS, Karpe SP, Nalawade SV, Kakade RS, et al. Preparation of transdermal monolithic systems of indapamide by solvent casting method and the use of vegetable oils as permeation enhancer. Int J Green Pharm 2008; 2:129-33.

6. Patel HJ, Patel JS, Desai BG, Patel KD. Design and evaluation of amlodipine besilate transdermal patches containing film former. Int J Pharma Res Dev 2009; 7:1-12.

7. Kulkarni RV, Mutalik S, Hiremath D. Effect of plasticizers on the permeability and mechanical properties of eudragit films for transdermal application. Ind J Pharm Sci 2002; 64(1):28-31.

8. Murthy TEGK and Kishore VS. Effect of casting solvent and polymer on permeability of propranolol hydrochloride through membrane controlled transdermal drug delivery system. Indian J Pharm Sci 2007; 69(5):646-50.

9. Murthy TEGK, Kishore VS. Effect of casting solvent on permeability of antihypertensive drugs through ethyl cellulose films. J Sci Ind Res 2008; 67:147-50.

10.Subramanian K, Sathyapriya LS, Jayaprakash S, Prabhu RS, Abirami A, Madhumitha B et al. An Approach to the formulation and evaluation of transdermal DDS of isoxsuprine HCl. Int J Pharm Sci Tech 2008; 1(1):22-8.

11. Shinde AJ, Garala KC, More HN. Development and characterization of transdermal therapeutics system of tramadol hydrochloride. Asian J Pharm 2008; 2:265-69.

12. Devi KV, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev Ind Pharm 2003; 29(5):495-503.

13. Rao V, Mamatha T, Mukkanti K and Ramesh. Transdermal drug delivery system for atomoxetine hydrochloride – in vitro and ex vivo evaluation. Current Trends in Biotechnology and Pharmacy 2009; 3(2):188-96.