International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

ISSN:2347-6567

IJAMSCR |Volume 11 | Issue 2 | Apr - Jun - 2023
www.ijamscr.com

Research article *Medical research*

Fabrication and characterization of ace inhibitor loaded transdermal patches

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Published on: 05.05.2023

ABSTRACT

The aim of the study is to formulate and evaluate transdermal patches of Captopril In the present study, matrix type was prepared by molding techniques. This mode of drug delivery is more beneficial for chronic disorders such hypertension and some types of congestive heart failure, which require long term drug administration to maintain therapeutic drug concentration in plasma. Transport of drugs or compounds via skin is a complex phenomenon, which allows the passage of drugs or compounds into and across the skin. In the present work an attempt has been made to formulate and evaluate the transdermalpatches of Captopril using various blends of polymer.The polymeric Eudragit grade used for the formulation of transdermal patches showed good film forming property.The patches formed were thin, flexible, smooth and transparent. The weight variation tests showed less variation in weight and suggesting uniform distribution of drug and polymer over the mercury surface. The thicknesses of the transdermal patches were found to increase on increasing concentration of polymers.All the patches showed good flexibility and folding endurance properties. The result suggeststhat the formulations with increased polymer concentration showed long folding endurance.The *in-vitro* drug release studies showed that formulations F3 with increased concentration of polymer showed good release. The drug content analysis showed minimum variations suggesting uniform distribution of drug.

Keywords: Captopril,Transdermal drug delivery.

INTRODUCTION

Controlled drug delivery

Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release.

The term controlled release has a meaning that goes beyond scope of sustained release. The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically, but also reproducible from one unit to other[1].the difference between sustained release and controlled release is shown by fig.1.

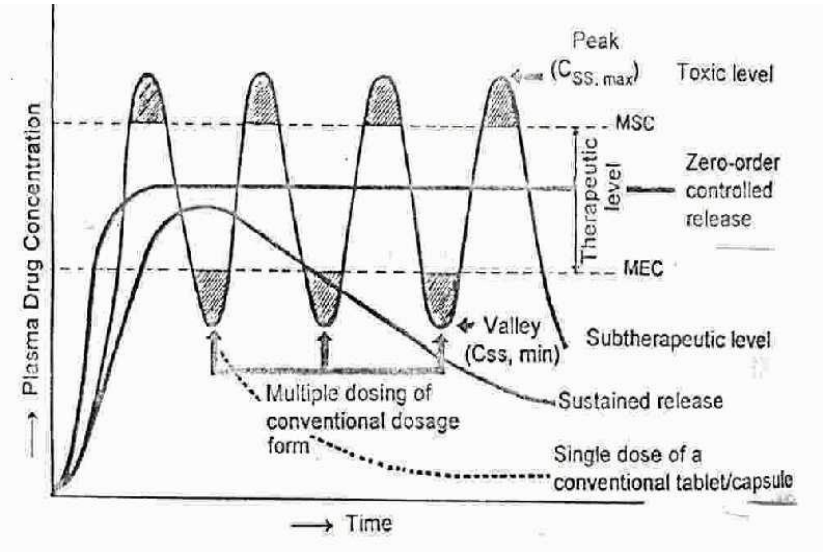

Fig. 1: Comparative graphs of conventional, sustained- and controlled release delivery systems.

The classification of controlled drug delivery can be given as follows.

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Out of these classes first class contains new drug delivery systems as transdermal delivery, intra uterine delivery, ocular inserts, and sub dermal implants. The transdermal drug delivery has advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time.

Transdermal drug delivery: An Introduction

The idea of delivering drugs through skin is old, as the use is reported back in 16th century B.C. Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation.

Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin typically cardiac drugs such as nitroglycerin and hormones such as estrogen.

Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation.

The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a one-day period.

Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories — therapeutic and cosmetic), aroma patches, and weight loss patches, and patches that measure sunlight exposure. Transdermal drug delivery has many advantages over conventional drug delivery and can be discussed as follows.

Advantages[2, 3, 4, 5]

- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
- They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea.
- They avoid the first-pass effect, that is, the initial pass of s drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
- They are noninvasive, avoiding the inconvenience of parenteral therapy.
- They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
- The activity of a drugs having s short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
- They are easily and rapidly identified in emergencies (e.g., unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.
- They are used for drugs with narrow therapeutic window. At the same time transdermal drug delivery has few disadvantages that are limiting the use of transdermal delivery.

Disadvantages[3, 4, 6]

- Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- The delivery system cannot be used for drugs requiring high blood levels.

- The use of transdermal delivery may be uneconomic. For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.

The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers.[6,9,10.]

- **The epidermis** – thin protective outer layer.
- **The dermis** – the tough elastic second layer.
- **The hypodermis** – layer of fatty and connective tissue.

The Epidermis

The outer (epidermal) layer of the skin is composed of stratified squamus epithelial cells. The multilayered envelope of the epidermis varies in thickness, depending on cell size and then number of cells and then number of cell layers, ranging from about 0.8mm on the palms and the soles down to 0.66mm on the eyelids. Cells which provide epithelial tissue differ from those of all other organs provide epithelial tissue differ from those of all other organs in that as they change in an ordered fashion from metabolically active and dividing cells to dense, dead, keratinized protein.

Stratum germinativum (basal layer)

The basal cells are nucleated, columnar, and about 6 microns wide, with their long axis at right angles to the dermoepidermal junction; they connect by cytoplasmic intercellular bridges. Mitosis of the basal cells constantly renews the epidermis and this proliferation in healthy skin balances the loss of dead horny cells from the skin surface. The epidermis thus remains constant in thickness. Below the basal cell layer lies the complex dermoepidermal junction, which constitutes an anatomic functional unit. The junction serves three functions of dermal-epidermal adherence, mechanical support for the epidermis, and control of the passage of cells and some large molecules across the junction.

Stratum spinosum (prickle cell layer)

As the cells produced by the basal layer move outward, they alter morphologically and histochemically. The cells flatten and their nuclei shrink. These polygonal cells are called as prickle cells because they interconnect by fine prickles.

Stratum granulosum (granular layer)

As the Keratinocytes approach the surface, they manufacture basic staining particles, the keratohyalin granules. It was suggested that these granules represent an early form of keratin 3, 4. The term transitional zone is convenient region between living cells and dead keratin.

Stratum lucidum

In the palms and the soles an anatomically distinct, poorly staining hyaline zone forms a thin, translucent layer immediately above layer immediately above the granular layer. This region is the stratum lucidum.

Stratum corneum (horny layer):

As the final stage of differentiation, epidermal cells construct the most the superficial layer of the epidermis, the stratum corneum. On general body areas the membrane provides 10-15 layers of much flattened, keratinized dead cells (corneocytes). Ultimately these cells are sloughed off through desquamation.

The barrier nature of stratum corneum depends critically on its unique constituents; 75-80% is protein, 5-15% is lipid with 5-10% unidentified on a dry weight basis. The protein is located primarily within the keratinocytes and is predominantly alpha-keratin (around 70%) with some beta-keratin (approximately 10%) and a proteinaceous cell enveloping (around 5%). Enzymes and other proteins account for approximately 15% of the protein component. The cell envelop protein is highly insoluble and is very resistant to chemical attack.

MATERIALS

Double beam UV Visible Spectrophotometer (Lab India UV 3000), Digital weigh balance (Sartourious), FTIR Spectrophotometer (Bruker), Magnetic Stirrer (2MLH), Remi Equipments, Mumbai, India, Franz diffusion cell, Remi Equipments, Mumbai, India.

METHODOLOGY

Analytical method development

UV scan

A 100mg of Captopril was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH- 7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10µg/ml. 10µg/ml solution was scanned from 200-400nm.

Construction of calibration curve:

A 100mg of Captopril was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH-7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). It was further diluted with phosphate buffer pH – 7.4 to get solutions in concentration range of 5, 10, 15, 20 and 25µg /ml. The absorbances of these solutions were determined spectrophotometrically at 290 nm.

Preformulation study

A. Colour, Odour, Taste and Appearance: The drug sample was evaluated for its Colour, odour and appearance.

B. Melting point determination: Melting point of the drug sample was determined by capillary method by using melting point apparatus.

C. Determination of solubility: The solubility of Captopril was determined by adding excess amount of drug in the solvent.The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows.

Saturated solution of Captopril prepared using 10 ml. of distilled water/ phosphate buffer pH 7.4 in 25 ml volumetric flasks in triplicate. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flasks were shaken for 48 hours.

Formulation of transdermal patches

Preparation of blank patches

Polymers of single or in combination were accurately weighed and dissolved in respective solvent and then casted

in a Petri-dish with mercury as the plain surface. The films were allowed to dry overnight at room temperature.

Formulation of drug incorporated transdermal patches

Solvent evaporation technique

The matrix-type transdermal patches containing Captopril were prepared using different concentrations of Eudragit grade polymers. The polymers in different concentrations were dissolved in the respective solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Dibutyl phthalatewas used as plasticizers. Then the solution was poured on the Petri dish having surface area of 78 cm2 and dried at the room temperature.

Table 1: Formulation of Captopril patches

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Captopril	25	25	25	25	25	25	25	25	25
Eudragit-L100	40	80	120	-	-	-	-	-	-
Eudragit-S100	-	-	-	40	80	120	-	-	-
Eudragit RSPO	-	-	-	-	-	-	40	80	120
Dichloromethane	10	10	10	10	10	10	10	10	10
Methanol	10	10	10	10	10	10	10	10	10
Dibutylphthalate (in %w/v)	20	20	20	20	20	20	20	20	20
Dimethylsulphoxide (ml)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

All the quantities were in mg

RESULTS AND DISCUSSION

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

Analysis of drug

UV scan

The lambda max of Captopril was found to be 290nm.

Construction of calibration curve

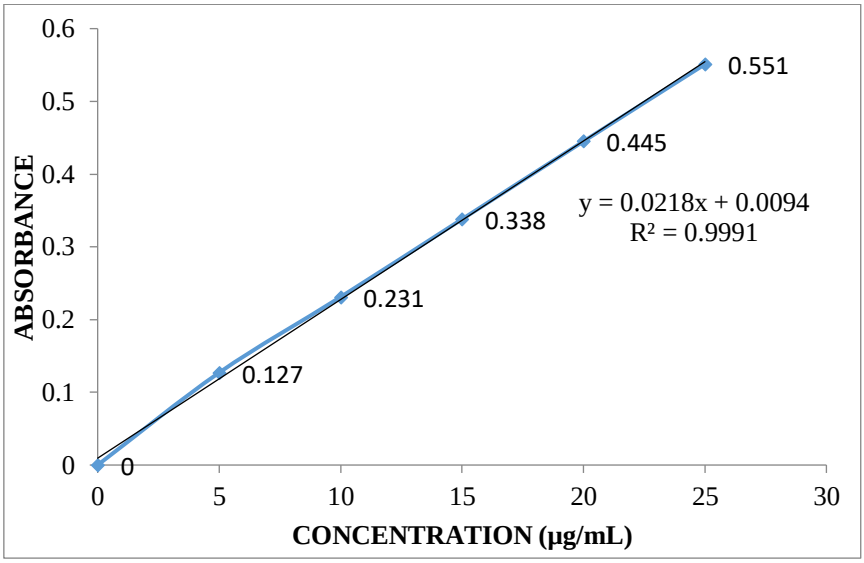

Fig2: Standard calibration curve of Captopril

Table 2: Evaluation of patches

Formulation Code	Average weight (mg)	Thickness (mm)	Folding endurance	Flatness (%)	Flatness (%)	% Drug Content
F1	97±2.85	0.043 ±0.002	74± 0.14	97	Transparent	96.53± 9.25
F2	98±4.64	0.049±0.006	73± 2.10	99	Transparent	98.65 ± 5.14
F3	96±1.25	0.051±0.002	75± 3.17	97	Transparent	98.24± 1.98
F4	97±0.18	0.046±0.006	76± 3.11	98	Transparent	98.30 ± 5.29
F5	100±2.34	0.048±0.001	77± 2.34	96	Transparent	96.56 ± 1.75
F6	99±3.92	0.050±0.005	71± 2.15	95	Transparent	98.17 ± 0.59
F7	98±1.76	0.049±0.003	75± 2.36	99	Transparent	99.93 ± 3.14
F8	97±2.12	0.047±0.002	74± 2.04	99	Transparent	97.47 ± 6.97
F9	97±4.57	0.051±0.004	75± 2.96	97	Transparent	98.38 ± 5.69

In Vitro Drug Release Studies

Table 3:*In vitro* drug permeation of Captopril containing different concentrations of Eudragit-L100

Time (hr)	F1	F2	F3
0	0	0	0
1	22.34	16.39	13.16
2	35.61	25.10	18.34
3	43.52	37.92	28.27
4	55.98	49.00	36.92
5	67.30	57.17	48.83
6	78.18	62.93	54.14
7	87.97	73.26	63.39
8	98.72	84.15	72.92
9		91.38	76.64
10		97.42	86.38
11			92.66
12			98.25

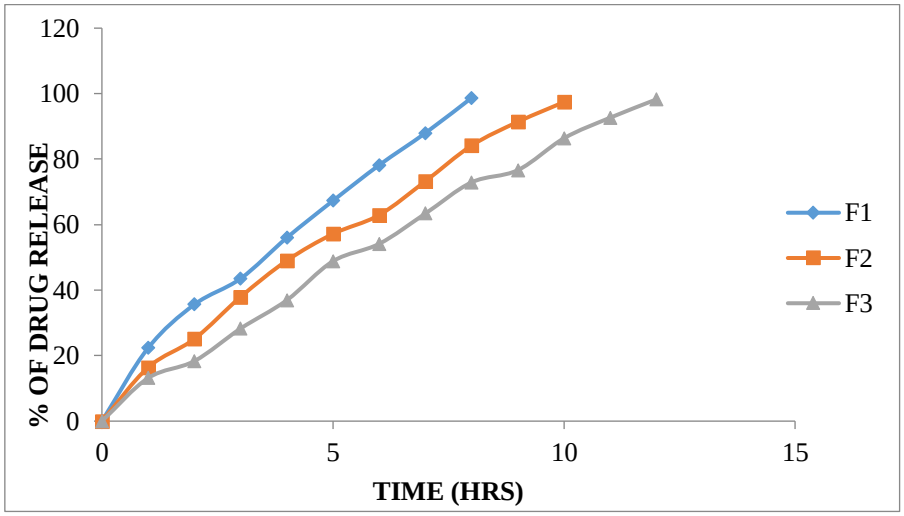

Fig3: Cumulative % drug permeation of Captopril patch (F1, F2, F3)

Table 4:*In vitro* drug permeation of Captopril containing different concentrations of Eudragit-S100

Time (hr)	F4	F5	F6
0	0	0	0
1	28.36	19.81	13.27
2	42.81	25.24	20.34

3	53.36	36.19	27.23
4	70.06	44.52	35.47
5	75.25	57.03	40.19
6	82.18	68.13	47.28
7	87.26	71.94	53.37
8	91.33	78.41	61.46
9	97.51	83.27	70.28
10		86.03	77.37
11		95.64	85.21
12			89.36

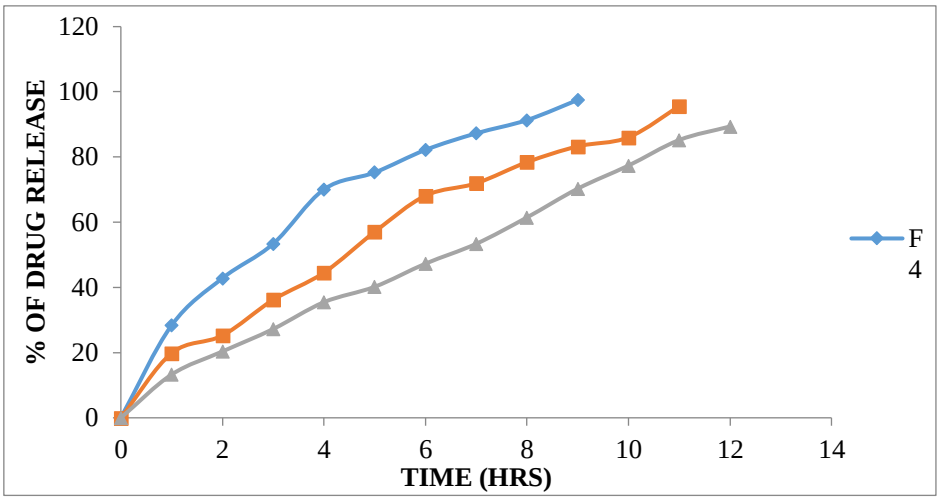

Fig4: Cumulative % drug permeation of Captopril patch (F4, F5, F6)

Table 5:*In vitro* drug permeation of Captopril containing different concentrations of Eudragit RSPO

Time	F7	F8	F9
0	0	0	0
1	15.47	13.15	10.28
2	24.03	22.06	19.46
3	34.43	30.52	26.52
4	42.56	39.37	30.47
5	51.27	47.46	36.61
6	59.84	55.08	42.07
7	67.34	62.31	50.36
8	78.25	70.49	56.13
9	89.38	79.30	61.23
10	98.04	86.21	68.31
11		91.55	75.43
12		98.12	81.37

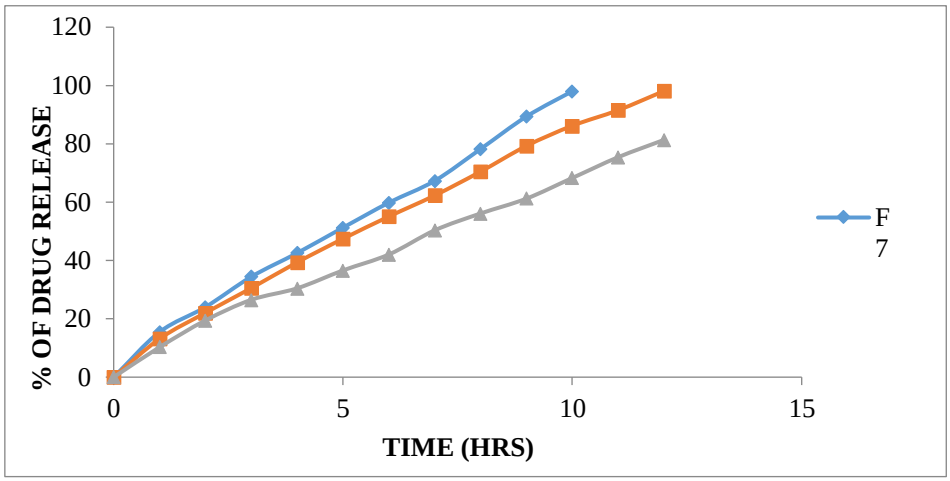

Fig5: Cumulative % drug permeation of Captopril patch (F7, F8, F9)

Table 6: Kinetics data of F3Captopril patch

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
13.16	1	1.000	1.119	0.000	1.939	13.160	0.0760	-0.881	86.84	4.642	4.428	0.213
18.34	2	1.414	1.263	0.301	1.912	9.170	0.0545	-0.737	81.66	4.642	4.338	0.303
28.27	3	1.732	1.451	0.477	1.856	9.423	0.0354	-0.549	71.73	4.642	4.155	0.487
36.92	4	2.000	1.567	0.602	1.800	9.230	0.0271	-0.433	63.08	4.642	3.981	0.661
48.83	5	2.236	1.689	0.699	1.709	9.766	0.0205	-0.311	51.17	4.642	3.713	0.929
54.14	6	2.449	1.734	0.778	1.661	9.023	0.0185	-0.266	45.86	4.642	3.579	1.062
63.39	7	2.646	1.802	0.845	1.564	9.056	0.0158	-0.198	36.61	4.642	3.320	1.321
72.92	8	2.828	1.863	0.903	1.433	9.115	0.0137	-0.137	27.08	4.642	3.003	1.639
76.64	9	3.000	1.884	0.954	1.368	8.516	0.0130	-0.116	23.36	4.642	2.859	1.783
86.38	10	3.162	1.936	1.000	1.134	8.638	0.0116	-0.064	13.62	4.642	2.388	2.253
92.66	11	3.317	1.967	1.041	0.866	8.424	0.0108	-0.033	7.34	4.642	1.943	2.698
98.25	12	3.464	1.992	1.079	0.243	8.188	0.0102	-0.008	1.75	4.642	1.205	3.437

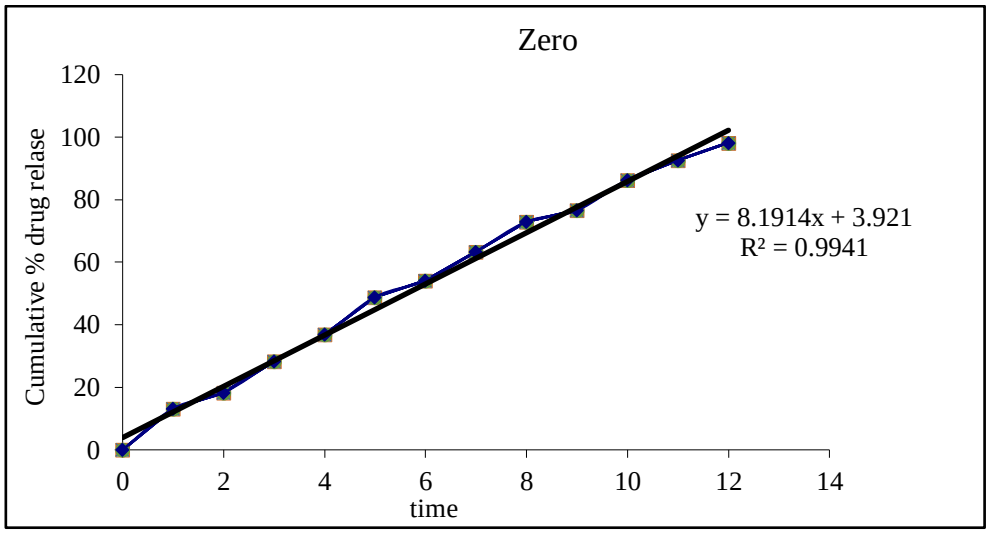

Fig 6: Zero order release kinetics graph

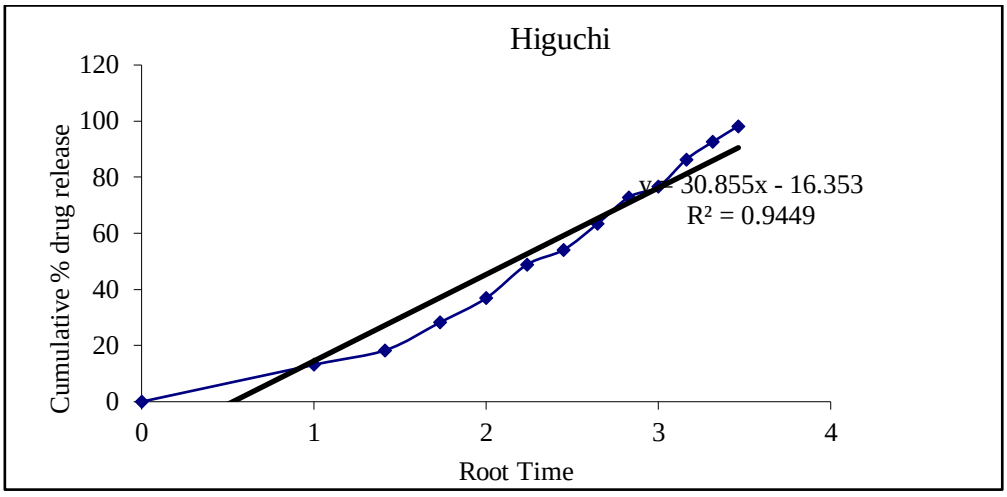

Fig7:Higuchi release kinetics graph

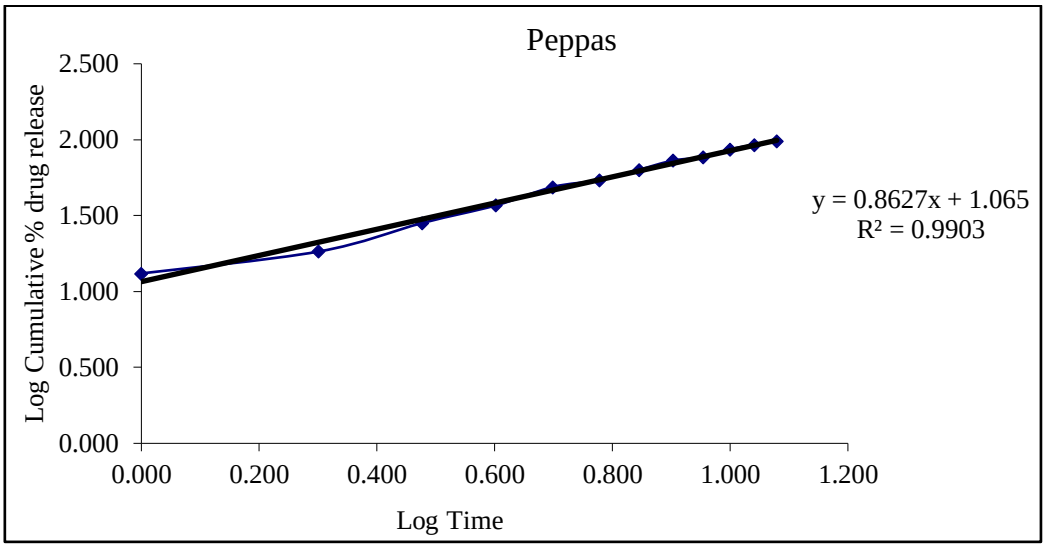

Fig 8:Peppas release kinetics graph

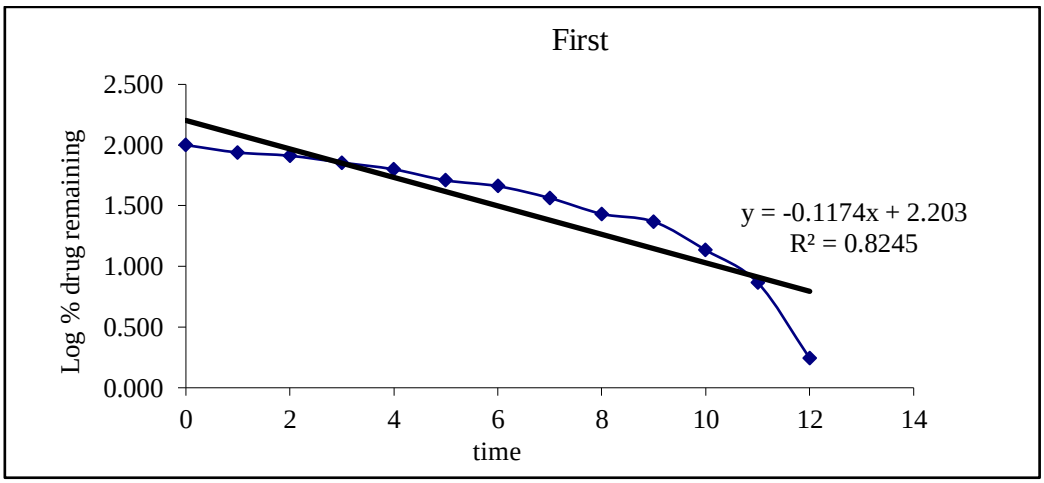

Fig9:First order release kinetics graph

Drug – Excipient compatibility studies

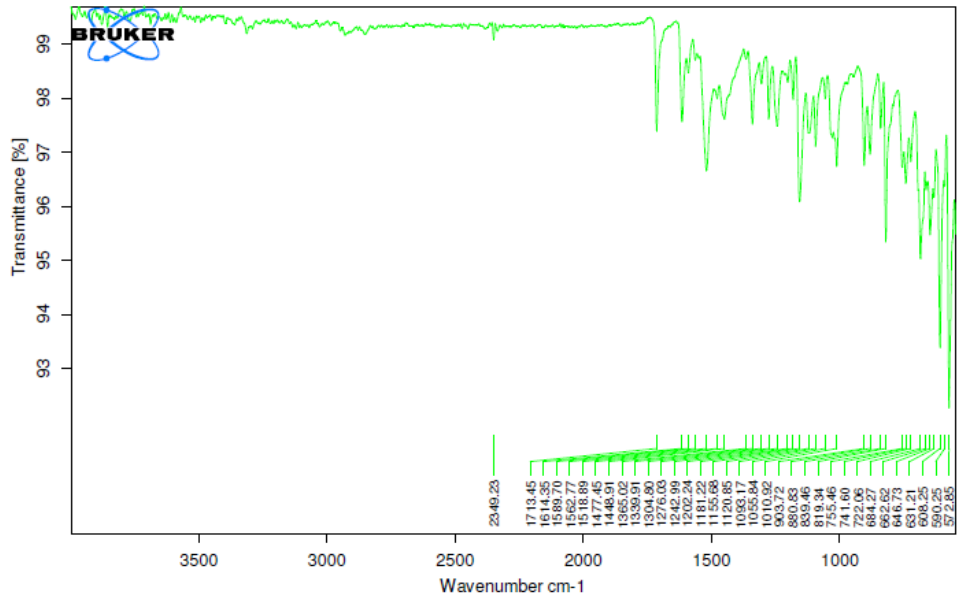

Fig10:FTIR Spectrum of pure Captopril drug

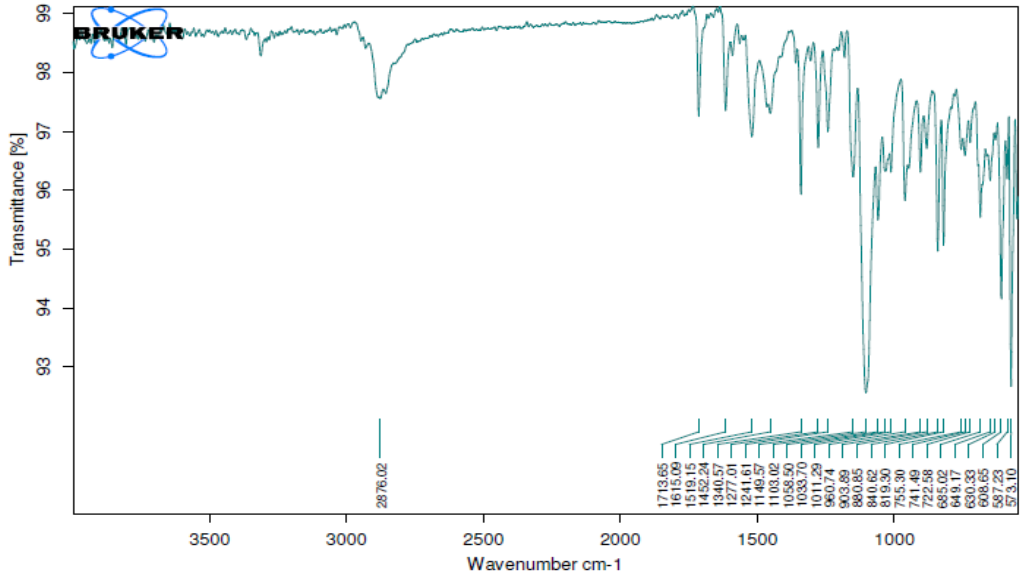

Fig 11: FTIR of Optimized formulation

CONCLUSION

The sustained release of drug from the transdermal patches suggests that the frequency of administration may be reduced. Further, the transdermal patches may improve the bioavailabilityof the drug by avoiding hepatic first pass metabolism. Hence we can conclude that the polymer matrix provide sustained delivery of drug and these systems can be used to deliver drugs with short half-life and low therapeutic index through transdermal drug delivery systems.

- In the present work an attempt has been made to formulate and evaluate the transdermal patches of Captopril using various blends of polymer.
- The Eudragit grade polymeric used for the formulation of transdermal patches showed good film forming property.
- The patches formed were thin, flexible, smooth and transparent.
- The weight variation tests showed less variation in weight and suggesting uniform distribution of drug and polymer over the mercury surface.
- The thicknesses of the transdermal patches were found to increase on increasing concentration of polymers.
- All the patches showed good flexibility and folding endurance properties. The result suggests that the formulations with increased polymer concentration showed long folding endurance.

- The *in-vitro* drug release studies showed that formulations F3 with increased concentration of polymer showed good release.

Based on the observations, it can be concluded that the attempt of formulation and evaluation of the Captopril patches was found to be successful in the release of the drug for an extended period of 12 hrs.

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