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TRANSDERMAL APPROACH OF ANTI -HYPERTENSIVE CAPTOPRIL BY EMPLOYING DIFFERENT POLYMERS

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Abstract:

The skin can be used as the site for drug administration for continuous transdermal drug infusion into the systemic circulation. For the continuous diffusion penetration of the drugs through the intact skin surface membrane-moderated systems, matrix dispersion type systems, adhesive diffusion controlled systems and micro reservoir systems have been developed. Various penetration enhancers are used for the drug diffusion through skin. In matrix dispersion type systems, the drug is dispersed in the solvent along with the polymers and solvent allowed to evaporate forming a homogeneous drug-polymer matrix.

Matrix type systems were developed in the present study. In the present work, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising of Captopril with different concentration of various polymers alone using solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. F3 formulation has been selected as the best formulation among all the other formulations. The in-vitro drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory. The data obtained from the in-vitro release studies were fitted to various kinetic models like zero order, first order, Higuchi model and peppas model. From the kinetic data it was found that drug release follows Zero order kinetics model release by diffusion technique from the polymer.

Keywords: *Captopril, Transdermal drug delivery.*

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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.

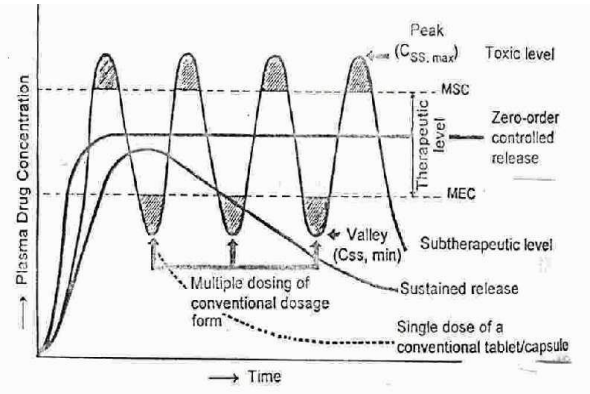

Figure1. 1: Comparative graphs of conventional, sustained- and controlled release delivery systems.

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.

1.1 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.

Definition: 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]

1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
2. They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea.
3. 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.
4. They are noninvasive, avoiding the inconvenience of parenteral therapy.
5. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
6. 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.
7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

8. They are easily and rapidly identified in emergencies (e.g., unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.
9. 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]

1. Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
2. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
3. The delivery system cannot be used for drugs requiring high blood levels.
4. 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.

METHODOLOGY:

7.1. Analytical method development:

A.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.

B. 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 25 µg /ml. The absorbances of these solutions were determined spectrophotometrically at 290 nm.

7.2. 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. The sample withdrawn (1 ml after filtration) was diluted with appropriate medium and analyzed by using UV spectrophotometer at 290 nm and 292 nm for phosphate buffer and distilled water respectively.

7.3. 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 phthalate was used as plasticizers. Then the solution was poured on the Petri dish having surface area of 78 cm2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch. The formulation table is given in table no. 7.1.

Table 7.1: 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
Dibutyl phthalate (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

7
.4. Evaluation parameters of patches
7.4.1. Physical evaluations
a.
Thickness

The thickness of patches was measured by digital Verniers calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation.

b. Folding endurance

The folding endurance was measured manually for the prepared patches. A strip of patch (4x3 cm) was cut evenly 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 exact value of folding endurance.

c. Weight variation

The three disks of 2*1 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

d. Drug content Determination

The prepared drug contained patches specified surface area (2 cm^2) were cut and dissolved in (5% of methanol contained) 100ml of pH 7.4 phosphate buffer, and vigorously shaked for 12hrs, and then sonicated for 15 minutes, centrifuged at 5000 rpm for 30 min. Filter the drug contained polymeric solution through 42 number whatmann filter paper, then 1ml of the filtrate was taken in a test tube and dilute it for five times with same solvent by using double beam Uv-Visible spectrophotometer to determined drug content at λmax 290 nm. Respected Placebo patch was taken as a blank solution.

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

% constriction = I1 – I2 X 100

I2 = Final length of each strip

I1 = Initial length of each strip

7.4.2. *In-vitro* drug diffusion study:

The *in vitro* study of drug permeation through the semi permeable membrane was performed using a Franz type glass diffusion cell. The modified cell having higher capacity (25 ml) is used to maintain sink condition. This membrane was mounted between the donor and receptor compartment of a diffusion cell. The transdermal patch was placed on the membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with isotonic phosphate buffer of pH 7.4. The hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at

constant rpm and the temperature was maintained at 37±0.5ºC. The diffusion was carried out for 12 h and 1 ml sample was withdrawn at an interval of 1 h. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The samples were analyzed for drug content spectrophotometrically at 290 nm

7.5. Drug release kinetics:

Diffusion data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Zero-Order Kinetics:

Zero order as cumulative amount of Percentage drug released vs time

$$C=K0t$$

Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

First order kinetics:

First order as log cumulative percentage of log (%) cumulative drug remaining vs time,

$$L o g C = L o g C o - k t / 2.303$$

Where C0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi model:

Higuchi's model as cumulative percentage of drug released vs square root of time

$$Q = K t 1/2$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Kors meyer Peppas equations:

Korsmeyer peppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet. Log cumulative percentage of drug released VS Log time, and the exponent n was calculated through the slope of the straight line.

$$Mt/M\infty=Ktn$$

Where Mt/M∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n < 0.89, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

7.6. Compatibility study

FTIR study:

The infrared spectrum of the pure Captopril sample was recorded and the spectral analysis was done. The dry sample of drug was directly placed after mixing and triturating with dry potassium bromide.

8. 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.

8.1. Analysis of drug:

A. UV scan:

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

B. construction of calibration curve:

Table 8.1: Standard graph of Captopril

Concentration(µg/ml)	Absorbance (at 290nm)
0	0
5	0.127
10	0.231
15	0.338
20	0.445
25	0.551

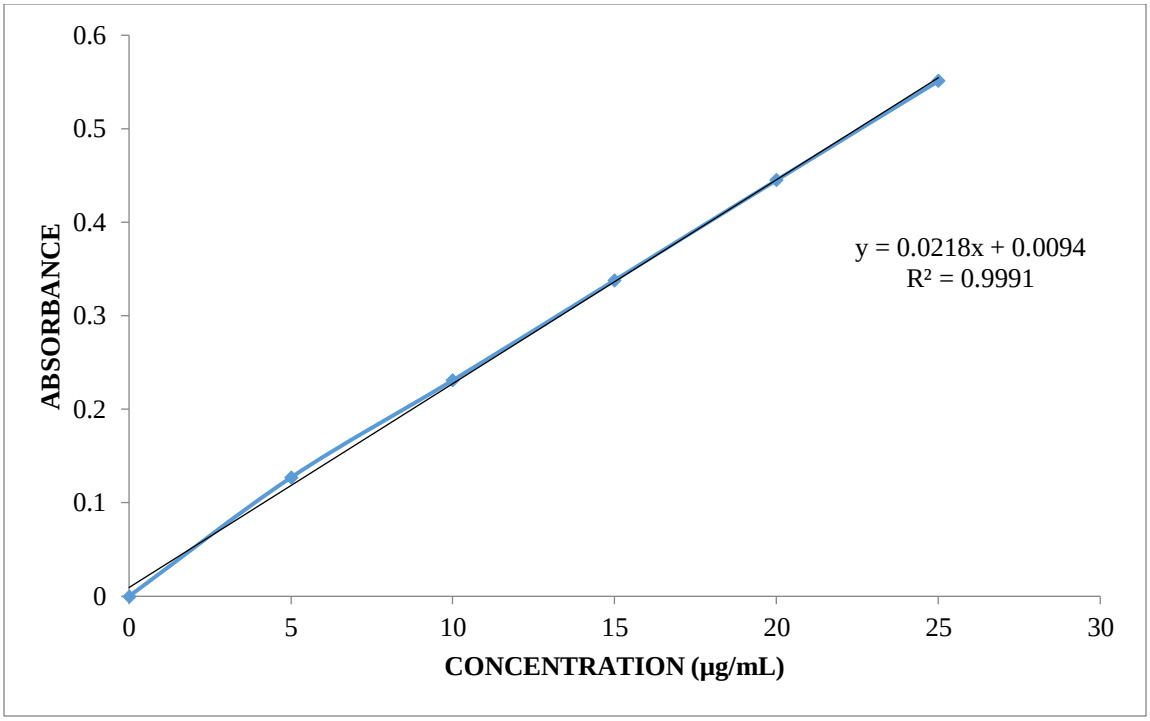

Figure 8.1: Standard calibration curve of Captopril

8.2. Preformulation study

Totally, nine formulation trials were done with the aim to achieve the successful matrix type Captopril transdermal patches. The blend trials prepared for the drug was evaluated for various physical parameters and content uniformity of drug by UV.

A. Colour, odour, taste and appearance

Table 8.2: Results of identification tests of drug

Parameter	Captopril
Color	White
Odor	Odorless
Taste	Bitter
Appearance	A white powder

B. Melting point determination:

Table 8.3: Results of melting point determination tests of drug

Drug	Reported melting point
Captopril	103-104 ^{0}C

C. Determination of solubility:

Table 8.4: Solubility Determination

Solvent	Drug solubility(mg/ml)
Distilled water	0.0403
Ph 7.4 phosphate buffer	78.3

8.3 Evaluation of Patch

The formulations F1 to F9 were varying in thickness when compared to other formulations which is due to the variation in the polymer concentration. Which shows the increase in polymer concentration increases the thickness of patch. For all other formulations it was found to be in between 0.043 ±0.002 to 0.051±0.004 mm.

All formulations from F1 to F 9 Shows weight variation in between 95±3.19 to 100±6.95mg.

Folding endurance from formulations F1 to F9 was found to be in between 71 ± 2.15 to 77 ± 2.34 which can withstand the folding of the skin.
All formulations showed % drug content from 95.32 ± 9.25 to 99.87 ± 1.98.

Table 8.5: 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* diffusion study:**
All the formulation *in vitro* diffusion study was carried out by using Franz type diffusion cell under specific condition such as temp maintained at 32 ± 0.5 ºC. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 8.6: *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

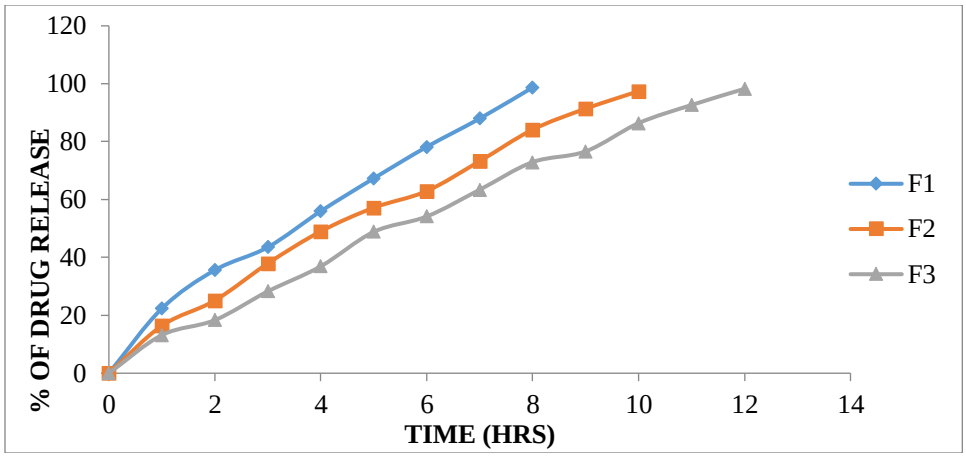

Figure: 8.2 Cumulative % drug permeation of Captopril patch (F1, F2, F3)

The formulations F1 to F3 were prepared by different concentrations of Eudragit-L100 (40, 80, 120mg) the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. At low polymer concentration the drug permeation is more within 8 hours it was total amount of drug was permeated.

Table 8.6: *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

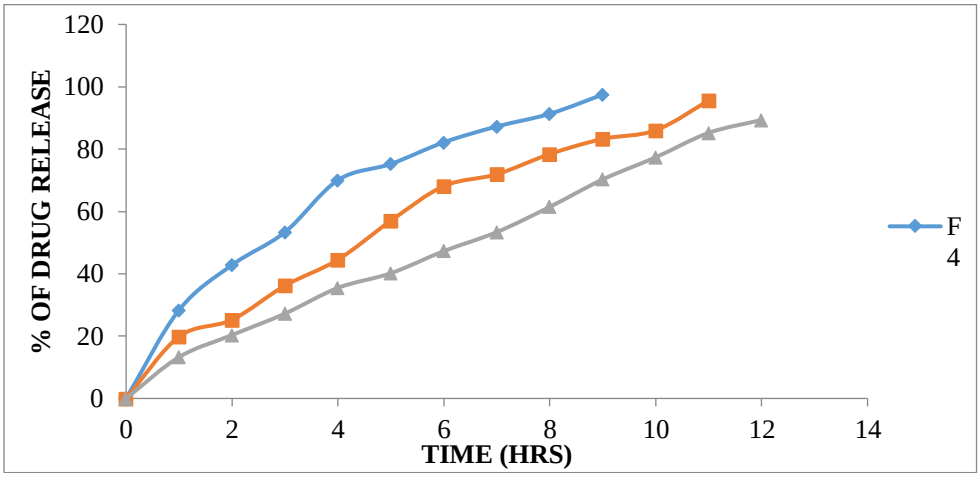

Figure: 8.3 Cumulative % drug permeation of Captopril patch (F4, F5, F6)

The 40mg concentration of polymer was showed maximum drug released at 9 hours 97.51 %. The 80mg concentration of polymer was showed maximum drug release 95.64 at 11 hours. Hence in that 3 formulations F6 formulations showed total drug release at desired time period.

Table: 8.8 *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

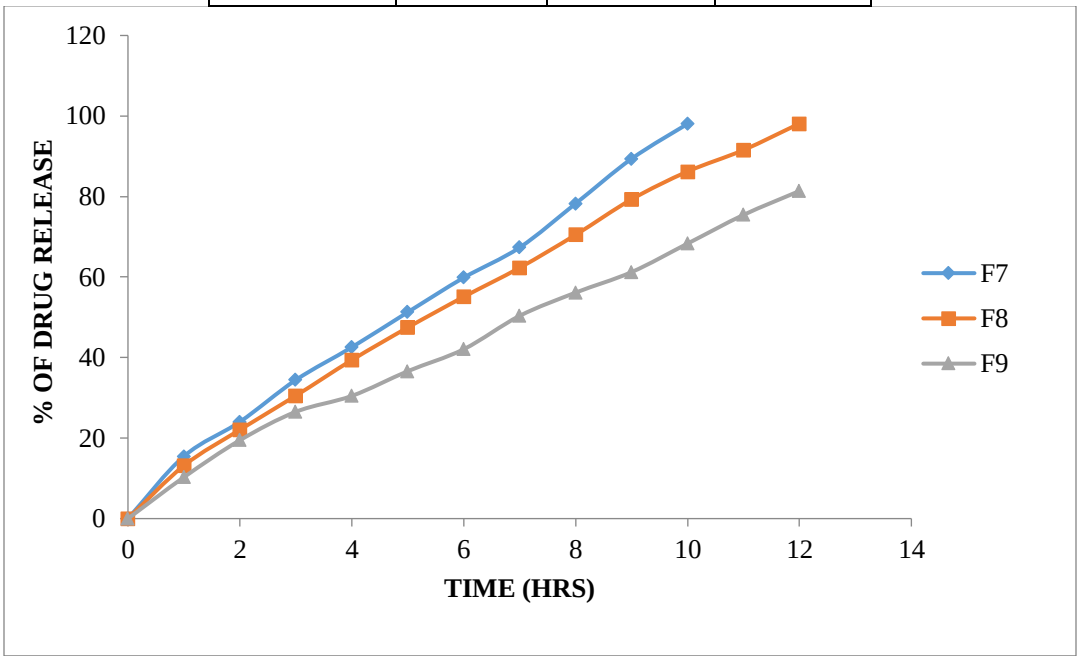

Figure: 8.4 Cumulative % drug permeation of Captopril patch (F7, F8, F9)

The formulations F7 to F9 were prepared by different concentrations of Eudragit RSPO (40, 80, 120mg) the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 40mg (F7) concentration of polymer was showed maximum drug release 98.04 within 10 hours. The 80mg (F8) concentration of polymer was showed maximum drug released at 12 hours 98.12 %. The 120mg (F9) concentration of polymer was showed less drug release 81.37 at 12 h.

Among all 9 formulations F3 formulation showed good drug permeation from the patch.
Among all *in vitro* evaluation parameters F3 formulation passed all evaluation parameters.

8.4 Kinetic models for Captopril

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table: 8.9 Kinetics data of F3 Captopril 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

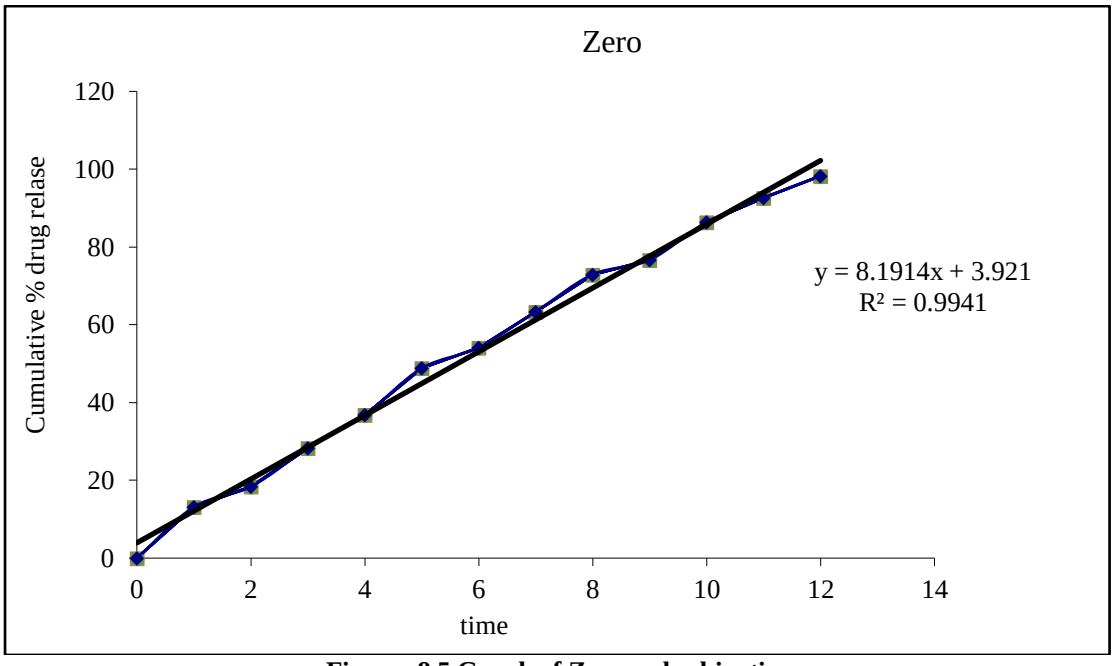

Figure: 8.5 Graph of Zero order kinetics

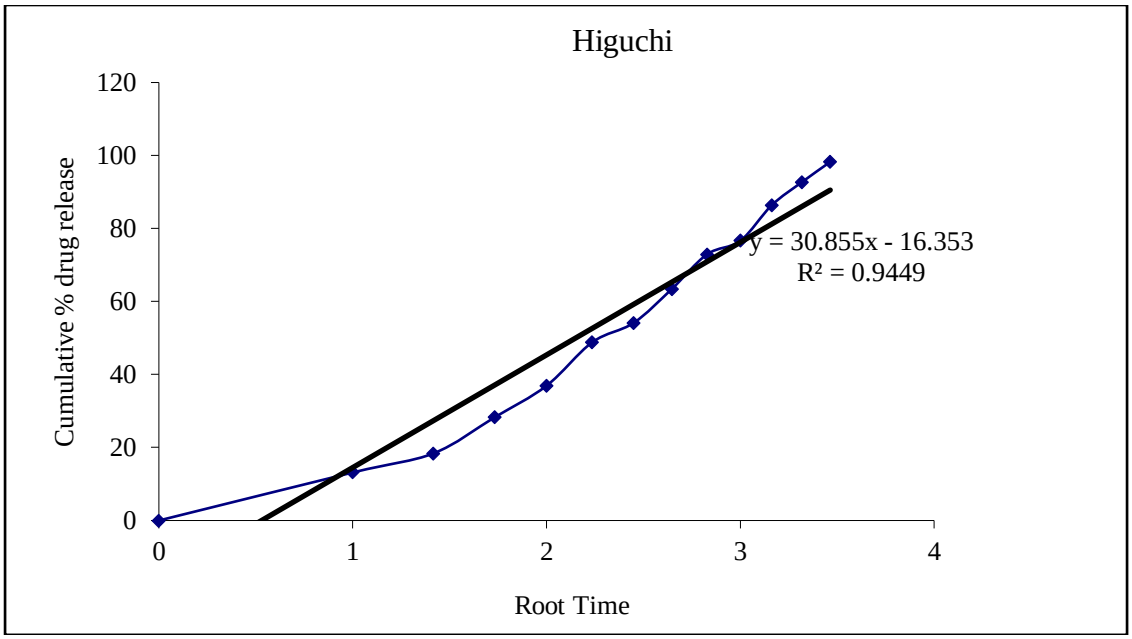

Figure: 8.6 Graph of Higuchi release kinetics

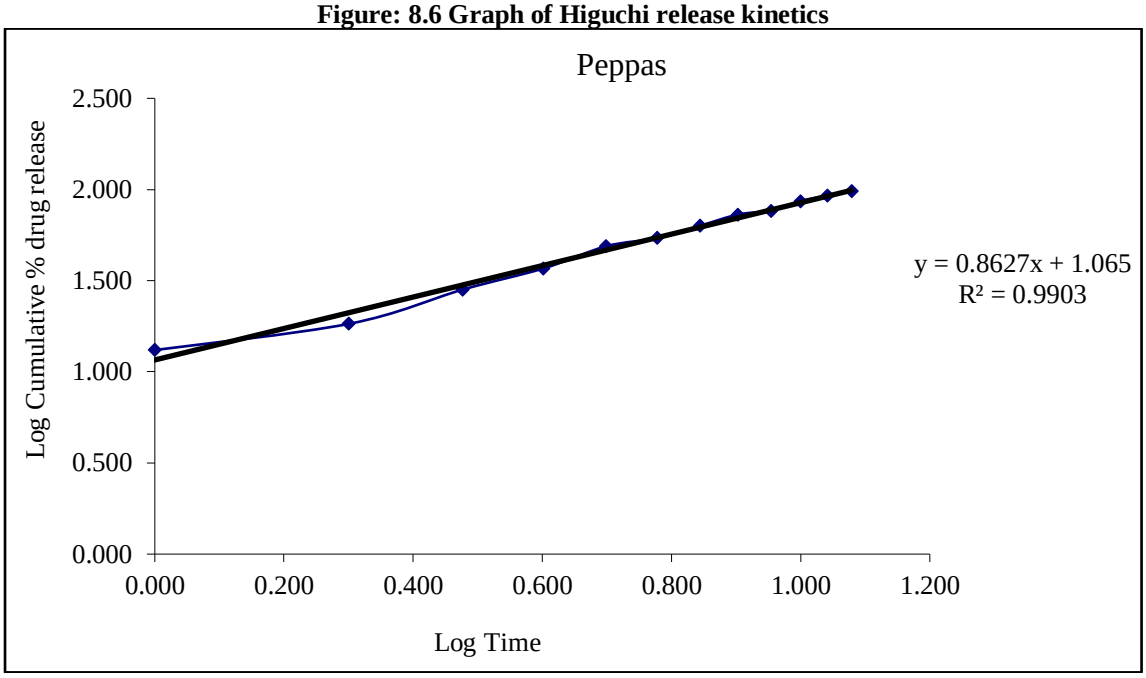

Figure: 8.7 Graph of peppas release kinetics

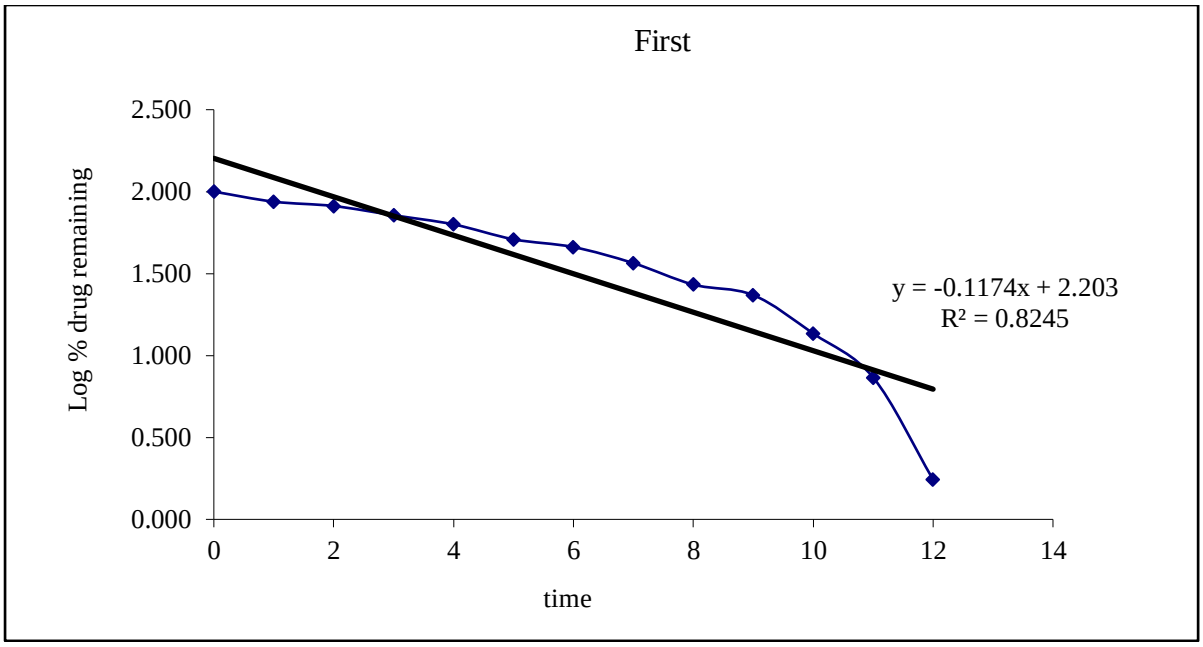

Figure: 8.8 Graph of First order release kinetics

From the above data the optimized formulation followed Zero order kinetics model rule.

8.2. Compatibility studies:

IR SPECTROSCOPY:

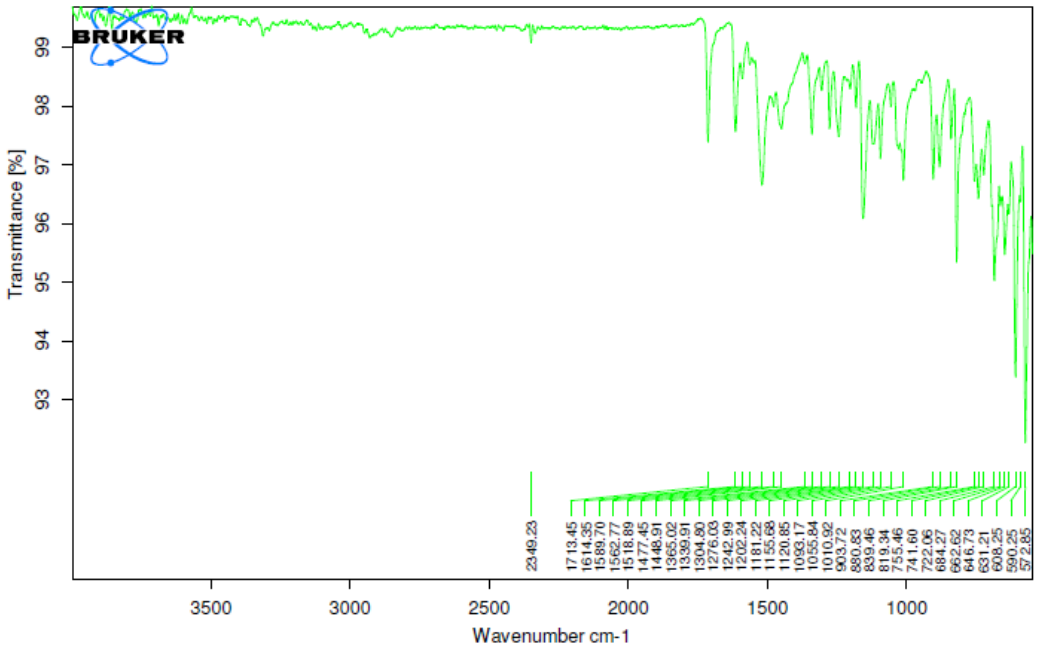

Figure 8.9: FTIR Spectrum of pure Captopril drug

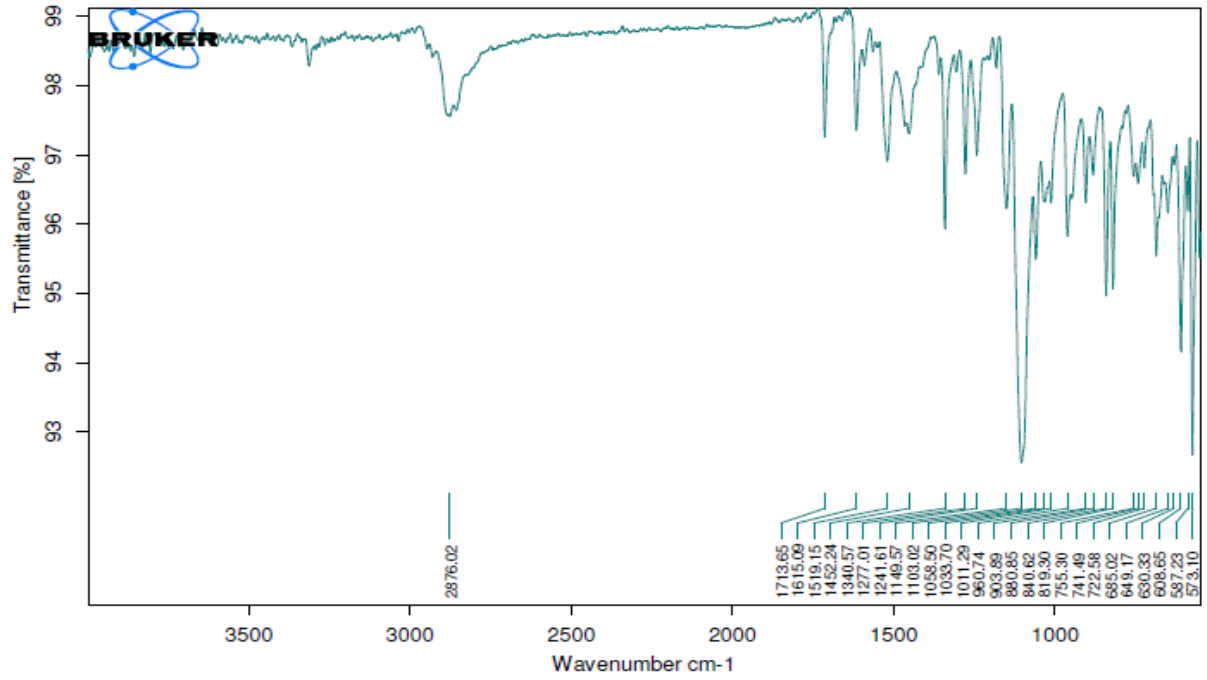

Figure 8.10: FTIR of Optimized formulation

The compatibility studies of the drug with excipients indicate no characteristic visual changes and no additional peaks were observed during FT-IR studies.

9. CONCLUSION:

In the present investigation an attempt has been made to design and develop the formulation of Captopril patches using different types of polymers by solvent evaporation technique method. The drug used is the best studied for therapy in treating hypertension and some types of congestive heart failure.

Captopril was successfully formulated as controlled release transdermal patches, which prevents the frequency of administration and gives good patient compliance.

From the experimental results obtained, F3 formulation has been selected as the best formulation among all the other formulations. The *in-vitro* drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory.

The data obtained from the *in-vitro* release studies were fitted to various kinetic models like zero order, first order, Higuchi model and Pappas model.

From the kinetic data it was found that drug release follows Zero order kinetics release by diffusion technique from the polymer.

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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