Research Article

Formulation And Evaluation Of Sustained Release Tablet Of Captoprilusing Cross-Linked Alginate

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ABSTRACT

Over the past three decades, formulation technology has significantly advanced, particularly in drug delivery systems. Innovations include novel dosage forms and new uses for existing drugs, offering benefits like improved patient compliance, sustained drug concentration, reduced dosing frequency, targeted delivery, and minimized side effects. Transdermal drug delivery systems (TDDS) are key developments, allowing controlled, continuous medication administration through the skin, bypassing gastrointestinal degradation and hepatic first-pass metabolism, and enhancing bioavailability and patient compliance. The FDA approves roughly one transdermal product every 2.2 years, with the first patch approved four decades ago. This research examines the skin's role as a barrier, clinical trials, patents, commercialization, and the benefits and limitations of TDDS. Various TDDS methods are reviewed, highlighting their advantages, disadvantages, and potential applications. Recent advancements demonstrate TDDS's effectiveness and potential across diverse sectors, emphasizing their transformative impact on drug delivery and therapeutic practices.

INTRODUCTION

Research in the field of sustained release delivery system is extremely fertile and produced many discoveries. Different drug has basic goal is to achieve steady state blood level that is therapeutically effective and non toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Over recent years, as the expense and complication involved in marketing new entities have increased with accompanying recognition of the therapeutic use of controlled drug delivery,

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greater attention has been focused on the development of sustained or controlled drug delivery system.Sustained release, sustained action, prolonged action, controlled release, extended action and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of the oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT. Captopril belongs to class Angiotensin Converting Enzyme inhibitor (ACE inhibitor).The impact is on the renin-Angiotensin system, where it hinders the transformation of Angiotensin I, which is relatively inactive, into the active Angiotensin II. Interaction of Captopril with iron and other transition metals has been documented in literature. It has been postulated by the researchers that this interaction might be peculiar to Captopril within the class of ACE inhibitors due to the presence of a sulfhydryl functional group. Consequently, in cases where a patient necessitates an ACE inhibitor and is also taking iron salts, alternative agents to Captopril should be contemplated. Captopril is highly soluble in water and possesses a half-life of 1.9 hours. The primary objective of this research endeavour was the formulation of sustained release tablets of Captopril by employing different proportions of Xantham gum and Ethyl cellulose.

MATERIALS & METHODS:

MATERIALS:

Captopril was purchased from Balaji Drugs B20, Varachha Road, Surat – 395010 (GUJ)., HPMC K 100,Xantham gum, PVP K30 purchased from Balaji Drugs. Magnesium stearate, Aerosil 200 are from Research lab fine chem industries (Mumbai). Formulation of Captopril sustained release tablet: Sustained release tablets of Captopril were prepared by direct compression technique using varying proportions of polymers in combination. The composition of sustained release Captopril tablets is given in table -1. All the ingredients were individually passed through a 60 mesh sieve, except glidant and lubricant. For each formulation required quantities of Captopril, polymer (xanthan gum), were accurately weighed according to the composition and mixed in a polybag for about 30 to 45 minutes. s. The obtained blend was lubricated with aerosil and magnesium stearate for another 5 minutes. The appropriate amount of the mixture was weighed and then compressed using 8 station rotary tablet press equipped with 11 mm flat faced punches at a constant compression force required to produce hardness of tablets about 2-4 kg/ cm2.

Total weight of the tablet= 300mg

Each tablet contains= 25mg of the Captopril

Table 1: Formulation Design for Each Batch (Drug +Excipients)

Sr. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Captopril	25	25	25	25	25	25	25	25	25
2	Xanthum gum	45	60	75	-	-	-	22.5	30	37.5
3	HPMC K100	-	-	-	45	60	75	22.5	30	37.5
4	Calcium chloride	18	18	18	18	18	18	18	18	18
5	Sodium alginate	15	15	15	15	15	15	15	15	15
6	PVP K30	45	45	45	45	45	45	45	45	45
7	Avicel 200	143	128	113	143	128	113	143	128	113
8	Aerosil 200	6	6	6	6	6	6	6	6	6
9	Magnesium stearate	3	3	3	3	3	3	3	3	3

Pre-compression Parameters:

Angle of repose

The angle of repose of granules was determined by funnel method. It is a maximum angle possible between the surface of the pile and horizontal plane. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$Tan\ \theta=h/r$$

Where h and r is the height and radius of the powder cone.

Carr's compressibility index

The carr's are determined by compressibility index. % carr's index can be calculated by using the following formula

$$Carr's\ Index(\%) = TBD – LBD/ TBD \times 100$$

Post-Compression Parameters

Sustained release tablets of Captopril were prepared by direct compression technique. Total nine formulations were prepared. The tablet weight variation, hardness, friability and content uniformity for each formulation are shown in table 1. The prepared sustained release tablet were evaluated for their physical properties like hardness and friability, swelling index and drug content.

Hardness and friability:

For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester and roche friabilator.

$$Friability= Initial\ weight– Final\ weight / Initial\ weight\ x100$$

% Friability of tablets less than 1% is considered acceptable.

Swelling index

The swelling index of Captopril tablet is determined in 0.1 N HCL (pH 1.2) at R.T. After each interval the tablet was removed from beaker and then remove the excess buffer by using filter paper and weighed again upto7 hrs. The swelling index was calculated by following equation:

Swelling index (SI) = (Wt – W0)/ W0 x 100

Where Wt = Weight of tablet at time t

W0 = Initial weight of the tablet

Drug Content

The drug content of Captopril is following procedure take a 20 tablet and crush it then take a powder containing 0.1gm of Captopril with 150ml of phosphate buffer pH 6.8 to produce 200ml and filter this mixture by using whatman filter paper. Dilute 10ml of filterate to 100ml with water and measure the absorbance of filter a teat 205nm. The drug content of tablet was found to vary between 96.50% to 98.10%.

In vitro dissolution study

the dissolution profiles of formulation shows the comparative release profile with different concentration of different polymer from batches formulation (F1) to formulation (F9). In Vitro drug release studies of sustained release tablets of Captopril were done in USP type II dissolution test apparatus (Electro lab TDT-08, India) at 37°C ± 0.5°Cand 50 RPM speed in 900 ml of dissolution medium(0.1 N HCL). Dissolution medium consisted of 0.1N HcL for first 2 hrs and phosphate buffer pH 6.8 from 3 to 8 hrs. Take a Five mili litre sample were taken by filtration at predetermined time intervals then after each sampling the volume of dissolution medium was replaced by 5ml of phosphate buffer solution(pH 6.8). The amount of drug present in Captopril released is determined by UV spectroscopy. In formulation F1, F2 and F3 HPMC K100 is used as sustained released polymer. Then determination of Preformulation study and physiochemical properties of SR tablet of Captopril was conducted and results are shown in following table.4. In- vitro dissolution study results F1 showed 58.55% drug release within 8 hrs. F2 showed 68.59% and F3 showed 74.62% cumulative drug release in 8 hrs. Thus sustained release profile was not achieved. so the next batch

F4 the HPMC K100 are used as a polymer. Then F4 showed 65.58% and F5 showed 50.34% and F6 showed 72.90% drug release within 8 hrs. Then in F7, F8, F9 both xanthum gum and HPMC K100 are used ratio as 1:1. Hence f7 showed 77.01% and F8 showed 76.66 and F9 showed 57.39% drug release within 8 hrs. These result indicated that xanthum gum and HPMC K100 could control the release of Captopril up to 8 hr.

Zero Order Kinetics

A Zero order release of a drug is determined by the following equation:

$$Qt-Q0=K0t$$

Where Qt =Amount of drug release dissolved in time 't'

Co=Initial amount of drug concentration in solution.

Kot=Zero order rate constant.

First Order Kinetics:

A first order release would be predicted by the following equation

$$Log\ Qt=Log\ Q0-Klt/2.303$$

Qt=Amount of drug release in time 't'

Co= Initial concentration of drug in solution.

Klt=first order rate constant

Higuchi's Model:

This model states that the drug release from the matrix device by diffusion has been described by the following diffusion equation,

$$Ft=Q=VD5/T(2C-5Cs)Cst$$

Where, Q=Total amount of drug release dissolved in time 't'.

Co= Diffusion Coefficient of drug in the release matrix.

Cs= Solubility of drug in the matrix.

5= Porosity of matrix

t=Tortuosity

T=Time (hr)

Stability study:

The stability study of this formulation was evaluated only through the stability studies in three different phases. The purpose of this stability testing was to obtain a stable product which assures drug safty and efficacy up to the end of shelf life at defined storage condition like Room temperature, cool and in freezer upto three months. The prepared sustained release Captopril tablet formulation (F7) of Captopril were placed on plastic tubes containing desiccant and stored at ambient conditions like R.T and cool temperature. Total 99.87% Drug content are present in API.

METHODS:

Drug-excipient compatibility studies:

Drug and excipients compatibility studies by using following instrument: Infra-red (IR) spectroscopy was conducted on FT IR 8201 PC Spectrophotometer (Tokiyo, Japan) and the spectrum was recorded in the wavelength region of 4000 to 400 cm−1. The procedure consist of dispersing a sample (mixture of drug and excipients) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

RESULTS AND DISCUSSION:

Pre compression parameters

Table 2: Pre-compression parameters for sustained release tablet of Captopril [F1 to F9]

Formulation	Bulk density	Tapped density	Carr's index	Hausner ratio	Angle of repose
F1	0.44±0.002	0.50±0.005	14.00±0.21	1.28±0.1	23.26±0.13
F2	0.48±0.005	0.54±0.004	11.11±0.22	1.07±0.4	21.80±0.2
F3	0.54±0.004	0.62±0.003	12.90±0.10	1.13±0.1	17.74±0.9
F4	0.51±0.003	0.58±0.002	12.06±0.22	1.13±0.2	19.79±0.2
F5	0.52±0.010	0.60±0.007	10.00±0.32	1.26±0.1	21.80±0.4

F6	0.53±0.004	0.60±0.006	11.66±0.43	1.21±0.1	23.74±0.3
F7	0.50±0.004	0.56±0.003	10.71±0.23	1.16±0.1	22.78±0.4
F8	0.47±0.004	0.54±0.002	12.96±0.42	1.23±0.2	23.50±0.3
F9	0.58±0.005	0.67±0.003	13.43±0.45	1.27±0.1	19.76±0.2

Table 3: Post-compression parameters for sustained-release Captopril tablets (Formulations F1 to F9).

Formulation	Hardness	Thickness	Friability	Weight variation
F1	3.0±0.18	2.62±0.01	0.72±0.12	201.2±0.32
F2	3.2±0.52	2.76±0.03	0.43±0.14	200.4±0.45
F3	2.8±0.56	2.83±0.11	0.64±0.15	201.6±1.43
F4	3.6±0.24	2.79±0.14	0.85±1.32	200.7±1.32
F5	3.5±0.65	2.45±0.43	0.60±0.05	200.3±0.85
F6	2.9±0.23	2.92±0.39	0.63±0.17	201.9±0.63
F7	3.5±0.46	2.26±0.56	0.73±0.43	200.3±0.71
F8	3.8±0.85	2.65±0.09	0.81±0.38	200.4±1.72
F9	3.9±0.76	2.72±0.26	0.67±0.49	200.3±1.68

Swelling Index of tablets of batch [F1 to F9]

The expansion characteristics of a pharmaceutical unit were assessed through the analysis of its weight gain. The degree of swelling exhibited by Captopril tablets was examined in a 0.1 N hydrochloric acid solution. The tablets were placed in a petri dish containing pH 6.8 phosphate buffer and observed at specific time points of 1, 2, 4, 6, and 8 hours. Subsequently, each tablet was carefully removed, dried with a tissue paper to eliminate excess moisture at each designated time interval.

Table 4: Swelling index of formulations

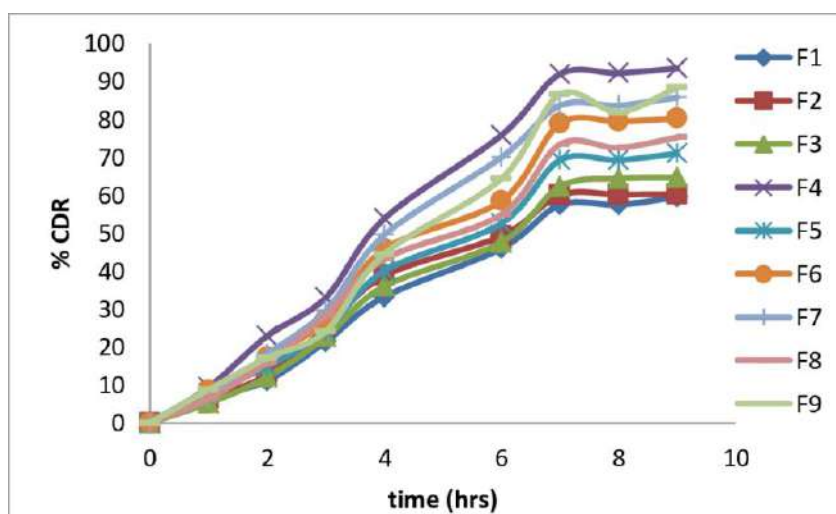| Time(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	00	00	00	00	00	00	00	00	00
2	58	25	58.2	47	48.4	38	49.3	62.1	47
3	63.2	34.63	69	49	51	42.5	52.3	66.4	57.56
4	74.5	45.54	76.5	53.5	61.5	50.8	65.2	74.2	67.4
5	86.1	56.1	94.5	68.5	74.1	62.2	80.5	88.2	75.5
6	98.2	64.3	102	79	84	68	92.5	98.5	92.2
7	107.5	72.3	114	90.5	92.5	74.5	118.2	103	104.5
8	118.3	85.5	125.5	103.5	110.1	91.55	125.6	111.3	111.3
9	124.5	96.1	131.7	107.5	115.5	99.01	126.5	119.2	119.2

Fig.1: Swelling index of Captopril SR tablet

In-vitro release study:

Table 4: In vitro dissolution profile of Captopril.

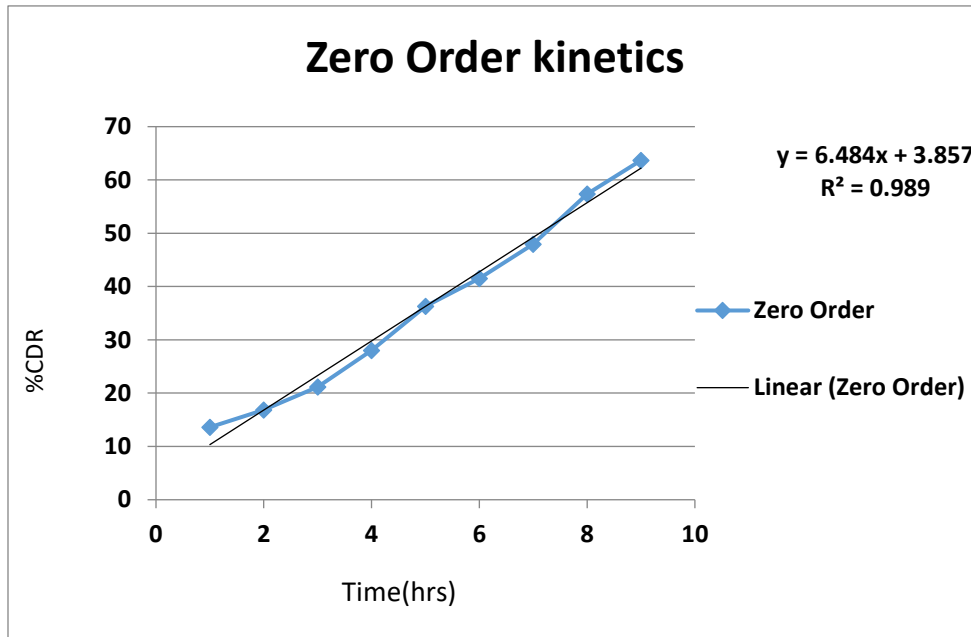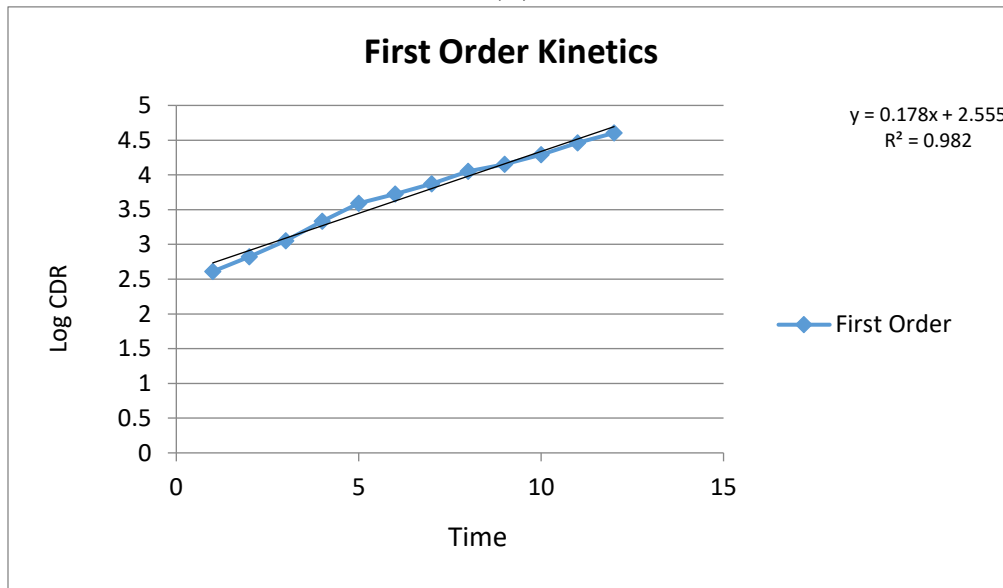| Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	10.710	15.616	13.109	14.435	11.931	22.960	20.774	12.009	13.607
2	20.159	26.602	18.821	18.097	14.337	32.125	28.510	16.855	16.828
3	28.981	35.460	31.153	21.071	17.040	36.451	39.556	25.119	21.167
4	38.941	42.265	41.222	28.166	21.043	43.500	51.643	41.143	28.034
5	43.597	47.004	49.975	32.337	26.069	47.778	56.772	45.746	32.325
6	47.135	54.862	58.840	42.325	29.260	58.928	62.145	57.964	41.506
7	53.979	62.805	68.951	50.504	42.650	66.110	70.585	68.081	47.972
8	58.552	68.591	74.629	65.589	50.342	72.904	77.012	76.663	57.390
9	65.599	77.641	81.720	76.824	65.523	78.711	81.022	79.159	63.680
10	76.515	83.538	85.767	85.191	76.181	87.978	86.577	85.141	73.063
11	88.896	87.255	93.514	94.364	86.995	93.581	91.681	91.535	86.700
12	95.833	97.404	98.835	96.605	94.327	98.407	98.422	98.071	99.853
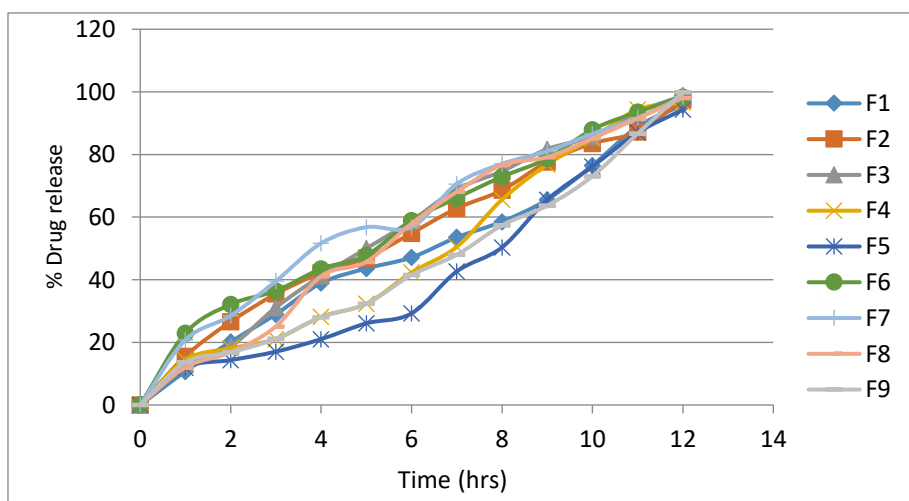
Fig. 2: In-vitro Release study

Kinetic study:

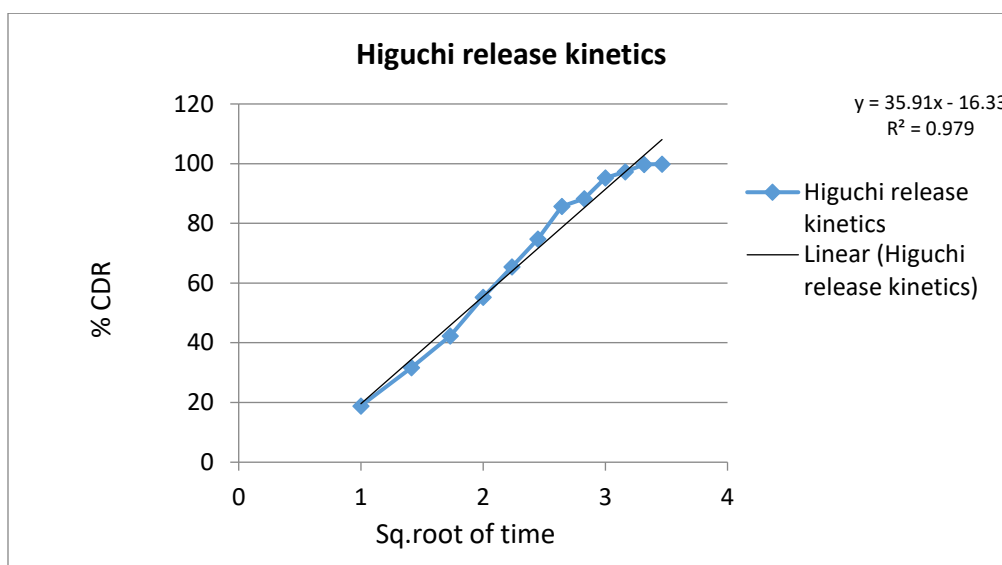The release kinetics data for the various formulations of sustained release captopril tablets are presented in the following table, with correlation coefficients (R^2) for Zero order, First order, Higuchi model, and Korsmeyer-Peppas model:
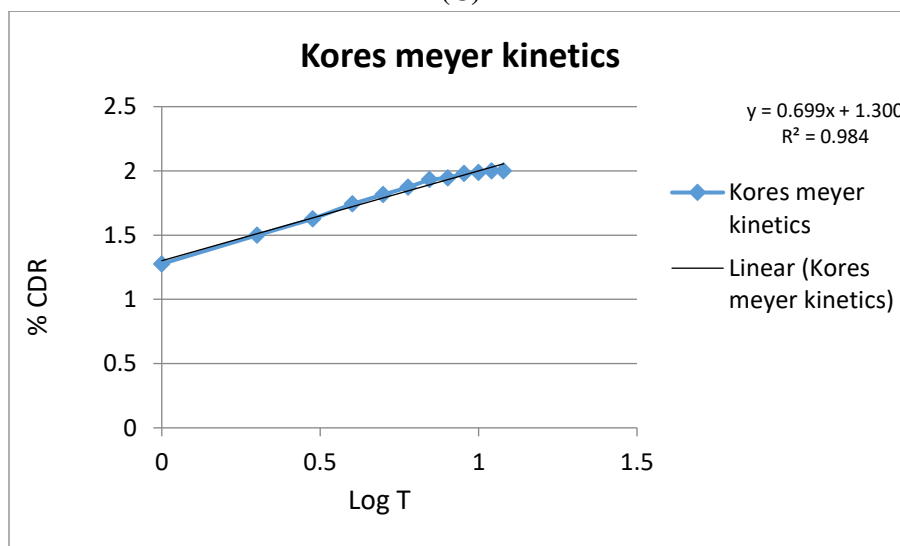

Zero Order kinetics

$y = 6.484x + 3.857$
$R^2 = 0.989$

(A)

First Order Kinetics

$y = 0.178x + 2.555$
$R^2 = 0.982$

(B)

(C)

(D)

Fig. 3:Drug release kinetic study (A) Zero order drug release kinetics, (B) First order release kinetics, (C) Higuchi model drug release kinetics, (D) Korsemyer peppas model drug release kinetics.

Table 5. Release kinetics data optimized Captopril sustained release tablet (f9)

Formulation	Model	R^2	Slope	K
F9	Zero order	0.989	6.484	3.857
	First order	0.982	0.178	2.555
	Higuchi Model	0.979	35.91	16.33
	Korsmeyer Model	0.984	0.699	1.300

The in vitro release data of F9 was fitted with various kinetics equations. From the table.5. it was shown that the regression coefficient (r2=0.989) value was more in zero order and korsmeyer model (r2=0.984). The 'n' was found to be 1.300 which indicates that the drug release follows Fickian diffusion.

COMPATIBILITY STUDY OF DRUG:

Infrared spectrophotometer is useful analytical technique utilized to check the chemical interaction between drug and excipients used in formulation. The sample 1mg was powdered and mixed with 10mg of dry powdered potassium bromide. The scanning in the wavelength region of 4000-400 cm−1. IR spectroscopy studies revealed that the pure Captopril showed typical band at1743.33 cm-1. Due to C=0 stretching of carboxylic group and a band at 1594.84 cm-1 due to C=O stretching of amide group, C-H stretching of 2877.27 cm-1. There is no significant shifts of reduction in intensity of the FTIR bands of Captopril were observed as shown in figure.4.

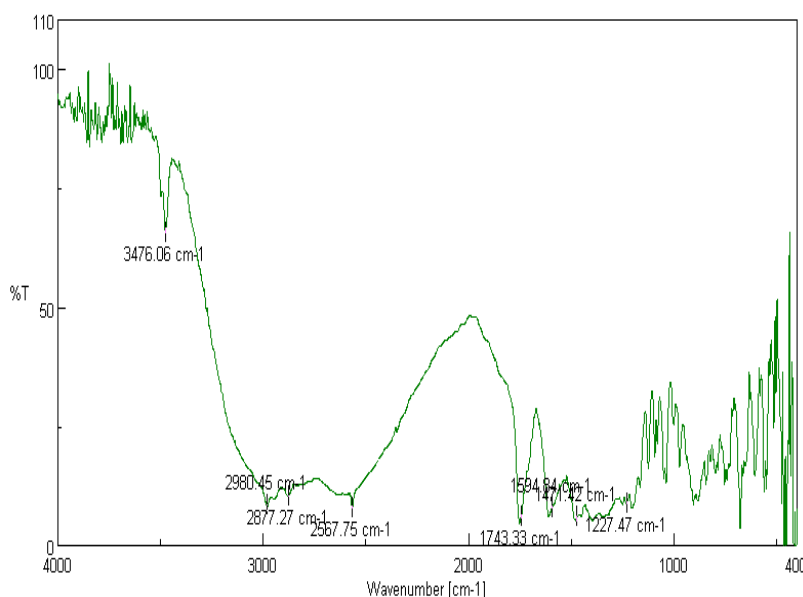**Figure 4: FTIR Spectra of Captopril**
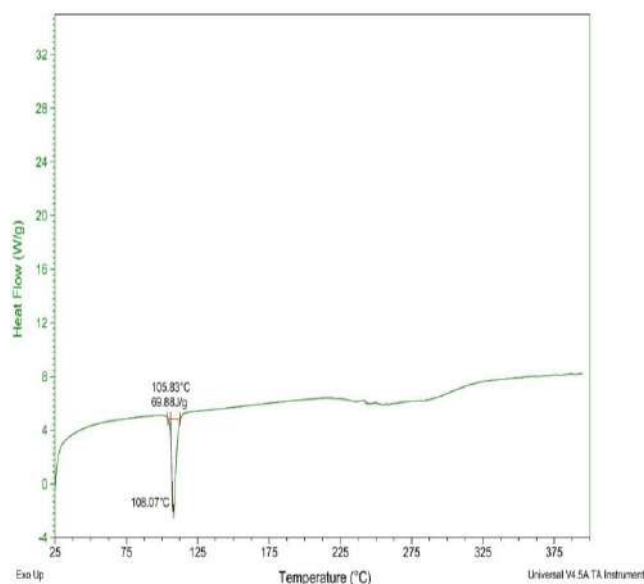
Differential Scanning Calorimetry(DSC):

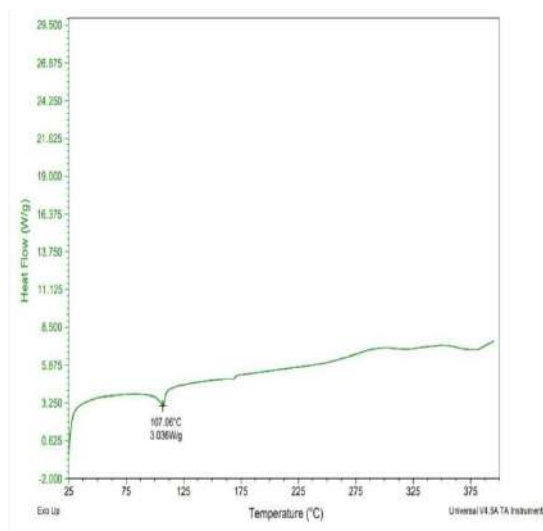**Fig.5. DSC Thermogram of Captopril Differential scanning Calorimetry**

Fig.6. DSC of Captopril+ Excipients

Thermal analysis of the drug was conducted using Differential Scanning Calorimetry (DSC). The DSC curve of Captopril exhibited a sharp exothermic peak at 105.07°C corresponding to its melting point, indicating its crystalline nature and the purity of the sample. The DSC thermogram is presented in the figure.

CONCLUSION

From the above results it is concluded that sustained release tablet of Captopril containing Different ratio of Xanthum gum and HPMC K100 By direct compression method. The results state that the xanthum gum and HPMC K100 control the Captopril release effectively for 12hrs. It is concluded that sustained release of Captopril over a period of 12 hours was obtained with formulation (F9) containing high amount of xanthum gum and HPMC K100. From the present research it is concluded that a successful sustain release tablet of Captopril can be formulated.

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