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Formulation, development and evaluation of Polysaccharide based Gastro-retentive Formulation for Delivery of Anti-Hypertensive Drug

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ABSTRACT

In situ gel forming systems have been widely investigated as vehicles for sustained drug delivery. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. So, In situ gelling system via different route such as oral, nasal, ophthalmic etc can be formulated. In the present research work Oral Floating Insitu gel of Captopril was formulated using Sodium alginate. The optimized batch gave drug release for 7 hrs in the polymer combination of Sodium Alginate 1% and sodium bicarbonate 1.25%. It was found to be floating for more than 12 hrs. The batch was found to be stable for 2 months in stability study.

Keywords— *Captopril, In-situ gel, In-vitro study, Sodium Alginate*

1. INTRODUCTION

Captopril is an Angiotensin Converting Enzyme (ACE) inhibitor. Captopril's main uses are based on its vasodilation and inhibition of some renal function activities. These benefits are most clearly seen in:

(a) Hypertension
(b) Cardiac conditions such as congestive heart failure and after myocardial infarction
(c) Preservation of kidney function in diabetic nephropathy.

Insitu gels are drug delivery systems that are in solution before administration but undergo gelation insitu after administration inside the body, therefore ease of administration & reduced frequency of administration improved patient compliance & comfort.

2. FORMULATION AND EVALUATION OF POLYSACCHARIDE BASED GASTRORETENTIVE SYSTEM OF CAPTOPRIL

The formulations were designed by varying the polymer sodium alginate and sodium carbonate concentration. In the present study the floating in-situ gel of captopril was prepared by "ion-crosslinking method".

2.1 Formulation of Floating In-situ gel of captopril

In-situ gel formulations were prepared according to the method reported earlier with slight modification (Archana D Kajale, 2016) by using different concentrations of sodium alginate and sodium bicarbonate as shown in table 1. The various ingredients used in formulation of in situ gel was displayed in table 1. These ingredients were selected to enhance the floating and gelling properties based on their attribute to the formulation.

Table 1: Ingredients of in situ gel formulation and their uses

S.No	Ingredients	Attribute
1.	Sodium alginate	Gelling Agent
2.	Calcium chloride	Cross linking agent
3.	Tri-sodium citrate	Fluidity to the solution
4.	Sodium bicarbonate	Gas generating agent, buoyancy enhancer
5.	Calcium carbonate	Cross linking agent, gas generating agent
6.	Captropril	Therapeutic action

2.2 Method of preparation of polysaccharide based In-situ gel of Capropril

In-situ gel of formulation of captopril was prepared by "ion-crosslinking method" as reported earlier with slight modification (Archana D. Kajale). Calcium chloride solution was prepared along with trisodium citrate. Both the solutions were mixed in appropriate quantities and to the above solution mixture, calcium carbonate was added and heated up to 60℃ with continuous stirring. Different concentrations of sodium alginate (0.5, 0.75, 1, 1.25% w/v) was added upon cooling at 4 ℃. To the above mixture drug solution was added and neutralized with 0.1N NaOH to maintain pH.

Table 2: Formulation composition of Floating In-situ gel of Captopril

F	a	b	c	d	e	f	g
F1	0.5	1	0.5	0.01	0.01	0.01	Qs to100 mL
F2	0.75	1	0.5	0.01	0.01	0.01	
F3	1	1	0.5	0.01	0.01	0.01	
F4	1.25	1	0.5	0.01	0.01	0.01	
F5	1.5	1	0.5	0.01	0.01	0.01	
F6	1	1	0.5	0.015	0.01	0.01	
F7	1	1	0.5	0.02	0.01	0.01	
F8	1.25	1	0.5	0.0075	0.01	0.01	
F9	1	1	0.5	0.0125	0.01	0.01	

Where F= Formulation

a. Composition of Sodium alginate (%w/v)
b. Composition of Calcium carbonate (%w/v)
c. Composition of Trisodium citrate (%w/v)
d. Composition of Sodium bicarbonate (%w/v)
e. Composition of Calcium chloride (%w/v)
f. Composition of Captopril (%w/v)
g. Composition of deionised water (%w/v)

Note: All the formulations were made up to volume 100mL with deionised water i.e by adding quantity sufficient (Qs) to 100mL.

2.3 Evaluation of Floating In-situ gel of captopril

(a) Physical Appearance: The physical appearance of the formulation was inspected visually for clarity under black and white background.

(b) pH: The pH of the formulations was determined using digital pH meter by bringing the electrode of the pH meter in contact with the surface of the formulation and allowing it equilibrate for 1min.

(c) Viscosity: The viscosity of the formulation before and after gelling was determined by Ostwald's viscometer.

(d) Floating lag time: In this test, 5ml of in-situ gel was added into 500ml of dissolution vessel containing 0.1N HCl at 37 ℃. It is the time taken for the formulation to emerge at the surface of dissolution media is called floating lag time.

(e) Floating duration: Floating duration was determined by adding 5ml of in situ gel into 500ml of dissolution vessel containing 0.1N HCl at 37℃. The time that formulation took to remain constantly floating on surface of dissolution medium is referred as duration of floating

(f) Drug content estimation: Drug content of formulations was determined in triplicate by using double beam UV spectrophotometer (Shimadzu UV-1800) (Gaikwad, 2010). 10ml of formulation was taken in 100 ml volumetric flask and 50 ml of 0.1 N HCl (pH 1.2) was added with continuous shaking. Final volume was adjusted up to 100 ml with the help of 0.1 N HCl (pH 1.2) and filtered the solution. Sample was analyzed for determination of drug content spectrophotometrically at λ max 218nm.

(g) FTIR studies: FT IR spectroscopy of the formulation was carried out to assure the integrity of the drug.

(h) Scanning Electron Microscopy (SEM): The shape and surface characteristics of the prepared microspheres were evaluated by means of SEM. The in-situ gel is lyophilized with Virtis lyophilizer for24hours. The specimens were coated under vacuum with gold in argon atmosphere maintain 30kv voltage to determine morphology.

(i) Water uptake study: A simple method was adopted to determine the water uptake by the gel. The insitu gel formed in 0.1 N Hydrochloric acid was used for this study. From each formulation the gel portion from the 0.1 N Hydrochloric acid was separated and the excess solution was blotted out with a tissue paper. The initial weight of the gel taken was weighed and to this gel 10 ml of distilled water was added and after every 30 minutes of the interval water was decanted and the weight of the gel was recorded and the difference in the weight was calculated and reported.

(j) In-vitro drug release study: The drug release was determined using USP XXVI dissolution basket apparatus. 500ml of SGF (pH 1.2) acts as dissolution medium, was placed in the dissolution jr and the formulation 10ml was suspended into the medium by means of a basket. Dissolution was carried out at 37±0.5℃ at a rotation speed of 50rpm.

2.4 Drug Release Kinetics

Table 3: Representative Equations of Release kinetic models

Kinetics	Expression
Zero order	Qo – Qt = Ko t
First order	LogQt = log Qo+ K1 t / 2.303
Higuchi Hixson Crowell	Qt = KH * t ½ $W_o^{1/3} – W_t^{1/3} = K_s t$
Krosemeyr Peppas Release Model	$Mt / M\infty = K_P t^n$

2.5 Stability studies

The purpose of stability testing is to provide evidence on how the quantity of a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and to establish a re-test period for the drug substance or a shelf-life for the drug product and recommend storage conditions. Stability studies of the formulations were carried out as per ICH guidelines, at room and refrigerated conditions for a period of 2 months. (Tingstad et al,1964) The final selected formulation was packed in amber coloured glass containers and closed tightly with the cap. They were stored at the stated conditions for two months. Samples were analysed after 0, 15, 30, days and evaluated for viscosity, drug content and in-vitro dissolution studies (Tamizharasi S et al, 2008).

3. RESULTS AND DISCUSSION

3.1 Pre-formulation Studies

3.1.1 Physicochemical properties

(a) Organoleptic characters: The colour and appearance of the drug was found to be white, crystalline powder on visual inspection.

(b) Melting point: The melting point range of captopril was found to be 100˚C by capillary tube method within the range that is, 100-107.

(c) Solubility: The solubility of the drug was tested in various solvents listed below in table 4, table 5 and figure 1.

Table 4: Solvents used to check solubility of the drug

Solvent used	Solubility
Water	++
Methanol	+
Ethanol	+
Acetone	++
0.1N HCl	+++

(+) indicates poorly soluble
(++) indicates sparingly soluble
(+++) indicates readily soluble.

Table 5: solubility profile of the drug

Solvents	Absorbance (µg/ml)
Water	26.714
Methanol	102.166
Ethanol	37.725
Acetone	31.949
0.1 N HCl	45.667

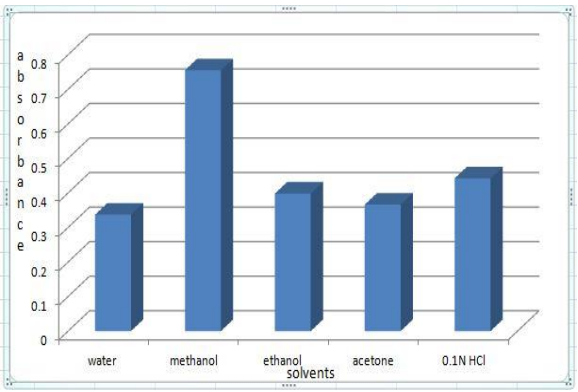


Fig. 1: Graphical representation of solubility data of captopril

3.1.2 Identification of the drug:

3.1.2.1 By (UV-Visible Spectroscopy)

(a) Determination of absorption maxima (λ_{max}): The absorption maximum (λ_{max}) of drug was determined by scanning the drug solution of 10µg/ml over the range of 200-400nm by UV spectroscopy and spectra was recorded as shown in figure 2. Results displayed that absorption maxima of drug were found to be 218 nm in 0.1N HCl as shown in figure 2.

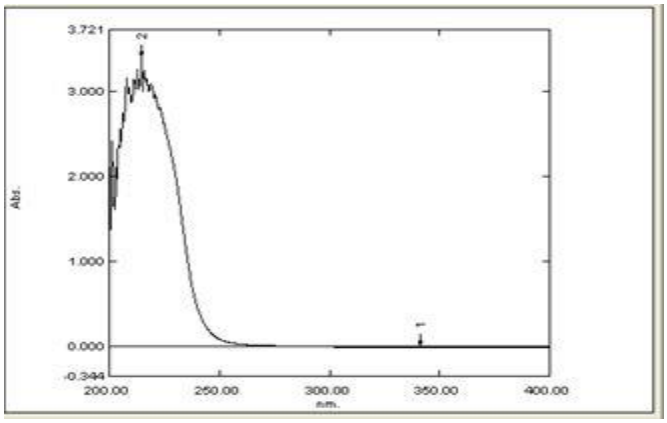


Fig. 2: U V Spectra of Captopril

(b) Preparation of calibration curve of Captopril: The calibration curve of Captopril was prepared in 0.1 N HCl (pH 1.2) in the concentration range of 2.0, 4.0, … up to 20 µg/ml. Absorbance of the corresponding concentration was determined at 218nm by using UV spectrophotometer and absorbance was shown in table 3. A calibration curve was plotted between the concentrations versus absorbance as shown in figure 3 Linearity was obtained within the concentration range of 2-20µg/ml. This indicates that beer's lamberts law was followed over this range. R2 value of the curve was found to be 0.9911in 0.1N HCl (pH 1.2).

Table 3: Calibration curve of Captopril in 0.1N HCl at λ_{max} 218nm

Concentration(µg/ml)	Absorbance
0.0	0.00
2.0	0.184 ± 0.02
4.0	0.205± 0.04
6.0	0.308± 0.06
8.0	0.433± 0.08
10.0	0.501± 0.021
12.0	0.602± 0.022
14.0	0.675± 0.042
16.0	0.750± 0.053
18.0	0.892± 0.046
20.0	0.920± 0.048

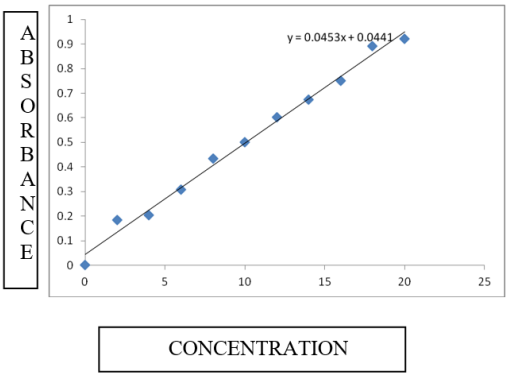


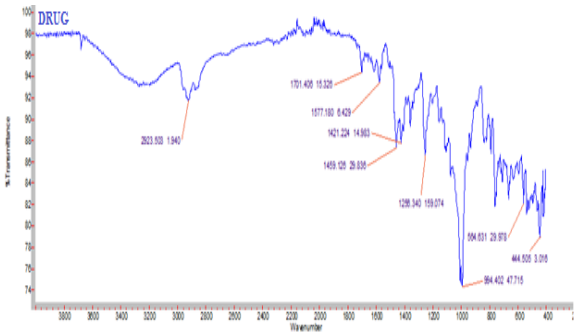
Fig. 3: Standard Calibration curve of Captopril in 0.1N HCl

3.1.2.2 Partition co-efficient of the drug

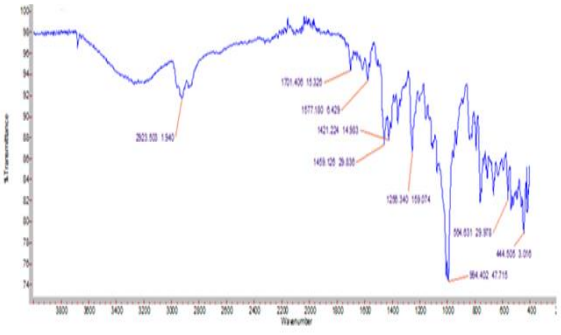
Partition co-efficient of the drug in chloroform and 0.1N HCl (1.2 pH) solvent system was determined in ambient conditions as discussed in methodology section. Log P of the drug was found to be 0.483 which indicates that hydrophilic in nature.

3.1.2.3 FTIR Spectroscopy:

Drug was further identified by FTIR technique and FTIR spectra of captopril sample and reference (I.P., 2010) was shown in Figure 4. The characteristic peaks for all functional groups of the drug C=N, C-S-C, C=O (ketone), C=O (ester linkage), -C=C- stretching aromatic carbons were found sample of Captopril and shown in table 4. and at different storage condition room, refrigerated conditions were shown in table 6.4 and Fig 6.4 A, 6.4 B and respectively.



(a)



(b)

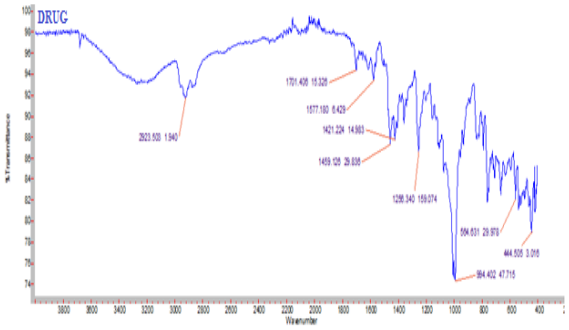
Fig. 4: FT-IR Spectra of a) Captopril b) Reference (from IP 2007 Vol II)

3.1.2.3 (a) Drug excipient Interaction Studies: The FT-IR spectra of the drug samples were compared with FT-IR spectra of excipients individually and with the physical mixture of polymer and drug and mixture of drug and excipient.

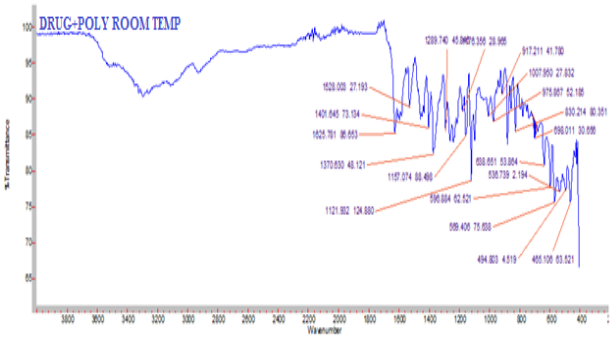
3.1.2.3 (b) Physical mixture of drug and polymer: Peaks of all functional groups such as a ketone group, thiol group, hydroxyl group and pyrimine of drug were observed at 1701.406, 2923.503, 1577.180 and 1258.340cm-1 respectively in the FTIR spectra of drug and polymer as shown in table 4 and Fig. 5 and 6 (a, b and c). It was clearly shown that peaks of drug were remain present in the physical mixture of drug and polymer in both the temperature condition shows no interaction between the drug and excipient as there is no disappearance of functional group of drugs.

Table 4: Analysis of FT-IR Spectra

S.no	1	2	3	4
	Streching			
Vibration	C=O	S-H	O-H	N-H
Reference peaks	1690-1750	2600-3000	1500-1800	1150-1480
Peaks of pure drug	1701.406	2923.503	1577.180	1258.340
Peaks of sodium alginate	1694.25	2758.64	1680.681	-



(a)



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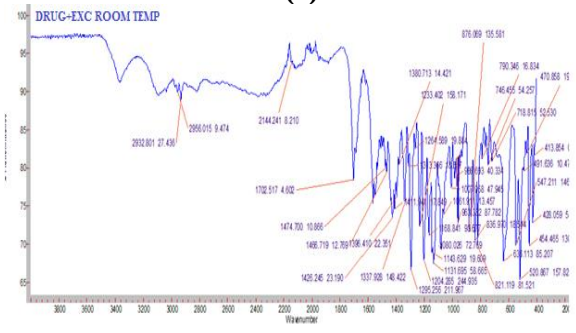
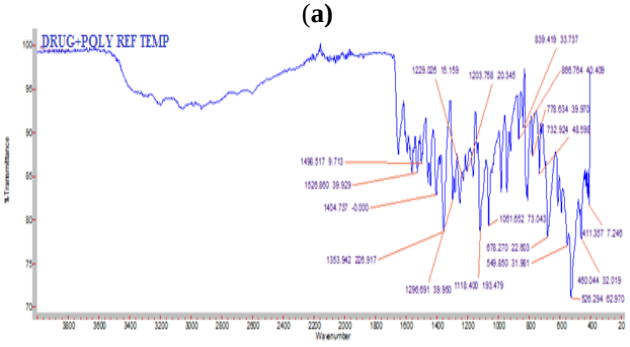


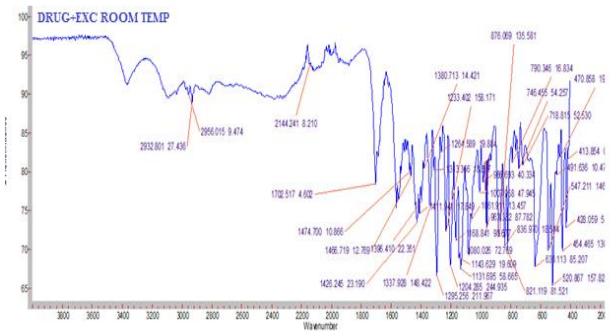
(c)

Fig. 5: FT-IR Studies of (a) Drug (Captopril) (b) Drug + Polymer (c) Drug + Room Temperature

(a)



(b)



(c)

Fig. 6: FT-IR studies of (a) Drug (Captopril) (b) Drug + Polymer (c) Drug + Excipients at Refrigeration temperature

3.3 Formulation of in-situ gel of Captopril

Based on the results of preliminary investigation, the formulations were designed by varying the polymer sodium alginate and sodium carbonate concentration. The polysaccharide based floating In-situ gel was formulated by using ion-cross linking method

Table 5: Formulation of polysaccharide based Floating In-situ gel of Captopril

F	a	b	c	d	e	f	g
F1	0.5	1	0.5	0.01	0.01	0.01	Qs to 100 mL
F2	0.75	1	0.5	0.01	0.01	0.01	
F3	1	1	0.5	0.01	0.01	0.01	
F4	1.25	1	0.5	0.01	0.01	0.01	
F5	1.5	1	0.5	0.01	0.01	0.01	
F6	1	1	0.5	0.015	0.01	0.01	
F7	1	1	0.5	0.02	0.01	0.01	
F8	1.25	1	0.5	0.0075	0.01	0.01	
F9	1	1	0.5	0.0125	0.01	0.01	

Where F= Formulation

a. Composition of Sodium alginate (%w/v)
b. Composition of Calcium carbonate (%w/v)
c. Composition of Trisodium citrate (%w/v)

d. Composition of Sodium bicarbonate (%w/v)
e. Composition of Calicum chloride (%w/v)
f. Composition of Captopril (%w/v)
g. Composition of deionised water (%w/v)

Note: All the formulations were made up to volume 100mL with deionised water that is by adding quantity sufficient (Qs) to 100 mL.

3.4 Evaluation of in-situ gel

In-situ gel formulations were prepared by using different concentrations of sodium alginate and characterized for various parameters such as physical appearance, pH, viscosity, gelling behaviour, floating time, water uptake, drug content, in-vitro drug release etc.

3.4.1 (a) Physical Appearance: All the formulations were white and clear in appearance as in Figure 7.

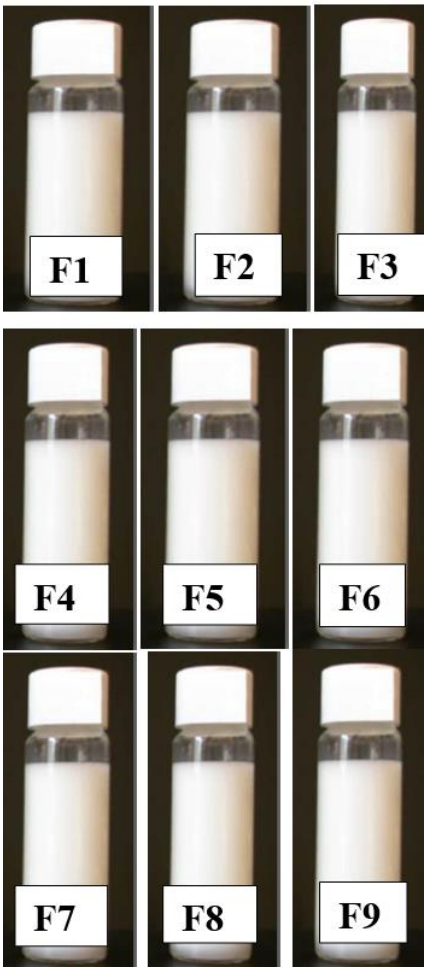


Fig. 7: Physical appearance of Formulations of F1 - F9

3.4.1 (b) pH determination:

pH values of all formulations were determined by using digital pH meter. It was observed from the data as shown in table 6 and figure 8 that pH of all developed formulations was found to be in the range of 7.5-7.9.

Table 6: Characterization of In-situ gel

F	Physical Appearance	pH	Viscosity (cp)		Gelling behaviour
			Before gelling	After gelling	
F1	Clear and white	-	2.33±0.8	3.1±0.4	-
F2		7.8	3.17±0.4	4.0±0.6	-
F3		7.6	3.79±0.2	4.5±0.5	++
F4		7.7	3.42±0.5	4.1±0.3	+++
F5		7.7	3.6±0.4	4.04±0.2	+++
F6		7.6	3.72±0.5	4.96±0.3	++
F7		7.5	3.84±0.5	5.14±0.4	+++
F8		7.4	3.91±0.2	5.1±0.2	+++
F9		7.8	3.96±0.4	5.91±0.3	++++

Where F-Formulation

Note: (-) No gelation, (+) weak gel dissolves rapidly, (++) gelation immediately remains for few hours, (+++) gelation immediately remains for extended period and forms stiff gel.

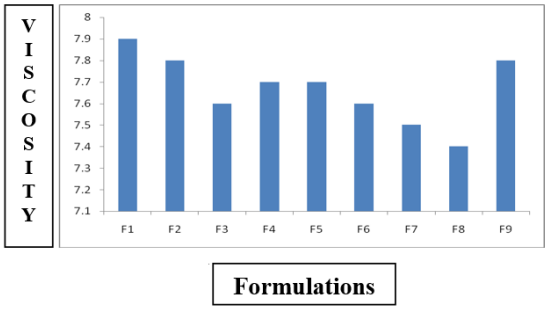
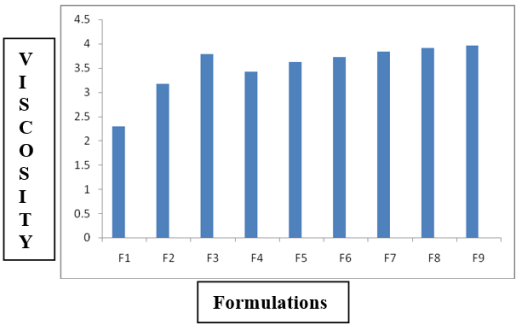
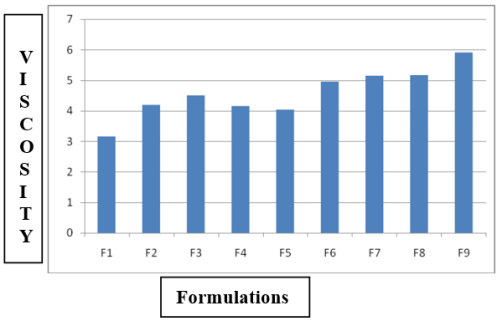


Fig. 8: pH of various In-situ Gel formulations prepared at different concentration of sodium alginate

3.4.1 c) Viscosity: The viscosity values of all formulations were determined by using Ostwald's viscometer. It was observed from the data that the viscosity of all developed formulations was found to be in the range of 2.01cp to 3.96cp and 2.61cp to 5.14cp before Gelling and after gelling respectively as shown in table 7.



(a)



(b)

Fig. 9: (a) Viscosity of the formulations before gelling, (b) Viscosity of the formulations after gelling

3.4.1 (d) Gelling behaviour: It was observed from the data shown in the table 7. The gelation behaviour shows that formulation F9 shows very stiff gel.

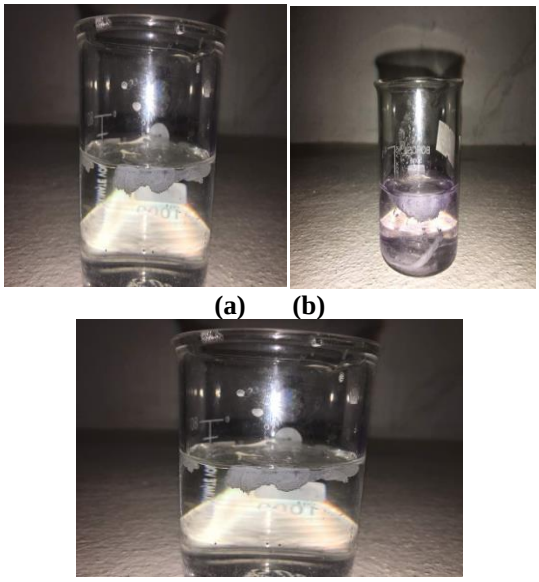
Fig. 10: Gelling behaviour of (a) F9 formulation (b) Formation of stiff gel.

3.4.1 (e) Floating lag time: Floating lag time was determined by adding 5ml of in-situ gel into 500ml of dissolution vessel containing 0.1N HCl at 37 and results were illustrated in the table 7 and figure 11.

3.4.1 (f) Floating duration: In this test, 5ml of in situ gel was added into 500ml of dissolution vessel containing 0.1N HCl at 37℃. It was illustrated in the table 7 and fig. 3.10.

Table 7: In vitro floating lag time and floating duration of floating in situ gel

Formulation	Floating lag time (sec)	Floating duration	Drug content (%w/v)
F1	16	> 24 hours	89.98±1.5
F2	18	> 24 hours	87.02±0.71
F3	17	>24 hours	91.21±1.08
F4	14	>24 hours	91.21±0.85
F5	9	> 24 hours	95.37±0.76
F6	12	> 24 hours	92.05±1.58
F7	7	> 24 hours	94.24±1.58
F8	9	>24 hours	88.70±0.74
F9	14	> 24 hours	97.8±0.96



(a) (b)

(c)

Fig. 11: Floating time and duration characteristic of F9 formulation (a) Floating lag time, (b) Buoyancy up to 12hr (c) Buoyancy up to 24hr

3.4.1 (g) Drug content: The percent drug content for all the formulations were determined UV spectrophotometer and results were shown in table 8 and figure 12. The drug contents of all the formulations were found to be in the range of 87-97%.

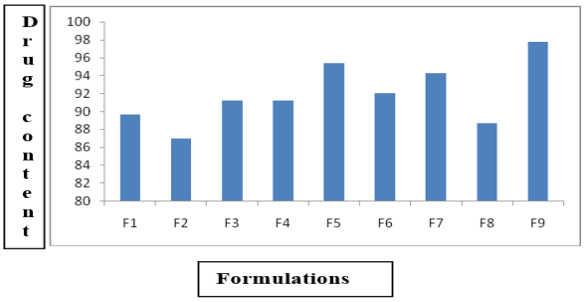


Fig. 12: Percent drug content of various in situ gel formulations prepared at different concentrations of sodium alginate

3.4.1 (h) FTIR of the formulation: FTIR of the formulation (F9) was performed vs. integrity of the drug. The results displayed in figure 13 shows that all the functional group peaks were observed which confirmed the integrity of the drug.

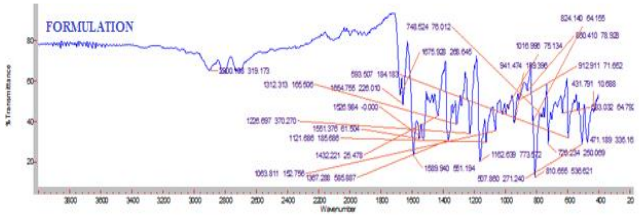


Fig. 13: FTIR Spectra of Formulation (F9)

3.4.1 (i) Scanning electron microscopy: Surface and morphological characteristic of the developed in-situ gel formulation was carried out by SEM. The result of final optimized formulation (F9) as shown in Figure 14 revealed the porous, smooth nature of the gel.

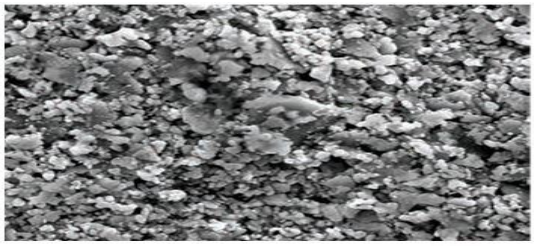


Fig. 14: Scanning electron microscopy of captopril floating insitu gel of optimized formulation F9

3.4.1 (j) Water uptake: The water uptake of F9 formulation was performed by using the gel, dipped in excess water and determined the water uptake capacity of the formulation.

Fig. 15: Water uptake of F9 formulation

3.4.1. (j) In-vitro Drug release studies: In vitro release study was carried out by dissolution apparatus USP type I (basket method) and results were shown in table 8. The results show sustained release study was carried out for 7 hours and samples were taken after different intervals. Percentages cumulative drug release profile was shown sustained release profile.

Table 8: In-vitro drug release data of Captopril floating gel using sodium alginate

Time(hr)	F1	F2	F3	F4	F5	F6
0.5	10±0.3	11±0.5	10±0.8	9 ±0.5	11±0.4	12±0.8
1	20±0.8	23±1.2	25±0.6	25±0.5	24±0.3	28±0.8
2	36±0.3	36±0.5	39±1.4	35±0.6	33±0.6	34±0.8
3	39±0.5	41±0.16	42±1.6	40±0.4	42±0.6	44±0.6
4	42±0.3	47±0.2	49±0.6	43±0.6	49±1.2	51±0.6
5	52±0.2	50±0.4	56±0.4	54±0.6	55±0.6	62±0.5
6	61±0.2	68±0.5	69±0.8	65±0.9	69±0.7	71±0.7

Time(hr)	Time(hr)	F7	F8	F9
0.5	0.5HR	17±0.2	16±0.5	18±0.2
1	1HR	28±1.2	29±0.6	27±1.4
2	2HR	36±1.2	38±0.6	35±0.2
3	3HR	43±0.8	41±0.6	42±0.4
4	4HR	49±0.8	50±1.0	49±0.6
5	5HR	57±1.2	59±0.6	58±0.5
6	6HR	65±0.6	68±0.4	70±0.2
7	7HR	78±0.3	74±0.3	79±0.5

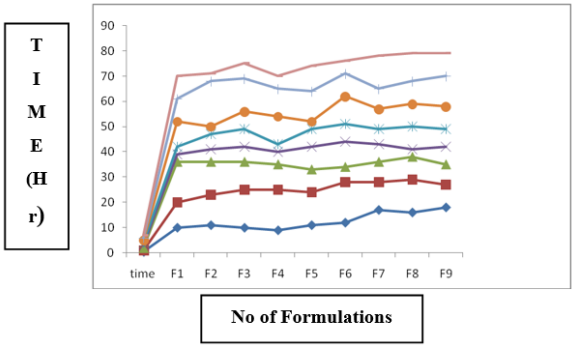


Fig. 16: In-Vitro drug release of Floating in-situ gel formulations

3.5 Kinetic Release Data

On the basis of in-vitro release study kinetic models were applied to final formulation (F7). The percent cumulative drug release data was fitted into various kinetic models viz. Zero order, first order, Higuchi, Hixson-Crowell, Peppas model to determine mechanism of drug release from the formulation and has been presented in the table 3.9

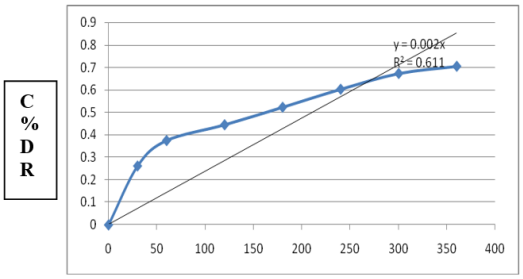


Fig. 17: In-vitro release kinetic data of the in-situ (F9) by zero order kinetic release

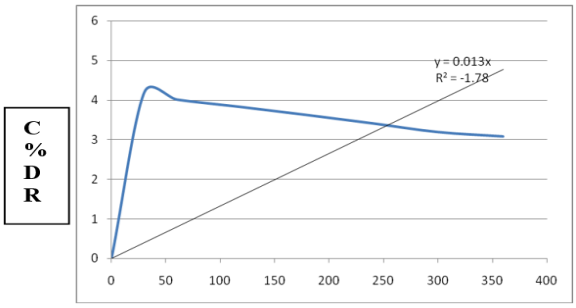


Fig. 18: In-vitro release kinetic data of in-situ gel (F9) by First order kinetic release

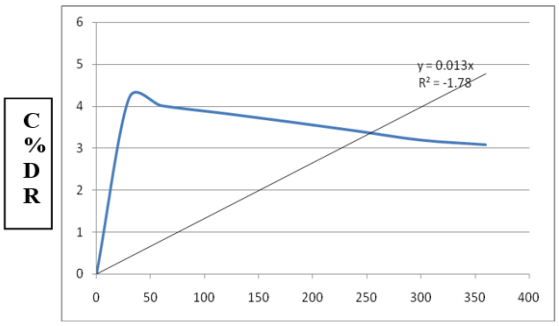


Fig. 19: In-vitro release kinetic data of in-situ gel (F9) by Hixson Crowell kinetic release

Table 9: Kinetic modelling parameters of F9 formulation

Time (min)	Cumulative Percent drug release	Time (min)	Log Cumulative Percent drug release	√time (min)	Cumulative Percent drug release	Log time	Log Cumulative Percent drug release	Time (min)	Cumulative Percent drug unreleased
30	0.262	30	1.86	5.47	26.2	1.47	1.41	30	4.19
60	0.375	60	1.81	7.7	35.1	1.77	1.51	60	4.01
120	0.445	120	1.74	10.95	44.5	2.0	1.64	120	3.82
180	0.523	180	1.67	13.41	52.3	2.25	1.71	180	3.62
240	0.603	240	1.59	15.49	60.3	2.38	1.78	240	3.41
300	0.673	300	1.51	17.32	67.3	2.47	1.82	300	3.19
360	0.705	360	1.47	18.97	70.5	2.55	1.84	360	3.08

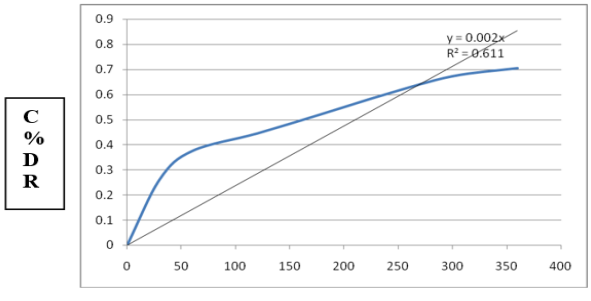


Fig. 20: In-vitro release kinetic data of in-situ gel (F9) by Higuchi kinetic release

Table 10: Kinetic Modeling of parameters of F9

Regression parameter	Zero order	First order	Hixson Crowell model	Higuchi model
Slope	0.002	0.013	0.013	0.002
R2	0.611	0.178	1.78	0.611

From the results it was found that regression coefficient value of Higuchi model was more i.e. 0.661 as compared to other models.

3.6 Stability Study

On the basis of result of in vitro characteristics of in-situ formulation, F9 formulation was selected for further stability

studies. Stability of F9 in situ gel formulations were carried out at different storage conditions as given in table 11. Samples were withdrawn and physical appearance and percent drug content was determined by UV spectrophotometer. After 60days, there was no significant change in the physical appearance; percent drug content was observed in in-situ gel formulation as shown in table 11. Thus, the in-situ gel formulation was found to be stable up to one month at different storage conditions.

Table 11: Stability Studies Profile at Different Storage Standard Conditions

	Physical appearance		Percent drug content	
	At room temperature	At 5°C	At room temperature	At 5°C
0days	Clear white solution	Clear white solution	97.90± 1.08	97.90± 1.08
15days	Clear white solution	Clear white solution	97.4± 0.60	95.12± 0.30
30days	Clear white solution	Clear white solution	95.15± 0.21	94.1±0.54
45days	Clear white solution	Clear white solution	94.11± 0.62	94.09± 0.67
60days	Clear white solution	Clear white solution	93.5± 0.67	92.87±0.97

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