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Research Article

Formulation and Evaluation of Rabeprazole Oral Floating *In-Situ* Gel

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ABSTRACT

Present study was conducted for formulation and evaluation of oral floating Rabeprazole in -situ gel for Gastroesophageal reflux disease (GERD). It refers to symptoms of damaged mucosal layer caused by stomach acid coming up from the stomach into the esophagus. Pre formulation studies was done that included API characterization, solubility, melting point, determination of λmax, standard calibrative curve, drug and excipient compatibility study. Ion activated method was used for the formulation of Rabeprazole oral floating in-situ gel. Various formulations (F1-F9) has been developed using different concentration of polymers like sodium alginate and HPMC K100M .Different physicochemical parameters were evaluated for the formulations like appearance, clarity, in-vitro gelling capacity, gelling time, in-vitro floating behaviour, viscosity, drug content and in-vitro drug release studies. As the polymer concentration increases properties like gel strength, viscosity also increased. Best formulation selected was F4 on the basis of good gelling capacity and optimum viscosity. Drug content was found to be 97.6%. F4 showed 95.16% in vitro drug release for 12h. Selected formulation follows first order kinetic that describes the rate of drug release is dependent on its concentration and is best fit for higuchi kinetic model. Stability studies were carried out for F4 formulations as per ICH guidelines for a period of 90 days and the stability was confirmed that there were no significant changes observed in physicochemical parameters.

Keywords: GERD, in situ gel, Sodium Alginate, ion activated method.

INTRODUCTION

In-situ is a Latin word meaning 'in its original place' or 'in position'. Sustained drug release and constant plasma profiles can be maintained by in-situ gelling drug delivery system.In situ gelling systems encounter gelation when comes in contact with body fluids and change in pH while they are liquid at room temperature. There ease of administration is good in liquid form at the site of administration as compared to strong gels. These gels prolong the residence time of drug at the absorption site as they form strong gels after swelling. Different methods like pH triggered, Ion activated, Photo polymerisation, Temperature triggered and enzymatic cross linking can be used for the formulation of in-situ gel[1].

Gastro esophageal reflux disease (GERD) is a chronic situation of mucosal layer damage caused by acid in stomach coming up from the stomach into the esophagus. Major cause of GERD is changes in stomach and esophagus barrier symptoms include heart burn and regurgitation. Proton pump inhibitors, H2 receptor blockers and antacids are some of the treatments used during GERD[2].

Rabeprazole trades under the name of Aciphex and helps in reducing the stomach acid. Erosive esophagitis can be healed by rabeprazole. It does not exhibit anticholinergic or histamine H2 -receptors. Rabeprazole suppress gastric acid secretion by inhibiting the gastric H+/K+ATPase at the secretory surface of the gastric parietal cell. Final step of gastric acid secretion is blocked by rabeprazole[3].

MATERIALS AND METHODS

Material

Rabeprazole was collected as gift sample from SAMCHEM Health Care Pvt. Ltd., Sodium Alginate, HPMC K100M, Sodium Citrate, Calcium Carbonate, D. Sorbitol was collected from Balaji Drugs. All chemicals and solvents used were of analytical grade.[4]

Methodology

Preformulation Studies

Solubility: The solubility of the selected drug was determined in Distilled water, Methanol, 0.1N HCL with the standard method.

Melting point: Rabeprazole powder was added in a glass capillary tube (previously sealed at one end) and attached to a thermometer with a rubber band, immersed in the Thiel's tube containing liquid Paraffin. Heating was commenced. The melting temperature was determined.[4]

Estimation of Rabeprazole: A Spectrophotometric method based on the measurement of extinction at 254 nm in 0.1N Hcl was used for the estimation of Rabeprazole.[4]

Standard Calibaritve curve of Rabeprazole in 0.1N HCl: Rabeprazole weighing 100mg added in 100ml of volumetric flask and 0.1N HCl was dissolved and desired volume was made up making it stock1. From the stock 1 pipette out 10ml solution and transfer to volumetric flask and make up the volume to 100 ml with 0.1N HCl. From this solution pipette out solution in a way the concentration comes out to be 5, 10, 15, 20, 25µg/ml. Absorbance was noted on the UV Spectrophotometer at 254nm.[4]

Fourier Transform Infrared Radiation (FT IR): FT IR spectroscopy studies were carried out with pure drug and along with different excipients to check the affinity between drug and Sodium Alginate, HPMC K100M, Sodium Citrate, Calcium Carbonate, D. Sorbitol which were used in the formulation of In-situ gel. Spectrum peaks of drugs were compared with different polymer mixture peaks. Tensor 27 was the instrument used for these studies using KBr pellets method.[5]

Method of preparation of In-situ gel

Rabeprazole In-situ gel was prepared by Ion activated method. It is prepared by adding sodium Alginate, HPMC K100M & Sodium Citrate in a beaker with 1/3rd water and stir it on magnetic stirrer at 60°C. In another beaker add Rabeprazole, calcium carbonate and D. Sorbitol and stir it on the magnetic stirrer. Mix both the solutions and make up the volume to 100ml.[6]

EVALUATION of *In-situ* Gel

A) Physical Appearance & Clarity

Appearance of all the prepared formulations were checked, clarity (visually).[6]

B) Floating Behaviour

Time taken by the gel to reach the top from the bottom position of the dissolution flask is termed as Floating lag time / buoyant time. Visual inspection can be done on USP dissolution apparatus that contains 900 ml of 0.1N HCl at 37±0.5°C.[6]

C) Gelling Time

5ml of prepared formulation was mixed with 0.1N HCl in a beaker and gelation was observed. Time was noted down that was required for the detection of gelation of *in situ* gelling system termed as gelling time and the gel integrity was also observed. [6]

D) In Vitro Gelling Capacity

Formulation was mixed with the 0.1N HCl in the ration of 3:15 and gelation was observed.

Different symbols used for indicating gelling capacity

(+) Gelation after few min, weak gel formation.

(+ +) Immediate gelation, good gel formation.

(+ + +) Immediate gelation, stiff gel formation. [8]

E) Viscosity Study

Brookfield DVT viscometer with LV-3 spindle was used for viscosity determination. Sample holder was used for holding the sample and gradually increasing the angular velocity from 0.3, 0.6, 1.5, 3, 6, 12, 30 and 60 rpm after a period of 30 seconds. It was performed at room temperature. [7]

F) Drug Content Uniformity

1 ml solution was added to 100ml 0.1N HCl and stirred for 1 hour on a magnetic stirrer. The solution was filtered and diluted with 0.1N HCl and drug content was determined using U.V Visible Spectrophotometer at 254 nm against a blank solution. [6]

Drug Content= (Absorbance/Slope) x (Dilution Factor/1000)

% Drug Content= (Drug Content/Label claim)/100

G) In Vitro Dissolution Studies

USP type II apparatus was used for drug release studies at 37 ±0.5°C and at 50 rpm 0.1N Hcl (900ml) was used as dissolution medium. 10 ml of the formulation was added and 1 ml of the sample was withdrawn at predetermined time intervals. Immediately volume was made upto the mark in dissolution medium with 0.1N HCl. Samples were analysed at 254 nm with the help

of UV spectrophotometer.[8]

Kinetics of drug release

To study the in-vitro drug release kinetics, obtained from in-vitro release of drug studies were plotted in various kinetic models: Zero-order plotted as % drug released Vs time, First

RESULTS

Ingredients (mg)	Formulation Codes and Quantities (per100ml)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rabeprazole	200	200	200	200	200	200	200	200	200
Sodium Alginate	1000	2000	3000	1000	2000	3000	1000	2000	3000
HPMC K100M	300	300	300	400	400	400	500	500	500
Sodium Citrate	250	250	250	250	250	250	250	250	250
Calcium Carbonate	250	250	250	250	250	250	250	250	250
D. Sorbitol	2000	2000	2000	2000	2000	2000	2000	2000	2000
Distilled Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 1: Formulation of In-situ Gel of Rabeprazole

Drug	Rabeprazole
Nature	Solid
Colour	White
Odour	Odourless

Table 2: Description about drug

Drug	Solvents	Amount of Drug	Solubility
Rabeprazole	Water	150 mg/ml	Freely
	Methanol	150 mg/ml	Freely
	0.1 N	>1000mg/ml	Very

Table 3: Solubility Studies

S.NO.	Actual Melting Point	Observed Melting Point
1	Melts & Decomposes at 100°C	98°C
2		100°C
3		103°C
	Average Melting Point	100.3°C

Table 4: Melting point of Rabeprazole

Conc	Trial 1	Trial 2	Trial3	Average Absorbance
0.5	0.1458	0.1459	0.1459	0.1459
1.0	0.3121	0.3122	0.3121	0.3121
1.5	0.4823	0.4822	0.4822	0.4822
2.0	0.5864	0.5863	0.5863	0.5863
2.5	0.7648	0.7647	0.7648	0.7648

Table 5: Standard Calibrative Curve of Rabeprazole in 0.1N HCl

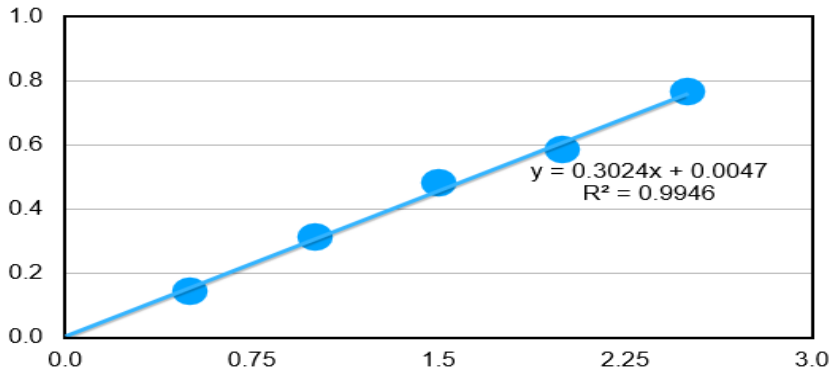


Figure 1: Standard Calibration Curve of Rabeprazole

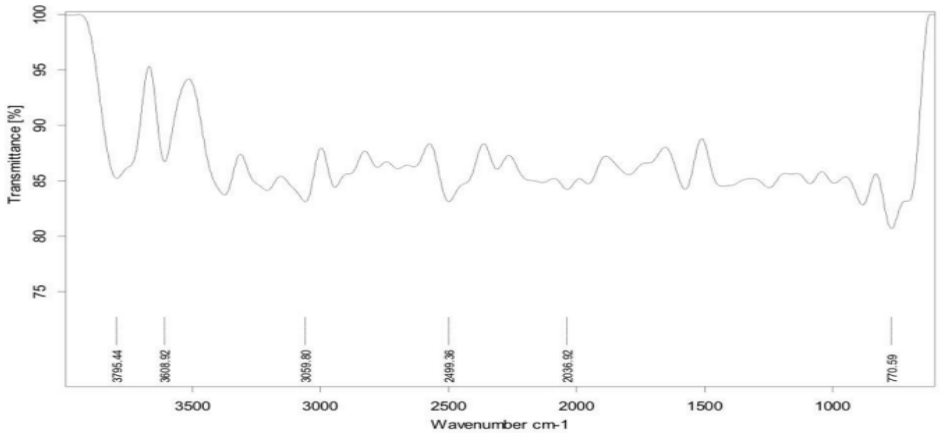


Figure 2: Ft-IR Spectra of Rabeprazole

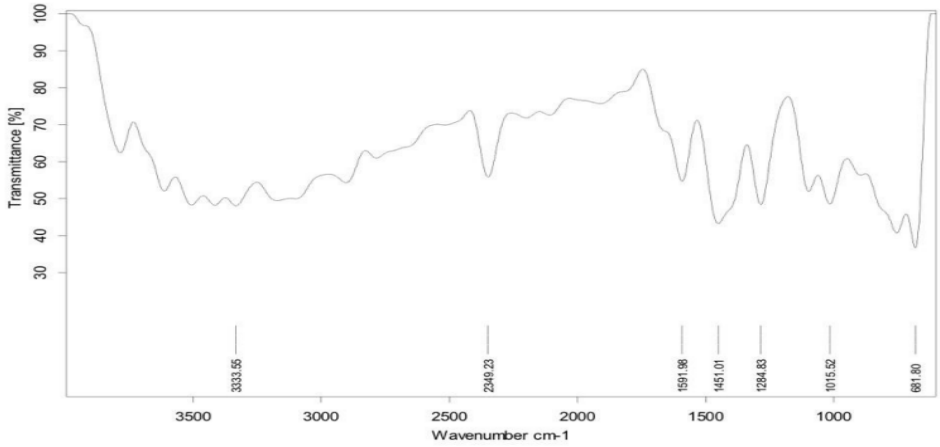


Figure 3: FT-IR Rabeprazole+ Sodium Citrate

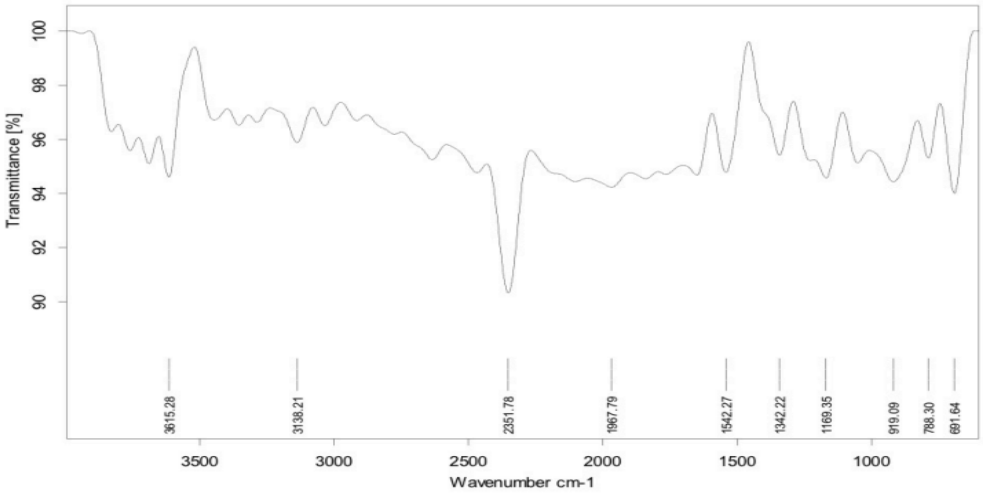


Figure 4: FT-IR Rabeprazole+ HPMC K100M

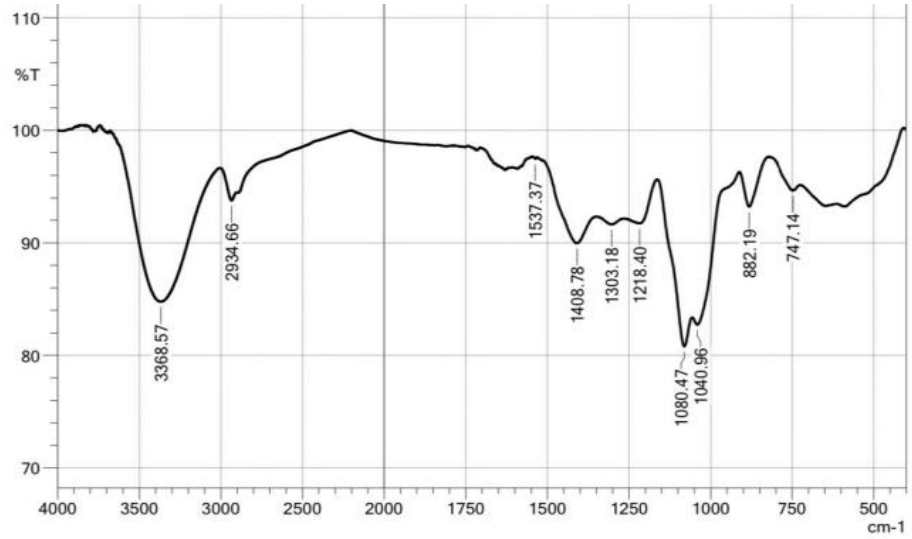
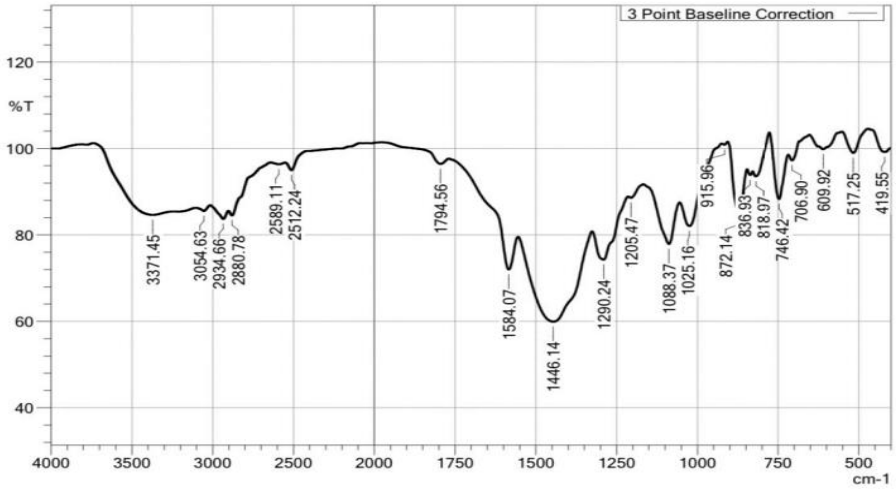


Figure 5: Rabeprazole + Calcium carbonate



6: FT-IR Rabeprazole + Sodium Alginate

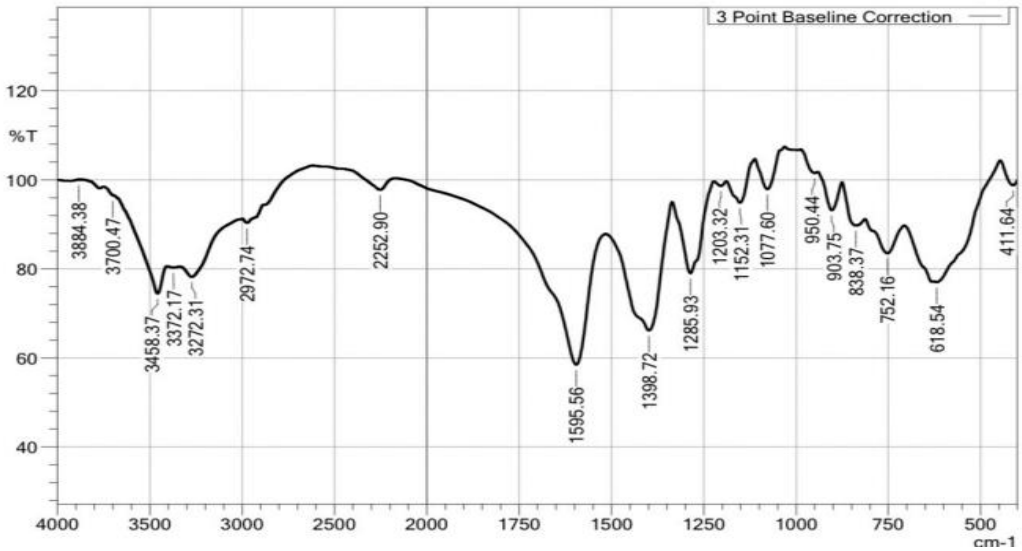


Figure 7: Rabeprazole + D. Sorbitol

Functional Group	Drug frequency	Drug +Sodium Alginate	Drug + Sodium Citrate	Drug +Calcium Carbonate	Drug + D.Sorbitol
C-H	2848.13	2934.66	2814.18	2880.78	2892.38
N-H	3353.32	3368.57	3333.55	3371.07	3458.37
S=O	1038.32	1040.96	1015.52	1025.16	1077.60

Table 6: Interpretation of FT-IR Spectral data of Rabeprazole

Formulation Code	Appearance	Clarity
F1	Transparent	Clear
F2	Transparent	Clear
F3	Transparent	Clear
F4	Transparent	Clear
F5	Transparent	Clear
F6	Transparent	Clear
F7	Transparent	Clear
F8	Transparent	Clear
F9	Transparent	Clear

Table 7: Physical appearance & clarity (F1-F9)

Formulation Code	Floating Lag Time (sec)	Floating Duration (hrs)
F1	32	>12hrs
F2	25	>12hrs
F3	19	>12hrs
F4	29	>12hrs
F5	22	>12hrs
F6	17	>12hrs
F7	27	>12hrs
F8	20	>12hrs
F9	15	>12hrs

Table 8: Floating Lag time & Floating Duration of in situ gelling formulation (F1-F9)

Formulation Code	Gelling Time	In-vitro gelling capacity
F1	18	++
F2	20	++
F3	24	+++
F4	19	++
F5	21	++
F6	27	+++
F7	21	++
F8	25	++
F9	28	+++

Table 9: Gelling Time, In-Vitro Gelling Capacity F1-F9

Shear Rate	Viscosity (cps)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0.3	8000	10000	12000	10000	12000	18000	12000	16000	20000
0.6	6000	7000	8000	6000	9000	12000	8000	12000	15000
1.5	3600	4000	4400	4800	4400	6000	4400	6000	7200
3	2000	2600	2800	2600	2800	3600	2800	3600	4800
6	1400	1700	1800	1700	1800	2300	2400	2400	2600
12	700	850	1000	850	1000	1250	1000	1250	1450
30	340	360	380	360	400	460	420	440	460
60	200	210	230	210	240	220	230	240	260

Table 10: Viscosity of formulation F1- F9

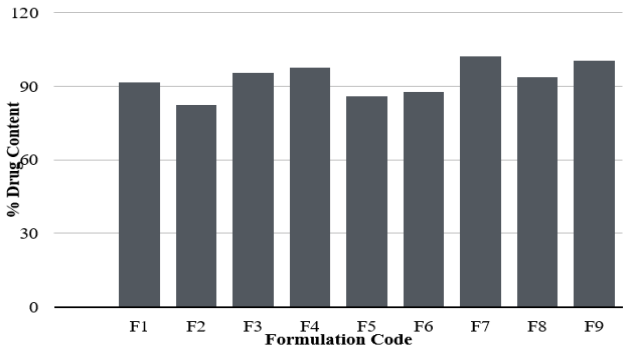


Figure 9: Bar Graph for Drug Content

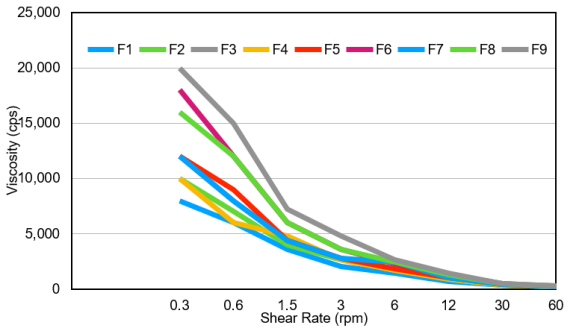


Figure 8: Viscosity of Formulation F1-F9

Formulation Code	% Drug Content
F1	94.62
F2	96.3
F3	95.5
F4	97.6
F5	98.9
F6	99.89
F7	102.4
F8	94.7
F9	100.5

Table 11: % Dug Content for Formulation F1-F9

Time (hr)	CDR%								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	16.84	16.74	20.56	17.32	9.01	6.30	13.8	8.55	4.95
2	30.06	32.67	29.95	28.54	18.03	14.86	25.69	19.05	17.15
3	44.01	41.06	55.73	49.07	28.14	25.67	37.48	26.91	22.06
4	65.51	50.42	64.04	58.40	40.15	37.43	46.75	40.19	32.95
5	72.11	72.95	78.30	66.32	47.81	48.74	49.78	54.51	36.46
6	77.96	85..02	86.32	71.24	54.16	56.05	65.64	62.82	54.02
8	83.40	90.03	95.15	80.17	62.78	61.86	75.49	68.34	61.38
10	84.08	95.89	-	87.61	75.91	75.90	78.14	79.18	70.11
12	91.25	-	-	95.16	85.41	82.29	90.39	89.04	89.32

Table 12:%CDR for formulations (F1-F9)

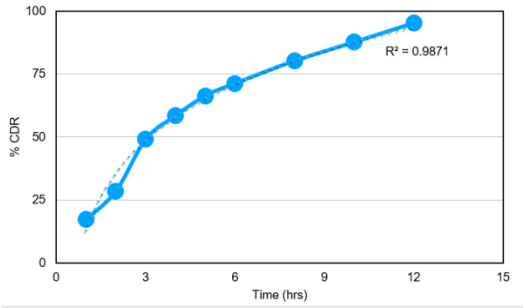


Figure 10: Zero Order Kinetics

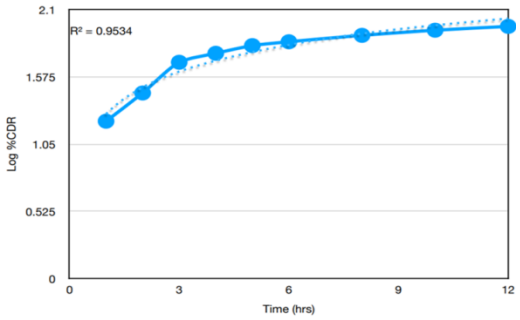


Figure 11: First order kinetics

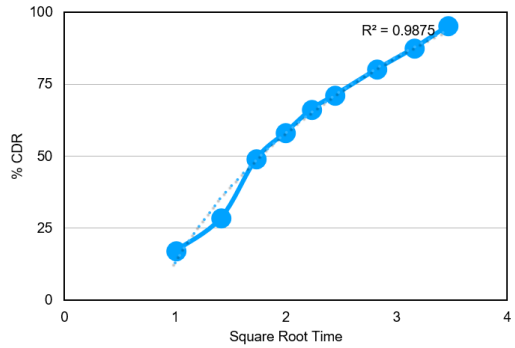


Figure 12: Higuchi plot

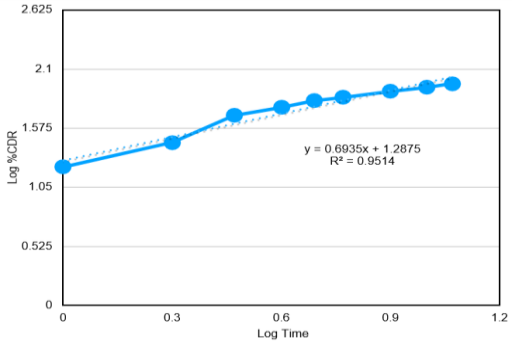


Figure 13: Korsmeyer Peppas

Formulation	Kinetics Of Drug Release	Mechanism Of Release			
	Zero Order	First Order	Higuchi Plot	Korsmeyer Peppas Plot	
	Correlation Coefficient (r2)				Slope 'n' Value
F4	0.9871	0.9534	0.9875	0.9514	0.6935

Table 13: Regressional analysis of the in vitro release data according to various release kinetic model of optimized formulation F4

Days	Physicochemical parameters						
	Physical appearance	Floating Lag Time (Sec)	Floating Duration (hrs)	Gelling Time(sec)	In Vitro Gelling Capacity	Gel Strength	Drug content
30	Transparent, Clear	27	12 hr	19	++	Good	97.15%
60	Transparent, Clear	29	12 hr	16	++	Good	98.99%
90	Transparent, Clear	25	12 hr	14	++	Good	100.2%

Table 14: Physicochemical parameters of best F4 Formulation at 1st, 2nd and 3rd month

Time	% CDR		
	1st month	2nd month	3rdmonth
1	17.32	15.32	18.82
2	28.54	25.67	29.91
3	49.07	50.99	38.98
4	58.40	59.87	49.99
5	66.32	65.12	58.67
6	71.24	73.87	73.33
8	80.17	79.99	86.66
10	87.61	85.86	89.91
12	95.16	93.99	94.56

Table 15: %CDR of best F5 Formulation at 1st, 2nd and 3rd month

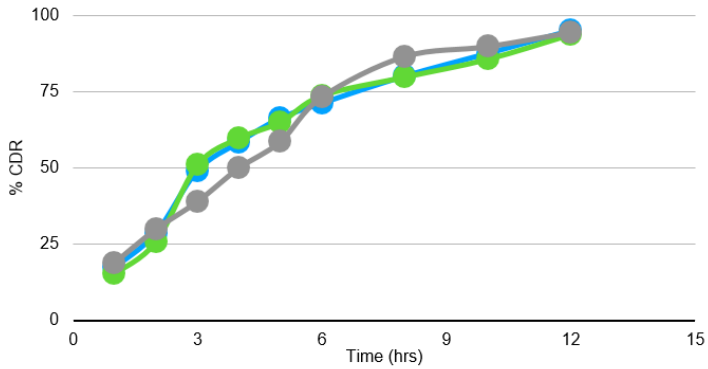


Figure 14: In vitro drug release of best formulation (F4) at 1st, 2nd and 3rd month

order plotted as log % drug retained Vs time, Higuchi plotted as % drug released Vs √time, Korsmeyer-Peppas plotted as log % drug released Vs log time. Comparing the r2 values obtained, the best-fit model was selected.[9,10]

Stabilitystudies

The purpose of stability studies was to determine the period for which the in-situ gel remains viable and usable. Stability is tested according to ICH guidelines at 40±2°C and 75±5% RH for 3 months.[11]

CONCLUSION

Oral floating *in situ* gel formulation was prepared and evaluated in the present study for treating Gastro esophageal reflux disease (GERD). The main criteria is to prepare a targeted drug delivery in stomach for an extended period of time. Pre formulation studies for the drugs included API characterization for their organoleptic properties & other properties such as solubility and melting point and all these characteristics were in harmony with their specifications as per the standards. standard calibration curve was determined by using UV-Visible Spectrophotometer. *FT-IR* technique was used for the drug and excipient compatibility and found out that there was no interaction between each other & drug and excipients used were compatible with each other. Ion activated method was used for the formulation of Oral floating *in-situ* gel of Rabeprazole. This method was used for the development of different formulation (F1-F9) using excipients in various concentration of sodium alginate. Sodium Alginate was used as gelling agent, HPMC K100M as viscosity enhancer, Calcium carbonate act as cation induced gelation and sodium citrate is added to avoid gelation before reaching the stomach. Formulations were evaluated on the basis of various physicochemical parameters like appearance, clarity, gel strength, viscosity, *in-vitro* gelling capacity, gelling time, *in-vitro* floating behaviour, drug content and *in-vitro* release studies. Result analysis showed the various properties of the prepared gelling system were found to be proportional to that of the concentration of polymer that has been used in the formulation. Best formulations F4 because of its good gelling capacity and optimum viscosity. Drug content was found to be 97.6% for F4 formulation. It showed 95.16 cumulative drug release for 12h. The formulation F4 best fitted for first order kinetic for drug release with R2=0.9534 that describes the rate of drug release is dependent of its concentration and follows higuchi kinetic mechanism with R2=0.9875. Stability studies were carried out for F4 formulations as per ICH guidelines for a period of 3 months and the stability was confirmed that no significant changes observed in physicochemical parameters.

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