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Design and development of floating *In-Situ* gel of pantoprazole

Ramana B. V.*, S. Jalalu Sana, L. Clement Swapna, S. Chandra Sekhar, G. Ademma and T. E. G. K. Murthy[1]

Department to Pharmaceutics, Dr. K. V. Subba Reddy Institute of Pharmacy, Dupadu, Kurnool, Andhra Pradesh-518218
[1]Bapatla College of Pharmacy, Bapatla, Guntur Dist, Andhra Pradesh-518218

ABSTRACT

The present investigation deals with the formulation, optimization and evaluation of sodium alginate based floating oral In situ gel of Pantoprazole. Sodium alginate used as a polymer and Calcium carbonate was used as a cross-linking agent. In-situ forming polymeric formulation drug delivery systems is in sol form before administration in the body, but once administered, undergoes gelation in-situ to form a gel. The formulation of gel depends upon factors like temperature modulation, pH changes, presence of ions and ultraviolet irradiation from which drug gets released in sustained and controlled manner. The objective of this study was to develop a novel in- situ gel system for sustained drug delivery using natural biodegradable polymer. The system utilizes polymers that exhibit sol-to-gel phase transition due to change in specific physicochemical parameters. In-situ gel was formed at a gastric p^H from designed set of experiments, it was evident that formulation containing 2 % of sodium alginate control the release of drug for longer duration. The in-situ gel exhibited the expected, viscosity, drug content, p^H, in vitro gelling capacity, in vitro floating ability and sustained drug release. The formulated in situ gel for Pantoprazole was found to be stable in situ gel. It was found to have better floating efficacy and in vitro release profile characteristics. Better efficiency and results of batch F-6 gives newer alternative use of natural biodegradable polymers in situ gel formulation.

Key-words: Oral *In-situ* gel, Sustained Release, Sodium alginate, Calcium Carbonate, Pantoprazole.

INTRODUCTION

Peptic ulcers are open craters or sores that develop in the inner lining (mucosa) of the stomach or the duodenum (the first section of the small intestine). A coating of mucus and other chemicals normally shield the stomach and duodenum from digesting themselves. When these protective mechanisms are disrupted, powerful digestive acids can erode into the lining of these organs and cause peptic ulcers**.**[1]

In situ is a Latin word which means in position. In situ gel formation of drug delivery systems can be defined as a liquid Formulation generating a solid or semisolid depot after administration. *In-situ* activated gel forming Systems are those which are when exposed to physiological conditions will shift to a gel phase. This new concept of producing a gel in situ was suggested for the first time in the early 1980s. Gelation occurs via the cross-linking of polymer chains that can be achieved by covalent bond formation (chemical cross-linking) or Non-covalent bond formation (physical cross-linking) [2].Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery systems is desirable for drugs with an

absorption window in the stomach or in the upper small intestine6. This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach.[3].

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H^+, K^+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).[4]

EXPERMINENTAL INVESTIGATIONS

Materials:
Pantoprazole(Ranbaxy Pharmaceuticals Ltd (India). Sodium Alginate (Lobachemie (P) Ltd.), Calcium carbonate (Central Drug House (P) Ltd.), Sodium citrate (Central Drug House (P) Ltd.), D-sorbitol (Central Drug House (P) Ltd.). All the other chemicals used were of Analytical grade.

Methods:
Preformulation Studies:
Identification of Drug by FTIR- Compatibility of Pantoprazole with gelling agent and other excipients was established by infrared spectral analysis IR Spectral analysis of samples (Ranitidine hydrochloride, Sodium Citrate, Sodium alginate, calcium carbonate, sorbitol) was carried out to investigate the changes in chemical composition of the drug**[5]**

Preparation of Formulations
Preparation of Pantoprazole in-situ gelling solutions – The polymeric dispersion was prepared by dispersing required quantity of gums and polymers in water using a magnetic stirrer and allowing it to swell overnight**.**SA (sodium alginate) Solutions were prepared in distilled water by heating to 60^0C under continuous stirring. After cooling below 40^0C ingredients including drug, gelling agent and other excipients were weighed accurately and formulations were prepared as per the table 3.The resulting six formulations (F1-F6) were finally stored in amber coloured bottles until further use.

Table no.1 Composition of Floating in situ gel:

Ingredients	Formulation code & Quantities					
	F1	F2	F3	F4	F5	F6
Pantoprazole	400mg	400mg	400mg	400mg	400mg	400mg
Sodium Alginate	1gm	1.5 gm	2 gm	1 gm	1.5 gm	2 gm
Sodium Citrate	250 mg	250 mg	250 mg	500 mg	500 mg	500 mg
CaCo3	250 mg	250 mg	250 mg	500 mg	500 mg	500 mg
D. sorbitol	1gm	2gm	3gm	1gm	2gm	3gm
Distil Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total Weight(ml)	100ml	100ml	100ml	100ml	100ml	100ml

Physical Appearance and p^H:- [6]
All the prepare sodium alginate based **in-situ** solution were checked for their clarity and the type of the solution. After administration of the prepared solution in (0.1N HCL, p^H 1.2) also checked the time required for gel formation and type of gel formed. The p^H was measured in each of the solution of sodium alginate based **in-situ** solution using a calibrated digital p^H meter at 27^0C. The measurement of p^H of each data was in triplicate**.**

Viscosity of in situ gelling solutions – The viscosity of formulations was determined by a Brookfield viscometer DV-III (Brookfield, USA) using spindle number 21 with cup and bob setting at 50 rpm.

Floating behavior – The floating ability of the prepared formulations was evaluated in (0.1N HCl, pH 1.2) Solution. The floating time of the prepared formulation took to emerge on the medium surface (floating lag time) was found to be 60sec.The time the formulation constantly floated on the dissolution medium surface (duration of floating) was evaluated to be 12hrs resulting the formation of thick gel with good floating tendency.

In-vitro gelling capacity - To evaluate the formulations for their in-vitro gelling capacity by visual method, solutions of in-situ gel forming drug delivery system were prepared. The in-vitro gelling capacity of prepare formulations was measured by placing 5 ml of the gelation solution (0.1N HCL, p^H 1.2) in a 15 ml borosilicate glass test tube and maintained at 37±1ºC temperature. One ml of formulation solution was added with the help of pipette. The formulation was transferred in such a way that places the pipette at surface of fluid in test tube and formulation was slowly released from the pipette. As the solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity of solution was evaluated on the basis of stiffness of formed gel and time period for which the formed gel remains as such. The in-vitro gelling capacity was graded in three categories on the basis of gelation time and time period for which the formed gel remains.

(+) Gels after few minutes, dispersed rapidly
(++) Gelation immediate remains for 12 hours
(+++) Gelation immediate remains for more than 12 hours**.**

Drug content:
Preparation of standard calibration curve of Pantoprazole: - Pantoprazole (10 mg) was dissolved in (0.1 N HCl, p^H 1.2) and volume was made up to 100 ml in 100 ml volumetric flask. This solution (100 mcg/ml) was further diluted with (0.1 N HCl, p^H 1.2) to obtain solution of 10 to 100 mcg/ml. The absorbance of each solution was measured at 283.4 using UV spectrophotometer. The standard curve was obtained by plotting absorbance v/s. concentration (µg/ml) .

Ten ml of the solution was added to 900 ml (0.1N HCl, p^H 1.2) Solution and stirred for 1 hr. on a magnetic stirrer. The solution was filtered, suitably diluted with (0.1N HCl, p^H 1.2) and the drug concentration was determined by using a UV-visible spectrophotometer a (Shimandzu UV 1700 Pharmaspec) at 284nm against a suitable blank solution**.**

In-vitro release studies: An in-vitro release study was carried out using dissolution test apparatus USP Type II (Paddle Method). The following procedure was followed throughout the study that is shown in (table 2) to determine the in vitro dissolution rate for the formulations. The release of Pantoprazole from the formulations was determined using dissolution test apparatus USP Type II with a paddle stirrer at 50 rpm. The dissolution medium used 900 ml of (0.1N HCL, p^H 1.2) solution and temperature was maintained at 37 ± 0.2 °C. Ten ml of the formulation were placed into a Petri dish (4.5cm i.d.) which was kept in the dissolution vessel and 0.1N HCL solution was carefully added to the vessel avoiding any disturbance of the Petri dish. At each time interval, a precisely measured sample of the dissolution medium was pipette out and replenished with fresh medium. Pantoprazole concentration in the aliquot was determined spectrophotometrically**.[6]**

Table: 2 Dissolution of Floating In Situ Gel

Dissolution medium	900 ml of (0.1N HCL,1.2 pH) solution
Temperature	37 ^{0}C±0.2 ^{0}C
RPM	50
Volume withdrawn	10 ml every 1 hrs.
λ_{max}	284nm
Sol. taken	Ten ml sol. (Known drug content)

Evaluation of in-vitro release kinetics:[34]
To study kinetics data obtained from in-vitro release were plotted in various kinetic models.

➢ **Zero-order equation:**

$$\%R = Kt$$

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs.

➢ **First order equation:**

$$\text{Log\% unreleased} = Kt / 2.303$$

This model is applicable to study hydrolysis kinetics and to study the release profiles of pharmaceutical dosageforms such as those containing water soluble drugs in porous matrices.

➢ **Higuchi equation:**

$$\%R = Kt0.5$$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrixtablets with water soluble drug.

➢ **Hixson and Crowell equation:**

$$(\%\text{unreleased})\ 1/3 = Kt$$

This expression applies to pharmaceutical dosage forms such as tablets, where the dissolution occurs in planes that are parallel to drug surface if the tablet dimensions diminish proportionality in such a manner that the initialgeometrical form keeps constant all the time. When this model is used, it is assumed that release rate is limitedby drug particles dissolution rate and not by diffusion that might occur through the polymeric matrix.

➢ **Korsmeyer-Peppas equation:**

$$\%R = Kt\ n$$

This model is widely used, when the release phenomenon could be involved. The end value could be used to characterize different release mechanisms as

Table No:-3

N	**Mechanism**
0.5	Fickian diffusion(Higuchi matrix)
0.5<n<1	Anomalous transport
1	Case- II transport(zero order release)
n>1	Super case- II transport

The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r' value is considered as the best fit of the release data. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined**.[6]**

Accelerated Stability Study of optimized formulation:
Accelerated stability study was carried out for optimized formulation, to assess its stability as per ICH guidelines. The optimized formulation were kept in amber coloured bottles and was placed in the accelerated stability chamber at elevated temperature and humidity of 40^0 c /75% RH and a control sample was placed at an ambient condition for a period of 1 month. Samplings was done at a predetermined time of initial 0,1,2,3 and 4 weeks interval respectively. At the end of study, samples were analyzed for the appearance , pH and drug content.

RESULTS AND DISCUSSION

Identification of Drug by FTIR:
Identification study was performed using FTIR spectrophotometer. The characteristic absorption peaks of Pantoprazole were obtained at different wave numbers. The peaks obtained in the spectra of pure drug correlates with the peaks of official spectrum of British Pharmacopeia which confirms the purity of drug.

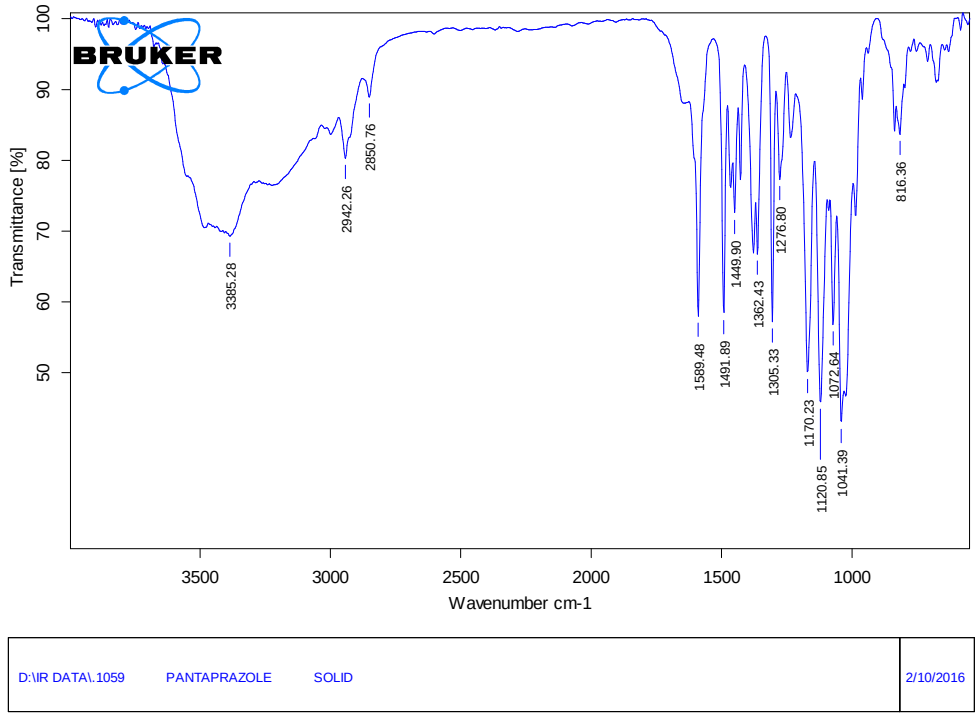

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Figure 1: IR spectra of Pantoprazole

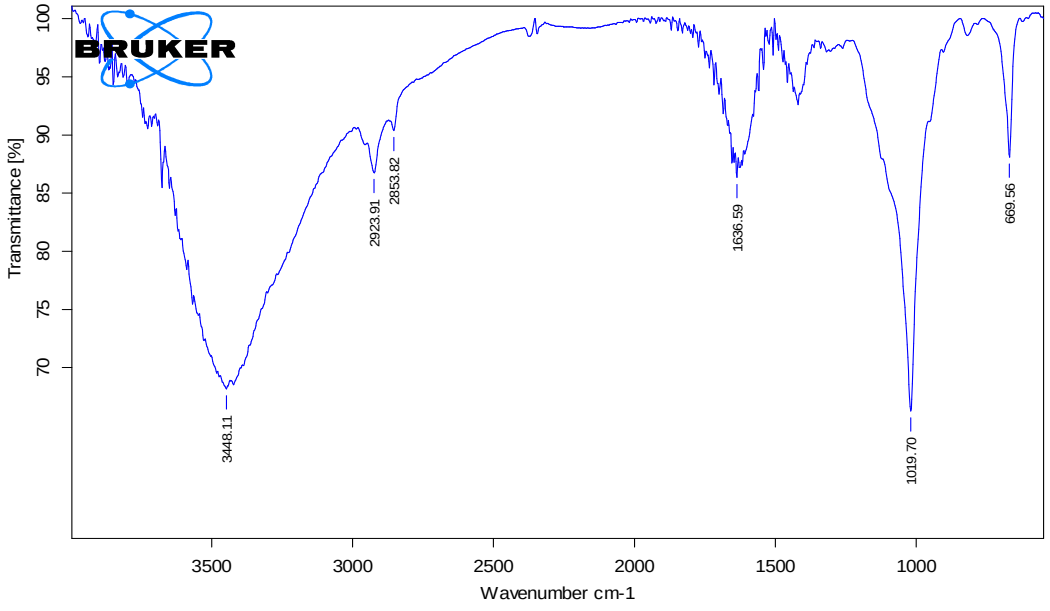

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Figure 2: IR spectra of Sodium alginate

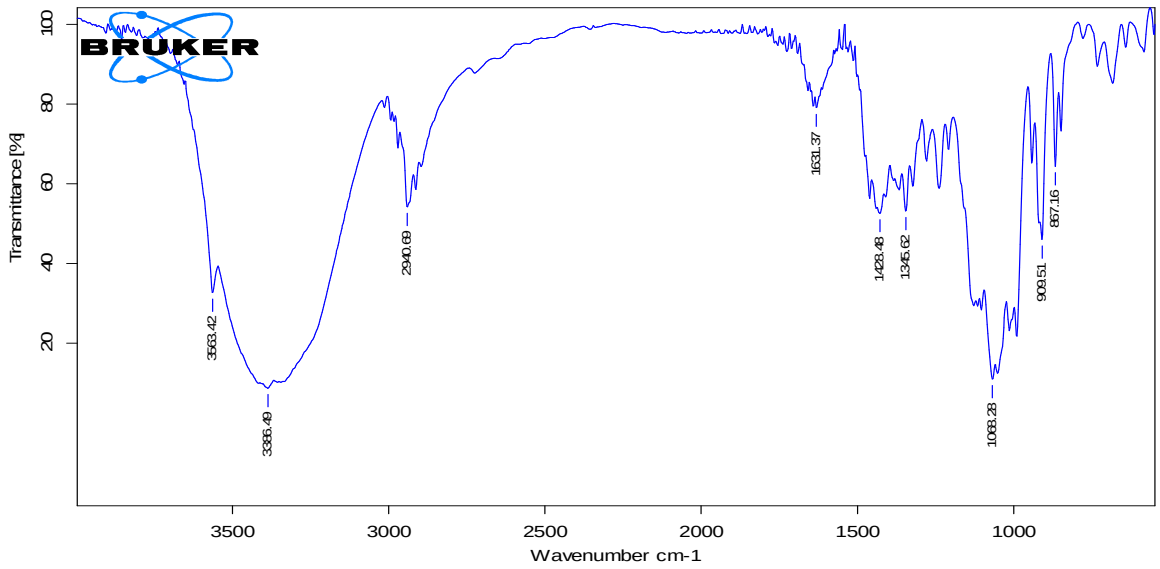


Figure 3: IR spectra of Sodium Citrate

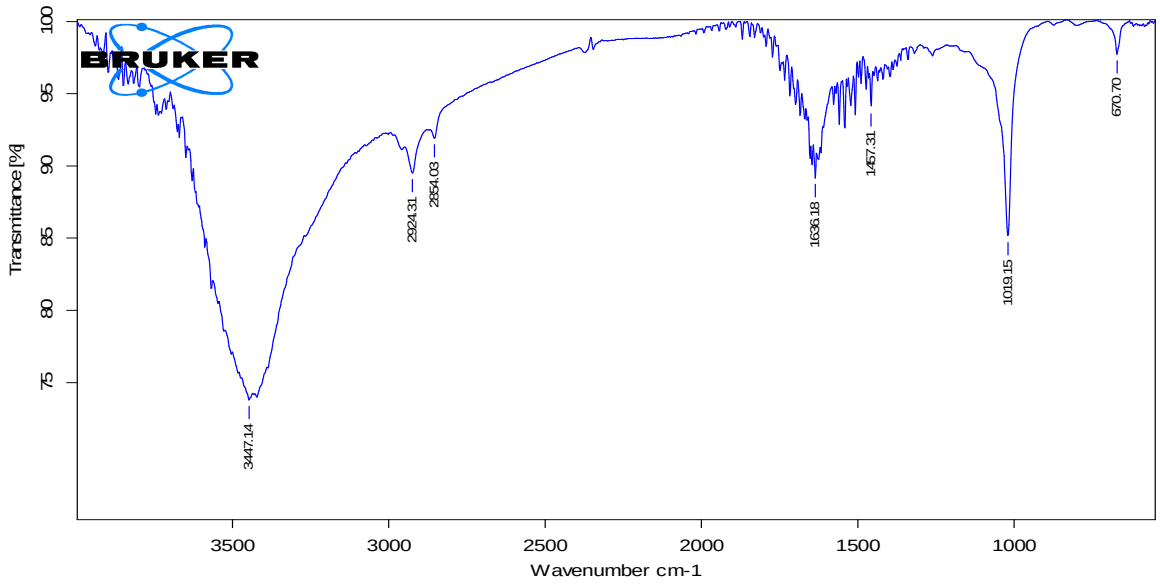


Figure 4: IR spectra of Calcium Carbonate

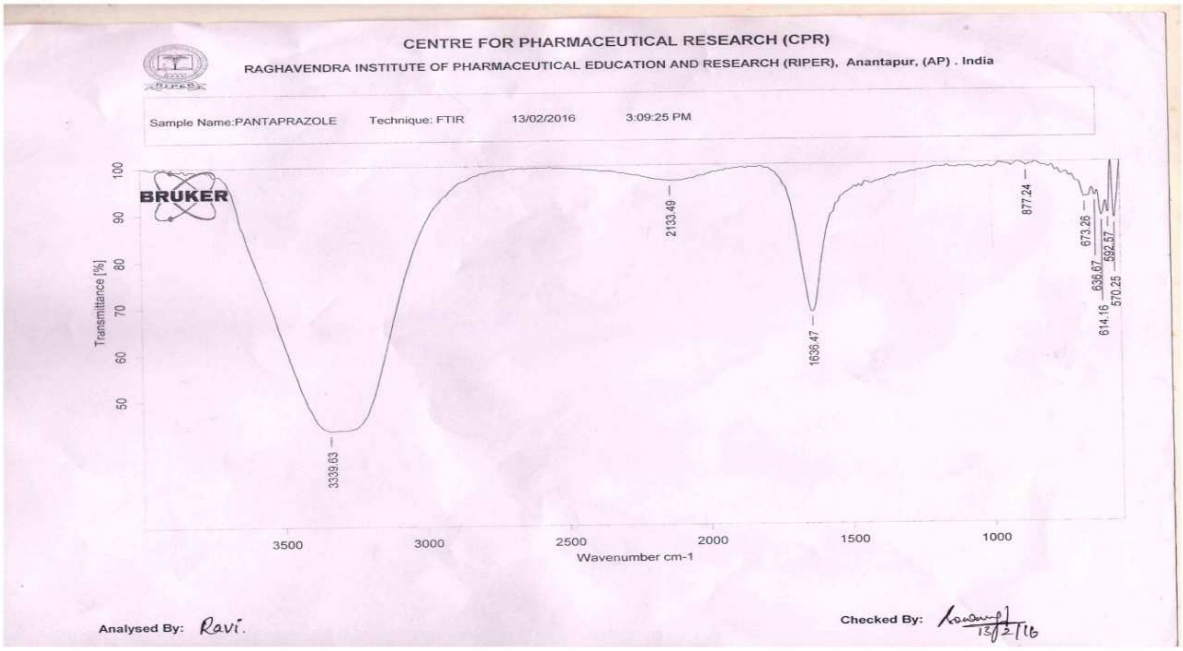


Figure 5: IR spectra of Pantoprazole with Excipients

Physical Appearance and p^H [6]:

All the prepared sodium alginate based in situ solution of Pantoprazole were checked for their clarity and the type of the solution. All the solutions are light brown in appearance and showed no visible particles or lumps in the preparation. After administration of the prepared solution in (0.1N HCL, p^H1.2) also checked the time required for gel formation and type of gel formed. The p^H was measured in each of the solution of sodium alginate based in situ solution ofPantoprazole, using a calibrated digital pH meter. The measurement of pH of data were in triplicate and the Average values given in **Table6.** All the formulations are within required pH range suitable for absorption.

Table 4: p^H of prepared In-situ gel formulation

Formulation code	F1	F2	F3	F4	F5	F6
p^H	9.3±0.11	9.2±0.47	8.9±0.28	9.4±0.36	9.2±0.34	8.9±0.22

All the values are mean of 3 and S.D

Viscosity :

The viscosity of the formulations increased with an increase in sodium alginate concentration. This phenomenon is a consequence of increasing chain interaction with an increase in polymer concentration. Calcium carbonate, which is the source of cations, increased the viscosity of the formulation. This change in viscosity is due to the proportional increase in the amount of dispersed calcium carbonate. All the values are tabulated in the table 7. The increase in order of viscosity was observed form which F6 shown the higher viscosity value and the order of increase of formulations is as **F1<F2<F3<F4<F5<F6 .**

Table 5: Viscosity of prepared In-situ gel formulation

Formulation code	F1	F2	F3	F4	F5	F6
Viscosity	91±0.29	132±0.58	156±0.63	192±0.52	220±0.62	240±0.18

Floating Behavior:

The buoyancy lag time varied with the formulation variables. Formulation F6 exhibited the least buoyancy lag time (70 s) while formulation F2 exhibited the highest lag time (82 s). The decrease in the buoyancy lag time of a formulation F6 can be attributed to the availability of an increased the concentration of calcium carbonate, being entrapped in the formed gel to give rapid buoyancy. Irrespective of formulation variables, buoyancy duration was > 12 hours.

Table 6: Floating behavior of prepared In-situ gel formulation

Formulation code	F1	F2	F3	F4	F5	F6
Floating lag time(sec)	72±0.35	82±0.41	74±0.56	76±0.09	72±0.83	70±0.24
Floating time(hr)	10	>10	>10	>10	>12	>12

Gelling Capacity:

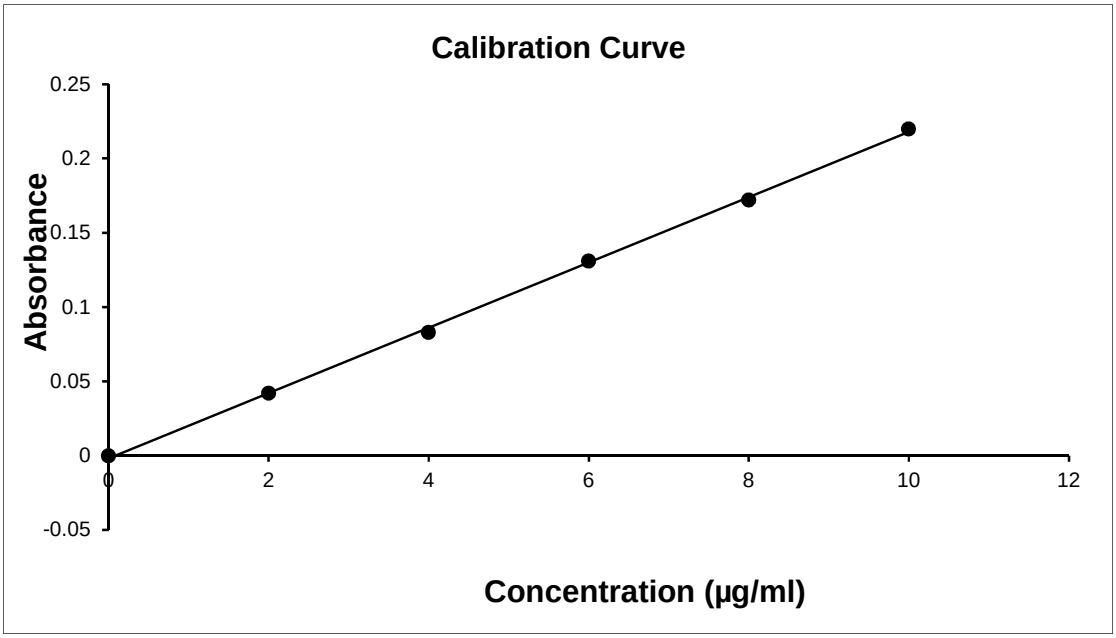
In vitro gelling capacity of various formulation of in-situ floating gel is reported in table

Table 7: Gelling capacity of prepared In-situ gel formulation

Formulation code	F1	F2	F3	F4	F5	F6
Gelling capacity	++	++	++	++	+++	+++

Drug Content:

Determination of Calibration Curve:



Date :			08.02.2016				
Calibration curve for :			Pantoprazole				
Solvent / Mobile Phase :			0.1N HCL				
Wavelength (nm) :			284				
Unit for Concentration:			mcg/ml				
Analytical Response :			0				
Done By :			R				
Equation for the standard curve :				Conc. =	45.48	0	+	0.088
				R =	0.9997			

The Drug content of all (F1-F6) formulations is given in table no 10, It ranges in between 97.03% - 98.62%. The values are acceptable as per united state pharmacopeia standards.

Table 8: Results of Drug Content of all formulation of Pantoprazole

Formulation code	F1	F2	F3	F4	F5	F6
Content uniformity (%)*	97.03±0.38	98.03±0.38	98.54±0.40	97.08±0.40	98.09±0.42	98.62±0.42

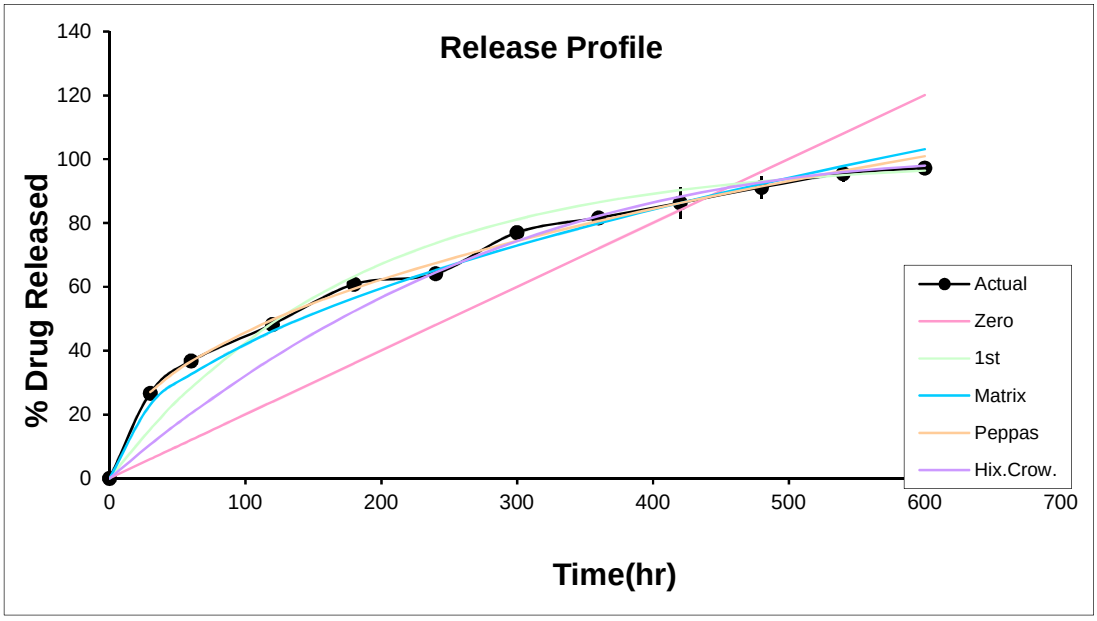
5.8 In-Vitro Drug Release:

The in-vitro drug releases of the in situ floating gel were carried in (0.1N HCl, 1.2 p^H) solution from 0 to 12 hrs by using dissolution test apparatus USP Type II (Paddle Method). The samples were withdrawn at different time intervals and analyzed at 284 nm. Percentage Cumulative drug release was calculated on the basis of mean amount of Pantoprazole present in the respective solution. The results obtained in the in vitro drug release for the formulations F1 to F6 in (Table 11). The plots are shown in (Figure no. 9) for % cumulative drug release VS time. Formulation F1, F2, F3, F4, F5 and F6 released about 93.01 %, 97.60 %, 98.56%, 96.68%, 97.92% ,98.88 of drug after 12 hrs. respectively. The results are shown in figure 9 indicate that the formulation, F6 which was prepared by the Sodium alginate (2%) with Pantoprazole showed drug release evenly and completely upto 12 hrs. Thus, the formulation (F6) has better result as comparison to others formulations as sustained release.[6]

Table 9: In-Vitro Drug release of Pantoprazole *in-situ* gel Formulations (F1- F6)

Sl.no:	Time	%R1	%R2	%R3	%R4	%R5	%R6
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	30	24.82	25.90	27.72	26.21	26.83	28.60
3	60	35.31	36.33	37.33	36.13	36.61	39.13
4	120	46.71	47.95	48.84	48.11	48.39	49.71
5	180	59.62	60.92	61.38	60.14	61.46	61.44
6	240	63.01	63.69	64.91	63.55	64.45	65.17
7	300	75.91	76.35	77.51	76.07	77.53	79.00
8	360	84.34	79.37	80.42	84.63	80.34	80.89
9	420	93.56	81.39	82.55	94.40	82.40	83.87
10	480	93.02	96.72	90.98	94.39	85.30	86.93
11	540	93.43	97.07	98.24	96.37	97.39	90.72
12	600	93.91	97.60	98.56	96.68	97.92	98.88

Figure 10: In-vitro Release Profile of Pantoprazole (F1 To F6)[25]



Release Kinetics:

The % cumulative drug release (%CDR) was calculated**.** The data obtained was further subjected to PCP DISSO software for curve fitting for drug release data . The best fit model was found to be First order and Krosmeyers pepp as with the regression in the range of 0.4755 – 0.4998 and 0.9532-0.9969 and the formulation exhibited fickinian diffusion mechanism with a value of 0.1095-0.1609.Formulation F6 exhibited required release characteristics with the regression value of 0.9969, as show in table 11.The F6 formulation was further subjected to accelerated stability study.

Table 11: Release Kinetics of all prepared formulations

Model		F1	F2	F3	F4	F5	F6
Zero order	K	0.0812	0.0745	0.0693	0.0834	0.0912	0.0939
	R	0.4523	0.4326	0.4122	0.4643	0.4851	0.4932
First order	K	-0.006	0.0124	-0.008	0.2321	-0.009	-0.009
	R	0.4755	0.4852	0.4672	0.4912	0.4936	0.4998
Higuchi	K	0.2322	0.2125	0.1913	0.1956	0.1817	0.2071
	R	0.9121	0.8856	0.9190	0.8952	0.9021	0.8725
Hixon Crowell	K	-0.0002	-0.0003	-0.0006	0.0123	0.0011	-0.0003
	R	0.5236	0.4875	0.4232	0.5189	0.4758	0.4758
Krosmeyer – Peppas	K	0.2456	0.2836	0.2925	0.2268	0.2861	0.3411
	n	0.1612	0.1324	0.1248	0.1536	0.1600	0.1274
	R	0.9532	0.9658	0.9875	0.9647	0.9855	0.9969

Accelerated stability study of Optimized Formulation:

In pantoprazole preparations formulation F8 was to be stable during accelerated stability studies for Appearance , clarity, pH and % Drug content as shown iin the Table 12. Finally it was observed that there was no change in Physical and Chemical properties as well as in drug release profile even after storage at 40^0 C and 75 % RH for 1 month.

Table 12 : Results of accelerated stability study of optimized formulation

Optimized Formulation			
	Appearance& Calrity	**pH**	**% Drug Content**
Initial	No Change	8.9	98.62
First week Ambient	No Change	8.9	98.62
40^0 C /75% RH	No Change	8.9	98.62
Second week Ambient	No Change	8.9	98.62
40^0 C /75% RH	No Change	8.9	98.62
Third week Ambient	No Change	8.9	98.62
40^0 C /75% RH	No Change	8.9	98.62

CONCLUSION

The present work was carried out to develop a novel gel based *in-situ* drug delivery system of Pantoprazole. The methodology adopted for preparation of *in-situ* gel solution was very simple and cost effective. It is newer approach to improve easy instillation, residence time and bioavailability and prolong drug release. From the study conducted, the following conclusions were drawn, by varying the concentration of polymer, it is to obtain the increased residence time and sustained drug release. Among the novel gum systems used sodium alginate was found to be best gum and viscosity enhancer in combination with polymers with respect to increased duration of action and drug release. The study revealed that an appropriate concentration is an important factor in achieving increased duration of action and also release from the dosage form to achieve sustained effect. The gel formed in situ afforded sustained drug release over 8 hrs periods. The formulations exhibited therapeutic efficacy. The developed formulation is a viable alternative conventional solution by virtue of its ability to enhance bioavailability through its longer gastric residence time and ability to sustain drug release.

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