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Formulation and Evaluation of Floating *In Situ* Gel Based Gastro Retentive Drug Delivery of Cimetidine

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ABSTRACT

The present investigation deals with the formulation and evaluation of sodium alginate and pectin based *In situ* gel of Cimetidine. Sodium alginate and pectin were used as a polymer and $CaCO_3$ was used as a cross-linking agent. In-situ forming polymeric formulations 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 ultra-violet 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 polymers. The system utilizes polymers that exhibit sol-to-gel phase transition due to change in specific physico-chemical parameters. In-situ gel was formed at a biological pH. *In vitro* release studies were conducted in simulated gastric fluid and cumulative amount of drug release was analyzed by spectrophotometry. From designed set of experiments, it was evident that formulation containing 1.2% of sodium alginate and 1.5% of pectin control the release of drug for longer duration. The in-situ gel exhibited the expected, viscosity, drug content, pH, *in vitro* gelling capacity, *in vitro* floating ability, water uptake ability and sustained drug release.The drug release from the *in situ* gels follows the fickian diffusion type of release.

KEYWORDS

In-situ gel, gelation, natural biodegradable polymers, simulated gastric fluid, Cimetidine.

INTRODUCTION

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating drug delivery systems (FDDS), swelling and expanding systems, bioadhesive systems, modified shape systems, high-density systems and other delayed gastric emptying devices[1]. FDDS are widely explored for gastroretention purposes and have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time[2].

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While the system is floating on gastric contents, the drug is released slowly at a desired rate from the system[3]. Sodium alginate (SA) is a widely used natural polymer in various drug delivery systems. It exhibits favourable biological properties such as non-toxicity, biocompatibility, biodegradability and ulcer healing traits. Moreover, gelation of dilute solutions of SA occurs on addition of di- and trivalent metal ions by a co-operative process involving consecutive G-residues in the a-L-guluronic acid blocks of the alginate chain in a manner described by the 'egg-box' model[4].

The procedure by which gelation is achieved is similar to the previously reported *in situ* gelling formulations of sodium alginate[5,6]. H_2-

antagonists or proton pump inhibitors are clinically used in treating chronic conditions like peptic ulcer and reflux oesophagitis. H_2-antagonists competitively inhibit histamine actions at all H_2-receptors, but are mainly used clinically as inhibitors of gastric acid secretion[7,8].

Local availability of H_2-antagonists in stomach has a greater clinical significance in treatment of peptic ulcer. Cimetidine (CT), a H_2-antagonist, is widely prescribed in active duodenal ulcers, gastric ulcers and gastroesophageal reflux disease[9,10]. A conventional dose of 200 mg can inhibit gastric acid secretion up to 5 hours and frequent administration leads to plasma fluctuations; hence, a sustained release dosage form of ranitidine is desirable[11]. The short biological half-life of the drug (~2.5–3 hours) also favors development of a sustained release, gastroretentive formulation [7,8]. In the present study, an attempt was made to develop a gastroretentive *in situ* gelling liquid formulation using cimetidine for local release in the stomach. Gastroretentive *in situ* gelling liquid formulations were formulated using different grades and concentrations of sodium alginate and pectin.[12,13,14]

MATERIALS AND METHODS

MATERIALS

Pectin, $CaCl_2$ and $CaCO_3$ were obtained from S.D.Fine chemicals, Mumbai. Sodium alginate and Sodium citrate were supplied from RANKEM Ltd. Gift sample of Cimetidine was kindly provided by Acron pharmaceuticals Ltd. Ahmedabad. Deionized water was supplied from Surni pharmaceuticals, Baroda.

METHOD

Preparation of Cimetidine *In Situ* Gel

Polymer solution was prepared in deionized water by heating to 60°C under continuous stirring. After cooling below 40°C, various concentration of cross linking ($CaCO_3$) and the drug will dispersed/dissolved under continuous stirring. Finally, Preservative will be added and stored.

Table 1: Cimetidine *in situ* gel

Ingredients	F1	F2	F3
Cimetidine	2.5%	2.5%	2.5%
Sodium alginate	0.5%	1.0%	1.5%
Pectin	1.0%	1.0%	1.0%
$Caco_3$	2.0%	2.0%	2.0%
$Cacl_2$	0.15%	0.15%	0.15%
Sodium citrate	0.45%	0.45%	0.45%
Deionized water	Up to 100 ml	Up to 100 ml	Up to 100 ml

Determination of UV Absorbance Maxima of Cimetidine

Stock solution of Cimetidine in methanol was prepared and diluted till appropriate concentration. The solution was then scanned in UV visible spectrophotometer within wavelength of 200-300 nm.

Preparation of Standard Calibration Curve of Cimetidine in 0.1 N HCl[15]

100 mg of Cimetidine was dissolved in100 ml of 0.1N HCl. The solution was then diluted with 0.1 N HCl to obtain 2, 4, 6, 8 and 10 µg/ml solution. It was then measured by UV visible spectrophotometer at 218nm.

Identification of Drug by FTIR

Fourier-transform infrared **(**FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The pure Cimetidine were mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.[16]

Table 2: Cimetidine *in situ* gel

Ingredients	F4	F5	F6	F7	F8	F9	F10	F11
Cimetidine	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Sodium alginate	0.8%	1.2%	0.8%	1.2%	0.8%	1.2%	0.8%	1.2%
Pectin	1.5%	1.5%	2.0%	2.0%	1.5%	1.5%	2.0%	2.0%
$CaCO_3$	1.5%	1.5%	1.5%	1.5%	2.0%	2.0%	2.0%	2.0%
$CaCl_2$	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%
Sodium citrate	0.45%	0.45%	0.45%	0.45%	0.45%	0.45%	0.45%	0.45%
Deionized water	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml

Identification of Drug By DSC

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The drug were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.[17]

Physical Appearance and pH

All the prepared sodium alginate based *in situ* solutions of Cimetidine were checked for their clarity and the pH of the solutions. After administered of the prepared solutions in 0.1 mol L^{-1}HCl, pH 1.2, the time required for gel formation and consistency of gel formed was checked visually. The pH was also measured in each of the solution of sodium alginate based *in situ* solutions of cimetidine, using a calibrated digital pH meter at 25°C.[18]

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.[19]

Floating Behavior

The buoyancy lag time and buoyancy duration of the formulations were determined in simulated gastric fluid (0.1 mol L^{-1}HCl, pH 1.2). The time in minutes taken by the formulation to emerge on the dissolution medium surface (buoyancy lag time) and buoyancy duration was noted.[20]

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 prepared formulations was measured by placing five ml of the gelation solution (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube and maintained at 37±1°C 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.[21]

(+) Gels after few minutes, dispersed rapidly

(++)Gelation immediate remains for 12 hours

(+++) Gelation immediate remains for more than 12 hours

Drug Content

Ten mL of the solution was added to 900 mL of simulated gastric fluid (0.1 mol L^{-1}Cl, pH 1.2) and stirred for 1 h on a magnetic stirrer. The solution was filtered, suitably diluted with simulated gastric fluid and the drug concentration was determined by using a UV-visible spectrophotometer a (UV-1601 Shimadzu, Japan) at 226 nm against a suitable blank solution.[22]

***In Vitro* Release**

The release of ranitidine from the formulations was determined using a USP/24 dissolution test apparatus (Tab Machines, India) with a paddle stirrer at 50 rpm. The dissolution medium used was 900 mL of simulated gastric fluid (0.1 mol L^{-1}HCl, pH 1.2) and temperature was maintained at 37 ± 0.2 °C. Ten mL of the formulation were placed into a Petri dish (4.5 cm i.d.) which was kept in the dissolution vessel and simulated gastric fluid 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 pipetted out and replenished with fresh medium. Ranitidine concentration in the aliquot was determined spectrophotometrically. Each study was conducted in triplicate (9).[23]

Kinetic of Drug Release

The cumulative amount of drugs released from the systems at different time intervals was fitted to different kinetic model of Zero order, First order, Higuchi model, Hixson-Crowell model and Korsmeyer-Peppas model to find out whether the drug release from the systems provides a constant drug release pattern. The correlation coefficient (R2), Sum of square (SSQ) and Release constant also calculated to find the fitness of the data to different kinetic models.[24,25]

Stability Study

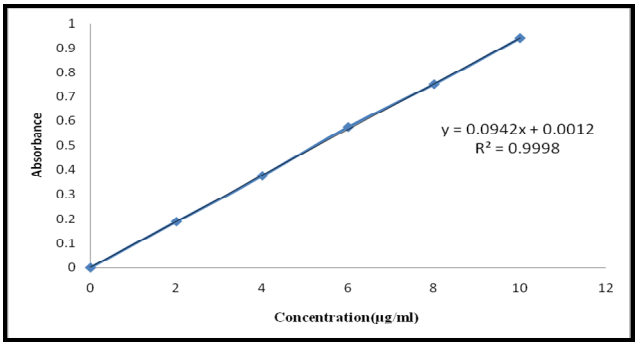
The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 25ºC/60%RH and 40ºC/75%RH for 1 month and evaluated for their physical appearance, drug content, drug release, and drug excipients compatibility at specified intervals of time.[26,27]

RESULTS AND DISCUSSION

UV ABSORBANCE MAXIMA OF CIMETIDINE

The sample containing Cimetidine was scanned in the range of 200-300 nm by UV spectrophotometer. From the obtained spectrum of Cimetidine absorbance maxima was found to be at 218.2 nm which is very close to its reported λ_{max} value that is 218nm.

Standard Calibration Curve of Cimetidine



Identification of Drug by FTIR

Identification study was performed using FTIR spectrophotometer. The characteristic absorption peaks of Cimetidine 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.

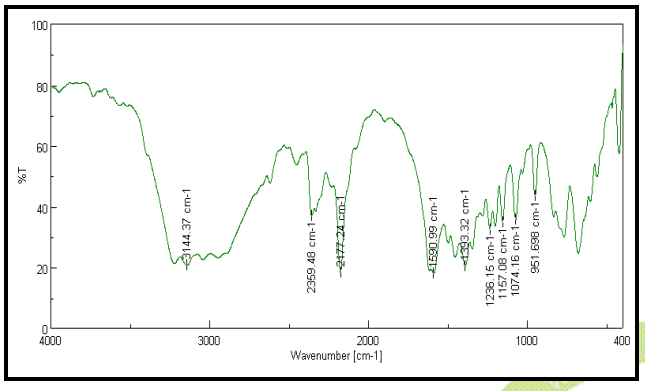


Figure 1: FTIR spectra of Cimetidine

Identification of Drug by DSC Spectra

The DSC thermogram of Cimetidine analyses was conducted to explore the melting activities of drug. DSC analysis showed a sharp endothermic peak at 142.5^{o}C which is an indication of melting point of Cimetidine. The melting range of Cimetidine is 139-144^{o}C as per United States pharmacopeia. So it was found to be very close to authentic range of official standards. The identity of a compound was also confirmed by verification of the presence of functional groups in Cimetidine by IR spectra**.**

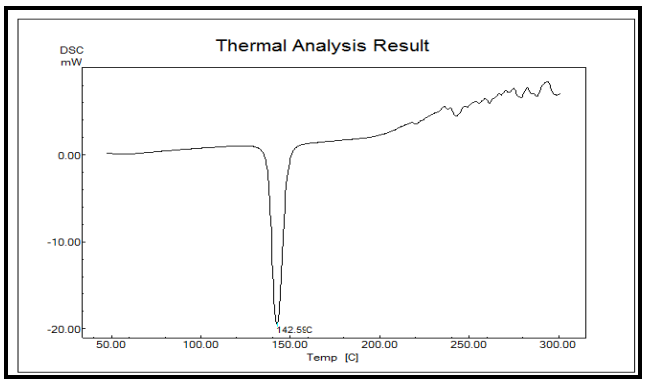


Figure 2: DSC spectra of Drug

Physical Appearance and pH

Physical characterization parameters are reported in table 3. All the formulation had off white to pale yellow colored solution. They had pH in the range of 6.84-7.20.

Viscosity of *In Situ* Gelling Solutions

The viscosity of the formulations increased with an increase in sodium alginate and pectin 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.

Floating Behavior

The buoyancy lag time varied with the formulation variables. Formulation F8 exhibited the least buoyancy lag time (26 s) while formulation F11 exhibited the highest lag time (219 s). The decrease in the buoyancy lag time of a formulation F8 can be attributed to the availability of an increased amount of CO_2 as the concentration of calcium carbonate was increased, being entrapped in the formed gel to give rapid buoyancy. Irrespective of formulation variables, buoyancy duration was > 12 hours.

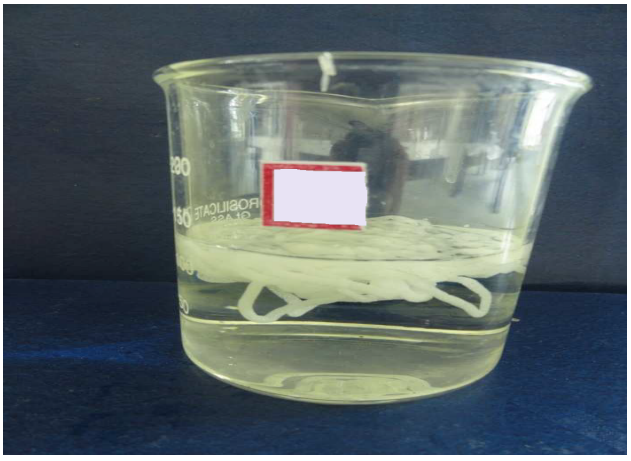


Figure 3: Floating behavior of *In situ* gel formulation

Table 3: pH of prepared *In situ* gel formulation

Formulation Code	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
pH	7.05	7.11	7.14	6.84	7.11	7.20	7.09	7.12

Table 4: Viscosity of prepared *In situ* gel formulation

Formulation Code	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
Viscosity(cp)	260	268	280	240	242	275	296	308

Table 5: Floating behavior of *In situ* gel formulation

Formulation Code	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
Floating lag time(Sec)	50	66	45	72	26	35	196	219
Floating time(hr)	>12	>12	>12	>12	>12	>12	>12	>12

Table 6: *In vitro* gelling capacity of *In situ* gel formulation

Formulation Code	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
Gelling capacity*	++	++	++	++	++	++	+++	+++

***(++) Gelation immediate remains for 12 hours, (+++) Gelation immediate remains for more than 12 hours

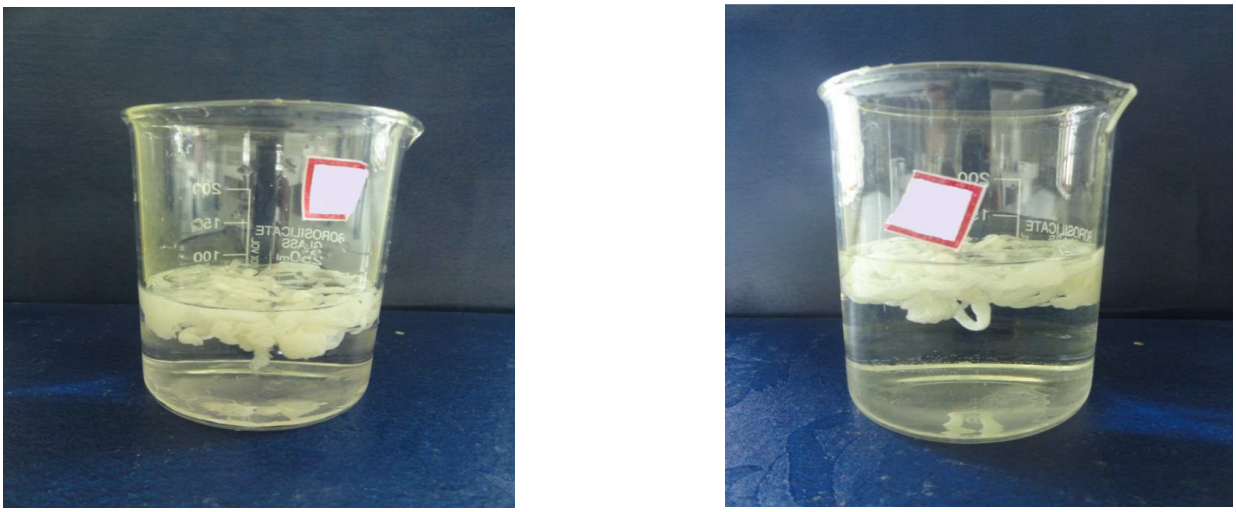


Figure 4: Gelling capacity of *in situ* floating gel formulation

In Vitro Gelling Capacity

In vitro gelling capacity of various formulation of *in situ* floating gel is reported in table no.6.

Drug Content (%)

The Drug content of all (F4-F11) formulations is given in table no 7. It ranges in between 97.68% - 98.94%. The values are acceptable as per united state pharmacopeia standards.

In-Vitro Drug Release

The *in-vitro* drug release of the *in situ* floating gel were carried in 0.1N HCl from 0 to 8 hrs by USP type-II apparatus and the values are shown in table no. The plot of % Cumulative drug release v/s time (hrs) was plotted and depicted as shown in figure no.8. *In vitro* drug release study was conducted on the formulations for a period of 8 hours during which the highest drug release of 99.75±1.28 % (n=3) was observed with formulation F9 and the least drug release of 80.66±4.36 % with F6 during the 8 hour dissolution study. The influence of SA and pectin on *in vitro* drug release is shown in Figure. As the concentration of SA and pectin used in the formulation were increased from low to high, a decrease in the amount of drug release was observed. The drug release from the formulations with higher concentration of SA and pectin were slower compared to formulations with medium and low concentration of SA and pectin.

Kinetic of Drug Release

The dissolution of drug from prepared *In situ* gel at different time periods was plotted as cumulative % drug release v/s time curve as shown in figure.

The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, Korsmeyer-Peppas models. Results were shown in table 9.

Mechanism of drug release

By incorporating the first of release data mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release.

Fickian diffusional release and a case-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient.

Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. Table 9 describes the limits of this analysis for cylindrical shape, e.g. a capsule. The value of the release exponent in cimetidine *in situ* floating gel (F9) obtained as 0.306 which indicates the fickian diffusion type of release. Other all batches show the range of release exponent in between 0.5-1.0, indicates fickian diffusion type of release.

Table 7: Results of Drug Content of all formulation of Cimetidine

Batches	F4	F5	F6	F7	F8	F9	F10	F11
Content uniformity (%)*	98.94 ±0.40	98.94 ±0.40	99.75 ±0.33	99.75 ±0.33	97.68 ±0.27	97.68 ±0.27	98.75 ±0.42	98.75 ±0.42

*Values are expressed as mean ± SD of 3 readings (n=3).

Table 8: % Drug release of all formulation of *in situ* floating gel

Time (Hr)	% Drug Release							
	F4	F5	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0	0	0
1	51.90±0.38	47.99±0.83	61.62±1.46	52.91±1.64	54.74±1.74	55.84±1.37	46.93±2.02	40.91±1.36
2	73.30±0.86	64.13±1.57	67.30±1.36	57.73±1.93	63.95±1.83	62.92±1.84	54.92±1.84	48.74±1.75
3	77.93±1.52	73.35±1.84	68.46±2.68	65.82±2.45	70.16±2.37	68.04±1.48	61.03±2.67	53.17±2.54
4	79.08±1.87	82.48±2.4	69.70±1.36	71.38±2.24	76.32±1.56	77.95±2.94	67.94±2.38	65.63±2.87
5	80.24±2.67	96.28±1.28	70.57±2.94	75.39±1.84	81.47±3.32	84.05±2.28	72.94±3.94	74.39±2.36
6	81.18±3.63	97.43±3.64	72.58±3.74	79.02±3.63	86.53±3.26	89.75±4.18	78.93±1.45	78.57±1.81
7	84.17±2.19	98.62±2.68	78.8±2.97	81.93±3.18	93.84±2.62	93.94±1.68	81.93±2.16	82.63±2.36
8	88.91±4.25	99.77±2.49	80.66±4.36	83.73±2.89	98.53±2.68	99.75±1.28	85.94±2.98	84.62±2.84

*Values are expressed as mean ± SD of 3 readings (n=3).

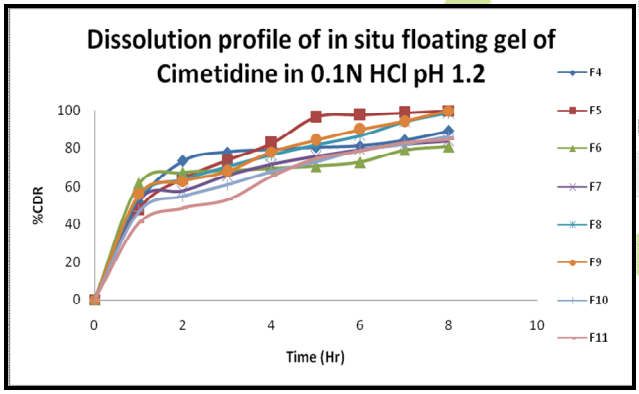


Figure 5: Dissolution profile of *in situ* floating gel of cimetidine

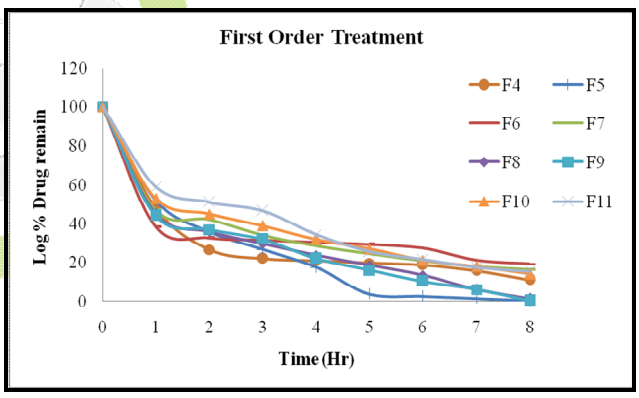


Figure 7: First order release kinetic of *In situ* gels

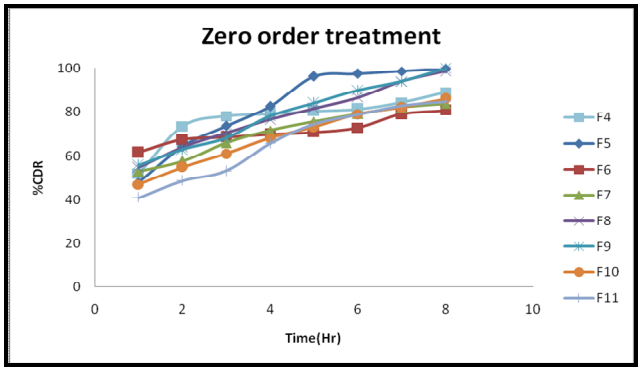


Figure 6: Zero order release kinetic of *In situ* gels

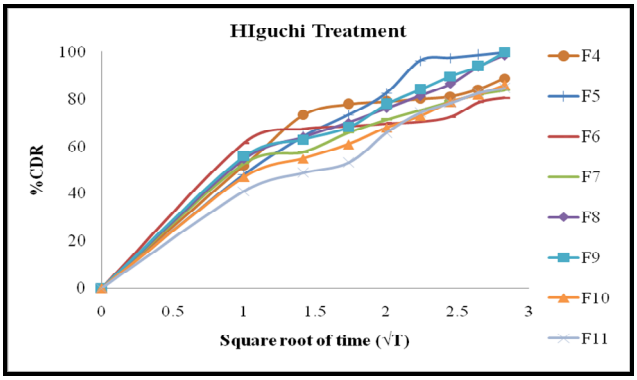


Figure 8: Higuchi model kinetic of *In situ* gels

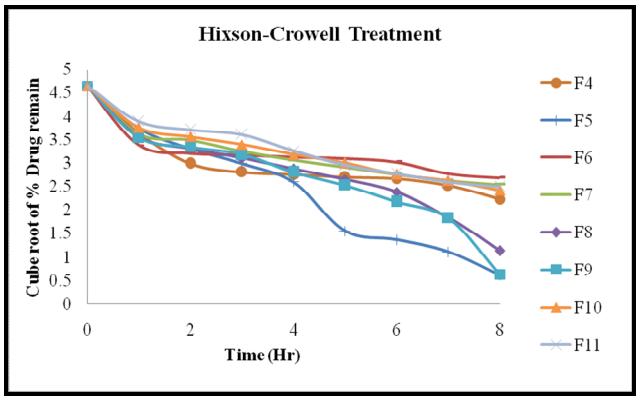


Figure: 9 Hixson-Crowell model kinetic of *In situ* gels

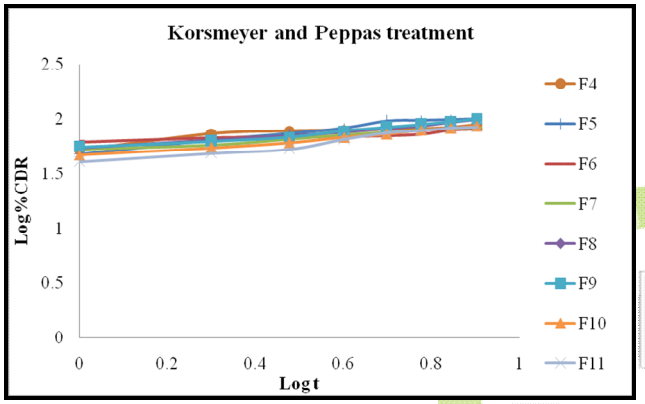


Figure 10: Korsmeyer-Peppas model kinetic of *In situ* gels

Stability Study

The selected Formulation F9 were evaluated for stability studies which were stored at 25ºC±2ºC/60%RH±5%RH and 40ºC±2ºC/75%RH±5%RH tested at 1 month, and were analyzed for their drug content and drug release. The residual drug contents of formulations were found to be within the permissible limits.

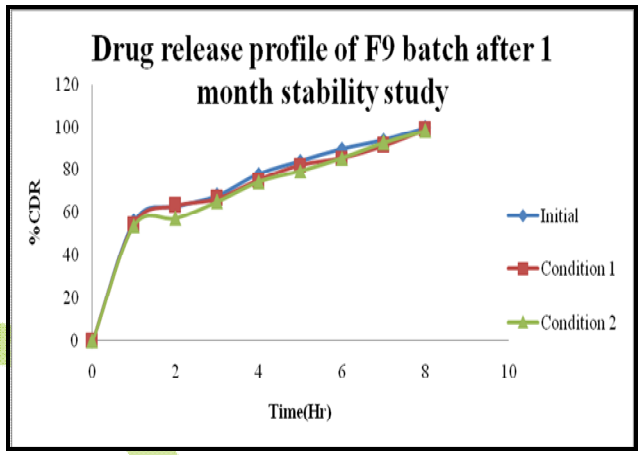


Figure 11: *In vitro* Drug release of F9 batch after stability study

Table 9: Different kinetic models applied on In situ gel formulations

Batch Code	Zero Order Model			First Order Model			Higuchi Square Root Model			Korsmeyer-Peppas Model				Hixson-Crowell Model			Best Fit Model
	K_0	SSQ	R^2	K_1	SSQ	R^2	K_H	SSQ	R^2	n	K_{KP}	SSQ	R^2	K_{HC}	SSQ	R^2	
F4	14.399	6121.4998	0.0048	0.487	887.9546	0.8556	36.145	1386.4923	0.7746	0.197	58.937	120.0295	0.9805	0.137	1521.5600	0.7526	First
F5	16.082	4281.5124	0.5041	0.521	133.0157	0.9846	39.659	417.2003	0.9517	0.351	50.534	96.7243	0.9888	0.135	268.0822	0.9689	First
F6	13.067	6003.6729	-0.2575	0.365	2069.1265	0.5666	32.972	1697.6168	0.6444	0.119	60.608	35.6786	0.9925	0.089	2971.3506	0.3776	First
F7	13.460	4253.5261	0.2086	0.344	937.4681	0.8256	33.529	739.7647	0.8624	0.241	50.957	11.1626	0.9979	0.089	1548.6359	0.7119	First
F8	15.049	4270.1513	0.3895	0.453	544.4029	0.9222	37.234	562.4510	0.9196	0.294	51.990	30.1963	0.9957	0.116	995.6180	0.8577	First
F9	15.255	4205.8080	0.4209	0.463	511.5475	0.9296	37.695	523.1720	0.9280	0.306	51.690	42.5428	0.9941	0.119	906.0068	0.8753	First
F10	13.289	3182.3295	0.4243	0.311	637.8059	0.8846	32.846	368.0493	0.9334	0.309	44.803	11.2018	0.9960	0.081	1097.9768	0.8014	First
F11	13.035	2216.5285	0.6195	0.281	364.5012	0.9374	31.943	146.0646	0.9749	0.396	37.866	52.4629	0.9910	0.075	654.4846	0.8877	First

Table 10: Stability testing data of optimized batch (F9)

Results of stability testing			
Condition (1)	25ºC±2ºC/60%RH±5%RH		
Condition (2)	40ºC±2ºC/75%RH±5%RH		
Batch No.	F9		
In Vitro drug release			
Time (Hrs)	**Initial**	**After 1 month at25ºC±2ºC/60%RH±5%RH**	**After 1 month at40ºC±2ºC/75%RH±5%RH**
0	0	0	0
1	55.84±1.37	54.68±1.73	53.68±1.28
2	62.92±1.84	63.24±1.92	62.18±2.27
3	68.04±1.48	66.48±2.84	65.24±1.83
4	77.95±2.94	75.24±2.11	74.19±1.30
5	84.05±2.28	82.17±1.27	79.35±2.39
6	89.75±4.18	87.44±2.59	85.39±2.14
7	93.94±1.68	91.28±2.94	92.68±2.75
8	99.75±1.28	98.63±4.10	98.24±3.72
Drug Content			
% Potency	98.75	98.57	98.48
Physical appearance*			
Morphology	+++	+++	++

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