FORMULATION AND EVALUATION OF FLOATING IN-SITU GELLING SYSTEM FORSTOMACH SPECIFIC ORAL DELIVERY OF CEPHALEXIN

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Abstract:

Objective: The objective of this study was to develop a floating in-situ gel system for the stomach-specific oral delivery of cephalexin. Cephalexin, an antibiotic with a narrow absorption window primarily in the proximal areas of the gastrointestinal tract (GIT), requires targeted and sustained release to effectively treat infections like Helicobacter pylori (H. pylori) and urinary tract infections.

Methods: In situ gel formulations were prepared using varying concentrations of sodium alginate, a biodegradable polymer that forms gels in situ, and calcium carbonate as a cross-linking agent. The formulations underwent a comprehensive evaluation encompassing physical appearance, pH, in vitro drug release, viscosity, in vitro floating behavior, in vitro gelling capacity, and drug content. Fourier-transform infrared (FTIR) spectroscopy was employed to analyze cephalexin, excipients, and the optimized formulation for potential interactions.

Results: All formulations exhibited optimal viscosity, facilitating easy administration and swallowing. The formulations displayed floating lag times between 32-70 seconds and maintained floating for more than 12 hours. In vitro gelling capacity correlated with increased polymer and gelling agent concentrations. Higher polymer concentrations were associated with decreased drug release rates and extents. Notably, formulation F4, containing 4% w/v sodium alginate and 4% w/v calcium carbonate, demonstrated sustained in vitro drug release (95.6%) over 12 hours. FTIR analysis indicated no significant interactions between the drug and excipients. The drug release kinetics followed first-order kinetics with Fickian diffusion.

Conclusion: Conclusion: This study successfully formulated cephalexin into a pH-triggered floating in-situ gel system using sodium alginate and calcium carbonate. Such a system holds promise for stomach-specific oral delivery, potentially enhancing the therapeutic efficacy of cephalexin against infections.

Keywords: In situ gel, Sodium alginate, Calcium carbonate, Cephalexin.

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INTRODUCTION

In the realm of pharmaceutical advancements, the development of innovative drug delivery systems has revolutionized the field of medicine, facilitating enhanced therapeutic outcomes and patient compliance. Among these cutting-edge strategies, the concept of in-situ gelling systems holds remarkable potential, particularly for the targeted delivery

of drugs to specific anatomical regions. One such noteworthy application is the utilization of a floating in-situ gelling system for the stomach-specific oral delivery of cephalexin, a potent antibiotic widely prescribed for the treatment of various bacterial infections [(1)].

cephalexin, a third-generation cephalosporin antibiotic, exhibits potent antimicrobial properties against a broad spectrum of pathogens. However, its oral delivery often encounters challenges related to variable absorption, suboptimal bioavailability, and dose regimen adherence. Conventional oral dosage forms of cephalexin face limitations in achieving sustained drug release and targeted delivery to the stomach, which is a crucial site for drug absorption and action against gastrointestinal infections.

The innovative approach of a floating in-situ gelling system addresses these challenges comprehensively. This unique drug delivery system combines the benefits of both floating and in-situ gelling technologies, offering a multifaceted solution to the complex problem of stomach- specific drug delivery. Upon oral administration, the dosage form remains buoyant in the gastric contents, ensuring prolonged residence time within the stomach. This not only facilitates the localized drug release but also enhances the contact time of cephalexin with the gastric mucosa, optimizing its absorption and therapeutic efficacy.

The in-situ gelling property of the system further accentuates its potential. The formulation is designed to undergo a phase transition in response to specific physiological cues encountered in the stomachs. microenvironment. Factors such as pH variation, which occur upon gastric emptying, trigger the transformation of the liquid dosage form into a gel-like consistency. This gel formation not only provides a sustained release mechanism but also helps to anchor the dosage form within the stomach, reducing the risk of unintended gastric emptying and ensuring prolonged drug exposure [(2)].

In-situ gelling embodies a synergistic approach that significantly enhances the therapeutic performance of cephalexin. By harnessing the power of this technology, clinicians can potentially achieve improvement. Patient outcomes, reduced dosing frequency, and minimized adverse effects, leading to enhanced patient compliance and overall treatment efficacy.

In conclusion, the introduction of a floating in-situ gelling system for stomach-specific oral delivery of cephalexin heralds a new era in pharmaceutical research and development. This groundbreaking approach demonstrates the potential to overcome long-standing challenges associated with conventional oral drug delivery, promising optimized therapeutic outcomes for patients suffering from bacterial. infections. As research and innovation continue to propel the field forward, the integration of advanced drug delivery systems like the floating in-situ gelling system is poised to reshape the landscape of modern medicine, offering hope for more effective and patient-centric treatments.

MATERIALS AND METHODS:

Materials: Cephalexin was procured from a reputable pharmaceutical supplier. Polymers used for in-situ gel formation, such as sodium alginate, polycarbophil, and Carbopol, were sourced from recognized manufacturers. Additional excipients and surfactants were of pharmaceutical grade.

Methods:

Pre-formulation Study:

Preformulating may be described as a stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is an important part of the drug development process. Infra-red spectroscopy is widely used in pharmaceutical research. IR spectroscopy is routinely used for compound identification as a fingerprinting tool. IR spectroscopy also has its application in studies of drug excipient interaction, contaminant analysis etc.IR spectrum with high quality is acquired with KBr pellet method. Compatibility study of drug with the excipients was determined by using FTIR. The sample powder of drugs, excipients, and mixture of both were subjected to FTIR study. The mixture spectra were compared with that of the original spectra.

Determination of Melting point:

Melting point of cephalexin was determined by open capillary method. Melting-point apparatus is most frequently used for the determination of the melting point of a solid. A few crystals of the compound are placed in a thin-walled capillary tube 10- 15 cm long, about 1 mm in inside diameter, and closed at one end.

Fourier Transform infrared Spectroscopy (FTIR) study:

The compatibility study was carried out by using Fourier transform infrared spectrophotometer (Shimadzu). FTIR study was carried out on pure drug. Physical mixture of drug and polymers were prepared, and samples kept for 1 month at 400C. The infrared absorption spectrum of physical mixture of drug and polymers was recorded using KBr disc over the wave number 4000 to 650 cm -1[3,4].

Calibration curve of Cephalexin:

A Standard Solution of cephalexin was prepared by dissolving accurately weighed 100 mg of cephalexin with little quantity of 0.1N HCl solution, in a 100 ml volumetric flask. The volume was made up to 100 ml with 0.1N HCl, to obtain a stock solution of 1000µg/ml. From the above solution several dilutions are made to obtain 50, 75, 100, 125, 150 µg/ml solutions. The absorbencies of these drug solutions were estimated at λmax 236 nm.

Preparation of floating in-situ gels of Cephalexin:

The floating in-situ gelling system for stomach-specific oral delivery of cephalexin was prepared using sodium alginate and hydroxypropyl methylcellulose (HPMC K4M) as polymers, mixed with cephalexin and other excipients such as calcium carbonate, sodium bicarbonate, and sodium citrate in a drug-loaded liquid pre-gel formulation. The pre-gel solution was then combined with Poloxamer 407 and Carbopol 974P to induce gelation. The formulation's floating behavior was assessed using USP Dissolution Apparatus II in simulated gastric fluid (SGF), and in vitro drug release studies were conducted to evaluate drug release behavior. Rheological studies, pH measurement, and drug content uniformity analysis were performed to characterize the system. The developed in-situ gelling system shows promise as a stomach-specific drug delivery. system for cephalexin, potentially improving drug bioavailability and patient compliance. a composition of different formulations of cephalexin were shown in table 1&2[5,6].

Table 1: Composition of Floating in-situ gels of Cephalexin (F1 to F6)

Formulation Code	COMPOSITION							
	CEPHALEXINMg	Sodium alginate %	HPMC 100M %	Carbopol %	CaCo3 %	Sodium Citrate %	Propyl Paraben (Mg)	Distilled water (ml)
F1	500	-	0.4	0.6	0.5	0.2	45	50
F2	500	-	0.4	0.9	0.5	0.2	45	50
F3	500	-	0.4	1.2	0.5	0.2	45	50
F4	500	-	0.4	1.2	0.75	0.2	45	50
F5	500	-	0.4	1.2	1	0.2	45	50
F6	500	-	0.4	1.2	1.25	0.2	45	50

Table 2: Composition of Floating in-situ gels of Cephalexin (F7 to F12)

Formulation Code	COMPOSITION							
	Drug Mg	Sodium alginate %	HPMC 100M %	Carbopol %	CaCo3 %	Sodium Citrate %	Propyl Paraben (Mg)	Distilled water (ml)
F7	500	0.5	0.4	-	0.5	0.2	45	50
F8	500	1	0.4	-	0.75	0.2	45	50
F9	500	1.5	0.4	-	1	0.2	45	50
F10	500	-	0.4	1.2	0.5	0.2	45	50
F11	500	-	0.4	1.2	0.5	0.2	45	50
F12	500	-	0.4	1.2	0.5	0.2	45	50

EVALUATION OF CEPHALEXIN FLOATING IN-SITU GELS:

Physical Appearance and PH measurement:

All the formulations were visually inspected for their appearance and clarity. The pH for each of the formulations was measured using a calibrated pen pH meter. The readings were recorded three times for each of the formulations and the averages of the readings were considered [(7)].

Drug content:

5 ml of the formulation equivalent to 10 mg of the drug was added to 80 ml of 0.1N HCl, pH 1.2, and stirred for 1 h in a magnetic stirrer. After 1 h, the solution was filtered and diluted with 0.1 N HCl, pH 1.2. The drug concentration was then determined by ultraviolet (UV) visible spectrophotometer at 287 nm against a suitable blank solution [(8)].

In Vitro Floating Study:

The studies were conducted in a USP Type II dissolution apparatus using simulated gastric fluid (0.1N HCl, pH) as the dissolution medium at 37±0.5°C. About 10 ml of the in-situ gel formulation was placed in the dissolution medium. The time taken by the in-situ gel formulation on the surface of the medium (floating lag time) and time period for which the formulation remained buoyant (duration of floating) was noted.

Floating lag time:

The floating lag time is defined as time taken by the gel to reach the top from bottom of the dissolution flask. The floating lag time is determined by visual inspection of a USP (Type II) dissolution test apparatus containing 900 ml of 0.1N HCl at 37^0C[(9)].

In vitro Floating duration:

The in vitro floating study was determined using USP dissolution apparatus II having 900 ml of simulated gastric fluid (pH 1.2). The medium temperature was kept at 370 C. 10 ml prepared InSitu gel formulations were drawn up using disposable syringe and placed into the petri dish (4.5mm internal diameter) and finally petri dish containing formulation was kept in the dissolution vessel containing medium without much disturbance. The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on the dissolution medium surface (duration of floating) were noted [(9)].

In vitro gelation study:

5ml of the simulated gastric fluid (0.1N HCl, pH 1.2) in a 15ml test tube maintained at 37°C followed by the addition of 1 ml of the formulation using a pipette. The pipette was positioned facing the surface of the fluid in the test tube and slowly the formulation was released from the pipette. When the formulation came in contact with the gelation medium, it was quickly converted into a gel-like structure. Based on the stiffness of gel as well as the duration for which the gel remains as such, the in vitro gelling capacity was investigated [(12,10)].

The in vitro gelling capacity was mainly divided into three categories based on gelation time and time period the formed gel remains.

- (+): Gels in few second and disperse immediately.
- (++): Immediate gelation does not disperse rapidly.
- (+++): Gelation after few minutes remains for extended periods.

In vitro drug release studies:

The release rate of drug from in situ gel was determined using USP dissolution rate testing apparatus I (basket covered with muslin cloth) at 50 rpm. [5, 6, 7] 900 ml of 0.1N HCl was used as the dissolution medium and temperature of 37±0.5o C was maintained. 10 ml samples were withdrawn at the interval of 1 hour for estimating the drug release using UV-Visible spectrophotometer. The same volume of fresh medium was replaced every time the sample had been withdrawn. Dissolution study was carried out for 8 hours[(11)].

Kinetics of drug release:

Dissolution profile of all the formulations were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson- Crowell, Korsmeyer and Peppas to ascertain the kinetics modelling of dug release by using a PSP Dissolution version 2.08 and the model with higher correlation was. Considered to be the best model observation were submersed. In order to know drug release mechanism the data was further analyzed by korsmeyer pepas equation and value if n i.e. release exponent was calculated. The n value is used to interpret the release mechanism[(12)].

RESULTS & DISCUSSION:

Determination of melting point

The melting point of cephalexin was found to be 3250C, which complied with the BP standards.

Fourier Transform Infrared Spectroscopy (FT-IR):

In the FT-IR drug – excipients interaction study, it was found that cephalexin was compatible with all the excipients used in the formulations. There were no extra peaks observed. Thus the chosen excipients for the formulations were found to be compatible with the active ingredient and have no physical interaction with the active pharmaceutical ingredient.

Appearance:

All the prepared batches was found to be clear in appearance.

pH:

The pH was measured of each polymer formulation based on in-situ solution using a calibrated digital pH meter at 27 °C. The pH of all the prepared batches was found in the range of 9.2 to 10.8. The optimized batch T12 showed pH 10.8.

Drug Content Uniformity:

All the prepared formulations show drug content uniformity in the range of 97.96% to 100.06 %. The values are acceptable as per Indian pharmacopeia standards.

Floating lag time:

Floating lag time of all the prepared formulations was observed by visual examination. All the prepared formulations show Floating lag time from 4-5 sec to immediate. And the optimized batch T12 shows immediate floating after entering in 0.1 N HCl and show floating for more than 12 h.

Floating Duration:

All prepared formulation shows floating duration more than 12 h.

Gelling time:

The gelling capacity of prepared formulations was observed by visual examination. All the prepared batches show gelling time from 4-5 seconds to immediate after entering in 0.1 N HCl. The optimized batch T12 showed immediate gelling after getting in contact with 0.1 N HCl and remained in the form of gel for more than 12 h.

In vitro drug release:

The in vitro drug release study of cephalexin from all formulations was carried out by USP type II dissolution apparatus containing 900 ml of 0.1N HCl at 37±0.5º C at 50 rpm for 12 hrs.. A significant decrease in the rate and extent of the drug release was observed with the increase in polymer concentration in in situ gelling preparation. The Carbopol, sodium alginate and HPMC with a primary role in the sol-gel phenomenon and buoyant also affected the release rate to some extent. Carbopol gel formulations released the drug 92.26%-99.82% in 12 hrs. and Carbopol in combination with HPMC K100 shown the drug release. from 96.78%-99.67%, whereas sodium alginate containing formulations release the drug in a sustained manner i.e., in the range of 89.95%-95.81%.

Kinetics of Drug Release:

The above obtained data was fitted to different kinetic models such as zero order, first order, Higuchi model and Korsmeyer peppas model. From the data obtained and graphs plotted, it can be said that the floating in-situ gels follow zero order kinetics where drug release is not dependent on the concentration.

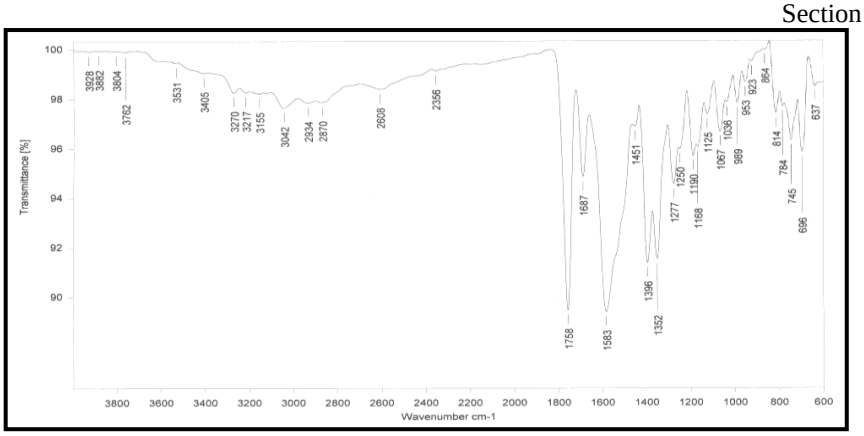


Figure 1 : FTIR of Cephalexin drug

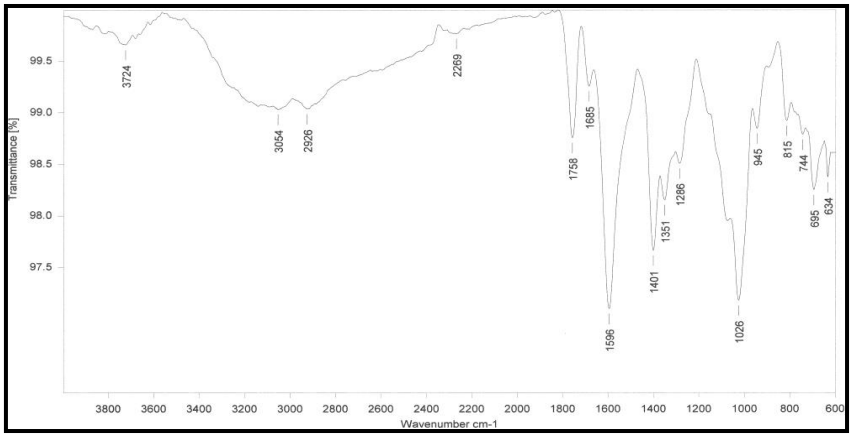


Figure 2 : FTIR of Cephalexin + Sodium alginate

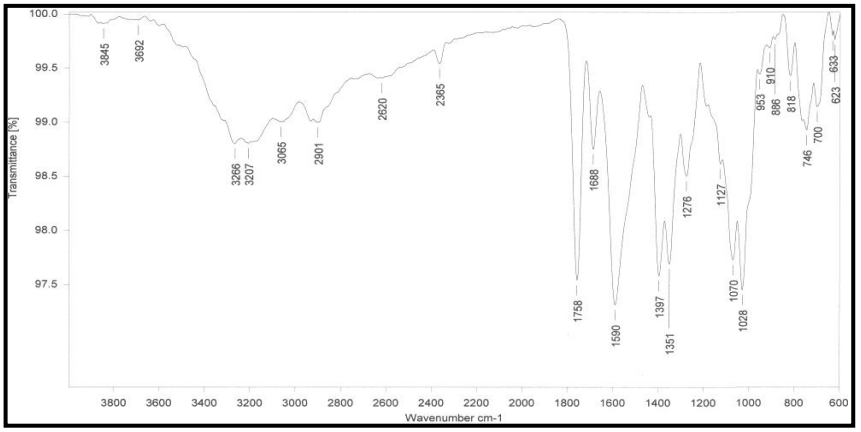
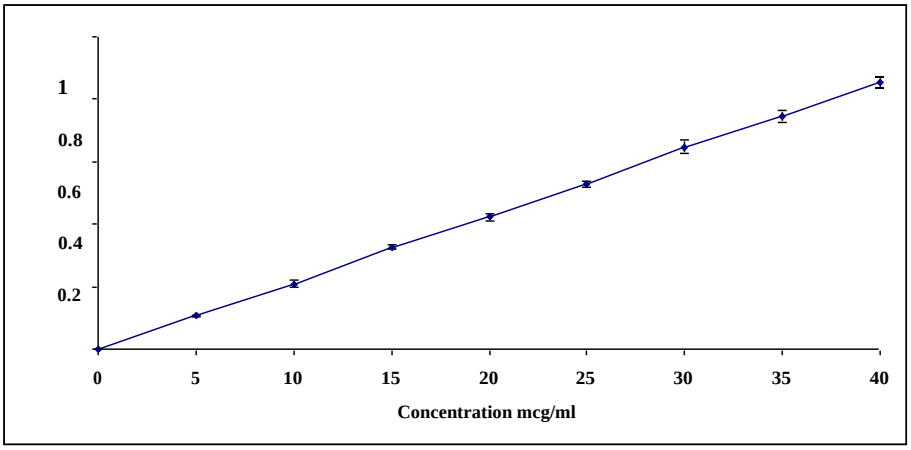


Figure 3: FTIR Spectra of pure Cephalexin + All Excipients

Preparation of standard curve of CEPHALEXIN:

Table 3: Calibration Curve data for CEPHALEXIN at 278nm

S. No	Aliquots (ml)	Vol. made upto (ml)	Concentration(mcg/ml)	Avg. Absorbance	SEM (±)
1	2.5	50	5	0.108	0.0025
2	5.0	50	10	0.209	0.0121
3	7.5	50	15	0.326	0.0075
4	10.0	50	20	0.423	0.0110
5	12.5	50	25	0.526	0.0093
6	15.0	50	30	0.646	0.0214
7	17.5	50	35	0.745	0.0186
8	20.0	50	40	0.854	0.0180



The slope = 0.021
The intercept = 0.000
The correlation coefficient = 0.999

Figure 4: Calibration curve of CEPHALEXIN

S. No	Time(hr)	% Cumulative drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	10.87	12.19	10.21	11.26	11.50	11.82
3	2	18.44	19.70	17.66	19.25	20.25	20.93
4	3	27.91	28.64	26.04	27.71	28.55	29.14
5	4	36.92	38.98	36.75	38.54	39.17	36.91
6	5	48.31	49.81	43.76	45.62	46.57	46.50
7	6	62.07	63.94	52.64	55.06	56.74	55.19
8	7	73.95	74.79	64.77	67.79	68.77	66.17
9	8	80.18	82.85	77.39	80.53	78.04	76.25
10	12	98.70	99.82	95.12	97.98	94.23	92.26

Table 4: *In-vitro* diffusion data for formulation F1 to F6

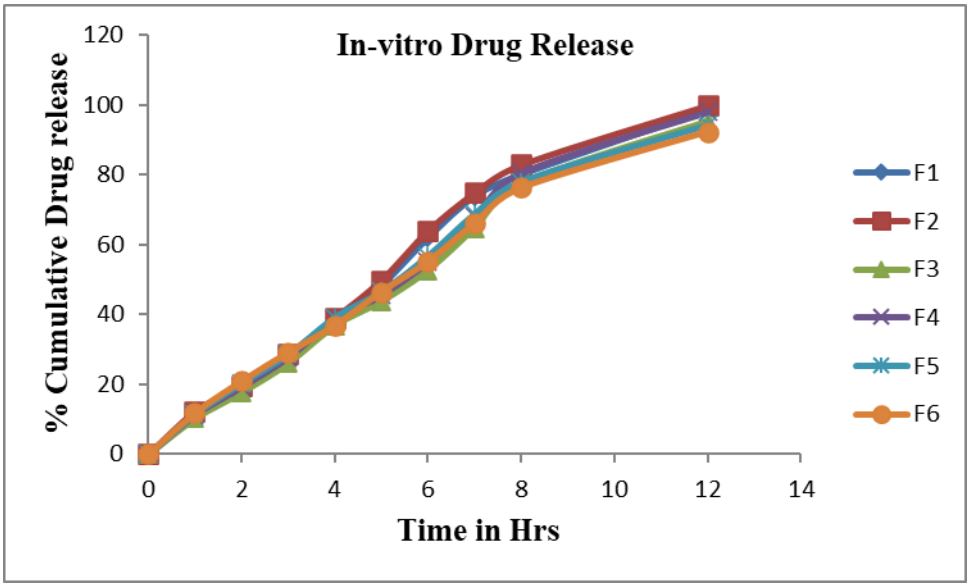


Figure 5: *In-Vitro* Diffusion studies for F1 to F6

S.No	Time(hr)	% Cumulative drug release					
		F7	F8	F9	F10	F11	F12
1	0	0	0	0	0	0	0
2	1	14.67	10.90	11.27	12.40	11.69	12.32
3	2	23.40	18.49	19.44	21.61	20.25	20.69
4	3	35.81	28.94	30.36	32.66	31.07	31.28
5	4	42.73	38.93	37.51	40.97	41.01	41.00
6	5	51.49	49.40	44.66	50.21	50.05	50.28
7	6	62.55	59.41	54.19	59.00	59.10	59.58
8	7	70.88	67.53	64.20	68.72	68.17	68.01
9	8	78.75	75.66	72.80	78.90	77.69	77.77
10	12	95.81	91.86	89.95	99.67	97.12	96.78

Table 5: *In-vitro* diffusion data for formulation F7 to F12

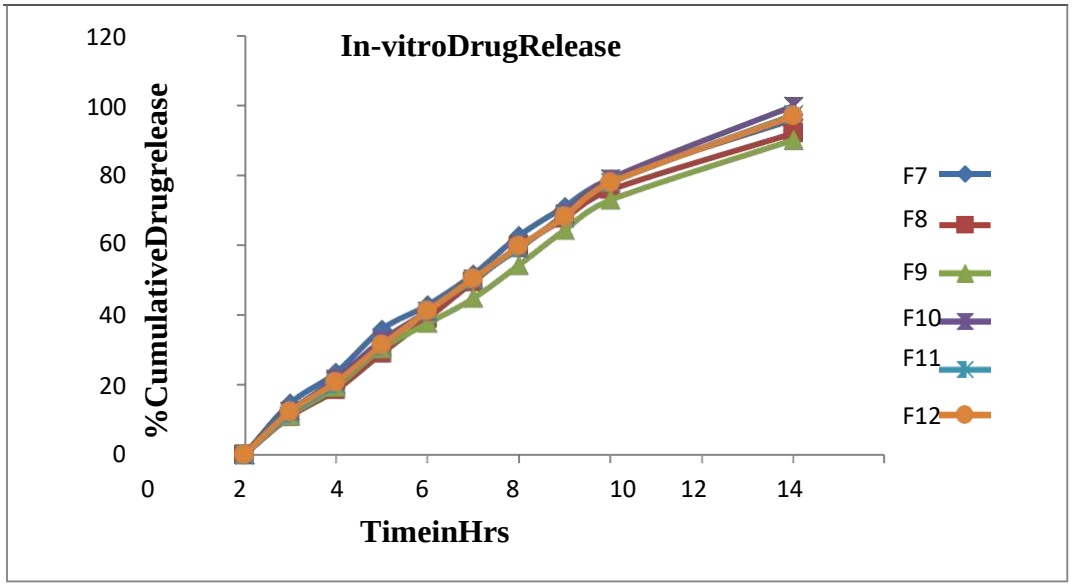


Figure 6: Time vs Drug retained (First order Kinetics) of formulations F7 to F12

Table 6 : Release Kinetics Data of the Formulations F1 to F12

Formulation code	Zero order R^2	First order R^2	Higuchi's R^2	Korsemeyer Peppa's	
				n	R^2
F1	0.9697	0.8533	0.9206	0.9581	0.9882
F2	0.9671	0.7674	0.9253	0.9200	0.9862
F3	0.9821	0.9019	0.9174	0.9479	0.9931
F4	0.9799	0.8556	0.9216	0.9192	0.9927
F5	0.9376	0.9348	0.9349	0.8933	0.9933
F6	0.9757	0.9464	0.9385	0.8648	0.9945
F7	0.965	0.9298	0.9604	0.7936	0.9936
F8	0.9673	0.9644	0.9408	0.9176	0.9902
F9	0.9772	0.9594	0.9442	0.8707	0.9950
F10	0.9823	0.7575	0.9455	0.8674	0.9971
F11	0.9784	0.8857	0.9449	0.8916	0.9952
F12	0.9773	0.8949	0.9469	0.8710	0.9951

CONCLUSION:

The in-situ gel containing cephalexin was effectively prepared by using sodium alginate and xanthan gum. The formulation F6 could be the most capable gastro retentive in situ gel formulation and provide a site- specific delivery of cephalexin for 12 h. It suggests that the in situ formed gel preserved its integrity without dissolving or eroding for a prolonged period to facilitate sustained release of drugs. The prepared floating in situ gel of cephalexin has the feasibility of sustaining the drug release while remaining in the stomach.

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