FORMULATION AND EVALUATION OF FLOATING *IN SITU* GEL OF CIPROFLOXACIN

SHAILAJA PASHIKANTI[1*], JYOTHSNA B.[2]

[1]AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, 530003. Andhra Pradesh, India, [2]Pullareddy Institute of Pharmacy, Hyderabad, Telangana, India
Email: dr.pshailaja@andhrauniversity.edu.in

ABSTRACT

Objective: The objective of the study was to develop floating *in situ* gel formulations of Ciprofloxacin that has a narrow absorption window and mainly absorbed in the proximal areas of GIT. These formulations increases the targeted action on bacteria for a longer time that can be used in the treatment of *Helicobacter pylori* (*H. pylori*) infections and urinary tract infections.

Methods: *In situ* gel formulations were prepared by varying concentrations of sodium alginate as *in situ* gel forming bio-degradable polymer and calcium carbonate as a cross-linking agent. The formulations were evaluated for Physical appearance, pH, *in vitro* drug release, viscosity, *in vitro* floating behaviour, *in vitro* gelling capacity and drug content. FTIR was conducted for Ciprofloxacin, excipients used and optimized formulation.

Results: All the formulations showed an optimum viscosity that will allow ease of administration and swallowing. Floating lag time of all formulations was between 32-70 seconds and floated for>12 h. The *in vitro* gelling capacity increased with increasing the polymer and gelling agent concentrations. Increase in polymer concentration decreased the rate and extent of the drug release. Among all the formulations, F4 containing 4% w/v of sodium alginate and 4% w/v of calcium carbonate showed sustained *in vitro* drug release (95.6%) over an extended period of 12 h. FTIR studies revealed no interaction between drug and excipients used. Drug release from the formulations followed First order kinetics with Fickian diffusion.

Conclusion: Ciprofloxacin was successfully formulated as a pH-triggered floating *in situ* gelling system using sodium alginate.

Keywords: *In situ* gel, Sodium alginate, Calcium carbonate, Ciprofloxacin

INTRODUCTION

Oral administration is the most convenient and preferred means of drug delivery to the systemic circulation. Oral controlled release drug delivery has recently been of increasing interest to achieve improved therapeutic advantages, such as ease of administration, patient compliance, and flexibility in formulation. *In situ* gel-forming polymeric formulations is in sol form before administration undergo gelation *in situ* to form a gel [1]. These *in situ* solutions are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent, pH-dependent and cation induced gelation. Compared to conventional controlled release formulations, *in situ* forming drug delivery systems possess potential advantages like simple manufacturing process, ease of administration, reduced frequency of administration, and improved patient compliance and comfort [2-4]. Floating *in situ* gel drug delivery systems have been used to deliver many drugs which are used either for their systemic or for their local effects in the stomach [5]. A major constraint in the oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract (GIT), and some drugs are absorbed only in a particular portion of GIT or absorbed to a different extent in various segments of the GIT. The pH-dependent solubility and stability levels of a drug play an important role in its absorption. In the case of the drug Ciprofloxacin HCl (CPF HCl), it has a narrow absorption window and mainly absorbed in the proximal areas of GIT [6]. Therefore, the researchers were developed certain gastro retentive systems of CPF HCl such as floating systems [7, 8]. Ciprofloxacin belongs to the family of quinolones (the term refers to potent chemotherapeutic antibacterial agents) [9]. Ciprofloxacin is a broad-spectrum antibiotic active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a Type II topoisomerase and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division and also affect mammalian cell replication [10]. The objective of the present study was to develop ciprofloxacin floating in situ gel that remains in the stomach, resulting in increased gastric residence time and thus increases the local concentration of the drug for complete eradication of *H. pylori* [5]. The present investigation deals with the formulation, optimization, and evaluation of Sodium alginate, HPMC K100M based floating oral *in situ* gel of CPF HCl in which calcium carbonate, sodium alginate were used as a cross-linking agent. The gel was evaluated for parameters like floating lag time, floating duration, gel strength, density, viscosity, pH, *in vitro* drug release, drug content, and *in vitro* gelling capacity.

MATERIALS AND METHODS

Materials

Ciprofloxacin HCl (Gift sample procured from Dr. Reddy's Laboratories, India), sodium alginate and Hydroxyl propyl methyl cellulose (HPMC K100M) (Yarrow Chem, India), sodium citrate, methylparaben and propylparaben (Himedia Laboratories, India). All other reagents were of analytical grade.

Methods

Preparation of floating *in situ* gels of ciprofloxacin

Sodium alginate form pH-triggered *in situ* gel in the presence of calcium ions as a cross-linking agent in the gastric fluid. Sodium alginate solutions of different concentrations were prepared by dissolving the specified amount of sodium alginate in 100 ml of distilled water. The appropriate amount of sodium alginate, 0.4% w/v of HPMCK100M and 0.5% w/v of sodium citrate were dissolved in sufficient amount of distilled water and stirred for 20 min on the mechanical stirrer (M/s. Remi, Model: RQ-124 A/D) for complete swelling of polymers. Drug solution containing 500 mg of the drug in 17 ml of 0.1N HCl was slowly added to 20 ml of polymer solution with continuous stirring on the mechanical stirrer for 15 min. Specified concentrations of $CaCO_3$ were prepared in distilled water and add to the polymer solution while stirring, continue stirring for 10 min. For the final preparation directly add 0.09% w/v of methylparaben, 0.09% w/v of propylparaben and continue stirring for 2 min. Finally, make up the volume to 50 ml with distilled water. A composition of different formulations of ciprofloxacin were shown in table 1.

Table 1: *In situ* gel compositions of different formulations of ciprofloxacin

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Ciprofloxacin	500	500	500	500	500	500	500	500
HPMC K100M	200	200	200	200	200	200	200	200
Sodium alginate	500	1000	1500	2000	500	1000	1500	2000
Calcium carbonate	500	1000	1500	2000	250	500	750	1000
Sodium citrate	250	250	250	250	250	250	250	250
Methylparaben	45	45	45	45	45	45	45	45
Propylparaben	45	45	45	45	45	45	45	45
Distilled water up to (ml)	50	50	50	50	50	50	50	50

Evaluation

Fourier Transform Infrared (FTIR) compatibility studies

Compatibility studies of drug and the polymer were carried out by using fourier transform infrared spectroscopy (FTIR). Fourier transform infrared spectra of the samples were obtained in the range of 4000 to 450 cm^{-1} using an FTIR (M/s Shimadzu, Model: IR Spirit) by the KBr disc method [11].

Determination of drug content

Accurately, 10 ml of the formulation (containing the equivalent of 30 mg CPF HCl) from completely different batches was measured and transferred to a 100 ml volumetric flask. To the current 50-70 ml of 0.1N, HCl was sonicated for 30 min. Volume was adjusted to a 100 ml. Complete dispersion of the contents was ensured visually, and therefore the dispersion was filtered through Whatman's paper. From this answer, 10 ml of the sample was withdrawn and diluted to a 100 ml with 0.1N HCl. The contents of the compound were measured at most absorbance at 237 nm using double beam UV Visible Spectrophotometer (M/s. Elico, Model: SL210) [12].

pH measurement

The pH of the prepared formulations was measured using a calibrated digital pH meter (M/s. Elico, Model: LI120) [13].

The viscosity of *in-situ* gelling solutions

A viscosity of the all the prepared in situ gel formulations are studied by using Brookfield Viscometer.

In vitro gelation study

To evaluate *in vitro* gelling capability, accurately measured 10 ml of formulation was added to a 100 ml of 0.1N HCl at 37 ° C in a beaker with gentle agitation that avoids breaking of farmed gel. The *in vitro* gelling capability was categorized into 3 classes on the idea of the stiffness of farmed gel, gelation time and period that the gel remains intrinsically [14].

(+) Gels after few minutes dispersed rapidly

(++) Gelation immediate remains for few hours

(+++) Gelation immediate remains for an extended period

In vitro floating study

The *in vitro* floating study was administered by introducing 10 ml of the formulation into a beaker containing 900 ml of 0.1N HCl (pH 1.2) at 37℃ without much disturbance. The time the formulation took to emerge on the medium surface (floating lag time) and also the time the formulation perpetually floated on the surface of the dissolution medium (Duration of floating) were recorded [15, 16].

In vitro drug release study

The dissolution studies were performed using type USP II (paddle method) dissolution apparatus (M/s. Labindia, Model: DS 8000). The dissolution medium used was 900 ml of 0.1N HCl maintained at 37 ° C. The stirring rate was adjusted to 50 rpm. This speed was believed to stimulate the *in vivo* existing delicate agitation and was slow enough to avoid the breaking of the gelled formulation. At the predetermined time intervals, 1 ml samples were withdrawn and replaced by fresh dissolution medium, filtered through Whatman's paper, diluted and assayed at 237 nm using double beam UV Visible Spectrophotometer [17, 18].

RESULTS AND DISCUSSION

FTIR interpretation studies

Spectra's of drug and drug, polymer mixtures were given in fig. 1,2,3 and 4. No interaction was observed between drug and polymer. In FTIR spectra of ciprofloxacin, one prominent characteristic peak was found between 3500 and 3450 cm^{-1}, which was assigned to stretching vibration of OH groups and intermolecular hydrogen bonding. Another band at 3000-2950 cm^{-1} represented alkene and aromatic C-H stretching, mainly C-H. 1950 to 1450 cm^{-1} region exhibited FTIR absorption from a wide variety of double-bonded functional groups. The band at 1750 to 1700 cm^{-1} represented the carbonyl C=O stretching, i.e., C=O. The peak between 1650 and 1600 cm^{-1} was assigned to quinolones. The band from 1450 to 1400 cm^{-1} represented C=O and at 1300 to 1250 cm^{-1} suggested bending vibration of the O-H group which proved the presence of carboxylic acid. A strong absorption peak between 1050 and 1000 cm^{-1} was assigned to a C-F group. From FTIR studies, it is clear that there is no interaction between drug and polymers.
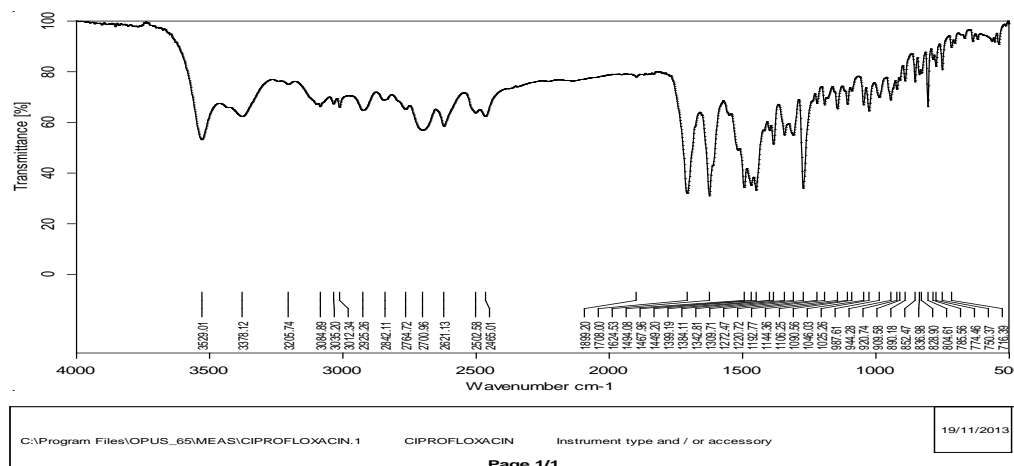

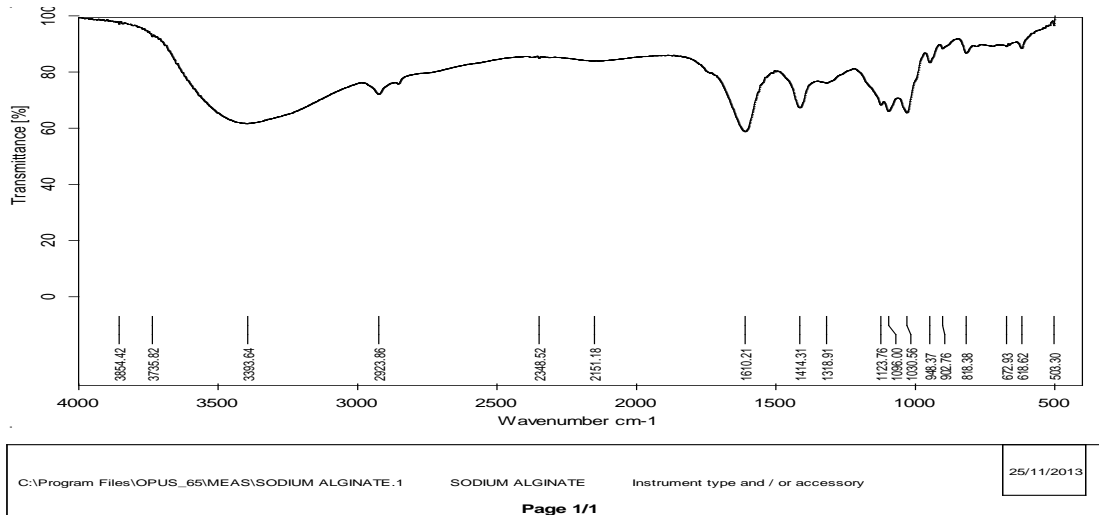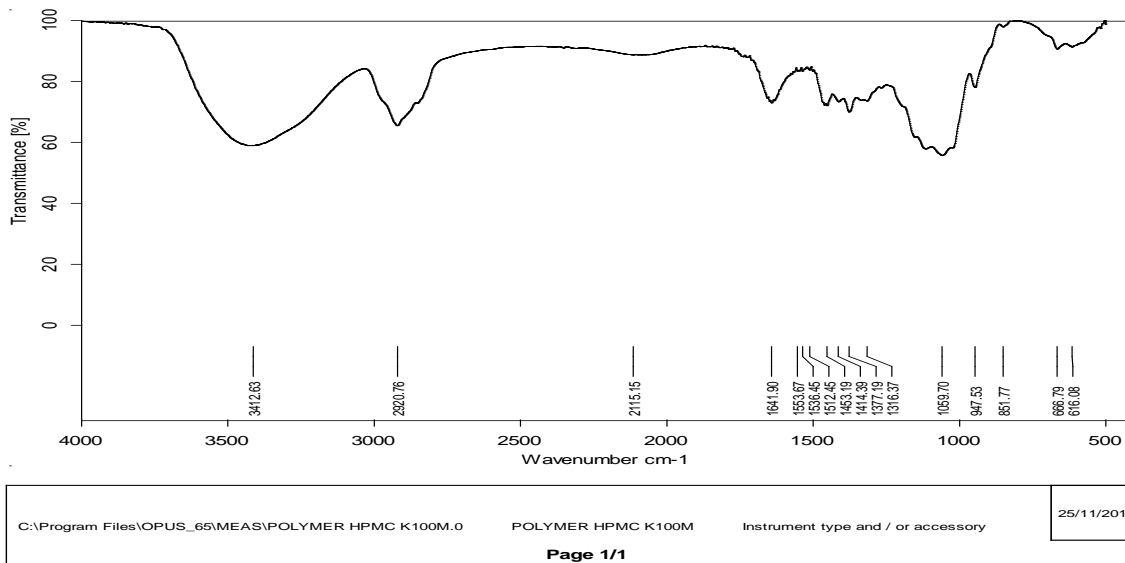**Fig. 1: FTIR spectra of ciprofloxacin**

C:\Program Files\OPUS_65\MEAS\SODIUM ALGINATE.1   SODIUM ALGINATE   Instrument type and / or accessory   25/11/2013

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Fig. 2: FTIR spectra of sodium alginate

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Fig. 3: FTIR spectra of HPMC K100M

C:\Program Files\OPUS_65\MEAS\DRUG + POLYMER.0   DRUG + POLYMER   Instrument type and / or accessory   25/11/2013
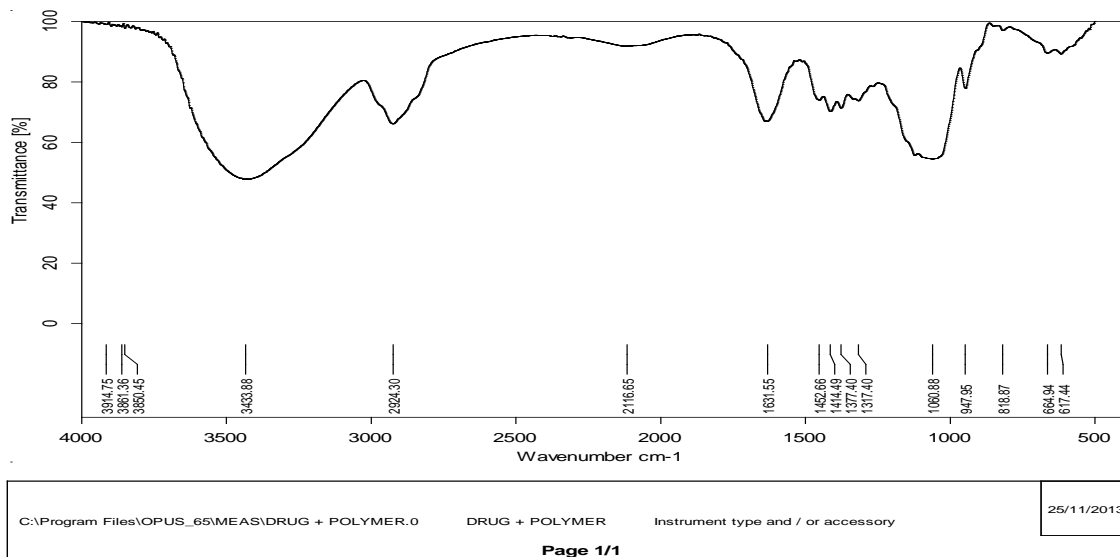
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Fig. 4: FTIR spectra of the formulation

Physical appearance and pH

The measurement of pH is very important for oral preparations, otherwise, it leads to irritation to the throat. All the formulations had a slightly acidic pH. The pH of formulations was found in the range of 5.80-5.93 as shown in table 2.

The viscosity of *in situ* gelling solutions

The formulation should have an optimum viscosity that will allow ease of administration and swallowing as a liquid and produce satisfactory gel strength for use as a delivery vehicle. Results of viscosity for formulations F1 to F8 are shown in table 2. The formulations showed an increase in viscosity with increasing the concentration of gel forming polymer sodium alginate as a consequence of the increase in chain interaction. The concentration of sodium alginate (2000 mg and 1500 mg) was found to produce a satisfactory viscosity increase which provides sustained release of the drug. Calcium carbonate also contributes to increasing the viscosity of the formulations. The viscosity of formulation increased with an increase in sodium alginate and calcium carbonate concentration. As calcium carbonate increases cross-linking tendency of sodium alginate, increase in calcium carbonate concentration also increases viscosity. The viscosity of formulations was in between 140-390 centipoise.

In vitro floating behaviour

The time is taken by the formulation to emerge on the surface of the medium (floating lag time) and the time for which the formulation constantly floated on the dissolution medium surface (duration of floating) is shown in (table 2). In contact with the gastric environment, calcium carbonate effervesced, releasing carbon dioxide and calcium ions. Then, gelation and complexation by Ca^{+2} ions took place to provide a gel barrier at the surface of the formulation. The released carbon dioxide was entrapped in the gel network producing a buoyant preparation, which resulted in extended floating. The floating properties of the formulation, mainly depend on calcium carbonate, on increasing the calcium carbonate concentration, the floating lag time was reduced, and the duration of floating was extended [21]. The increasing amounts of Ca^{+2} and CO_2 Gel strength resulted from the increase in calcium carbonate concentration, are responsible for the observed reduction in floating lag time and increasing duration of floating.

Floating lag time and floating time were shown in table 2. The floating lag time is minimum for F1 and highest to F8. This is because F4 and F8 contain the highest concentration of calcium carbonate. Increase in polymer concentration results in an increase in viscosity. Hence time taken from the sol to form a cohesive gel mass and to emerge on the surface of the medium was lowered. The *in vitro* floating test revealed the ability of all formulations to maintain buoyancy for more than 12 h. All formulations exhibited total floating time of>12 h. Floating lag time varied with formulation variables. Floating lag time of all formulations were in between 32-70 s.

In vitro gelling capacity

Gelling studies were carried out using 0.1N HCl (pH 1.2), and the obtained data were represented in table 2. Gelation occurs when the insoluble calcium carbonate solubilize when it comes in contact with acidic medium releasing carbon dioxide and calcium ions. The calcium ions interact with the anionic polymer (sodium alginate) in the formulation causing instantaneous gelation and provide a gel barrier that restricts drug release [20]. As the concentration of the polymer and calcium carbonate increases the *in vitro* gelling capacity also increases. F1 and F5 formulations had somewhat less stiff gels when compared to other formulations.

Drug content

The percentage of drug content for all formulations was determined and shown in table 2. The drug content was found to be in the range of 96.5-98.5% for all the formulations indicating a uniform distribution of the drug.

Table 2: Evaluation parameters of *in situ* gel formulations of ciprofloxacin

Batch	pH	Viscosity (centipoise)	Floating lag time(s)	Total floating time(h)	Gelling capacity	Drug content (%)
F1	5.83	180	35±2	>12	++	98.2±1.1
F2	5.93	250	38±1	>12	+++	97.4±1.3
F3	5.80	310	45±2	>12	+++	96.5±1.2
F4	5.86	390	61±2	>12	+++	97.5±1.3
F5	5.83	140	37±3	>12	++	98.5±1.1
F6	5.80	210	43±2	>12	+++	97.9±1.0
F7	5.83	270	52±3	>12	+++	96.8±1.5
F8	5.82	315	70±2	>12	+++	97.7±1.6

(n = 3, mean±SD)

Table 3: Dissolution data of ciprofloxacin *in situ* gel formulations

Time (h)	% Cumulative drug released (n = 3, mean±SD)								
	F1	F2	F3	F4	F5	F6	F7	F8	M
0.5	55.6±1.2	50.4±1.3	43.7±1.7	38.5±1.9	60.2±1.6	54.6±1.9	46.8±1.4	41.2±1.5	38.5±1.3
1	60.8±1.7	54.2±1.5	49.2±1.2	42.7±1.6	67.3±1.4	57.6±1.4	50.6±1.2	45.5±1.2	64.2±1.4
2	69.6±1.5	59.6±2.0	54.9±1.5	49.5±1.7	74.6±1.3	65.7±1.3	58.7±1.5	51.2±1.5	82.5±1.5
3	77.8±2.4	66.7±2.1	59.3±1.4	53.8±1.4	85.4±1.2	72.8±1.5	64.4±1.8	58.8±1.7	99.9±1.1
4	86.2±1.2	70.4±2.3	64.9±1.7	57.6±1.5	94.7±1.7	79.5±1.7	71.3±1.9	65.3±1.4	
5	96.5±1.6	75.9±1.1	70.5±1.8	62.8±1.6	99.5±1.7	84.6±1.8	76.5±1.2	72.3±1.5	
6		83.5±1.4	74.4±1.7	68.4±1.2		90.3±1.2	82.7±1.5	77.5±1.6	
7		89.2±1.2	78.3±1.9	73.9±1.9		98.5±1.1	87.5±1.7	83.8±1.9	
8		97.2±1.5	83.9±1.7	77.3±1.6			93.7±1.6	88.6±1.7	
9		99.3±1.7	89.5±2.3	81.5±2.3			99.8±1.2	92.6±1.5	
10			95.1±1.2	86.6±2.2				98.9±1.3	
11			99.5±1.3	91.7±1.2					
12				95.4±1.2					

In vitro drug release

The *in vitro* drug release study of ciprofloxacin from all formulations was carried out by USP type II dissolution apparatus containing 900 ml of 0.1N HCl at 37±0.5 °C at 50 rpm for 12 h, and the result was shown in fig. 6. Dissolution data is represented in table 3. 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 sodium alginate and HPMC with a primary role in the sol-gel phenomenon and buoyant also affected the release rate to some extent. F1, F2 and F3 released 96.5%, 99.3% and 99.5% in 5, 9 and 11 h of dissolution. Formulations F4 to F6 released 95.4%, 99.5% and 98.5% in 12, 5 and 7 h of dissolution. Formulations F7, F8 released 99.8%, 99.9% in 9 and 10 h of dissolution respectively. Commercially available product (M), CIFRAN showed 99.9% drug release in 4 h.

Kinetics of drug release

The cumulative amount of drug released from the systems at different time intervals was fitted to different kinetic models of zero order, first order, Higuchi model, Korsmeyer-Peppas model, and

Hixson-Crowell model to find out the mechanism of drug release. The *in vitro* release profile was fitted to various kinetic models in order to find out the mechanism of drug release. The goodness of fit was evaluated using the correlation coefficient (r^2) values. The correlation coefficient (r^2) for all the formulations using different kinetics equation is listed in table 4. The values of r^2 for all formulations were found higher for the first order model. It was found that all formulations mostly followed the first order models as the best fit model because of the higher value of r (correlation coefficient). The release profile of *in situ* gelling formulations was treated with Korsmeyer-Peppas equation, and slope value $n \leq 0.45$ were indicating fickian diffusion [19]. Kinetic profiles of various formulations were shown in fig. 5,6,7 and 8.

Table 4: Different kinetic models applied on *in situ* gel formulations

atch B	Zero-order plot		First order plot		Higuchi plot	Korsmeyer Peppas plot	Hixson crowell plot
	K_0 (mg. ml^{-1}h^{-1})	r^2	K_1 (h^{-1})	r^2	r^2	n	r^2
F1	14.35	0.85	0.54	0.95	0.9539	0.23	0.9518
F2	7.99	0.88	0.42	0.91	0.9644	0.25	0.9602
F3	6.62	0.92	0.33	0.88	0.9747	0.25	0.9565
F4	5.53	0.91	0.16	0.98	0.9813	0.28	0.9813
F5	15.40	0.83	0.65	0.90	0.9608	0.25	0.9554
F6	8.67	0.87	0.38	0.93	0.9513	0.23	0.9396
F7	6.89	0.89	0.31	0.88	0.9685	0.32	0.9439
F8	6.16	0.93	0.26	0.94	0.9798	0.29	0.9766
M	24.40	0.98	1.97	0.81	0.9920	0.69	0.9482
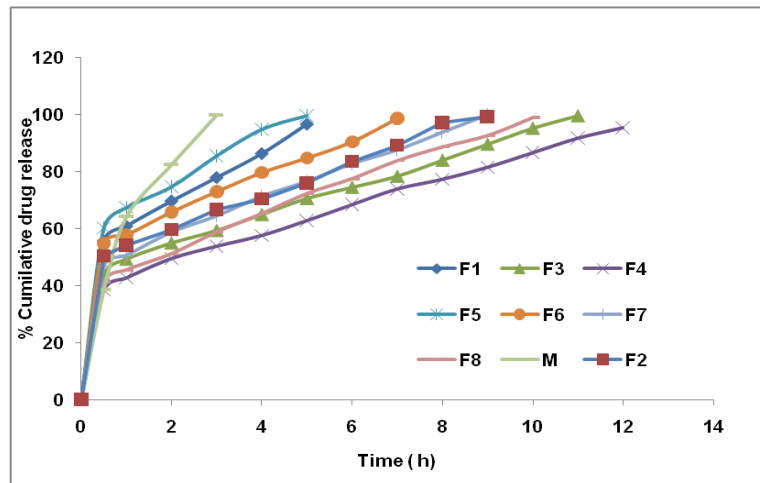
Fig. 5: Comparison of dissolution profiles of ciprofloxacin *in situ* gel formulations with CIFRAN
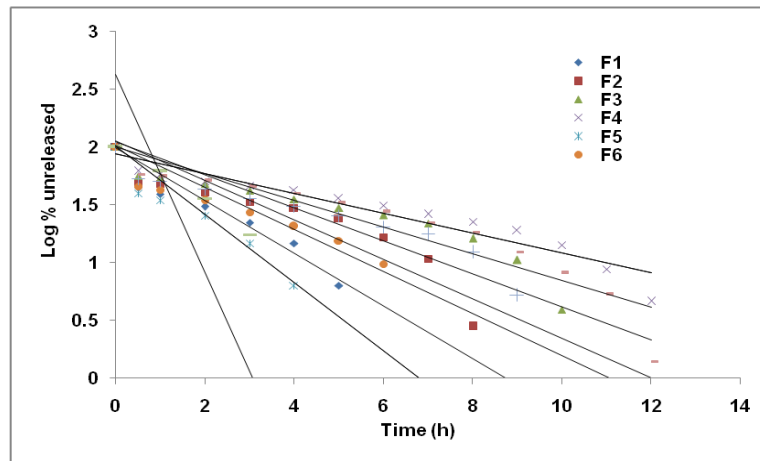
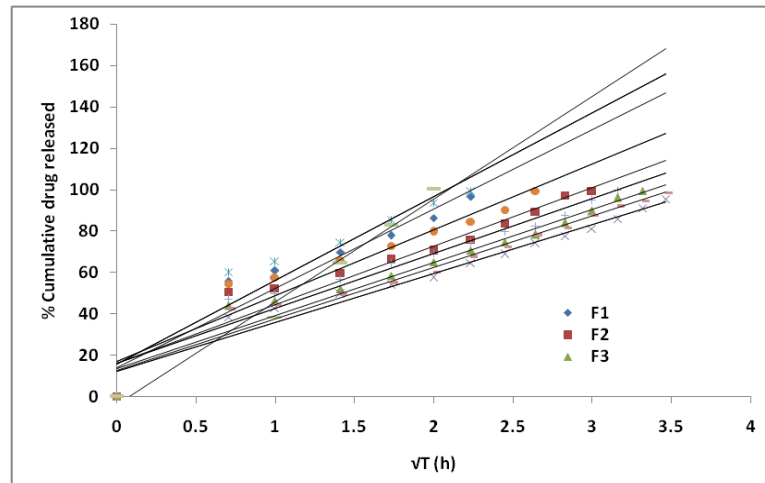Fig. 6: First order plots of various formulations and marketed product

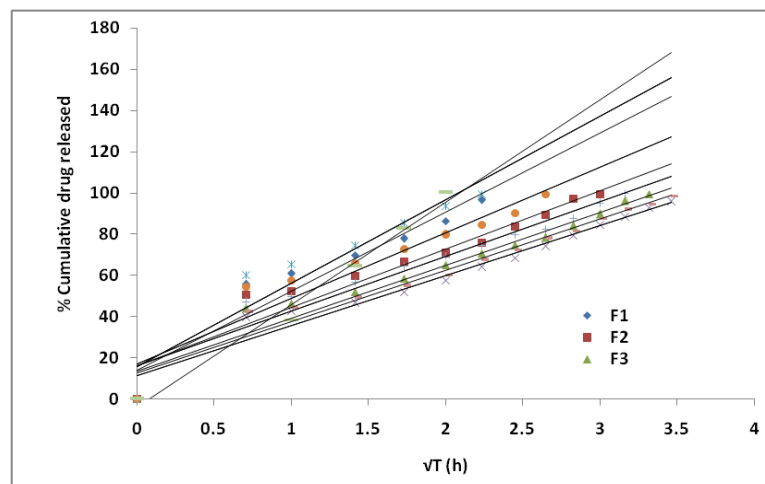**Fig. 7: Higuchi plots of various formulations and marketed product**

Fig. 8: Korsmeyer-peppas plot

CONCLUSION

The prepared formulations m*et al.* l pre-requisites to become an *in situ* floating system, gelled and floated instantaneously in stomach pH. The high concentration of calcium carbonate increased cross-linking of sodium alginate and form egg case like structures, more the cross-linking density less the penetration of water into the matrix and limited amount of drug that enters into dissolution fluid. Thereby the high concentration of sodium alginate along with HPMC K100M (increases strength of the gel) and calcium carbonate had sustained effect. Ciprofloxacin was successfully formulated at a pH-triggered floating *in situ* gelling system using sodium alginate. The F4 formulation containing 4% w/v of sodium alginate, 0.4% w/v of HPMC K100M and 4% w/v of calcium carbonate shows more sustained *in vitro* release (95.7%) than other formulations over an extended period of 12 h. The drug release from a gel structure follows a first-order type, and release pattern was fickian diffusion type.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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