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Formulation and Evaluation of Ciprofloxacin Hydrochloride Loaded Gastro Retentive in Situ Gel for Treating Peptic Ulcer

[1]Sowmya Devarakonda, [2*]Venu Madhav Katla, [3]Somnath De, [4]Kiranmai Mandava [5]Naga Raju K, [6]Deepika B

[1] MPharmacy Student, Department of Pharmaceutics, St. Pauls College of Pharmacy, R.R District, Telangana, India- 501510.

[2] Professor, Department of Pharmaceutics, St. Pauls College of Pharmacy, R.R District, Telangana, India-501510.

[3] Professor, Department of Pharmacology, St. Pauls College of Pharmacy, R. R District, Telangana, India-501510.

[4] Professor, Department of Pharmaceutical Chemistry, St. Pauls College of Pharmacy, R. R District, Telangana, India-501510.

[5] Associate Professor, Department of Pharmaceutics, St. Pauls College of Pharmacy, R. R District, Telangana, India-501510.

[6] Assistant Professor, Department of Pharmaceutics, St. Pauls College of Pharmacy, R. R District, Telangana, India-501510.

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KEYWORDS

Ciprofloxacin, Gastro retentive, In-situ gel, Floating time, Invitro study.

ABSTRACT:

The objective of the present investigation was to design and evaluate ciprofloxacin hydrochloride loaded gastro retentive in situ gel using different polymers and calcium carbonate as cross-linking agents. Ciprofloxacin hydrochloride is an antibiotic belongs to the class of fluroquinolones and is used as a drug of choice for treating the helicobacter pylori. Various polymers like sodium alginate, HPMC K 100, Xanthum gum, sodium carboxy methyl cellulose and Gellan gum were used. F1-F12 formulations were prepared with the concentration difference 0.3% and 0.6%. The prepared formulations were assessed for various characteristic tests like viscosity, floating behavior, gelling capacity, invitro dissolution test etc. The percentage drug release of all the formulations between 70-80% and the drug content was found to be between 70-90%. Amongst all these formulations the formulations of F3 is selected as optimized one as it has shown the floating lag time 2.6±0.5, Floating time greater than 12 hours, viscosity 358±1.28, drug content 95.2±0.1 and cumulative drug release of 93.1±1.2. So, F3 formulation has been selected as the optimized one.

INTRODUCTION

Oral drug administration is widely preferred due to its simplicity, but the effectiveness of oral dosage forms can vary due to several factors. One significant factor influencing drug bioavailability in oral forms is the duration they remain in the stomach, known as gastric residence time (GRT). Recently, there has been a growing interest in enhancing gastric retention, as many conventional oral delivery systems are limited by their tendency to empty from the stomach quickly. Gastro retentive dosage forms represent an innovative approach to drug delivery, designed to extend the time drugs stay in the stomach [1]. This extended gastric retention can significantly improve drug bioavailability.

Gastroretentive drug delivery systems (GRDDS) have demonstrated their effectiveness in achieving systemic and localized therapeutic effects, particularly in the treatment of gastric or duodenal ulcers [2].

Medications that are readily taken up in the digestive system and have brief durations in the body are rapidly eliminated, requiring more frequent administration. To address this issue, gastroretentive drug delivery systems are developed to maintain efficient drug levels in the bloodstream for longer durations, reducing the need for regular dosing. These systems also offer the advantage of delivering drugs in a controlled and consistent manner, minimizing fluctuations in drug concentration in the bloodstream [3].

The in situ gel forms are the systems that are in solution form before administration and converts into gel form after administration. A sol-gel transition takes place depending on the mechanism [4]. The spontaneous creation of gel within biomaterials can begin via various mechanisms: Natural stimuli like temperature and pH shifts, Physical changes within the biomaterials involving solvent shifts and swelling,

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and Chemical responses such as enzymatic, chemical response.

Ciprofloxacin, an antibiotic belonging to the fluoroquinolone class, is used to treat various bacterial infections such as urinary tract infections, pneumonia, and sexually transmitted infections like gonorrhea and chancroid. Most of the drugs undergo rapid absorption and has a shorter half-life. The drug ciprofloxacin which is an antibiotic helps in the treatment of helicobacter pylori. Helicobacter pylori, often referred to as H. pylori, stands as one of the prevalent bacterial infections [5]. It is linked to the emergence of significant gastrointestinal disorders, like peptic ulcers, gastric lymphoma and both sudden and prolonged gastritis. H. pylori mainly reside within the gastric mucosa or position themselves at the boundary between the mucus layer and the epithelial cells, usually found in the antral area of the stomach. So, to eradicate the bacterial infection of H. pylori the antibiotics are required in high and frequent dosing. The standard form of ciprofloxacin has a short half-life of approximately 4 hours and a limited absorption range mainly in the upper gastrointestinal tract (GIT) [6,7]. However, when ciprofloxacin is formulated into a gastro retentive in situ gel, the resulting formulation remains in the stomach for an extended period, displaying characteristics akin to a sustained-release dosage. This modification eliminates the necessity for frequent dosing and can lead to increased bioavailability and a longer half-life for the drug. Consequently, this gastro retentive formulation offers an extended period of therapeutic effectiveness compared to the conventional ciprofloxacin dosage form.

MATERIALS AND METHODS

Materials:

Ciprofloxacin was obtained from St. Paul's College of Pharmacy, sodium alginate from adhunik industries, HPMC K 100 from S.D fine chemicals Ltd, Mumbai, Xanthum gum from Akshar chemical, India Pvt Ltd, Maharashtra, SCMS from Patel Industries, Hyderabad, Pectin from CP kelco, USA Guar gum from Penta Italia, Italy, from Calcium carbonate from Indo Chemicals Pvt. Ltd, Delhi and Sodium citrate from Lead citrate manufacturer, Maharashtra.

Methods:

In situ gel Preparation

The insitu gel formation commenced by adding the necessary quantity of sodium alginate to the initial 20 ml of water, ensuring complete dissolution using a magnetic stirrer. Maintain the temperature at 65-70°C.Then add the required polymers like HPMC K 100, Xanthum gum, pectin and guar gum to the above solution. Let the polymer get dissolved completely and add the calcium carbonate and sodium citrate. Then the drug is added to the above polymer solution. The entirety of the formulation is kept at a temperature of 70°C. Adjust the volume to 50ml with distilled water. Let the formulation get cooled down to below 40°C and then store it in a ambered colored bottle [8].

Table 1: Composition of formulations

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Ciprofloxacin (Milligrams)	250	250	250	250	250	250	250	250	250	250	250	250
Sodium alginate (Grams)	0.3	0.3	0.3	0.3	0.3	0.3	-	-	0.3	0.3	0.3	0.3
HPMC K 100 (Grams)	0.3	0.6	-	-	-	-	-	-	-	-	-	-
Xanthum gum (Grams)	-	-	0.3	0.6	-	-	-	-	-	-	-	-
SCMC (Grams)	-	-	-	-	0.3	0.6	-	-	-	-	-	-
Sodium alginate (alone) (Grams)	-	-	-	-	-	-	0.3	0.6	-	-	-	-

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Pectin (Grams)	-	-	-	-	-	-	-	-	0.3	0.6	-	-
Guar gum (Grams)	-	-	-	-	-	-	-	-	-	-	0.3	0.6
Calcium carbonate (Grams)	1	1	1	1	1	1	1	1	1	1	1	1
Tri sodium citrate (Grams)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Methyl paraben (Grams)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Water (Milliliter)	50	50	50	50	50	50	50	50	50	50	50	50

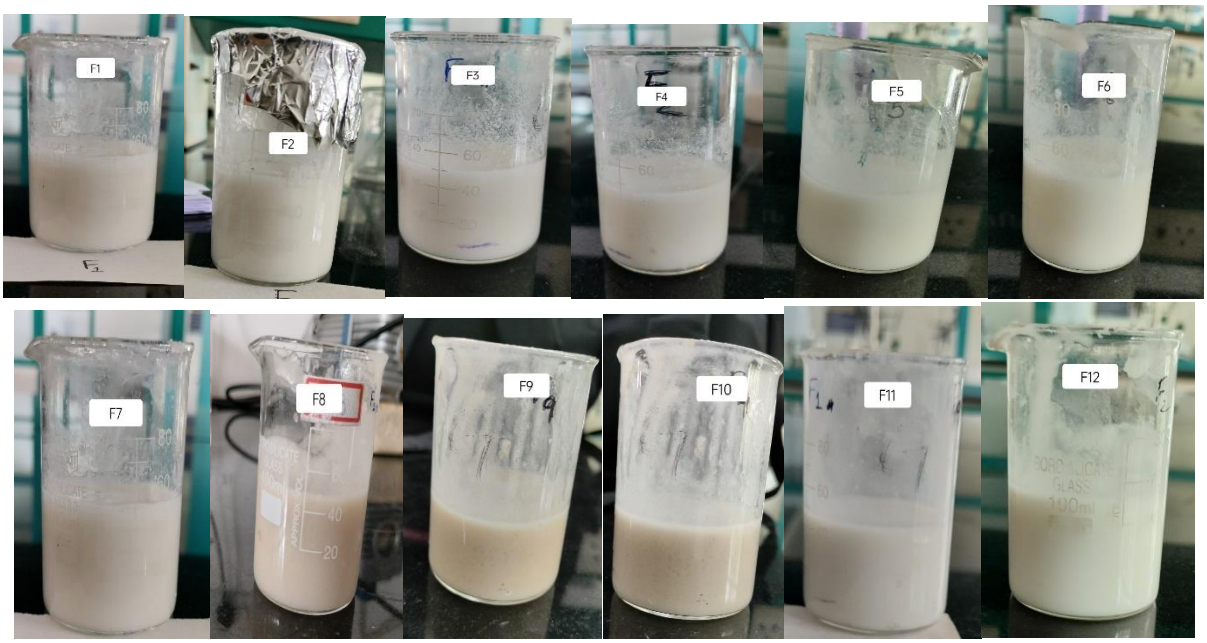

Fig 1: Photographs of all the prepared formulations

EVALUATION TESTS

Physical Characteristics and pH-[9]

The evaluation of the appearance and texture of all formulated products was conducted. The pH measurement for each formulation was carried out at a temperature of 25°C using a digital pH meter.

Viscosity:

The viscosity was assessed by using DV-III Brookfeild viscometer. To measure viscosity using a Brookfield viscometer, start by setting up and calibrating the instrument. Prepare the sample at room temperature and load it into the viscometer chamber. Choose an appropriate spindle based on the expected viscosity. Control the sample temperature if necessary and immerse the spindle into the sample. Start the viscometer, record the reading, and repeat measurements for consistency.[10]

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Floating behavior:

Buoyancy Lag Time Evaluation:

- Take 50ml of the specified medium (often 0.1N HCl) in a suitable container.
- Using a syringe, gently dispense a predetermined volume of the in-situ gel formulation (e.g., 5ml) onto the surface of the medium from a minimal distance.
- Start timing immediately upon release of the formulation into the medium.
- Observe and record the time it takes for the formulation to rise and float on the surface of the medium. This duration represents the floating lag time.

Buoyancy Time Evaluation:

Record the total duration or the length of time that the formulation consistently remains buoyant without sinking or dispersing within the medium. This duration is termed the floating time [11].

Drug content:

The drug content of all formulated preparations was assessed using a magnetic stirrer. A 5ml sample of the in-situ gel was introduced into 50ml of 0.1N HCl, and the mixture was subjected to stirring on a magnetic stirrer for one hour to ensure complete dissolution of the in-situ gel. After this duration, the solution underwent filtration using Whatman filter paper. From the resulting filtrate, 1ml was extracted and diluted with 0.1N HCl to a final volume of 10ml. Subsequently, the absorbance was checked by UV spectrophotometer at 278nm [12].

***In vitro* gelling capacity:[11]**

The evaluation of the in vitro gelling ability involved visually assessing the process. Initially, 50 ml of 0.1N HCl served as the medium, and 5 ml of the in-situ gel was introduced using a syringe. The time taken for gel formation was noted. The in vitro gelling capacity was categorized into three stages:

- (+) Formation of gel occurred after a short duration and dispersed rapidly.
- (++) Gel formation was immediate and endured for a limited number of hours.
- (+++) Gel formation was immediate and sustained for an extended period.

***In vitro* drug release studies:**

The *in vitro* drug release was evaluated by using the apparatus called USP Type-II dissolution apparatus. The procedure for carrying out the *invitro* drug release involved 900ml of 0.1N HCl taking in the baskets. Before filling the baskets with the medium initially place the petri dish in the basket and transfer 10ml of the insitu gel into the petri dish with the help of syringe. Then carefully add the medium into the basket without disturbing the petri dish. Then place the baskets in the apparatus and ensure to turn on the heater. Then the paddle goes running at 50RPM. The temperature was kept constant at 37°C. once the paddle starts running the samples were withdrawn at different intervals like 0.5,1,2,4,6,8 and12 hours. At the time of these intervals the samples were withdrawn and simultaneously the fresh medium was added. The absorbance was checked at 278nm by using UV spectrophotometer [13].

Drug Release kinetics:

The results obtained from the in vitro drug release experiments were analyzed using several kinetic equations, including zero-order kinetics, first-order kinetics, and the Higuchi model. These analyses were conducted to better understand the underlying mechanisms governing the release kinetics of the drug. Moreover, the Peppas equation, formulated as $Mt/M\infty=ktn$, was applied for further evaluation. In this equation, Mt represents the quantity of drug released at a given time (t), $M\infty$ signifies the proportion of drug released at time (t), K stands for the kinetics constant, and n denotes the diffusional exponent that characterizes the primary mechanism of drug release. Subsequently, regression coefficient values were calculated from the linear curves derived through regression analysis. This was performed to determine the most suitable model for explaining the drug release behavior of the formulation [14].

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RESULTS AND DISCUSSION

Table 2: Characterization of in situ gel

Characterization	pH	Floating lag time (S)	Viscosity (centipoise)	Gelling capacity	Floating time(H)
F1	6.58±0.04	64.3±4.04	174±1.23	+++	>12
F2	6.6 ±0.03	76±0.7	245±1.15	+++	>12
F3	6.53± 0.01	2.6±0.57	358±1.28	+++	>12
F4	6.28±0.02	1.6±0.57	376±1.26	+++	>12
F5	6.4±0.10	127±2.82	105±1.53	+++	>12
F6	6.54±0.05	189±5.03	119±1.12	+++	>12
F7	6.75±0.05	21±1.15	45±1.2	++	>12
F8	6.53±0.04	37±2	50±1.83	++	>12
F9	7.06±0.05	100±1.52	185±1.83	+++	>12
F10	6.7±0.11	111±3.21	203±3.05	+++	>12
F11	7.3±0.011	47±1.52	277±3.05	+++	>12
F12	6.5±0.34	58±1.8	290±0	+++	>12

The formulated products underwent a series of tests encompassing pH assessment, in vitro gelling capacity, in vitro drug release, floating duration, and drug content analysis. The pH values across all formulations fell within the 6.28±0.02 to 7.06±0.05 range. Concerning buoyancy behavior, the buoyancy lag time for all formulations was under 2 minutes, while the buoyancy duration surpassed 12 hours. The in vitro gelling capacity for all the formulations [+++] which indicate that the gel was formed immediately and sustained for long period. Particularly noteworthy was the exceptional performance of formulation F3, showcasing an impressive floating lag time of less than 2 seconds.

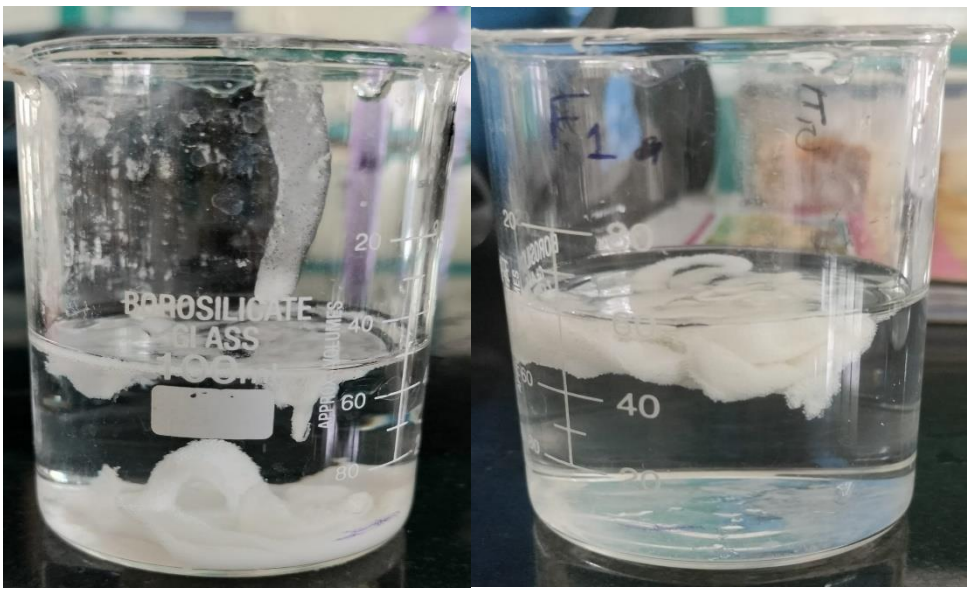

Fig 2: Pictures of Floating time of formulations

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Fig 3: Pictures of In vitro gelling capacity

Drug content:

The drug content for all the formulations were between 82.7 ± 0.9 to 95.1 ± 0.1. Notably, formulation F3 demonstrated superior performance with the highest drug content 95.1 ± 0.1.

Table 3: Cumulative % of drug release of all formulations

Time (H)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	5.78 ±1.53	6.02 ±1.24	5.95 ±1.33	6.09 ±1.12	6.61±1.14	6.43±2.12	6.37 ±1.38	6.13±1.48	6.28±1.49	6.28±1.23	6.46 ±1.27	6.42 ±1.32
1	13.73 ±1.22	12.45 ±1.58	13.26±1.22	12.34±2.16	13.65± 1.29	13.23± 1.27	12.98±1.23	12.51±1.28	12.93± 1.38	12.86± 1.12	13.34±2.28	13.24±1.38
2	35.24 ±1.35	33.37 ±1.48	23.54±1.48	22.35±1.28	22.12± 1.55	21.59± 1.23	20.47±1.28	19.82±1.28	21.69± 2.12	21.07± 1.57	20.54±1.17	20.23±1.48
4	48.83 ±1.25	40.36 ±1.28	37.23±1.38	34.52±1.58	31.52± 2.27	30.45±1.58	29.52±1.38	27.94±1.49	30.82± 2.12	29.99± 1.56	28.07±1.22	28.65±2.17

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6	59.62 ±1.55	58.54 ±1.27	54.14±1.27	53.13±1.46	41.87± 1.12	40.56±1.67	45.33±1.36	36.72±1.28	40.52± 1.27	39.41± 1.36	37.32±1.36	37.96±1.24
8	67.54 ±1.73	63.52 ±1.45	69.33±1.22	64.28±1.32	52.97± 1.12	50.63±1.64	58.32±1.46	45.92±1.26	50.86± 1.14	49.63± 1.25	46.99±1.42	48.76±1.24
10	73.54 ±1.62	71.64 ±1.65	83.52±2.17	82.11±1.45	64.56± 1.12	64.38±1.46	65.52±1.28	56.14±1.12	61.87± 2.18	60.22± 1.25	62.17±1.42	60.54±1.37
12	85.54 ±1.53	82.84 ±1.45	93.45±1.26	90.83±1.47	73.38± 1.36	71.13±1.38	72.25±2.18	70.11±1.28	73.55± 1.53	71.75± 1.29	72.52±1.17	70.64±1.58

Cumulative drug release percentages for the 12 formulations were between 73±1.3 to 93±1.2 whereas among all the prepared formulation F3 has a better drug release with 93±1.2. So the F3 was selected as an optimized one.

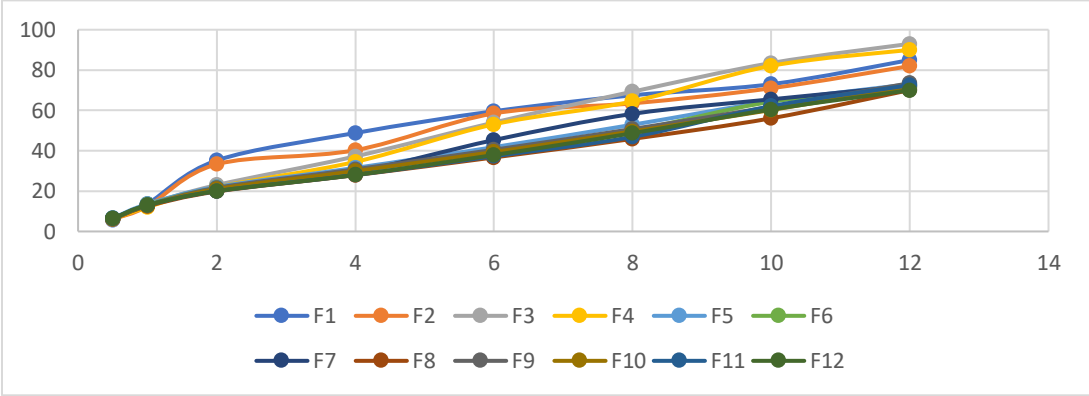

Fig 4: In vitro drug release of formulations (F1-F12)

Fig 5: Pictures of in vitro drug release

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Table 4: Kinetics of drug release

Formulation	Zero order	First order	Higuchi equation	Korsmeyers peppas equation		Hixon crowell
	R^2	R^2	R^2	R^2	n	R^2
F3	0.9932	0.9384	0.988	0.9954	0.8436	0.9819

Fig 6: Graph of Zero order kinetics

Fig 7: Graph of first order kinetics

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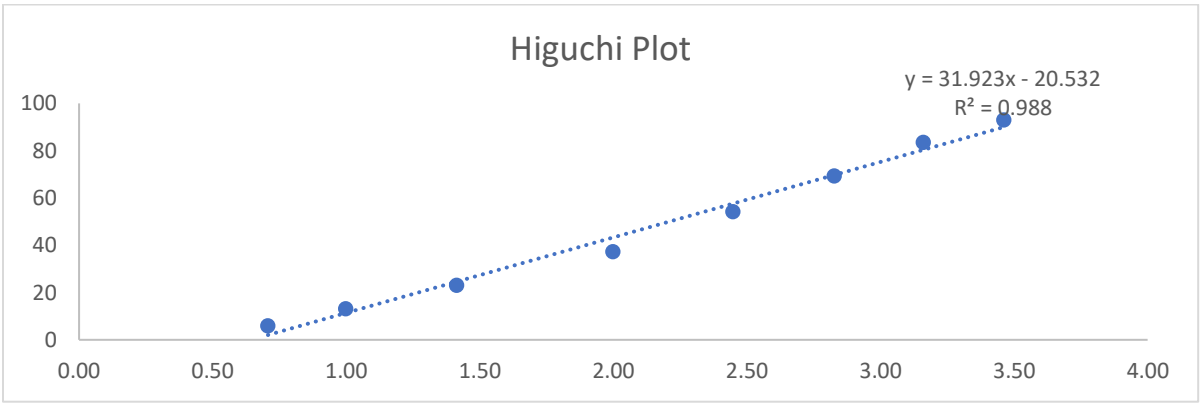

Fig 8: Graph of Higuchi kinetics

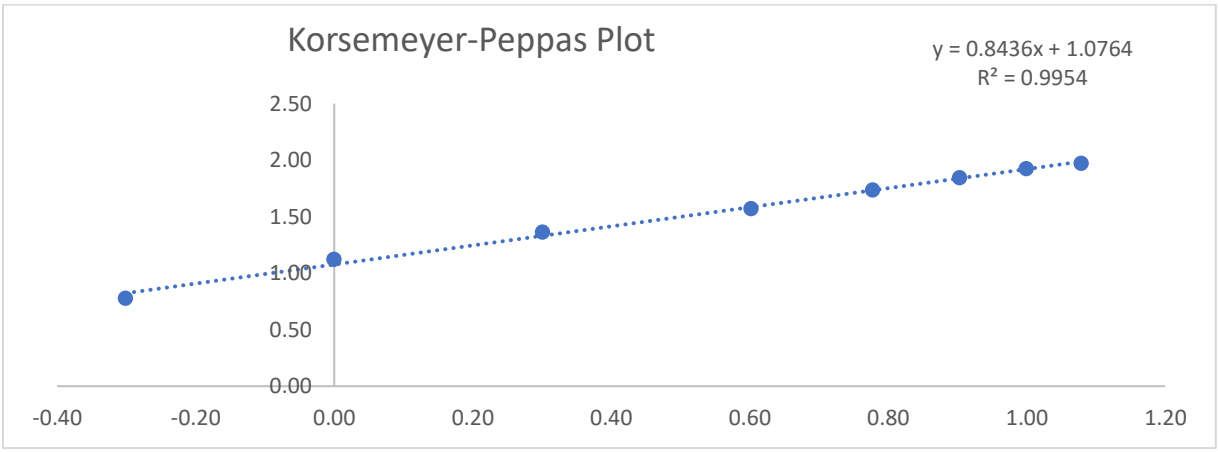

Fig 9: Graph of Korsmeyer- peppas kinetics.

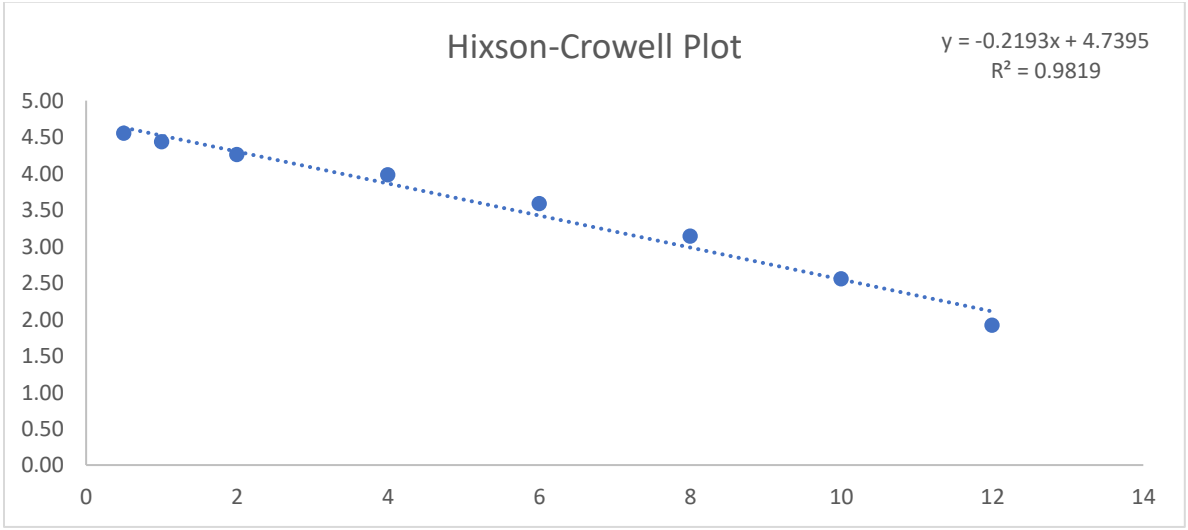

Fig 10: Graph of Hixson-Crowell Plot

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The release kinetics of Ciprofloxacin HCl was analysed by fitting drug release data to various models such as Higuchi's, zero order, first order, Hixson-Crowell, and Korsmeyer equations. These models were utilized to determine the underlying release mechanisms. Regression analysis was performed on the data using Microsoft Excel's statistical functions to understand the relationship between the drug release rate and time according to these different kinetic models. The R value is 0.9996. Since Korsemeyar Peppas' range of n value was less than 1, the drug release kinetics follow a non-Fickian kinetics process.

CONCLUSION

The study of gastro retentive in situ gel-based ciprofloxacin hydrochloride was formulated. F1-F12 formulations were prepared. All twelve prepared formulations have undergone various characteristic tests such as buoyancy lag time, viscosity, drug content and drug release. Amongst twelve prepared formulations the F3 has shown the optimized results. It has shown floating lag time 2.6±0.5, Floating time greater than 12 hours, viscosity 358±1.28, drug content 95.2±0.1 and cumulative drug release of 93.1±1.2. The in vitro tests have shown the optimized results which can be further investigated for *in vivo* study.

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