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Research Article

DESIGN AND DEVELOPMENT OF GASTRORETENTIVE DRUG DELIVERY SYSTEM OF CIPROFLOXACIN HYDROCHLORIDE

VIBIN BOSE R, JEGANATH S*, RAMYA SREE K, SHERNI PRITHIBA JHANSI RANI S

Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai, Tamil Nadu, India. Email: jeganaths@gmail.com

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ABSTRACT

Objective: The aim is to prepare the floating tablet of ciprofloxacin and to improve their bioavailability in the treatment against the Gram-positive and Gram-negative microorganisms. Ciprofloxacin HCL is an acidic drug used for respiratory tract infection, diarrhea, skin infection, thyroid fever, and urinary tract infection. The ciprofloxacin HCL is primarily absorbed in the stomach and it has low bioavailability. Due to its low availability, it was chosen as an appropriate drug for the scheme of the gastroretentive floating drug delivery system.

Method: Ciprofloxacin HCl is an acidic drug which was made by wet granulation process using various polymers, which include hydroxypropyl methylcellulose K4M, Eudragit, and Guar gum with a different composition. The gas generating agents such as saleratus and citric acid were used for the preparation. The prepared granules were subjected to pre-compression parameters technique and the formulated tablets were subjected to post-compression parameters, respectively.

Result: The Fourier-transform infrared analysis reveal that the drug and excipients used for the formulations were compatible with each other. All formulated granules having good flow properties and all the post-compression parameter are within the limit in which the F4 formulation shows optimum drug release of about 98.7% at 12 h and which has the buoyancy lag time of about 134 s and floating time about 12.5 h. Kinetic treatment revealed of the optimized preparation is based on Korsmeyer–Peppas model. The value n=0.861 states the process of non-Fickian diffusion.

Conclusion: Based on above observation found in the work, it was concluded that ciprofloxacin HCl can formulate as a floating drug delivery system which helps in increasing the gastric residence time, as a result, it increases the bioavailability and half-life of ciprofloxacin HCl.

Keywords: Floating tablets, Ciprofloxacin hydrochloride, Hydroxypropyl methylcellulose K4M, Buoyancy lag time.

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INTRODUCTION

The dynamically controlled system or floating system is low-density systems which possess enough buoyant property to float over the gastric contents and in the stomach they remain buoyant, and provide the prolonged action without changing the gastro emptying rate, which leads to an increase in gastroretention time, thereby it control the variation in plasma drug concentration [1]. Its importance includes lower dosing and fewer side effects and suitable for the drug which is easily absorbed in the stomach. The mechanism is that the floating drug delivery system has a bulk density lesser than the gastric fluids and thus they remain buoyant in the stomach for a long period of time without changing the gastro emptying rate. The major advantages are enhanced bioavailability, sustained release of drugs [2,3]. The hydroxypropyl methylcellulose (HPMC) K4M, Eudragit, and guar gum used as the polymers for the preparation of ciprofloxacin floating tablet.

METHODS

Ciprofloxacin was a gift sample obtained from the Micro Labs at Hosur. The HPMC K100M and Guar gum were buyed from Loba Chemicals, Mumbai. Saleratus, starch, citric acid, and Mg stearate were purchased from S.D. Fine Chemicals, Mumbai.

Drug-polymer compatibility studies

Fourier-transform infrared (FTIR) analysis

FTIR study is used to analyze the interactions between the drug, excipients, and the polymers. They should be compatible with each another to produce a safe, efficacious, and stable product.

The peaks and patterns of the pure drug and the peaks and patterns of the combination of drug and polymers were compared with each other [4].

Preparation of ciprofloxacin hydrochloride floating tablet

Ciprofloxacin HCl floating tablet was formulated by wet granulation technique, exploitation of numerous polymers such as HPMC K4M, Eudragit 100S, guar gum with a combination of sodium bicarbonate, and citric acid as the gas generating agent [5]. The various mixture of each formulated preparation is given in Table 1.

Ciprofloxacin Hcl is passed through sieve no.20. All the excipients were passed through sieve no. 40. Mg stearate is gone through sieve no 60. The shifted materials of ciprofloxacin HCl were geometrically mixed with the chemical compound and saleratus (sodium bicarbonate), and citric acid are blended for 10 min. Then, add starch mucilage slowly dropwise manner to create a coherent mass. The granules were prepared by passing the coherent mass through sieve no.16. The obtained granules are collected and using the hot air oven, it will be dried at 40°C±20°C for 2 h. The dried granule was gone through sieve no.20. Magnesium stearate is added to the dried granules then subjected to pre-formulation studies [6]. The granules of all formulations were compressed into tablets by exploitation tablets punching machine.

Preformulation studies

Bulk density

The bulk density is defined as the ratio between a given mass of granules or powder and its bulk volume [3]. The exactly weighed amount of granules was carefully placed into a 100 ml measuring cylinder, from

which the initial volume was measured, and it is calculated by the formulae [7].

Bulk density = Weight of granules/bulk volume of granules

Tapped density

Tapped density is defined as the ratio between a given mass of granules or powder and the constant or fixed volume of the granules or powder after tapping.

Tapped density = Weight of granules/tapped volume of granules

Angle of repose

The angle of repose is the maximum angle possible between the surface of the pile of powder and horizontal plane. The fixed funnel method is used to determine the angle of repose of the power or granules and to study the flow property of the powder or granules. The angle of repose (θ) can be determined by the formulae [8].

$$\theta = \mathrm{Tan}^{-1}(h/r)$$

Where,
θ = Angle of repose,
h = Height of the powder cone,
r = Radius of the powder cone.

Compressibility index (CI) and Hausner ratio

It is a popular method of predicting the flow characteristics of granules and powder. The Hausner ratio and the CI are obtained by evaluating the tapped density and bulk density of a powder or granules.

$$\text{C.I} = \frac{\text{Tapped density-bulk density} \times 100}{\text{Tapped density}}$$

Hausner ratio = Tapped density/bulk density

Characterization of ciprofloxacin HCl floating tablets

General appearance

The general appearance includes the measurement such as a tablets shape, size, color, presence or absence of odor and taste, physical flows, surface textures, and consistency [9].

Thickness

The thickness of ciprofloxacin HCl floating tablets was measured using Vernier calipers. The thickness must be controlled to facilitate packaging.

Hardness or crushing strength test

Hardness is defined as the force that required breaking a tablet across a diameter [3]. The hardness of the tablet is determined using the monsanto hardness tester.

Weight variation test

The under medication or overdose can be possible, if any variation in the weight of the tablet. Therefore, tablet of each batch should have uniform weight. From each formulation 20 tablets were selected randomly and weigh it individually, and the individual tablet weight is noted. From the total weight of all tablets, the average weight of the tablet was calculated. The individual weights were compared with the average weight. Not more than two tablets must differ from the average weight. The percentage deviation was determined by the following formulae [10].

$$\text{Percentage deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Friability test

It is studied to ensure the capacity of the tablets to withstand shock, while handling, transportation, processing, and packaging. It is usually measured using Roche Friabilator [11]. A maximal weight loss should not be exceeding 1% of the initial weight of the tablets after 100 evolutions (25RPM) are considered generally acceptable. The percent friability was obtained using the formula.

$$\text{friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where,
W_1 = Weight of tablets before the test
W_2 = Weight of tablets after the test

Estimation of drug content

From each formulation 10 tablets were taken and which is weighed and powered the amount of powered equivalent to 100 mg of ciprofloxacin HCl was transfer into 0.1N HCl containing volumetric flask of capacity 100 ml. From the prepared 1 ml of sample was withdrawn and diluted to 10 ml using 0.1N HCl and the resulting solution absorbance was observed at 277 nm [8].

Floating test

The formulated tablet was kept in 100 ml beaker having 0.1N HCl. The time difference between introducing the dosage form and there buoyancy on 0.1N HCl and the time at which the drug remain buoyant was observed [12].

Buoyancy lag time

The time required for a drug to emerge on the surface of the medium is known as floating lag time (FLT) [13]. Total duration of time during which the drug remains buoyant is known total floating time (TFT).

***In vitro* release studies**

The *in vitro* studies were done using USP Type II dissolution test apparatus, and it is allowed to rotate at a speed of 50 rpm. The 900 ml of 0.1 N HCl was poured in the dissolution medium and dissolution jar is maintained at 37±0.5°C. One of the formulated tablet was kept inside

Table 1: Formulation of ciprofloxacin HCl floating tablets

Formulations	Ciprofloxacin Hcl	HPMC K4M	Eudragit 100S	Guar gum	Sodium bicarbonate	Citric acid	Starch	Magnesium stearate
F1	250	150	-	-	50	15	25	10
F2	250	-	150	-	50	15	25	10
F3	250	-	-	150	50	15	25	10
F4	250	75	75	-	50	15	25	10
F5	250	-	75	75	50	15	25	10
F6	250	75	-	75	50	15	25	10
F7	250	50	50	50	50	15	25	10

HPMC: hydroxypropyl methylcellulose

the dissolution medium, after 1-h time interval 10 ml of sample was withdrawn, and the absorbance is noted. The sample is collected up to 12 h and replaced with the same volume of medium. After suitable dilution, the samples were analyzed at 277 nm using UV double beam spectrophotometer [6,14].

Release kinetics

The data observed from the *in vitro* studies were fitted to different kinetic equations which includes zero-order, first-order, Korsmeyer–Peppas model, and Higuchi model [15].

Zero-order equation: $(Q = Q_0 - k_0 t)$

First-order equation: $(\ln Q = Q_o - K_1 t)$

Higuchi equation: $(Q = K_2 t^{1/2})$

Korsmeyer–peppers: $(Q/Q_0 = K t^n)$

RESULTS AND DISCUSSION

Preformulation studies of granules of ciprofloxacin HCl floating tablets

The granules of ciprofloxacin HCl floating tablets were formulated by wet granulation method. The prepared granules are introduced to preformulation studies, and the results are presented in Table 2.

The bulk density of the granules ranges from 0.32 to 0.393. The tapped density of the granules ranged from 0.417 to 0.49. The angle of repose ranges from 22°71' to 26°15'. The CI and Hausner's ratio of the prepared granules ranged from 9.86 to 15.39 and 1.12 to 1.18, respectively. The results showed that the granules of all formulations showed excellent flow properties.

Characterization of ciprofloxacin HCl floating tablets

General appearance

The prepared tablets were estimated for organoleptic characters. The tablets are circular in shape, yellowish in color, with no characteristic odor. All tablets showed elegance in appearance.

The compressed tablet was estimated by various physical parameters. The results are presented in Table 3. The rigidity of the tablets ranges from 4.84 to 5.56 and percentage friability of all formulation within the range of 0.23–0.40%. The thickness ranged from 4.1 mm to 4.4 mm. Here, all the parameters are within the acceptable range. Hence, all the formulated tablets were falls within limits.

Weight variation test

All the formulated tablets undergo the weight variation test, and their percentage weight variations were within the pharmacopeial range. As a result, the weight of all tablets shows the low standard deviation values and found to be uniform, and the results are shown in Table 4.

Estimation of drug content

Drug content estimation shows that all the batches of formulated tablets are within the prescribed limits. It reveals that the drug and the excipients were mixed properly and the results are given in Table 4.

Buoyancy lag time

It is the time required during which the drug remains buoyant on 0.1N HCl was measured, and the results are given in Table 5. The buoyancy lag time value was seen in the range of 134–166 s.

TFT

It is defined as the total duration of time required during which the drug remains buoyant is measured, and the values were ranges between 356 and 485 min and the results are given in Table 5.

IR spectral analysis

The IR spectral studies of pure ciprofloxacin HCL, HPMC K4M, Eudragit, and Guar gum were done to study the drug-polymer interactions. It states that the IR spectrum of pure ciprofloxacin HCL and polymers have similar fundamental peaks and patterns. It reveals that there is no significant interaction within the drug and polymers. The results are shown in Figs. 1-8.

***In vitro* dissolution studies**

An *in vitro* study was done to evaluate the dissolution character of ciprofloxacin HCL from floating tablets using three polymers with different ratios. The *in vitro* evaluation results are presented in Table 6. The graphical representation of the data is shown in Fig. 9.

The percentage drug release of all prepared formulations after 12 h using HPMC K4M, Eudragit 100S, and guar gum was found to be 88.12% (F1), 90.68% (F2), and 73.45% (F3), respectively. Moreover,

Table 2: Preformulation studies of granules of ciprofloxacin HCl floating tablets

S. No	Formulation Code	Angle of repose	Bulk density (g/cm)	Tapped density (g/cm)	CI (%)	Hausner's ratio
1	F1	22°71′	0.32	0.49	11.22	1.16
2	F2	22°9′	0.386	0.435	11.34	1.12
3	F3	24°5′	0.393	0.436	9.86	1.12
4	F4	24°01′	0.375	0.429	12.59	1.14
5	F5	25°1′	0.371	0.417	11.16	1.13
6	F6	26°1′	0.380	0.448	10.714	1.10
7	F7	24°9′	0.391	0.455	15.39	1.18

CI: Compressibility index

Table 3: Evaluation of ciprofloxacin HCl floating tablets

S. No.	Formulation code	Hardness (kg/cm)	Friability (%)	Thickness (mm)	Diameter (mm)
1	F1	4.85	0.631	4.17	10.19
2	F2	4.8	0.413	5.14	10.8
3	F3	5.1	0.462	5.16	11.0
4	F4	4.75	0.381	4.4	10.7
5	F5	4.5	0.54	4.16	10.9
6	F6	5.0	0.761	4.5	11.0
7	F7	4.8	0.62	4.2	10.8

Table 4: Weigh variation and estimation of drug content of floating tablets

S. No	Formulation code	Weight variation	Drug content (%)
1	F1	498±2.5	98.12
2	F2	496±3.2	97.23
3	F3	497±2.7	98.63
4	F4	499±1.13	99.54
5	F5	498±3.5	97.83
6	F6	495±4.3	97.38
7	F7	497±4.2	99.17

Table 5: FLT and floating time of different formulations

S.No	Formulation code	FLT (Sec)	Floating time (h)
1	F1	150	10.0
2	F2	144	10.5
3	F3	151	8.0
4	F4	134	12.5
5	F5	154	9.0
6	F6	166	9.5
7	F7	140	11.0

FLT: Floating lag time

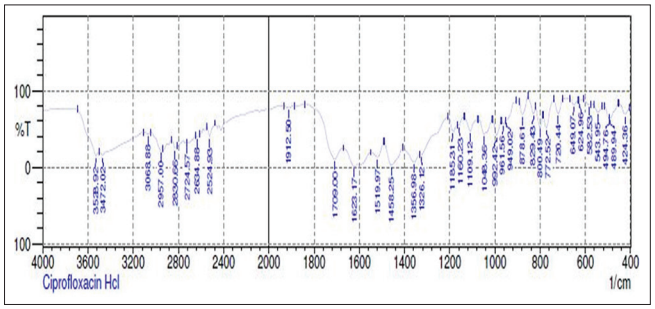

Fig. 1: Fourier-transform infrared spectrum of ciprofloxacin HCl

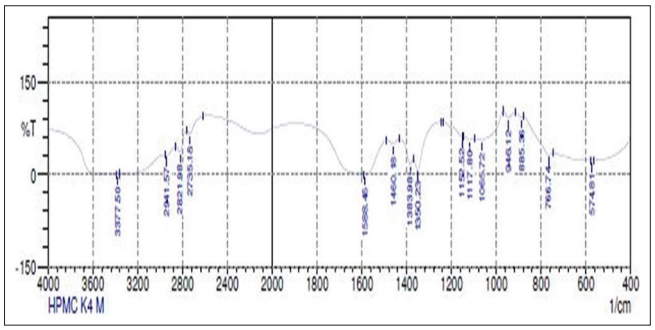

Fig. 2: Fourier-transform infrared spectrum of hydroxypropyl methylcellulose K4M

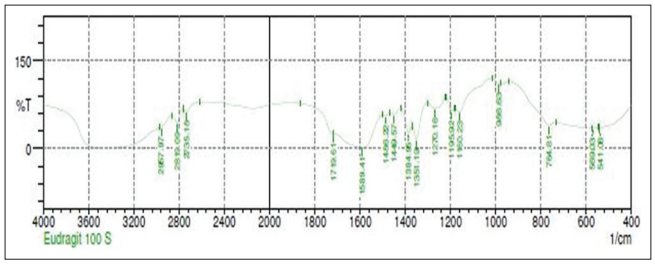

Fig. 3: Fourier-transform infrared spectrum of Eudragit 100S

the percentage drug release of a combination of HPMC K4M with Eudragit 100S is 98.87% (F4), Eudragit 100S with guar gum is 85.67% (F5), HPMC K4M with guar gum is 79.93% (F6), and HPMC K4M with Eudragit 100S and guar gum is 95.45% (F7).

From the *in vitro* evaluation study, it was observed that maximum drug release found in formulation F4 is 98.87%. It shows that F4 formulation exhibits optimized drug release when compared with other formulation.

Kinetic analysis of dissolution data

The absorbed data were treated in case of zero-order, first-order, Korsmeyer– Peppas model, and Higuchi's model to study the mechanism of drug release of prepared formulations. The release rate kinetic data for all the formulations were given in Table 7, the graphical representation of the data is shown in Figs. 10-13. The formulation showed high linearity when plotted in zero-order kinetics with regression coefficient values (R^2) between 0.993 and 0.998.

Diffusion is the process in which the drug moved from the dosage matrix into the *in vitro* study fluid based on the concentrations. This is governed by Higuchi's equations, as the plot reveals the high linearity with regression coefficient values (R^2) between 0.878 and 0.938.

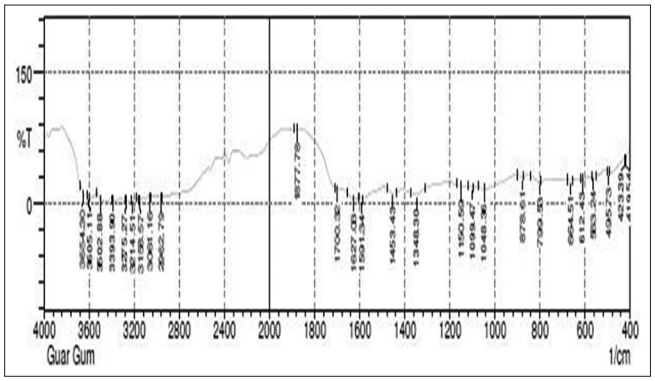

Fig. 4: Fourier-transform infrared spectrum of Guar gum

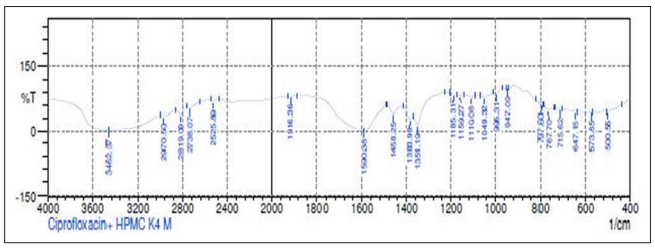

Fig. 5: Fourier-transform infrared spectrum of ciprofloxacin HCl and hydroxypropyl methylcellulose K4M

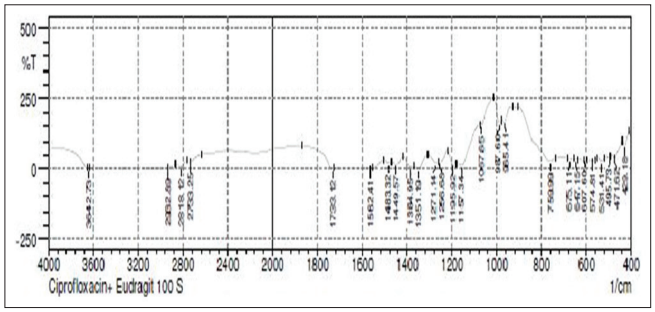

Fig. 6: Fourier-transform infrared spectrum of ciprofloxacin HCl and Eudragit 100S

Table 6: Comparative *in vitro* dissolution study of ciprofloxacin HCl floating tablets (F1-F7)

Time (h)	Cumulative % drug release						
	F1	F2	F3	F4	F5	F6	F7
1	11.22	9.43	8.24	12.18	9.91	10.51	10.98
2	14.3	16.13	10.38	20.9	12.83	12.22	19.06
3	19.8	21.51	13.68	27.13	16.86	15.27	24.81
4	27.01	29.94	18.7	36.78	24.2	21.38	31.04
5	33.73	35.93	25.66	44	31.16	29.82	39.23
6	39.84	41.8	30.18	52.43	37.4	36.17	45.58
7	47.3	50.23	36.3	60.74	41.8	40.94	51.08
8	53.04	58.17	42.04	69.05	50.23	48.15	61.47
9	63.92	68.68	51.45	77.24	58.91	54.02	70.52
10	71.98	75.28	57.81	85.43	68.07	62.57	81.64
11	79.81	82.13	69.91	91.91	76.14	72.47	87.02
12	88.12	90.68	73.45	98.87	85.67	79.93	95.45

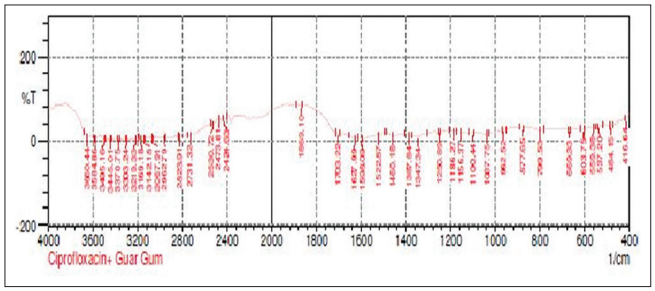

Fig. 7: Fourier-transform infrared spectrum of ciprofloxacin HCl and Guar gum

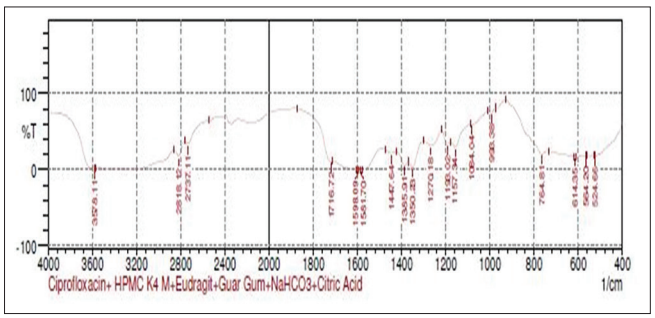

Fig. 8: Fourier-transform infrared spectrum of ciprofloxacin HCl, hydroxypropyl methylcellulose K4M, Eudragit 100S, Guar gum, sodium bicarbonate, and citric acid

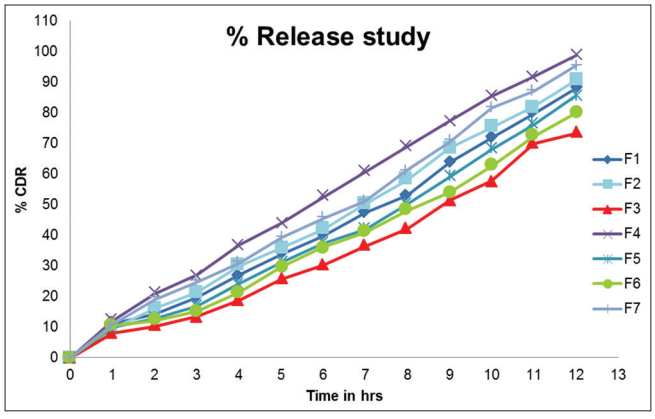

Fig. 9: Comparative *in vitro* dissolution study of ciprofloxacin HCl floating tablets (F1-F7)

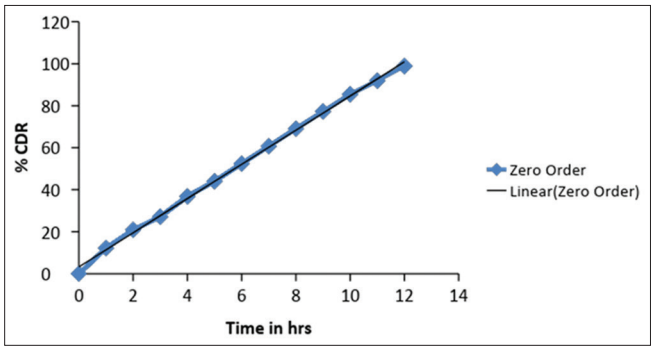

Fig. 10: Zero-order drug release kinetics of F4

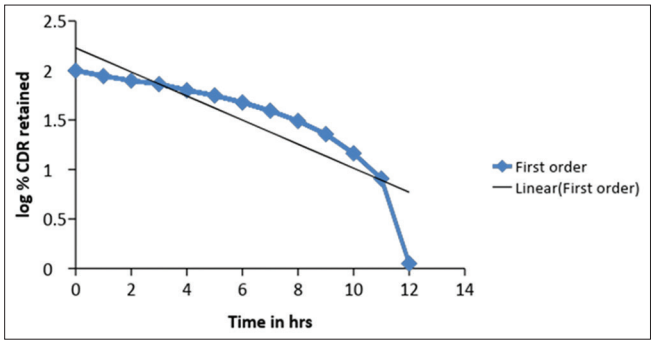

Fig. 11: First-order drug release kinetics of F4

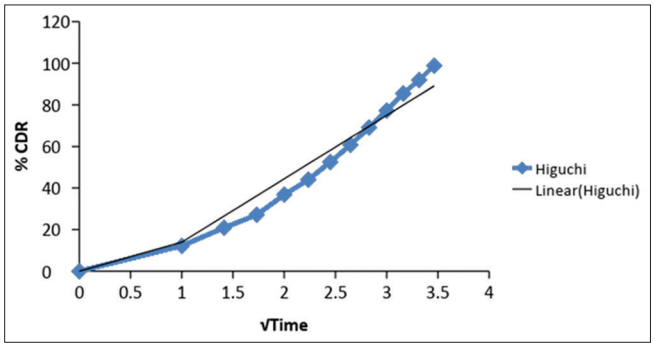

Fig. 12: Higuchi model of drug release kinetics for F4

Using Korsmeyer–Peppas model, if n=0.45, it is Fickian diffusion, if n=0.45–0.89 it is non-Fickian transport. Here, all the formulations showed "n" values between 0.806 and 0.929. Hence, all the formulations follow non-Fickian diffusion transport mechanism.

Table 7: Kinetic analysis of dissolution data

S. No	Formulation code	Regression coefficient (R^2)			Korsmeyer' plot	
		Zero-order plot	First-order plot	Higuchi's plot	R^2	Slope (n)
1	F1	0.993	0.886	0.896	0.970	0.887
2	F2	0.997	0.889	0.910	0.993	0.929
3	F3	0.988	0.880	0.878	0.997	0.868
4	F4	0.998	0.763	0.938	0.996	0.861
5	F5	0.988	0.880	0.878	0.998	0.806
6	F6	0.988	0.880	0.878	0.998	0.825
7	F7	0.995	0.832	0.912	0.990	0.877

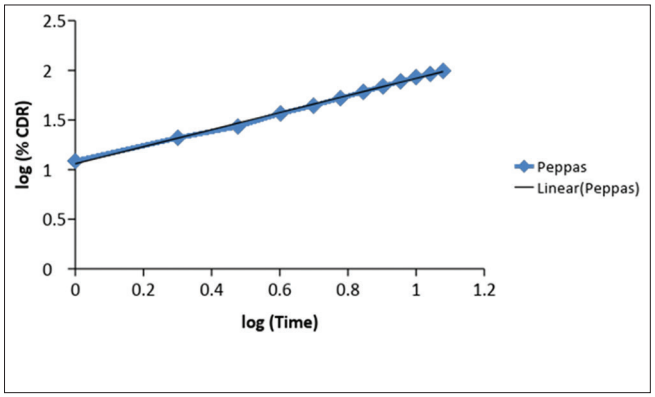

Fig. 13: Peppas model of drug release kinetics forF4

CONCLUSION

Hydrodynamically balanced tablets of ciprofloxacin HCl can be formulated with an approach to improve drug bioavailability and to increase gastric residence. The developed floating tablets of ciprofloxacin HCl were formulated using HPMC K4M, Eudragit100S, and guar gum as polymers and sodium bicarbonate combination with citric acid as the gas generating agent which is prepared by wet granulation technique and evaluated. The result states that all the parameters are within the range. When comparing all formulation, F4 showed optimized drug release of 98.87**%** at the end of 12 h. The optimized F4 formulation showed buoyancy lag time of 134 sec and floating time of 12.5 h, respectively. Data obtained from the kinetic treatment show F4 formulations follow Korsmeyer–Peppas model. The n=0.861 indicates the non-Fickian diffusion. From the above study, it was concluded that ciprofloxacin HCl can formulate as a floating drug delivery system with more bioavailable, safe, and economical drug and which helps to increase gastric residence time thereby it increases the bioavailability and half-life of ciprofloxacin HCl.

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