Available online on 15.08.2022 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Research Article

A study on Formulation and Evaluation of Gastroretentive tablet incorporating Ciprofloxacin Hydrochloride

Gautam D. Mehetre*, Raju R. Thenge, Pavan P. Chinchole, Mahesh B. Narkhede, Mukesh W. Babhulkar

Dr. Rajendra Gode College of Pharmacy, Malkapur, Dist. Buldana- 443101, Maharashtra, India

Article Info:

Article History:

Received 22 June 2022
Reviewed 29 July 2022
Accepted 09 August 2022
Published 15 August 2022

Cite this article as:

Mehetre GD, Thenge RR, Chinchole PP, Narkhede MB, Babhulkar MW, A study on Formulation and Evaluation of Gastroretentive tablet incorporating Ciprofloxacin Hydrochloride, Journal of Drug Delivery and Therapeutics. 2022; 12(4-S):53-60

DOI: http://dx.doi.org/10.22270/jddt.v12i4-s.5501

*Address for Correspondence:

Gautam D. Mehetre, Asst. Prof., Department of Pharmaceutics, Dr. Rajendra Gode College of Pharmacy, Malkapur, Dist- Buldhana, Pin code 443101, Maharashtra, India

Abstract

Ciprofloxacin is a broad spectrum fluoroquinolone antibiotic effective in a broad range of infections including some difficult to treat ones. Because of wide-spectrum bactericidal activity, oral efficacy and good tolerability, it is used in Urinary tract infection, Gonorrhea, Bacterial gastroenteritis, Typhoid, Bone, soft tissue and gynecological infection, Respiratory infection and tuberculosis. The main objective of formulating the floating system was to reduce the frequency of administration, to improve patient compliance and improve bioavailability of drug by preparing a gastroretentive drug delivery system. Floating tablets of Ciprofloxacin hydrochloride were prepared by employing two different grades of control releasing polymers HPMC K4M and HPMC K100M in different concentration. Sodium bicarbonate was incorporated as a gas-generating agent. The tablets were evaluated for uniformity of weight, hardness, friability, drug content, floating behavior, swelling studies and dissolution studies. Among tablet formulations, formulation F3 showed maximum drug release i.e. 92.25% at the end of 12 h compared with other formulations and was concluded as optimized one.

Keywords: Ciprofloxacin HCl, floating tablets, HPMC K4M, HPMC K 100M, FTIR.

INTRODUCTION

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery system (GRDDS). Gastroretentive drug delivery is one of the promising approaches for enhancing the bioavailability and controlled delivery of drugs that exhibit narrow absorption window. Gastroretentive techniques increase the gastric retention time of the dosage form and control drug release. These are the systems which can remain in gastric region for several hours and significantly prolong the gastric residence time of drug. After oral administration, such a delivery system would be retained in stomach. It will release the drug there in a controlled & prolonged manner, so that the drug could be supplied continuously to absorption site in GIT.[1]

A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular segment of GIT only or are absorbed to a different extent in various segments of GIT. Such drug candidates are said to have an „absorption window". But, in case of „narrow absorption window" drugs, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. Again after crossing the absorption window, the released drug drastically minimizes the time available for drug absorption after it, which is then accompanied by lesser bioavailability.[2] Thus, the success of oral controlled drug delivery has faced some difficulties related with physiological adversities, like short gastric residence time (GRT) and goes to waste with negligible or no absorption. This phenomenon is unpredictable gastric emptying time (GET). Prolonged GRT improves bioavailability, increases the duration of drug release, reduces drug waste and improves the drug solubility that are less soluble in a high pH environment.[2,3]

This has triggered the attention towards the development of various gastroretentive drug delivery technologies to deliver „narrow absorption window" drugs with improved bioavailability. Gastroretentive dosage forms are designed to be retained in the gastric region for prolonged time and release and prolonged input of the drug to the upper part of the GIT beyond the level of existing controlled release dosage thus ensuring its optimal bioavailability. Thus, they not only prolong the dosing intervals, but also increase the patient incorporated drug candidates and thereby enable sustained compliance forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs. Gastroretentive dosage forms greatly improved the pharmacotherapy of the GIT through local drug release.[4]

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need of repeated

dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited.[5]

Ciprofloxacin is a broad spectrum fluoroquinolone antibiotic. It is approved for the treatment of infectious diarrhea, urinary tract infections, bone and joint infections, lower respiratory tract infections. The drug is freely soluble in water and has a short elimination half- life of about 4h; various sustained release preparations were aiming to enhance its antibacterial activity. It has a narrow absorption window and is mainly absorbed in the proximal areas of GIT.[6]

An infection of stomach mucosa with *H. pylori,* a gram negative bacillus that causes chronic gastritis, is now generally considered as a risk factor of gastric cancer and duodenal ulcer. Ciprofloxacin is the drug of choice for the treatment of *H. pylori* infection. The drug does not readily cross blood brain barrier (BBB). Considering the above short comings, Ciprofloxacin HCl floating systemswere developed.

MATERIALS AND METHODS

Materials

Ciprofloxacin HCl obtained as a gift sample from Cipla (Goa). HPMC K 100M, HPMC K4M, Xanthan gum, and Talc purchased from Loba Chemie Pvt. Ltd. Mumbai. PVP K30, Magnessium stearate and Sodium bicarbonate purchased from SD Fine Chemicals, Mumbai.

Preparation of Floating Tablets of Ciprofloxacin HCl

The Gastroretentive tablet of Ciprofloxacin HCl was prepared by direct compression method. The steps involved in this method are weighing, screening, mixing, lubrication and compression. First accurately weighed all quantities of drug, excipients, and polymers like (Drug Ciprofloxacin HCl, HPMC K4M, HPMC K100M, Sodium bicarbonate, PVP K30, Xanthan gum). All the ingredients were sieved by #44 and then blended in mortar with pestle to obtain uniform mixing. Finally Magnesium stearate was mixed as glidant and talc added for lubrication. This was then compressed by chamunda Mini Press Compression machine using 12 mm flat punch. Different formulation batches were prepared as per the following table.

Table 1: Formulation batches for Ciprofloxacin HCl gastroretentive tablet

Sr. No.	Contents	F1	F2	F3	F4	F5	F6	F7	F8
1	Ciprofloxacin HCl	400	400	400	400	400	400	400	400
2	HPMC K 4 M	90	80	70	60	_	_	_	_
3	HPMC K 100 M	_	_	_	_	90	80	70	60
4	Xanthan gum	25	25	25	25	_	_	_	_
5	Tragacanth gum	_	_	_	_	25	25	25	25
6	PVP K-30	_	10	20	30	15	25	35	45
7	Sodium bicarbonate	115	115	115	115	100	100	100	100
8	Talc	10	10	10	10	10	10	10	10
9	Magnesium Stearate	10	10	10	10	10	10	10	10

*All the quantities expressed are in terms of milligrams.

Compatibility study

Compatibility studies were carried out to know the possible interactions between Ciprofloxacin HCl and excipients used in the formulation. Physical mixture of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using Fourier transform infrared spectroscopy. FTIR spectrum of pure drug and excipientswas seen in between 4000-400 cm^{-1}.

Precompression Parameters [7,8,9]

Bulk density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$D_b = M/V_0$

Where,

M is the mass of powder in gm.

V0 is the bulk volume of the powder in cm^3

Tapped Density (D_t)

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$D_t = M/V_t$Where,

M is the mass of powder.

V_t is the tapped volume of the powder.

Carr's Index (I)

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and isgiven by,

$I = (D_t - D_b)/D_t \times 100$

D_t is the tapped density of the powder. D_b is the bulk density of the powder.

Hausner's ratio

The Hausner's ratio of powder was calculated according to equation given below.

Hausner's ratio = D_t / D_bWhere,

D_t is the tapped density of the powder.D_b is the bulk density of the powder.

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose (θ) was calculated using the following equation.

$\tan \theta = h / r$

$\theta = \tan^{-1} h / r$Where,

θ = angle of repose,h = height of pile,

r = radius of pile.

Post Compression Parameters[10,11,12]

Thickness

Three samples were selected randomly from each batch and thickness was measured using Vernier Caliper. The tablet thickness should control within ±5% variation of standard value.

Hardness

The hardness of each of 3 tablets determined using a Phizer hardness tester till the tablet breaks under pressure at which time the reading in terms of kg/cm^2 is noted. Calculate the average hardness per tablet.

Limit: 3.0 kg/ cm^2 to 7.0 kg/ cm^2

Friability

Twenty tablets were weighed and placed in the Roche friabilator and tablets were rotated at 25 rpm for 4 minutes for 100 revolutions. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula.

% F =(Initial weight - Final weight) / Initial weight x100
Where,

% F = friability in percentageW_0 = Initial weight of tablets

W = Weight of tablets after revolution.

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight of 20 tablets was calculated. The batch was considered to pass the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in officials and none deviate by more than twice the percentage shown.

Content uniformity

Five tablets were taken and triturated. Weighed tablet powder equivalent to 100 mg of drug. This powder transferred into 100 ml volumetric flask, added with 60 ml of 0.1N Hydrochloric acid and shaked for 5 minutes and finally added 0.1 N HCl to make the volume up to 100 ml and solution was sonicated for 15 minute and filtered through whatman filter paper. Finally a solution was diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at the 276 nm using 0.1N Hydrochloric acid as blank.

Floating behavior

The tablets were placed in 100 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time.

Swelling studies

Three tablets were used from each formulation for the test. After recording the initial weights, the tablets were placed in purified water in petri dish at room temperature. After the time interval of 1,2,3,4,5,6,7,8,9,10,11 and 12 Hr the tablets were removed and weighed individually. The percent water sorption was calculated using following formula,

% Swelling index = $[(w_2 - w_1)/w_1] \times 100$ Where,

W_2 = weight of tablet after particular time interval.

W_1 = initial weight of tablet.

Dissolution studies [13,14]

The release rate of Ciprofloxacin hydrochloride from floating tablets was determined using The United States Pharmacopoeia (USP) dissolution testing apparatus (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and paddle speed 50 rpm. A sample (1 ml) of the solution was withdrawn from the dissolution apparatus at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and the samples were replaced with fresh dissolution medium maintained at 37 ± 0.5°C. The samples were diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 276 nm using a spectrophotometer. Percentage of drug release was calculated using the equation obtained from a standard curve.

Kinetic data analysis [15]

Drug release mechanism and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. To describe the kinetics of drug release from tablet, mathematical model such as zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models were used. The criteria for selecting the most appropriate model were chosen on the basis of the goodness or fit test.

RESULTS AND DISCUSSION

Precompression Parameter

Compatibility studies

The results of FTIR studies showed that there is no significant change in the properties of active drug (Ciprofloxacin HCl) by the addition of polymer. It showed that the active drug is compatible with polymer used. The FTIR spectra obtained are as below in Figures 1 and 2 and the interpretation is illustrated in given Table 2.

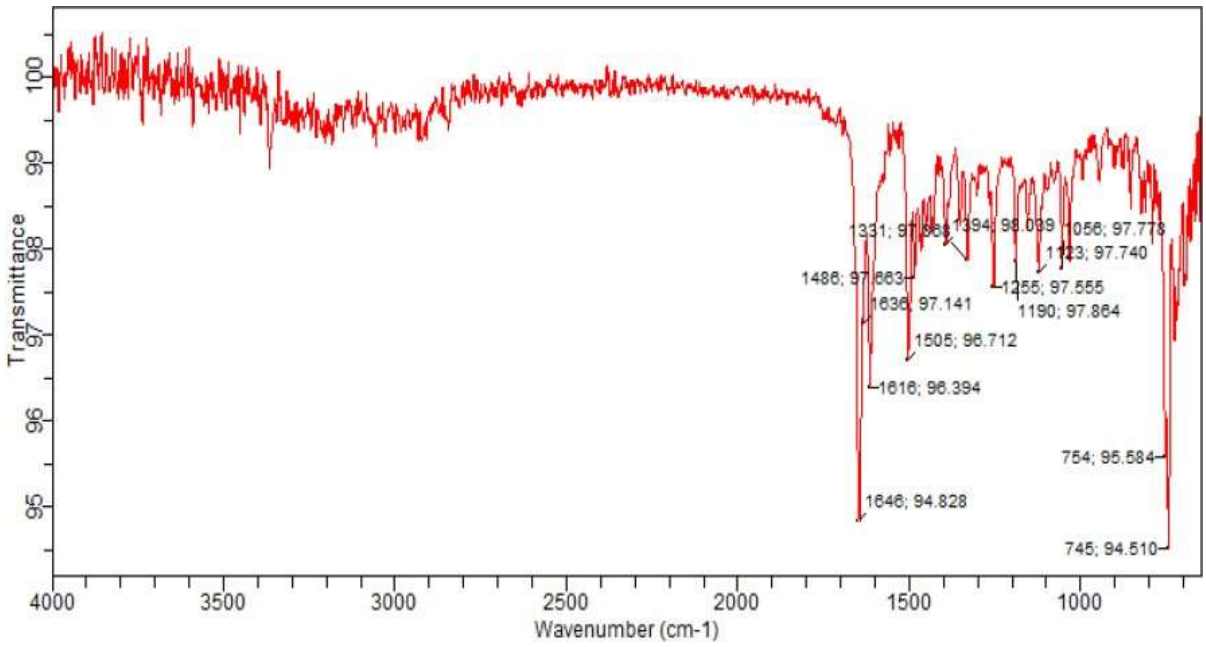

Figure 1: FTIR spectrum of Ciprofloxacin HCl

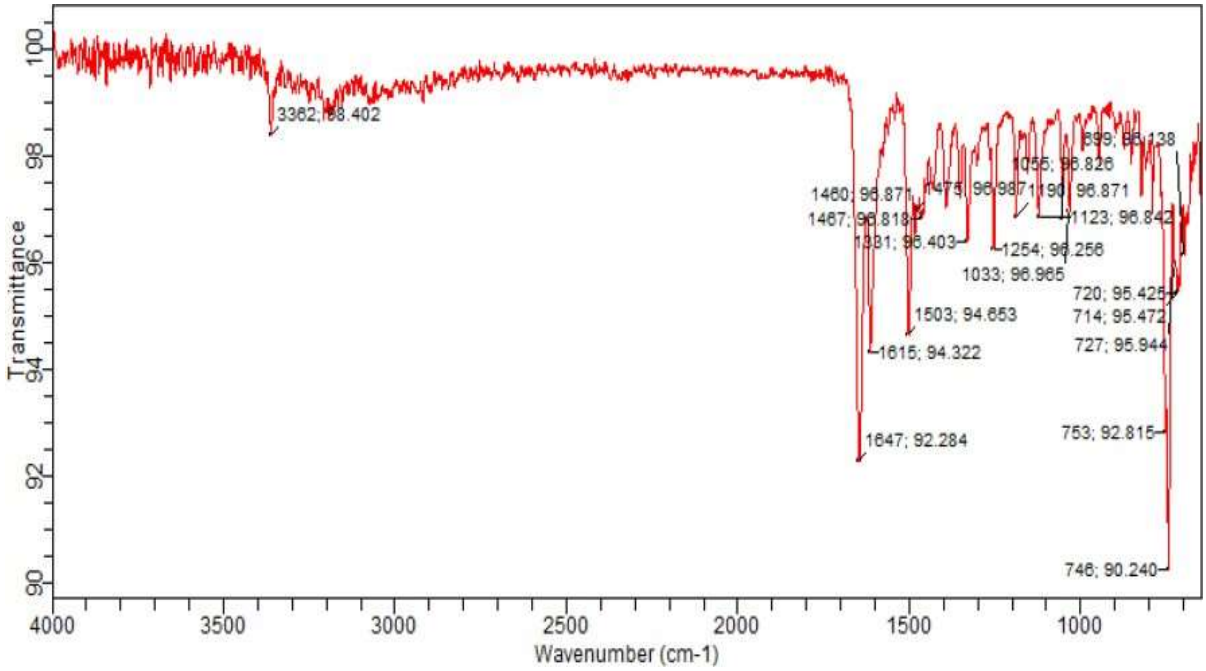

Figure 2: FTIR spectrum of physical mixture (Ciprofloxacin + excipients)

Table 2: Interpretation of FTIR spectra of Ciprofloxacin HCl

Interpretation	IR Range(cm^{-1})	Ciprofloxacin HCl Peak observed(cm^{-1})	Physical mixture
N-H stretching	3300-3500	3362;68.402	3362;68.402
O-H stretching	3000-3700	33.62;68.402	33.62;68.402
C=O stretching	3300-3600	33.62;68.402	33.62;68.402
N-H bending	1500-1700	1646;94.828	1647;92.284
C-N stretching	1180-1360	1255;97.555	1254;96.256

The bulk density values less than 1.2 gm/cm^3 indicate good packing and values greater than1.5 gm/cm^3 indicate poor packing. The bulk density values for all formulations of powder bulk varied in the range of 0.285±0.0265 gm/cm^3 to 0.375±0.0138 gm/cm^3. The values obtained lies within acceptable limits. The tapped density values for all formulation of powder bulk varied in the range of 0.363±0.0406 gm/cm^3 to 0.48±0.0184 gm/cm^3. The values obtained lies within acceptable limit.

The percent compressibility of formulation of powder bulk was determined by Carr's compressibility index. The percent compressibility for all formulation lies within the range of 20.87% to 22.48% indicates acceptable flow property.

Hausner's ratio was found to be in the range of 1.26 to 1.29 which shows acceptable flow property and good packing ability.

The angle of repose for all formulation of powder blend was found to be in the range of $32^0$61±0.340 to $39^0$40±0.340 indicating passable flow property. It can be concluded that the powder blend for all batches possess passable flow characteristic. The results of precompression parameters study are shown in Table 3.

Table 3: Precompression parameters of formulations.

Formulation	Bulk density(gm/cm³)	Tapped density (gm/cm³)	Carr·s index(%)	Hausner's ratio	Angle of repose(θ)
F1	0.292±0.0219	0.375±0.0317	22.13	1.28	$38^0$28±0.398
F2	0.315±0.0317	0.4±0.0513	21.25	1.26	$37^0$42±0.902
F3	0.324±0.0155	0.413±0.0210	21.54	1.27	$33^0$12±0.687
F4	0.285±0.0265	0.363±0.0406	21.48	1.27	$34^0$21±0.370
F5	0.307±0.0155	0.387±0.219	20.67	1.26	$39^0$40±0.340
F6	0.375±0.0138	0.48±0.0184	21.87	1.28	$34^0$21±0.604
F7	0.3±0.0210	0.387±0.0155	22.48	1.29	$33^0$02±0.687
F8	0.292±0.0317	0.375±0.0265	22.13	1.28	$32^0$61±0.340

*Value are expressed in mean ±SD (n=3).

Post compression parameters

The general appearance of tablets and overall elegance is essential for acceptability, the shape of all the formulation remained off white, smooth, flat faced circular and no visible cracks. The entire tablets passed the weight variation test as the percent weight variation was within the pharmacopoeial limits. The thickness of the tablet measured by Vernier calipers, twenty tablet from each batch were randomly selected and thickness was measured. The hardness of the tablet was measured by Monsanto tester and was ranged between 4.8±0.057 to 5.2±0.115 kg/cm².

The friability was measured by Roche friabilator and was found 0.492±0.205 to 0.870±0.102%, and this parameter given the satisfactory mechanical resistance of the tablet.

The drug content estimations showed values in the range of 95.82±0.416 to 99.21±0.498. These results showed the content uniformity of the tablet. Post compression parameters results are shown in Table 4.

Table 4: Post compression parameters of formulations.

Formulation	Thickness(cm)	Hardness (kg/cm²)	Friability (%)	Weight Variation (mg)	Uniformity ofcontent (%)
F1	0.5±0.0	5.2±0.208	0.638±0.101	650.1±0.592	97.91±0.180
F2	0.5±0.0	5.0±0.2	0.492±0.205	650.5±0.436	96.34±0.472
F3	0.5±0.0	4.8±0.100	0.676±0.306	650.4±0.681	98.42±0.203
F4	0.5±0.0	5.2±0.152	0.737±0.102	650.4±0.498	95.82±0.416
F5	0.4±0.0	4.8±0.057	0.515±0.208	649.7±0.723	98.95±0.877
F6	0.5±0.0	5.2±0.115	0.870±0.102	649.3±0.625	98.69±0.721
F7	0.5±0.0	5.2±0.102	0.722±0.100	650.3±0.436	99.21±0.498
F8	0.4±0.0	5.0±0.152	0.701±0.57	648.6±0.723	98.17±0.208

*Values are expressed in mean ±SD (n=3).

The time taken by the tablet to come up to the surface and float was determined. An average of three determinations from each batch was taken. The buoyancy time was found to be in between 42 to 72 sec. Also total floating time was noted. The results are shown in Table 5.

The photograph of floating tablet is as given in Figure 3.

Table 5: Floating behavior of formulations.

Formulation	Buoyancy time (sec.)	Total floating time (h)
F1	65	>12
F2	55	>12
F3	43	>12
F4	69	10
F5	72	>12
F6	62	>12
F7	56	11
F8	67	9

Figure 3: Floating photograph of ciprofloxacin table

Hydrophilic matrices in contact with water swell and increase their volume due to water diffusion through the matrix. As expected, matrices containing increasing polymer proportions show increasing swelling index. Table 6 shows cumulative percent swelling index of formulations.

Table 6: Cumulative percent swelling of formulations.

Time inHr	Cumulative percent swelling indexCumulative percent Swelling Index							
	F1	F2	F3	F4	F5	F6	F7	F8
1	25.69	23.38	22.61	21.84	31.07	25.07	22.15	20.61
2	38.92	37.84	38.30	36.46	44.30	38.00	35.07	33.38
3	50.61	49.38	50.30	48.15	55.69	48.92	42.61	40.30
4	56.76	55.53	57.69	57.84	64.15	55.69	51.84	50.30
5	62.15	60.46	59.84	60.30	78.00	63.38	56.46	54.46
6	75.84	76.46	74.15	73.53	81.38	74.92	68.61	68.00
7	80.61	79.84	77.84	77.38	91.38	79.84	73.53	72.61
8	88.46	87.53	88.00	85.69	104.15	88.76	84.46	81.07
9	98.46	96.76	94.15	91.84	127.38	99.53	91.84	89.07
10	107.84	106.76	105.69	106.30	134.92	107.23	100.76	99.53
11	125.87	126.46	125.23	124.76	142.92	124.30	106.46	105.53
12	137.23	136.76	136.00	135.69	145.69	138.00	121.23	119.84

The dissolution study was carried out by using USP dissolution testing apparatus II. Table 7 shows cumulative percent of drug release of formulations.

Table 7: Average cumulative percentage of drug released from F1-F8.

Time (h.)	F1	F2	F3	F4	F5	F6	F7	F8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	15.75	31.5	31.5	27	22.5	24.75	22.5	24.75
2	20.25	33.75	45	40	24.75	27	29.25	31.5
3	31.5	40.5	49.5	47.25	24.75	33.75	36	33.75
4	36	47.25	51.75	49.5	31.5	36	38	36
5	40.5	51.75	58.5	54	33.75	38.25	40	38
6	40.5	58.5	72	63	36	40.5	45	40
7	45	63	76.5	67.5	38.25	45	47	45
8	45	63	81	72	40.5	47.25	49	49
9	47.25	67	85.5	76.5	40.5	47.25	51	54
10	49.5	72	87.75	78.75	42.75	49.5	54	58
11	49.5	74	90	83.25	45	51.75	56	58.5
12	49.5	78.75	92.25	87.75	45	54	56	58.7

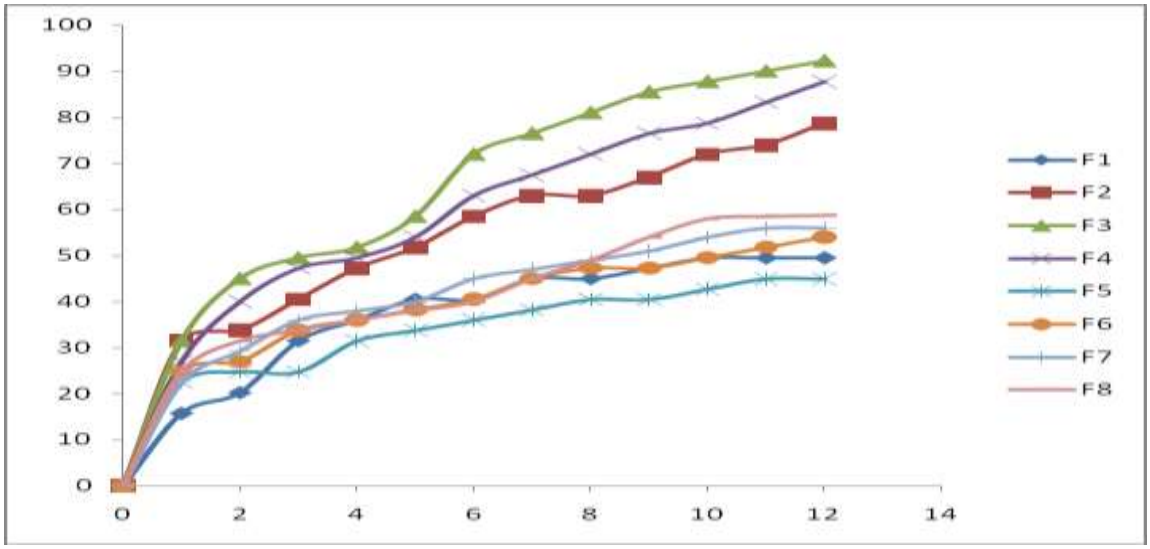

Figure 4: Cumulative percent drug release profiles of F1-F8

According to dissolution profiles of formulations, formulation F1, F5, F6, F7 and F8 showed relatively less drug release i.e. 49.5, 45, 54, 56, 58.7% respectively as high concentration of HPMC K4M and HPMC K100M was used in these formulations. The increase in HPMC K4M and HPMC K100M concentration leads to the formation of high-density polymer matrix into the tablet, which results in an increased diffusional path length and consequent retardation in drug release.

The release profiles of formulations F1, F2, F3, F4, F5, F6, F7 and F8 prepared by using HPMC K4M and HPMC K100M showed cumulative percentage drug release of 49.5, 78.75, 92.25, 87.75, 45, 54, 56, and 58.7% respectively at the end of 12 h. Drug release profiles shown in Fig. No.1. The difference in release was the result of difference in concentration of the polymers. Formulation F2, F3 and F4 yielded a faster initial release of 31.5, 31.5, and 27% respectively as it contains low viscosity polymer HPMC K4M. In vitro release profile showed on decreasing the concentration of polymer, released rate increased. In the formulation F1, F2, F4, F5, F6, F7 and F8 drug release profile is low as compared to formulation F3. The results are shown in Table 7. The drug release profile of formulations F1-F8 is given in Figure 4.

Above studies revealed that formulation F3 releases the drug at better rate than any other formulations. Formulation F3 was selected as optimized formulation and fitted to various kinetic models.

Kinetic model fitting of drug release data

The drug release data of the selected formulation (F3) was fitted to various models like zero order, first order, Higuchi's model, Hixon Crowell and Corsemeyer's model. The Kinetic model fitting of drug release data was done with the help of Microsoft excel based software PCP-Disso v2.08. The calculated slope, the intercept and R^2 are shown in Table 8. Formulation (F3) was best fitted for Higuchi's model with regression value, R^2 of 0.9935. Slope value suggested that the release of Ciprofloxacin HCl from floating tablets followed Non-Fickian or Anomalous transport mechanism.

Table 8: Drug release kinetics for selected formulation (F3)

Model	R^2	Slope	Intercept
Zero order	0.9438	6.6016	23.5631
First order	0.6732	0.0903	1.1324
Hixon Crowell	0.8180	0.5438	4.2858
Corsemeyer's-Peppa's model	0.0017	0..4455	-1.1100
Higuchi model	0.9935	0.0367	-0.072465

CONCLUSION

In the present work Gastroretentive drug delivery systems of Ciprofloxacin hydrochloride were successfully developed in the form of tablets to improve the local action and avoiding drug degradation, which reduces the wastage of drug. The release rate of the drug from the floating tablet was significantly influenced by the proportion as well as viscosity of the polymer. Floating system can improve the solubility for drugs that are less soluble in high pH environment.

In the present research work formulation F3 was found to satisfy necessary evaluation parameter and hence concluded as the optimized formulation. It can be finally concluded that such gastroretentive drug delivery system is a definite hope to improve bioavailability and patient compliance. It surely has a major future perspective.

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