

## FORMULATION DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING TABLET OF CIPROFLOXACIN HYDROCHLORIDE

MAULESH M. CHOKSHI<sup>1</sup>, MADAN MOHAN GUPTA<sup>1,2\*</sup>, MADHULIKA GUPTA<sup>3</sup>

<sup>1</sup>Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, India, <sup>2</sup>School of Pharmacy, Faculty of Medical Sciences, The University of the West Indies, St. Augustine, Trinidad and Tobago, WI, <sup>3</sup>Statistical Consultant, Aranguetz, San Juan, Trinidad & Tobago, WI  
Email: mmingupta@gmail.com

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### ABSTRACT

**Objective:** The aim of formulating floating tablets of ciprofloxacin hydrochloride was to prolong the gastric residence time after oral administration to achieve the controlled release of drug. Ciprofloxacin hydrochloride, a broad-spectrum fluoroquinolone antibacterial agent and it is use in the treatment of bone and joint infections, diarrhoeal infection, lower respiratory tract infections, urinary tract infections and meningococcal prophylaxis.

**Methods:** Floating tablets of Ciprofloxacin hydrochloride were prepared by wet granulation method using two different grades (K-100M & K-4M) of Hydroxyl Propyl Methyl Cellulose (HPMC) and Carbopol 934P using effervescent technique. Sodium bicarbonate was incorporated as a gas-generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies. The effect of citric acid on drug release profile and floating properties was also investigated.

**Results:** It was observed that tablet swelled radially and axially during *in vitro* buoyancy studies and remained buoyant for 10-14 h. The combination of sodium bicarbonate (70 mg) and citric acid (20 mg) was found to achieve the optimum *in vitro* buoyancy.

**Conclusion:** In the present work it was concluded that the floating duration of was more in tablet with HPMC K-100 as compared with formulations containing HPMC K-4M. Drug ciprofloxacin hydrochloride release could be prolonged about 14 h in the GIT by using blend of HPMC-K 100M with sodium bicarbonate as gas generating agent and formulate it as a gastro retentive floating tablet.

**Keywords:** Floating lag time, Ciprofloxacin hydrochloride, Total floating time, Hydroxyl Propyl Methyl Cellulose

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### INTRODUCTION

Gastro retentive drug delivery is an approach to prolong gastric residence time of the drug by floating the dosage form and thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects [1, 2]. Floating drug delivery systems (FDDS) is one of the important approaches to enhance gastric retention of the drug for better drug bioavailability [3]. FDDS is desirable for drugs having absorption window in the stomach or in the upper small intestine [4]. The FDDS should have a bulk density less than gastric fluids to remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly at a desired and controlled rate from the system. After the release of the drug, the residual system is emptied from the stomach. This floating drug release result in an increased gastric retention time (GRT) and a better control of the concentration drug fluctuation in blood plasma.

Ciprofloxacin hydrochloride, a broad-spectrum fluoroquinolone antibacterial agent. It is approved for use in the treatment of bone and joint infections, infectious diarrhea, lower respiratory tract infections, urinary tract infections, hospital-acquired infections and meningococcal prophylaxis [5]. Since the drug is freely soluble in water (1 g in 25 ml) and has an elimination half-life of about 4 h which is suitable to make a sustained-release dosage form aiming to enhance its antibacterial activity and provide a constant release of the drug without much fluctuation of plasma drug concentration in the blood. For the present study ciprofloxacin hydrochloride was selected due to broad spectrum and effective antibacterial agent and a drug of choice in various infections, as per the BCS classification ciprofloxacin hydrochloride is class 3 drug which is highly soluble and make it suitable for gastro retentive floating purpose and HPMC K-100 was used as polymer because of better-floating capacity.

The aim of this study was to get better drug release with less fluctuation of plasma drug concentration of ciprofloxacin

hydrochloride to the stomach, and the proximal parts of the small intestine floating tablet were prepared as compared to available dosage form and the drug release up to 12 hours with less fluctuation. This gastro retentive floating tablet increases the mean residence time (MRT) in the stomach and prolong the gastric emptying that provides the maximum drug at the site of absorption. Low viscosity hydrophilic polymer HPMC K-100 was found to be more beneficial to improving floating properties. The low concentration of hydrophilic polymer slowly forms a thick gel, which retains the integrity of the formulation and promotes drug release through thick gel which controls the burst release [6, 7]. The novelty of this work is prolonged release the drug (about 14 h) with less fluctuation and using less viscous polymer.

### MATERIALS AND METHODS

Ciprofloxacin HCl was received as a gift sample from Mars Remedies Pvt. Ltd. Vadodara, India. Hydroxypropyl methyl cellulose K-100M (HPMC K-100M) was obtained from Vishal Pharma, Vadodara, India and Carbopol 934P was received as a gift sample from Corel Pharma, Ahmedabad, India. Sodium bicarbonate and citric acid were purchased from Suvindhinath Laboratory and Harsh Pharma, Vadodara, India respectively.

#### Pre-compression parameters

##### Bulk density

Powder bulk density was determined by USP bulk density apparatus (Electrolab). It was measured by pouring the weighed granules into a measuring cylinder, and the volume was noted. It is expressed in gm/ml and is given by

$$Db = M/V_0$$

Where, M is the mass of powder, V<sub>0</sub> is the bulk volume of the powder

### Tapped density

The tapped density was measured USP bulk density apparatus (Electrolab) by tapping the drug granules of fixed mass for 50 and then 100 tapped until it reached a constant volume. It is expressed in gm/ml and is given by

$$DT = M/VT$$

Where, M is the mass of powder, VT is the tapped volume of the powder

### Carr's index

It is also known as % compressibility, and it was determined on the basis of bulk and tapped density data and given by

$$\text{Carr's Index} = (\text{Tapped density} - \text{Bulk density}) / \text{Tapped density} \times 100$$

### Hausner's ratio

It was calculated on the basis of bulk and tapped density data and given by

Tapped density/bulk density

### Preparation of floating matrix tablet

Different tablet formulations (table 1) were prepared by wet granulation technique. The required quantity of drug, polymer and filler were passed through 40 number sieves. The required quantity of PVP K-30 was dissolved in Isopropyl alcohol (IPA) to prepare a binder solution. The binder solution was added to the dry blend with constant kneading to form a homogeneous mass. After enough cohesiveness had been obtained, the granules were allowed to dry at 50°C for 15 min. Then granules were passed through 20 number sieves. Talc and magnesium stearate were finally added as glidant and lubricant respectively. The granules were compressed using double rotary tablet compression machine (Cad mach, India CMB4-35 stations) [8-11].

In order to evaluate the best matrix forming a polymer, different formulations of floating tablets were prepared by using HPMC K-4M (batches C1-C3), HPMC K-100M (batches C4-C6), Carbopol 934P (batches C7-C9), in 100, 125 and 150 mg amount and these were evaluated.

**Table 1: Formulation compositions of ciprofloxacin HCl floating tablets**

Ingredients	C1 (mg)	C2 (mg)	C3 (mg)	C4 (mg)	C5 (mg)	C6 (mg)	C7 (mg)	C8 (mg)	C9 (mg)
Ciprofloxacin HCl	582	582	582	582	582	582	582	582	582
HPMC K-4M	100	125	150	-	-	-	-	-	-
HPMC K-100M	-	-	-	100	125	150	-	-	-
Carbopol-934P	-	-	-	-	-	-	100	125	150
Sodium bicarbonate	75	75	75	75	75	75	75	75	75
Citric acid	20	20	20	20	20	20	20	20	20
PVP-K30	15	15	15	15	15	15	15	15	15
Isopropyl alcohol	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Lactose	94	69	44	94	69	44	94	69	44
Magnesium stearate	7	7	7	7	7	7	7	7	7
Talc	7	7	7	7	7	7	7	7	7
Total wt.	900	900	900	900	900	900	900	900	900

q. s.= Quantity sufficient, C1-C9 is the formulation codes

### Post-compression parameters

#### Weight variation test

Randomly twenty tablets of the formulation were selected and weighed using a Sartorius electronic balance and the test was performed according to the Indian Pharmacopoeia official method. Determinations were made in triplicate.

#### Hardness

The hardness of five tablets was determined using the Monsanto hardness tester and the average values were calculated. Determinations were made in triplicate.

#### Friability

The friability of the tablets was measured in a Roche friabilator. Randomly 20 tablets were selected and weighed ( $W_0$ ). After 100 revolutions (speed-25 RPM), the sample of 20 tablets was de-dusted and weighed ( $W$ ) again. Percentage friability was calculated from the loss in weight as per the given in equation below. Determinations were made in triplicate.

$$\% \text{ Friability} = \frac{W_0 - W}{W_0} \times 100$$

#### Drug assay

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (900 mg) was extracted in 100 ml of 0.1N HCl. The solution was filtered through 0.45µ membrane. The drug content was determined by UV-Visible

Spectrophotometer (Shimadzu UV-1800) at a wavelength of 276 nm after making suitable dilution with 0.1 N HCl [12].

#### In-vitro buoyancy study

The *in vitro* buoyancy was determined by floating lag time method [13]. 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.

#### In-vitro dissolution studies

The release rate of ciprofloxacin hydrochloride from floating tablets was determined using The United States Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 °C and 50 RPM. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at an interval of 1, 2, 3, 4, 6, 8, 10, 12, 14 h and the samples were replaced with fresh dissolution medium maintained at 37 °C. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable concentration with 0.1N HCl. The absorbance of these solutions was measured at 276 nm using UV-Visible Spectrophotometer (Shimadzu UV-1800). Cumulative percentage of drug release was calculated using the equation obtained from a standard curve [14-18].

#### Accelerated stability study

Ciprofloxacin hydrochloride gastro retentive tablets of batch C4 were packed in blister packing, and this packed tablet was kept for three months for the accelerated stability study at 40 °C and 75% RH. Periodically (0, 1, 2 and 3 mo interval) samples were removed and characterized by *in-vitro* drug release study and floating lag time.

**RESULTS**

The result of pre-compression parameters for the ciprofloxacin granules was recorded in table 2 and it was found that the angle of

repose of all batches except C8 is less than 30°. The bulk density of powder blend was found in the range of 0.1486-0.1683 g/ml. The value Carr's index was in the range of 14.68-18.86 and Hausner's ratio was in the range of 1.17-1.23.

**Table 2: Flow properties of ciprofloxacin HCl powder blend**

Batch	Loose bulk density (g/ml)	Tapped bulk density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
C <sub>1</sub>	0.1660	0.1990	16.55	1.19	29.68
C <sub>2</sub>	0.1584	0.1866	15.13	1.17	28.34
C <sub>3</sub>	0.1616	0.1957	17.44	1.21	28.67
C <sub>4</sub>	0.1563	0.1838	14.93	1.17	27.68
C <sub>5</sub>	0.1486	0.1783	16.66	1.20	28.01
C <sub>6</sub>	0.1514	0.1866	18.86	1.23	25.98
C <sub>7</sub>	0.1649	0.1990	17.12	1.20	29.68
C <sub>8</sub>	0.1594	0.1957	18.54	1.22	30.13
C <sub>9</sub>	0.1683	0.1973	14.68	1.17	28.56

\*n=3, Average of three determinations for loose bulk density, tapped bulk density, angle of repose, carr's index and hausner's ratio

The pre-compression parameters like angle of repose of all batches is less than 30° which shows that powder blend had good flow and suitable for tablet compression as well as the Carr's index values are in the range of good flow and all these shows that powder blend is good for tablet compression.

The post-compression parameters like weight variation test, hardness, friability, drug assay, *in-vitro* buoyancy study (floating time and floating leg time) data of batches C<sub>1</sub> to C<sub>9</sub> were recorded in table 3. The variation weight results varies between 899.6-904 mg, the hardness was found between 4.1 to 5.1 kg/cm<sup>2</sup>, the friability of all batches were less than 1% and the drug assay of all batches were

remained in the range 90-110%. The results of post-compression parameters (quality control evaluation) of a powder blend of all the formulation batches (C<sub>1</sub>-C<sub>9</sub>) were under the pharmacopeial limits which show that formulation development is good for further reproduction.

The floating leg time varies between 39-66 s and floating time varies between 10-14 h. When floating times was compared, it was found that C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub> having 14 h which is good for prolongation of drug release so on the basis of drug assay and floating time C<sub>4</sub> and C<sub>6</sub> batches were good and selected as optimum batches.

**Table 3: Post compression evaluation of ciprofloxacin HCl tablet**

Batch	Avg. weight	% Friability	Hardness (kg/cm <sup>2</sup> )	Drug assay (%)	Floating lag time (s)	Floating time(h)
C <sub>1</sub>	901.1±4.19	0.442±0.004	4.1±0.12	98.2±2.9	35±0.943	10±0.029
C <sub>2</sub>	903.5±5.548	0.551±0.017	4.4±0.05	101.6±2.6	41±0.471	12±0.081
C <sub>3</sub>	904±5.160	0.495±0.021	5.0±0.15	94.8±1.8	39±0.471	12±0.061
C <sub>4</sub>	902.2±5.125	0.444±0.016	4.5±0.43	101.3±1.9	47±1.414	14±0.032
C <sub>5</sub>	901.65±5.733	0.386±0.012	4.4±0.05	98±3.1	42±0.943	14±0.043
C <sub>6</sub>	900±4.180	0.605±0.043	5.0±0.15	101.1±1.9	49±0.942	14±0.067
C <sub>7</sub>	901.65±5.527	0.663±0.020	4.9±0.19	96.6±2.3	62±0.816	12±0.069
C <sub>8</sub>	900.6±4.816	0.606±0.016	4.8±0.09	98.4±2.7	59±0.471	13±0.035
C <sub>9</sub>	899.6±5.164	0.549±0.022	5.1±0.21	98.4±1.4	66±0.943	13±0.071

\*n=3, Average of three determinations for hardness, floating leg time, floating time Water absorption ratio, drug assay, friability, weight variation n=20. Sample size for friability and weight variation was 20

**Table 4: *In-vitro* drug release study of ciprofloxacin HCl tablets from different batches**

Time (h)	Cumulative % drug release								
	C <sub>1</sub>	C <sub>2</sub>	C <sub>3</sub>	C <sub>4</sub>	C <sub>5</sub>	C <sub>6</sub>	C <sub>7</sub>	C <sub>8</sub>	C <sub>9</sub>
0	0	0	0	0	0	0	0	0	0
1	21.10	19.20	17.20	21.30	13.90	12.10	10.10	9.10	7.60
2	39.20	23.40	24.60	23.80	16.00	18.20	18.00	16.00	14.10
3	46.10	29.10	35.10	29.20	20.20	25.12	26.32	21.45	19.30
4	58.40	34.20	44.20	31.14	25.30	29.10	32.57	28.14	26.34
6	68.30	41.20	49.20	39.50	33.26	35.10	39.00	33.65	31.40
8	80.00	55.50	57.90	48.90	45.30	40.20	42.13	38.00	34.30
10	100.20	88.00	87.40	64.00	69.30	64.00	54.64	53.36	54.28
12	-	90.70	89.30	81.70	73.10	80.20	65.00	61.03	62.10
14	-	-	-	98.50	89.10	86.14	75.23	73.13	70.41

\* n=3, Average of three determinations

The floating leg time varies between 39-66 s and floating time is up to 14 h both are significantly good for floating drug delivery system as well as better as compare to other available formulations [19]. The floating tablet will be retain in the GIT for the long time (about 14 Hour) with less drug plasma concentration fluctuation and deliver the drug for prolong period.

The *In-vitro* dissolution study of all batches (C<sub>1</sub>-C<sub>9</sub>) was performed in 0.1 N HCl and the data were recorded in the table 4. The batch C<sub>1</sub> released 100.2% of drug but the entire drug is released in 10 hour whereas in the case of batch C<sub>4</sub> of 98.5 % drug release in 14 h which is good for prolongation of drug release means tablet will be float for 14 h and will release the drug in controlled manner so batch C<sub>4</sub> was

selected as an optimum batch for the stability study to confirm the stability of the floating tablet of ciprofloxacin hydrochloride.

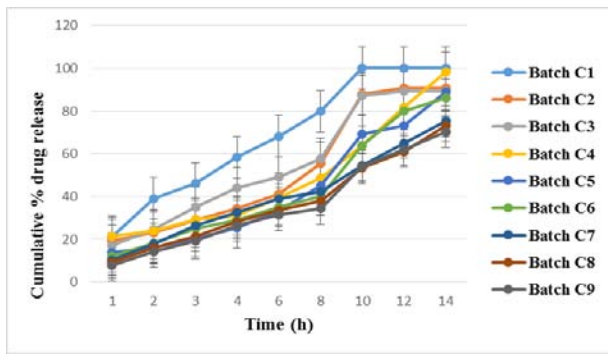


Fig. 1: *In-vitro* drug release of ciprofloxacin HCl tablets from different batches

\*\* n=3, Average of three determinations

The drug release from the all the formulation batches varies between 70-100 % and out of which batch C4 was selected as an optimized batch because as per the requirement for better release as compared to other available research [19] this batch releases the drug about 100% and up to 14 h which indicated long floating with less plasma drug concentration fluctuations.

Tablets containing different matrix forming agents (HPMC K-4M, HPMC K-100M and Carbopol 934 P) were prepared as per the formulation composition is given in table 1. The batches coded as C<sub>1</sub> to C<sub>9</sub> having 100, 125, 150 mg of HPMC K-4M, HPMC K-100M, and carbopol 934P respectively. In the case of HPMC K-4M, tablet prepared by using 100 mg of polymer almost 100% drug release at 10h whereas in 125 and 150 mg of polymer, 90% of drug release within 12 h but it fail to retard drug release after 12 h and the tablet loss its integrity. In the case of HPMC K-100M, 98.5 % of drug release at 14 h when the polymer is 100 mg, and the tablet retains its integrity whereas with carbopol 934P the drug release rate was found more retarded and carbopol has a negative effect on floating.

The concentration of HPMC K-100 M was 13.88% in the optimum powder blend which can float the tablet for 14 h. The effect of different concentration of sodium bicarbonate was checked, and the concentration was optimized to 8.33 %. Batch C<sub>4</sub> with 8.33 % of sodium bicarbonate shows a floating lag time of 47 s, floating time of 14 h and drug release up to 98.5% all these results show that batch C<sub>4</sub> is good because it is having good floating time and release the drug for a long time. After optimization, the formulation was kept for stability study.

In the formulations it was observed that carbopol has a high affinity towards water and promotes water penetration into tablet matrices increases the density which ultimately decrease the floating time that is not suitable for floating tablet so the formulation batches those are having carbopol were excluded, and only the formulation which is having HPMC K-100M with 100 mg polymer (13.88%) was selected for further study. The optimized formulation batch (C<sub>4</sub>) which is having floating time around 14 h and releases drug about 98 % gives a clear indication about the good formula for better floating in the GIT. The accelerated stability study of optimizing batch C<sub>4</sub> was conducted, and the *In-vitro* drug release study data were recorded in table 5 and expressed by fig. 2. The floating lag time data were recorded in table 6.

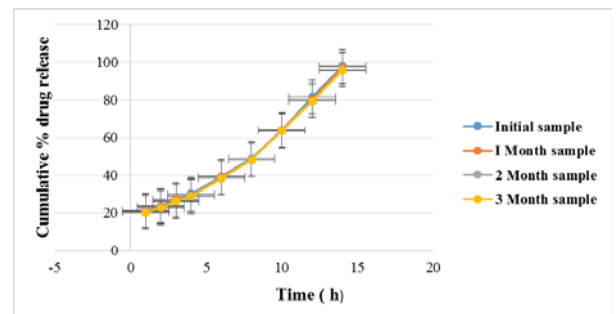


Fig. 2: *In-vitro* drug release study of ciprofloxacin HCl tablets from batch C4 (stability study batch)

\*\* n=3, Average of three determinations

Table 5: *In-vitro* drug release study of ciprofloxacin HCl tablets from batch C4 (stability study batch)

Time (h)	Outer appearance	Cumulative % drug release			
		Initial sample	1 Mo sample	2 Mo sample	3 Mo sample
0	White tablet	0	0	0	0
1	White tablet	21.30	21.10	20.80	20.10
2	White tablet	23.80	23.40	23.10	22.50
3	White tablet	27.20	27.20	26.50	26.10
4	White tablet	30.10	29.20	29.20	28.70
6	White tablet	39.40	39.10	38.40	38.40
8	White tablet	48.90	48.20	48.10	48.10
10	White tablet	64.00	64.10	64.10	63.60
12	White tablet	81.70	80.30	79.30	79.30
14	White tablet	98.10	97.50	96.30	95.80

\* n=3, Average of three determinations

Table 6: Floating leg time of batch C4 tablets (stability study)

Time duration	Floating leg time (s)
Initial	47
1 Mo	49
2 Mo	50
3 Mo	53

\*n=3, Average of three determinations

The *in-vitro* drug release profile of stability batches are same (about 98%) as compared to before stability which indicates that there was

no significant change in the dissolution profile which proves the reproducibility and stability of the formulation.

**CONCLUSION**

This research was concluded that drug ciprofloxacin hydrochloride release could be prolonged in the GIT by using a blend of HPMC-K 100M with sodium bicarbonate as gas generating agent and formulate it as a gastro-retentive floating tablet. This formulation could provide desired floating lag time and floating time along with the good drug release profile.

**CONFLICT OF INTERESTS**

Declare none

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