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FORMULATION AND EVALUATION OF A HYDRODYNAMICALLY BALANCED GASTRORETENTIVE DRUG DELIVERY SYSTEM INCORPORATING CIPROFLOXACIN HYDROCHLORIDE

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ABSTRACT
Drugs that have narrow absorption window in the gastrointestinal tract (GIT) will have poor absorption. For these drugs, gastroretentive drug delivery systems offer the advantage in prolonging the gastric emptying time. The present investigation concerns the development of hydrodynamically balanced tablets of Ciprofloxacin Hydrochloride,are designed to prolong the gastric residence time after oral administration and thereby increasing drug bioavailability. Floating tablets of Ciprofloxacin HCl were prepared by direct compression using HPMC K4M and HPMC K15M as polymers along with Sodium bicarbonate as gas generating agent. The tablets were evaluated for in- vitro buoyancy, dissolution studies and physical characteristic viz.Density, Hardness, Friability, Thickness and Weight variation. Further, tablets were evaluated for in-vitro release characteristic for 12 hrs. It is found that the hardness of the tablets affects the Buoyancy characteristic of the dosage form. All formulations possessed good floating properties with total floating time more than 12 hrs. The in-vitro release studiesindicated that the floating tablets of Ciprofloxacin HCl containing 200mg HPMC K15M (F4) showed sustained release when compared with the other formulation batches and provides a better option for controlled release action and improved bioavailability.

KEYWORDS: Ciprofloxacin hydrochloride, gastroretentive, HPMC, in vitro studies.

1. INTRODUCTION
Oral sustained release dosage forms deliver the drug for longer period and helps in producing the therapeutic effect for 24 h for those drugs which are having low plasma half life. Drugs that have narrow absorption window in the gastro intestinal tract (GIT) will have poor absorption.[1,2] For these drugs, gastroretentive drug delivery systems (GRDDSs) have been developed. Oral sustained release dosage form with prolonged residence time in the stomach helps in absorption of the drugs which are less soluble or unstable in the alkaline pH and those which are absorbed from the upper gastrointestinal tract.[3] GRDDSs help in maintenance of constant therapeutic levels for prolonged periods and produce therapeutic efficacy and thereby reduce the total dose of administration. Recently several gastroretentive approaches like swelling devices,[4,5] floating systems,[6] bioadhesive systems,[7] low density systems,[8] high density systems,[9] expandable systems,[10] super porous, biodegradable hydrogels,[11,12] and magnetic systems,[13] have been developed. To increase the gastric retention time (GRT), one should have a thorough knowledge about the physiology of GIT, and all the limitations should be well understood. To justify the in vitro studies, in vivo studies must be conducted.

The excellent floating system is effective only in the presence of sufficient fluid in the stomach; otherwise, buoyancy of the tablet may be hindered. This limitation can be overcomeby using a combination of a floating system with other gastroretentive approaches.[14] GRDDSs are formulated as floating microparticles, tablets, pellets, capsules, etc. among which the multiparticulate systems are more effective than the single unit dosage forms.[15,16] Ciprofloxacin hydrochloride, a broad-spectrum fluroquinolones antibacterial agent is moreabsorbed from the stomach and the proximal part of the small intestine.[17] Oral bioavailability is about 70% and reaches the peak plasma concentration to 2.5 μg/ml in 1 to 2h after administration of 500 mg. As the tablet passes down the GIT, the decrease absorption is the draw back with sustained release dosage form of ciprofloxacin hydrochloride. The extended release formulation of ciprofloxacin HCl (Cipro XR and Proquin XR) is used for complicated and uncomplicated urinary tract infections (UTIs).[18,19] Ciprofloxacin HClextended release (500 mg once daily) shows higher plasma concentration than the immediate

release (200 mg twice daily) formulation. The bioavailability is lower if Proquin XR tablets are given while fasting.[19]

The present study outlines a systematic approach for design and development of gastroretentive drug delivery system of Ciprofloxacin Hydrochloride using polymers such as HPMC K4M, HPMC K15M, which increases the gastric residence time, decreases the diffusion distance and allow more of the antibiotic to penetrate through the gastric mucus layer and act locally at the infectious site to enhance the bioavailability and therapeutic efficacy of the drug.[20] Formulations were evaluated invitro for its buoyancy, dissolution, physical characteristic viz. Density, Hardness, Friability, Thickness and Weight variation. Further, tablets were evaluated for in-vitro release characteristics in comparison to marketed product and effect of hardness on floating lag time.

2. MATERIALS AND METHODS

Ciprofloxacin Hydrochloride was obtained from FDC Ltd. Goa; HPMC K4M, HPMC K15M were obtained from S.D.Fine Chemicals Ltd. Mumbai. Lactose, Polyvinylpyrolidone (PVP) was supplied by Nice Chemicals Pvt. Ltd., Bangalore, India. Sodium bicarbonate, Talc and Magnesium stearate was supplied by Loba Chemie Pvt. Ltd., Mumbai, Maharashtra, India. Hydrochloric Acid was supplied by S.D. Fine Chem. Ltd., Mumbai, Maharashtra, India. All other reagents and solvents used were of analytical grade.[21]

Formulation of Floating Tablet of Ciprofloxacin HCl

Floating matrix tablets containing Ciprofloxacin Hydrochloride were prepared by direct compression method using variable concentrations of HPMC K4M, HPMC K15M with sodium bicarbonate. Accurate quantity of drug, HPMC K4M, HPMC K15M for each formulation (F1 to F6) was calculated, which was shown in Table 1. All the ingredients except magnesium stearate and talc were mixed well using mortar and pestle uniformly and passed through sieve No.60 and mixed with Magnesium stearate and talc. Powders obtained were compressed with 9mm concave punches to obtain tablets (Mini Press I, Karnavati Engineering Ltd., Mumbai). The weights of the tablets were kept constant for all formulations(F1 to F6).

Table 1: Composition of Floating Tablets of Ciprofloxacin Hydrochloride.

Ingredients (in mg)	F1	F2	F3	F4	F5	F6
Ciprofloxacin HCl	500	500	500	500	500	500
HPMC K4M	200	300	400	-	-	-
HPMC K100M	-	-	-	200	300	400
Lactose	15	15	15	15	15	15
Sodium Bicarbonate	50	50	50	50	50	50
Talc	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10
PVP	75	75	75	75	75	75

Evaluation of Ciprofloxacin HCl floating tablets

Physical evaluation

The formulated floating tablets of Ciprofloxacin HCl were evaluated for physical characteristic viz. Density, Diameter, Thickness, Hardness, Weight variation, Friability and Drug content uniformity.[22-23]

Floating Evaluation

The formulated Ciprofloxacin HCl floating tablets were evaluated for Buoyancy lag time, total floating time, and effect of hardness on Buoyancy Lag Time.

In-vitro Drug release studies

The standard calibration curve of Ciprofloxacin Hydrochloride was plotted by plotting absorbance values against concentration (µg/ml). In-vitro drug release studies of the prepared floating tablets of Ciprofloxacin were conducted for a period of 12 hrs using USP XXIII type II apparatus at 37± 0.5°C and at 50 rpm speed in 900ml of 0.1N HCl (pH 1.2). After withdrawing at predetermined time intervals for 12 hours, the samples were analyzed by a UV Spectrophotometer (Shimadzu, UV 1601) at 262 nm using dissolution medium in reference cell. The percent drug release was calculated and compared.

Drug Release Kinetics Study

Drug release kinetics study was performed with obtained data of in vitro drug release as applied to various pharmacokinetic modes. The statistics obtained was treated accordingly and concluded to understand the mechanism of drug release from the formulated floating typedosage form.

3. RESULTS AND DISCUSSION

Physical evaluation, Drug content uniformity

The formulated floating tablets of Ciprofloxacin were evaluated for Density, Diameter, thickness, hardness, friability, weight variation and Drug content uniformity for all the batches. The density for the all formulations range between 0.82 to 0.99 g/cm^3. The diameter of all tablets range between 9.05 mm to 9.09 mm. Tablets mean thickness were uniform in F1 to F6 formulations and found to be in the range of 5.12 mm to 5.18 mm. The hardness of tablets of each batch ranged between 4.5 to 9.1 kg/cm^2, which ensures good handling characteristics of all batches. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. All the formulated (F1 to F6) tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±5% of

the weight. The percentage of drug content for F1 to F6 was found to be 97.00% to 99.50% of Ciprofloxacin, which complies with official specifications. All values are expressed as mean ± SD (n=3) and the results are shown in Table 2.

Table 2: Physical Properties of Tablets of Batch F1 to F6.

Batch	Diameter(mm)	TabletDensity (g/cc)	Thickness(mm)	Hardness (Kg/cm2)	Friability(%)	Weight Variation (mg)	Content uniformity(mg)
F1	9.09±0.070	0.93±0.30	5.15±0.010	4.5±0.45	0.96±0.040	860.65 ±1.20	97.00
F2	9.08±0.060	0.82±0.40	5.14±0.012	5.2±0.30	0.72±0.055	961.50 ±1.75	99.50
F3	9.09±0.035	0.89±0.20	5.12 ±0.060	7.2±0.50	0.91±0.070	1060.55 ±1.15	98.65
F4	9.08±0.010	0.99±0.60	5.16±0.011	8.0±0.40	0.86±0.050	860.05 ±1.35	97.40
F5	9.08±0.070	0.97±0.44	5.18±0.012	9.1±0.35	0.79±0.050	960.65 ±1.40	98.50
F6	9.05±0.040	0.96±0.70	5.17±0.010	9.0±0.30	0.79±0.040	1060.80±1.25	97.10

Evaluation of floating properties

Prepared floating tablets of Ciprofloxacin were evaluated for its floating behavior such as Buoyancy lag time, total floating time. Formulations had shown floating lag time in the range of 32-68 sec, and total floating time more than 12 hr. The results were shown in Table 3.

Table 3: Floating properties like Buoyancy Lag Time, Total Floating Time of F1 to F6.

Batch	Buoyancy Lag Time (Sec)	Total Floating Time (hrs)
F1	32	>12
F2	65	>12
F3	24	>12
F4	40	>12
F5	62	>12
F6	45	>12

Effect of hardness on Buoyancy Lag Time

The formulation F4 was evaluated for effect of hardness on buoyancy/ floating lag time, since it had sustained activity and good buoyancy lag time (40 sec). The results of floating lag time of tablets with hardness of 4 kg/ cm^2 ,5kg/ cm^2, 7kg/ cm^2 and 8 kg/ cm^2 were 49,68,97and 146 sec respectively and the results were shown Table 4. Batch F4 was selected for the study because it showed buoyancy lag time of 146 sec at maximum hardness of 8kg/cm^2. The results showed that the floating lag time increased as hardness increased.

Table 4: Effect of Hardness on Buoyancy Lag Time of Batch F4.

Hardness in Kg/cm^2	Buoyancy Lag Time (sec)
4	49
5	68
7	97
8	146

***In-vitro* dissolution study of Ciprofloxacin floating tablets**

In-vitro drug release studies of the all formulations of prepared floating tablets were conducted for a period of 12 hrs using USP XXIII type II apparatus at 37± 0.5°C & 0.1N Hydrochloric acid (simulated gastric fluid, pH 1.2). Results of in vitro drug release studies are illustrated in Table 5. Results were plotted as percent drug released V/s time, was shown in Figure 1.

Table 5: *In vitro* drug release studies of Formulations F1 to F6.

Time (Hrs)	Percent drug release of Formulations F1 to F6					
	F1	F2	F3	F4	F5	F6
1	24.45	22.38	20.25	20.30	18.80	16.60
2	46.10	38.05	35.50	24.65	22.50	20.80
3	59.25	58.32	54.66	36.15	26.60	24.68
4	68.35	64.15	61.35	50.95	35.00	29.85
5	75.10	72.36	68.00	58.70	46.10	35.62
6	80.40	76.90	72.68	66.60	55.25	41.40
7	87.95	82.55	77.75	69.25	62.85	49.50
8	93.64	88.80	81.20	75.40	66.90	55.60
9	95.68	91.25	86.50	79.20	69.30	62.75

10	96.45	94.72	90.10	83.55	72.48	67.54
11	96.90	93.60	92.60	86.35	73.50	71.85
12	97.20	96.54	95.47	88.42	75.50	74.56

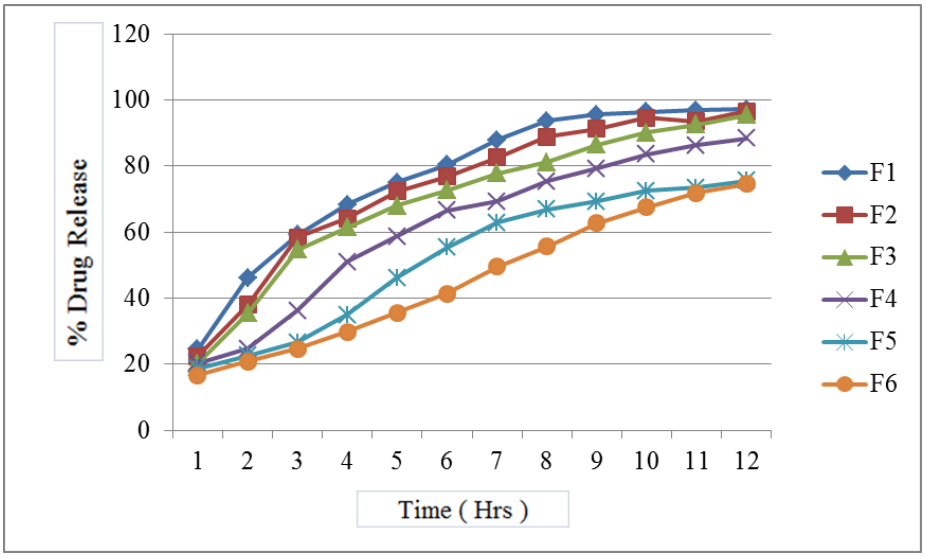

Fig. 1: *In-Vitro* Dissolution Profile for Tablets of Batches F1 to F6.

From the in-vitro dissolution data it was found that formulation F1, F2 and F3 containing HPMC K4M released 97.2%, 96.54% and 95.47% of drug within 12 hr of the study indicating that the polymer amount is not sufficient to control the drug release. F4, F5 and F6 containing HPMC K15M released 88.42%, 75.50% and 74.56% of drug within 12 hr. So, the results indicate that Hydrodynamically Balanced Tablets of Ciprofloxacin HCl containing only HPMC polymer showed good Buoyancy lag time (BLT) and Total floating time (TFT). Formulation F4 containing 200mg HPMC K15M showed good BLT of 40 sec, while the formulation containing HPMC K15M alone showed highest BLT and TFT of more than12 hrs. This may be due to the amount of polymer and gas generating agent, which were kept constant in the present study. The gas generated cannot be entrapped inside the gelatinous layer, and its escape leading to variation in BLT and TFT. So, F4 provides a better option for Controlled release action and improved bioavailability than the other formulations (F1-F6). It concludes that the F4 had better controlled release than other formulations of Ciprofloxacin Hydrochloride and is the optimized batch.

Drug Release Kinetics

The release kinetics of Ciprofloxacin HCl floating tablet followed Higuchi model. To understand the mechanism of release of Ciprofloxacin HCl from the floating tablet the drug release data was fit into Higuchi model and it showed the highest regression coefficient values for Higuchi model, indicating diffusion to be the predominant mechanism of drug release. The graph as in figure 2 was plotted between cumulative percent release and square root of time. The regression value for drug release profile of formulation F4 was found to be 0.983, other formulations values as in table 6. These indicate that, diffusion is the mechanism of drug release from the system.

Table 6: Drug release kinetics parameters of Formulation F4.

Kinetics Model	Regression value (R^2)
Zero order	0.973
First order	0.748
Hixon order	0.958
Korsemeyer Pappas	0.260
Higuchi plot	0.983
Best model	Higuchi model

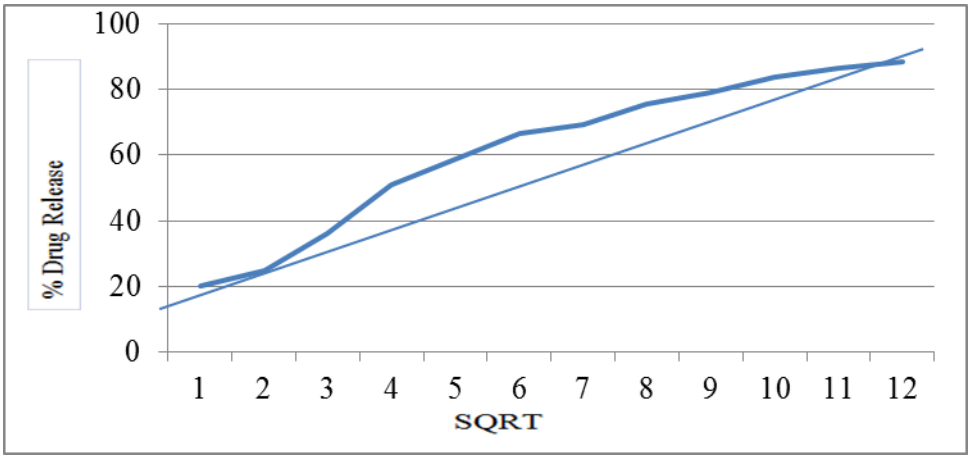

Fig. 2: Higuchi plot of Formulation F4.

4. CONCLUSION

The principle of hydrodynamically balanced controlled drug delivery systems offers a suitable and practical approach to obtain controlled release of Ciprofloxacin with enhanced bioavailability and reduced dosing frequency. The ciprofloxacin floating tablets were prepared by using polymers such as HPMC K4M, HPMC K15M. Formulations were evaluated for floating behaviour, which showed floating lag time in the range of 32-65 sec, and total floating time more than 12hr. *In-vitro* drug release study was performed in simulated gastric fluid (1.2 pH), the optimized batch (F4) shows drug release in a controlled manner for 12 hr. From results, it concludes that the floating lag time increased as hardness increased and F4 had better controlled release than the other formulations (F1-F6). Formulation F4 followed diffusion mediated drug release which was proved by applying drug release kinetics study; resulted that best suited model of drug release mechanism is Higuchi's model. So, formulation F4 provides a better option for Controlled release action and improved bioavailability of Ciprofloxacin Hydrochloride.

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