ORIGINAL ARTICLE

Formulation Development and *In-vitro* Evaluation of Floating Tablets of Ciprofloxacin HCl

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Abstract

Aim: In the present investigation, the hydrodynamically balanced tablets of Ciprofloxacin (CPF) HCl were prepared by direct compression method. **Materials and Methods:** CPF HCl floating tablets were formulated using various viscosity grades of hydroxypropyl methyl cellulose (HPMC) and sodium bicarbonate as a gas generating agent. **Results and Discussion:** The prepared CPF HCl tablets were evaluated for weight variation, hardness, friability, drug content, tablet density, floating test, swelling index, *in-vitro* drug release, stability studies, and showed satisfactory results. Formulations F2, F5, F6 and F7 were showed satisfactory drug release of 91.38%, 90.66%, 94.65% and 95.10%, respectively, for 10 h and those formulations were selected for further studies. **Conclusion:** From the kinetic studies, it was confirmed that the drug release from its dosage forms (F2, F5, F6, and F7) follows non-Fickian diffusion. Stability studies indicated that the suitable temperature for storage of CPF HCl tablets was refrigerator temperature (2-8°C).

Key words: Direct compression method, floating system, hydrodynamically balanced system, hydroxy propyl methyl cellulose, sodium bicarbonate

INTRODUCTION

Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance, and flexibility in formulation.[1] Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over the drug delivery.[2] These systems achieve and maintain drug concentration within the therapeutic level needed for the better treatment when taken several times a day. It causes significant fluctuations in drug level occurs and to overcome these demerits, nowadays most of the pharmaceutical scientists are involved in developing an ideal drug delivery systems (IDDS). An IDDS should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period.[3,4] Controlled release drug delivery systems provide drug release at a predetermined, predictable rate and optimize the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dosing.[2,4]

A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract (GIT), and some drugs are absorbed only in a particular portion of GIT or absorbed to a different extent in various segments of the GIT. The pH dependent solubility and stability levels of a drug play an important role in its absorption.[2] In the case of the drug Ciprofloxacin (CPF) HCl, it has a narrow absorption window[5] and mainly

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Received: 27-07-2016
Revised: 12-08-2016
Accepted: 25-08-2016

absorbed in the proximal areas of GIT.[5] Therefore, the researchers were developed certain gastroretentive systems of CPF HCl such as floating systems,[6,7] bio/mucoadhesive systems,[6,8] swelling and expanding systems,[9] high density systems,[10] ion exchange resins,[11] incorporation of passage delaying food agents,[12] low density systems,[13] raft systems,[14] biodegradable hydrogels,[15] and magnetic systems.[16] The floating drug delivery is developed for the drugs which have narrow absorption window, primarily absorbs and acts locally in the stomach, poor solubility in alkaline pH and unstable at the colonic and intestinal environment.[17] CPF, i.e., 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride monohydrate belonging to the family of quinolones (term refers to potent chemotherapeutic antibacterial agents).[18] CPF is a broad-spectrum antibiotic active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a Type II topoisomerase and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division and also affects mammalian cell replication.[19] It is used in the treatment of infections such as lower respiratory tract, urinary tract, bone and joint infections, hospital acquired infections, and diarrheal infections.[20]

In this study, floating tablets of CPF were prepared by direct compression method using different viscosity grades of hydroxypropyl methylcellulose (HPMC) and sodium bicarbonate (SBC) as a gas generating agent. The scope of this work was to evaluate the effect of SBC on buoyancy and effect of different grades of HPMC on drug release.

MATERIALS AND METHODS

Materials

CPF HCl was purchased from Sreepathi Pharmaceuticals Ltd., India, and HPMC (K100M, K4M, E50), SBC, Talc, and magnesium stearate (MS) were obtained from Taian Ruitai Cellulose Co., Ltd., China, Avantor Performance Materials Ltd., India, Golcha Group, India, and Loba Chemie Pvt. Ltd., India, respectively, and remaining chemicals used were analytical grade.

Fourier transform infrared (FTIR) studies

The compatibility of the drug and polymer under experimental conditions is an important prerequisite before the development of new formulation. It is necessary to confirm that the drug does not react with the polymer and affect the shelf life of the product. This can be confirmed by FTIR studies (Perkin Elmer IR spectrophotometer, North America). In this study, potassium bromide disc (pellet) method was employed, and the obtained IR spectra were compared with the reference spectrum of CPF HCl.

Preparation of floating tablets of CPF HCl

Floating tablets of CPF HCl were prepared by direct compression technique using varying ratios of polymers such as different grades of HPMC (K100M, K4M, and E50) with SBC as gas generating agent. Different grades of HPMC were used in the ratios of 1:2:3, 1:3:2, 1:1:1, 2:1:3, 2:3:1, 3:1:2, 3:2:1 with respect to the formulations F1, F2, F3, F4, F5, F6 and F7, respectively. CPF HCl was sifted by passing through the sieve No. 20, HPMC K100M, HPMC K4M, HPMC E50, SBC through the sieve No. 40, Talc and MS were passed through the sieve No. 60 and collected. CPF HCl was geometrically mixed with HPMC K100M, HPMC K4M, HPMC E50 and SBC for 10 min followed by the talc was added and further mixed for 5 min. After sufficient mixing of powder blend, SBC was added and further mixed for additional 2 min. Then, this lubricated mixture was compressed by RIMEK 10 stationary Rotary tablet punching machine. The weight of the tablet was kept constant (730 mg) for all the formulations [Table 1].

Precompression evaluation studies

These studies were aimed to know the flow properties of powder blend and the blend was analyzed to know the bulk and tapped density,[21] angle of repose,[22] Hausner's ratio, and Carr's index[23] according to the standard procedures.

Postcompression evaluation studies

The manufactured tablets were subjected to appearance, weight variation, thickness, hardness, friability, drug content,[24] tablet density,[25] floating time,[26] and swelling index[27] according to the standard procedure.

In-vitro dissolution study

It was performed by Electro Lab TDT-06N USP dissolution apparatus Type-II (paddle method) using 0.1 N HCl buffer at 37 ± 0.5°C and rotated at 50 rpm. One tablet was placed in each of the six dissolution vessels, and the system was run. Aliquots of samples were withdrawn at specific intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10 h), and the same volume of fresh dissolution medium was replaced to maintain the original volume. The withdrawn aliquots were filtered, suitably diluted with 0.1 N HCl to obtain the concentration of 10 µg/ml and its absorbance measured spectrophotometrically at 276 nm to determine the drug release.

Release kinetics study

The data obtained from *in-vitro* dissolution studies was subjected to zero order, first order, Higuchi, and Korsmeyer-Peppas models to determine the release kinetics and mechanism of drug release from the optimized formulations.[27]

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing was to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage and packing conditions. The prepared floating tablets of CPF HCl were placed in plastic tubes containing desiccant and stored at ambient humidity conditions, at room temperature, oven temperature (40 ± 2°C) and in refrigerator (2-8°C) for 60 days. The samples kept for stability studies were evaluated for hardness, friability, floating time, drug content and *in-vitro* dissolution studies after 15, 30, 45 and 60 days for selected formulations F2, F5, F6 and F7.[28]

RESULTS AND DISCUSSION

Hydrodynamically balanced tablets of CPF HCl were prepared and evaluated for their use as gastroretentive drug delivery systems to increase its bioavailability. In this study, seven formulations were prepared, and the compositions of all the batches were shown in Table 1. Controlled release CPF HCl floating tablets were prepared using different grades of HPMC with effervescent agent SBC. Most of the formulations were found to have good buoyancy properties [Table 2 and Figure 1]. They floated on immersion in 0.1 N HCl at 37°C and remained buoyant for >10 h. SBC used as a gas forming agent who is essential for rapid floating of CPF HCl on acidic medium. The concentration of SBC was kept constant for all the formulations and when comes in contact with acidic medium which starts to react, thereby generates CO_2, which entrapped by gel layer formed by the hydration of the polymer HPMC. The entrapment of CO_2 within the gel layer leads to decreased tablet density thereby tablet become buoyant.[28] The mechanism involved in buoyancy of CPF HCl tablets was rapid hydration of polymer leads to swelling of polymeric matrices, thereby forms a gel layer and this gel layer prevents the escape of CO_2 facilitates floating of tablet on the acidic medium.[17,29]

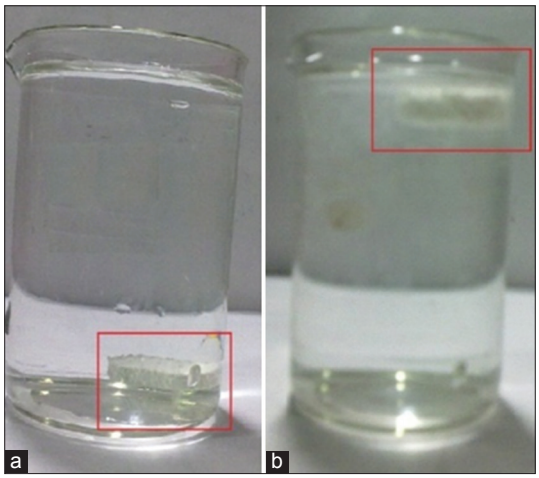

Figure 1: Buoyancy character of formulated tablets. (a) Initial, (b) after 20 s

Table 1: Composition of CPF HCl floating tablets

Ingredients (mg/tablet)	Batch code						
	F1	F2	F3	F4	F5	F6	F7
CPF HCl	500	500	500	500	500	500	500
HPMC K100M	20	20	40	40	40	60	60
HPMC K4M	40	60	40	20	60	20	40
HPMC E50	60	40	40	60	20	40	20
SBC	100	100	100	100	100	100	100
Talc	5	5	5	5	5	5	5
MS	5	5	5	5	5	5	5
Total weight	730	730	730	730	730	730	730

CPF: Ciprofloxacin, HPMC: Hydroxy propyl methyl cellulose, MS: Magnesium stearate, SBC: Sodium bicarbonate

Table 2: Regression analysis of the *in-vitro* release data (F2, F5, F6, F7) according to the various release kinetic models

Batch	Regression coefficient (R^2)			
	Zero order	First order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	N
F2	0.9860	0.9511	0.9930	0.612
F5	0.9920	0.9514	0.9928	0.633
F6	0.9727	0.9342	0.9918	0.542
F7	0.9366	0.9701	0.9837	0.521

Hydrophilic polymers form a "gel layer" at the surface of tablets on exposure to aqueous media by the mechanism of hydration, thereby the tablet swells due to the plasticization of HPMC.[30] The overall effect is that the thickness of gel layer was increased which retards the disintegration, drug release and prevents the further penetration of water into the matrix tablets.[31] Gel thickness depends on the rate of water penetration and movement within the matrix, swelling characteristic of the polymer, dissolution rate of drug and excipients, gel removal by erosion.[32,33] When the outermost layer of the gel becomes fully hydrated, gradually polymer dissolves and contributes to erosion of matrix surface. This process is continued up to the matrix become completely erodes [Figure 2].

FTIR studies

Compatibility studies were performed using FTIR spectrophotometer and the FTIR spectrum of the obtained drug and drug with polymers were studied. The characteristic absorption peaks of CPF HCl obtained at 3327.32, 1327.07, 1379.15, 1712.54, 1728.33, 3084.28 and 2976.26/cm were mainly because of N-H stretching, C-N stretching, C-F stretching, C=C stretching, C=O carboxylic stretching, C-H stretching and O-H carboxylic stretching, respectively. All the characteristic absorption peaks of pure drug were observed in the IR spectra of drug physical mixture [Figure 3].

Micromeritic study

The bulk density and tapped density of granules were used for determination of compressibility index and Hausner's ratio. Compressibility index of formulations ranged from 12.60% to 18.19%, which indicates the fair to good flowability of physical mixture. Hausner's ratio values of formulations were showed from 1.14% to 1.22% indicates acceptable to good flowability. All the seven formulations showed good to excellent flow properties as indicated by the angle of repose values (28.30-32.65°) [Table 3].

Post compression evaluation

Microscopic examination of tablets from each batch showed white, caplet shape, biconvex, uncoated tablets plain on both sides. The tablets passed weight variation test as % weight variation was within the pharmacopoeial limits of ±5% of the

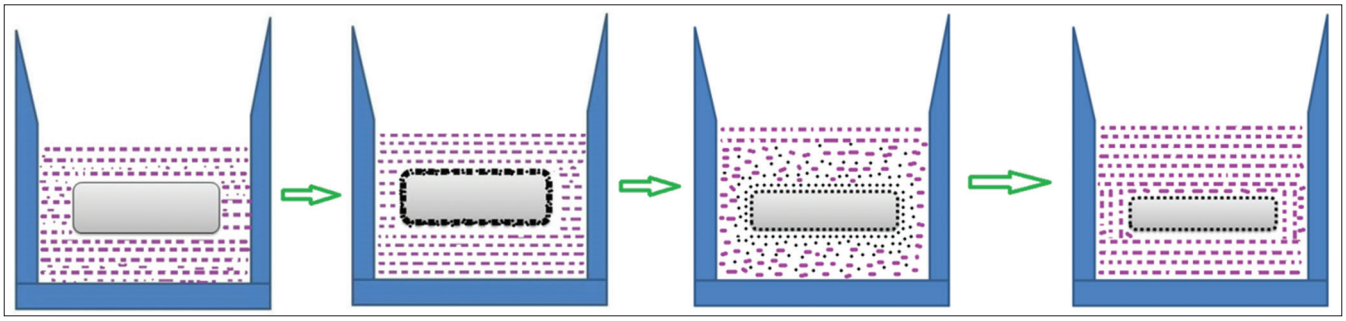

Figure 2: Process of gel formation and drug release after drug administration precompression evaluation

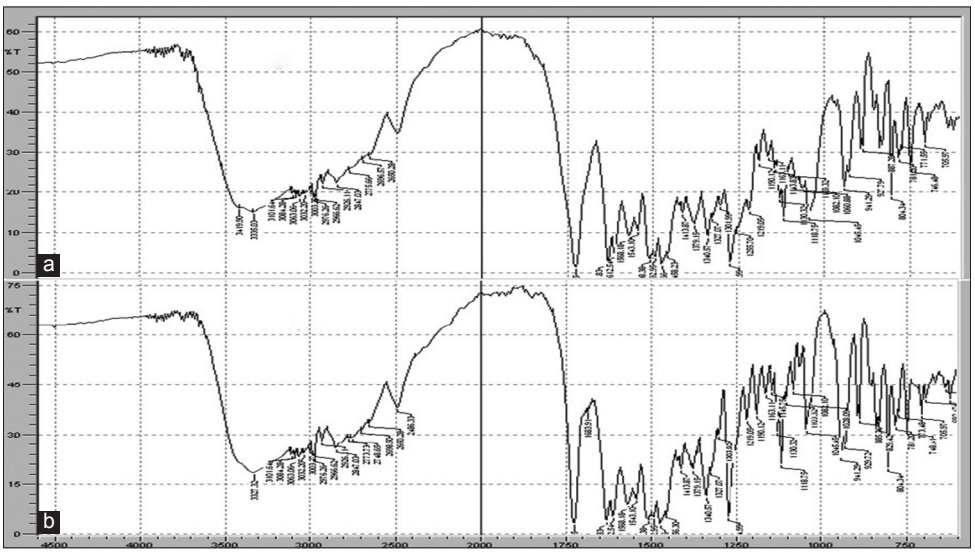

Figure 3: Fourier transform infrared studies. (a) Infrared (IR) spectra of pure drug ciprofloxacin HCl, (b) IR spectra of physical mixture

average weight. The thicknesses of all the seven formulations obtained from 5.58 to 5.64 mm and were consumer acceptable. The hardness of all the formulations ranged from 3.5 to 6.5 kg/cm^2 and it is sufficient to withstand mechanical shocks. Percent friability values obtained were <1% ensuring the tablets were mechanically stable. The drug content was found to be 97.43-99.90%, which complies with the acceptable limits indicating dose uniformity in each batch [Table 4].

Tablet density

To have good floating behavior in the stomach, density of the system should be less than that of the gastric contents. All the seven batches showed density in the range of 0.92-0.94 g/cm^3 [Table 4]. In this study, it was clearly observed that the tablets of all batches showed good floating characteristics after Buoyancy lag time and indicated when the tablets comes in contact with test medium, it expands (because of swellable polymer) and generates CO_2 gas (because of effervescent agent). The tablet was floated as density dropped below the 1.0 g/cm^3 due to the expansion of polymer and upward force of CO_2 gas generation.[28]

Floating time

On immersion in 0.1 N HCl at 37°C, it expands and CO_2 was formed within the tablets thereby floated and remained buoyant without disintegration. Formulations consists of high concentration of HPMC K100M showed good floating lag time (FLT) and total floating time (TFT), which might be due to the rapid hydration of the polymer, thereby it forms gelatinous layer when exposed to aqueous medium. This gelatinous layer prevents the escape of CO_2 from dosage form thereby decreases the density which leads to floating of tablets within a short period of time. In the case of formulations consists of the polymer HPMC E50 showed faster FLT but failed to show the TFT of >10 h, which might be due to the rapid hydration and solubilization or dispersion of gelatinous layer of the polymer leads to escape of CO_2 from the matrix, so these formulations showed less TFT.[34] The results of FLT of all seven formulations were lies within 1 min. TFT of F1 and F4 formulations were more than 6 h and the formulations F2, F3, F5, F6 and F7 showed more than 10 h [Table 4]. Figure 1 represents the buoyancy character of formulated tablets.

Swelling study

The swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of the network of structure, hydrophilicity, and ionization of the functional groups. Swelling study was performed on all the batches for 8 h and the swelling of tablets increased up to 5 h but thereafter it was decreased [Table 5]. Different grades

Table 3: Precompression parameters

Parameters	Formulation						
	F1	F2	F3	F4	F5	F6	F7
Bulk density (g/ml)	0.454±0.13	0.476±0.36	0.454±0.41	0.400±0.18	0.416±0.81	0.434±0.53	0.476±0.49
Tapped density (g/ml)	0.546±0.35	0.555±0.86	0.555±0.75	0.482±0.51	0.476±0.37	0.500±0.96	0.555±0.43
Compressibility Index (%)	16.84±1.36	14.23±1.56	18.19±0.99	17.01±0.87	12.60±1.41	13.20±1.63	14.23±0.83
Hausner's ratio	1.20±0.56	1.16±0.81	1.22±0.93	1.21±0.38	1.14±0.48	1.15±0.74	1.16±0.53
Angle of repose (θ)	31.24±1.60	28.42±1.89	32.65±2.19	31.37±1.45	29.14±1.96	27.34±0.99	28.30±1.68

Results were expressed in mean (*n*=3)±SD. SD: Standard deviation

Table 4: Physicochemical properties, density and floating behavior of CPF HCl tablets

Parameters	Formulation						
	F1	F2	F3	F4	F5	F6	F7
Weight variation (g)*	0.733±0.01	0.729±0.01	0.728±0.02	0.731±0.02	0.731±0.01	0.733±0.01	0.732±0.01
Thickness (mm)*	5.62±0.05	5.60±0.57	5.58±0.43	5.64±0.07	5.62±0.86	5.58±0.37	5.60±0.55
Hardness (kg/cm^2)*	3.5±1.56	4.5±1.43	6.5±1.89	3.5±1.47	4.5±1.68	5.0±1.93	5.0±1.54
Friability (%)*	0.94±0.31	0.52±0.41	0.32±0.39	0.92±0.54	0.52±0.14	0.56±0.89	0.54±0.53
Drug content (%)*	99.90±1.35	98.67±1.43	97.43±1.58	99.63±1.63	98.12±1.34	98.82±1.68	99.09±1.99
Tablet density (g/cc)*	0.93±00.31	0.93±0.54	0.94±0.35	0.93±0.43	0.92±0.68	0.93±0.81	0.94±0.97
FLT or BLT (s)	12	30	50	10	35	15	20
TFT (h)	>6	>10	>10	>6	>10	>10	>10

Results were expressed in mean (*n*=3)±SD.*±5% SD: Standard deviation, FLT: Floating lag time, BLT: Buoyancy lag time, TFT: Total floating time, CPF: Ciprofloxacin

of the polymer HPMC gradually absorbs the water due to its hydrophilicity, thereby the outermost layer of polymer hydrates, swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration, swelling, release processes are repeated toward new exposed surfaces, thus maintaining the integrity of the dosage form.[7] From the results, it was observed that the formulations consist of the polymer HPMC K100M and HPMC E50 in high concentrations (F6, F7 and F1, F4, respectively) showed greater swelling index than the polymer HPMC K4M, which might be due to the more hydrophilic characteristic of the polymers HPMC K100M, HPMC E50.[34,35] Formulations F1, F4, F6 and F7 showed good swelling index than that of F2, F3 and F5.

In-vitro dissolution study

Two mechanisms mainly involved in drug release of water-soluble and water-insoluble drugs from their dosage form are diffusion and erosion, respectively. Hydrophilicity of the polymer leads to hydration causes the burst release of drug might be happens at the initial stage of hydration, but thereafter, it was controlled by the diffusion in the case of soluble drugs and erosion in case of insoluble drugs through the gel layer.[30,36]

In-vitro drug release profile of tablets from each batch using USP dissolution apparatus Type II were listed in Table 6. In this study, HPMC used was hydrophilic in nature, drug release involves: (1) Hydration and swelling of polymer and dissolution of active ingredients and (2) transfer of the dissolved drug and soluble components into the bulk. The results of formulation F3 (HPMC K100M, K4M, and E50) in the ratio of 1:1:1 was showed the drug release of 79.98% in 10 h. Formulation F1, F4 in the ratio 1:2:3 and 2:1:3 were showed faster drug release of 99.82% and 99.34%, respectively, in 6 h. Formulations F2, F5, F6 and F7 used HPMC (K100M, K4M and E50) in the ratio of 1:3:2, 2:3:1, 3:1:2 and 3:2:1 exhibited the drug release of 91.38%, 90.66%, 94.65% and 95.10% respectively. The formulations F2, F5, F6 and F7 were found to be satisfactory, hence these formulations were selected for future studies.

Drug release kinetics

The results of dissolution data were fitted to various drug release kinetic models. All the optimized formulations showed R^2 value highest for Higuchi model followed by zero order and first order. From the Korsmeyer-Peppas plot, the

Table 5: Swelling index of CPF HCl floating tablets

Time (h)	Swelling index (%)						
	F1	F2	F3	F4	F5	F6	F7
1	51.38±1.31	30.14±1.45	24.54±1.56	49.27±1.63	30.06±1.35	32.55±1.96	34.68±1.64
2	61.77±1.53	47.33±1.86	32.51±1.34	60.51±1.64	44.18±1.06	49.92±1.53	51.33±1.04
3	79.56±1.36	54.83±1.67	39.83±1.08	76.81±1.69	51.34±1.34	67.37±1.61	74.92±1.87
4	89.92±1.98	65.44±1.45	46.41±1.33	88.56±1.83	64.29±1.96	77.11±1.49	81.29±1.83
5	88.21±1.78	78.33±1.73	50.10±1.58	88.17±1.65	76.14±1.33	82.54±1.61	87.16±1.53
6	63.11±1.35	55.42±1.66	48.23±1.88	63.43±1.57	57.55±1.61	76.44±1.36	79.13±1.59
7	32.15±1.86	39.22±1.38	41.11±1.93	32.98±1.58	42.18±1.34	59.15±1.39	54.24±1.68
8	17.18±1.33	27.93±1.54	39.87±1.91	17.26±1.49	29.46±1.79	30.29±1.86	29.35±1.65

Results were expressed in mean (n=3)±SD. SD: Standard deviation, CPF: Ciprofloxacin

Table 6: *In-vitro* dissolution study of CPF HCl floating tablets

Time (h)	Cumulative % drug release						
	F1	F2	F3	F4	F5	F6	F7
1	32.69±1.36	22.93±1.65	17.72±1.43	30.39±1.69	22.12±1.67	27.25±1.96	29.40±1.78
2	45.08±1.36	32.20±1.56	21.45±1.97	42.16±1.89	30.55±1.39	38.71±1.74	40.85±1.96
3	59.26±1.13	46.25±1.17	29.83±1.76	51.73±1.19	43.14±1.11	50.22±1.65	54.62±1.46
4	72.37±1.18	51.07±	35.76±1.68	69.98±1.87	49.72±1.18	55.34±1.76	61.73±1.14
5	81.61±1.69	59.14±1.11	40.41±1.37	80.93±1.15	56.43±1.71	63.66±1.64	74.43±1.93
6	99.82±1.83	67.31±1.18	49.92±1.65	99.34±1.69	65.18±1.69	75.76±1.37	80.17±1.57
7		72.43±1.82	57.33±1.46		70.92±1.83	79.38±1.97	82.59±1.49
8		80.27±1.93	65.04±1.74		78.71±1.41	80.70±1.65	85.10±1.43
9		88.79±1.96	74.37±1.78		86.12±1.68	89.26±1.73	91.48±1.87
10		91.38±1.35	79.98±1.96		90.66±1.44	94.65±1.38	95.10±1.97

Results were expressed in mean (n = 3)±SD. SD: Standard deviation, CPF: Ciprofloxacin

"*n*" value obtained was ranged from 0.521 to 0.633 indicates the mechanism of non-fickian diffusion [Table 2].

Stability studies

Results were revealed that there was no significant change occurs in appearance, floating test and drug content up to 60 days but it was up to 30 days in case of evaluation parameters such as hardness, friability, and drug release. Thus, it is evident from the results that F2, F5, F6, and F7 formulations were stable at all three storage conditions up to the period of 30-day. However, F2, F5, F6, and F7 showed decrease in hardness after the period of 30-day, with subsequent increase in friability and *in-vitro* drug release for samples stored at prevailing room temperature (34 ± 2°C) and at 40°C, whereas there was no significant change occurs in F2, F5, F6 and F7 formulations stored in refrigerator (2-8°C). Thus, from the above results, it could be concluded that the CPF HCl floating tablets are stable when stored at 2-8°C.

CONCLUSION

It could be concluded from the results that the hydrodynamically balanced tablets of CPF HCl were formulated with an approach to increase in gastric residence and thereby improves its bioavailability. All seven formulations showed satisfactory results for tablet density, floating time, and swelling studies. It follows the Higuchi model with the mechanism of non-fickian diffusion. The results of stability studies indicated that the most suitable storage temperature for CPF HCl floating tablets was 2-8°C for 60 days. Formulations F2, F5, F6 and F7 showed satisfactory drug release, hence there is a lot of scope for future *in-vivo* studies.

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Source of Support: Nil. **Conflict of Interest:** None declared.