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Formulation and *In-vitro* evaluation of ciprofloxacin HCl floating matrix tablets

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ABSTRACT

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process. Gastroretentive drug delivery system was developed in pharmacy field and drug retention for a prolonged time has been achieved. The goal of this study was to formulate and *in-vitro* evaluate Ciprofloxacin HCl controlled release matrix floating tablets. Ciprofloxacin HCl floating matrix tablets were prepared by wet granulation method using two polymers such as HPMC K100M (hydrophilic polymer) and HPMC K15M. All the Evaluation parameters were within the acceptable limits. FTIR spectral analysis showed that there was no interaction between the drug and polymers. *In-vitro* dissolution study was carried out using USP dissolution test apparatus (paddle type) at 50 rpm. The test was carried out at 37 ± 0.5 0C in 900ml of the 0.1 N HCl buffer as the medium for eight hours. HPMC K100M shows a prolonged release when compared to HPMC K15M. These findings indicated that HPMC K100M can be used to develop novel gastroretentive controlled release drug delivery systems with the double advantage of controlled drug release at GIT pH. On comparing the major criteria in evaluation such as preformulation and in vitro drug release characteristics, the formulation F8 was selected as the best formulation, as it showed the drug content as 99±0.4% and swelling index ratio was 107.14, and *in-vitro* drug released 61.31±0.65% up to 8 hours. Results indicated that controlled Ciprofloxacin HCl release was directly proportional to the concentration of HPMC K100M and the release of drug followed non-Fickian diffusion. Based on all the above evaluation parameters it was concluded that the formulation batch F8 was found to be best formulation among the formulations F1 to F8 were prepared.

Keywords: Ciprofloxacin HCl, HPMC K100M, *In-vitro* drug delivery, Gastroretentive drug delivery.

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INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process [1].

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as [2, 3].

Sustained release (SR) - gastroretentive dosage forms (GRDF) enable prolonged and continuous input of the drug to stomach and upper parts of the gastrointestinal (GI) tract. These systems are designed to be retained in the stomach for longer period of time and hence significantly prolong the gastric residence time of drugs. Therefore, different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems, swelling and expanding systems, floating systems and delayed gastric emptying devices [4, 5, 6].

Among these, the floating dosage form has been used most commonly. This technology is suitable for drugs with an absorption window in the stomach or in the

upper part of the small intestine, drugs acting locally in the stomach, and for drugs that are poorly soluble or unstable in the intestinal fluid. The floating systems include single, multiple and raft forming systems. The principle of these systems offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release [7, 8, 9].

The present investigation is concerned about the development of effervescent floating drug delivery systems that generate CO_2, thus reduces the density of the system in the stomach for prolonged period of time and releases the drug slowly at desired rate. Formulation of extended release effervescent floating tablets of Ciprofloxacin HCl improves patient compliance and minimizes the dose related side effects. Therefore, this study aims at formulating once-a day floating hydrophilic matrix tablets using hydroxypropyl methylcellulose (HPMC K15 and K100) as a release rate modifying polymer, NaHCO3 and talc were used as floating aid and release modifier.

In order to optimize the therapy research efforts have been focused on the development of oral sustained release (SR) preparations as well as controlled release gastro retentive dosage forms. A conventional oral SR formulation releases most of the drug content at colon, thus requiring that the drug will be absorbed from colon.

The above drawbacks provide a rationale for developing Ciprofloxacin Hydrochloride as a gastro retentive dosage form, which is retained in the stomach and produces a constant input of drug to the absorption site. This improves the bioavailability of the drug, reduces frequency of dosing, thus minimizes side effects and enhances patient compliance. The present study a systematic approach for the development of intra gastric Buoyant tablets of Ciprofloxacin Hydrochloride with a view to enhance its oral bioavailability and efficacy.

MATERIALS AND METHOD

Ciprofloxacin Hydrochloride and all the polymers were procured from SD Fine Chemicals Ltd., Mumbai. All other chemicals and ingredients for study were of analytical grade.

Preparation

Effervescent floating tablets containing drug (50mg) were prepared by wet granulation technique (slugging) using varying concentrations of polymers i.e. hydroxy propylmethyl cellulose HPMC K15, HPMC K100 and sodium bicarbonate as effervescent component. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except magnesium stearate and talc all other ingredients were blended uniformly in polyethylene bag for 5-6 min. Slugging the powder blend and sifted through sieve no. #22. Granules were lubricated with magnesium stearate and talc (1-2%) for additional 3min., compressed in to tablets using a 16 station rotary tablet machine (Cadmach, Ahmedabad, India.) using 8mm standard flat face punch, compression force was adjusted to obtain tablets with hardness in range of 5.1 ± 0.51- 5.8 ± 0.23 kp. The tablet weights were 300±2 mg with average diameter of 9.0±0.2 mm.

Evaluation of granules

Pre-compression parameters of granules

The flow properties of granules (before compression) were characterized in terms of angle of repose, tapped density, bulk density and Carr's index [10, 11].

Evaluation of tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods [12]. The weight variation was determined by taking 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to average of tablet. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics) for 4 minutes at 25 rpm. Acceptance criteria are not more than 1 % of their weight.

In Vitro drug release study

The release rate of the drug from floating tablets was determined using USP testing apparatus II (Paddle Type DISSO 2000). The dissolution test was performed using 900ml of 0.1N HCl at 37±0.5°C and 50 rpm. 5ml of aliquots were withdrawn at specific time intervals and the level of the dissolution media was maintained by replacing the same which was already maintained at sink conditions. The samples were filtered through a 0.45 µm membrane filter. Absorbance of these samples were taken at 277nm using UV visible spectrophotometer (Shimadzu UV 1700) against 0.1N HCl as blank. Cumulative percent drug release was calculated.

Assay of tablets

The drug content in each formulation was determined by triturating 10 tablets and a quantity of powder equivalent to the mass of one tablet was extracted with pH 1.2 buffer and the solution was filtered through 0.45 µ membranes. The absorbance was measured at 277nm after suitable dilution.

Floating lag time and total floating time

The time between the introduction of a floating tablet of the drug in to the medium and its buoyancy to the upper one third of the dissolution vessel was measured as floating lag time which is a part of dissolution studies. The time for which FDDS constantly float on the water surface is total floating time. It is performed

by visual observations during the dissolution studies [13, 14].

Kinetics of drug release

A gel layer is formed around the tablet core when the tablet containing a polymeric matrix comes in contact with water, which governs the drug release. Drug release from HPMC matrix tablets is controlled by diffusion through the gel layer in case of water soluble drug or by erosion of the outer polymer chains for water insoluble drugs. Hence, the kinetics of swelling is important because the gel barrier is formed with water penetration. The drug release rate kinetics was calculated for zero order, first order and Higuchi models [15, 16, 17].

Mechanism of drug release

The mechanism of drug release was determined by fitting the drug release data of drug release to Korsmeyer *et al*'s equation and graphs were plotted as log cumulative percentage of drug release vs. log time and the exponent *n* was calculated through the slope of the straight line and finding the R^2 values of the release profile corresponding to each model $Mt/M\infty = at^n$, Where $Mt/M\infty$ is the fractional solute release, t is the release time, a is constant incorporating structural and geometrical characteristics of the drug dosage form and n is the release exponent indicative of drug release mechanism and function of time, t. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n <0.89, then it is non-Fickian or anomalous diffusion. An exponent's value of 0.89 is indicative of case-II Transport or typical Zero order release [17].

Stability studies

The stability studies were carried out on optimized formulation i.e. F8. The formulations were stored at 40^oC/ 75 % RH for three months to assess their long term stability. Samples were withdrawn after 1, 2 & 3 months and retested for physical properties, drug content, floating lag time and *in vitro* drug release.

RESULTS AND DISCUSSION

The present study was aimed to prepare and evaluate effervescent floating matrix tablets of Ciprofloxacin Hydrochloride with HPMC K15 and HPMC K100 as polymer using wet granulation technique. HPMC was chosen because it is widely used as a low density hydrocolloid system upon contact with water a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in intestinal pH. Magnesium stearate acts as buoyancy increasing agent and also improves the gelling property of polymer. Magnesium stearate was used in combination with HPMC to slow the drug release.

The granules prepared for compression of floating tablet were evaluated for their flow properties (Table 2). Angle of repose (ø) was in the range of 23.73 ± 1.2 to 26.22. Bulk density ranged between 0.345 ±0.03 to 0.435 ± 0.04 gm/cm^3. Tapped density ranged between 0.372 ± 0.04 to 0.480 ± 0.02 gm/cm^3. Carr's Index was found to be 21.88 ± 0.18 to 23.86 ± 0.32. These values indicate that the prepared granules exhibited good flow properties.

The average weight and hardness of the tablets were found in the range of 283 ± 0.6 to 320 ± 0.9mg and 7.2 ± 0.2 - 8.0 ± 0.3kg/cm^2 respectively as shown in table3. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet.

On immersion in 0.1 N HCl, pH 1.2 solution at 37 ± 0.5^0C all effervescent floating tablets floats immediately and remain buoyant up to 8hr without disintegration. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (HPMC K 100M), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies. The cumulative percent drug release was found to be 61.31 ± 0.65% at 8hr. Among all the formulations F8 was found to be the optimized one in terms of floating lag time and drug release at the end of 8hr as shown by results in table 3. The dissolution profiles of all the formulations are shown in (Figure 1, Figure 2, Figure 3 and Figure 4).

The assays of tablets of all the formulations were found within the range as per the requirement of pharmacopoeia. When the concentration of polymer was increased, the lag time was increased but total drug release was decreased. The data clearly indicate the drug release can be effectively controlled by varying the polymer and its ratio. Incorporated sodium bicarbonate into the HPMC matrix could increase the drug release rate. The increase in the quantity of sodium bicarbonate decreases the lag time but increases the drug release. As magnesium stearate is hydrophobic in nature and when it was increased extra granularly then floating lag time was increased slightly but no effect on initial drug release from the matrix tablets.

The data obtained from *in-vitro* dissolution studies were fitted in different models viz. Zero order, First order, Higuchi and Korsmeyer Peppa's equation (shown in Table 4). The Higuchi plots were found to be followed as indicated by their high regression values (r^2 = 0.929 to 0.996). To confirm the exact mechanism of drug release from these tablets, the data was fitted to Higuchi and Korsmeyer Peppa's equation. The formulation F8 with HPMC K 100 M (20%) shows maximum release of 61.31±0.65 % at a time period of 8 hours in a controlled manner. The *in-vitro* release

Table 1: Formulation batches of effervescent floating tablets of Ciprofloxacin Hydrochloride

Ingredients	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Ciprofloxacin HCl	50	50	50	50	50	50	50	50
HPMC K15M	50	100	150	200	-------	------	------	-----
HPMC K100M	-----	------	------	------	50	100	150	200
$NaHCO_3$	45	45	45	45	45	45	45	45
Magnesium Stearate	3	3	3	2.5	3	3	3	2.5
Microcrystalline cellulose	154	99	49	___	154	99	49	___
Talc	3	3	3	2.5	3	3	3	2.5

**All the quantities are in mg*

Table 2: Granule properties of formulation F1 to F8 of Ciprofloxacin Hydrochloride matrix tablets

Parameters	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Angle of Repose (ø)	25.16 ±1.2	25.35 ±1.4	26.12 ±1.6	24.43 ±1.3	23.73 ±1.2	26.22 ±1.6	24.18 ±1.0	25.30 ±1.4
Bulk Density (gm/cm^3)	0.435 ±0.04	0.358 ±0.06	0.420 ±0.02	0.376 ±0.02	0.345 ±0.03	0.425 ±0.02	0.409 ±0.03	0.369 ±0.02
Tapped Density (gm/cm^3)	0.476 ±0.03	0.427 ±0.01	0.386 ±0.03	0.462 ±0.02	0.418 ±0.03	0.385 ±0.02	0.480 ±0.02	0.372 ±0.04
Carr's Index (%)	22.26 ±0.14	21.88 ±0.18	22.46 ±0.40	23.86 ±0.32	22.82 ±0.42	23.81 ±0.45	22.92 ±0.32	23.76 ±0.18

**Each reading is an average of three determinations (Avg.± S.D)*

Table 3: Different properties of tablets of batch F1 to F8

Formulation No.	Avg. Weight (Mean ± S.D) (n=20)	Hardness (kg/cm^2) (n=3)	Friability (Mean±S.D) (n=20)	% Drug content (mg)	Buoyancy lag time (min)	Total floating Time (hrs)	Matrix integrity
F1	283±0.6	7.2±0.2	0.546	97±0.7	4	8	+
F2	320±0.9	7.5±0.2	0.612	99±0.5	10	8	+
F3	297±0.3	8.0±0.3	0.827	100±0.6	8	8	+
F4	291±0.4	7.6±0.2	0.611	99±0.6	6.1	8	+
F5	286±0.8	7.6±0.2	0.625	99±0.6	5.0	8	+
F6	304±0.8	7.3±0.4	0.655	98±0.5	3	8	+
F7	294±0.4	8.0±0.2	0.711	100±0.3	8.5	8	+
F8	292±0.4	7.7±0.5	0.702	99±0.4	8.6	8	+

**Each reading is an average of three determinations (Avg.± S.D)*

Table 4: Release kinetic parameters of floating tablets of Formulation F1 to F8

Formulation Code	Zero order	First order	Higuchi's	Korsmeyer Peppa's
F1	0.976	0.870	0.929	0.934
F2	0.975	0.915	0.954	0.971
F3	0.937	0.940	0.996	0.994
F4	0.971	0.990	0.994	0.995
F5	0.983	0.923	0.957	0.966
F6	0.992	0.954	0.966	0.975
F7	0.975	0.955	0.970	0.985
F8	0.979	0.981	0.986	0.994

plot has shown drug release followed by Higuchi plot, which was also confirmed from the regression value in Table 4. From the regression and slope value of Higuchi's (0.986) and Peppa's (n = 0.994) plot respectively, the drug release was confirmed to followed by diffusion mediated non-Fickian transport mechanism.

The optimized F8 formulation was subjected to stability studies for 3 months. At the interval of 30 days the tablets were withdrawn and evaluated for hardness, thickness, weight variation, friability. All the parameters have not shown much variation when compared to the initial data**.** The *in-vitro* dissolution was also carried out for specified time intervals. Based on the results, we observed that, drug release profiles were not affected by exposing to temperature and the specified humidity conditions.

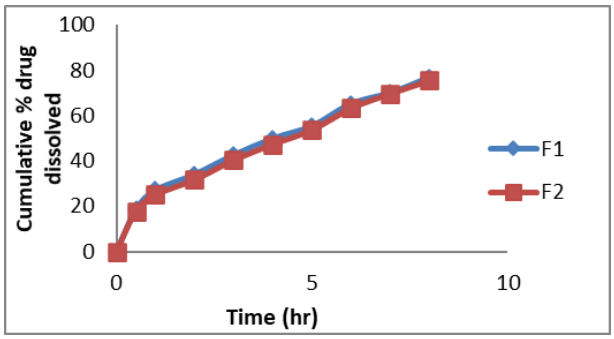

Figure 1: Dissolution profile of Ciprofloxacin HCl floating tablets (F1, F2) formulations.

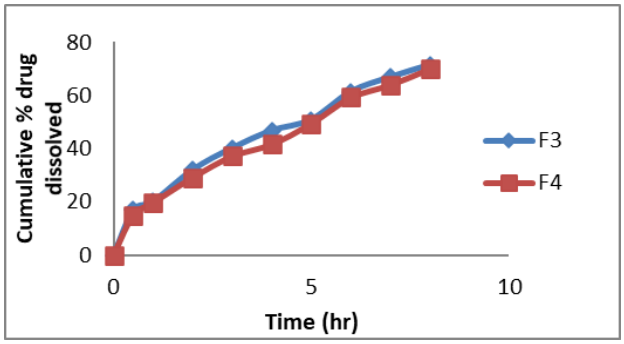

Figure 2: Dissolution profile of Ciprofloxacin HCl floating tablets (F3, F4) formulations.

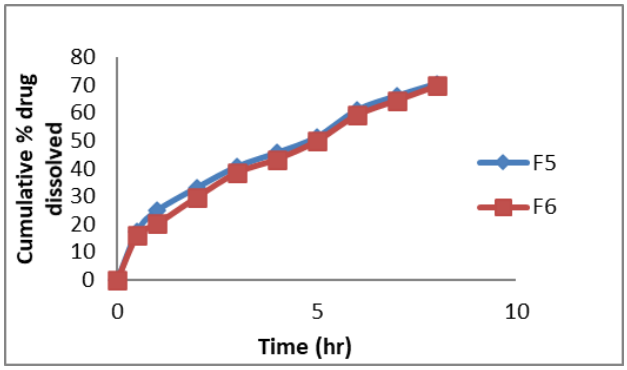

Figure 3: Dissolution profile of Ciprofloxacin HCl floating tablets (F5, F6) formulations.

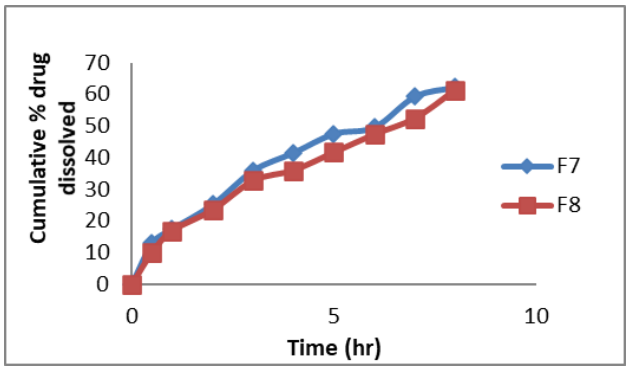

Figure 4: Dissolution profile of Ciprofloxacin HCl floating tablets (F7, F8) formulations

CONCLUSION

Based on the results and discussion, we can concluded that controlled release tablets of Ciprofloxacin HCl were prepared successfully by wet granulation using different concentration of polymers like HPMC-K15, HPMC-K100 and other excipients such as magnesium stearate as lubricant, talc as glidants and microcrystalline cellulose as diluent were found to be good without chipping, capping and sticking. There are various approaches to increase the gastric retention time of dosage form and floating system is one of the approaches for delivery of drugs which are absorbed from stomach and upper small intestine. Ciprofloxacin HCl has high solubility in stomach pH and is formulated as effervescent floating drug delivery system. For antibiotic therapy, the drug has to administer for long period of time and due to this more drug will be accumulated in the body, which ultimately increases the side effects. This targeted delivery of the drug through FDDS reduces the dose, duration of therapy and also the side effects.

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