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Formulation Development and In-Vitro Evaluation of Sustained-Release Gastro Retentive Tablets of Ciprofloxacin Hydrochloride by Using HPMC and Sodium CMC

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Keywords: Gastro retentive matrix tablets; HPMC K_4M; HPMC $K_{100}M$; Sodium CMC; Ciprofloxacin hydrochloride.

ABSTRACT

The present investigation concerns the development of Hydrodynamically balanced tablets of Ciprofloxacin Hydrochloride 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 K_4M, HPMC $K_{100}M$, and Sodium CMC as the retardant polymers each with two different levels. All the tablets were prepared by the effervescent approach in which Sodium bicarbonate was added as a gas generating agent. Tablets were evaluated for their physical characteristics, viz., hardness, thickness, friability, and weight variation, drug content and floating properties. Further tablets were studied for *in-vitro* drug release pattern over the dissolution medium and showed satisfactory results. Floating lag time of all the formulations was within 1 minute and Total floating time of all the formulations were more than 12 hours. *In-vitro* release studies revealed that the release rate decreased with increase polymer proportion of retarding polymers. Formulation F_2 sustained release of drug for 12 hrs by incorporating 4% of HPMC K_4M, 4% of HPMC $K_{100}M$ along with 2% of Sodium CMC and Formulation F_4 sustained release of drug for 12 hrs by incorporating 8% of HPMC K_4M, 4% of HPMC $K_{100}M$ along with 2% of Sodium CMC. The formulations F_2 and F_4 sustained release of drug for 12 hrs with 27% and 21% release of drug after 1hr and more than 95% and 93% at the end of 12 hrs. The release kinetics was analyzed using Zero-order model equation, Higuchi's square root equation, and Korsmeyer and Peppas' empirical equation. The regression coefficient obtained for Higuchi's square root equation for optimized formulation F_2 was found to be highest (R^2: 0.995) and for F_4 formulation (R^2: 0.952). The mechanism of drug release from formulation F_2 (n: 0.494) and formulation F_4 (n: 0.603) showed the behavior of Fickian and non-Fickian diffusion respectively.

INTRODUCTION:

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[1]. Floating drug delivery systems are good promising options for drugs which show good absorption in the stomach and which are degraded, less efficient in the intestine. These drug delivery systems are beneficial to achieve the more local action in the gastric environment. Floating systems are one type of gastro retentive drug delivery systems (GRDDS) which are retained in the stomach for a longer period of time and thereby improving the bioavailability, local action of drugs that are preferentially absorbed from upper GIT. The gastric retention of the dosage form in the stomach depends upon various factors like pH, size of the dosage form, food intake, and biological factors which include age, body mass index, gender, posture, and diseased states. Out of all available gastro retentive systems floating tablets, floating beads, floating granules, and floating microspheres have gained major importance in the formulation development more recently. These floating systems will improve the contact time of drug with gastric mucosa and thereby providing the beneficial results[2, 3]. Floating dosage forms are dosage forms with a bulk density lower than that of the gastric content. This allows them to remain buoyant on the surface of the gastric content for a certain period of time without affecting the intrinsic rate of emptying. They are also referred to as hydrodynamically balanced systems (HBS) as they are able to maintain their low density while the polymer hydrates and builds a gelled barrier at the outer surface[4]. Ciprofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It belongs to the family of fluoroquinolones. It functions by inhibiting DNA gyrase, a type II topoisomerase, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division. It is rapidly absorbed orally and shows 60-70% oral bioavailability and 3-4 hours elimination half life. Due to its short elimination half life, Ciprofloxacin is administered twice to thrice daily[5, 6].

MATERIALS AND METHODS:

Materials:

Ciprofloxacin Hydrochloride was obtained as a gift sample from Dr. Reddy's Lab (Hyderabad, India), HPMC $K_{100,}$ HPMC $K_{4,}$ and Sodium CMC were obtained from Aurobindo Pharma Ltd, (Hyderabad, India), Micro Crystalline Cellulose and Mg. Stearate

from Loba Chem (Mumbai, India). All other chemicals and ingredients were used for the study are of commercial grade.

Methods:

Matrix embedded Sustained release floating matrix tablets of Ciprofloxacin Hydrochloride were prepared by direct compression technique using various concentrations of HPMC K_{100} HPMC K_4 and Sodium CMC. All ingredients except magnesium stearate and talc were blended in glass mortar uniformly. After the sufficient mixing of the drug as well as other components, magnesium stearate and talc were added and mixed for an additional 5 minutes and finally compressed on a rotary tableting machine using 7.96-mm punches.

Table 1: 2^3 Full Factorial Design for the Preparations of Batches

Formulation No	Factors in Coded form		
	HPMC K_4M	HPMC $K_{100}M$	Sodium CMC
F_1	-1	+1	+1
F2	-1	-1	-1
F3	+1	+1	+1
F4	+1	-1	-1
F5	+1	+1	-1
F6	-1	+1	-1
F7	+1	-1	+1
F8	-1	-1	+1

Table 2: 2^3 Full Factorial Design for the Preparations of Batches with coded level

Factors used	Coded Level	
	-1	+1
HPMC K_4M (mg)	20	40
HPMC $K_{100}M$ (mg)	20	40
Sodium CMC (mg)	10	20

Table 3: Preparation of Matrix Tablets of Ciprofloxacin Hydrochloride

Formulation Ingredients (mg)	Formulation batch							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Ciprofloxacin Hydrochloride	250	250	250	250	250	250	250	250
HPMC K_4M	20	20	40	40	40	20	40	20
HPMC $K_{100}M$	40	20	40	20	40	40	20	20
Sodium CMC	20	10	20	10	10	10	20	20
Sodium Bicarbonate	100	100	100	100	100	100	100	100
MCC	60	90	40	70	50	70	60	80
Talc	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5
Total wt	500	500	500	500	500	500	500	500

Evaluation of Matrix Tablets [7, 8]

Physical Characterization of the Designed Tablet

The properties of the compressed matrix tablets, such as hardness, friability, weight variation, and content uniformity were determined using the reported procedure. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester. Friability was determined by testing 10 tablets in a Roche friability tester for 4 min at 25 rpm. The weight variation was determined by taking the weight of 20 tablets using an electronic balance (Sartorius Electronic Balance, BT-2245). The drug content of the manufactured tablets of each batch was determined in triplicate. For each batch, 10 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved and analyzed after making appropriate dilutions.

Table 4: Physical Characterization of Floating Sustained Release Matrix Tablets of Ciprofloxacin Hydrochloride

Formulation batch	Avg. Wt. (mg)	Hardness (kg/cm^2)	Drug Content (%)	Friability (%)
F_1	502.25±6.257	5.13±0.337	97.292±2.282	0.587
F_2	505.79±6.63	5.22±0.288	97.654±2.246	0.571
F_3	498.77±6.63	5.07±0.265	97.932±2.064	0.582
F_4	497.55±6.634	5.17±0.188	99.051±2.102	0.566
F_5	497.76±5.491	5.26±0.219	98.83±2.21	0.549
F_6	498.46±5.321	5.19±0.129	96.63±2.54	0.556
F_7	498.31±5.6.13	5.09±0.316	99.84±2.74	0.564
F_8	497.19±6.519	5.26±0.3785	98.734±2.654	0.634

Values are represented as mean ± S.D. (n = 3)

In-vitro Drug Release Studies

The release rate of all the designed formulations was studied up to 12 hours using USP- type II (Paddle) dissolution apparatus at 50 rpm. The dissolution medium (900ml) consisted of 0.1N HCl maintained at 37°C ± 0.5°C. A sample of 5 ml was withdrawn at specific time intervals throughout the dissolution study of 12 hours for analysis and replaced with fresh dissolution medium. After appropriate dilution, the samples were analyzed for Ciprofloxacin Hydrochloride using a double beam UV-Visible spectrophotometer at 276nm using 0.1N HCl. The release studies were conducted in triplicate.

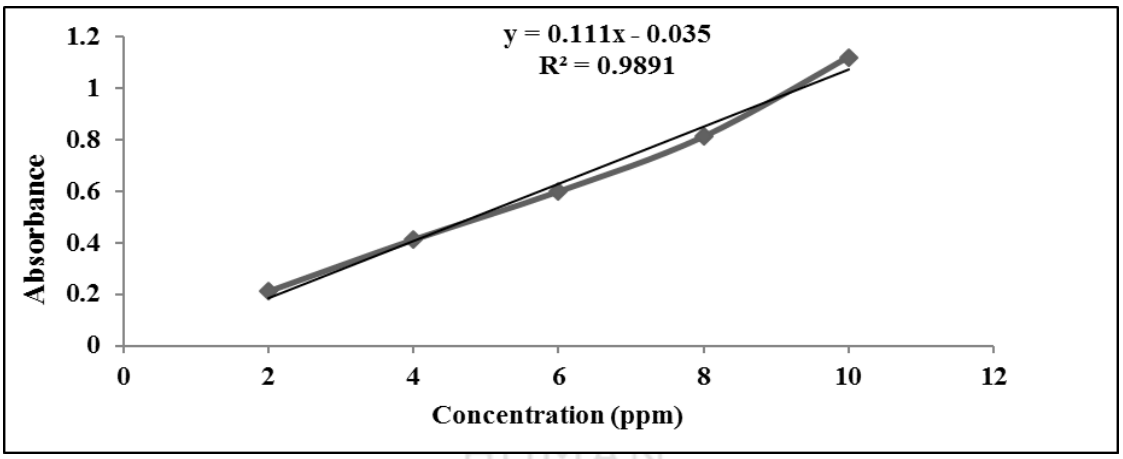

Fig. 1: Standard Curve of Ciprofloxacin Hydrochloride in 0.1 N HCl

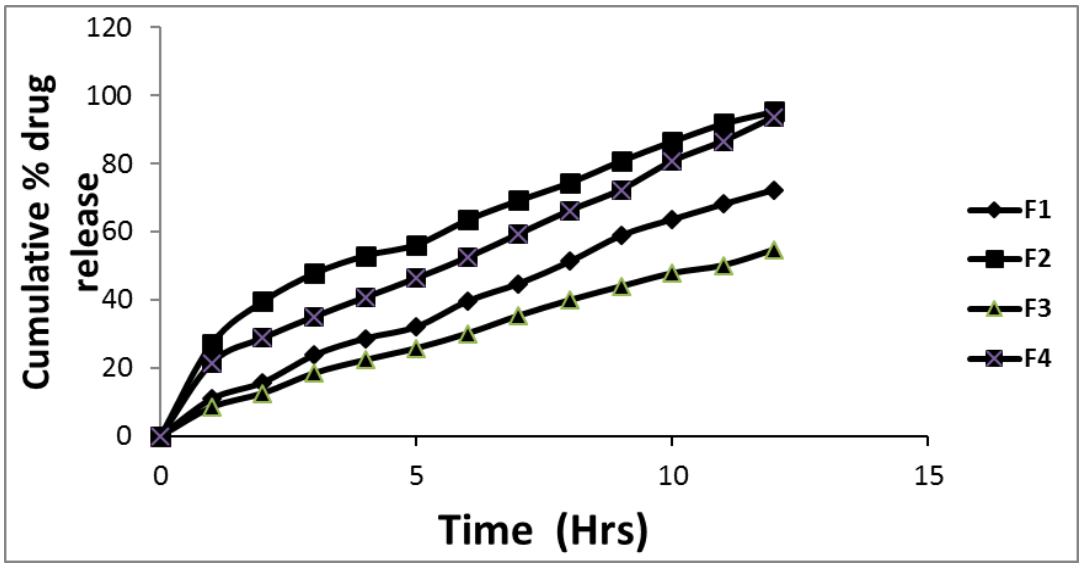

Fig. 2: *In-vitro* Drug Release Profile of Floating Sustained Release Matrix Tablets of Ciprofloxacin Hydrochloride Using HPMC and Sodium CMC

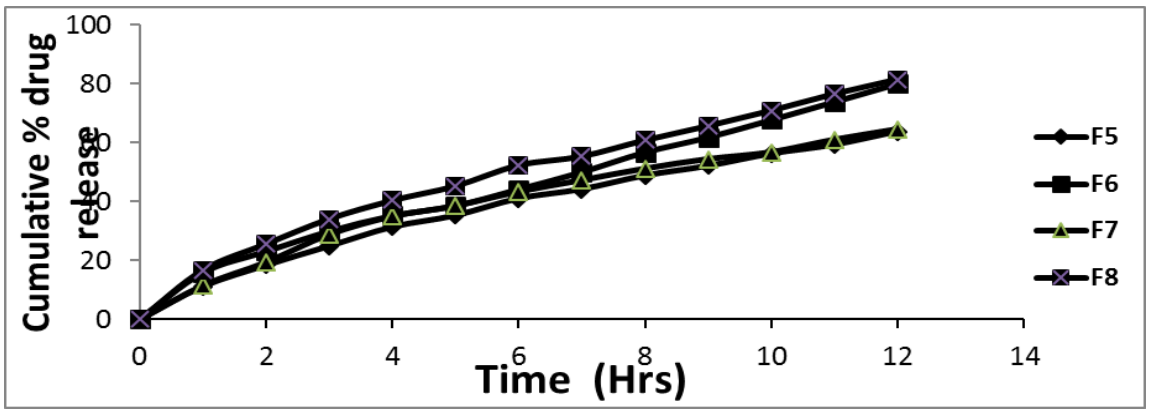

Fig. 3:- ***In-vitro*** **Drug Release Profile of Floating Sustained Release Matrix Tablets of Ciprofloxacin Hydrochloride Using HPMC and Sodium CMC**

Kinetic analysis of given data [9, 10, 11]

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$W_0 - W_t = K_0 t$$

Where $W_0$is the initial amount of drug in the pharmaceutical dosage form, $W_t$is the amount of drug in the pharmaceutical dosage form at time **t**and $K_0$is proportionality constant. Dividing this equation by $W_0$and simplifying:

$$f_t = K_0 t$$

Where f_t = 1- (w_t/ w_0) and f_t represents the fraction of drug dissolved in time t and k_0 the apparent dissolution rate constant or zero order release constant.

First order kinetics:

The relation expressing this model:

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t/2.303$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and $K_1$is the first order release rate constant.

Korsmeyer Peppas model:

It can be represented by the following equation:

$$Q_t/Q_\infty = K_k t^n$$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and *n* is the release exponent, indicative of the drug release mechanism. For matrix tablets, an *n* value of ~0.5 indicates a diffusion-controlled mechanism while an *n* value of ~1.0 indicates erosion-controlled release. Intermediate values suggest a dual mechanism of both diffusion and erosion.

Higuchi Model:

It can be represented by the following equation:

$$Qt = K_H t^{1/2}$$

Where Q_t = the amount of drug released at time t and

K_H= the Higuchi release rate;

Table 5: Release Exponent and Drug transport mechanism

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.5<*n*<1.0	Anomalous transport
1.0	Case-II transport
Higher than 1.0	Super Case-II transport

Table 6: Kinetic analysis of Dissolution Profile from Batches F_1 to F_8

Models		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Peppas Model	n	0.792	0.494	0.773	0.603	0.693	0.648	0.676	0.628
	R^2	0.991	0.992	0.995	0.977	0.998	0.989	0.989	0.998
	K_1	9.84	27.03	7.81	19.05	11.48	14.75	12.50	16.67
Higuchi Model	R^2	0.908	0.995	0.924	0.952	0.969	0.948	0.980	0.978
	K_2	18.17	26.89	13.83	23.90	17.06	20.26	17.78	21.73
Zero- Order	R^2	0.986	0.779	0.979	0.935	0.923	0.948	0.878	0.901
	K_3	6.358	9.153	4.821	8.267	5.882	7.019	6.102	7.473
First- Order	R^2	0.978	0.914	0.995	0.877	0.998	0.954	0.994	0.976
	K_4	0.046	0.097	0.027	0.086	0.034	0.052	0.034	0.055

RESULTS AND DISCUSSION:

The oral floating sustained release matrix tablets of Ciprofloxacin were formulated by using HPMC K_4M, HPMC $K_{100}M$, and Sodium CMC as the retardant polymers each with two different levels. All the tablets were prepared by the effervescent approach in which Sodium bicarbonate was added as a gas generating agent. Floating Matrix tablets were prepared by direct compression method and prepared tablets were evaluated for weight variation, percentage friability, hardness, and drug content studies. All the formulations showed compliance with pharmacopeia standards. Formulations were evaluated for floating behavior. Floating lag time of all the formulations was within 1 minute and Total floating time of all the formulations were more than 12 hours. *In-vitro* release studies revealed that the release rate decreased with increase polymer proportion of retarding polymers. Formulation F_2 sustained release of drug for 12 hrs by incorporating 4% of HPMC K4M, 4% of HPMC K100M along with 2% of Sodium CMC and Formulation F_4 sustained release of drug for 12 hrs by incorporating 8% of HPMC K_4M, 4% of HPMC $K_{100}M$ along with 2% of Sodium CMC. It can be concluded that stable formulation could be developed by incorporating in a definite proportion of HPMC and Sodium CMC So that sustained released profile is maintained for an extended period of time. The release kinetics was analyzed using Zero-order model equation, Higuchi's square root equation, and Korsmeyer and Peppas' empirical equation. The regression coefficient obtained for Higuchi's square root equation for optimized formulation F_2 was found to be highest (R^2: 0.995) and for F_4 formulation (R^2: 0.952). The mechanism of drug release from formulation F_2 (n: 0.494) and formulation F_4 (n: 0.603) showed the behavior of Fickian and non-Fickian diffusion respectively.

CONCLUSION:

It can be concluded that stable formulation could be developed by incorporating in a definite proportion of HPMC and Sodium CMC, So that sustained released floating profile is maintained for an extended period of time.

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