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DESIGN AND EVALUATION OF GASTRORETENTIVE DRUG DELIVERY OF OFLOXACIN TABLETS

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Abstract:
The objective of the work is to develop floating tablets of ofloxacin having prolonged gastric residence time after oral administration. Floating tablets of ofloxacin have shown controlled release thereby proper duration of action at a particular site. Floating tablets of ofloxacin were prepared by direct compression technique using polymers like HPMC K4M, HPMC K15M, HPMC K100M, compritol, and xanthum gum as swelling polymers with sodium bicarbonate as a gas generating agent. All formulations were evaluated for their pre and post-compression studies, buoyancy lag time, duration of floating time, in-vitro drug release, and swelling studies. The effect of different concentrations of HPMC on drug release profiles and floating characteristics was studied. The formulation F10 showed drug release 98.45% in 12 hrs; floating lag time was found to be 24 sec and release of drug followed by first order with non-fickian diffusion.

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1. INTRODUCTION:

Oral controlled release (CR) dosage forms (DFs) have been developed for the past 3 decades due to their considerable therapeutic advantages [(1)]. However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the GIT i.e. stomach and small intestine [(2)]. After oral administration, such a DF would be retained in the stomach and released the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper GIT. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs for these drugs [(3)]. The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry toward the development of such drug delivery systems [(4)].

Ofloxacin belongs to fluoroquinolone antibiotic and is used for the treatment of upper and lower respiratory tract infections. It exhibits pH-dependent solubility, more soluble acidic pH, slightly soluble alkaline pH conditions, and has an absorption window confined to the upper part of the gastrointestinal tract [(5)]. Hence, it was considered a suitable candidate for formulation as a floating drug delivery system. To study the effect of concentration of different polymers (HPMCK4M, HPMC K15M, HPMC K100M, compritol 888 & xantham gum), on the drug release from ofloxacin floating tablets.

2. MATERIALS & METHODS:

2.1. Materials

All the materials used in the current study were of pharmaceutical grade. Ofloxacin was chosen as a model drug (Gift sample from Hetero labs, Pvt ltd, Hyderabad). Polymers like HPMC K4M, HPMC K15, HPMC K100 (Signet Chemical Corporation, Mumbai), Compritol888 (Matrix labs, Pvt ltd, Hyderabad), Microcrystalline cellulose, Sodium bicarbonate, Xanthum gum, and Magnesium stearate were procured from S.D. Fine chemical Pvt Ltd, Mumbai.

2.2. Methods

2.2.1. Evaluation of precompression parameters

The powder blend of all formulations was evaluated for Bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose.

2.2.2. Formulation development

Preparation of floating tablets of ofloxacin

Preparation of ofloxacin floating tablets by direct compression method. Drug, polymer, sodium bicarbonate, and diluent were weighed and mixed in geometrical order in a mortar; this powder mixture was passed through sieve #60 & homogeneously blended in a polybag for about 5 to 10 min. Then lubricated with the previously weighed magnesium stearate was added to obtain the blend for compression. Then the lubricated blend was subjected to compression by 12.7mm standard flat-faced punches on an eight-station rotary tablet punching machine [(6)].

Table 1: Composition of floating tablets of ofloxacin

Code	Ofloxacin	HPMC K4M	HPMC K15M	HPMC K100M	Compritol 888	Xanthum gum	MCC	$NaHCo_3$	Mg stearate
F1	400	100	-	-	-	-	120	120	10
F2	400	150	-	-	-	-	70	120	10
F3	400	200	-	-	-	-	20	120	10
F4	400	-	100	-	-	-	120	120	10
F5	400	-	150	-	-	-	70	120	10
F6	400	-	200	-	-	-	20	120	10
F7	400	-	-	100	-	-	120	120	10
F8	400	-	-	150	-	-	70	120	10
F9	400	-	-	200	-	-	20	120	10
F10	400	-	-	-	100	-	120	120	10
F11	400	-	-	-	150	-	70	120	10
F12	400	-	-	-	200	-	20	120	10
F13	400	-	-	-	-	100	120	120	10
F14	400	-	-	-	-	150	70	120	10
F15	400	-	-		-	200	20	120	10

(Weight in mg)

2.2.3. Evaluation of post-compression studies

2.2.3.1. Weight variation test

Twenty (20) tablets from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with the average weight.

2.2.3.2. Thickness test

The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets by using vernier calipers.

2.2.3.3. Hardness test

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness each was recorded in kg/cm^2 and the average hardness and the standard deviation were reported.

2.2.3.4. Friability test

The six (6) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25rpm for 4min (100 rotations) in the Roche friabilator [7 & 8].

2.2.3.5. Drug content

Three tablets were taken, powdered and the powder equivalent to one dose each was transferred to a 100ml volumetric flask, and this 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and diluted suitably and drug content in the samples was estimated using UV-spectrophotometer at 294nm [9].

2.2.3.6. *In vitro* drug release studies

The *in vitro* drug release study was performed for the single and multiple-unit tablets using USP type II dissolution apparatus was used. At predetermined time intervals samples (5 ml) were collected and replenished with the same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 294nm. The floating time is determined by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as the testing medium maintained at 37°C & 50 rpm. The study was monitored for up to 12 hrs [10].

2.2.4. Dissolution profile modeling

There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and reference dissolution profiles as follows zero-order kinetics, first-order kinetics, Korsmeyer-Peppas, and Higuchi model [11].

3. RESULTS AND DISCUSSION:

3.1. Pre-compression studies

The results of the pre-compression studies of power blends are carr's index, angle of repose, and Hausner's ratio was within the limits and comply with the standards. The results are specified in Table 2.

Table 2: Physical properties of powder blends of tablet formulations

Formulation	CI	Angle of repose	Hausner's ratio
F1	13.4	26.7º	1.14
F2	14.6	27.5º	1.12
F3	12.8	28.2º	1.16
F4	14.7	28.4º	1.18
F5	13.5	27.5º	1.14
F6	12.4	27.4º	1.18
F7	13.8	28.8º	1.07
F8	11.6	28.5º	1.14
F9	14.6	27.4º	1.16
F10	13.3	28.6º	1.15
F11	12.9	28.4º	1.17
F12	11.2	27.8º	1.12
F13	12.6	27.6º	1.15
F14	11.8	28.1º	1.17
F15	13.7	26.8º	1.14

3.2. Evaluation of post-compression studies

All the prepared formulations were tested for physical parameters like hardness, thickness, weight variation, and friability and found to be within the pharmacopeia limits. The drug content of all the formulations was determined and was found to be within the permissible limits. The results of the tests were tabulated in Table 3.

Table 3: Physical properties of powder blends of tablet formulations

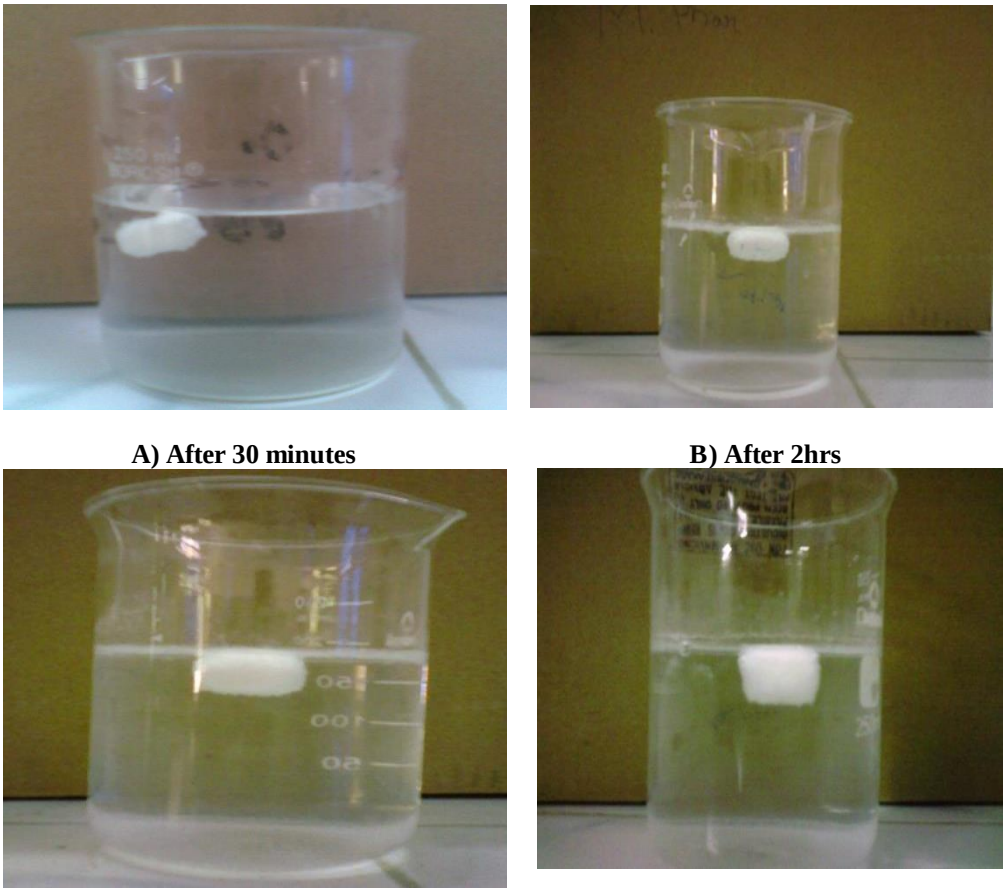
Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (Mm)	Friability%	Drug content
F1	736 ± 2.1	6.55 ± 0.71	4.51 ± 0.01	0.22 ± 0.18	97.25 ± 0.87
F2	739 ± 1.9	6.67 ± 0.85	4.42 ± 0.04	0.29 ± 0.21	96.91 ± 1.07
F3	752 ± 2.3	6.48 ± 0.59	4.61 ± 0.07	0.41 ± 0.35	99.81 ± 1.54
F4	740 ± 2.4	6.01 ±1.63	4.56 ± 0.05	0.19 ± 0.16	98.33 ± 0.15
F5	741 ± 1.25	6.27 ± 1.08	4.80 ± 0.02	0.21 ± 0.15	97.90 ± 1.09
F6	757 ± 2.91	5.97 ± 0.58	4.73 ± 0.03	0.14 ± 0.11	97.40 ± 0.54
F7	743 ± 1.8	5.92 ± 1.53	4.64 ± 0.09	0.21 ± 0.17	99.81 ± 1.54
F8	740 ± 3.95	6.10 ± 1.43	4.89 ± 0.05	0.23 ± 0.19	96.1 ± 1.15
F9	738 ± 2.6	6.61 ± 1.12	4.77 ± 0.04	0.15 ± 0.12	98.31 ± 0.76
F10	**741 ± 1.61**	**6.35 ± 1.56**	**4.68 ± 0.08**	**0.12 ± 0.09**	**98.16 ± 0.65**
F11	759 ± 3.75	6.29 ± 1.10	4.72 ± 0.06	0.24 ± 0.19	98.83 ± 0.20
F12	737 ± 1.36	6.38 ± 1.12	4.65 ± 0.04	0.20 ± 0.18	99.31 ± 1.85
F13	741 ± 2.1	6.20 ± 0.54	4.79 ± 0.07	0.17 ± 0.14	97.33 ± 1.15
F14	750 ± 3.9	5.79 ± 0.85	4.37 ± 0.05	0.11 ± 0.87	98.71 ± 0.76
F15	742 ± 1.8	6.12 ± 1.06	4.64 ± 0.08	0.13 ± 0.76	99.85 ± 0.98

3.3. Floating properties of ofloxacin tablets

The formulations were tested for floating properties like floating lag time and total floating time. The results of the tests were tabulated in Table 4 and Figure 1. All the developed formulations showed well *in vitro* buoyancy.

Table 4: Floating properties of ofloxacin tablets

Formulation	Lag time (sec)	Total floating time (hrs)
F1	25	7
F2	36	8
F3	41	9
F4	50	10
F5	62	10
F6	68	10
F7	120	>12
F8	140	>12
F9	250	>12
F10	**24**	**>12**
F11	37	11
F12	57	10
F13	170	>12
F14	270	>12
F15	250	>12



A) After 30 minutes **B) After 2hrs**

C) After 6 hrs **D) After 12hr**

Figure 1: *In vitro* buoyancy of floating tablets in 0.1 NHCl

3.4. *In vitro* drug release studies

The formulations F1 to F3, prepared with HPMC K4M and drug release were found to be 99.42% 98.03%, and 98.41% in 6 hrs. The formulations F4 to F6, prepared with HPMC K15M and drug release showed 99.43%, 99.14%, and 98.05% in 10 hrs. The formulations F7 to F9, prepared with HPMC K100M and drug release were 85.38%, 71.52%, and 57.25% in 12 hrs. These studies indicated that as the viscosity increases the drug release from the floating tablets is decreased. The formulations F10 to F12 were prepared with compritol 888 and release was released 98.45%, 99.24%, and 98.05% in 12 hrs. Compritol 888 has a very low density than HPMC polymers hence the high concentration of polymer required for the release of the drug maintains well *in vitro* buoyancy. *In vitro* dissolution studies of formulations F13 to F15, prepared with xanthum gum and drug release were 51.35%, 46.52%, and 57.25% in 12 hrs respectively. The results are represented in Figure 2.

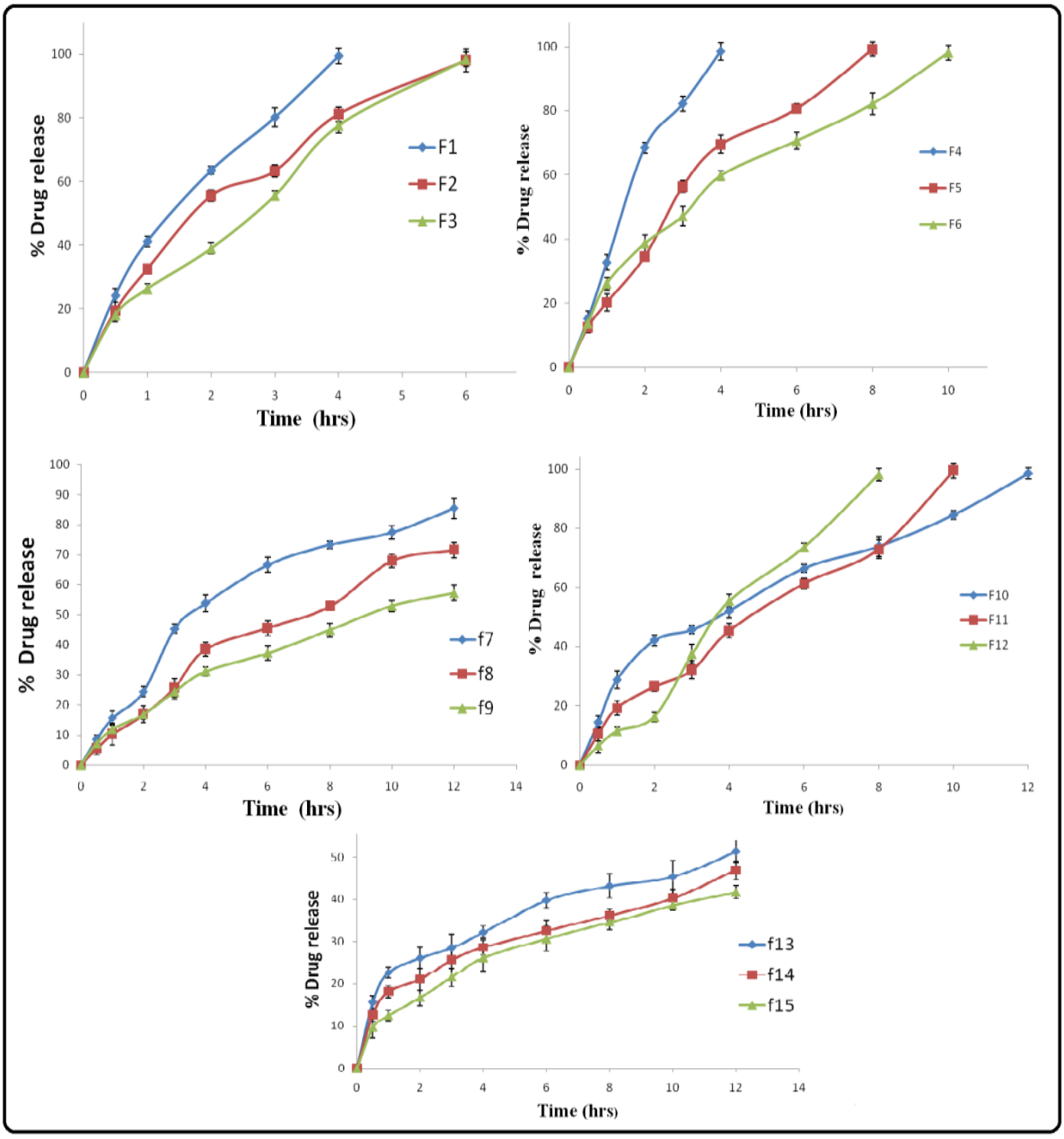


Figure 2: *In vitro* drug release profiles of formulations (F1 to F15)

3.5. Kinetic modeling of the data

The mechanism of release for the optimized formulations was determined by finding the R^2 value for each kinetic model, corresponding to the release data of formulations. The results are tabulated in Table 5. The formulation F10 showed a high regression value of 0.985 for the first order with non-fickian diffusion of drug release.

Table 5: Regression coefficient (R^2) values of different kinetic models

Formulation	Zero-order	First order	Higuchi	Peppas	n value
F1	0.610	0.451	0.864	0.905	0.453
F2	0.685	0.516	0.911	0.960	0.515
F3	0.825	0.394	0.971	0.963	0.654
F4	0.805	0.886	0.961	0.984	0.435
F5	0.817	0.961	0.966	0.976	0.327
F6	0.903	0.967	0.987	0.975	0.431
F7	0.863	0.972	0.983	0.981	0.427
F8	0.979	0.891	0.922	0.905	0.675
F9	0.968	0.968	0.960	0.992	0.787
F10	0.826	0.985	0.981	0.979	0.588
F11	0.932	0.982	0.985	0.982	0.666
F12	0.946	0.978	0.965	0.923	0.539
F13	0.839	0.910	0.973	0.975	0.436
F14	0.856	0.913	0.913	0.989	0.662
F15	0.831	0.862	0.862	0.933	0.320

4. CONCLUSION:

The ofloxacin floating tablets were prepared by using gel-forming polymer HPMC K4M, HPMC K15M, HPMC100M, Compritol 888, xantham gum, and gas generating agent sodium bicarbonate to enhance the gastric retention time. The formulation with compritol 888 (F10) showed the best result in terms of the required lag time (24 sec) and floating duration time of 12 hrs. The drug release from the tablet was carried out for 12 hrs and the drug release mechanism was non-fickian diffusion.

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