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Formulation Development And In-Vitro Evaluation Of Intragastric Floating Drug Delivery System Of Ofloxacin

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Abstract: The study describes the formulation development and *in-vitro* evaluation of intragastric floating drug delivery of Ofloxacin. The 3^2 full factotial design was employed to evaluate the contribution of hydroxypropyl methyl cellulose (HPMC) K 15 M / HPMC K 100 LV ratio and sodium lauryl sulfate (SLS) on drug release from HPMC matrices. Floating tablets were prepared by using direct compression method. Formulations were evaluated for *in-vitro* buoyancy studies, swelling index and drug release study using paddle type dissolution apparatus using 0.1 N HCl as a dissolution medium. All formulations had total floating time of more than 12hours.Formulation F1 had the highest floating lag time of 36.5seconds.The swelling index of formulation F1 showed highest results of 2.648 for 12 hours. Formulation F1 showed the highest percentage drug release of 99.12 for 12 hours. In the kinetics studies it was concluded that the peppas model was the best fit model. Formulation F1 was considered to be stable after stability studies conducted for 3 months.
Key Words: Gastroretentive drug delivery, Antibiotic, Ofloxacin.

INTRODUCTION

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), by using gastro-retentive dosage forms (GRDFs). GRDFs can remain in the gastric region for several hours and hence, prolong the gastric residence time of drug.[1]

Quinolones are similar to sulfonamides, totally synthetic chemical compounds with a significant antibacterial activity. Ofloxacin is a synthetic chemotherapeutic antibiotic of fluroquinolones drug class considered to be a second generation fluroquinolones. Ofloxacin is the broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative. Ofloxacin is more potent against gram positive organism and certain anaerobes when compared with other fluroquinolone antibiotics.[2]

The objective of this study was to develop a gastroretentive floating drug delivery system containing Ofloxacin. The 3^2 full factorial design were chosen, in this the amount of HPMC K15, HPMC K100 (X1), solubulising agent SLS (X2) were selected. Regressional analysis was performed to conclude the best formulation.[3]

MATERIALS AND METHODS

Ofloxacin was supplied as a gift sample from Goodman Pharmaceuticals, Pondicherry, HPMC K15,Lactose were received from Loba Chemie, Mumbai, HPMC K 100,SLS, Sodium bicarbonate from Cipla Labs, Mumbai.

PRELIMINARY TRIALS: PREPARATION OF OFLOXACIN FLOATING TABLETS

The floating tablets were prepared by direct compression method using (9 mm diameter, round flat faced punches) multiple punch tablet compression machine (Cadmach Machinery Ltd., Ahmedabad, India). Each tablet contained 400 mg of Ofloxacin, the batch size for each formulation was 100 tablets.[4]

EXPERIMENTAL DESIGN

The experimental design with corresponding formulations is outlined that Content of polymer blend was 15% of the total tablet weight. Blends of HPMC K15 and HPMC K100 were evaluated at 85:15, 75:25 and 65:35, while content of SLS was evaluated at0%, 1%, 2% of the total tablet weight. [3]

The experimental design was formulated in the tables 1,2,3.

Table.1: Ratio's of polymer used in the formulation

Sl.No	Code values	Actual values in mg	
		HPMC K15:HPMC K100	SLS
1	-1	85:15	0%
2	0	75:25	1%
3	1	65:35	2%

Table.2: Formulation of ofloxacin using 3^2 full factorial design

S.NO	BATCH CODE	Variable level in Code	
		X1	X2
1	F1	+1	+1
2	F2	+1	0
3	F3	+1	-1
4	F4	0	+1
5	F5	0	0
6	F6	0	-1
7	F7	-1	+1
8	F8	-1	0
9	F9	-1	-1

Table.3: Composition of floating Tablets of Ofloxacin:

Sl. No.	Ingredients (mg/tablet)	Formulations Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Ofloxacin	400	400	400	400	400	400	400	400	400
2	HPMCK15 HPMCK100	58.5 31.5	58.5 31.5	58.5 31.5	67.5 22.5	67.5 22.5	67.5 22.5	76.5 13.5	76.5 13.5	76.5 13.5
3	Sodium lauryl sulfate	12	6	0	12	6	0	12	6	0
4	Sodium bicarbonate(10%)	60	60	60	60	60	60	60	60	60
5	Magnesium stearate(1%)	6	6	6	6	6	6	6	6	6
6	Lactose	32	38	44	32	38	44	32	38	44
7	Total	600	600	600	600	600	600	600	600	600

EVALUATION OF TABLETS

A. SWELLING INDEX:

The extent of swelling was measured in terms of percentage weight gain by the tablet. The swelling behaviour of formulation F1-F9 was studied. One tablet from each formulation was kept in a petritdish

containing 0.1N HCl. The tablet was withdrawn in time intervals, soaked with tissue paper, and weighed. Weights of the tablet were noted and the process was continued till the end 12 hrs. Percentage weight gain by the tablet was calculated by formula.[5]

$$\text{Swelling Index} = \frac{\text{Weight of swollen tablet - Initial weight of tablet}}{\text{Initial weight of tablet}}$$

B. *IN-VITRO* BUOYANCY STUDIES :

The time taken for tablet to emerge on the surface of the medium is called the floating lag time or buoyancy lag time and duration of time the dosage form constantly remains on the surface of the medium is called total floating time. The buoyancy of the tablets was performed by using 0.1 N HCl. The time of duration of floatation was observed visually.[5]

C. *IN-VITRO* DRUG RELEASE STUDIES:

The release rate of Ofloxacin from floating tablets was determined using USP Dissolution Testing Apparatus type-II (paddle method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5°C and 100 rpm. The samples were withdrawn and replaced with fresh medium at specific time intervals. The samples withdrawn were diluted and the amount of drug released was estimated using UV Spectrophotometer.[6]

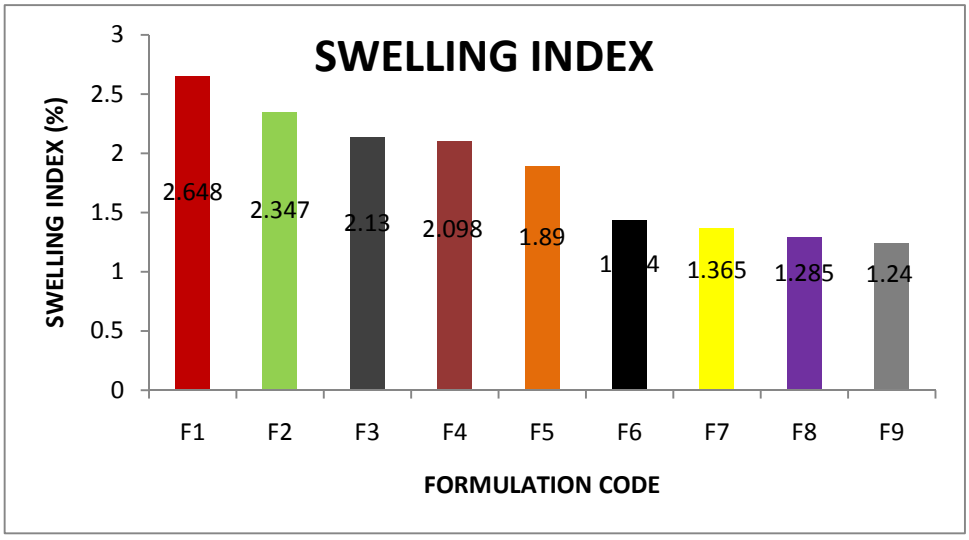
D. Kinetics of *in-vitro* drug release studies:

To analyze the mechanism of drug release from the tablets the *In-vitro* drug release, data were fitted to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas.[1]

E. STABILITY STUDIES:

To assess the drug and formulation stability, stability studies were done according to International Conference on Harmonization and World Health Organisation guidelines. The tablets were stored at 40ºC/75% relative humidity in closed high-density polyethylene bottles for 3 months. Tablets were analyzed at specific time intervals for hardness, drug content, *in vitro* buoyancy studies, *in vitro* drug release studies.[7]

Figure.1: Comparison of swelling Index of formulations F1-F9



RESULTS AND DISCUSSION

SWELLING INDEX:

The floating and drug release profile are dependent upon swelling behaviour of the tablets. Swelling index increased as the weight gained by the tablet increased proportionally with the rate of hydration. Swelling is also a vital factor to ensure buoyancy and drug dissolution of matrix tablet. The floating tablet containing HPMCK15 and HPMCK100. Results were illustrated in the figure 1.The swelling Index of different formulations decreased in the following order.

F1> F2 > F3 > F4 > F5 > F6 > F7 > F8>F9

IN-VITRO BUOYANCY STUDIES:

The floating lag time of formulation F1, F2 and F3 was found to be 36.5, 34.6, 32.5 respectively. 30.8, 29.4 and 28.2 for F4, F5 and F6. 26.2, 25.4 and 24.6 for F7,F8 and F9 respectively.This above phenomena might be due to the generation of large amounts of effervescence with 10% sodium bicarbonate. This would lead to an increasing rate of pore formation and consequently rapid hydration of tablets. Results for *in-vitro* buoyancy studies were shown in the figures 2, 3**.**

Figure.2: *In-vitro* buoyancy studies

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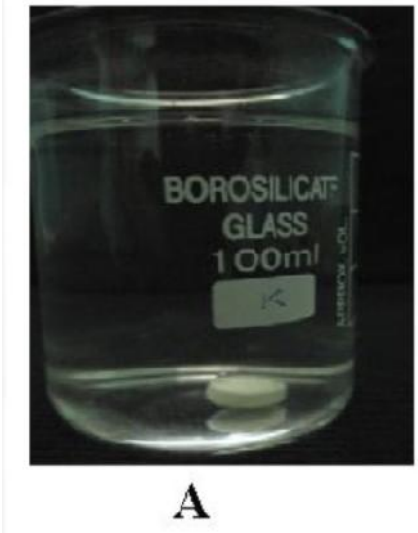
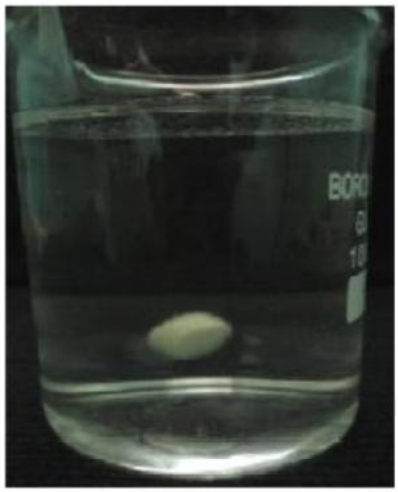
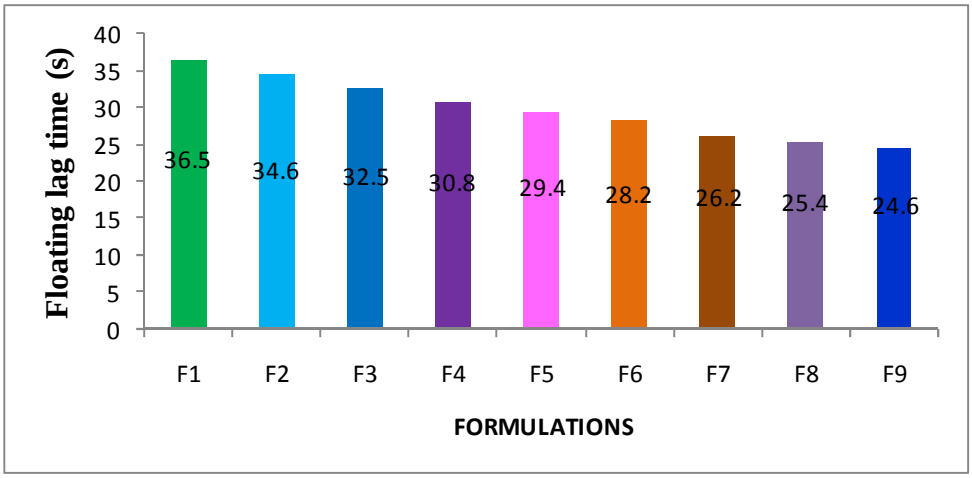
<tr><td> 

A</td><td> 
B</td></tr>
<tr><td>Floating lag time at initial stage</td><td>Tablet start to rise up to the surface</td></tr>
<tr><td> 
C</td><td> 

D</td></tr>
<tr><td>Floating lag time at 36.50 sec</td><td>Floating lag time after 12 hrs</td></tr>
</table>

Figure.3: Comparison of Floating lags time studies for different formulations (F1-F9)



***IN-VITRO* DRUG RELEASE:**

In-vitro drug release studies of all the formulation of Ofloxacin intragastric tablets were carried out in 0.1 N HCl. The study was performed for 12 hrs and cumulative drug release was calculated at different time interval**.** This showed that HPMC hydrated more rapidly with high amount of SLS in the presence of 0.1 N HCl. The formulation F1, F2 and F3 showed the drug release 99.12, 96.52 and 94.91% upto 12 hrs but F4, F5 and F6 showed the drug release 92.12, 90.06 and 89.80% upto 10 hrs and F7, F8 and F9 showed the drug release 87.81, 85.64 and 84.61 upto 8hrs. Results were given in the table 4 and figure 4.

Figure.4: Comparison of Floating lags time studies for different formulations (F1-F9)

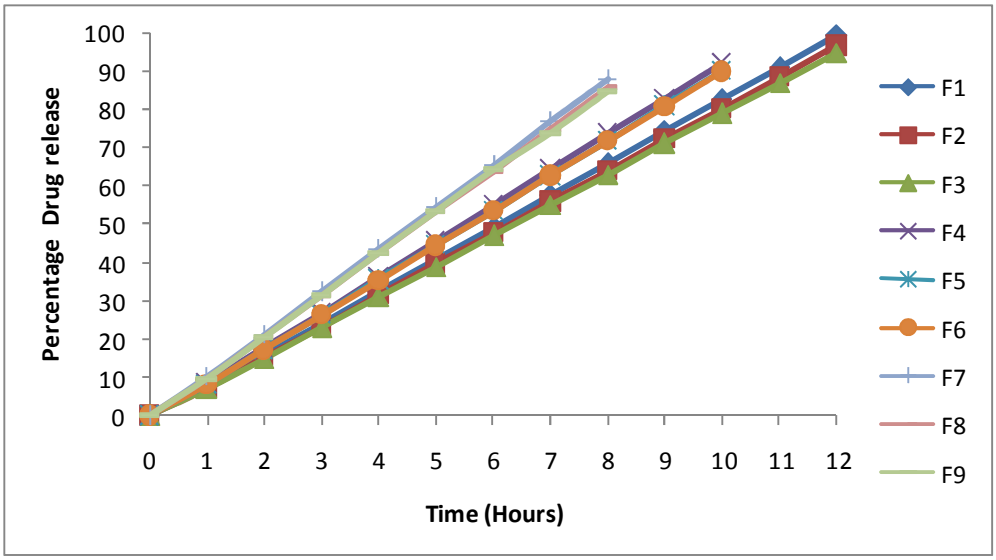


Table.4. In-vitro drug release studies

S.NO	Medium	Time(hrs)	% drug release (F1)	% drug release (F2)	% drug release (F3)	% drug release (F4)	% drug release (F5)	% drug release (F6)	% drug release (F7)	% drug release (F8)	% drug release (F9)
1	0.1 N Hydrochloric acid	0	0	0	0	0	0	0	0	0	0
2		1	07.38± 0.040	07.16± 0.030	07.02± 0.031	08.35± 0.020	08.13± 0.030	08.11± 0.905	10.14± 0.050	9.78±0. 030	09.73± 0.051
3		2	15.72± 0.010	15.28± 0.011	15.01± 0.041	17.67± 0.010	17.23± 0.031	17.19± 0.110	21.24± 0.031	20.70± 0.041	20.31± 0.012
4		3	24.06± 0.041	23.41± 0.032	23.00± 0.041	26.98± 0.050	26.33± 0.061	26.27± 0.036	32.34± 0.041	31.53± 0.042	31.46± 0.041
5		4	32.40± 0.090	31.53± 0.043	30.99± 0.012	36.30± 0.040	35.45± 0.040	35.34± 0.026	43.45± 0.031	42.36± 0.020	42.23± 0.022
6		5	40.74± 0.030	39.66± 0.051	38.98± 0.030	45.61± 0.030	44.55± 0.072	44.42± 0.032	54.55± 0.020	53.20± 0.010	53.50± 0.021
7		6	49.08± 0.033	47.78±. 0410	46.97± 0.010	54.93± 0.041	53.63± 0.051	53.50± 0.041	65.65± 0.081	64.03± 0.031	64.21± 0.030
8		7	57.42± 0.060	55.90± 0.030	54.96± 0.060	64.24± 0.030	62.73± 0.030	62.58± 0.040	76.75± 0.030	74.86± 0.031	73.92± 0.033
9		8	65.76± 0.030	64.03± 0.050	62.94± 0.042	73.56± 0.041	71.83± 0.050	71.65± 0.031	87.86± 0.051	85.69± 0.021	84.61± 0.050
10		9	74.11± 0.010	72.15± 0.021	70.93± 0.053	82.81± 0.031	80.93± 0.041	80.73± 0.051	-	-	-
11		10	82.42± 0.080	80.28± 0.043	78.92± 0.041	92.19± 0.012	90.02± 0.020	89.81± 0.11	-	-	-
12		11	90.78± 0.021	88.40± 0.080	86.91± 0.032	-	-	-	-	-	-
13		12	99.12± 0.020	96.52± 0.030	94.90± 0.029	-	-	-	-	-	-

IN-VITRO DRUG RELEASE KINETICS:

The data obtained from *in vitro* drug release studies were fitted to zero order, first order, Higuchi, korsmeyers-peppas equation. To confirm the exact mechanism of the drug release korsmeyer and peppas equqtion superposes two apparently independent mechanism of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer. Results were given in the table 5.

STABILITY STUDIES:

No statistically significant differences were observed in Hardness, percentage drug content and percentage drug release in optimized formulation at the end of months of stability studies. So, it can be concluded that the formulation is stable for short term storage conditions. Results were given in the table 6 and figure 5,6.

Table 5 : Kinetics of In-vitro drug release

Code	Zero order		First order		Higuchi		Korsemayer-Peppas		Best fit model
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K ($mg\ h^{-1/2}$)	R^2	N	
F1	0.9999	0.0100	0.9999	0.0001	0.9237	0.025	0.9999	1.0356	Peppas
F2	0.9999	0.0102	0.9999	0.0001	0.9236	0.0220	0.9999	1.0367	Peppas
F3	0.9999	0.0103	0.9999	0.0001	0.9233	0.0290	0.9999	1.0347	Peppas
F4	0.9999	0.0120	0.9999	0.0001	0.9259	0.0310	0.9999	1.0346	Peppas
F5	0.9998	0.0117	0.9998	0.0001	0.9266	0.0304	0.9998	1.0367	Peppas
F6	0.9994	0.0118	0.9994	0.0001	0.9226	0.0305	0.9999	1.0413	Peppas
F7	0.9996	0.0141	0.9996	0.0001	0.9304	0.0328	0.9997	1.0220	Peppas
F8	0.9997	0.0141	0.9997	0.0001	0.9308	0.0328	0.9997	1.0422	Peppas
F9	0.9998	0.0138	0.9998	0.0001	0.9302	0.0322	0.9999	1.0367	Peppas

Table.6: Stability studies

Characteristics	Initials	1 Month	2 Month	3 Month
Hardness (kg/cm2)	3.49	3.42± 0.032	3.40± 0.095	3.39± 0.035
Drug Content (mg/Tab)	99.20± 0.040	99.12± 0.060	99.10± 0.030	99.08± 0.031
Floating lag time (s)	36.5± 0.25	36.46± 0.036	36.39± 0.005	36.0± 0.005
Total floating time	>12hrs	>12hrs	>12hrs	>12hrs
***In-vitro* drug released at end of 12th hour.**	99.12± 0.020	99.07± 0.032	99.04± 0.025	99.0± 0.030

Figure.5: Floating lag time of F1 after stability studies for 3 months

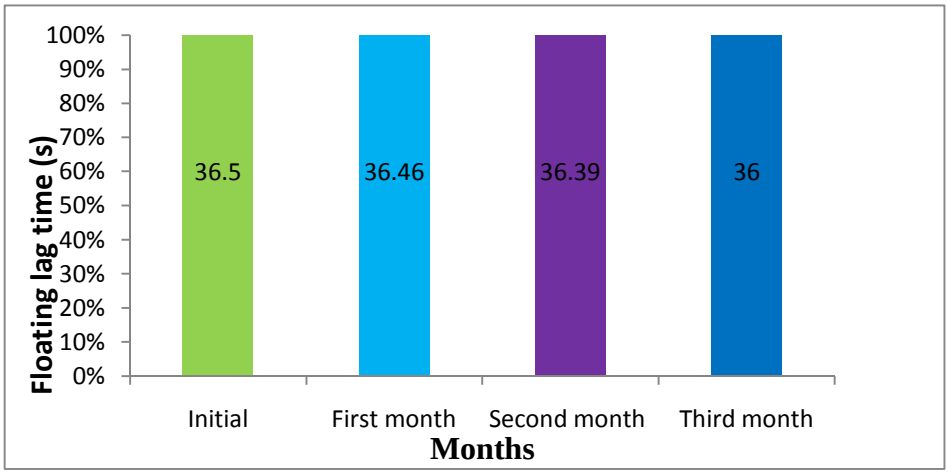
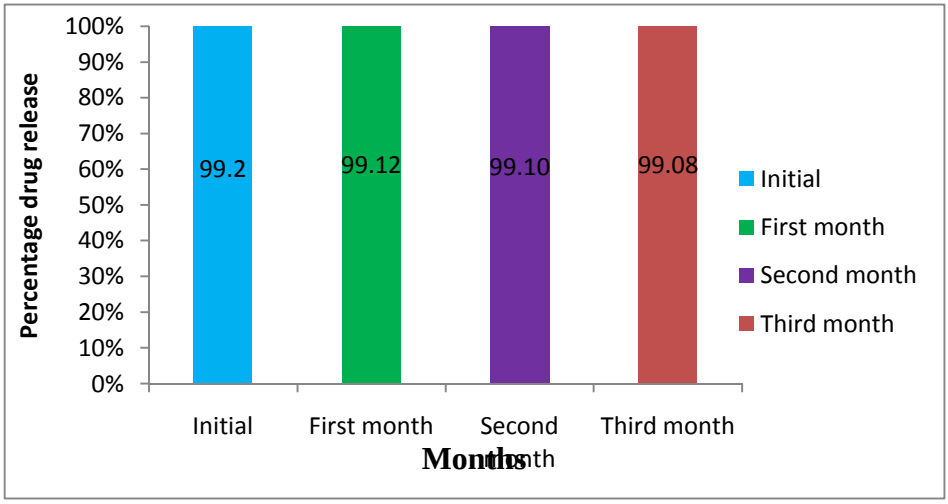


Figure.6: Comparisons of percentage drug content for formulation F1 with initial and different periods of stability



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