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Original Article

Formulation Development and Evaluation of Gastro Retentive Floating Drug Delivery System for Novel Fluoroquinolone using Natural and Semisynthetic Polymers

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Abstract

The purpose of present research work is to develop gastro retentive formulation for Moxifloxacin using various release retardants. Moxifloxacin, that is a novel synthetic fluoro quinolone, is an iantibacterial agent. Floating tablets of Moxifloxacin. HCl were prepared using variable amounts of HPMCK4M, HPMCK15M and HPMCK100M with effervescent mixtures by direct compression technique. Totally 9 formulations were designed, prepared and are evaluated for various pharmacopoeial tests like uniformity of weight, thickness, Hardness, friability, floating lag time, Total floating time. Drug release profiles of formulation trails subjected to kinetic modeling. Parameters like correlation coefficient(r), slope (b), intercept (a) were determined. The results reveal that floating lag time decreases with decreased viscosity of polymer composites. According to SUPAC guidelines formulation (F_4) containing 12.5% HPMCK15M was found to be most identical formulation (similarity factor f_2= 70.997, dissimilarity factor f_1= 6.007 to marketed product (AVELOX). Trail F_4 drug release found to be first order kinetics, Non-Fickian Diffusion Anomalous Transport. (n= 1.065).

Keywords: Moxifloxacin. HCl, Gastroretentive, Floating Lag Time, HPMCK15M, Anomalous transport, First order kinetics.

1. Introduction

The effective oral drug delivery practice depends on numerous factors like gastric emptying process, GI transit time, release of drug from dosage form and absorption site for drug [1-3]. The design of oral controlled drug delivery systems (DDS) is aimed to obtain desirable and enhanced bioavailability. Gastric emptying is a dynamic process and gastro retentivity of dosage form results improved clinical response.

Several difficulties were present in front of researchers (Formulation Scientist) for designing controlled release systems for better

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absorption, improved bioavailability [4]. The controlled gastric retention of solid dosage forms was obtained by numerous mechanisms such as flotation, bioadhesion, High density, modified shape systems, or by drug interactions which act through decreased gastric motility [4-6].

Floating drug delivery system is also known as hydrodynamically balanced system (HBS). Floating Drug Delivery Systems (FDDS) have a bulk density is lower than gastric fluids and thus remain buoyant in gastric environment for prolonged period of time, without affecting the gastric emptying rate. Dosage form is stayed in stomach due to flotation mechanism, which results controlled rate of drug release. After the release of drug, the residual system is run out from the gastro environment; this will increases GRT and a better control of fluctuations in plasma drug concentrations [5, 7-9].

Moxifloxacin, A 4th generation synthetic fluoroquinolone belongs to broad spectrum antibacterial agent. It has a narrow absorption window. It was absorbed in the proximal areas of gut, hence it is selected for formulating gastroretentive drug-delivery system that will prolong the gastric transit time of formulation, and results enhanced bioavailability [10-11].

An attempt is made in current study to develop gastro retentive drug delivery system (preferably by Flotation) using various release rate modifiers (Natural- Xanthan Gum, Semisynthetic- HPMCK4M, HPMCK15M, HPMCK100M) and effervescent mixtures [12-13].

A systemic approach for design and development of gastro retentive drug delivery system of Moxifloxacin using polymers which increases the gastric transit time, improve penetrability of drug via mucosa thereby improving the clinical efficacy of the active ingredient.

2. Materials and Methods

2.1. Materials

A gift sample of Moxifloxacin HCl was procured from Macleods Pharmaceutical Ltd, Mumbai, India. HPMCK4M, K15M and K100M were obtained from Loba Chemie Pvt. Ltd, Mumbai, India. Xanthan Gum was gifted from MSN Labs Ltd, Hyderabad. All other excipients such as Sodium bicarbonate, Magnesium stearate were obtained from S.D. Fine Chem. Ltd, Mumbai, India.

2.2. Preparation of Moxifloxacin HCl Floating Tablets

Direct compression technique was utilised for the preparation of floating tablets, each containing 400 mg Moxifloxacin HCl. Accurately weighed ingredients (except Moxifloxacin HCl) were screened for obtaining uniform size to ensure proper mixing, to obtain polymer mixture. The drug was then mixed with the polymer mixture for

10 minutes for uniform mixing of powder blend. Blend was lubricated with magnesium stearate. The formulae for Moxifloxacin HCl floating tablets were shown in table 1. Powder blend was subjected to preformulation analysis.

Powder blend was subjected to compression with the help of rotary tablet compression machine (Tablet Minipress). Compressed tablets were processed for Quality Control measures as per Pharmacopoeia. Final formulations were transferred to airtight and light resistance containers.

2.3. Evaluation of Moxifloxacin.HCl Floating Tablets

2.3.1. Hardness

The breaking/ crushing strength of the tablets was determined by measuring diametric breakdown of tablet using a Monsanto Tablet Hardness Tester. A hardness of about 2-4 kg/cm^2 is considered as preferable for optimal mechanical stability [14].

2.3.2. Friability

The friability of the tablets was carried with the help of Roche friabilator. 20 tablets were weighed noted as initial weight (W_0), these were subjected to 100 free falls from a fixed height and weighed (W) again. % friability was calculated by using following formula. The friability result should not be more than 1 %.

$$\text{Weight loss (\%)} = [W_0 - W / W_0] \times 100$$

2.3.3. Assay

Assay was performed by triturating stated number of tablets in pharmacopoeia (20) converted to powder, powder equivalent to 100mg of drug was added in 100 ml of 0.1 N HCl, followed by sonication. The solution was filtered through a 0.45 µ membrane filter, suitable aliquots were prepared, and the absorbance of the resultant solution was measured spectrophotometrically at 288 nm using 0.1 N HCl as blank [11, 12, 15].

2.3.4. Thickness

Thickness formulations were determined by using vernier calipers, by placing tablet between two arms it.

2.3.5. In vitro Buoyancy Studies

This test is performed by placing the tablets in a beaker containing 100 mL of 0.1 N HCl (SGF). The time required for the upward movement of tablet to float on the 0.1 N HCl (SGF) was noted to be floating lag time [16-18].

2.3.6. In-vitro Drug Release Study

The *In vitro* dissolution rate study for formulation trails were performed using USP XXIII type-II dissolution test apparatus containing 900 ml of 0.1 N HCl operated under conditions like temperature 37 ± 0.5°C and rotated at a speed of 50 rpm. At predetermined time intervals, 5 ml of the samples were withdrawn as per the pharmacopoeial procedure. The resultant samples were analyzed for estimation of drug release by measuring the absorbance at 288

nm using UV-Visible spectrophotometer after suitable aliquots. The samplings were performed in triplicate manner (n = 3).

The dissolution profile of all the formulations was subjected to kinetic modeling such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to know the drug release mechanisms [15,19-21].

2.3.7 Swelling Index Study

To evaluate swelling index, tablet was placed in USP dissolution apparatus II with 900 ml 0.1N HCl after measuring the weight of tablet (W_1). Then weight of tablet (W_2) was determined by virtue of time i.e at different time intervals viz. 1, 2, 3, 4, 5, 6, 7, 8hrs after using blotting paper to remove surplus fluid. Swelling Index was calculated using following formula.

Swelling Index (%) = $[(W_2 - W_1) / (W_2)] \times 100$

3. Results and Discussion

Gastro retentive floating tablets of Moxifloxacin.HCl were prepared by using various polymers such as HPMCK4M, HPMCK15M and HPMCK100M along with effervescent mixtures. The formulae for Moxifloxacin HCl floating tablets were presented in table 1.

Powder blends were subjected to flow analysis. Results were summarized in table 2. Pre-formulation Results reveals that all formulations are passed the limits and blends shows good flow properties.

All formulations containing 400 mg Moxifloxacin HCl. Floating tablets were prepared by direct compression method. All the prepared tablets were subjected to various quality control tests such as drug content, floating lag time, mean hardness, total floating time, mean thickness, friability as per pharmacopoeial methods, and subjective results were summarized (Table 3). The hardness of tablets was in the range of 4.485±0.14-5.501±0.17 Kg/Cm^2. Weight loss in the friability test was less than 0.11%. Results for Drug content of final batches was found to be within the acceptable range only. All formulation batches passed the Weight variation test.

The purpose of swelling study is to determine the water uptake capability of the retardant. Swelling study was performed on all formulation Trials about 12 hours. From the swelling study it is found that, All formulation trails were shown swelling phenomenon when come in contact with 0.1 N HCl but stayed without breaking during the study period. Formulation F_4 prepared with HPMCK15M was found to have highest swelling property and the data for swelling evaluation was presented in table 4.

In vitro drug release studies were performed for formulation trials using 0.1 N HCl as a dissolution fluid as per pharmacopoeial procedures. Comparative zero order plots for formulations are shown in Figure 1-3. % Cumulative drug release (CDR) of formulations F_1-F_9 at 24 hr was found to be in the range of 92.75±0.23-99.91±0.02. % CDR against to time for formulations F_1-F_9 were presented in table 5. From the results, it reveals that amount of retardant was inversely proportional to the release rate of drug due to viscosity gradient of polymer composite.

Hence predicted drug release can be achieved by manipulating the composition of retardants [22-23].

Variations were observed in dissolution parameters ($t_{10\%}$, $t_{25\%}$, $t_{50\%}$, $t_{75\%}$ $t_{90\%}$) due to formulation variables. Formulation (F_4) containing 75 mg of HPMCK15M showed favorable dissolution parameter, which helps in meeting the objective of research by providing gastro retentivity and optimum drug release. The initial eruption of drug release (burst release) is due to change in viscosity of the polymeric mixtures. The *in vitro* drug release profile of formulation trails was subjected to the goodness of fit test by linear regression analysis, with the aid of various kinetic models to know the drug release pattern from the formulation. The results were presented in table 6 and the plots are shown in figures 1-12. From the results concluded that all formulations belong to first order kinetics, R^2 values was found to be in the range of 0.948-0.998. r values of Higuchi's kinetics for factorial formulations was found to be in the range of 0.965- 0.988. n values for Peppas model, ranges from 0.964 to 1.103 confers drug release mechanism was non-Fickian diffusion (Super Case-II Transport) dissolution parameters for final batches was summarized in table 7. Dissolution profile of formulation (F_4) is compared with marketed product (AVELOX) shows similarity of (f_2) 70.997, difference factor (f_1) 6.007 (t_{cal} is <0.05).

4. Conclusion

On the basis of the current research study, the use of polymer (Natural and Semisynthetic) in combination had its own advantages of maintaining integrity and buoyancy of tablets. The effervescent based FDDS is a promising formulation to obtain gastro retentivity by using gel forming polymers such as HPMCK4M, HPMCK15M and HPMCK100M employing sodium bicarbonate as gas generating agent. Among the various FDDS formulations studied, the optimized formulation (F_4) prepared with HPMCK15M, Xanthan Gum showed the best result in terms of the required % Cumulative drug release, Floating lag time and total floating time was 99.85% within 24 hrs and is considered as the ideal formulation**.**

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Figures:

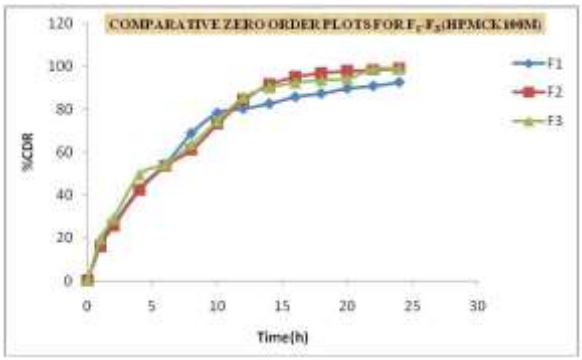

Figure 1. Comparative Zero order plots for F_1-F_3.

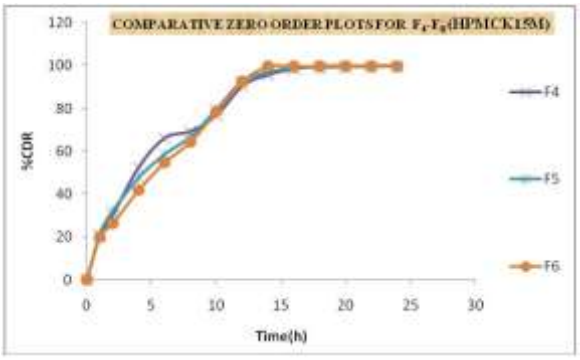

Figure 2. Comparative Zero order plots for F_4-F_6.

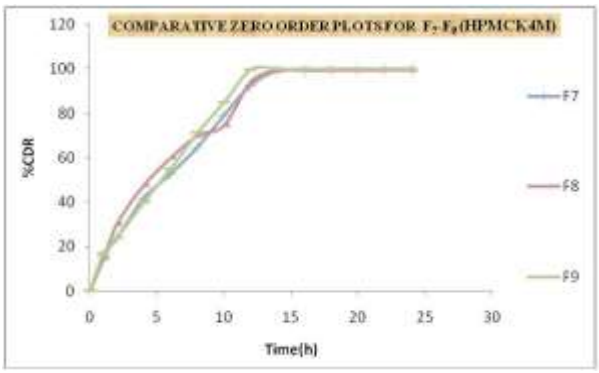

Figure 3. Comparative Zero order plots for F_7-F_9.

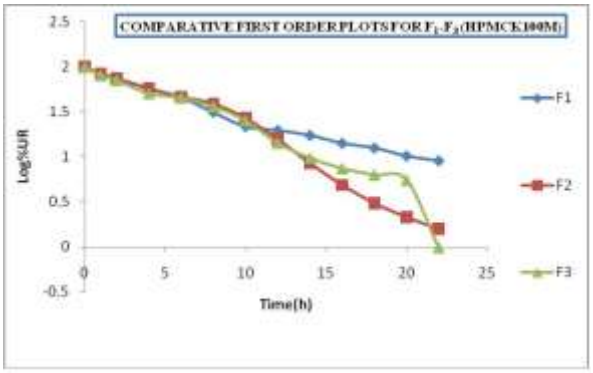

Figure 4. Comparative First order plots for F_1-F_3.

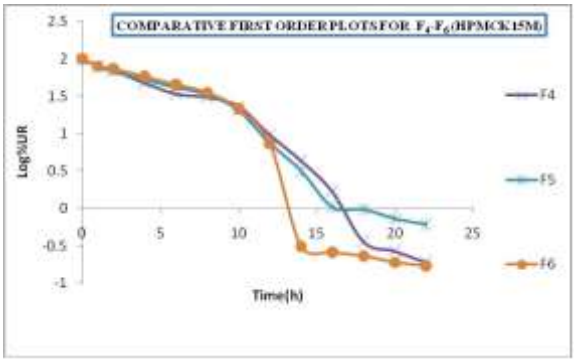

Figure 5. Comparative First order Plots for F_4-F_6.

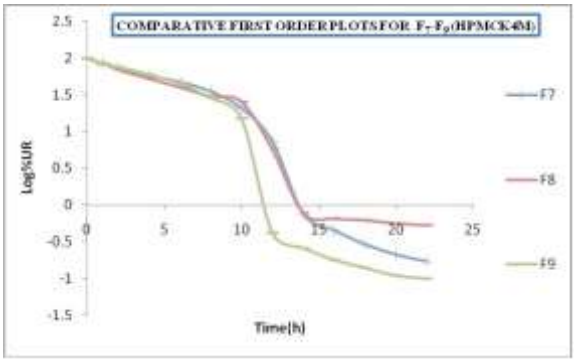

Figure 6. Comparative First Order plots for F_7-F_9.

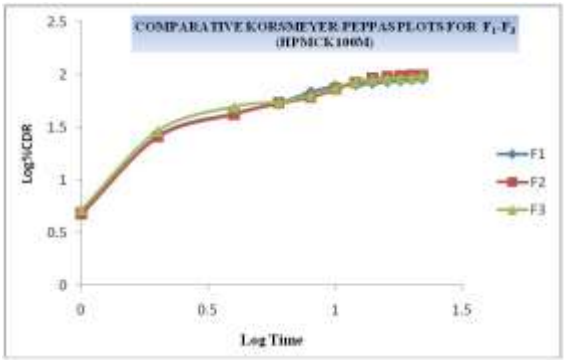

Figure 7. Comparative Korsmeyer-Peppas Plots for F_1-F_3.

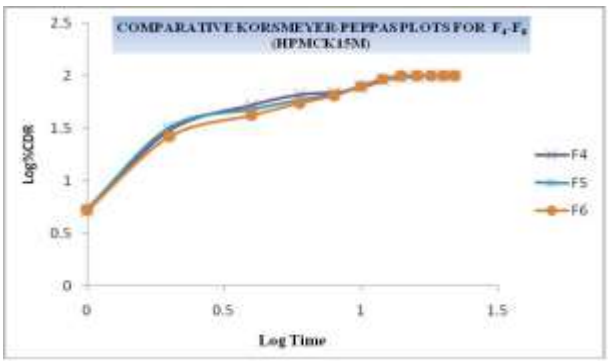

Figure 8. Comparative Korsmeyer-Peppas plots for F_4-F_6.

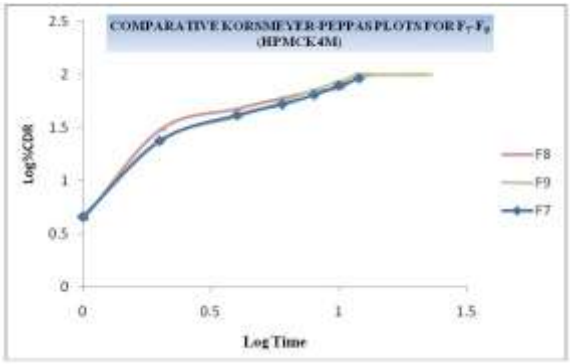

Figure 9. Comparative Korsmeyer-Peppas Plots for F_7-F_9.

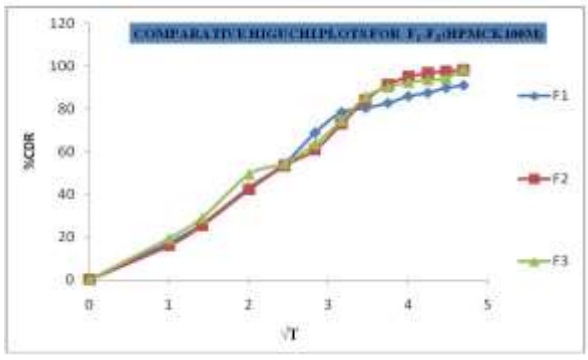

Figure 10. Comparative Higuchi plots for F_1-F_3.

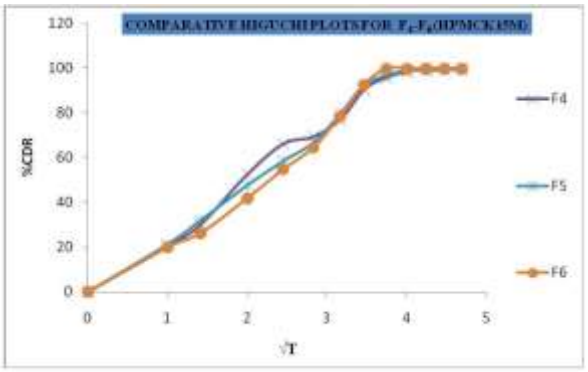

Figure 11. Comparative Higuchi plots for F_4-F_6.

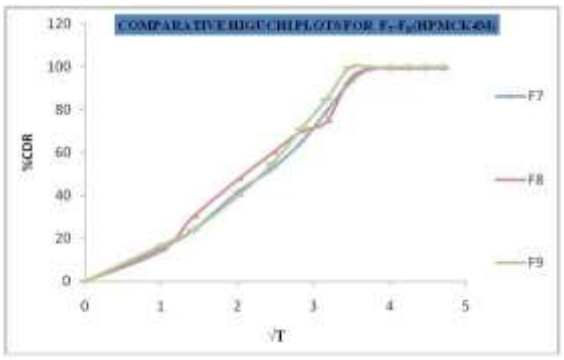

Figure 12. Comparative Higuchi plots for F_7-F_9.

Tables:

Table 1. Formulae for the preparation of Moxifloxacin HCl floating tablets.

Name of the Ingredients	Quantity for single Tablet (mg)								
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Moxifloxacin.HCl	400	400	400	400	400	400	400	400	400
Emcompress	20	35	50	20	35	50	20	35	50
HPMCK100M	75	60	45	-	-	-	-	-	-
HPMCK15M	-	-	-	75	60	45	-	-	-
HPMCK4M	-	-	-	-	-	-	75	60	45
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Xanthan Gum	50	50	50	50	50	50	50	50	50
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total Weight	600	600	600	600	600	600	600	600	600

Table 2. Pre-Formulation studies for Formulation Blends.

S.No	Formulation Code	Angle of Repose (°)	Compressibility Index (%)
1	F_1	28.56	16.34
2	F_2	28.45	15.35
3	F_3	27.08	14.59
4	F_4	26.77	15.67
5	F_5	25.28	14.58
6	F_6	25.41	14.48
7	F_7	24.30	12.30
8	F_8	24.72	14.12
9	F_9	24.53	14.01

Table 3. Final product quality assurance parameters (n=3).

nulation Code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Average Weight (mg)	Drug Content (%)	Floating lag time (sec)	Total floating time (h)
F_1	5.15±0.165	6.39±0.01	0.15±0.12	601.21±2.1	97.21±0.25	48.05±1.3	> 12
F_2	5.305±0.134	6.24±0.02	0.12±0.13	603.02±2.3	96.38±0.30	50.22±1.4	> 12
F_3	5.745±0.20	6.31±0.01	0.11±0.1	601.21±2.1	98.29±0.50	55.26±1.6	> 12
F_4	4.785±0.14	6.11±0.01	0.13±0.12	602.51±2.22	97.21±.40	48.45±1.4	> 12
F_5	5.399±0.29	6.12±0.03	0.144±0.13	600.22±2.48	98.38±0.90	53.67±1.5	> 12
F_6	5.110±0.45	6.23±0.06	0.15±0.05	602.29±2.31	97.698±0.70	57.63±1.7	> 12
F_7	5.31±0.19	5.817±0.01	0.121±0.13	603.11±1.12	98.19±0.25	42.98±1.2	> 12
F_8	5.501±0.17	5.93±0.03	0.143±0.132	602.24±1.21	98.48±0.30	46.21±1.5	> 12
F_9	5.212±0.37	6.20±0.03	0.126±0.140	601.22±2.28	97.31±0.50	51.72±1.6	> 12

Table 4. Swelling Idex of Moxifloxacin HCl Floating tablets.

S.no	Formulation Code	% swelling with respect to Time (h)					
		2	4	6	8	10	12
1	F_1	30	50.5	85	92	102	115
2	F_2	31	52.5	76	84	101	114
3	F_3	30	51.5	73	82	100	112
4	F_4	31	52.8	78	84.6	101	115
5	F_5	36	59.5	72	91.5	100	115
6	F_6	34	56	74	85.7	102	116
7	F_7	38	61	72	95	106	112
8	F_8	37.5	62	75	95	101	113
9	F_9	34	56	72	96	105	112

Table 5. *In-vitro* dissolution profile for Moxifloxacin.HCl Floating Tablets.

S.No	Time (H)	IN-VITRO DISSOLUTION PROFILE %CDR								
		F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
1	0	0	0	0	0	0	0	0	0	0
2	1	17.46±0.64	16.16±0.88	19.515±0.87	20.19±0.88	21.27±0.22	19.89±0.12	15.67±0.17	14.4±0.11	16.67±0.15
3	2	26.27±0.32	25.63±0.85	29.09±0.92	30.07±0.33	32.01±0.17	26.23±0.16	23.82±0.18	30.04±0.56	23.93±0.12
4	4	43.12±0.16	42.29±0.75	49.44±0.66	52.43±0.17	47.68±0.53	41.875±0.88	41.61±0.19	47.39±0.77	39.78±0.98
5	6	54.46±0.15	53.59±0.67	54.595±0.18	66.05±0.72	58.48±0.15	54.705±0.97	52.55±0.99	59.74±0.75	54.83±0.77
6	8	68.84±0.26	61.04±0.43	63.69±0.54	69.25±0.19	66.69±0.11	64.385±0.11	64.68±0.13	69.83±0.47	70.99±0.55
7	10	78.40±.18	73.15±0.11	74.65±0.49	76.78±0.11	79.54±0.55	78.545±0.34	79.11±0.12	74.51±0.76	84.8±0.87
8	12	80.38±0.17	84.33±0.18	85.725±0.54	90.33±0.17	92.54±0.19	92.64±0.15	92.65±0.94	94.28±0.77	99.58±0.91
9	14	82.73±0.18	91.55±0.15	90.26±0.55	95.65±0.57	96.82±0.15	99.69±0.11	99.24±0.01	99.23±0.05	99.74±0.01
10	16	85.90±0.14	95.16±0.13	92.53±0.77	98.31±0.22	98.96±0.35	99.74±0.13	99.55±0.02	99.35±0.05	99.82±0.01
11	18	87.49±0.17	96.96±0.11	93.67±0.28	99.64±0.06	99.03±0.11	99.77±0.01	99.71±0.01	99.38±0.04	99.86±0.01
12	20	89.82±0.11	97.88±0.21	94.42±0.31	99.73±0.07	99.27±0.16	99.81±0.08	99.79±0.01	99.44±0.05	99.89±0.01
13	22	90.99±0.46	98.43±0.14	99.01±0.05	99.81±0.09	99.39±0.35	99.83±0.07	99.83±0.01	99.47±0.03	99.90±0.01
14	24	92.75±0.23	99.07±0.02	99.19±0.08	99.85±0.05	99.54±0.18	99.84±0.04	99.89±0.01	99.49±0.01	99.91±0.02

Table 6. Regression analysis of Moxifloxacin HCl floating tablet formulations (Kinetic Modeling).

S.no	Formulation Code	KINETIC PARAMETERS											
		Zero order			First Order			Higuchi			Korsemeyer-Peppas		
		a	b	r	a	b	r	a	b	r	a	b	R
1	F_1	25.182	3.478	0.909	1.927	0.047	0.989	2.909	20.250	0.979	1.012	0.783	0.920
2	F_2	22.070	3.989	0.938	2.117	0.087	0.990	1.860	22.691	0.987	0.985	0.823	0.938
3	F_3	25.403	3.759	0.928	2.089	0.081	0.971	2.181	21.604	0.988	1.045	0.772	0.923
4	F_4	28.701	3.798	0.907	2.235	0.129	0.975	4.280	22.145	0.979	1.065	0.776	0.911
5	F_5	27.661	3.847	0.912	2.124	0.109	0.980	3.310	22.304	0.979	1.066	0.771	0.918
6	F_6	24.404	4.046	0.919	2.235	0.142	0.948	0.482	23.220	0.976	1.010	0.816	0.940
7	F_7	22.775	4.135	0.920	2.272	0.142	0.970	2.528	23.687	0.975	0.964	0.855	0.940
8	F_8	26.074	3.959	0.907	2.115	0.116	0.953	0.987	22.961	0.974	1.008	0.824	0.911
9	F_9	24.665	4.104	0.901	2.197	0.156	0.949	1.198	23.757	0.965	0.969	0.859	0.936
10	MP	28.150	3.611	0.916	1.970	0.067	0.978	5.404	20.898	0.981	1.103	0.724	0.911

Where *r*- correlation coefficient, a- intercept, b- slope, Mp- Marketed product

Table 7. Kinetic Parameters for Formulations F_1-F_9.

S.no	Formulation Code	KINETIC PARAMETERS				
		$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{1/2}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
1	F_1	0.976	2.665	6.421	12.841	21.335
2	F_2	0.527	1.439	3.468	6.937	11.525
3	F_3	0.565	1.544	3.720	7.440	12.361
4	F_4	0.356	0.971	2.340	4.680	7.777
5	F_5	0.419	1.144	2.756	5.512	9.158
6	F_6	0.321	0.876	2.112	4.224	7.018
7	F_7	0.323	0.882	2.125	4.251	7.063
8	F_8	0.395	1.078	2.597	5.194	8.630
9	F_9	0.294	0.802	1.933	3.865	6.422
10	MP	0.682	4.490	4.490	8.979	14.919