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Development and evaluation of gastroretentive floating matrix tablets of moxifloxacin HCL

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ABSTRACT

The present study was undertaken with an aim to formulate, develop and evaluate gastroretentive floating tablets of Moxifloxacin HCl which release the drug in a sustained manner over a period of 12 h. Different hydrophilic and hydrophobic retardants were used in different combinations at different ratios for the preparation of tablets. The tablets were prepared by direct compression method and evaluated for tablet thickness, hardness, weight variation, friability, floating lag time and in vitro drug release. Formulation F11 with hydrophilic polymer (Methocel® K100M) and hydrophobic retardant (carnauba wax) considered as an optimized formulation. The optimized formulation showed satisfactory sustained drug release and remained buoyant on the surface of the medium for more than 12 h. It can also be concluded that floating drug delivery system of Moxifloxacin HCl can be successfully formulated as an approach to increase gastric residence time and thereby improving its bioavailability.

Keywords: Moxifloxacin HCl**,** floating drug delivery system, carnauba wax, WSR 301, buoyancy period.

INTRODUCTION

Oral route of administration is the most convenient and widely used method of drug administration, and the development of stomach specific oral controlled-release drug delivery systems is a challenging job due to the variation of pH in different segments of the gastrointestinal tract, the fluctuation in gastric emptying time and the difficulty of localizing an oral delivery system in a selected region of the gastrointestinal tract [1, 2].

Sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose, since the majority of drugs are absorbed in stomach or the upper part of small intestine [3, 4]. Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability [5].

FDDS have lower density than gastric fluids and thus remain buoyant in the stomach fluid without affecting the gastric emptying for a prolonged period of time. While the system is floating in the gastric fluid, the drug is released slowly from the system at a desired rate. Materials used for FDDS include carbon dioxide gas-forming agents (carbonate or bicarbonate compounds [6, 7] highly swellable hydrocolloids and light mineral oils [8, 9]. Multiple unit systems and floating systems prepared by solvent evaporation methods have also been developed [10].

Moxifloxacin HCl is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria with a narrow absorption window and is mainly absorbed in proximal areas of GIT [11].

The objective of the present research work was to provide gastroretentive formulation that will provide once daily, sustained release dosage form. The swellable hydrophilic polymers like HPMC with different grades and hydrophobic polymers like carnauba wax were tried at different ratios to prepare various formulations of Moxifloxacin HCl.

MATERIALS AND METHODS

Materials:

Moxifloxacin HCl pure drug was generous gift from Macleods Pharmaceutical Ltd, Mumbai, India. HPMC K 4M, K 15M and K100M were obtained from Rubicon labs, Mumbai, India, POLYOX WSR 301 was obtained from Dow chemical's, New York. Gelucire 44/14 and Carnauba wax was gifted from MSN Labs Ltd, Hyderabad. All other excipients and chemicals used were of analytical grade.

Methods

Preparation of Moxifloxacin HCl floating tablet

The floating tablets, each containing 400 mg Moxifloxacin HCl were prepared by direct compression method. All the ingredients except Moxifloxacin HCl were passed through # 40 mesh prior to mixing. The ingredients were weighed separately and mixed to get a uniform polymer mixture. The drug was then mixed with the polymer mixture for a period of 10 minutes to ensure uniform mixing of the drug using mortar and pestle. These powder mixtures were lubricated with magnesium stearate and compressed to obtain tablets. The composition of Moxifloxacin HCl floating tablets was shown in **Table 1.**

Table 1: Composition of Moxifloxacin HCl floating tablets

Formulation code	Moxifloxacin HCl (mg)	HPMC K 4M (mg)	HPMCK 15M (mg)	HPMC K 100M (mg)	WSR 301 (mg)	$NaHCO_3$ (mg)	Gelucire 44/14 (mg)	Carnauba wax (mg)	Magnesium stearate (mg)
F1	400	60	---	---	25	42	30	40	3
F2	400	65	---	---	20	47	20	45	3
F3	400	70	---	---	15	52	10	50	3
F4	400	75	---	---	7.5	55	7.5	52	3
F5	400	---	60	---	25	42	30	40	3
F6	400	---	65	---	20	47	20	45	3
F7	400	---	70	---	15	52	10	50	3
F8	400	---	75	---	7.5	55	7.5	55	3
F9	400	---	---	60	25	42	30	40	3
F10	400	---	---	65	20	47	20	45	3
F11	400	---	---	70	15	52	10	50	3
F12	400	---	---	75	7.5	52	7.5	55	3

Evaluation of floating tablets

a) Thickness

The thickness of the prepared tablets was tested using vernier calipers. The test was done in triplicate and average was determined.

b) Hardness

Hardness of prepared tablets was determined using Monsanto hardness tester and measured in terms of kg/cm^2.

c) Weight variation

The weight variation test was performed as per the I.P. guidelines. Twenty randomly taken tablets were weighed together and the average weight was determined. Each tablet was then weighed individually and deviation from average weight was calculated.

d) Friability
A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche friabilator. It was operated for 4min at a speed of 25 rpm, and then the tablets were removed, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,

%Friability= (Loss in weight/ Initial weight) x 100.

e) Drug content
Ten tablets for each batch was taken and triturated. Powder equivalent to 100mg of drug was weighed and was transferred to breaker and 0.1N HCl was added and it was then shaken for 5 minutes and finally 0.1N HCl was added to make the volume up to 100ml and solution was then sonicated for 15 minutes and filtered through Whatman filter paper. Finally a solution was diluted suitably and the absorbance of resultant solution was measured to determine the drug content spectrophotometrically at 288nm using UV/Visible spectrophotometer Shimadzu 1800 against 0.1N HCl blank.

f) Swelling studies
The extent of swelling was measured in terms of % of weight gained by the tablet. One tablet from each formulation was weighed and kept in petridish containing 50 ml of 0.1N HCl buffer solution. At the end of specified time intervals tablets were withdrawn from petri dish and excess buffer blotted with tissue paper and weighed. The % of weight gained by the tablet was calculated by using the following formula:

Swelling Index (%) = M_t-M_0/M_0 X 100[12]

Buoyancy lag time & total floating time
The in vitro buoyancy was determined by the floating lag time. The tablet was placed in a 250 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the buoyancy lag time and further total floating time of all tablets was determined by visual observation[13].

***In vitro* dissolution studies**
In vitro drug release studies for the prepared immediate release tablets were conducted for a period of 12 hrs using USP XXIV type-II (Paddle) dissolution apparatus at 37±0.5oC at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. At predetermined interval of time, 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium. After filtration and appropriate dilution, the samples were analyzed for cumulative percentage drug release of Moxifloxacin HCl by UV/Visible spectrophotometer Shimadzu 1800 at 288 nm.

Kinetic modeling of drug release
To analyze the mechanism of drug release from the tablets the in vitro dissolution data was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas model.

Zero order equation
This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fitted into zero order equation.

$Q=Q_{\circ}K_{\circ}t$,

Where
Q=Amount of drug released at time t
$Q_{\circ}$= Amount of drug release initially
$K_{\circ}$ t =Zero order rate constant

A graph of concentration vs. time would yield a straight line with a slope equal to $K_{\circ}$ and the intercept at the origin of the axes. The zero order plot is derived from plotting the cumulative percent drug dissolved Vs time.

First order Equation
The first order equation describes the release from systems where dissolution rate is dependent upon the concentration of the dissolving species release behavior

Generally follows the following first order release equation.

In M= In M0-K1t

Where
M is the amount of drug dissolved at time t,
M0 is the amount of drug dissolved at t=0 and
M1 is the first order rate constant.
A graph of log concentration of drug release Vs time yields line.

Higuchi Square Root law
A form of the Higuchi Square Root Law is given by equation

$Q=KS\sqrt{t}$

Where
Q= Amount of drug dissolved at time t,
Ks=Higuchi rate constant

The Higuchi square root law equation describes the release from system where the solid drug is dispersed in a insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

Korsmeyer and Peppas release model
The release rate data were fitted to the following equation

$Mt/M\alpha = K.t^n$

Where

$Mt/M\alpha$= the fraction of drug released,

K=the release constant‘t’ is the release time.

‘n’ is diffusion exponent, if n is equal to 0.89, the release is Zero order. If n is equal to 0.45 the release is best explained by Fukien diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non fickian diffusions (Swellable & Cylindrical Matrix)

In this model, a plot of log ($Mt/M\alpha$) vs. log time was plotted and slope was noted to explain release pattern.

Drug- Excipient compatibility studies
Fourier transforms infrared spectroscopy (FTIR)
FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons.

Differential scanning calorimetry (DSC)
Differential scanning calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5ºC /min, over a temperature range of 0 to 250ºC.

Stability studies
The stability studies were carried out as per ICH guidelines. The best formulation F15 was subjected to accelerated stability test by storing at 40 ± 2^0C/75±5% relative humidity in an accelerated stability chamber (Remi, Mumbai). After specified period of time (1, 2, 4 & 6 months) samples were withdrawn and floating lag time, total floating time and in vitro dissolution studies were conducted.[14]

RESULTS AND DISCUSSION

Evaluation of physicochemical parameters

All the formulations were tested for physicochemical parameters like weight variation, hardness, thickness, friability and % drug content and found to be within the limits. The results are tabulated in **Table 2.**

Table 2: Physical properties of prepared formulations

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	601±5	5.2±0.4	6.2	0.12	97.3
F2	602±3	55±0.2	5.9	0.14	985
F3	599±8	5.8±0.3	6.3	0.11	97.6
F4	602±4	5.2±0.2	5.8	0.13	97.8
F5	600±6	5.4±0.3	6.1	0.14	98.4
F6	602±2	5.1±0.5	6.2	0.15	97.7
F7	603±1	5.3±0.2	5.8	0.12	98.2
F8	602±3	4.8±0.4	6.1	0.13	97.2
F9	601±6	5.7±0.2	6.3	0.11	98.3
F10	603±2	5.3±0.3	6.2	0.12	96.4
F11	600±3	5.2±0.4	6.0	0.13	99.3
F12	601±5	5.0±0.6	6.3	0.15	97.2

Study of swelling characteristics of Moxifloxacin HCl floating tablets:

The purpose of swelling study is to determine the water uptake capability of the polymer. Swelling study was performed on all the batches of floating tablet for 12 hours. All the floating tablets swelled but remained intact without breaking throughout the period of swelling in 0.1 N HCl. The order of swelling index observed with the polymers was HPMC K100 M > HPMC K15M > HPMC K15M. Formulation F11 prepared with HPMC K 100M was found to have highest swelling property and the results are summarized in **Table 3.**

Table 3: Swelling Index of Moxifloxacin HCl floating tablets

Formula code	Time in h. (% Swelling)					
	2	**4**	**6**	**8**	**10**	**12**
F1	34	56	72	96	105	112
F2	37.5	62	75	95	101	113
F3	39.6	64	78	97	104	115
F4	38	61	72	95	106	112
F5	36	59.5	72	91.5	100	116
F6	34	56	74	85.7	102	115
F7	33	54	76	85.8	104	110
F8	31	52.8	78	84.6	101	115
F9	30	51.5	73	82	100	112
F10	31	52.2	76	84	101	114
F11	40	58	85	98	112	128
F12	30	50.5	85	92	102	115

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Floating properties for the prepared formulations

All the formulations were evaluated for in vitro buoyancy lag time and total floating period. The time required for the tablet to rise to the surface (when the tablets were placed in a beaker containing 0.1 N HCl) for floating was described as the buoyancy lag time. $NaHCO_3$ induces CO_2 generation in the presence of HCl. All the formulations had buoyancy lag time in the range of 32 to 70 sec. The total floating period for all the formulations was found to be more than 12 hrs, which indicates a stable gel layer formation by all polymers and that $NaHCO_3$ remains for a longer time. Formulation F11 was found to be less floating lag time i.e. 32 sec when compared with other formulations and the results are depicted in **Table 4 & Figure 1.**

Table 4: Floating properties of Moxifloxacin HCl floating tablets

Formulation code	Floating lag time (sec)	Total floating time (hrs)
F1	70	>12hrs
F2	61	>12hrs
F3	52	>12hrs
F4	43	>12hrs
F5	68	>12hrs
F6	57	>12hrs
F7	48	>12hrs
F8	41	>12hrs
F9	65	>12hrs
F10	48	>12hrs
F11	32	>12hrs
F12	35	> 12hrs

At time 0 **After 32 sec**

Figure 1: In vitro buoyancy lag time of the optimized formulation (F11)

In vitro dissolution studies:

Table 5: *In vitro* cumulative % drug Moxifloxacin release formulations F1 to F6

Time(h)	F1	F2	F3	F4	F5	F6
0	0±0	0±0	0±0	0±0	0±0	0±0
1	16.01±0.15	17.04±0.11	21.71±0.17	19.53±0.66	21.15±0.12	18.95±0.22
2	25.51±0.12	28.16±0.56	29.29±0.17	29.64±0.43	31.86±0.15	23.93±0.16
3	33.49±0.61	34.50±0.87	35.24±0.11	42.35±0.43	42.18±0.65	38.92±0.42
4	41.32±0.97	48.06±0.77	49.87±0.18	51.46±0.97	46.81±0.87	43.72±0.53
6	52.83±0.76	51.94±0.75	55.52±0.98	65.52±0.53	57.496±0.98	59.77±0.14
8	60.49±0.55	61.88±0.47	64.69±0.34	68.73±0.52	66.574±0.11	66.36±0.11
10	72.28±0.87	72.74±0.76	75.69±0.11	76.23±0.55	79.212±0.33	77.23±0.54
12	83.35±0.98	84.6±0.77	85.11±0.97	89.68±0.65	92.4±0.14	94.64±0.18

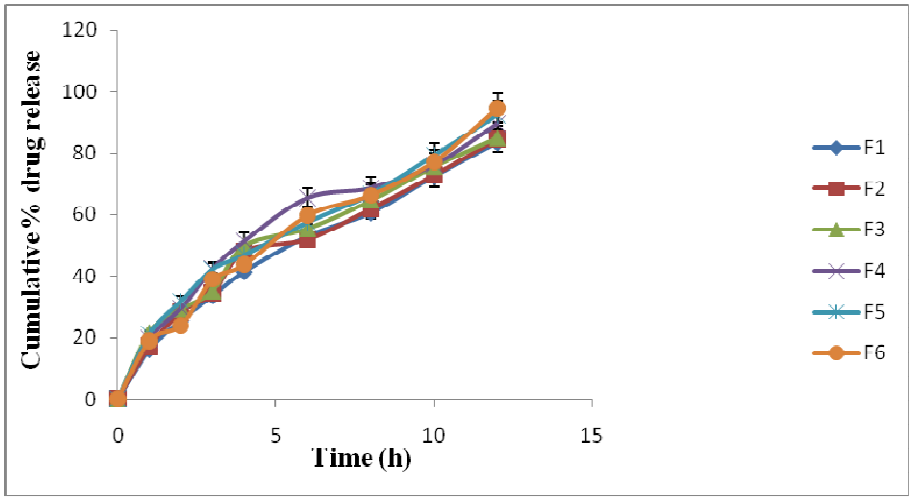

Figure 2: Percentage drug release of Moxifloxacin formulations F1-F6

Table 6: Percentage drug release of Moxifloxacin HCl tablet

Time (h)	F7	F8	F9	F10	F11	F12	Innovator
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	19.76±0.85	16.72±0.74	14.80±0.87	13.52±0.88	16.03±0.64	14.34±0.43	24.45±0.11
2	28.05±0.32	26.16±0.11	22.91±0.91	29.19±0.85	23.61±0.32	27.22±0.88	36.12±0.54
3	34.11±0.18	35.83±0.65	30.28±0.15	35.2±0.18	31.34±0.23	33.19±0.18	48.34±0.43
4	39.33±0.17	42.36±0.76	40.96±0.65	46.63±0.76	39.62±0.16	41.21±0.76	54.23±0.18
6	48.77±0.73	54.29±0.17	52.38±0.17	59.09±0.65	54.68±0.15	51.44±0.18	64.56±0.54
8	62.12±0.18	68.19±0.65	64.15±0.53	69.4±0.43	70.73±0.26	60.39±0.24	72.34±0.87
10	79.21±0.11	78.22±0.18	78.64±0.47	74.4±0.11	84.62±0.18	79.68±0.13	84.16±0.77
12	90.29±0.17	80.20±0.18	92.10±0.55	94.10±0.18	99.41±0.17	92.75±0.65	94.23±0.29

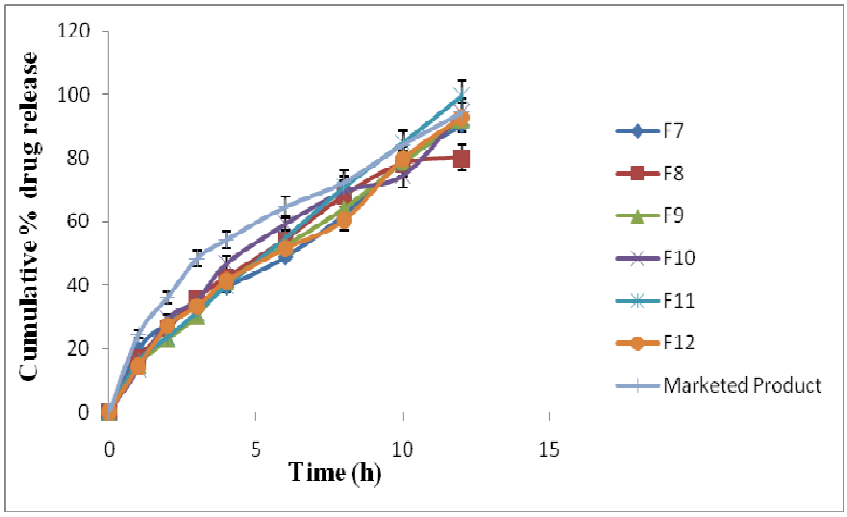

Figure 3: Percentage drug release of Moxifloxacin formulations F7 to F12

All the formulations (F1-F12) were prepared with polymers like HPMC with different grades, POLYOX WSR 301 and lipid excipient Gelucire 44/14. The release of Moxifloxacin HCl from different formulations was carried out in 0.1N HCl and the results are depicted in **Table 5&6.** The highest drug release was found in the formulation F11 i.e. 99.41% within 12h when compared with other formulations. F11 was found to be optimized formulation based on the dissolution and other evaluation parameters. The comparison of marketed product Moxicip SR tablet and optimized formulation F11 was shown in **Figure 3.** The drug release from marketed product was 94.23% within 12h.

Mathematical modeling of optimized formula of Moxifloxacin HCl tablets (F11):

Table 7: Release kinetics of optimized formulation of Moxifloxacin HCl floating tablets

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
F11	0.995	7.896	0.767	0.130	0.950	29.11	0.561	2.168

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.995 indicates that the drug release follows a zero order mechanism. This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics. Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer plots. The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one i.e. 0.549 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 2.168 suggest that the drug release from floating tablet was anomalous Non fickian diffusion.

Drug- Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

FTIR spectra of Moxifloxacin hydrochloride (**Figure 4**) showed aromatic C=C stretching at 1621, 1515 and 1454 cm–^{1} and C–H bending for substituted benzene at 873 cm–1. Besides, spectra also showed carboxylic acid C=O stretching at 1705 cm–^{1}, C–N stretching at 1350 cm–^{1}, stretching of monofluorobenzene at 1183 cm–^{1}. All the coated inserts showed aromatic C=C stretching at usual positions, indicating incorporation of Moxifloxacin and peaks for ester at 1730 cm–^{1}, since acrylate polymers are esters. The spectrum of physical mixture was also shown in **Figure 5**. Major characteristic peaks of Moxifloxacin were found in the optimized formulation (F11) (**Figure 6**), confirming the presence of the drug in the polymer without interaction.

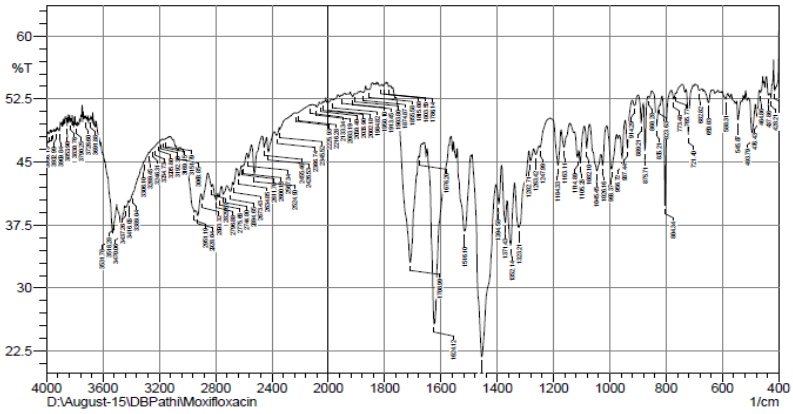

Figure 4: Moxifloxacin HCl pure drug

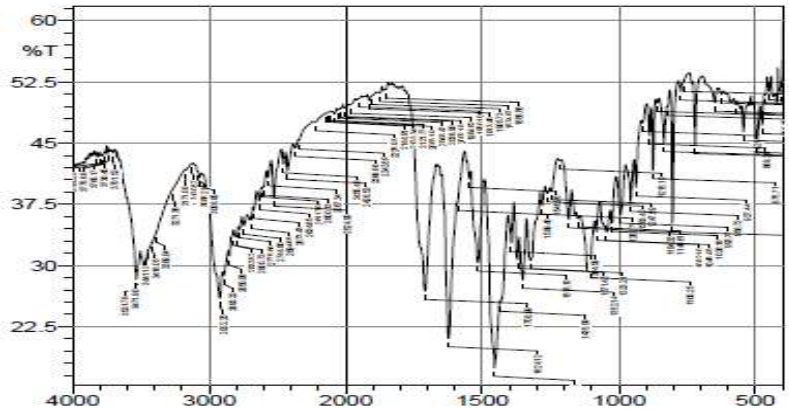

Figure 5: Physical mixture of Moxifloxacin HCl

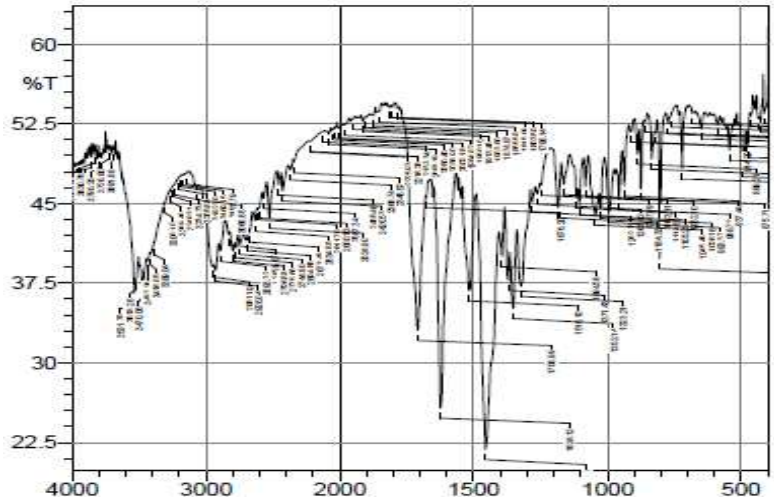

Figure 6: Moxifloxacin HCl optimized formulation (F11)

Stability studies:

Optimized formulation (F11) was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for In vitro % drug release and floating lag time for 6 months according to ICH guidelines and retained the same properties. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences which depicted in **Table 8.**

Table 8: Stability studies of optimized formulation (F11):

Retest time for optimized formulation (F11)	*In-vitro* (%) drug release	Floating lag time (sec)
0 days	99.41	32
30 days	98.86	34
60 days	98.12	35
120 days	97.92	36
180 days	97.68	38

CONCLUSION

On the basis of the present study, the use of hydrophobic retardant and hydrophilic polymer in combination had its own advantages of maintaining integrity and buoyancy of tablets. The effervescent based FDDS is a promising approach to achieve *in vitro* buoyancy by using gel forming polymers such as HPMC K4M, HPMC K15M and HPMC K 100M employing sodium bicarbonate as gas generating agent. Among the various FDDS formulations studied, the optimized formulation (F11) prepared with HPMC K100, WSR 301 and Gelucire 44/14 showed the best result in terms of the required lag time (32sec), total floating time of 12 hrs and cumulative % drug release was 99.41% within 12hrs and is considered as the ideal formulation**.** The compatibility study (FT-IR) showed that the drug has no interactions with polymers and other excipients.

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