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Full Length Original Research Paper

Formulation and Evaluation of effervescent floating matrix tablets of Ofloxacin

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Abstract:
The aim of present study was to develop Effervescent floating matrix tablets of Ofloxacin by wet granulation method using gas generating agents like Sodium bicarbonate, Citric acid and polymers like HPMC K100M, HPMC K4M, Psyllium husk and Xanthan gum. The prepared tablets evaluated in terms of their pre-compression parameters, physical characteristics, buoyancy lag time and dissolution studies. Optimization of formulation was done by studying effect of polymer on drug release. FT-IR studies indicated absence of any interaction between Ofloxacin, polymer (HPMC K100M, HPMC K4M, Psyllium husk and Xanthan gum) and excipients. The *in vitro* release studies showed that optimized formulation F8 could sustain drug release (92.31%) for 12 hrs and total floating greater than 12 hrs and fitted best to be Higuchi model with R^2 value 0.9850. As the n value for the Korsmeyer-Peppas model was found be greater than 0.45, it follows Non-Fickian diffusion mechanism.

Keywords: Ofloxacin, effervescent floating tablets, psyllium husk

Introduction:

The real challenge in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hours, but to prolong the presence of the dosage forms in the stomach or upper gastrointestinal tract until all the drug is released for the desire period of time[1]. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose[2]. Therefore, various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include floating system[3] (gas generating systems), Swelling and expanding systems[4&5], Mucoadhesive systems[6&7], High density systems[8], Modified shape systems[9&10], Gastric emptying delaying devices and co-administration of gastric delaying drugs.

Gastric retentive dosage forms are designed to be retained in the stomach and prolong the gastric residence time of the drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment[11].

Based on the mechanism of buoyancy, two types of technologies are developed in the floating systems. They are non effervescent and effervescent systems. Non effervescent systems prepared by using polyacrylate, polycarbonate, polystyrene as excipients swells unrestrained via inhibition of gastric fluid to an extent which will prevent their exit from stomach[12]. Effervescent system utilizes matrices prepared by using swellable polymers like methocel, polysaccharides

and effervescent compounds like sodium bicarbonate, citric acid or tartaric acid[13].

Ofloxacin is a fluoroquinolone antibacterial agent which is highly effective against gram positive and gram negative bacteria[14]. Ofloxacin exhibits pH dependent solubility. The solubility of Ofloxacin in water is 60 mg/ml at pH value ranging from 2 to 5, falls to 4 mg/ml at pH 7 (near isoelectric pH). Thus it is more soluble in acidic pH environment and slightly soluble at neutral or alkaline condition[15] (intestinal environment). The tablet form of Ofloxacin has bioavailability approximately 98% following oral administration reaching maximum serum concentrations within one to two hours. Between 65% and 80% of an administered oral dose of Ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Therefore, elimination is mainly by renal excretion. Plasma elimination half-life is approximately 4 to 5 hours in patients. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms, it is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa[16].

The objective of present study was to develop matrix floating tablets of Ofloxacin using HPMC K4M and HPMC K100M alone and combination with Psyllium husk and Xanthan gum and evaluating the prepared tablets for physicochemical properties, floating lag time, total floating time, swelling index, dissolution study and FT-IR studies.

MATERIALS AND METHODS:

Materials:

Ofloxacin was obtained as a gift sample from Dr. Reddy's Pharmaceuticals, Hyderabad, HPMC K4M and HPMC K100M were obtained from Aurobindo Pharma Pvt, Ltd, Hyderabad, Psyllium husk was obtained from Cambridge Health Care Ltd, Gujarat and Xanthan gum was obtained from Himedia Laboratories, Mumbai.

Preparation of Floating tablets:

Floating tablets were prepared by conventional wet granulation method. Ofloxacin (200 mg) , required amount of polymers and other excipients were accurately weighed. Ofloxacin was well mixed with weighed quantity of polymer and then mixed with remaining ingredients i.e., sodium bicarbonate, citric acid and microcrystalline cellulose in geometric proportions. All the excipients were passed through #60 mesh, mixed and granulated with 5% solution of PVP K30 in isopropyl alcohol. The wet mass passed through #16 mesh and dried at 60°C for 1 hour. Dried granules were passed through #24 mesh and mixed with magnesium stearate and talc. Granules were compressed in to tablets on a sixteen station rotary tablet punching machine using 12 mm circular standard caplet shaped punches.

Table 2: Composition of floating tablets of Ofloxacin containing HPMC K4M

Ingredients (weight in mg)	Formulations						
	F1	F2	F3	F4	F5	F6	F7
Ofloxacin	200	200	200	200	200	200	200
HPMC K4M	70	80	90	70	80	90	100
Psyllium husk	30	20	10	–	–	–	–
Xanthan gum	–	–	–	30	20	10	–
Citric acid	55	55	55	55	55	55	55
Sodium bicorbonate	82.5	82.5	82.5	82.5	82.5	82.5	82.5
Micro cristalline cellulose	81	81	81	81	81	81	81
PVP K30	27.5	27.5	27.5	27.5	27.5	27.5	27.5
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2
Total weight	550	550	550	550	550	550	550

Table 3: Composition of floating tablets of Ofloxacin containing HPMC K100M

Ingredients (weight in mg)	Formulations						
	F8	F9	F10	F11	F12	F13	F14
Ofloxacin	200	200	200	200	200	200	200
HPMC K100M	100	70	75	80	70	75	80
Psyllium husk	–	30	25	20	–	–	–
Xanthan gum	–	–	–	–	30	25	20
Citric acid	55	55	55	55	55	55	55
Sodium bicorbonate	82.5	82.5	82.5	82.5	82.5	82.5	82.5
Micro cristalline cellulose	81	81	81	81	81	81	81
PVP K30	27.5	27.5	27.5	27.5	27.5	27.5	27.5
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2
Total weight	550	550	550	550	550	550	550

EVALUATION OF FLOATING TABLETS OF OFLOXACIN

Pre-Compression of Ofloxacin granules

Angle of repose

Angle of repose for prepared granules was determined by fixed funnel method. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface to which a graph paper was placed. The granules were carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using the formula[17],

$$\theta = \tan^{-1}(h/r)$$

Where, 'θ' is the angle of repose 'h' is height of pile, 'r' is radius of base of the pile

Bulk density

Loose bulk density (LBD) and Tapped bulk density (TBD) were determined for the prepared granules. LBD and TBD was calculated using the formula,

LBD = Wt of Powder / Vol. of Powder

TBD = Wt of Powder / Tapped Vol. of Powder

Compressibility Index

Carr's Compressibility Index[18] for the prepared granules was determined by the equation, Carr's Index (%) = TBD – LBD/TBD x 100

Hausner's ratio

Hausner ratio is an indirect index of ease of measuring the powder flow. It is calculated by the following formula[19].

Hausner's ratio = Tapped density / Bulk density

Post-Compression parameters of Ofloxacin Floating tablets

Thickness

Thickness of 10 tablets randomly selected were measured using vernier calipers and expressed in millimeters.

Hardness Test

The crushing strength kg/cm^2 of prepared tablets was determined for tablets of each batch by Pfizer tablet hardness tester. Hardness indicates the ability of a tablet to withstand mechanical shocks while handling.

Friability Test

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets randomly selected were initially weighed (W_0 initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W final). The percentage friability (%F) was then calculated by

$$\%F = (1 - W/W_0) \times 100$$

Where, W_0 = weight of tablet before test,

W = weight of tablet after test.

Weight Variation Test

Twenty tablets were selected randomly from each batch and weighed individually using electronic balance to check for weight variation[20]. Pharmacopoeial limits are shows in below Table 1.

Table 1: IP standards of percentage of weight variation

Percentage deviation allowed under weight variation test	
Average weight of tablet	**Percentage deviation**
80 mg or less	10
More than 60 mg but less than 250 mg	7.5
250 mg or more	5

In vitro Buoyancy Studies

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface for floating was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained buoyant is determined as Total Floating Time (TFT)[21].

Determination of Swelling Index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 5 h. The swelling index (SI), expressed as a percentage, and was calculated from the following equation.

$$\text{Swelling index} = \frac{(Wt - Wo)}{Wo} \times 100$$

Where, Wt = Weight of the tablet at time t.

Wo = Initial weight of tablet.

Drug Content Estimation

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 294nm using 0.1N HCl as blank[22].

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In vitro Drug Release Studies

The release rate of Floating tablets of Ofloxacin was determined using USP Type 2 Apparatus. The dissolution test was performed in triplicate, using 900ml of 0.1 N HCl at 37± 0.5˚C at 50 rpm for 12 hrs. A 5ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted if necessary. Absorbance of these solutions was measured at 294nm using a U.V-Visible Spectrophotometer. Cumulative drug release was calculated from the developed methods.

Drug release kinetics:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order[23], first order[24], Higuchi[25] and Korsmeyer-Peppas[26] release model.

Fourier Transform Infrared (FTIR) Spectroscopy

Fourier transform Infra red analysis (FT-IR) measurements of pure drug, polymers and drug loaded floating tablets formulations were obtained using a model name BX- Perkinelmer System 200 FT-IR Spectrophotometer. The pellets were prepared on KBr press under hydraulic pressure of 150 kg /cm^2, the spectra were scanned over the wave number range of 4000-500 cm^{-1} at an ambient temperature[27].

Results and Discussion

Pre-compression parameters of Ofloxacin granules:

Results of the pre-compression parameters performed for the granules of Ofloxacin formulations F1 to F14 are tabulated in Table 4. The bulk density and the tapped density for all the formulations varied from 0.32±0.01 to 0.40±0.02 g/ml and 0.37±0.02 to 0.52±0.02 g/ml respectively. The percentage compressibility of granules was determined using Carr's index. Carr's index lies within the range of 12.19±0.84 to 21.73±0.56 %. All formulations show good compressibility. Angle of repose of all the formulations found to be less than 27.86° which indicates a good flow property of the granules. The values were found to be in the range of 22.43°±0.05 to 27.86°±1.03. Hausner ratio was found to be in the range of 1.14±0.06 to 1.30±0.03.

Table 4: Evaluation of Pre-Compressional parameters of Ofloxacin granules

Formulation Code	Bulk density (gm/ml) ± S.D	Tapped density (gm/ml) ± S.D	Carr's Index (%) ± S.D	Hausner Ratio ± S.D	Angle of repose (θ) ± S.D
F1	0.33±0.02	0.40±0.01	17.5±1.88	1.21±0.06	27.86±1.03
F2	0.40±0.02	0.52±0.02	15.38±0.92	1.30±0.03	25.67±1.28
F3	0.33±0.01	0.38±0.01	13.15±1.04	1.15±0.07	24.84±1.07
F4	0.35±0.26	0.40±0.04	12.50±2.12	1.14±0.06	25.79±0.09
F5	0.32±0.01	0.37±0.02	13.51±0.53	1.15±0.12	23.46±1.43
F6	0.33±0.02	0.41±0.03	19.51±0.45	1.24±0.03	25.11±2.09
F7	0.40±0.02	0.46±0.03	13.04±0.60	1.15±0.05	22.73±1.76
F8	0.36±0.05	0.42±0.02	14.28±0.61	1.16±0.05	24.18±0.84
F9	0.36±0.04	0.43±0.02	16.27±0.72	1.19±0.04	26.87±1.05
F10	0.40±0.01	0.47±0.01	14.89±2.10	1.17±0.01	23.54±0.12
F11	0.35±0.02	0.42±0.03	16.60±0.55	1.2±0.08	22.43±0.05
F12	0.36±0.01	0.41±0.02	12.19±0.84	1.13±0.06	26.32±1.58
F13	0.35±0.01	0.41±0.04	14.63±0.67	1.17±0.05	25.76±2.32
F14	0.36±0.04	0.46±0.03	21.73±0.56	1.27±0.04	26.71±0.09

S.D = Standard Deviation (n=3)

Post-compression parameters of Ofloxacin floating tablets:

All of the Ofloxacin formulations were tested for Physical parameters like Hardness, Thickness, Weight Variation, Friability drug content. The results of the tests were tabulated in Table 5. The Hardness of the tablets was found in the range of 5±0.05 - 5.7±0.11 Kg/cm^2 indicating satisfactory mechanical strength. The thickness of the tablets was found to be between 4.20±0.03 and 4.40±0.04 mm. The variation in weight was within the range ±5% complying with pharmacopoeial specifications. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. Assay of the prepared matrix tablets was found in the range of 98-100% clearly indicating the good content uniformity. This study indicated that all the prepared formulations were good.

The results of the physical tests of many of the formulations were within the limits and comply with the standards.

Table 5: Evaluation of Post-Compressional parameters of Ofloxacin floating tablets

Formulation code	Thickness (mm) ±S.D	Hardness (Kg/cm^2) ±S.D	Weight Variation (mg) ±S.D	Friability (%)±S.D	Drug Content (%) ±S.D
F1	4.35±0.06	5.5±0.05	549.80±0.04	0.546±0.03	99.78±1.02
F2	4.30±0.04	5.3±0.15	549.60±0.04	0.424±0.06	99.83±0.86
F3	4.40±0.04	5.7±0.11	550±0.03	0.423±0.02	98.65±2.12
F4	4.30±0.02	5.5±0.28	550.60±0.03	0.302±0.05	99.85±1.32
F5	4.25±0.05	5.5±0.05	550±0.03	0.363±0.03	99.27±1.67
F6	4.40±0.04	5±0.05	549.30±0.02	0.312±0.07	98.11±1.14
F7	4.40±0.03	5.7±0.05	549.70±0.02	0.423±0.04	99.08±0.08
F8	4.35±1.72	5.6±0.05	551.20±0.01	0.541±0.02	98.16±1.27
F9	4.20±0.03	5.6±0.15	550.90±0.01	0.302±0.03	99.19±0.83
F10	4.35±0.01	5.4±0.11	549.50±0.01	0.241±0.05	98.86±0.67
F11	4.28±0.02	5.7±0.15	549.60±0.03	0.242±0.03	99.27±0.43
F12	4.28±0.05	5.5±0.05	550.80±0.03	0.279±0.06	99.84±1.27
F13	4.32±0.02	5.7±0.11	550.40±0.02	0.181±0.07	99.53±0.07
F14	4.30±0.01	5.5±0.04	550.40±0.03	0.242±0.05	99.06±0.09

S.D = Standard Deviation (n=3)

In vitro Buoyancy studies:

In vitro buoyancy of the tablets from each formulation (F1 to F14) was evaluated and the results are mentioned in Table 6. Where, the highest and lowest floating lag time (FLT) was observed with the formulation F1 and F8 respectively. The concentration of the natural polymers increases the floating lag time also increases and total floating time observed for all the formulations was >12 hours.

Table 6: Floating Lag Time and Total Floating Time of Designed Formulations (F1 to F14)

Formulation Code	Floating lag time (seconds)	Total floating time (hours)
F1	153	>12
F2	129	>12
F3	124	>12
F4	123	>12
F5	114	>12
F6	93	>12
F7	91	>12
F8	65	>12
F9	112	>12
F10	116	>12
F11	104	>12
F12	96	>12
F13	84	>12
F14	88	>12

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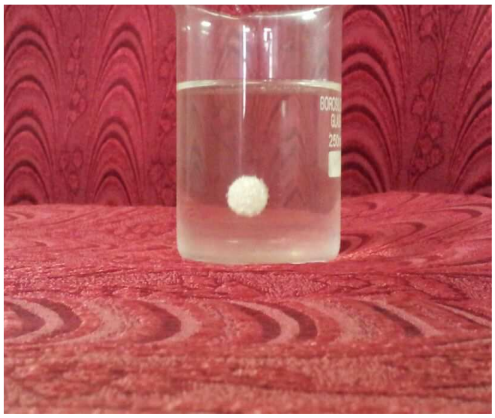
At initial time



After 58 Sec

After 12hrs

Fig 1: Floating lag time of F7

Swelling index:

The swelling index of the formulations (F5, F7, F8, and F10) was evaluated and the results are mentioned in Table 7 and plot of % swelling index vs. time (hrs) is depicted in Fig.2. Where, the highest and lowest swelling was observed with the formulation F7 and F10 after 5 hrs respectively. The swelling index increases by increasing the contact time with pH 1.2 buffer, as the polymer gradually absorbs buffer due to hydrophilic nature of the polymer, resultant swelling of the tablets is also observed.

Table 7: Swelling Index of floating tablets (F5, F7, F8 and F10)

Time(hrs)	Swelling Index (%)			
	F5	F7	F8	F10
1	21.96	21.02	31.95	30.50
2	26.49	34.91	52.42	45.36
3	33.93	51.55	62.65	52
4	53.35	62.52	74.17	59.45
5	65.88	85.37	81.68	64.72

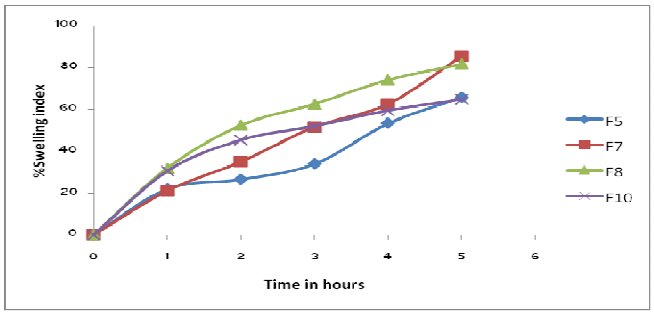


Fig 2: Swelling Index floating tablets (F5, F7, F8 and F10)

In vitro release studies

In vitro dissolution studies of all the floating tablets formulations of Ofloxacin were carried out in 0.1N HCl. The study was performed for 12 hours and cumulative drug release was calculated at every one hour time interval. *In vitro* dissolution studies of all the formulations are shown in Fig 3 & 4. The different polymers like HPMC K4M, HPMC K100M, Psyllium husk and Xanthan gum table 2 & 3 were used to prepare floating tablets. It was observed that the type of polymer influences the drug release pattern. HPMC K4M and HPMC K100M are hydrophilic polymers, upon contact with aqueous fluid is able to form quite viscous gel, and hence retard the drug release from hydrophilic matrix. The concentration of the polymers like HPMC K100M and HPMC K4M increased, slow drug release was observed. The formulation containing HPMC K100M (F8) gave the best results, which retarded the drug release

92.31% for 12 hours and hence it was considered as the optimized formulation.

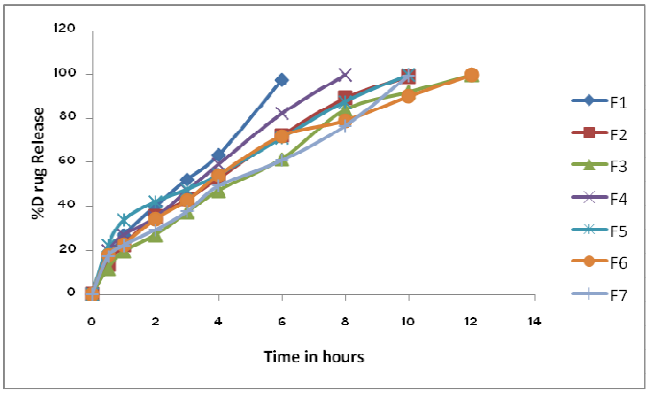


Fig 3: Comparison of *in vitro* dissolution profiles of F1 to F7

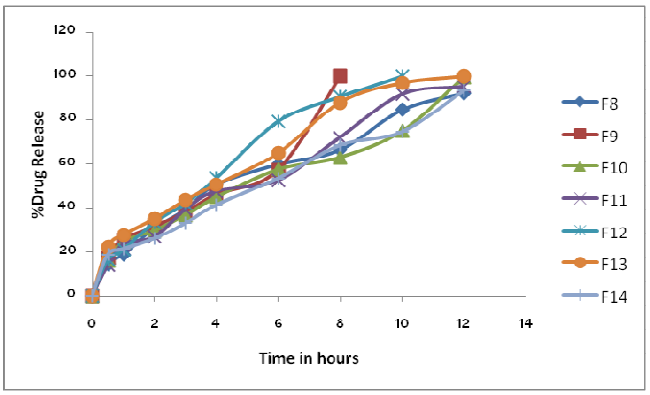


Fig 4: Comparison of *in vitro* dissolution profiles of F8 to F14

Drug release kinetics:

The drug release data were fitted to models representing zero order (cumulative amount of drug released vs. time), first order (log percentage of drug unreleased vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time), and Korsmeyer's equation (log cumulative percentage of drug released vs. time) kinetics to know the release mechanisms. The results of all formulation were shown in table 8. The release profile of optimized formulation F8, fitted best to Zero order kinetics with R^2 value of 0.9514. As the n value for the Korsmeyer-Peppas model was found to be greater than 0.45 it follows Non-Fickian diffusion mechanism, while all other formulations also follows Zero order kinetics and Non-Fickian diffusion mechanism.

Table 8: Regression coefficient (R^2) values for different kinetic models

Formulation Code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer R^2	Korsmeyer N	Similarity Factor (F2)
F1	0.9827	0.805	0.9437	0.9808	0.6971	39.57
F2	0.9684	0.8376	0.9795	0.9966	0.6543	52.37
F3	0.9710	0.7342	0.9697	0.9901	0.6953	52.36
F4	0.977	0.6851	0.9657	0.9787	0.6532	44.22
F5	0.9346	0.6578	0.9855	0.9630	0.4796	58.37
F6	0.9419	0.6565	0.9916	0.9957	0.6036	60.90
F7	0.9787	0.6937	0.9551	0.9773	0.6463	52.73
F8	0.9514	0.9472	0.9850	0.992	0.6269	52.49
F9	0.9347	0.5995	0.8727	0.8860	0.6002	45.41
F10	0.9541	0.6148	0.9576	0.9635	0.5486	49.94
F11	0.9634	0.9141	0.9626	0.9613	0.6049	52.57
F12	0.9632	0.7508	0.9701	0.9927	0.7042	47.89
F13	0.9452	0.8208	0.9798	0.9763	0.5599	59.78
F14	0.9747	0.8839	0.9673	0.9739	0.6100	45.98

Fourier Transform Infrared (FTIR) Spectroscopy:

Potential chemical interaction between drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibility of chemical interaction between drug and polymer FTIR spectra of pure Ofloxacin, pure polymers and optimised formulations were analyzed over the range 4000–500 cm^{-1}. The peaks obtained in the

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spectrum of formulation correlated with the peak of drug spectrum and there were no significant extra peaks. This indicates that the drug was compatible with the formulation components. The spectra of pure drug and drug with excipients are shown in Fig 5 & 6.

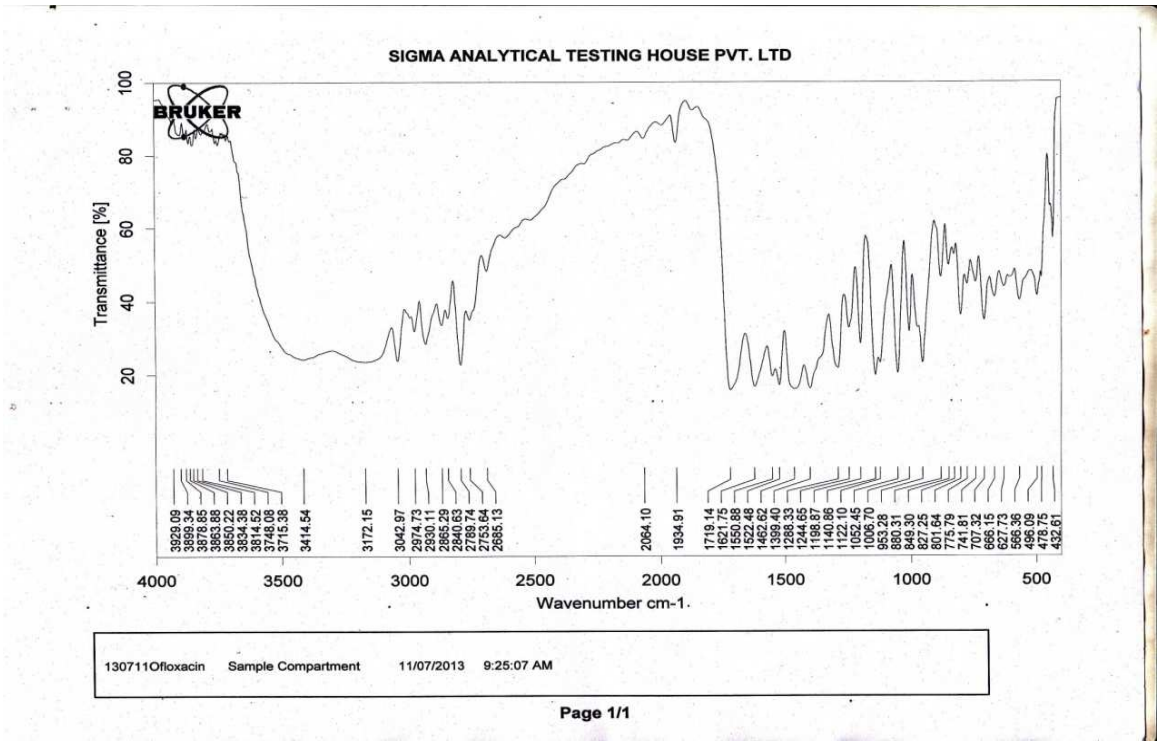

Fig 5: FT-IR Spectra of Ofloxacin

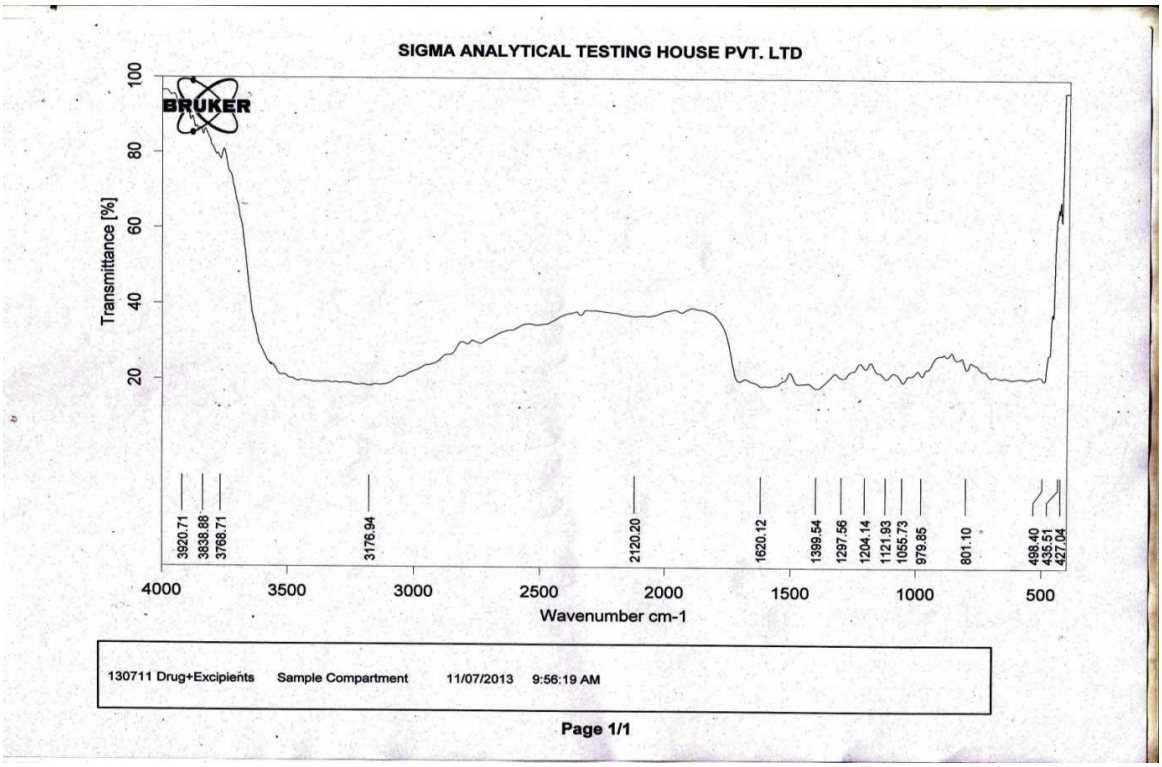

Fig 6: FT-IR Spectra of Ofloxacin and excipients

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Conclusion

The present study was aimed at developing an oral floating system for Ofloxacin with the use of different polymers such as HPMC K100M, HPMC K4M individually and combination with other polymers such as Psyllium husk and Xanthan gum, as it released the drug in a controlled manner for extended period of time by maintaining the buoyancy. This formulation may overcome the problem of poor solubility and its associated problems. Since the formulation showed sufficient release for prolonged period, the dose can be reduced and possible incomplete absorption of the drug can be avoided

Acknowledgement

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