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FORMULATION, DEVELOPMENT AND OPTIMIZATION OF OFLOXACIN FDDS SUSTAINED RELEASE FOR UTI'S AND H-PYLORI

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ABSTRACT

Objective: Development & Optimization of Ofloxacin Floating tablets to enhance gastric retention time. Sustained release effect of formulation will reduce the dosing frequency for UTIs and prolonged local effect will benefit against H-pylori infection. **Materials:** Pre formulation tests were performed which include bulk characteristics and flow properties. Post formulation studies include weight variation, thickness, content uniformity, hardness, friability, dissolution studies, release kinetics and compatibility & stability analysis. Kinetic studies were done and models were applied to understand the drug release mechanism. Accelerated stability analysis was also done for time period of 6 months. **Results:** All pre formulation tests were within range of USP standards, all the formulations showed good buoyancy. The in-vitro dissolution testing showed that F2 released drug at much slower rate, 64.97% within 24 hrs. F3 & F4 released ofloxacin at faster rate, 98.6% & 99.90% respectively, however, F1 released 91.66% drug within 24 hrs. F1 followed Higuchi model, F2 & F3 followed 1st order kinetics and F4 followed 1st order & Higuchi model. For F1, FTIR & DSC analysis curves showed no interaction or change of state of ofloxacin. **Conclusion:** Formulation F1 was proved to be the optimized formulation and followed non-Fickian release independent of concentration of drug also confirmed from Korsmeyer-Peppas equation. The Stability analysis also proved that F1 is the best fit formulation to be used as Floating Drug Delivery System of Ofloxacin. Stability analysis proved that polymers used in F1 formulation were effective effervescent agents and made the formulation optimized and efficacious.

Keywords: Ofloxacin FDDS, Optimized Ofloxacin FDDS, FDDS Development & Evaluation.

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INTRODUCTION

Urinary tract infections (UTIs) the most prevailing infections among young and mature adults due to unhealthy hygienic conditions. Females are more prone to those infections than men as they have shorter but wider urethra thus giving more space for microbes to grow in and develop an infection **[1]**. The prevalence of infection is higher in females i.e., 62.1% than that of males 37.9%, the main causative agent for UTIs is E-coli and is now multidrug resistant. **[2]**. H.-pylori is the most common gastric infection with prevalence of 40% globally **[3]**. H-pylori infects both adults and children all over the world and cost them with low life quality **[4]**. This infection is now becoming resistant to most of the drug therapies like that of clarithromycin **[3]**. The success of a therapy to eradicate the infection depends on various factors and the most important is being the sustain drug level **[5]**.

Ofloxacin a broad-spectrum antibiotic effective against many of gram positive and gram negative bacterial species **[6]**. The antibacterial activity being spread over wide variety of bacteria so ofloxacin shows excellent effect against prolonged Urinary Tract Infections **[7]**. For its local action in Stomach ofloxacin is effective in eradicating *H. pylori* much effectively, its activity also encompasses some local actions of small intestine **[8]**. Being utilized in combination therapy along with other anti-biotics produces synergistic effect in removing bacterial Ulcer from stomach by local action **[9]**. Being acidic in nature it requires acidic media to dissolve and get absorb in order to achieve better and nearly 100% bioavailability the ofloxacin has to be retained into stomach fluid **[10]**. If the system containing Ofloxacin remained in stomach for a bit longer period it showed better bioavailability of Ofloxacin **[11]**. Ofloxacin on oral administration has smooth absorption and good bioavailability 85%-95% within stomach **[6]**. Elimination half -life of 9hrs require multiple dosing as to maintain effective plasm concentration levels in order to treat various infections effectively thus mostly given two – three times daily, reducing

patient compliance **[12]**.

Floating Drug Delivery Systems (FDDS) is a new developing approach & is developed to retain the drug in the stomach fluid, this system is suitable for enhancing the absorption of drug and to provide local effect **[13]**. The basic principle behind the system was to lower the bulk density so that it floats in the stomach above the fluid **[14]**. Ofloxacin Floating System was developed to increase the Gastric Retention time for sustain effect and minimize the dosing interval **[11]**. This system also provides additional benefit of Local effect of drug due to prolong stay of system in stomach **[15]**. Such systems that can float in the gastric fluid and prolong the stay of drug in stomach can help to achieve both local effects & sustained release effect **[16]**. Floating system can be achieved by utilizing various approaches either by forming beads, rafts, effervescent, non-effervescent systems and many other forms **[16, 17]**. So for the approach of developing such a system it has to be incorporated with some excipients that help in forming that special sort of system that make the delivery system to float above the gastric fluid in the fundus region of stomach **[14, 18]**.

Floating System containing ofloxacin will give better outcomes as combined with various polymers giving specific floating mechanism increase the buoyancy of tablet thus providing local effect and sustain release **[10]**. This enhanced effect of ofloxacin will reduce the dosing interval as the drug in system was release controlled by utilizing various sort of chemicals like that of polymers to control the dissolution and release characteristics of drug from the floating system **[18, 19]**. Ofloxacin in a floating system will produce better antibacterial activity and increases the dosing interval thus ultimately providing better compliance and acceptability **[20]**.

This study was aimed to make the Gastric Retention System of Ofloxacin to enhance the gastric retention time by making a Floating Tablet by effervescent mechanism. This can be achieved by adding swellable polymers like Hydroxy Propyl Methyl cellulose and Effervescent chemicals that will generate gas and float the system. then the evaluations were evaluated by various methods of Post Formulation Studies to get the optimized formulation with enhanced floatability and better drug release kinetics.

MATERIAL AND METHODS

Materials

Ofloxacin was gifted from CCL Pharmaceuticals Ltd., Lahore, while other ingredients i.e., HPMC K100M (Hydroxy Propyl Methyl Cellulose), HPMC K40M, Eudragit, Carbopol, PVP K30 (Poly Vinyl Pyrrolidone), Gas forming agents (Sodium Bicarbonate, Citric acid), Talc, Magnesium Stearate, Lactose were purchased from Merck chemical laboratories, Lahore, all ingredients were of analytical grade.

Method of Floating Tablet Formulation

A slurry of PVP K30 was prepared in Isopropyl alcohol, all the ingredients were added into the mortar and mixed except for Magnesium Stearate, Lactose and Gas forming agents. Then the above binder slurry was poured drop wise and mixed continuously till the dough was formed. Gas generating agents were added and mixed in the dough for another 3-5 mints. The dough was passed through the sieve No 25. The granules formed by wet granulation were dried. The granules and Magnesium Stearate & Lactose were tumbled and passed through Sieve No. 10. Then the granules formed were again mixed with magnesium stearate as post lubricant was punched into a tablet with average weight of 650 mg using single punch punching machine with a force of 60 N. The composition of all Formulations was given in **Table 1**.

Pre-Formulation Studies

Pre formulation studies of the powder blend were evaluated for their bulk characteristics by utilizing bulk and tapped densities hausner's ratio and compressibility index were calculated. To evaluate flow properties angle of repose was performed on powder mix. Solubility analysis were also performed which involve gravimetric analysis & partition co-efficient. Melting point was also determined to check the purity of ofloxacin by using Fisher John's Melting point apparatus.

Table 1. Formulation Composition of ofloxacin FDDS sustained release tablets

FDDS	F1	F2	F3	F4
Ofloxacin	400	400	400	400
HPMC K 100M	115	20	-	25
HPMC K 15M	35	-	-	-
Carbopol 940p	30	-	-	-
PVP K 30	10	10	40	-
Cross Povidone	-	-	107.8	-
Karaya Gum	-	-	-	75
Linseed	-	20	-	-
B-Cyclodextrin	-	130	-	-
NaHCO3	90	70	67.7	36
Citric Acid	20	-	30	-
Mg- Stearate	-	20	15	3
Lactose	-	-	83.9	100
MCC	-	-	-	15
Talc	10	15	-	-

Table 2: Pre formulation Study of ofloxacin FDDS sustained release tablets.

Formulation	Bulk Density Mean ± S.D	Tapped Density Mean ± S.D	Carr's Index Mean ± S.D	Hausner Ratio Mean ± S.D	Angle of Repose Mean ± S.D
	(g/cc)	(g/cc)	(%)		(θ)
F1	0.46 ± 0.5	0.51 ± 0.5	18.9 ± 1.2	1.32 ± 0.5	26.97 ± 0.57
F2	0.38 ± 0.4	0.43 ± 0.4	17 ± 1.6	1.19 ± 0.3	25.78 ± 0.45
F3	0.41 ± 0.5	0.49 ± 0.3	16.4 ± 1.7	1.34 ± 0.24	27.32 ± 0.4
F4	0.53 ± 0.3	0.64 ± 0.4	20.5 ± 1.2	1.21 ± 0.2	24.33 ± 0.5

Gravimetric Analysis

In this analysis solubility of drug was checked in different pH solution of 1.2 pH HCl buffer, 5.8 pH potassium phosphate buffer, 7.4 pH potassium phosphate buffer and 8.0pH potassium phosphate buffer solutions. This method determines how much milliliters are required to dissolve 1g of drug.

Table 3: Gravimetric analysis.

Buffers (pH)	Solubility (ml/mg)
1.2	2.6
5.8	26.3
7.4	30.86
8.0	33.12

Partition co-efficient

This determines the partition of drug in two different solvents i.e., aqueous and oil phase. For this, two phases (1.2 pH HCl buffer & chloroform) in equal proportions were taken in separating funnel and drug is dissolved. The samples were taken and analyzed for drug content in both phases and log-p value was calculated.

Post Formulation Studies

Quality control test for our formulated tablets were applied which include weight variation, thickness, hardness, friability, content uniformity, buoyancy testing, in-vitro dissolution studies, release kinetic studies & stability studies.

Weight Variation

From each formulation batch ten tablets were selected randomly and weighed accurately individually, the average weight was calculated and then the individual weigh was compared with average weight. Percentage weight variation was calculated and checked with USP specifications.

Hardness

Randomly selected ten tablets from each formulation batch were taken and hardness was checked by Monsanto Hardness Tester. The mean and Standard Deviation were calculated.

Friability

Roche Friabilator was used for friability testing of our tablets randomly selected from formulation batches. Tablets were weighed and placed in the rotating plastic chamber that applied continuous attrition at 25rpm for 4 mints. After that the dust from tablets was cleaned and weighed again to calculate percentage friability.

Tablet Thickness

Tablet thickness was calculated by utilizing Micrometer for all randomly selected ten tablets from each batch of formulation. Mean and standard deviation were calculated and reading were taken in mm.

Content Uniformity

Five tablets from each formulation were selected, weighed individually and crushed. For drug content from fine powder calculated amount was taken that contains 10 g of Ofloxacin. Then added to a 100ml volumetric flask and diluted with 1.2 pH HCl Buffer. After dissolving the powder appropriate amount of solution was taken into a test tube ad diluted up to 10ml with buffer. The absorbance was measured by using Shimadzo UV-visible Spectrophotometer at wavelength of 294nm. The content of ofloxacin was then determined by utilizing linearity equation obtained from calibration curve **[20]**.

In-vitro Buoyancy Studies

It was determined by the floating lag time of tablets. In a 500ml beaker 250ml 1.2 pH HCl buffer was takes and then tablets were added individually from all formulations and time was noted till the tablet swells and begin to rise above the surface, this was the Floating lag time. After that beaker was left and after continuous time periods the tablet was observed till it remained buoyant as a whole, was determined as the floating time **[21]**.

In-vitro Dissolution Studies

For this USP Type II (paddle) apparatus was used, the tablets were placed in multiple dissolution beakers containing 900ml 1.2 pH HCl buffer solution. The apparatus particulars were set at 100rpm & temperature at 37 °C ± 0.5. 1ml sample from each beaker was taken in separate test tubes after appropriate time intervals for 24 hrs. and each sample was further diluted with 10ml 1.2 pH HCl buffer solution. The samples were than analyzed by UV spectrophotometer at wavelength of 294nm and calibration curve was obtained for further release studies **[20]**.

Release Kinetic Studies

Ofloxacin release mechanism from matrix system was determined by utilizing the dissolution data of the optimized formulation F1 by applying zero order, first order, Higuchi model & Korsmeyer-Peppas model. The R^2 value and slope obtaining by above data the release kinetics of drug was determined **[22]**. The value of n from Korsmeyer-Peppas equation provides the mechanism of release by superposing the two independent mechanisms of drug transport. The value of n from Korsmeyer-Peppas equation for cylindrical tablets demonstrates the release mechanism. If n<o.45 the drug follows the Fickian release, if n=0.45-0.9 there is non-Fickian release or anomalous diffusion release of drug from the formulation. If n=0.9 drug release is independent of time (case II transport) & if n>0.9 the drug follows supercase II.

Table 4: Post formulation study of ofloxacin FDDS sustained release tablets.

Formulation	Hardness Mean ± S.D	Thickness Mean ± S.D	Friability Mean ± S.D	Weight Variation Mean ± S.D	Drug Content Mean ± S.D
	(Kg/cm)	(mm)	(%)	(mg)	(%)
F1	4.6 ± 0.52	4.7 ± 0.01	0.32 ± 0.04	663 ± 2.54	99.86 ± 1.5
F2	4.9 ± 0.23	4.3 ± 0.05	0.65 ± 0.06	765 ± 3.52	94.32 ± 2
F3	4.1 ± 0.58	4.9 ± 0.03	0.47 ± 0.02	576 ± 1.34	96.43 ± 4
F4	5.3 ± 0.47	3.7 ± 0.06	0.72 ± 0.03	620 ± 4.45	97.56 ± 2.3

Table 5: Buoyancy Testing of ofloxacin FDDS sustained release tablets.

Formulation	Floating Lag Time	Tablet Floating Time
F1	120 sec	>24 hrs.
F2	300 sec	24 hrs.
F3	60 sec	24 hrs.
F4	260 sec	>24 hrs.

Table 6: Kinetics of in-vitro release of ofloxacin FDDS sustained release tablets.

Models and parameters		F1	F2	F3	F4
Zero Order	k0	4.911	3.031	4.460	5.252
	R^2	0.389	0.945	0.949	0.753
	AIC	84.936	56.471	62.592	80.424
	MSC	0.293	2.694	2.772	1.197
1st Order	k1	0.131	0.045	0.080	0.128
	R^2	0.953	0.998	0.968	0.992
	AIC	59.390	24.657	58.012	45.883
	MSC	2.847	5.876	3.230	4.651
Higuchi	kH	20.231	11.658	17.171	20.975
	R^2	0.972	0.917	0.924	0.961
	AIC	54.237	60.560	66.558	61.877
	MSC	3.363	2.285	2.375	3.052
Korsmeyer Peppas	kKP	23.159	6.218	9.216	17.372
	n	0.545	0.746	0.743	0.575
	R^2	0.979	0.993	0.998	0.970
	AIC	51.865	36.088	28.233	60.287
	MSC	3.600	4.733	6.208	3.211

Compatibility Studies

For stability of ofloxacin in tablet with other excipients was checked by using FTIR (Fourier Transformed Infra-Red) and DSC (Differential Scanning Calorimetry) analysis. For analyzing using FTIR small amount of powdered sample was placed at the stage of the spectrometer (Bruker FTIR Alpha spectrometer). It was then analyzed by placing the diamond tip of spectrometer on the sample. A beam of Infrared was passed through the sample and the curves were obtained against 4000-400 cm^{-1} spectra wavelength. On DSC tablets were weighed and crushed, 5mg of sample from each formulation was weighed accurately and were placed in aluminum pans & pans were crimped. Inert gas was used to avoid overheating of the heating chamber. The Enthalpy was calculated by utilizing Q1000 software. The thermal behavior was investigated at thermal rate of 5°C/min between temperatures of 0°C - 350°C. the curves obtained from both procedures were then analyzed to check for any physical or chemical interactions.

Stability Studies

Optimized formulation F1 was packed in aluminum foil strip packing of 0.05mm thickness and stored at 75% RH (relative humidity) and 40°C temperature for 6 months. After 6 months the samples were tested for hardness, content uniformity & in-vitro drug release studies.

RESULTS AND DISCUSSION

In our work, ofloxacin, an oral antibiotic acting as the active ingredient used in the treatment of various bacterial infection. It was chosen to be a good candidate of Floating system as to give a sustained release effect and to reduce the dosing frequency to improve patient compliance. Multiple polymers were incorporated in order to make polymeric matrix system that swells in gastric fluid and entraps the gas generated by effervescent ingredients added to make it float. This will help to control the release kinetics of drug from the polymeric system.

Floating tablets of ofloxacin were prepared by using varied amounts of polymers and effervescent ingredients (sodium bicarbonate & citric acid).

Pre-formulation Studies

The results of pre-formulation parameters as shown in *Table 2.* All the pre-formulation parameters were evaluated and were within the USP pharmacopeial standards. Ofloxacin was found to be pure with melting point 254°C **[23]**.

Gravimetric Analysis

The solubility of ofloxacin as shown in **Table 3**, has shown that the ofloxacin was freely soluble in 1.2 pH buffer and required 2.6ml per 1g, soluble in 5.8 pH and sparingly soluble in 7.4 pH & 8.0 pH **[24]**.

Partition Co-efficient

The log-p value for ofloxacin was determined to be 0.65 which showed us that the drug was more soluble in organic solvent. Thus being lipophilic **[25]** in nature the drug is highly permeable.

Post-formulation Studies

Floating Tablets of ofloxacin are smooth, white in color and cylindrical in shape. The results of post formulation parameters are shown in *Table 4*. The thickness of all the tablets (n=3) from each formulation was uniform and was measured by micrometer. The standard deviation values show that all the tablets were within range of uniform thickness without much deviation.

All the tested tablets fall within the range of 4.5 - 5.5 kg/cm^2. The values showed that all the tablets had shown good resistance to mechanical stress and show better hardness.

The weights of all the tested tablets fall into the percentage weight variation range of Pharmacopeial standard that is ±5 % variation, thus all the tablets passed the weight variation test.

Friability test values were also presented in **Table 4**, and showed that all the values fall less than 1% of weight change. Thus, all the formulation tablets are good in terms of friability and possess good strength against abrasion and shock.

Content Uniformity showed variation in uniformity among different formulations, F1 & F4 fall within the normal range i.e., 97.17 – 100.71%. but for F2 & F3 formulations had values below the normal content range that's might be due to physical or chemical interaction of drug with other excipients [**26-29**].

In-vitro Buoyancy Testing

All floating formulations were prepared by incorporating effervescent mechanism. On buoyancy testing the tablets were immersed in 1.2pH HCl buffer solution at 37°C. All the tablets stayed float for 24 hrs. while floating lag time differs for different formulations as shown in *Table 5.* F1 formulation showed best results with lag time of 120 sec and stayed float for more than 24 hrs., that's might be because of incorporation of Carbopol 940p along with HPMC K100M & HPMC K15M, this led to early hydration of Carbopol and HPMC which formed better gel structure and began swelling radially and axially. F3 contains Cross povidone in higher ratio that gives lag time of 60 sec. F2 contains HPMC K100M but also Linseed oil and B-Cyclodextrin that retarded the swelling of tablet and retarded the release of drug. F4 however also contain Karaya gum along with HPMC K100M there was controlled hydration of HPMC K100M due to Kraya gum that slowed the swelling of tablets.

In-vitro Dissolution Studies

Dissolution studies were performed in 1.2pH HCl buffer solution by taking the samples at regular intervals for 24 hrs. the in-vitro release profile was tabulated in **Table 6**, from the above data the percentage release plot against release rate and time was obtained as illustrated in **Fig. 2**.

It was observed that the incorporation of different polymers and also in varied ratios affects the release of drug from the polymeric system due to difference in swelling characteristics. The incorporation of Carbopol gave better results along with HPMC K100M & HPMC K15M showed better and controlled release of drug from the matrix as in F1 and had better selling integrity all over the time of floating and released 91.66% of drug within 24hrs. However, F3 & F4 released the drug rapidly i.e., 98.6% & 99.9% within 24 hrs., however F2 containing HPMC K15M along with Linseed oil & B-Cyclodextrin showed retard release with 64.97% drug released within 24 hrs.

Thus, due to presence of Carbopol the tablet retained good swelling integrity and released drug within time as compared to other formulations that do not contain Carbopol in any ratio [**30**].

Release Kinetic Studies

The release kinetics of optimized formulation F1 was recorded. To ascertain drug release kinetics of the formulation models were applied as zero order, first order, Higuchi model and Korsmeyer-Peppas model.

The data obtained was then plotted against cumulative percent release verses time as in **Fig. 2**. The sustained and controlled release also effects the release of drug as swelling increases the diffusion distance and thus the release kinetics is also affected by other factors like that of polymer which effects the time based, concentration based, and time factor-based release so Korsmeyer-Peppas equation was used to determine the exact release of the drug from the formulation, the values were shown in **Table 6**.

For best fit formulation F1 values of n and R^2 were tabulated in *Table 6.* The value of n for F1 is greater than 0.45 which was 0.545, formulation also follows the Higuchi model. The n value confirmed that the drug release was non-Fickian release, drug release was independent of the drug concentration and was released by anomalous diffusion. Thus, first the solvent will penetrate the swelled matrix and drug dissolves and diffuses out of the system and there was another factor that controlled the drug release that might be the polymer [**31**].

Compatibility Studies

Compatibility studies for F1 were performed by utilizing FTIR and DSC analysis. The curves of FTIR & DSC curves were illustrated in **Figure 3 & Figure 4** respectively. The FTIR curve for Ofloxacin and Ofloxacin polymeric mixture in formulation showed no physical or chemical interaction as there is no transformation in peaks.

The Ofloxacin compound seemed to be more thermally stable and its decomposition, associated with weight loss, started just after reaching the melting point T = 264.8°C. The DSC curves obtained for samples exposed to UVA light differ significantly from those not exposed.

Stability Studies

Accelerated stability studies were carried out for 6 months time period, the results shown in *Table 7*, showed no significant change in hardness, content uniformity and buoyancy testing. In-vitro release of drug from formulation after 6 months was also good and released 89.7% drug within 24 hrs. the percentage release of drug after stability studies compared with initial formulation 6 months was illustrated in **Fig. 5**. There was no significant change in parameters and polymers used i.e., HPMC K100M, HPMC K15M and Carbopol proved to be effective for optimized formulation **[32]**.

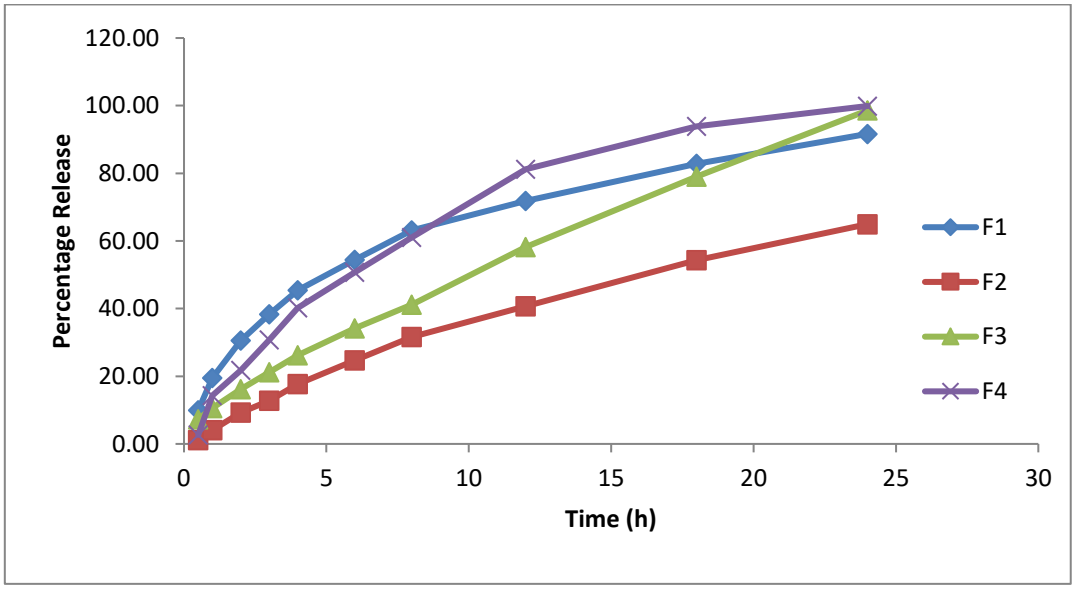

Figure 2: Release kinetics of ofloxacin FDDS sustained release tablets.

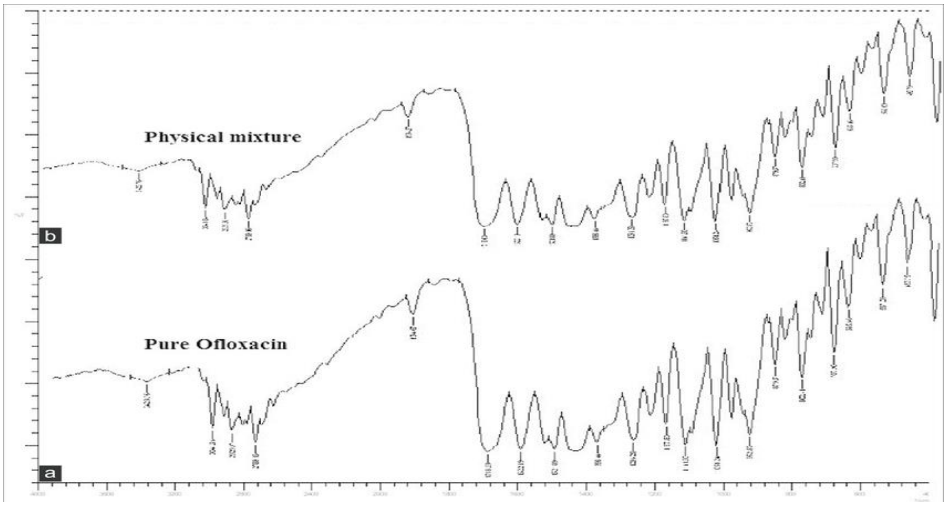

Figure 3: FTIR curve of a) Ofloxacin and b) Ofloxacin & HPMC K100M.

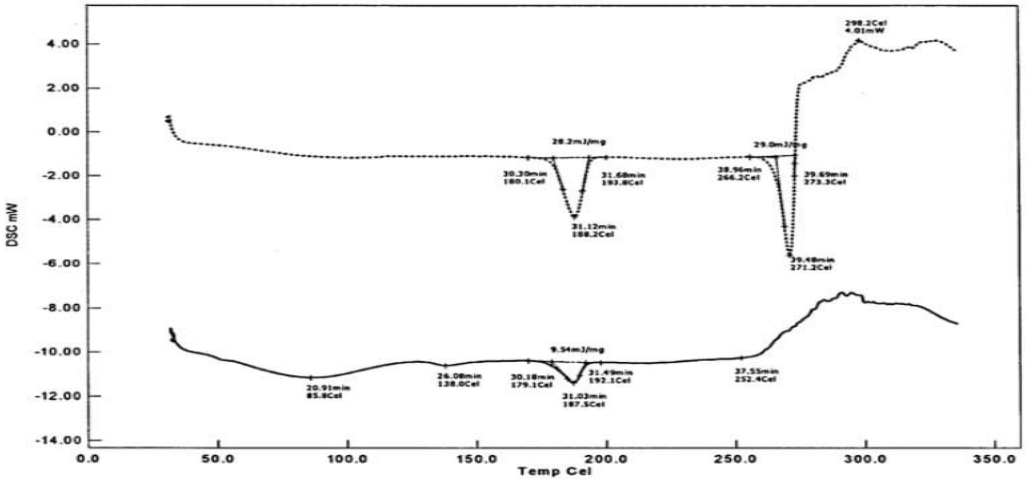

Figure 4: DSC curve a) Ofloxacin and b) Ofloxacin & HPMC K100M.

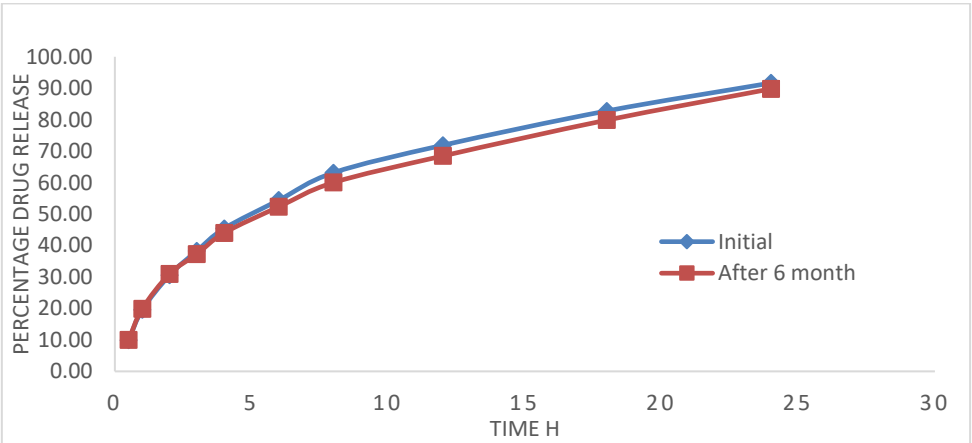

Figure 5: Ofloxacin release from FDDS sustained release tablets.

Table 7: Stability studies of ofloxacin FDDS sustained release tablets.

Parameters	Initial	After 6 months
Hardness	4.6 ± 0.52	4.5 ± 0.54
Drug content	99.86	99.45
Floating lag time	120 sec	124 sec
Drug release for 24h	91.66	89.79

CONCLUSION

The floating drug delivery system of ofloxacin will help to reduce the dosing frequency and also helps in providing local effect. The formulations prepared showed good results for this system of ofloxacin the best being F1 formulation provided excellent results and is optimized for the Floating system providing effective results with best floatability and drug release kinetics giving sustained release effect.

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