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# Development and Evaluation of Gastroretentive Formulations for Moxifloxacin Hydrochloride

**Raghavendra Kumar Gunda[1], A.Vijayalakshmi[1], K. Masilamani[2]**

*[1]Department of Pharmacognosy, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Chennai, Tamil Nadu, India, [2]Department of Pharmaceutics, Jaya College of Paramedical Sciences, College of Pharmacy, Thiruninravur, Chennai, Tamil Nadu, India*

**Corresponding Author:**
Mr. Raghavendra Kumar Gunda, Department of Pharmacognosy, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai - 600 117, Tamil Nadu, India.
Phone: +91-9666705894.
E-mail: raghav.gunda@gmail.com

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## ABSTRACT

**Purpose:** The objective of the current study is to develop gastroretentive formulation for moxifloxacin HCl (hydrochloride) using various drug release modifiers and performing *in vitro* and *in vivo* evaluations. Moxifloxacin is a novel synthetic compound having antibacterial activity. **Materials and Methods:** Floating and mucoadhesive tablets of moxifloxacin HCl were prepared using variable amounts of HPMC K100M and *Lannea coromandelica* gum (LCG) by direct compression technique and wet granulation technique, respectively. **Results and Discussion:** Formulations were developed, optimized and are checked for pharmacopoeial tests. Results show that all the factorial batches were lying within the standard limits. Dissolution parameters of all formulations were subjected to kinetic fitting, various statistical parameters were determined. Formulation (GRSOF) containing 50 mg of HPMC K100M and 50 mg of LCG, is the best formulation showing similarity $f_2$ = 71.734, $f_1$ = 4.271 with the marketed product (AVELOX). It follows Higuchi's kinetics and non-Fickian diffusion first-order kinetics ($n$ = 0.717). *In vivo* studies were performed for the GRSOF with six healthy rabbits and pharmacokinetic parameters were determined, compared with Avelox and found that GRSOF produced similar results. Stability studies were performed for GRSOF as per International Conference on Harmonization (ICH) guidelines. Results found to be satisfactory. **Conclusion:** GRSOF expected to improve patient compliance by means of providing good clinical outcome.

**Keywords:** Gastroretentive, HPMC K100M, *in vitro*, *in vivo*, *Lannea coromandelica* gum, moxifloxacin hydrochloride

## INTRODUCTION

The effective oral drug delivery practice depends on numerous factors such as 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 gastroretentivity of dosage form results improved clinical response.

Gastric transit time in humans, influences absorption of drugs, can result inappropriate drug release from formulation, leading to diminished clinical response. Gastric transit time is a dynamic process and ability to sustain the release of drug at predictive rate, which retain in the acidic environment for a longer period of time than prompt release formulations. Gastroretentive dosage forms are suitable for local drug delivery to the stomach and small intestine.[4] In case of many drugs which are released in the stomach have the greatest therapeutic effect while their release is prolonged in a continuous and controlled manner. This type of DDS will have relatively less side effect and removes the need of repeated dosages.[5]

Several difficulties were present in front of researchers for designing controlled release systems for better absorption, improved bioavailability.[6] The controlled gastric retention of solid dosage forms was obtained by numerous mechanisms such as flotation, bioadhesion, high density (sedimentation), modified shape systems, expansion, or by simultaneous administration of pharmacological agents that delay gastric emptying.[7,8]

Bioadhesive delivery systems produce many more benefits over other oral modified release systems by virtue of gastroretentivity, localization by targeting drug product at a specific site. It also proven that bioadhesive systems, they provide intimate contact between absorptive mucosa and dosage form which results high flux of drug through the GI mucosa.[9-13]

Materials for mucoadhesive delivery are polymers of either natural, semi-synthetic or synthetic, and water-insoluble or hydrophilic polymers; semi-synthetic polymers play a key role in the formulation of bioadhesive systems due to the formation of hydrogen bonds. Hydrogen bonding is directly proportional to the adhesion strength.[14,15]

Floating DDS (FDDS) is also known as hydrodynamically balanced system. FDDSs 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 increase gastric retention time and a better control of fluctuations in plasma drug concentrations.[16-19] They also offer maintenance of $C_{ss}$ longer period of time and minimizing the risk of resistance, this is very useful for delivery of antibiotics.[20]

Moxifloxacin HCl (hydrochloride), synthetic broad-spectrum antibacterial agent, belongs to the class of the fourth-generation fluoroquinolone. It has a narrow absorption window and absorbed primarily in the proximal portions of gut, an ideal candidate for a gastroretentive drug delivery system that will prolong the gastric transit time of formulation, results enhanced bioavailability.[21,22]

An attempt is made in the current study to develop gastroretentive DDS (preferably by flotation) with the help of drug release rate modifiers (natural – *Lannea coromandelica* gum [LCG] and semi-synthetic – HPMC K100M) and effervescent mixtures.[23-26] From literature, very less work reported for LCG, though it is natural more benefits observed from economy point of view as well as risk incidence also low. Hence, LCG selected as polymer for the formulation development of moxifloxacin HCl gastroretentive delivery.

Most of the tablets were manufactured by utilizing direct compression technique. However, drug release retardation also influenced by the method of manufacture; literature survey proved that gastroretentive formulations were prepared by wet granulation technique also.[27]

The development of gastroretentive DDS of moxifloxacin HCl using polymers which increases the gastric transit time improves penetrability of drug through mucosa, thereby improving the clinical efficacy of the active ingredient.

Hence, an attempt is made in this research work to formulate gastroretentive floating (GRF) and mucoadhesive tablets of moxifloxacin HCl using HPMC K100M and LCG by direct compression technique and wet granulation method, respectively.

## MATERIALS AND METHODS

### Materials

A gift sample of moxifloxacin HCl was procured from Macleods Pharmaceutical Ltd., Mumbai, India. HPMC K100M was obtained from Loba Chemie Pvt. Ltd., Mumbai, India. LCG was gifted from Sarada Pharmaceuticals, Guntur. All other excipients such as sodium bicarbonate, lactose, Emcompress, magnesium stearate, and talc were obtained from S.D. Fine-Chem. Ltd., Mumbai, India.

### Formulation Development of Moxifloxacin HCl GRF Tablets

*Preparation of moxifloxacin HCl mucoadhesive tablets (GMAF)*

Granules were prepared by wet granulation method. Moxifloxacin HCl and polymers were dry mixed for a period of 15 min. Distilled water was added as granulating liquid. The cohesive mass obtained was passed through sieve no #12. The wet granules were dried at 60°C for 15 min. The dried granules were passed through sieve no #16 and were mixed with lubricants. Granules showing promising preformulation properties were subjected to compression using rotary tablet punching machine (RIMEK), Ahmadabad. The composition is shown in Table 1.1.

*Preparation of moxifloxacin HCl floating tablets (GRSOF)*

Direct compression technique was utilized for the preparation of floating tablets, each containing 400 mg moxifloxacin HCl. Accurately weighed ingredients (except moxifloxacin HCl) were screened (#40 mesh) for obtaining uniform size to ensure proper mixing, to obtain polymer mixture. The drug was then mixed with the polymer mixture for 10 min for uniform mixing of powder blend. Blend was lubricated with magnesium stearate. The formulae for moxifloxacin HCl floating tablets are shown in Table 1.2. Powder blend was subjected to preformulation analysis. Results show good flow properties. Powder blend was subjected to compression with the help of rotary tablet compression machine (tablet Minipress).

Based on the dissolution profile, gastroretentivity the formulations further processed in mucoadhesive delivery, floating delivery systems for optimization and reproducibility of results again formulated, and compositions are presented in Table 1.3.

**Table 1.1:** Formulae for the preparation of moxifloxacin HCl mucoadhesive tablets (WG)

| Name of ingredients | Quantity of ingredients per each tablet (mg) | | | | | |
|---|---|---|---|---|---|---|
| | $FA_1$ | $FA_2$ | $FA_3$ | $FA_4$ | $FA_5$ | $FA_6$ |
| Moxifloxacin HCl | 436.8 | 436.8 | 436.8 | 436.8 | 436.8 | 436.8 |
| Lactose | 101.2 | 71.2 | 41.2 | 101.2 | 71.2 | 41.2 |
| HPMC K100M | 90 | 120 | 150 | - | - | - |
| *Lannea coromandelica* gum | - | - | - | 90 | 120 | 150 |
| Talc | 6 | 6 | 6 | 6 | 6 | 6 |
| Magnesium stearate | 6 | 6 | 6 | 6 | 6 | 6 |
| Total weight | 640 | 640 | 640 | 640 | 640 | 640 |

**Table 1.2:** Formulae for the preparation of moxifloxacin HCl floating tablets (DC)

| Name of ingredients | Quantity of ingredients per each tablet (mg) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $FS_1$ | $FS_2$ | $FS_3$ | $FS_4$ | $FS_5$ | $FS_6$ | $FS_7$ | $FS_8$ | $FS_9$ |
| Moxifloxacin HCl | 436.8 | 436.8 | 436.8 | 436.8 | 436.8 | 436.8 | 436.8 | 436.8 | 436.8 |
| Emcompress | 17.2 | 32.2 | 47.2 | 32.2 | 47.2 | 62.2 | 47.2 | 62.2 | 77.2 |
| HPMC K100M | 65 | 65 | 65 | 50 | 50 | 50 | 35 | 35 | 35 |
| *Lannea coromandelica* gum | 65 | 50 | 35 | 65 | 50 | 35 | 65 | 50 | 35 |
| Sodium bicarbonate | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Total weight | 640 | 640 | 640 | 640 | 640 | 640 | 640 | 640 | 640 |

**Table 1.3:** Formulae for the preparation of moxifloxacin HCl gastroretentive tablets

| Name of the ingredients | Quantity for single tablet (mg) | |
|---|---|---|
| | GMAF | GRSOF |
| Moxifloxacin HCl | 436.8 | 436.8 |
| Emcompress | | 47.2 |
| Lactose | 47.2 | - |
| HPMC K100M | - | 50 |
| HPMC K15M | - | - |
| *Lannea coromandelica* gum | 150 | 50 |
| Sodium bicarbonate | - | 50 |
| Talc | 3 | 3 |
| Magnesium stearate | 3 | 3 |
| Total weight | 640 | 640 |

Compressed tablets were examined as per official standards and unofficial tests. Tablets were packaged in well-closed light resistance and moisture-proof containers.

## Evaluation of Moxifloxacin HCl Gastroretentive Tablets[28]

*Hardness*

The breaking/crushing strength of the tablets was determined by measuring diametric breakdown of tablet using a Monsanto tablet hardness tester.

*Friability*

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

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

*Assay*

Assay was performed by triturating stated number of tablets in Indian pharmacopeia (20) converted to powder, powder equivalent to 100 mg of drug was added in 100 ml of 0.1 N HCl, followed by sonication. The solution was filtered through a 0.45 $\mu$ 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.[29]

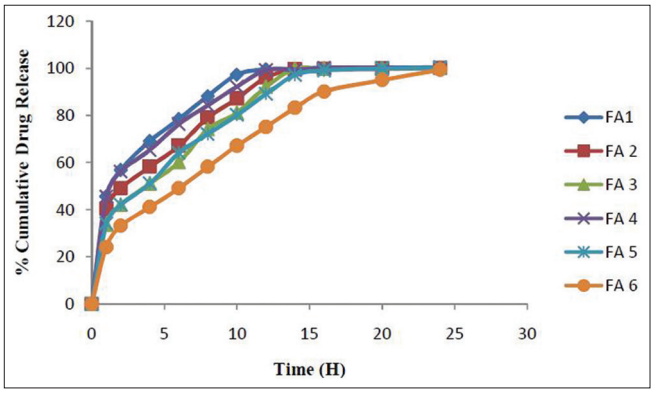


**Figure 1.1:** *In vitro* dissolution profiles for $FA_1$-$FA_6$ (mucoadhesive tablets)

*Thickness*

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

*In vitro buoyancy studies*

This test is performed by placing the tablets in a beaker containing 100 mL of 0.1 N HCl (simulated gastric fluid [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.[30]

*Measurement of detachment force (mucoadhesion strength)*

Measurement of detachment force is a measure of adhesion strength. It is determined with the help of texture analyzer.[19]

*In vitro drug release study*

The *in vitro* dissolution rate study for formulation trails was 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 pharmacopeial

procedure. The resultant samples were analyzed for the estimation of drug release by measuring the absorbance at 288 nm using ultraviolet-visible spectrophotometer after suitable aliquots. The samplings were performed in triplicate manner ($n = 3$).[21,22,29]

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.[31-34]

*Swelling index study*

To evaluate swelling index, tablet was placed in USP dissolution apparatus II with 900 ml 0.1 N 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, namely, 0, 2, 4, 6, 8, 10, and 12 h after using blotting paper to remove surplus fluid. Swelling index was calculated using the following formula.

$$\text{Swelling index (\%)} = [(W_2 - W_1)/(W_1)] \times 100$$

*In vivo evaluation*

To ascertain the pharmacokinetic parameters and clinical outcome, the *in vivo* evaluation of GRSOF (optimized) containing 436.8 mg of moxifloxacin HCl equivalent to 400 mg of moxifloxacin was performed. A single-dose crossover, non-blended, open-label, and randomized block study was designed and conducted using six healthy rabbits with a washout period of 15 days. Prior ethical clearance was obtained from the Institutional Animal Ethical Committee which is certified by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and approved by the Institutional Animal Ethical Committee ref. no. 1987/PO/Re/S/17/CPCSEA.Exp.No.5. Blood samples were collected at 0, 0.5, 1, 2, 4, 8, 12, 16, 20, and 24 h from the marginal vein. Collected samples were subjected to centrifugation using Remi MicroCentrifuge-209 operated at 3000 ± 500 rpm for 10 min. After centrifugation, the samples were preserved at refrigeration conditions until the analysis was carried out. After analysis data processed for the determination of pharmacokinetic parameters such as $C_{Max}$, $T_{Max}$, and area under curve (AUC). The pharmacokinetic data obtained for GRSOF are compared with Avelox-400.[35,36]

*Stability studies*

An ideal controlled release dosage form should provide consistency of drug release throughout its shelf life. In the present investigation, stability studies were performed on optimized formulation (GRSOF). In each case, all formulations were packed in high-density polyethylene screw capped bottles and kept in humidity chambers maintained at 25 ± 2°C, 60 ± 5% RH, 30 ± 2°C, 60 ± 5% RH, and 40 ± 2°C, 75 ± 5% RH as per the stability protocol of ICH guidelines.[37,38]

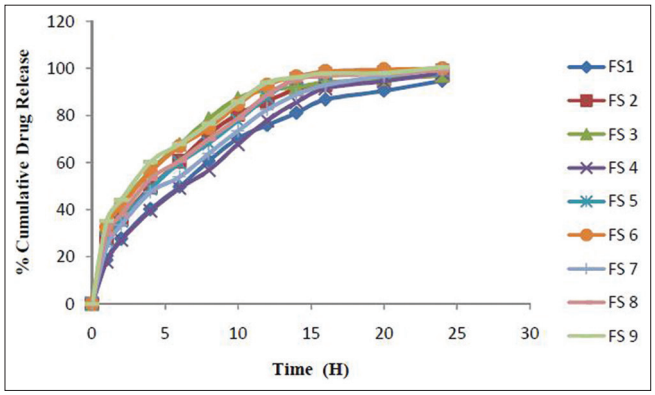


**Figure 1.2:** *In vitro* dissolution profiles for $FS_1$-$FS_9$ (floating tablets)

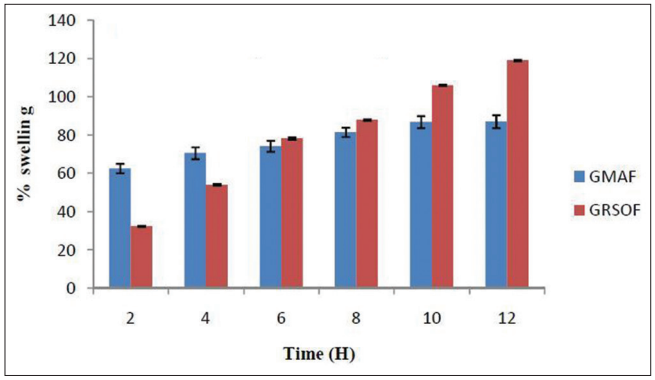


**Figure 2:** Percentage swelling with respect to time chart

## RESULTS AND DISCUSSION

Gastroretentive tablets of moxifloxacin HCl were formulated with the help of various drug release modifiers (HPMC K100M and LCG) along with effervescent mixtures. Formulation design is presented in Tables 1.1-1.3. Dissolution profiles of mucoadhesive and floating formulations are presented as Figures 1.1-1.2, respectively. The best formulation in each set

**Table 2.1:** Pre-formulation studies for gastroretentive mucoadhesive formulations

| Formulation code | Angle of repose (°) | Compressibility index (%) | Hausner's ratio |
|---|---|---|---|
| $FA_1$ | 22.15±1.2 | 20.09±0.9 | 1.23±0.2 |
| $FA_2$ | 24.12±1.2 | 15.11±0.7 | 1.24±0.2 |
| $FA_3$ | 23.15±1.1 | 19.16±0.6 | 1.23±0.3 |
| $FA_4$ | 24.12±1.1 | 18.07±0.6 | 1.22±0.2 |
| $FA_5$ | 24.12±0.6 | 17 0.11±0.8 | 1.24±0.2 |
| $FA_6$ | 23.15±0.7 | 18 0.16±0.2 | 1.25±0.3 |
| Moxifloxacin HCl | 35.21±0.6 | 28.05±0.15 | 1.24±0.36 |

**Table 2.2:** Pre-formulation studies for gastroretentive floating formulations

| Formulation code | Angle of repose (º) | Compressibility index (%) | Hausner's ratio |
|---|---|---|---|
| $FS_1$ | 25.155±0.7 | 16.95±0.3 | 25.155±0.7 |
| $FS_2$ | 25.855±0.6 | 16.725±0.2 | 25.855±0.6 |
| $FS_3$ | 26.34±1.1 | 17.205±0.2 | 26.34±1.1 |
| $FS_4$ | 25.1±0.7 | 16.455±0.3 | 25.1±0.7 |
| $FS_5$ | 26.285±0.6 | 16.23±0.2 | 26.285±0.6 |
| $FS_6$ | 26.285±1.1 | 16.71±0.2 | 26.285±1.1 |
| $FS_7$ | 25.815±0.7 | 16.675±0.3 | 25.815±0.7 |
| $FS_8$ | 26.2±0.6 | 16.05±0.2 | 26.2±0.6 |
| $FS_9$ | 26.2±1.1 | 16.53±0.2 | 26.2±1.1 |
| Moxifloxacin HCl | 35.21±0.6 | 28.05±0.15 | 1.24±0.36 |

**Table 2.3:** Pre-formulation studies for gastroretentive formulations

| Formulation code | Angle of repose (º) | Compressibility index (%) | Hausner's ratio |
|---|---|---|---|
| GMAF | 23.16±0.4 | 18.16±0.4 | 1.21±0.29 |
| GRSOF | 22.31±0.19 | 16.25±0.19 | 1.17±0.03 |
| Moxifloxacin HCl | 35.21±0.6 | 28.05±0.15 | 1.24±0.36 |

**Table 3.1:** Post-compression parameters for mucoadhesive formulations ($n$=3)

| Formulation code | Hardness (kg/cm²) | Thickness (mm) | Friability (%) | Weight variation (mg) | Drug content (%) | Force of detachment (mN) | Adhesion time (hr) |
|---|---|---|---|---|---|---|---|
| $FA_1$ | 5.11±0.86 | 6.39±0.01 | 0.35±0.12 | 642±1 | 96.90±0.61 | 244.75±6.25 | 20 |
| $FA_2$ | 4.91±0.49 | 6.24±0.02 | 0.37±0.01 | 643±2 | 97.21±0.87 | 336.22±6.78 | 23 |
| $FA_3$ | 5.10±0.15 | 6.31±0.01 | 0.42±0.02 | 642±3 | 96.51±0.14 | 494.71±6.29 | 26 |
| $FA_4$ | 5.33±0.22 | 6.11±0.01 | 0.32±0.12 | 640±4 | 94.91±0.51 | 211.73±6.27 | 20 |
| $FA_5$ | 5.22±0.21 | 6.12±0.03 | 0.54±0.05 | 646±6 | 98.22±0.47 | 319.54±5.46 | 21 |
| $FA_6$ | 5.62±0.23 | 6.23±0.06 | 0.24±0.13 | 642±2 | 97.53±0.36 | 453.39±9.61 | 25 |

**Table 3.2:** Post-compression parameters for floating formulations ($n$=3)

| Formulation code | Hardness (kg/cm²) | Thickness (mm) | Friability (%) | Average weight (mg) | Drug content (%) | Floating lag time (s) | Total floating time (h) |
|---|---|---|---|---|---|---|---|
| $FS_1$ | 5.39±0.198 | 6.31±0.04 | 0.195±0.125 | 641.61±2.05 | 97.37±0.31 | 48.25±1.35 | >12 |
| $FS_2$ | 5.19±0.188 | 6.26±0.02 | 0.345±0.085 | 643.62±4.05 | 97.715±0.36 | 50.86±1.4 | >12 |
| $FS_3$ | 5.24±0.193 | 6.25±0.01 | 0.235±0.12 | 640.61±3.05 | 97.26±0.38 | 52.84±1.5 | >12 |
| $FS_4$ | 5.46±0.18 | 6.24±0.04 | 0.18±0.13 | 642.5±2.15 | 98.96±0.33 | 49.34±1.4 | >12 |
| $FS_5$ | 5.263±0.17 | 6.18±0.03 | 0.33±0.09 | 644.5±4.15 | 99.3±0.39 | 51.95±1.45 | >12 |
| $FS_6$ | 5.32±0.18 | 6.18±0.01 | 0.22±0.125 | 641.5±3.15 | 99.95±0.41 | 53.93±1.55 | >12 |
| $FS_7$ | 5.68±0.22 | 6.27±0.04 | 0.175±0.115 | 641.61±2.05 | 99.91±0.43 | 51.86±1.5 | >12 |
| $FS_8$ | 5.48±0.21 | 6.22±0.02 | 0.325±0.075 | 643.62±4.05 | 99.26±0.49 | 54.47±1.55 | >12 |
| $FS_9$ | 5.54±0.21 | 6.21±0.01 | 0.215±0.11 | 640.6±3.05 | 100.6±0.51 | 56.45±1.65 | >12 |

as further studied for the optimization and reproducibility of results again formulated, the formula for the composition is summarized in Table 1.3. All formulations showed promising results for pre-formulation studies. Results are summarized in Tables 2.1-2.3.

All trials have 436.8 mg of moxifloxacin HCl (equivalent to 400 mg of moxifloxacin) as a gastroretentive tablet dosage form prepared by direct compression technique as well as wet granulation techniques. All final batches were subjected to various finished product evaluation tests such as drug content, floating lag time, adhesion time, mean hardness, mucoadhesion strength, total floating time, mean thickness, friability as per pharmacopeial methods, and subjective results which are summarized in Tables 3.1-3.4. Hardness for finished batches

**Table 3.3:** Final product quality assurance parameters for the formulations ($n$=3)

| Formulation code | Hardness (kg/cm²) | Thickness (mm) | Friability (%) | Average weight (mg) | Drug content (%) |
|---|---|---|---|---|---|
| GMAF | 5.62±0.23 | 6.23±0.06 | 0.24±0.13 | 642±2 | 97.53±0.36 |
| GRSOF | 5.263±0.17 | 6.18±0.03 | 0.33±0.09 | 644.5±4.15 | 99.3±0.39 |

**Table 3.4:** Final product quality assurance (gastroretentive) parameters ($n$=3)

| Formulation code | Floating lag time (s) | Total floating time (h) | Force of detachment (mN) | Adhesion Time (h) |
|---|---|---|---|---|
| GMAF | - | - | 453.39±9.61 | 25 |
| GRSOF | 51.95±1.45 | 24 | - | - |

**Table 4.1:** Swelling index of moxifloxacin HCl mucoadhesive formulations

| Formulation code | % swelling with respect to time (h) | | | | | |
|---|---|---|---|---|---|---|
| | 2 | 4 | 6 | 8 | 10 | 12 |
| $FA_1$ | 0 | 57.62±3.2 | 58.53±4.1 | 65.62±2.3 | 69.36±3.1 | 71.79±3.3 |
| $FA_2$ | 0 | 61.53±2.7 | 67.59±3.1 | 72.09±3.3 | 77.56±2.8 | 81.63±3.4 |
| $FA_3$ | 0 | 63.30±3.3 | 69.23±2.5 | 72.10±3.5 | 80.20±2.5 | 84.14±3.1 |
| $FA_4$ | 0 | 52.43±2.6 | 51.80±4.1 | 53.57±3.7 | 58.94±3.1 | 64.28±2.4 |
| $FA_5$ | 0 | 63.47±2.6 | 69.71±3.5 | 73.58±3.8 | 81.16±2.4 | 84.75±2.4 |
| $FA_6$ | 0 | 62.60±2.4 | 70.58±3.3 | 74.30±2.7 | 81.48±2.5 | 86.84±3.4 |

**Table 4.2:** Swelling index of moxifloxacin HCl floating formulations

| Formulation code | % swelling with respect to time (h) | | | | | |
|---|---|---|---|---|---|---|
| | 2 | 4 | 6 | 8 | 10 | 12 |
| $FS_1$ | 31.97±0.1 | 53.4±0.2 | 88.49±0.3 | 96.0.38±0.3 | 107.7±0.4 | 120.83±0.4 |
| $FS_2$ | 31.43±0.3 | 52.4±0.4 | 87.28±0.2 | 95.9±0.5 | 106.95±0.4 | 119.92±0.3 |
| $FS_3$ | 30.9±0.4 | 51.47±0.4 | 85.95±0.2 | 93.23±0.4 | 103.5±0.3 | 117.15±0.3 |
| $FS_4$ | 32.97±0.2 | 55.4±0.1 | 79.49±0.2 | 88.8±0.2 | 106.7±0.3 | 119.83±0.2 |
| $FS_5$ | 32.43±0.3 | 54.4±0.4 | 78.28±0.5 | 87.9±0.4 | 105.95±0.3 | 118.92±0.4 |
| $FS_6$ | 31.9±0.3 | 53.47±0.5 | 76.95±0.6 | 85.23±0.4 | 102.5±0.3 | 116.15±0.3 |
| $FS_7$ | 31.97±0.2 | 54.4±0.1 | 76.49±0.2 | 86.8±0.2 | 105.7±0.3 | 117.83±0.2 |
| $FS_8$ | 31.43±0.3 | 53.4±0.4 | 75.28±0.5 | 85.9±0.4 | 104.95±0.3 | 116.92±0.4 |
| $FS_9$ | 30.9±0.3 | 52.47±0.5 | 73.95±0.6 | 83.23±0.4 | 101.5±0.3 | 114.15±0.3 |

**Table 4.3:** Swelling index of moxifloxacin HCl gastroretentive formulations

| Formulation code | % swelling with respect to time (h) | | | | | |
|---|---|---|---|---|---|---|
| | 2 | 4 | 6 | 8 | 10 | 12 |
| GMAF | 62.60±2.5 | 70.59±3.1 | 74.31±2.9 | 81.49±2.51 | 86.85±3.15 | 87.07±3.33 |
| GRSOF | 32.43±0.3 | 54.4±0.4 | 78.28±0.5 | 87.9±0.4 | 105.95±0.3 | 118.92±0.4 |

**Table 5:** Regression analysis of moxifloxacin HCl gastroretentive tablet formulations (kinetic modeling)

| Formulation code | Kinetic parameters | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Zero order | | | First order | | | Higuchi | | | Korsmeyer–Peppas | | |
| | a | b | r | a | b | r | a | b | r | a | b | r |
| GMAF | 22.637 | 3.581 | 0.962 | 2.096 | 0.067 | 0.924 | 2.035 | 20.079 | 0.998 | 1.072 | 0.716 | 0.932 |
| GRSOF | 29.247 | 3.576 | 0.924 | 2.071 | 0.082 | 0.984 | 6.699 | 20.703 | 0.990 | 1.116 | 0.717 | 0.912 |
| MP | 30.379 | 3.578 | 0.915 | 2.214 | 0.109 | 0.935 | 7.465 | 20.831 | 0.987 | 1.122 | 0.718 | 0.897 |

**Table 6:** Kinetic parameters for gastroretentive formulations

| Formulation code | Kinetic parameters | | | | |
|---|---|---|---|---|---|
| | $t_{10\%}$ (h) | $t_{25\%}$ (h) | $t_{1/2}$ (h) | $t_{75\%}$ (h) | $t_{90\%}$ (h) |
| GMAF | 0.682 | 1.861 | 4.485 | 8.970 | 14.903 |
| GRSOF | 0.559 | 1.526 | 3.678 | 7.365 | 12.221 |
| MP | 0.420 | 1.146 | 2.762 | 5.524 | 9.178 |

**Table 7:** Study design (*in vivo*) for the determination of pharmacokinetic parameters

| Treatments | Subject codes | | | | | |
|---|---|---|---|---|---|---|
| | S-I | S-II | S-III | S-IV | S-V | S-VI |
| Avelox | √ | - | √ | - | - | - |
| GMAF | - | √ | - | - | √ | - |
| GRSOF | - | - | - | √ | - | √ |
| After washout period (15 days) | | | | | | |
| Avelox | - | - | - | √ | √ | - |
| GMAF | - | - | √ | - | - | √ |
| GRSOF | √ | √ | - | - | - | - |
| After washout period (15 days) | | | | | | |
| Avelox | - | √ | - | - | - | √ |
| GMAF | √ | - | - | √ | - | - |
| GRSOF | - | - | √ | - | √ | - |

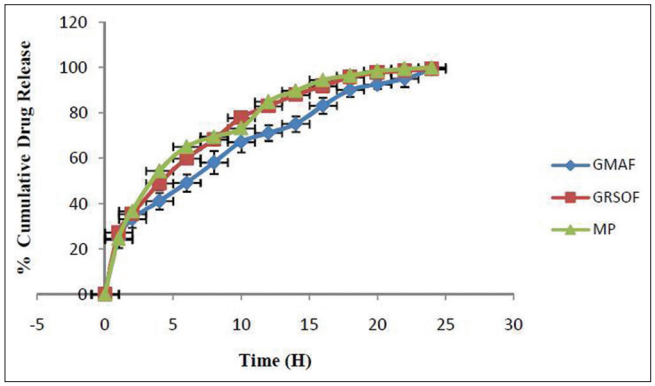


**Figure 3:** Comparative zero-order plots

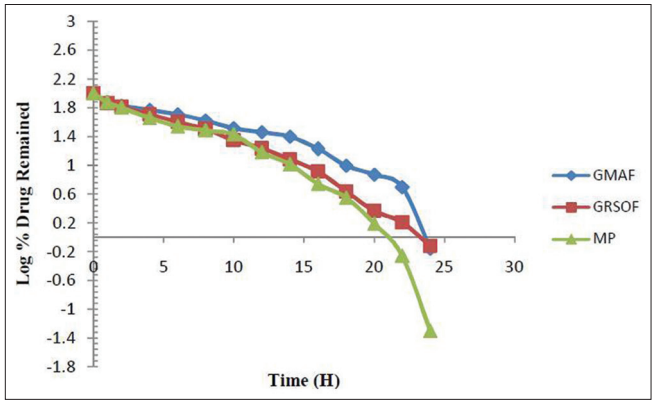


**Figure 4:** Comparative first-order plots

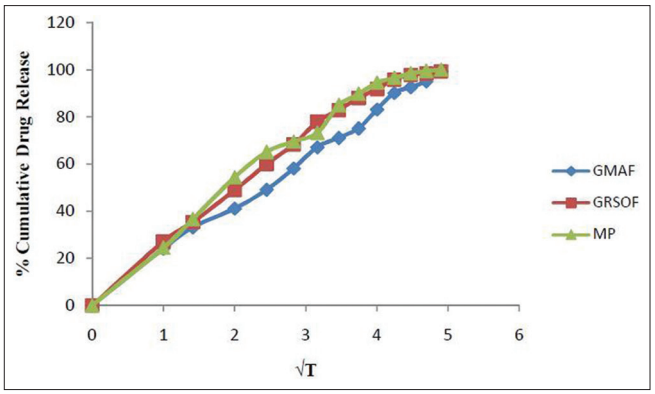


**Figure 5:** Comparative Higuchi plots

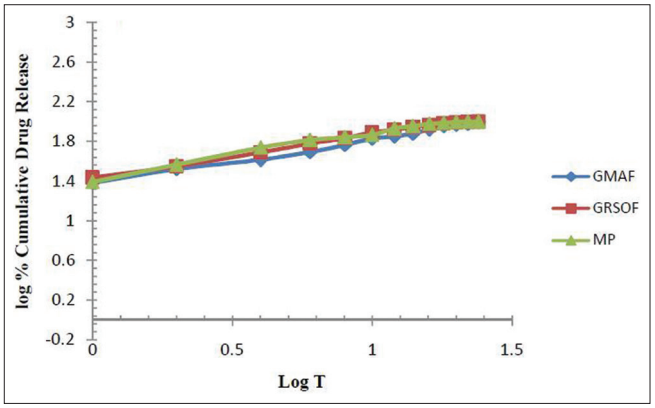


**Figure 6:** Comparative Korsmeyer–Peppas plots

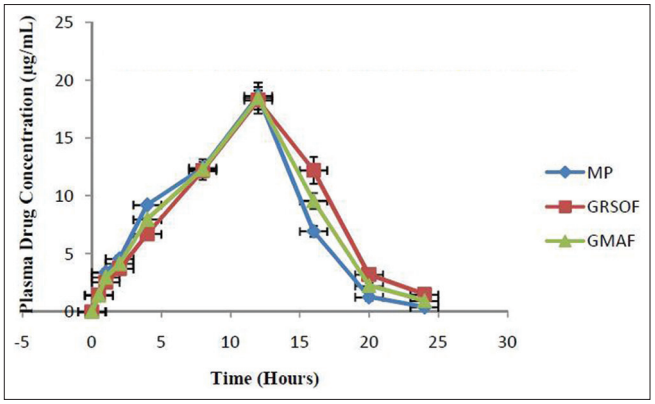


**Figure 7:** Comparative Plasma drug profiles

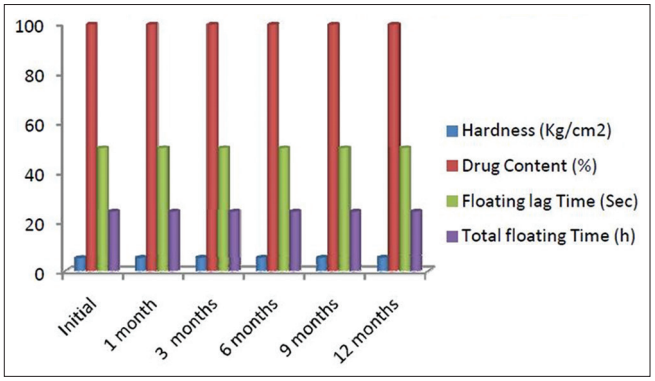


**Figure 8:** Stability data at 25 ± 2°C, 60 ±5% RH for 1 year (LST)

was founded to be in the range of 5.26 ± 0.17–5.62 ± 0.23 kg/cm$^2$. Thickness for finished batches was founded to be in the range of 6.18 ± 0.03–6.23 ±0.06 mm. Results for friability test were founded to be <0.34%. Drug content for finished batches was founded to be within acceptance criterion. 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 h. 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 GRSOF was found to have highest swelling property and the data for swelling evaluation are presented in Tables 4.1-4.3 and Figure 2.

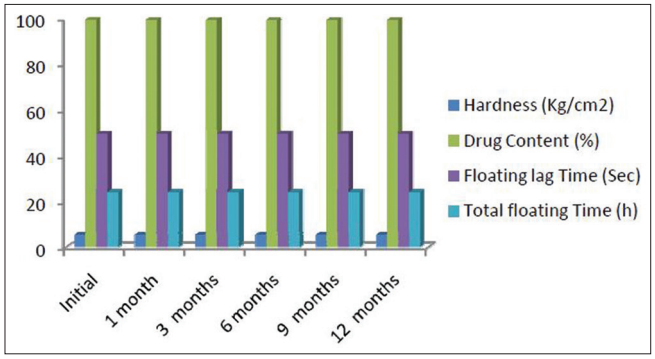


**Figure 9:** Stability data at 30 ± 2°C, 65 ± 5% RH for 1 year (IST)

Drug release studies were performed for finished batches using pH 1.2 buffer (0.1 N HCl) as a dissolution fluid as operated under standard set of conditions at 50 rpm (Paddle), 37 ± 0.5°C. Dissolution plots are presented in Figures 3-6 (Kinetic Plots). Percentage Cumulative drug release (CDR) for finished batches $F_1$-$F_9$ at 24 h was found to be 99.25 ± 0.66–99.31 ± 2.1%. The result revealed that the release rate of drug was inversely proportional to quantity of polymers and vice versa.[37] Hence, desired drug release was achieved by manipulating composition of independent variables.

Dissolution profiles of moxifloxacin HCl tablets were subjected to kinetic modeling. The results were presented (statistical parameters and kinetic parameters) as Tables 5 and 6. Results reveal that all formulation batches best fitted to first-order kinetics, quantification of $r^2$ wasfounded to be in the range of 0.924–0.984. They also fitted to Higuchi's kinetics, $r^2$ was found to be in the range of 0.990–0.998. From the Peppas treatment, it reveals that all batches follow that shows non-Fickian diffusion ($n$ = 0.716). Formulation (GRSOF) is the identical product

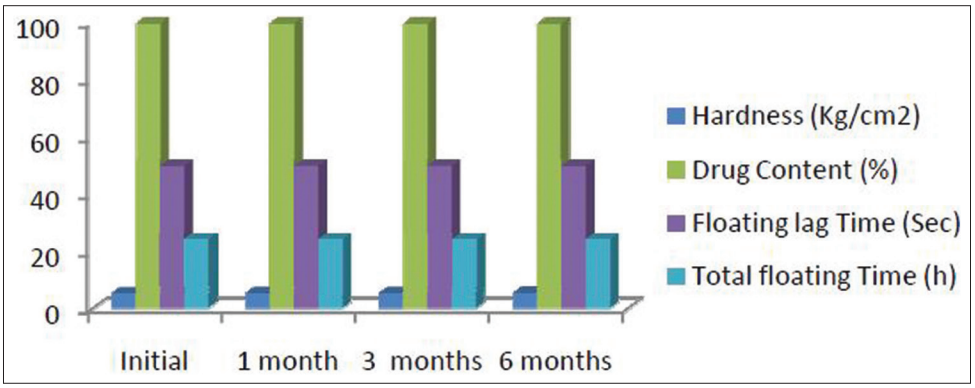


**Figure 10:** Stability data at 40 ± 2°C, 75 ± 5%RH for 6 months (AST)

**Table 8:** *In vivo* pharmacokinetic data for moxifloxacin HCl gastroretentive formulations

| Formulation | Pharmacokinetic parameters | | | | |
|---|---|---|---|---|---|
| | $C_{max}$ (μg/mL) | $T_{max}$ (H) | $AUC_{0-t}$ (μg.H/mL) | $AUC_{0-\infty}$ (μg.H/mL) | $K_E$ ($H^{-1}$) |
| MP | 18.65±0.4 | 12±0 | 195.79±12.51 | 196.79±12.55 | 0.332±0.001 |
| GRSOF | 18.29±0.5 | 12±0 | 209.62±15.78 | 214.78±16.29 | 0.222±0.002 |
| GMAF | 18.47±0.31 | 12±0 | 199.47±9.751 | 205.22±9.75 | 0.261±0.001 |

**Table 9:** Stability data at 25±2°C, 60±5% RH for 1 year (LST)

| Parameter | Initial | 1 month | 3 months | 6 months | 9 months | 12 months |
|---|---|---|---|---|---|---|
| Physical appearance | NC | NC | NC | NC | NC | NC |
| Hardness (kg/cm$^2$) | 5.27±0.13 | 5.34±0.12 | 5.38±0.11 | 5.39±0.10 | 5.39±0.09 | 5.40±0.10 |
| Average weight (mg) | 644.6±4.13 | 644.2±4.9 | 645.21±2.9 | 645.25±2.5 | 644.91±2.9 | 645.21±3.2 |
| Drug content (%) | 99.38±0.40 | 99.35±0.35 | 99.34±0.35 | 99.33±0.35 | 99.33±0.35 | 99.33±0.30 |
| Floating lag time (s) | 49.54±0.6 | 49.55±0.7 | 49.55±0.7 | 49.54±0.7 | 49.54±0.5 | 49.55±0.5 |
| Total floating time (h) | 24 | 24 | 24 | 24 | 24 | 24 |

**Table 10:** Stability data at 30±2°C, 65±5% RH for 1 year (IST)

| Parameter | Initial | 1 month | 3 months | 6 months | 9 months | 12 months |
|---|---|---|---|---|---|---|
| Physical appearance | NC | NC | NC | NC | NC | NC |
| Hardness (kg/cm$^2$) | 5.27±0.13 | 5.24±0.12 | 5.28±0.11 | 5.30±0.10 | 5.31±0.09 | 5.30±0.10 |
| Average weight (mg) | 644.6±4.13 | 644.32±5.0 | 645.22±3.9 | 645.23±3.7 | 644.95±2.9 | 645.22±3.5 |
| Drug content (%) | 99.38±0.40 | 99.33±0.37 | 99.34±0.36 | 99.33±0.35 | 99.33±0.37 | 99.34±0.31 |
| Floating lag time (s) | 49.54±0.6 | 49.54±0.7 | 49.55±0.65 | 49.55±0.64 | 49.54±0.49 | 49.54±0.5 |
| Total floating time (h) | 24 | 24 | 24 | 24 | 24 | 24 |

**Table 11:** Stability data at 40±2°C, 75±5% RH for 6 months (AST)

| Parameter | Initial | 1 month | 3 months | 6 months |
|---|---|---|---|---|
| Physical appearance | NC | NC | NC | NC |
| Hardness (kg/cm$^2$) | 5.27±0.13 | 5.34±0.13 | 5.37±0.13 | 5.40±0.12 |
| Average weight (mg) | 644.6±4.13 | 644.38±4.2 | 645.38±3.2 | 645.40±3.61 |
| Drug content (%) | 99.38±0.40 | 99.30±0.35 | 99.32±0.38 | 99.31±0.35 |
| Floating lag time (s) | 49.54±0.6 | 49.55±0.1 | 49.55±0.55 | 49.54±0.54 |
| Total floating time (h) | 24 | 24 | 24 | 24 |

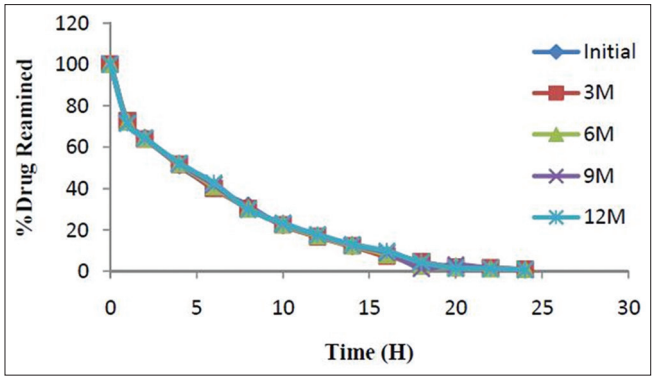


**Figure 11:** Percentage drug remained at 25 ± 2°C, 60 ± 5% RH for 1 year (LST)

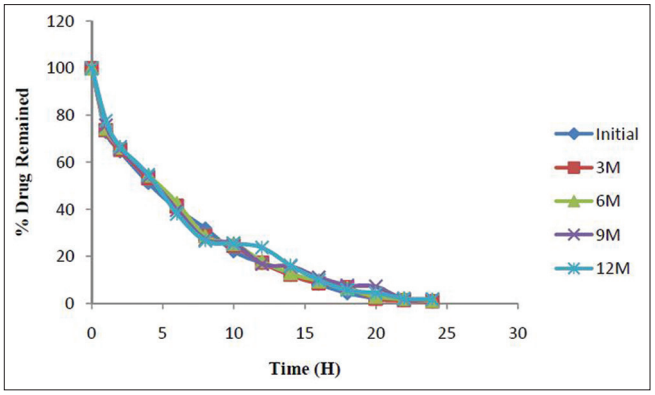


**Figure 12:** Percentage drug remained at 30 ± 2°C, 65 ± 5% RH for 1 year (IST)

shows similarity factor ($f_2$) 71.73, difference factor ($f_1$) 4.27, $t_{cal}$ is <0.05 when compared with marketed product (AVELOX).

Design for performing *in vivo* test is presented in Table 7. The mean plasma drug concentration profile of (*in vivo*) GRSOF, marketed product shows similarity or nearly superimposable. Results for pharmacokinetic evaluation are summarized in Table 8 and Figure 7. $C_{max}$ of formulations was founded to be in the range of 18.29 ± 0.5–18.65 ± 0.4. $T_{max}$ was founded to be 12 h. $AUC_{0-t}$ was founded to be in the range of 195.79 ± 12.51–209.62 ± 15.78 and $AUC_{0-\infty}$ 196.79 ± 12.55–214.78 ± 16.29. $K_E$ values were founded to be in the range of 0.222 ± 0.002–0.332 ± 0.001.

No visible physical changes were observed in GRSOF withdrawn from the humidity chambers. The hardness, moisture content, and drug content in all the formulations were found to be satisfactory. The release profiles of all the formulations have not changed significantly after storage at 25 ± 2°C, 60 ± 5% RH and 30 ± 2°C, 60 ± 5% RH for a period of 12 months and 40 ± 2°C, 75 ± 5% RH for a period of 6 months. The slow and controlled drug delivery

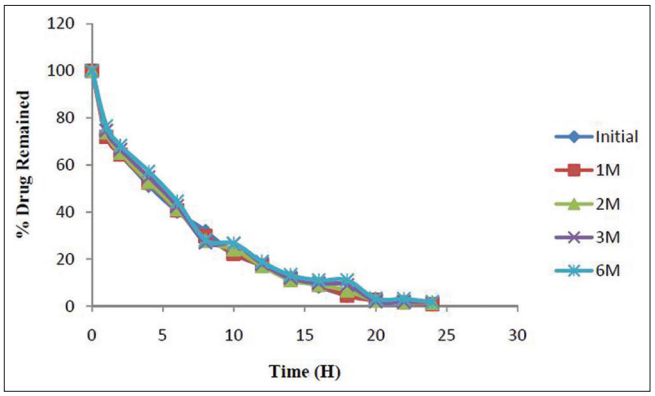


**Figure 13:** Percentage drug remained at 40 ± 2°C, 75 ± 5% RH for 6 months (AST)

of the moxifloxacin remained constant. Results for finished product assurance tests are summarized in Tables 9-11 and Figures 8-10. Comparative percentage drug remained versus time plots at different conditions are shown in Figures 11-13.

## CONCLUSION

On the basis of the current research study, the use of macromolecules (natural and semi-synthetic polymers) in combination had its own advantages of maintaining integrity and buoyancy of tablets. Gastroretentive tablet dosage form of moxifloxacin HCl was formulated successfully using HPMC K100M and LCG. The effervescent-based FDDS is a promising formulation to obtain gastroretentivity using gel-forming polymers employing sodium bicarbonate as gas-generating agent. Among the various gastroretentive formulations studied, the formulation (GRSOF) showed the best result in terms of the required percentage cumulative drug release, floating lag time, and total floating time and is considered as the ideal formulation**.** Best formulation GRSOF follows first-order release, non-Fickian diffusion. It shows good retaining characteristics. Plasma drug concentrations were maintained well. Results for stability studies of GRSOF found to be satisfactory. It also avoids first-pass effect and also improves patient compliance by reducing the dosing frequency, which will ultimately improve the clinical outcome.

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