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Formulation and evaluation of gastroretentive floating tablets of moxifloxacin

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Abstract
The objective of the current study is to develop gastroretentive formulation for moxifloxacin using various drug release modifiers, moxifloxacin, novel synthetic fluoroquinolone, and antibacterial agent. Floating tablets of moxifloxacin. HCL were prepared using variable amounts of Eudragit RS with effervescent mixtures as per 32 factorial designs by direct compression technique. Amount of release modifiers required to obtain the prolonged release of drug was chosen as independent variables, X1 and X2, respectively, whereas time taken for 10%, 50%, 75%, and 90% of drug release were chosen as dependent variables. Nine formulations were developed and are checked for pharmacopeial tests. Results show that all the factorial batches were lie within the standard limits. Dissolution parameters of all formulations were subjected to kinetic fitting; various statistical parameters were determined. Polynomial equations were developed and verified for dependent variables. Formulation (F5) containing 50 mg of Eudragit RS is the best formulation showing similarity f2 = 71.733 and f1 = 4.272 with the marketed product (AVELOX). Formulation F5 follows Higuchi's kinetics, Non-Fickian Diffusion, and first-order kinetics (n = 1.098).

Keywords: 32 factorial design, first-order kinetics, gastroretentive, Eudragit RS, moxifloxacin, non-Fickian diffusion mechanism

1. Introduction
The effective oral drug delivery practice depends on numerous factors such as gastric emptying process, gastrointestinal (GI) transit time, release of drug from dosage form, and absorption site for the 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.
Numerous factors show the impact on the effectiveness of oral delivery practice such as gastric emptying process, GI transit time, drug release pattern from the formulation and absorption site for the drug. The design of oral controlled DDS is targeted to obtain predictable and improved *in vivo* availability. 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 a predictive rate, which retains in the acidic environment for a longer period of time than prompt release formulations.
Several difficulties were present in front of researchers for designing controlled release systems for better absorption, improved bioavailability [4]. 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 [5, 6].
Floating drug delivery system (FDDS) is also known as hydrodynamically balanced system. FDDS have a bulk density is lower than gastric fluids and thus remain buoyant in the gastric environment for a prolonged period of time, without affecting the gastric emptying rate. The dosage form is stayed in the stomach due to the flotation mechanism, which results in controlled rate of drug release. After the release of the drug, the residual system is run out from the gastro environment; this will increases GRT and better control of fluctuations in plasma drug concentrations [7-10].
Moxifloxacin, synthetic broad-spectrum antibacterial agent, belongs to the class of 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 [11, 12].

An attempt is made in the current study to develop gastroretentive drug-delivery system (preferably by flotation) with the help of drug release rate modifiers (natural – Eudragit RS [13-16] From the literature, very less work reported for LCG, though it is natural more benefits observed from an economy point of view as well as risk incidence also low. Hence, Eudragit RS selected as a polymer for the formulation development of moxifloxacin gastroretentive delivery.

A systemic approach for formulation of gastroretentive drug-delivery system of moxifloxacin with the help of polymers which prolong the gastric transit time, improve penetrability of the drug through mucosa thereby improving the clinical efficacy of the active ingredient.

Response surface methodology (RSM) with a polynomial equation has been extensively applied in the design and development of pharmaceutical products. Variables of RSM include 32 factorial design, central composite design), and Box- Behnken design. RSM is applied when only a few significant factors are involved in the optimization procedure. Advantage of this method is less experimentation and time, results in more effective and cost-effective than tradition experimentation models [17, 18].

Direct compression is a widely used manufacturing method for the preparation of tablets [19].

Hence, an attempt is made in this research work to formulate gastroretentive floating (GRF) tablets of moxifloxacin using Eudragit RS. Instead of the heuristic method, a standard statistical tool design of experiments is utilized to study the effect of formulation variables on the release properties.

A 32 factorial design was utilized to study the effect of polymers on the drug release profile (effect of independent variables or factors), i.e., the quantity of Eudragit RS on the dependent variables (t10%, t50%, t75%, and t90%) [18, 20].

A systemic approach for design and development of gastroretentive drug-delivery system of moxifloxacin using polymers which increases the gastric transit time, improve penetrability of drug through mucosa thereby improving the clinical efficacy of the active ingredient.

2. Materials and Methods

Formulation Development of Moxifloxacin GRF Tablets

Quantities required for the Eudragit RS for the preparation of moxifloxacin floating tablets was selected as independent variables (X1 and X2, respectively). t10%, t50%, t75%, and t90% were selected as dependent variables. Polynomial equations were developed for dependent variables as per backward stepwise linear regression analysis [21].

The three levels of X1 (EUDRAGIT RS were 8.75%, 12.5%, and 16.25%. Three levels of X2 (LCG) were 8.75%, 12.5%, and 16.25% (percentage with respect to dose of active ingredient). Nine moxifloxacin floating tablet formulations were designed using selected combinations of X1 and X2, checked for the selection of optimum composition required to meet the primary objective of the study.

Preparation of moxifloxacin HCl floating tablets

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 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 the powder blend. The blend was lubricated with magnesium stearate. The formulae for moxifloxacin HCl floating tablets are shown in Table 1. The powder blend was subjected to preformulation analysis.

The powder blend was subjected to compression with the help of rotary tablet compression machine (Tablet Mini-press). Compressed tablets were processed for quality control measures as per pharmacopeia. Final formulations were transferred to airtight and light resistance containers.

Experimental Design

Experimental design used in the current research study is 32 factorial designs, quantity of Eudragit RS was labeled as X1, and quantity of LCG was labeled as X2 Three levels for both X1 and X2 chosen and coded as −1 = 8.75%, 0 = 12.5%, +1 = 16.25%, formulations for factorial trials are presented in Table 2.

Evaluation of Moxifloxacin. HCl GRF Tablets [22]

Hardness

The breaking/crushing strength of the tablets was determined by measuring the 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 (W0); 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%.

$$\text{Weight loss (\%)} = [W0–W/W0]\times100$$

Assay

The assay was performed by the triturating stated number of tablets in Indian Pharmacopoeia (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 µ membrane filter, suitable aliquots were prepared, and the absorbance of the resultant solution was measured spectrophotometrically at 288 nm using 0.1 N HCl as blank.

Thickness

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

In vitro buoyancy studies

This test is performed by placing the tablets in a beaker containing 100 mL of 0.1 N HCl (SGF). The time required forthe upward movement of the tablet to float on the 0.1 N HCl (SGF) was noted to be floating lag time [23].

In vitro drug release study

The *in vitro* dissolution rate study for formulation trials was performed using USP XXIII type-II dissolution test apparatus containing 900 ml of 0.1 N HCl operated under conditions such as 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 estimation of drug release by measuring the absorbance at

288 nm using ultraviolet-visible spectrophotometer after suitable aliquots. The samplings were performed in the triplicate manner (n = 3) [11, 12, 24].

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 [25-28].

Swelling index study

To evaluate swelling index, the tablet was placed in USP dissolution apparatus II with 900 ml 0.1N HCl after measuring the weight of tablet (W1). Then, the weight of tablet (W2) 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.

$$\text{Swelling index (\%)} = [(W2–W1)/(W2)]\times100$$

3. Results and Discussion

GRF tablets of moxifloxacin were formulated with the help of 32 factorial designs, for identifying the best composition of drug release modifiers (Eudragit RS) along with effervescent mixtures. Formulation design is presented in Table 1. Two factors involved for the design are that the quantity of Eudragit RS was labeled or chosen as independent variables (X1 and X2, respectively), and kinetic parameters labeled as dependent variables (t10%, t50%, t75%, and t90%). Nine factorial batches were designed.

Powder blends were subjected to flow analysis. Results are summarized in Table 3. Pre-formulation results reveal that all formulations are passed the limits and blends show good flow properties.

All trials have 400 mg of moxifloxacin as a GRF tablet dosage form by direct compression technique. All final batches were subjected to various finished product evaluation tests such as drug content, floating lag time, mean hardness, total floating time, mean thickness, and friability as per pharmacopeial methods, and subjective results are summarized in Table 4. Hardness for finished batches was founded to be in the range of 5.19 ± 0.188–5.68 ± 0.22 kg/cm2. The thickness for finished batches was founded to be in the range of 6.12 ± 0.03–6.31 ±0.04 mm. Results for friability test were founded to be <0.35%. Drug content for finished batches was founded to be within the acceptance criterion. All formulation batches passed the weight variation test. The purpose of the swelling study is to determine the water uptake capability of the retardant. The 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 F1 was found to have the highest swelling property and the data for swelling evaluation. Drug release studies were performed for finished batches using pH 1.2 buffer (0.1 N HCl) as a dissolution fluid is operated under a standard set of conditions at 50 rpm (paddle), 37 ± 0.5 °C. Dissolution plots were presented in Figures 1-4 (kinetic plots), and statistical parameters are summarized in Table 6. Percentage cumulative drug release for finished batches F1-F9 at 24 h was found to be 94.815–100.39%. The result revealed that the release rate of the drug was inversely proportional to the quantity of polymers and vice versa [29]. Hence, desired drug release was achieved by manipulating the composition of independent variables.

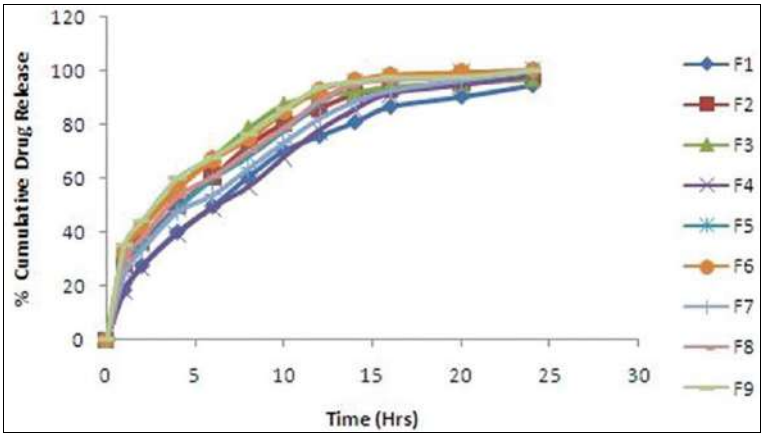

Fig 1: Comparative zero-order plots

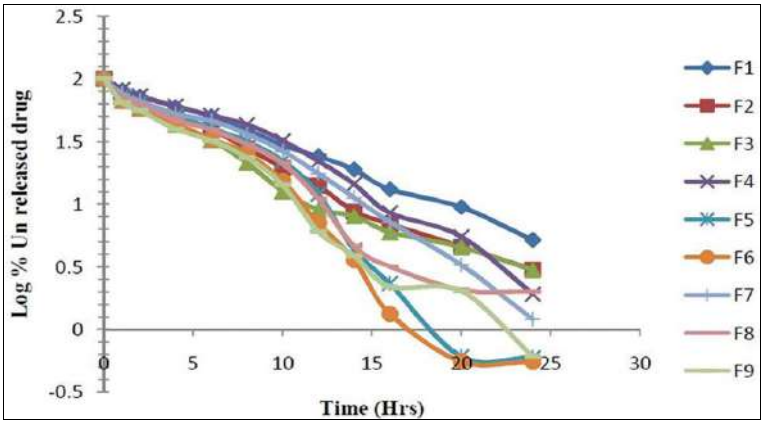

Fig 2: Comparative first-order plots

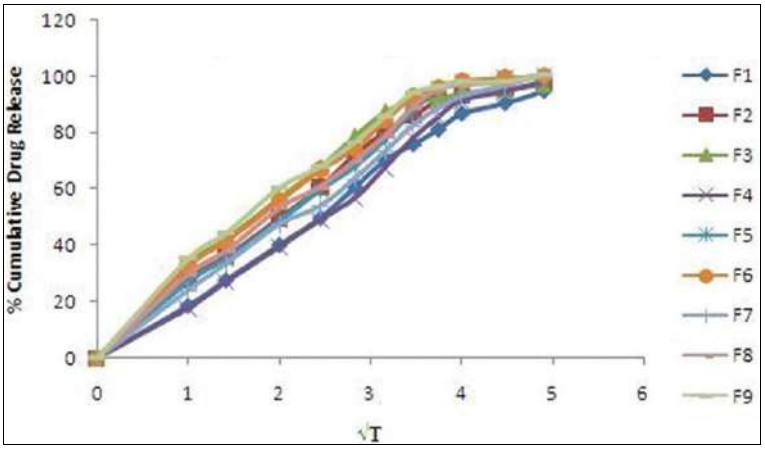

Fig 3: Comparative Higuchi plots

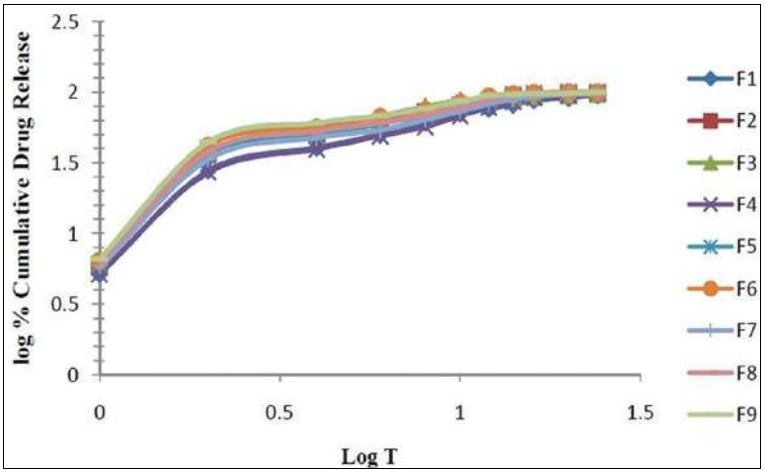

Fig 4: Comparative Korsmeyer–Peppas plots

The difference was seen independent variables due to the change in proportions of X1 and X2. Formulation coded F5 containing 50 mg of Eudragit RS produced promising dissolution characteristics, which helps in meeting the objective of research by gastric retentive and optimum drug release (t10% = 0.453 h, t25% = 1.236 h, t50% = 2.979 h, t75% = 5.958 h, and t90% = 9.899 h). The initial burst release of drug from the formulation was due to change in viscosity of polymer matrix. As the increase in viscosity of stagnant layer results in a corresponding decrease in the drug release (occurred due to thicker gel layer formation). Dissolution profiles of moxifloxacin floating tablets were subjected to kinetic modeling. Results reveal that all formulation batches best fitted to first-order kinetics, quantification of r2 was founded to be in the range of 0.977–0.998. They also fitted to Higuchi's kinetics, r2 was found to be in the range of 0.964–0.994. From the Peppas treatment, it reveals that all batches follow that shows non-Fickian diffusion super Case-II path (*n* values 0.986–1.187). Polynomial equations were developed for all dependent variables by linear stepwise backward regression analysis with the help of PCP Disso software, and response morphological plots were constructed using Design-Expert 7.0. The response morphological plots are presented as Figures 5-9 for t10%, t25%, t50%, t75% and t90% using X1 and X2 on both the axes, to show the effects of independent variables on the dependent variables. Polynomial equation for 3^2 full factorial designs was presented as follows:

$$Y= b0+b1\ X1+b2\ X2+b12\ X1X2+b11\ X1^2+b22\ X2^2\ldots$$

Y – dependent variable, b0 – mean response of 9 trials, b1 – estimated coefficient for X1, b2 – estimated coefficient for X2, b12 – interaction term, $X1^2$ and $X2^2$ coefficients for non-linearity.

The equations for dependent variables developed as mentioned below,

Y1 = 0.617+0.102X1+0.084X2+0.017X1X2+0.142 X12+ 0.055X22 (for t10%)

Y2 = 1.683+0.279X1+0.227X2+0.046 X1X2+0.388 X12+ 0.152 X22 (for t25%)

Y3 = 4.056+0.672X1+0.547X2+0.111 X1X2+0.936 X12+ 0.364 X22 (for t50%)

Y4 = 8.111+1.344X1+1.095X2+0.222 X1X2+1.871 X12 +0 729 X22 (for t75%)

Y5 = 13.477+2.233X1+1.820 X2+ 0.368 X1X2+3.11 X12+ 1.21 X22 (for t90%)

The positive sign for coefficient of X1 in Y1–Y5 notifies that, as the amount of X1 increases, all independent variables values were also increases. In other words, the data demonstrate that both X1 and X2 affect dependent variables. From the results, it can be concluded that increase in the amount of the polymer leads to decrease in release rate of the drug and drug release pattern may be altered by changing the quantities of X1 and X2 to appropriate levels. The dissolution parameters for predicted from the polynomial equations and those actual observed from experimental results are summarized in Table 8. Closeness of results were seen between actual values and predicted

values. This proves that developed polynomial equation was valid. The response surface/surface morphological plots were presented to show the effects of X1 and X2 on dependent variables. The final best (based on desirability factor above 0.999) formulation (F5) is the identical product and shows similarity factor (f2) 71.733, difference factor (f1) 4.272, tcal is <0.05 when compared with the marketed product (AVELOX). Comparative dissolution plots for best formulation (F5) and marketed product.

4. Conclusion

On the basis of the current research study, the use of macromolecules (Natural and Semisynthetic polymers) in combination had its own advantages of maintaining integrity and buoyancy of tablets. The effervescent based FDDS is a promising formulation to obtain gastroretentivity using gel-forming polymers such as Eudragit RS employing sodium bicarbonate as gas generating agent using 32 factorial design. Among the various FDDS formulations studied, theformulation (F5) showed the best result in terms of the required percentage cumulative drug release, floating lag time and total floating time were 99.245% within 24 h and are considered as the ideal formulation. Best formulation F5 follows first-order release, Non-Fickian Diffusion super Case-II transport. The best formulation shows good retaining characteristics. It also avoids the first-pass effect and also improves patient compliance by reducing the dosing frequency, which will ultimately improve the clinical response.

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