

Design and Optimization of Guar Gum-Carboxymethyl Cellulose-Based Gastro-Retentive Floating Tablets of Levofloxacin through Melt Granulation Technique

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Abstract Gastroretentive delivery of therapeutics has gained considerable attention from researchers in recent times due to its effectiveness in localizing the delivery system in the stomach. Stomach-specific delivery of antibiotics is essential to eradicate *Helicobacter pylori*. The aim of the present investigation is to optimize and evaluate the effect of guar gum (GG) and carboxymethyl cellulose (CMC) on sustaining the release of levofloxacin from the formulated gastroretentive floating matrix tablets. Optimization of the formulation was done using Design Expert 13 software Trial Version. Thermoplastic granulation technique was employed using stearic acid for granule preparation. The developed matrix tablets were evaluated through several evaluation techniques. The Fourier transform infrared (FTIR) technique was used to investigate the compatibility between levofloxacin and the used polymers. The pre-compression and post-compression parameters were also evaluated. The FTIR spectra reflected excellent compatibility between the drug and other excipients. The floating lag time was found to decrease with increasing polymer concentration. The total floating duration was reported up to 456 ± 14.4 mins for F6 (10% GG & 15% CMC).

The drug release study in 0.1 N HCl buffer showed a gradual decrease in cumulative drug release % with increasing guar gum concentration. The drug release mechanism was found to follow Korsmeyer-Peppas kinetics, and the n value indicated Fickian diffusion of the dissolved drug from the tablet matrix. The obtained results indicated the suitability and effectiveness of the developed floating matrix tablets for gastroretentive and sustained release of levofloxacin.

Keywords Gastroretentive Tablets, Hot Melt Granulation, Guar Gum, Carboxymethyl Cellulose, Central Composite Design

1. Introduction

Tablets are the most conventional dosage form for delivering active pharmaceutical ingredients in order to receive the intended action within the body [1,2]. It is the most commonly used formulation due to its stability, ease of administration, cost-effectiveness for production, and enhanced elegance [3,4]. Drugs having short half-lives

when absorbed rapidly from the gastrointestinal tract (GIT) are excreted from the systemic circulation swiftly. Therefore, in order to obtain the desired therapeutic effect, the dosing frequency is increased [5, 6]. Oral sustained-release formulations have been developed in order to release the drugs at an optimal rate, thereby maintaining the therapeutic level of concentration for an extended period of time [7, 8]. Hence the release of medicament from the matrix can be controlled after oral administration of these sustained-release dosage forms [9]. The site-specific oral administration of the sustained release formulations is necessary for enhancing the gastric residence time (GRT) [10]. Sustained release formulations enable the distribution of a certain drug at a previously determined rate, leading to prolonged drug delivery [11, 12]. This drug release mode is particularly helpful for drugs that are metabolized and rapidly eliminated from the body after administration. Sustained release of the therapeutic agent can maintain required drug concentration in plasma for desired pharmacological efficacy [13]. Longer gastric retention enhances drug bioavailability, and lengthens the time to pass through gastric region that increases the possibility to solubilize in GI fluid and subsequent absorption of drugs [14].

Floating drug delivery approaches which include floating tablets have several advantages for poorly bioavailable drugs and drugs having narrow absorption window in the upper GI tract [15,16]. Since the dosage form is intended to reach the site of absorption, the bioavailability of the dosage form increases. As floating drug delivery systems have a lower bulk density than gastric fluids, they float freely in the stomach without slowing down the rate at which the stomach empties [17]. The floating drug delivery system progressively releases the drug at the specified rate, and after the drug has been released, the residual system is eliminated from the stomach. This facilitates extended gastric residence time with better control over the plasma concentration [18].

Guar gum is a natural non-ionic galactomannan polysaccharide isolated from *Cyamopsis tetragonolobus* seeds of the Leguminosae family [19]. It is a water-soluble polymer and comprises linear chains of β -(1-4)-D-mannan, having side chains of α -(1-6) linked galactose. Being a natural polysaccharide guar gum, it shows several properties like biocompatibility, biodegradability, and sustainability in pharmaceutical formulations and drug release studies. Guar gum has a wide variety of applications in pharmaceutical industries like stabilizer, emulsifier, thickener, and suspending agent [20]. Moreover, it is frequently used as a binding and dissolving agent in the preparation of several solid preparations. Intermolecular chain entanglement in the guar gum structure takes place in the presence of water, which improves the gelling and thickening capabilities and can create high viscosity at low concentrations. The hydroxyl groups in guar gum allow it

to form hydrogen bonds with other molecules in an aqueous solution. In cold water, guar gum swells and becomes a colloidal dispersion [21]. Moreover, it has the ability to form gelled networks, which can increase the drug release rate. The diverse chemical and physical functionalization of guar gum aids in gaining control over the polymer's extended swelling behavior in physiological buffer solution [22].

Carboxymethyl cellulose is a cellulose derivative of an anionic water-soluble polymer. It has several characteristics of bio-adhesiveness, hydrophilicity, pH sensitivity, non-toxicity, and gel-forming capacity which can be employed in various drug delivery and biomedical research [23]. Polar carboxyl groups from organic acids make cellulose liquid and chemically reactive [24]. CMC can also be created from cellulose-based textiles, like cotton and viscose rayon [25]. Moreover, a "semi-purified" intermediate grade is created, which is commonly employed in paper applications like document restoration for historical records. CMC can also act as a thickening agent that is also used for stabilizing emulsions in a wide range of products, both food- and non-food-related [8, 26]. CMC is extensively used in several applications such as laxatives, toothpaste, water-based paints, detergents, diet pills, textile sizing, reusable heat packs and different paper goods [27].

Levofloxacin is a third-generation fluoroquinolone antibiotic with broad-spectrum antibacterial activity that is an optically active L-isomer of ofloxacin. Levofloxacin works by inhibiting the bacterial topoisomerase II (DNA gyrase) enzyme, which is necessary for RNA transcription, bacterial DNA repair, and DNA replication [28]. It permeates the cell wall of the bacteria. The normal functioning of DNA gyrase is hindered, hence inhibiting bacterial cell proliferation. Levofloxacin binds to serum plasma proteins (mostly albumin) 24–38% of the time; serum protein binding occurs regardless of blood drug concentrations. In individuals with common renal function, the plasma elimination half-life ($t_{1/2}$ beta) ranges from 6h to 8h [29]. A linear two-compartment open model with first-order elimination characterizes the pharmacokinetics of levofloxacin [30]. After oral administration of 250 mg and 500 mg levofloxacin tablets, plasma drug concentrations reach mean peak levels of approximately 2.8 mg/L and 5.2 mg/L, respectively within 1h to 2h. Levofloxacin displays good oral bioavailability, and its absorption is not significantly influenced by food intake [29].

In this research work, the hot melt granulation technique was employed, which is a solvent-free process. The developed granules were compressed into tablet formulation using varying concentrations of guar gum and carboxymethyl cellulose [22, 23]. The sustained release ability of the polymeric composition developed through hot melt granulation was investigated in this work.

2. Materials and Methods

2.1. Materials

Levofloxacin was commercially procured from Jiyan Chemicals, India. Guar gum and carboxymethyl cellulose were purchased from Loba Chemie, India. Stearic acid was purchased from Sigma Aldrich. Talc and magnesium stearate were commercially purchased from SD Fine Chemicals.

2.2. Methods

2.2.1. Fourier Transform Infrared Spectroscopy (FT-IR)

The pure levofloxacin, guar gum, carboxymethyl cellulose, and formulation were analyzed using FTIR spectroscopy. KBr was mixed with the powdered sample which was then compressed into pellets using a hydraulic press. The scan range for the pellets was 4000 cm^{-1} to 400 cm^{-1} using the FTIR spectrophotometer (Bruker, Germany, ALPHA II) [31].

2.2.2. Experimental Design

The experimental design was statistically evaluated employing Design Expert (v.13.0.3.0, Stat-Ease Inc., Trial Version) software. Central composite design (CCD) was selected for this study.

With a 3-level design, formulation optimization was dependent on composition of tablet batches. 9 formulation batches were developed using 2^3 factorial designs for investigating the effects of guar gum (X_1) and carboxymethyl cellulose (X_2) as independent variables on various dependent variables including floating lag time (sec), total floating duration (min), and drug release (mg/ml). The coded levels were translated into corresponding experimental units, and experimental trials, and factor combinations employed in this study are summarized in Table 1. ANOVA was employed to analyze the obtained data and indicate a suitable significant model [32, 33].

Table 1. Selection of the independent variables

Coded values level	Independent Variables	
	Guar gum % (X_1)	Carboxymethyl cellulose % (X_2)
-1	2.5	2.5
0	5	5
+1	7.5	7.5

2.2.3. Optimization of Formulation

CCD was employed to find suitable variables. As described in Table 2, 9 experimental runs were performed. CCD was applied not only for establishing a correlation between the independent and dependent variables, but also for optimizing formulation batches.

Table 2. Composition of formulations based on central composite design.

Formulation Code	Factor 1	Factor 2
	A:Guar gum %	B:Carboxymethyl cellulose %
F1	2.5	2.5
F2	2.5	5
F3	2.5	7.5
F4	5	2.5
F5	5	5
F6	5	7.5
F7	7.5	2.5
F8	7.5	5
F9	7.5	7.5

2.2.4. Preparation of Levofloxacin Granules Using Hot Melt Granulation Technique

The levofloxacin incorporated granules were developed through hot melt granulation technique (as shown in Table 3). Stearic acid, guar gum, carboxymethyl cellulose, citric acid, sodium bicarbonate, lactose, talc and magnesium stearate were weighed individually. A weighed quantity of stearic acid was taken in a china dish which was placed in a water bath. The other ingredients including drug and excipients were mixed together following geometric order. The resultant physical mixture of drug and excipients was added to the molten stearic acid and stirred with a glass rod to make a homogenous dispersion. Upon cooling and solidification of the mass, it was passed through sieve no. 10 to obtain granules. The granules were lubricated using the remaining amount of talc and magnesium stearate. The resulting granules were kept in a petri-dish and air-dried by keeping an inverted glass funnel on it. The dried granules were subjected to a tablet compression machine (Kambert Mini Tablet Press, KMPc D8) using dies having an 8 mm diameter and flat punch sets. The weight of each tablet was maintained at 400 mg containing 100 mg of levofloxacin [33].

Table 3. Formulation of levofloxacin floating tablets through hot melt granulation

Formulation no.	Drug (mg)	Stearic acid (mg)	Guar gum (%)	CMC (%)	NaHCO ₃ (mg)	Citric acid (mg)	Talc (mg)	Mg stearate (mg)	Lactose (mg)
F1	100	100	2.5	2.5	50	25	12.5	12.5	80
F2	100	100	2.5	5	50	25	12.5	12.5	70
F3	100	100	2.5	7.5	50	25	12.5	12.5	60
F4	100	100	5	2.5	50	25	12.5	12.5	70
F5	100	100	5	5	50	25	12.5	12.5	60
F6	100	100	5	7.5	50	25	12.5	12.5	50
F7	100	100	7.5	2.5	50	25	12.5	12.5	60
F8	100	100	7.5	5	50	25	12.5	12.5	50
F9	100	100	7.5	7.5	50	25	12.5	12.5	40

2.2.5. Pharmacotechnical Evaluation

2.2.5.1. Evaluation of Granules

2.2.5.1.1. Bulk Density

Bulk density is the mass-to-volume ratio of a sample, including the volume of interparticulate voids. A measuring cylinder was used to determine the bulk density of the sample by measuring the volume of a known mass of the sample. 10 g of granules were taken into a measuring cylinder and bulk volume was measured. This process was done thrice in a repetitive manner and average bulk density was determined [31].

$$\text{Bulk density of granules} = \frac{\text{Mass of granules taken}}{\text{Bulk volume of granules}}$$

2.2.5.1.2. Tapped Density

Tapped density is the ratio of weight of granules to the volume employed by the granules after it has been tapped for certain times. By manual tapping of a graduated measuring cylinder containing granules, the tapped volume shown in the measuring cylinder and tapped density are determined. 10 g of granules were taken into a measuring cylinder. Then it was tapped for certain times and the tapped volume was measured. This process was performed in a triplicate manner and average tapped density was determined [34].

$$\text{Tapped density of granules} = \frac{\text{Mass of granules taken}}{\text{Tapped volume of granules}}$$

2.2.5.1.3. Compressibility Index

The compressibility index is a procedure to calculate the intensity of granules to consolidate. As a result, it is a measurement of inter-particle interactions. The values of the bulk densities and tapped densities will be closer

together in free-flowing powder, where inter-particle interactions are usually less significant. There are usually more inter-particle interactions in materials with poor flow property, which leads to lower bulk densities and a wider gap between the bulk and tapped densities as a result of particle bridging. A lower compressibility index shows better flow property. This compressibility index was done three times and the average compressibility index was calculated [35].

$$\text{Compressibility index} = \frac{(\text{Initial bulk volume} - \text{Tapped bulk volume})}{\text{Initial bulk volume}} \times 100$$

2.2.5.1.4. Hausner's Ratio

The Hausner's ratio (HR) is similar to the compressibility index [36]. It can be determined by using

$$\text{Hausner's ratio} = \frac{\text{Tapped density of the granules}}{\text{Bulk density of the granules}}$$

2.2.5.1.5. Angle of Repose

Angle of repose can be used for the characterization of bulk solids. This is a property associated with interparticulate friction or resistance to motion between particles. Angle of repose can be termed as the angle between the horizontal plane and the materials to be piled without collapsing [37].

$$\theta = \tan^{-1} \frac{\text{height of the heap}}{\text{radius of the heap}}$$

2.2.5.2. Evaluation of Tablets

2.2.5.2.1. Weight Variation

Weight variation test also known as content uniformity test. Weight variation can be performed to determine uniformity in different batches. 20 tablets were weighed individually, the average weight was determined, and the individual tablet weights were compared [38].

2.2.5.2.2. Hardness

The Monsanto hardness tester can be used to measure the hardness of the tablets. Hardness is the force required to break or crush a tablet in compression. It can be measured in kg/cm² [39].

2.2.5.2.3. Friability

Friability can be performed by using Roche friabilator. To measure the mechanical strength of tablets, a friability test can be done. Tablets that have been previously weighed can be placed in a friabilator. Friabilator contains a plastic chamber which rotates at 25 rpm, with dropping of tablets from 6 inches of height in each revolution. This process can be done for 4 mins and then tablets can be reweighed [40]. Friability can be measured by the following formula-

$$\text{Percentage friability} = \frac{W_0 - W_f}{W_0} \times 100$$

2.2.5.2.4. Thickness

Thickness of tablets is one of the essential parameters for evaluation of tablets. This test can be performed to check uniform size of each tablet. Thickness can be measured by Vernier calipers [41].

2.2.5.2.5. Diameter

Diameter can also be measured by using Vernier Callipers. Diameters of the tablets are performed to get uniform sized tablets [42].

2.2.6. Determination of Drug Content

Three tablets were randomly selected and taken from each batch for determining drug content. An individual tablet had been placed in a beaker with 100 millilitres of 0.1 N HCl buffer. The beaker was kept for 24 h and then sonicated using a probe sonicator (LABMAN PRO650) followed by filtration through Whatman filter paper. The filtrate was collected and spectrophotometrically analyzed at 294 nm using a UV-Visible Spectrophotometer (SHIMADZU, UV-1900i) after suitable dilution [43].

2.2.7. *In-vitro* Buoyancy Study

5 individual tablets of each formulation were kept in individual beakers containing 200 ml of 0.1 N HCl buffer. The *in vitro* floating lag time was determined by measuring the time in seconds required to float back to the surface of the beakers after dropping the tablets into the beaker. The average floating lag time was calculated from the obtained data. The total floating time was also noted for individual tablets from which the mean floating time was calculated [44].

2.2.8. Determination of *In-vitro* Drug Release Study

The *in-vitro* dissolution study for the developed floating tablets was carried out in USP type II dissolution apparatus (LAB INDIA DS800). 0.1 N HCl buffer (pH 1.2). The rpm

was selected at 50 with a preheated bath temperature of 37.4 ± 0.5°C. Randomly picked tablets were taken from each batch and weighed accurately, before placing into the dissolution vessel containing 900 ml of HCl buffer. 5 ml of medium was withdrawn with replacement of fresh buffer solution having same pH at predetermined time intervals up to 8 h. The samples were diluted with the dissolving media whenever necessary while being passed through Whatman filter paper. The diluted aliquot was subjected to spectrophotometric analysis at 294 nm utilizing UV-Visible Spectrophotometer (SHIMADZU, UV-1900i). The experiments were performed in triplicate and the mean cumulative percentage release of levofloxacin from the tablet core against respective time intervals was calculated [45].

2.2.9. Kinetic Evaluation of Drug Release Data

To understand the drug release mechanism from the tablet core, the dissolution data were fitted in different mathematical models including zero order (time Vs cumulative percentage of drug released), first order (time Vs log of percentage of drug released), Higuchi's model (square root of time Vs cumulative percentage of drug released), Hixon-Crowell model (time Vs cube root of fraction remaining to release) and Korsmeyer-Peppas model (log of time Vs log of percentage of drug released). The r² (correlation coefficient) values were obtained from the graph based on which the drug release mechanism was proposed [46].

In pharmacokinetics and drug release studies, different mathematical models are used to manifest and analyze the relationship between time and the cumulative percentage of drug release from the polymer matrix so as to achieve the optimum effective concentration in the plasma [47].

Zero-Order kinetics: In zero-order kinetics, the rate of drug release is constant over time, resulting in a linear relationship between time (t) and the cumulative percentage of drug released (Q) [48]. It describes the mechanism by which a drug is continuously released from a drug delivery device, despite its concentration. Mathematically, it can be represented as:

$$Q_t - Q_0 = K_0 t$$

where: Q_t = Cumulative percentage of drug released at time t. Q₀ = Cumulative percentage of drug released at time zero minutes. K₀ = Zero-order release rate constant.

In this model, the graph of cumulative percentage drug release versus time would be a straight line with a constant slope. This is primarily represented by osmotic pump systems, transdermal systems, matrix tablets containing low-soluble drugs, and coated forms.

First-Order Model: In the first-order model, the rate of drug release is proportional to the amount of drug remaining to be released. This leads to an exponential decrease in drug concentration over time [49]. The first-order equation, which states that the release rate is concentration dependent, describes the release from the

system.

$$\text{Log } Q_t = \text{Log } Q_0 - \frac{K_1 t}{2.303}$$

where: Q_0 = Initial amount of drug in the dosage form. Q_t = Final amount of drug in the dosage form. K_1 = First-order release rate constant (units: time^{-1}).

Higuchi Model: Drug release is described by the Higuchi model as a matrix-based diffusion-controlled process. It is commonly used for solid dosage forms like tablets and can be mathematically expressed as [50]:

$$Q = K_H t^{0.5}$$

where: Q = Cumulative percentage of drug released at time t . K_H = Higuchi release rate constant (units: $\%/\text{time}^{1/2}$).

The Higuchi model typically shows a linear relationship between the cumulative percentage of drug release and the square root of time.

Hixson-Crowell Model: The Hixson-Crowell model is applicable to systems where the surface area of the drug particles changes with time. It is often used for drug release from solid particles that erode or dissolve over time. The mathematical equation for the Hixson-Crowell model is:

$$Q^{1/3} = Kt + Q_0^{1/3}$$

where: Q = Cumulative percentage of drug released at time t . Q_0 = Initial amount of drug in the dosage form. K = Hixson-Crowell release rate constant.

Korsmeyer-Peppas Model: The Korsmeyer-Peppas

model describes the way drugs are released from polymeric matrices, particularly when more than one drug release mechanism is involved.

$$Q = Kt^n$$

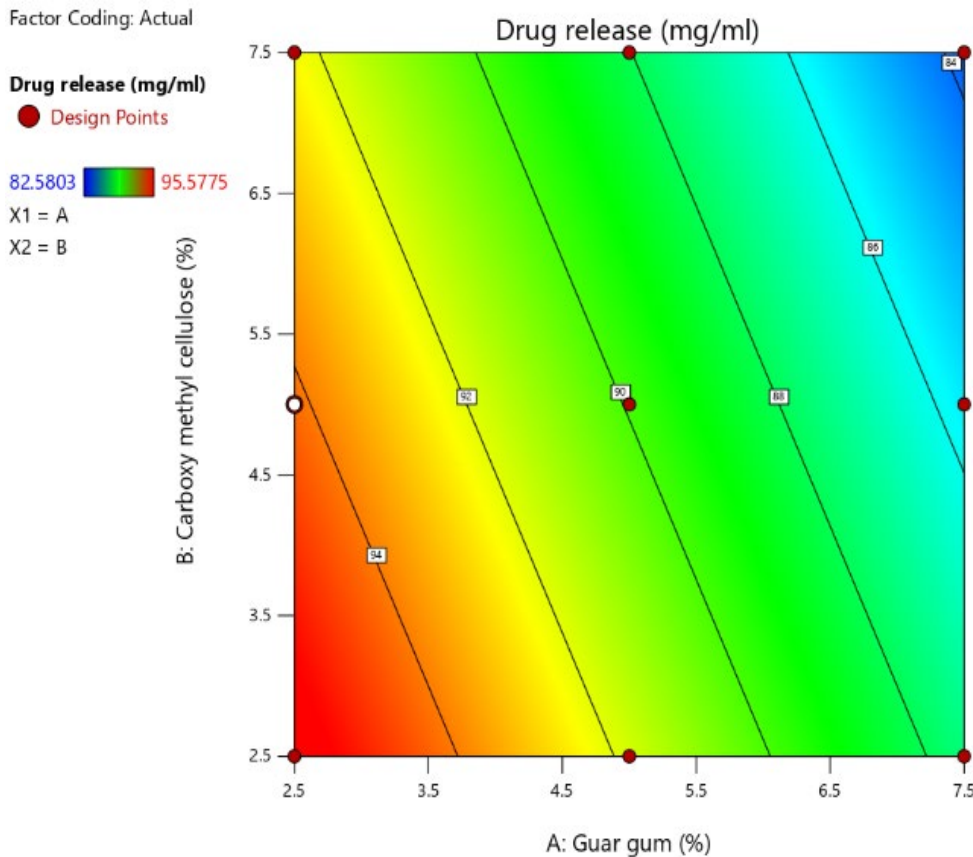
Where, Q = dissolved amount of drug at time t ; K = rate constant; n = diffusional exponent. This kinetic model helps predict the drug release mechanisms including Fickian mechanism ($n \leq 0.43$), non-Fickian diffusion ($0.43 < n < 0.85$) or case-II transport ($n \geq 0.85$).

3. Results and Discussion

3.1. Analysis of Obtained Response through Polynomial Equations

3.1.1. Effect of Variables on Drug Release

The obtained data were analyzed to fit the linear model suggested for correlation of the various study responses with investigated variables. The 2D and 3D plots in the figure below indicate low guar gum and carboxymethyl cellulose concentration demonstrated a positive influence on drug release. A decrease in levofloxacin release is observed with increasing concentration of guar gum and carboxymethyl cellulose. The dissolution study report suggested the lowest concentration of both polymers resulted in a faster drug release rate.



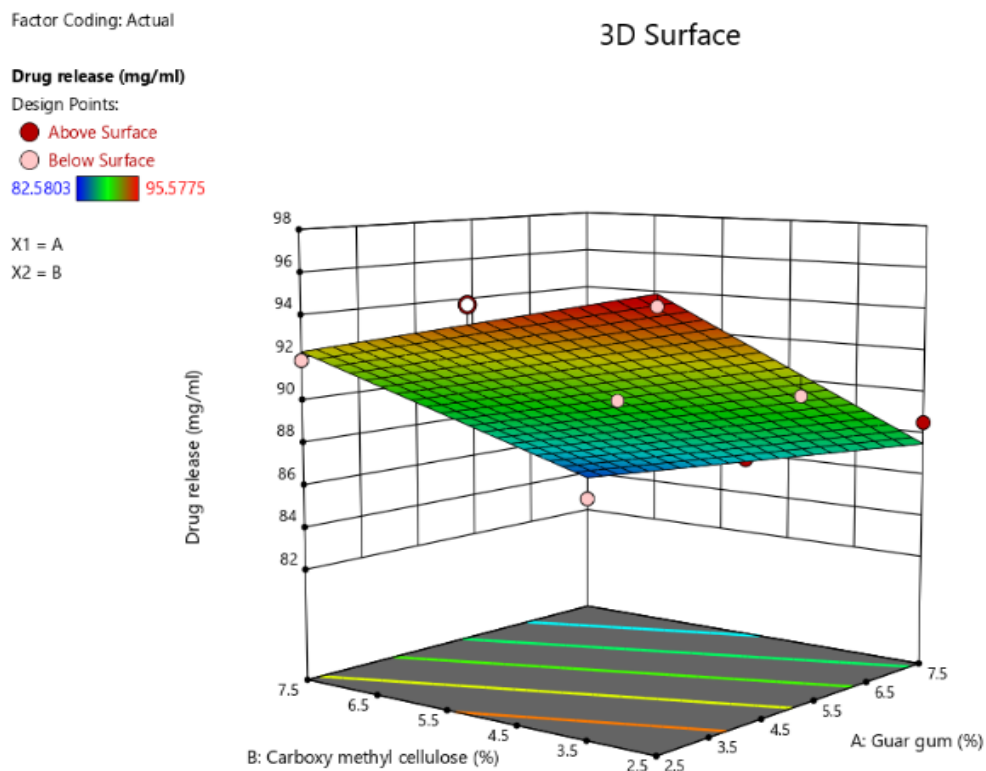


Figure 1. 2D and 3D representation reflecting contour plots and response surface plots respectively for assessing the influence of guar gum (X1) and carboxymethyl cellulose (X2) on drug release (Y1)

The mathematical model with respect to coded factors determined by Design Expert software is given below in Equation (1).

Response 1: Drug release, Y1

$$Y1 = 89.92 - 4.29 X1 - 1.89 X2 \quad (1)$$

The ANOVA result of the model with *p*-values less than 0.05, specifically *p*-value of 0.0001 indicated the significance of the model terms. The model F-value (67.59) indicates the significance of the model including the model terms A and B. The predicted determination coefficient value (*R*²) and adjusted *R*² were 0.8912 and 0.9433, respectively. The signal-to-noise ratio value is 21.671 indicating an adequate signal [51].

3.1.2. Effect of Variables on Floating Lag Time

The floating lag time of the formulated tablets was positively correlated with X1, Guar gum concentration, and X2, carboxymethyl cellulose concentrations, as indicated in the 2D and 3D plots in Figure 2.

The mathematical model with respect to coded factors determined by Design-Expert software is given below in Equation (2).

Response 2: Floating lag time, Y2

$$Y2 = 14.12 - 2.02 X1 - 5.37 X2 \quad (2)$$

The ANOVA study result of the model with *p*-values

less than 0.05, specifically *p*-value of 0.0001 indicated significant model terms. Model terms A and B are significant model terms, with a model F-value of 1106.84 reflecting that the model is significant. The predicted *R*² value and adjusted *R*² value were reported as 0.9950 and 0.9964, respectively. The differences were less than 0.2 and signal-to-noise ratio value was 85.734, indicating an adequate signal.

3.1.3. Effect of Variables on Total Floating Time

The total floating time of the formulated tablets was positively correlated with X1, Guar gum concentration, and X2, carboxymethyl cellulose concentration, as depicted in Figure 3.

The mathematical model with respect to coded factors as determined using Design-Expert software is given below in Equation (3).

Response 2: Total floating time, Y3

$$Y3 = 310.67 + 106.00 X1 + 43.00 X2 \quad (3)$$

The ANOVA result of the model with *p*-values less than 0.05, specifically *p*-value of 0.0001 indicated significant model terms with a model F-value of 137.90 indicating the significance of the model. The predicted *R*² and adjusted *R*² values were 0.9478 and 0.9716, respectively, with the difference of less than 0.2. The signal-to-noise ratio value was 30.592, indicating an adequate signal [52].

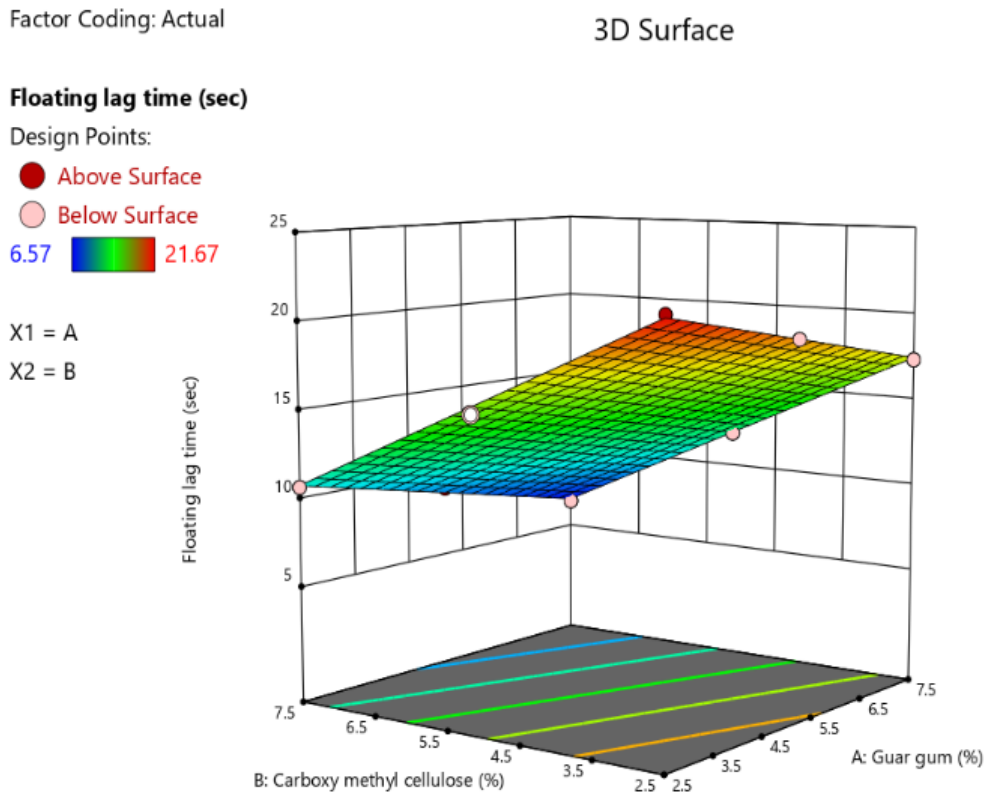
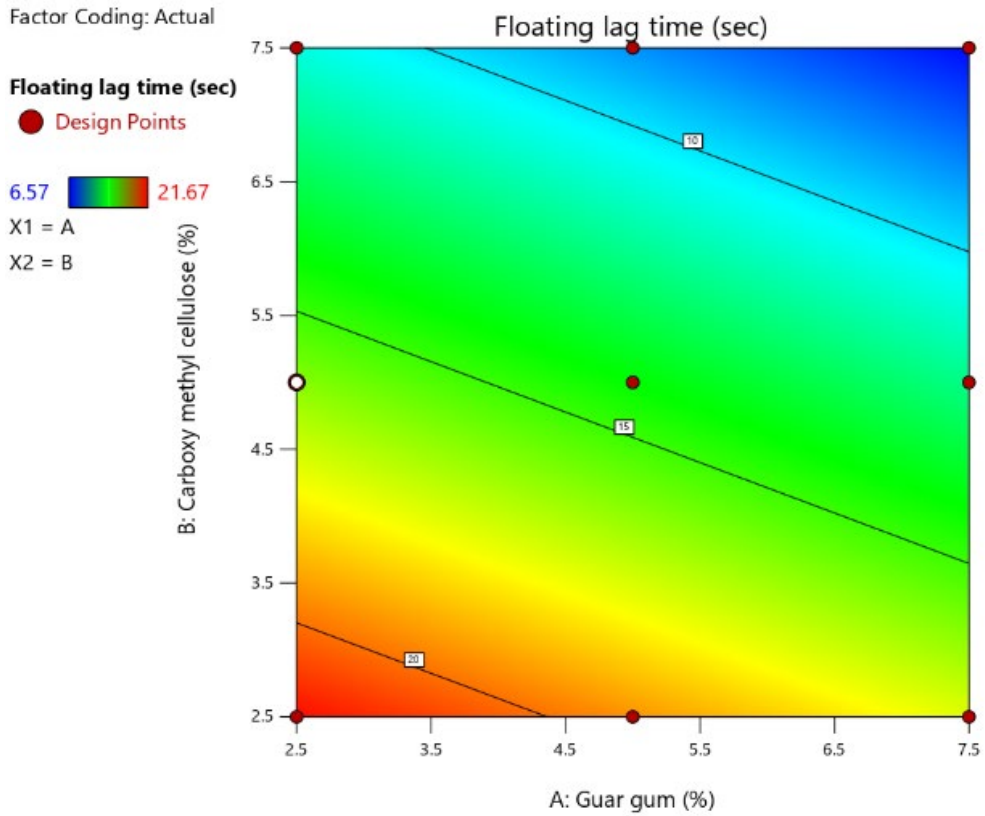


Figure 2. 2D contour plot and 3D response surface plot for evaluating the influence of guar gum (X1) and carboxymethyl cellulose (X2) on floating lag time (Y2)

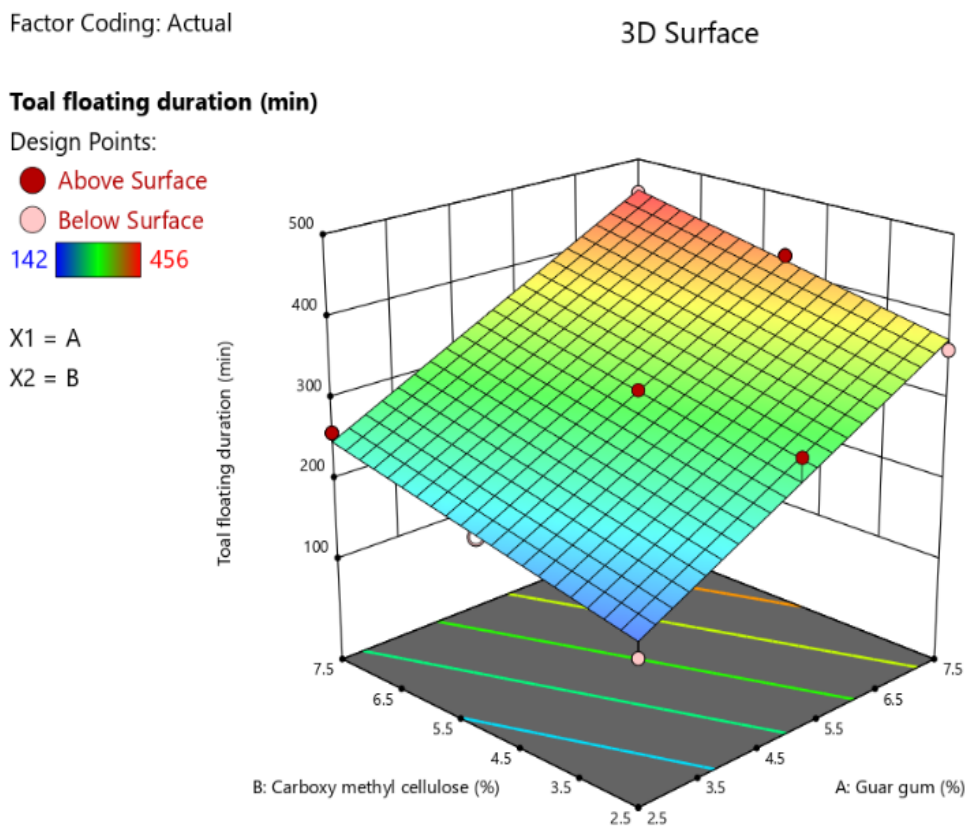
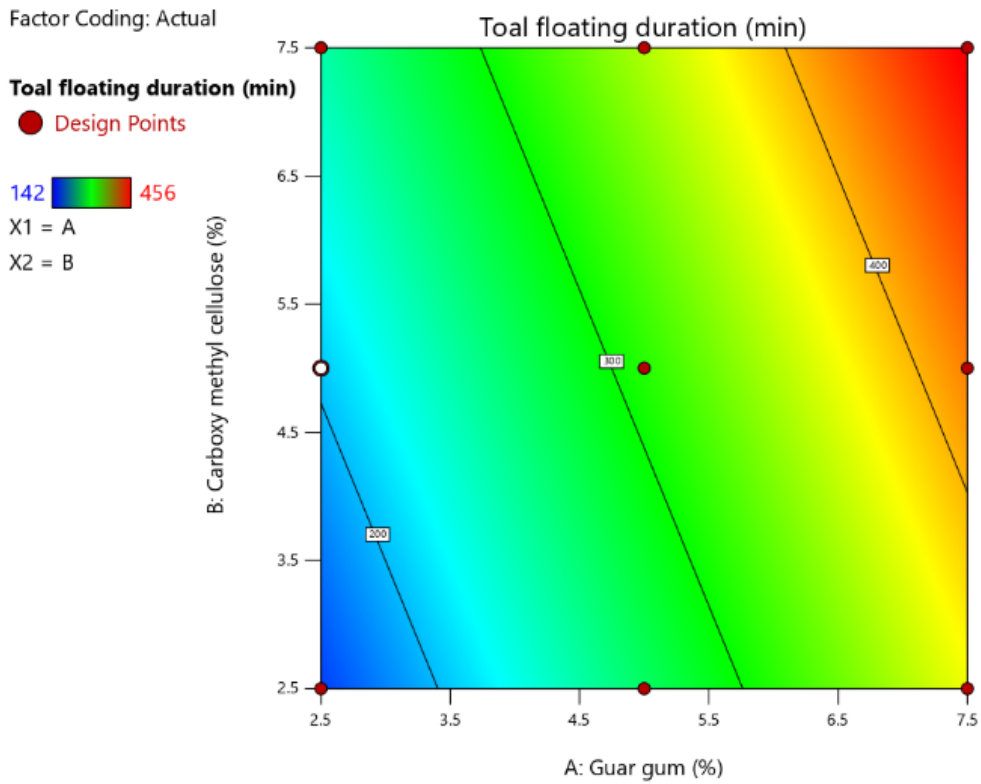


Figure 3. 2D contour plot and 3D response surface plot for evaluating the influence of guar gum (X1) and carboxymethyl cellulose (X2) on total floating time (Y3)

3.2. FTIR Analysis

FTIR analysis was performed for determination of possible physic-chemical interaction between drug and polymers during or after formulation. The FTIR spectra (shown in Figure 4) of pure levofloxacin, guar gum, carboxymethyl cellulose, and formulation were analyzed for drug-polymer interaction. The IR spectra of levofloxacin exhibited characteristic peaks for C=O at 1723.19 cm^{-1} , aromatic C-H group at 2933.08 cm^{-1} and for O-H bonding of existing -COOH moiety at 3261.89 cm^{-1} . The IR spectra of tablet formulation exhibited similar peaks at 1722.89 cm^{-1} , 2932.91 cm^{-1} , and 3262.78 cm^{-1} for the existing functional groups of levofloxacin. The study confirms the absence of physical and chemical interactions between levofloxacin and polymer used during or after processing [53].

3.3. Pharmacotechnical Evaluation of Granules

The average bulk densities of the formulations were respectively 0.5484 ± 0.0017 to $0.5525 \pm 0.0031\text{ g/ml}$. The average tapped densities of the formulations were respectively 0.7042 ± 0.0050 to $0.7076 \pm 0.0029\text{ g/ml}$. The average compressibility index of the formulations was respectively 22.1243 ± 0.0716 to 21.9191 ± 0.0789 . From the data of the compressibility index the flow property of granules was fair. Hausner's ratio was also determined for all the formulations. The average Hausner's index of the formulations was 1.2841 ± 0.0059 to 1.2807 ± 0.0088 . From this data the flow property of granules was fair [54]. Angles of repose for all the formulations ranged between $26.3333^\circ \pm 0.9074^\circ$ and $26.5666^\circ \pm 0.7767^\circ$. From this angle of repose data flow property of granules was excellent. All the pharmacotechnical parameters are reflected in Table 4.

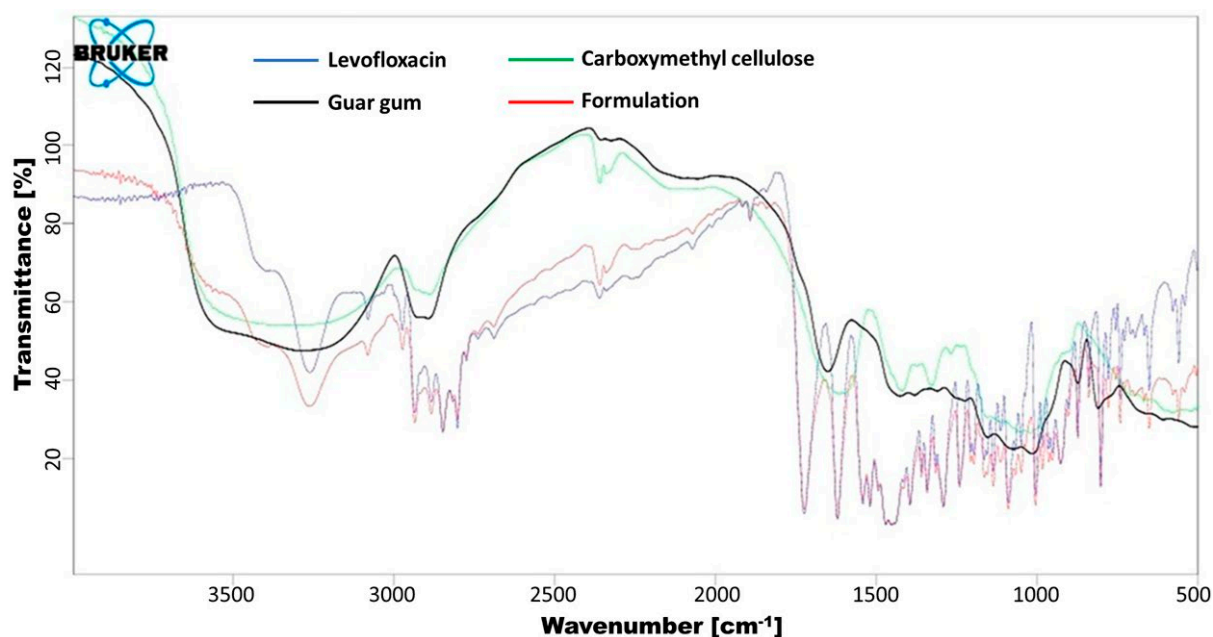


Figure 4. FTIR spectra of pure levofloxacin, guar gum, carboxymethyl cellulose, and the formulation

Table 4. Evaluation of granules of levofloxacin through melt granulation technique

Formulation Code	Bulk density (mean \pm S.D.; n = 5)	Tapped density (mean \pm S.D.; n = 5)	Compressibility index (mean \pm S.D.; n = 5)	Hausner's ratio (mean \pm S.D.; n = 5)	Angle of repose (mean \pm S.D.; n = 5)
F1	0.5484 ± 0.0017	0.7042 ± 0.0050	22.1243 ± 0.0716	1.2841 ± 0.0059	26.3333 ± 0.9074
F2	0.5505 ± 0.0018	0.7076 ± 0.0058	22.2018 ± 0.0513	1.2854 ± 0.0064	27.6333 ± 0.5033
F3	0.5484 ± 0.0017	0.7042 ± 0.0050	22.1243 ± 0.0625	1.2841 ± 0.0099	26.2666 ± 0.6028
F4	0.5495 ± 0.0030	0.7026 ± 0.0028	21.7904 ± 0.07561	1.2787 ± 0.0087	25.7666 ± 0.5508
F5	0.5495 ± 0.0030	0.7026 ± 0.0057	21.7904 ± 0.1115	1.2787 ± 0.0055	27.1333 ± 1.0116
F6	0.5525 ± 0.0031	0.7076 ± 0.0029	21.9191 ± 0.0789	1.2807 ± 0.0088	26.5666 ± 0.7767
F7	0.5484 ± 0.0017	0.7042 ± 0.0050	22.1243 ± 0.0625	1.2841 ± 0.0099	26.2666 ± 0.6028
F8	0.5495 ± 0.0030	0.7026 ± 0.0028	21.7904 ± 0.07561	1.2787 ± 0.0087	25.7666 ± 0.5508
F9	0.5505 ± 0.0018	0.7076 ± 0.0058	22.2018 ± 0.0513	1.2854 ± 0.0064	27.6333 ± 0.5033

3.4. Pharmacotechnical Evaluation of Levofloxacin Tablets

3.4.1. Weight Variation

The determination of weight uniformity for all the formulations of tablets was compliant within the IP specification with a deviation of less than 5% from the mean value [38].

3.4.2. Hardness

The hardness for several batches was observed to range in weight from 3.12 ± 0.0778 to 3.634 ± 0.2169 kg during the hardness test, indicating that the hardness of tablets was above the Pharmacopoeial limit of 3kg [39].

3.4.3. Friability

The friability of the tablets was in the acceptable range, or below 1%, as specified in the IP, ranging from 0.4233 to 0.0205% to $0.755 \pm 0.0043\%$. This shows that the tablets of all batches had adequate compactness and sufficient resistance to mechanical shock and abrasion [40].

3.4.4. Thickness

The thickness of all formulations was in the range 3.02 \pm 0.0008 to 3.0861 ± 0.0014 mm [41].

3.4.5. Diameter

The diameter of all formulations was in the range 5.1736 \pm 0.0278 to 6.3886 ± 0.0020 mm [42].

The results of the evaluation study of all the batches have been depicted in Table 5.

3.5. Drug Content

The drug content for all the batches was estimated using a spectrophotometric method. The obtained data indicated that the average drug content for all the formulations was within the range of $97.73 \pm 1.28 \%$ to $99.22 \pm 1.36 \%$. The obtained values were found within the limits specified for tablets [43].

3.6. *In-vitro* Buoyancy Study

Floating lag time and total floating duration were determined and the results are shown in Table 5. The floating lag time for all the formulations was reported below 30 secs. F1 exhibited the highest floating lag time, whereas, F8 and F9 showed excellent floating lag time of 12.03 ± 2.08 sec and 6.57 ± 1.52 sec respectively. The increase in polymer concentration helped entrap the liberated CO₂ gas which initiated the floating of tablets. The total floating time was found to vary between 142 ± 13.2 min and 456 ± 14.4 min. F1 (2.5% GG and 2.5% CMC) exhibited the least floating duration of 142 ± 13.2 min which is the result due to the decreased GG and CMC concentration in the formulation. The increased amount of CMC in F2 (2.5% GG and 5% CMC) exhibited a considerable increase in total floating duration (203 ± 9.4 mins). A subsequent increase in CMC and GG concentration has enhanced the total floating duration. The highest floating time was observed for F9 (7.5% GG and 7.5% CMC) of 456 ± 14.4 min [44].

Table 5. Evaluation of prepared levofloxacin tablets

Formulation Code	Hardness (Kg) (mean \pm S.D.; n = 5)	Friability (mean \pm S.D.; n = 3)	Thickness (mm) (mean \pm S.D.; n = 5)	Diameter (mm) (mean \pm S.D.; n = 5)	Floating lag time (Sec) (mean \pm S.D.; n = 3)	Total floating duration (Minutes) (mean \pm S.D.; n = 3)	Drug Content % (mean \pm S.D.; n = 3)
F1	3.12 ± 0.0778	0.4233 ± 0.0205	3.02 ± 0.0008	5.1736 ± 0.0278	21.67 ± 4.16	142 ± 13.2	99.22 ± 1.36
F2	3.214667 ± 0.0865	0.6116 ± 0.0163	3.0433 ± 0.0040	5.6713 ± 0.0053	15.73 ± 4.50	203 ± 9.4	98.21 ± 1.12
F3	3.3016 ± 0.0937	0.5646 ± 0.0046	3.0386 ± 0.0040	5.5746 ± 0.0020	10.67 ± 2.51	259 ± 13.2	97.91 ± 0.76
F4	3.225867 ± 0.0865	0.6126 ± 0.0163	3.0433 ± 0.0040	5.6713 ± 0.0053	19.47 ± 4.50	297 ± 9.4	98.21 ± 1.12
F5	3.304 ± 0.0818	0.6533 ± 0.0309	3.0476 ± 0.0024	5.8796 ± 0.0114	14.57 ± 2.51	312 ± 15.8	97.74 ± 1.07
F6	3.4156 ± 0.0822	0.7173 ± 0.0089	3.0639 ± 0.0023	6.2423 ± 0.0083	9.03 ± 2.08	343 ± 8.5	98.45 ± 0.83
F7	3.3016 ± 0.0937	0.5646 ± 0.0046	3.0386 ± 0.0040	5.5746 ± 0.0020	17.33 ± 4.50	361 ± 15.8	97.91 ± 0.76
F8	3.4156 ± 0.0822	0.7173 ± 0.0089	3.0639 ± 0.0023	6.2423 ± 0.0083	12.03 ± 2.08	423 ± 8.5	98.45 ± 0.83
F9	3.634 ± 0.2169	0.755 ± 0.0043	3.0861 ± 0.0014	6.3886 ± 0.0020	6.57 ± 1.52	456 ± 14.4	97.73 ± 1.28

3.7. In-vitro Drug Release Study

The release profiles of levofloxacin are shown in Figure 5. *In-vitro* drug release of levofloxacin gastroretentive tablets of F1 to F9 formulations showed 95.57% ± 1.0689% to 82.58% ± 2.56% at the end of 8 h. F1 formulations containing 2.5% of guar gum and 2.5% CMC showed 95.57% ± 1.0689% in 8 h, F2 formulations containing 2.5% of guar gum and 5% of carboxymethyl cellulose showed 95.085 ± 1.39, F3 formulations containing 2.5% of guar gum and 7.5% of carboxymethyl cellulose showed 91.909% ± 1.45%, F4 formulations containing 5% of guar gum and 2.5% of carboxymethyl cellulose showed 90.85% ± 2.493%, F5 formulations containing 5% of guar gum and 5% of carboxymethyl

cellulose showed 89.81% ± 1.107%, F6 formulations containing 5% of guar gum and 7.5% of carboxymethyl cellulose showed 89.17% ± 2.55%, F7 formulations containing 7.5% of guar gum and 2.5% of carboxymethyl cellulose showed 88.54% ± 2.56%, F8 formulations containing 7.5% of guar gum and 5% of carboxymethyl cellulose showed 85.73% ± 2.57%, and F9 formulations containing 7.5% of guar gum and 7.5% of carboxymethyl cellulose showed 82.58% ± 2.56% in 8 h. Sustained release ability was increased with increasing the guar gum concentration in formulations F1 to F9. The increased concentration of carboxymethyl cellulose has formed a relatively firm gelled layer, which may also slow down the diffusion of dissolved levofloxacin and sustain the release of drug in the bulk of the dissolution medium [45].

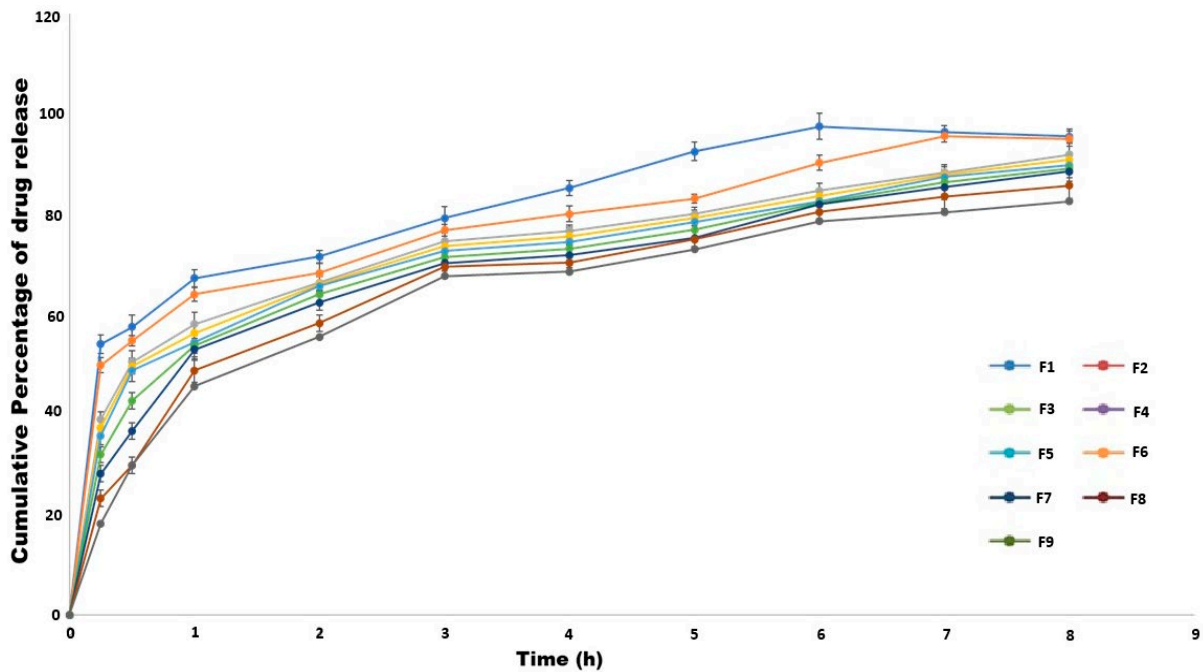


Figure 5. Cumulative release of levofloxacin in simulated gastric fluid for all the tablet batches (F1-F9)

Table 6. Kinetic evaluation of prepared levofloxacin tablet batches

Formulation Code	Zero-order	First order	Higuchi	Hixson-Crowell	Korsemeyer-Peppas		Best fit model
	R ²	R ²	R ²	R ²	R ²	n	
F1	0.6454	0.2684	0.8359	0.1434	0.1371	0.4268	Higuchi model
F2	0.6759	0.2768	0.8547	0.0825	0.1428	0.4309	Higuchi model
F3	0.7032	0.2988	0.8868	0.0316	0.1699	0.4652	Higuchi model
F4	0.7116	0.3041	0.8935	0.0267	0.1755	0.4717	Higuchi model
F5	0.7196	0.3098	0.8996	0.0225	0.1815	0.4787	Higuchi model
F6	0.7482	0.331	0.9216	0.023	0.205	0.5079	Higuchi model
F7	0.7706	0.3551	0.936	0.0234	0.233	0.5415	Higuchi model
F8	0.7955	0.3929	0.9513	0.0197	0.2785	0.5927	Higuchi model
F9	0.7977	0.4114	0.9524	0.011	0.3086	0.6241	Higuchi model

3.8. Kinetic Evaluation of Drug Release Data

Several kinetic models, including the zero-order equation, first-order equation, Higuchi square root equation, Hixon-Crowell equation, and Korsmeyer-Peppas equation, were used to fit the drug release data. Table 6 presents the release kinetics results. The R^2 value is close to 1.0, and the best fit model is chosen. Formulations F1, F2, F3, F4, F5, F6, F7, F8 and F9 followed Higuchi kinetic model of drug release. Fickian release occurred in all the formulations [46].

4. Conclusions

In present research, gastroretentive floating tablets of levofloxacin were successfully developed and evaluated for the required parameters. A polymeric combination of guar gum and carboxymethyl cellulose was employed for fabricating the tablet formulation. The increasing guar gum concentration helped achieve the sustained release of levofloxacin from the disintegrated tablets. The carboxymethyl cellulose has formed the gelled matrix after disintegration of the tablet, which helped the liberated carbon-dioxide to entrap, enabling the tablet content to float. The FTIR study has established the compatibility between the drug and the employed polymers. The *in vitro* buoyancy study has revealed shorter floating lag time with increasing carboxymethyl cellulose concentrations. It also has a positive impact on sustaining the drug release from the formed gelled layer due to relatively slower diffusion of dissolved drug. A firm gelled layer and higher guar gum concentration have resulted in increased floating duration up to 456 ± 14.4 min for F9 formulation (7.5% GG and 7.5% CMC). The drug release study revealed a sustained release ability of the developed tablet batches up to 8 h, maintaining a cumulative drug release of $82.58 \pm 2.56\%$ (F9 formulation). The kinetic analysis of drug release data indicated the suitable drug release mechanism is Higuchi kinetics in all the formulations. Depending on floating lag time, total floating duration and drug release F9 was selected as an optimized tablet batch. From the obtained experimental results, it can be concluded that the developed tablet formulations showed great potential in retaining the dosage form in the gastric region and sustaining the release of the drug for a longer time duration. This approach can be useful in achieving higher drug concentrations in gastric regions for stomach specific targeting of drug or drugs exhibiting preferred absorption window in gastric region.

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Credit Authorship Contribution Statement

Sreejan Manna: Planning, supervision, project administration, resources, investigation, writing, data analysis, editing; Sahabaj Ali Khan: Investigation, data analysis; Md Sanawaj Ali: Investigation, data analysis; Sucharita Hazra: Investigation, data analysis; Gouranga Nandi: Writing, editing; Sougata Jana: Writing, editing; Baishnabdas Pathak: Investigation; Olivia Sen: Writing, data analysis.

Conflict of Interest Statement

The authors declare no financial or competing interests that have influenced the reported research.

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