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Original Article

EXPERIMENTAL DESIGN APPROACH TO FABRICATE AND OPTIMIZE FLOATING TABLETS OF LEVOFLOXACIN FOR *HELICOBACTER PYLORI* INFECTION

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ABSTRACT

Objective: To improve the treatment of *H. pylori* infection, by achieving the required bactericidal concentrations of antibiotics in the stomach, by delivering the antibiotics to the mucus layer and release the drug at the site of infection for a prolonged period would be significantly more effective than conventional dosage forms.

Methods: The experimental method of the research was designed to prepare Levofloxacin floating by using Hydroxypropyl Methylcellulose (HPMC K4M), Hydroxypropyl Methylcellulose (HPMC K100M) and Xanthan gum by Three-level Box–Behnken design optimization method. The prepared tablets were evaluated for Thickness, Hardness, Friability, Weight variation, Swelling index (SI), Floating lag time (FLT) and Time required to release 90% of the drug from the tablet ($T_{90\%}$).

Results: It was found that the Thickness-3.12±0.11 mm to 3.28±0.10 mm, Hardness-4.52±0.36 kg/cm^2 to 4.81±0.24 kg/cm^2, Friability-0.81±0.02g to 0.86±0.12g, Weight variation-480±1.90 mg to 523±0.89 mg, Swelling index (SI)-61.9±0.624% to 99.95±0.226%, Floating lag time (FLT)-81.12±0.63 s to 119.7±0.567 s and Time required to release 90% of the drug from the tablet ($T_{90\%}$)-7.0±0.55 h to 10.33±0.289 h. HPMC K100M and Xanthan gum showed good swelling as compared to HPMC K4M. The study revealed that HPMC K100M grade had a significant effect on drug release.

Conclusion: The developed gastro-floating tablets can extend levofloxacin duration in the stomach and produce a prolonged release effect. The prepared levofloxacin floating tablet oral drug delivery system appears to be a promising choice for the efficient eradication of *H. pylori*

Keywords: Levofloxacin, Floating tablet, *Helicobacter pylori*, Box–Behnken design, HPMC K4M, HPMC K100M, Xanthan gum

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INTRODUCTION

Helicobacter pylori (H. pylori) is a gram-negative bacterium found in the stomach of about half of the world's population [1]. *H. pylori* infection is a strong risk factor for gastroduodenal ulcer disease, gastric cancer, and other types of gastric and extra gastric disease. This infection is linked up to 85% of gastric ulcers and 95% of duodenal ulcers, and eliminating the organism reduces the risk of ulcer recurrence dramatically [2]. The World Health Organization's (WHO) International Agency for Research on Cancer (IARC) classified *H. pylori* as a "category 1" pathogen (definite carcinogen) and suggested that *H. pylori* eradication is considered to lower the risk of stomach cancer, which kills 738,000 people worldwide each year. According to reports, eradicating *H. pylori* lowers the risk of stomach cancer [3, 4]. The Maastricht V Consensus Report and the guidelines established by the American College of Gastroenterology both suggested using levofloxacin-based triple therapy as a second-line treatment option [5, 6]. However, eradicating *H. pylori* successfully and completely has become a challenge in recent years.

Recent biopsy studies [7, 8] and cell culture infection models have indicated that *H. pylori* penetrate the gastric mucus layer and attach to various phospholipids and glycolipids in the mucus gel. As a result, both the lumen of the stomach and the gastric blood supply limit antibiotic availability in the mucus layer for a prolonged period. Also, the traditional drug delivery systems do not stay in the stomach for extended periods, and they are unable to deliver adequate concentrations and fully active antibiotics to the infection site. There is a need for new drug delivery systems to address the inadequacies of conventional delivery systems. Floating drug delivery systems have a bulk density lower than that of gastric fluids, allowing them to stay buoyant and deliver the drug for a longer period of time in the stomach without being impacted by the gastric emptying rate.

Hence, in the present study, gastro retentive floating Levofloxacin tablets for the eradication of *H. pylori*, were prepared using Xanthan gum, HPMC K100M and HPMC K4M and evaluated to overcome the shortcomings of conventional delivery of levofloxacin.

MATERIALS AND METHODS

Materials

Xanthan gum was purchased from SD Fine Chem Limited, Mumbai. HPMC K100M and HPMC K4M and Levofloxacin hemihydrate were gifted by MICRO LABS LIMITED, Bengaluru. All other used solvents were HPLC grade.

Experimental design

A three-factor, Three-level Box–Behnken design was used for the optimization procedure using Design-Expert® 13 software (Stat-Ease, Inc., USA). The investigated factors (independent variables) were HPMC K4M (A_1) content HPMC K100M (B_2) and Xanthan gum content (C_3). The levels for these three factors were determined from sufficient preliminary trials. The Swelling index (SI), Floating lag time (FLT) and Time required to release 90% of the drug from the tablet ($T_{90\%}$) were selected as dependent variables as shown in table 1. The experimental design with the corresponding formulations is outlined in table 2.

The statistical model:

$$Y = b_0 + b_1A + b_2B + b_3C + b_{11}AA + b_{22}BB + b_{12}AB + b_{23}BC + b_{13}AC + E$$

Compatibility studies

Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC) was used to study the compatibility of Levofloxacin with excipients.

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra of Levofloxacin, excipients and physical mixtures (drug: excipient ratio of 1:1) were recorded in the wavelength region 500-4,000 cm^{-1} using FTIR 8400S (Shimadzu, Japan).

Table 1: Layout of box-behnken experimental design

Independent variable	Levels		
	-1	0	1
A_1: HPMC K4M(mg)	40	60	80
B_2: HPMC K100M(mg)	30	45	60
C_3: Xanthan gum(mg)	15	30	45
Dependent variable			
Y_{FLT} = Floating Lag Time (min)			
Y_{SI} = Swelling Index (%)			
$Y_{T90\%}$ = Time required to release 90% of the drug from the tablet ($T_{90\%}$)			

Table 2: Factorial batch formula for levofloxacin floating tablets-box–behnken design

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Levofloxacin	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
HPMC K4 M	60	60	40	40	80	60	80	40	80	60	80	40	60	60	60
HPMC K100 M	30	60	45	30	45	60	30	60	45	30	60	45	45	45	45
Xanthan gum	15	45	15	30	15	15	30	30	45	45	30	45	30	30	30
Sodium bicarbonate	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Citric acid	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Microcrystalline cellulose	70	10	75	75	35	40	35	45	5	40	5	45	40	40	40
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Total (mg)	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500

Differential scanning calorimetry (DSC)

DSC measurements of Levofloxacin, and physical mixtures (drug: excipient ratio of 1:1) were carried out by using a differential scanning calorimeter (DSC 204 F1 Phoenix®). Samples of 5 mg taken in aluminium pans and sealed. The probes were heated from ambient to 400 °C at a rate of 10 °C/min under a nitrogen (50 ml/min) atmosphere.

Formulation of levofloxacin floating tablets

Levofloxacin was mixed with the required quantity of HPMC K4M, HPMC K100M, Xanthan gum, Sodium bicarbonate, Citric acid, Microcrystalline cellulose and Magnesium stearate in a mortar and triturated for 5 min Then the mixture was compressed on a 10-station rotary tablet compression machine (PROTON MINI PRESS) using a 9 mm standard flat-face punch.

Characterization of floating tablets

Weight variation test

The weight (mg) of 20 tablets was determined by using an electronic balance (Mettler AE240 Erweka Tap). The tablet weight data were analysed for standard deviation, sample mean and coefficient of variation (relative standard deviation) [9].

Hardness

The crushing strength of 20 individual tablets was determined by using an electronic hardness tester (Erweka). The standard deviation, sample mean and coefficient of variation (C. V) were calculated [9].

Thickness

The individual thickness of 20 tablets was determined by using Digital Vernier caliper. The measurements were recorded. The sample mean, standard deviation and coefficient of variation were calculated [9].

Friability

Friability of the prepared levofloxacin floating tablets was estimated by busing Roche-type Friabilator. It was determined by weighing 15 tablets after dusting, placing them in a Roche-type Friabilator and rotating the basket vertically at 25 rpm for 4 min (100 drops). After dusting, the total remaining weight of the tablets was recorded and the percentage friability was calculated according to the following formula

$$\% \text{ Friability} = \frac{\text{Weight final} - \text{Weight initial}}{\text{Weight initial}} \times 100$$

Content uniformity

The content uniformity was determined by using 10 individual tablets. Ten levofloxacin tablets were crushed, and the exact weight of the powder was measured. The crushed powder was mixed with 300 ml of 0.1 N HCl in a 500 ml volumetric flask and stirred. After stirring for 45 min, 200 ml of 0.1 N HCl was added and filtered. From the above solution, 2 ml of solution was collected, diluted into 50 ml with 0.1 N HCl and analysed spectrophotometrically using a spectrophotometer at 295 nm [9].

Measurement of floating lag time

Floating lag time was determined by the method reported by Rosa *et al.* [9]. Three tablets were selected from each batch for floating lag time determination. The selected floating tablets were placed in a 500-ml beaker containing 400 ml of 0.1N HCl. The floating lag time was calculated as the amount of time needed for the tablet to surface and float.

Measurement of total floating time

The total floating time of prepared tablets was determined using USP dissolution tester apparatus II, (Erweka, DPT6R, Germany). Tablets were placed in the vessels consists 900 ml of 0.1N HCl. The paddles were rotated at 50 rpm at the temperature of 37±0.2 °C. The duration of the tablet remaining buoyant was noted visually [10].

Swelling index

The prepared tablets were taken in a beaker containing 150 ml of 0.1 N HCl. Tablets were weighed before placing in the beaker (which was taken as the initial weight). After 12 h the swelled tablets were taken out and weighed after blotting at 12 h [11]. The swelling index was calculated using the formula

$$\text{Swelling index } \% = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

***In vitro* dissolution studies**

The dissolution studies of prepared floating tablets were carried out in a USP TYPE II paddle type apparatus (LAB INDIA), using 0.1 N HCl. At various time intervals, samples were taken out and replaced with fresh dissolution media. The collected sample solutions were diluted to 10 ml with 0.1 N HCl and analyzed spectrophotometrically at 295 nm [12].

Statistical analysis

To analyse the contribution of each factor with different levels on the response, the two-way analysis of variance (ANOVA) was

performed using Design-Expert® 13 software (Stat-Ease, Inc., USA). To graphically determine the effect of each factor on the response, the response surface plots were created using the Design-Expert® 13 software (Stat-Ease, Inc., USA).

RESULTS AND DISCUSSION

Box-Behnken experimental design

The RSM requires 15 experiments for a three-factor, three-level Box-Behnken statistical experimental design. Table 2 lists the independent variables and outcomes for each of the 15 experimental runs. The Levofloxacin floating were prepared by direct compression method.

Instrumental methods like FTIR and DSC were used to study the compatibility of drug with excipients. FTIR spectra of Levofloxacin, excipients and physical mixtures (drug: excipient ratio of 1:1)) were recorded. The results are shown in fig. 1. FTIR of levofloxacin showed the following characteristic peaks at 3266 cm^{-1} returns to the carboxylic group, 2933 cm^{-1} to alkanes group stretching, 1724 cm^{-1} to stretching of Carbonyl group, 1295 cm^{-1} to stretching of amines, 1100-1400 cm^{-1} to the presence of halogen group (fig. 1). These observations are in accordance with the observations of Numan R S *et al.*, confirming the identity and purity of levofloxacin. The physical mixture retains the key peaks in the pure drug FTIR spectrum without significant peak shift. This suggests no drug-excipient interactions or process incompatibilities [13].

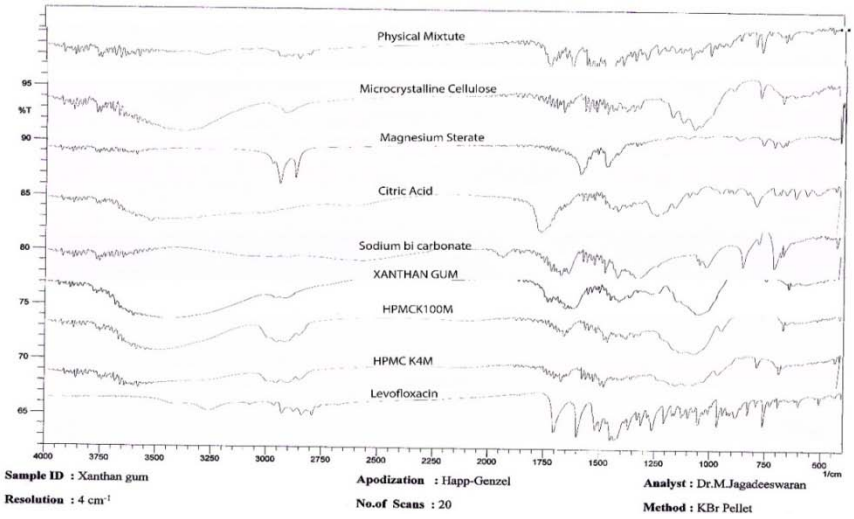

Fig. 1: FTIR spectra of levofloxacin, excipients (individual) and physical mixture

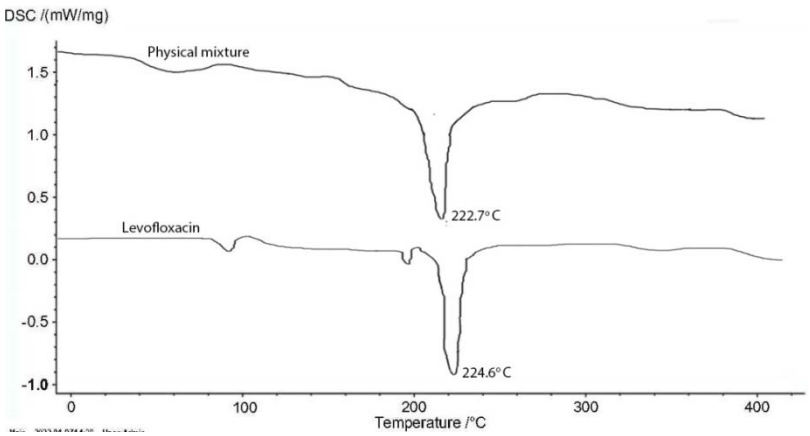

Fig. 2: DSC thermograms for levofloxacin and physical mixture

DSC experiments were also conducted to determine Levofloxacin's chemical compatibility with excipients. To understand the thermal behaviour, DSC thermograms of Levofloxacin, and physical mixtures (drug: excipient ratio of 1:1) were carried out and shown in fig. 2. Endothermic peaks of DSC thermograms Levofloxacin (fig. 2) showed a melting point 224.6 °C [14]. The sharp endothermic at 222.7 °C corresponds to the melting point of Levofloxacin and was retained in all the thermograms of 1:1 w/w physical mixtures of the Levofloxacin and selected excipients. DSC experiments showed that Levofloxacin did not interact with any excipients and was stable during formulation.

All formulations were evaluated for all physical parameters such as weight variation, thickness, hardness, friability and content uniformity. The weight variations result of the prepared tablets were within the permitted range of 5%, which is prescribed for tablets weighing more than 250 mg. Similarly, the hardness and friability of all batches of tablets were found within the limits of USP specifications. Tablet thickness was also used to assess the quality of tablets. Thickness values of all batches were between 3.12±0.11 mm to 3.28±0.10 mm, which was an allowable variation in thickness. The results are shown in table 3. The percentage of drug content of all the formulations was found to be in between 97.11 % to 99.69 % of Levofloxacin, it complies with official specifications.

Floating lag time

FLT is the time it takes for a tablet to float on a dissolution media. As FLT increases, the tablet may settle to the stomach's lower region and increase gastric emptying. FLT may affect the gastric retention time of the floating tablets and should be minimised. The FLT of

Levofloxacin floating tablets was carried out and the results were shown in table 4. From the results, it was found that the FLT (Y_{FLT}) range was from 81.12±0.63 s to 119.7±0.567 s. The experiments were conducted in triplicate.

Table 3: Post-compression characteristics of levofloxacin floating tablet formulations

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Weight variation (mg)
F1	3.17±0.14	4.81±0.12	0.83±0.05	500±0.22
F2	3.18±0.12	4.73±0.53	0.81±0.02	512±0.16
F3	3.16±0.12	4.55±0.40	0.86±0.03	496±0.02
F4	3.14±0.11	4.67±0.33	0.83±0.01	506±0.75
F5	3.20±0.10	4.71±0.17	0.81±0.08	521±0.46
F6	3.19±0.16	4.58±0.28	0.82±0.06	486±0.85
F7	3.17±0.14	4.58±0.31	0.81±0.03	523±0.89
F8	3.14±0.14	4.52±0.36	0.86±0.12	500±0.86
F9	3.16±0.11	4.64±0.35	0.84±0.10	480±1.90
F10	3.18±0.14	4.81±0.24	0.81±0.05	520±1.11
F11	3.17±0.12	4.72±0.29	0.81±0.08	486±0.16
F12	3.15±0.12	4.54±0.34	0.86±0.03	490±1.02
F13	3.28±0.10	4.64±0.41	0.82±0.01	500±0.75
F14	3.12±0.11	4.73±0.33	0.84±0.08	487±0.46
F15	3.23±0.16	4.57±0.62	0.86±0.06	493±1.82

mean±SD, *n*=3, SD: Standard Deviation

Table 4: Observed responses from batches in the box-behnken design

Formulation code	Independent variable			Dependent variables		
	A (mg)	B (mg)	C (mg)	FLT s	SI (%)	$T_{90\,\%}$ (h)
F1	60	45	30	89.65±0.492	69.63±0.321	7.00±0.550
F2	80	45	45	114.7±0.419	94.6±0.794	10.33±0.289
F3	40	60	30	109.2±0.124	89.8±0.529	10.17±0.289
F4	80	60	30	112.8±0.654	93.42±0.316	9.83±0.289
F5	80	30	30	104.1±0.513	84.23±0.666	9.50±0.500
F6	40	45	15	83.4±0.954	63.51±0.447	7.66±0.289
F7	60	60	15	89.98±0.511	70.64±0.481	8.66±0.289
F8	60	45	30	88.92±0.671	69.37±0.514	6.83±0.289
F9	60	45	30	91.98±0.437	72.7±0.557	6.66±0.289
F10	60	30	15	93.1±0.522	73.02±0.225	8.50±0.000
F11	60	30	45	81.12±0.63	61.9±0.624	7.50±0.500
F12	60	60	45	119.7±0.567	99.95±0.226	10.17±0.289
F13	40	45	45	100.6±0.437	81.79±0.278	10.17±0.289
F14	40	30	30	87.72±0.419	67.39±0.575	8.00±0.500
F15	80	45	15	95.05±0.492	75.47±0.578	8.83±0.289

mean±SD, *n*=3, SD: Standard Deviation

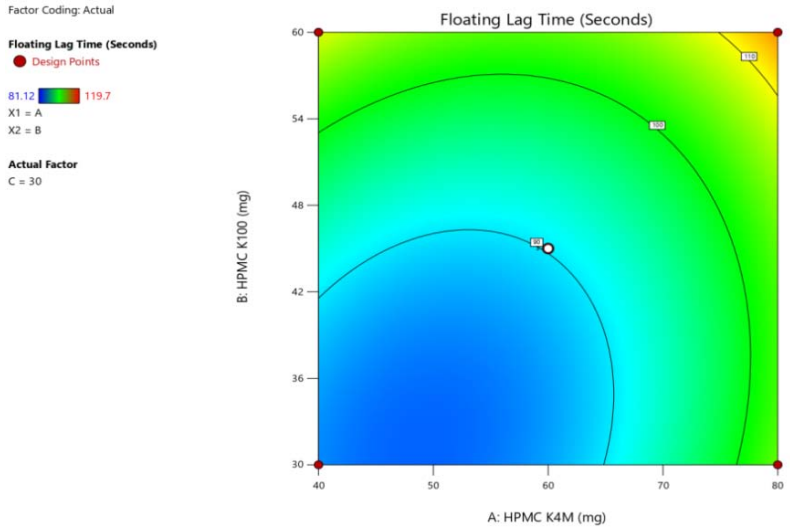

Fig. 3: Floating lag time contour plot of levofloxacin floating tablets (HPMC K4M vs HPMC K100M)

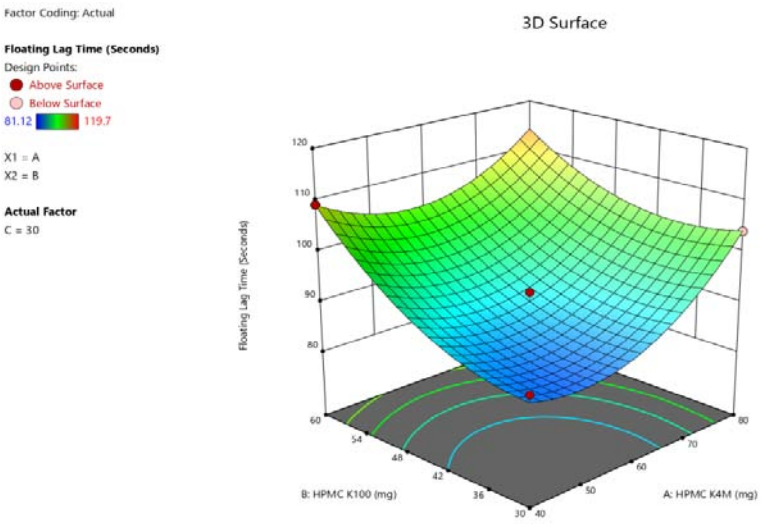

Fig. 3.1: Floating lag time 3D surface plot of levofloxacin floating tablets (HPMC K4M vs HPMC K100M)

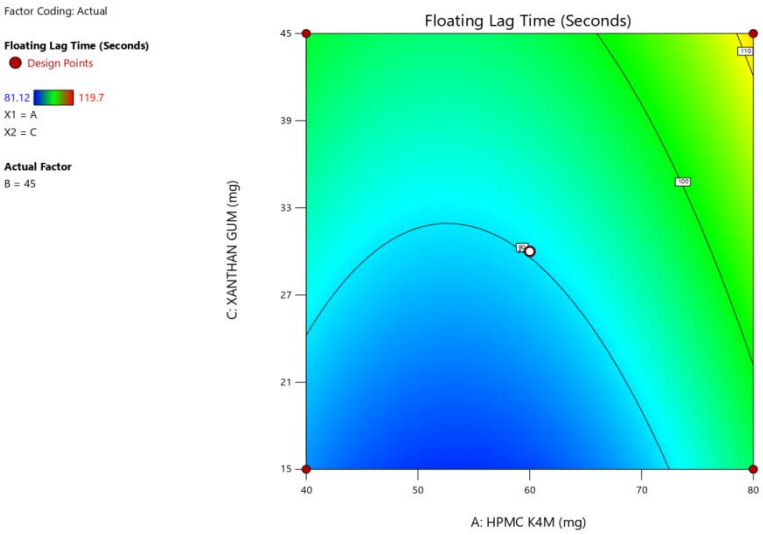

Fig. 4: Floating lag time contour plot of levofloxacin floating tablets (HPMC K4M vs Xanthan gum)

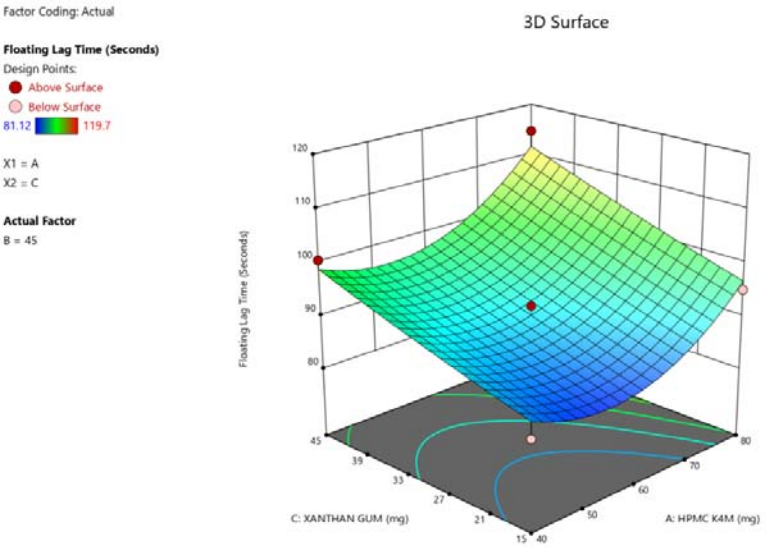

Fig. 4.1: Floating lag time 3D surface plot of levofloxacin floating tablets (HPMC K4M vs Xanthan gum)

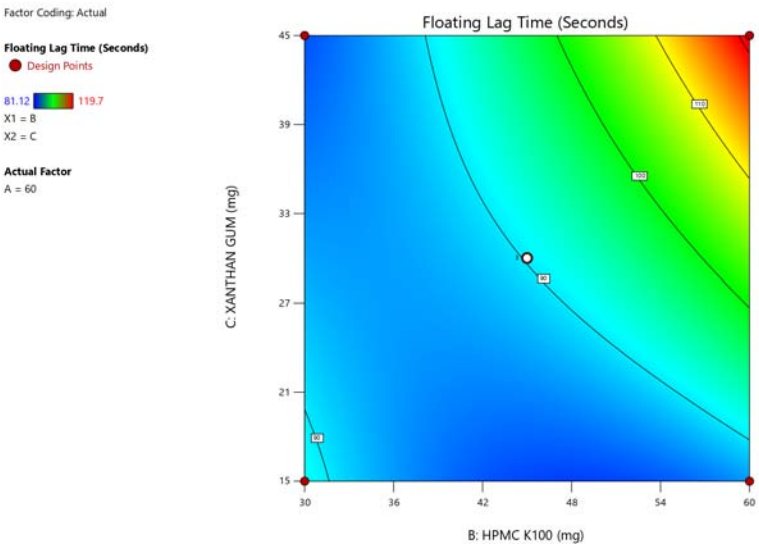

Fig. 5: Floating lag time contour plot of levofloxacin floating tablets (HPMC K100M vs Xanthan gum)

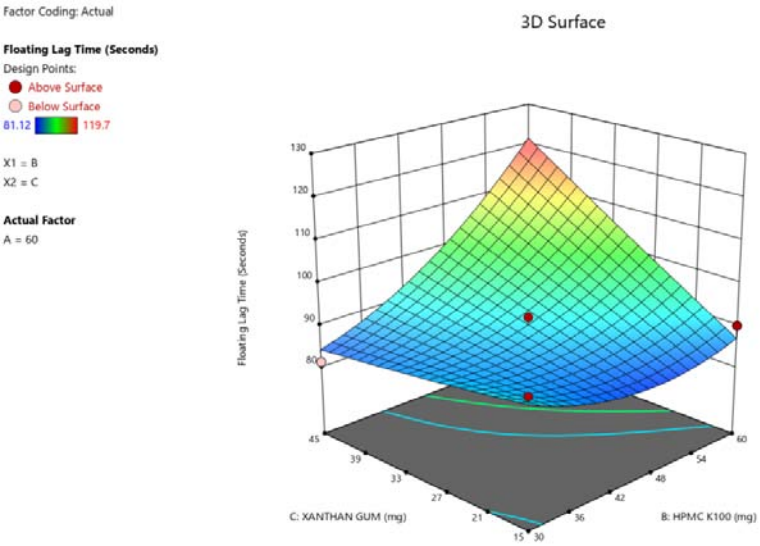

Fig. 5.1: Floating lag time 3D surface plot of levofloxacin floating tablets (HPMC K100M vs Xanthan gum)

It was observed that floating lag time increases with increasing the concentration of the polymers. As per the observations, higher polymer concentrations were linked to tablets longer floating lag time. The higher concentrations of polymer take longer time to hydrate with the dissolution medium. So, the gas is trapped within a gel-like barrier, induces an upward motion of the tablet. The tablets containing a high concentration of HPMC K100M showed an increased floating lag time compared to the tablets containing a high concentration of xanthan gum and HPMC K4M. The floating lag time observed in this study was in the order of HPMC K100M>xanthan gum>HPMC K4M. It may be due to the hydrophilic nature of the polymers used in this study. The hydrophilic nature of the polymers was reported as HPMC K100M>Xanthan gum>HPMC K4M [15].

It is important to highlight that HPMC K100M, the grade of HPMC employed in this work. It hydrates faster than HPMC K4M because it has more hydrophilic hydroxypropoxyl substitution than hydrophobic methoxyl substitution in comparison to HPMC K4M. So, HPMC K100M hydrates quickly and forms a protective gel barrier layer immediately, preventing the medium dissolution entry into the tablet matrix and decreasing the floating lag period. In general, when the HPMC molecular weight rises, the rate of fluid entry in polymer matrix decreases. Higher molecular weight HPMC has a tendency to expand more quickly, which could cause the pores to close prematurely, preventing further liquid intake [16].

The difference in their hydrophilicity can be used to explain the differences in hydration properties between Xanthan gum and HPMC K4M. Xanthan gum is more hydrophilic than HPMC K4M, it hydrates more quickly and forms a quick protective barrier layer, thereby reducing floating lag time.

The model equations relating FLT, as responses by eliminating nonsignificant terms,

$$FLT = 90.1833 + 5.71625^{*}A + 8.205^{*}B + 6.82375^{*}C - 3.195^{*}AB + 0.6125^{*}AC + 10.425^{*}BC + 7.86708^{*}A^2 + 5.40458^{*}B^2 + 0.387083^{*}C^2$$

$$R^2 = 0.9711; \text{F value} = 18.69; P < 0.05$$

Swelling index

The swelling degree in hydrophilic polymers employed in controlled drug delivery systems is connected with the diffusion rates of both the fluid into the matrix and the drug throughout the gel layer of the matrix. Swelling-controlled systems absorbs water or other body fluids and swells when introduced into the body. The swelling

increases the aqueous solvent concentration in the formulation as well as the polymer mesh size, allowing the drug to permeate into the external environment through the swollen network.

The molecular structure of HPMC consists of a linear polysaccharide cellulose chain with ether-linked methoxyl and hydroxypropyl side groups [17] HPMC is widely used in the development of controlled release formulations due to its ability to swell and form a gel layer that controls the rate of drug release on the surface of the matrix systems. Since HPMC-based matrices are not significantly influenced by the pH of the gastrointestinal (GI) fluids, the non-ionic nature of HPMC ensures a minimal risk of drug interactions and, in general, reproducible drug release profiles [18]. All of these factors make the HPMC polymer family the preferred pharmaceutical excipient for the production of hydrophilic matrix-based formulations. HPMC is a commonly used synthetic polymer in the biomedical industry. Due to their biocompatibility and biodegradability, natural polymers are also necessary in the biomedical industry, despite the fact that synthetic polymers are much simpler to use. Combining synthetic polymers with natural polymers is another method for preparing polymeric materials for biomedical applications. In the last three decades, there has been an increase in interest in new materials comprised of two or more polymer blends. Blends of synthetic and natural polymers can create a new class of biocompatible materials with enhanced drug release properties. Generally, natural polymers are biocompatible, whereas synthetic polymers may contain residual initiators and other impurities. Both synthetic and natural polymers can have their own properties that can be useful. But by mixing or combining them, new polymeric materials can be made that are both biocompatible and biodegradable, but also have the best drug release control properties [19]. Several studies have reported the prolonged drug release properties of natural polymer and HPMC blending [20-23]. Hence in this study Xanthan gum, HPMC K4M and HPMC K100M blend used to optimize the swelling property of Levofloxacin floating tablets.

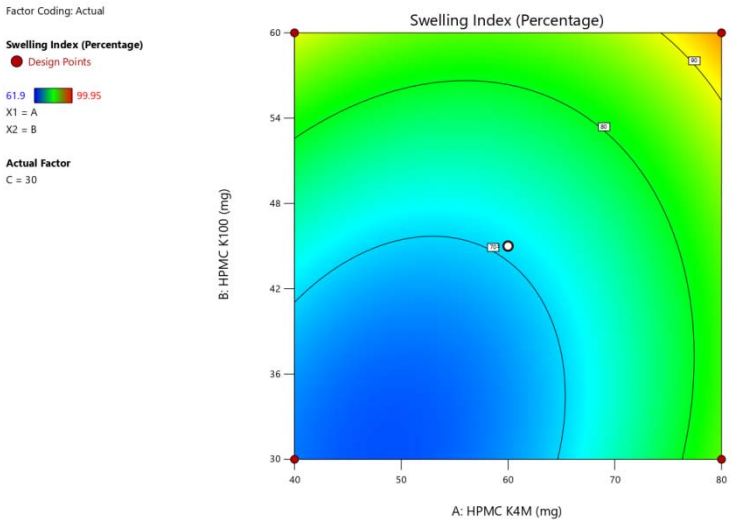

Fig. 6: Swelling index contour plot of levofloxacin floating tablets (HPMC K4M vs HPMC K100M)

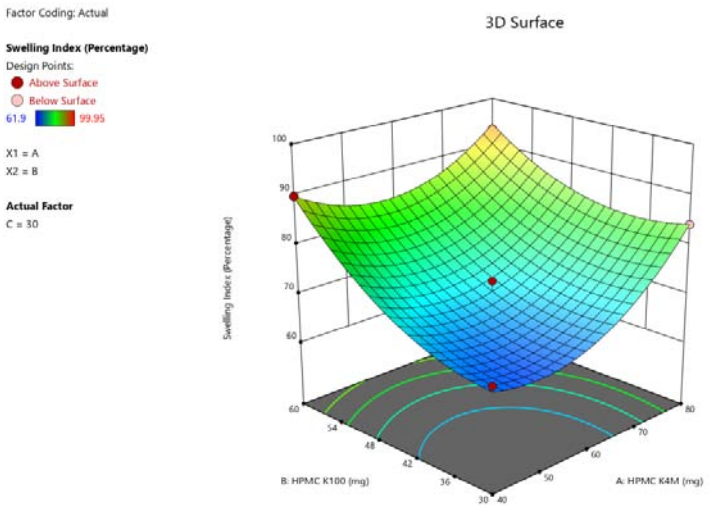

Fig. 6.1: Swelling index 3D surface plot of levofloxacin floating tablets (HPMC K4M vs HPMC K100M)

From the study, it was observed that HPMC K100M and Xanthan gum showed good swelling as compared to HPMC K4M. The difference in their hydrophilicity can be used to explain why Xanthan gum and HPMC K4M have different hydration properties. According to reports, Xanthan gum is more hydrophilic than HPMCK4M [16]. The study indicated that the rate of swelling is directly proportional to the viscosity of the polymer. It was reported that HPMC K100M and Xanthan gum have more viscosity than HPMC K4M. High-viscosity HPMC swells more than low-viscosity HPMC. Higher viscosity HPMC has better water uptake than lower viscosity [15]. The amount of water entry into the matrix plays a significant role in how quickly it swells. The swelling of the polymer is increased when the water

uptake into matrices is increased with more HPMC. The swelling index of prepared Levofloxacin floating tablets were ranges from 61.9±0.624% to 99.95±0.226%. The experiments were conducted in triplicate. The results are shown in table 4.

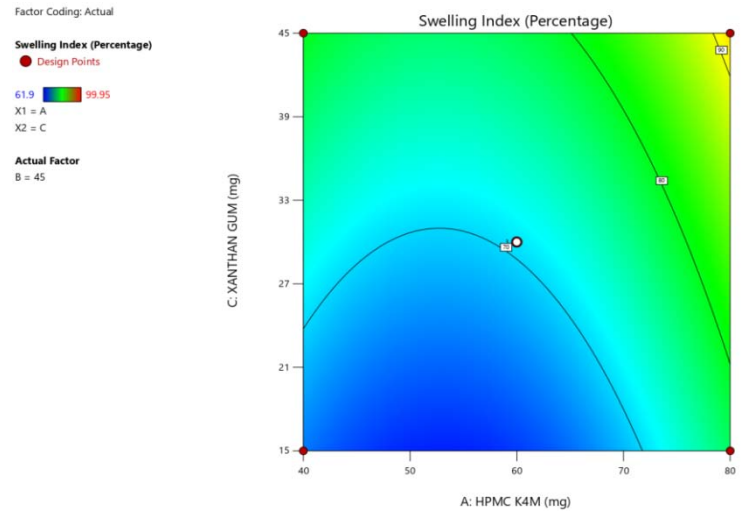

Fig. 7: Swelling index contour plot of levofloxacin floating tablets (HPMC K4M vs Xanthan gum)

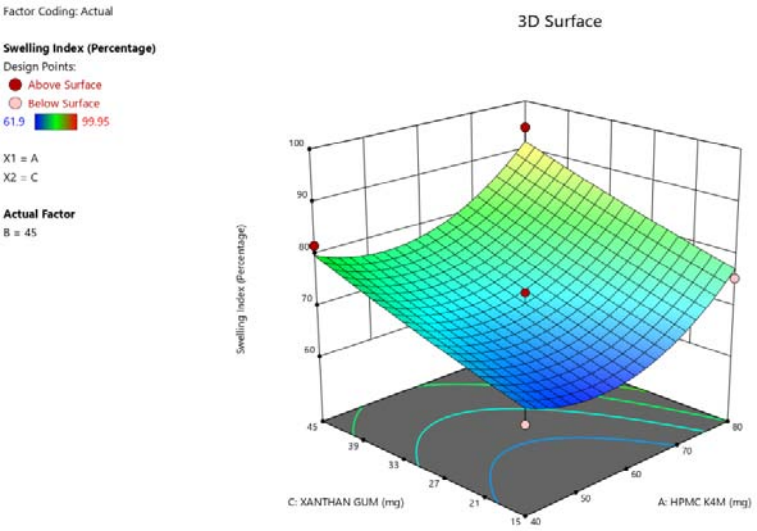

Fig. 7.1: Swelling index 3D surface plot of levofloxacin floating tablets (HPMC K4M vs Xanthan gum)

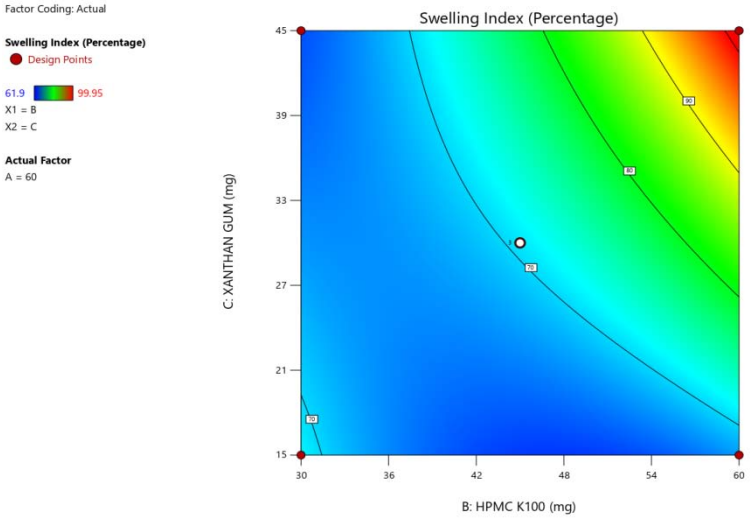

Fig. 8: Swelling index contour plot of levofloxacin floating tablets (HPMC K100M vs xanthan gum)

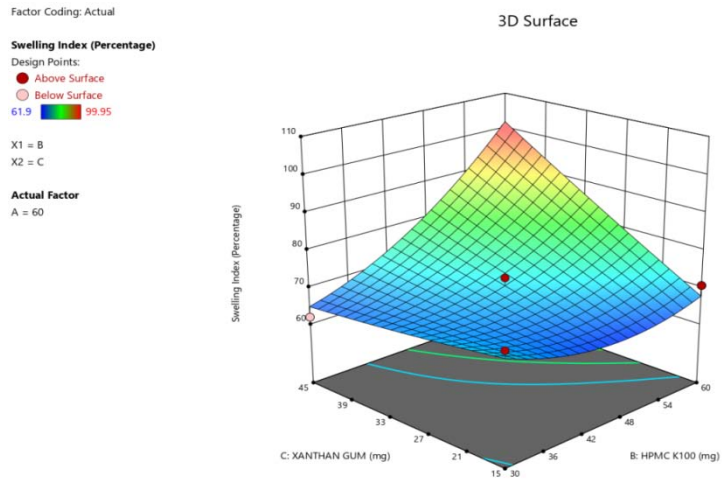

Fig. 8.1: Swelling index 3D surface plot of levofloxacin floating tablets (HPMC K100M vs xanthan gum)

The effect of polymers on swelling index can be explained by the following Quadratic equation.

$$SI = 70.5667 + 5.65375^{*}A + 8.40875^{*}B + 6.95^{*}C - 3.305^{*}AB + 0.2125^{*}AC + 10.1075^{*}BC + 7.80417^{*}A^{2} + 5.33917^{*}B^{2} + 0.471667^{*}C^{2}$$

$$R^{2} = 0.9717; \text{F value} = 19.05; P < 0.05$$

The model was found to be significant (F value = 19.05: P value<0.05. The value predicted 0.5932and adjusted R^2 value 0.9207 is reasonable agreement. Adequate Precision measures the signal-to-noise ratio is required. This ratio greater than 4 is desirable. The obtained ratio of 13.383 indicated an adequate signal. From the polynomial equation, it is clear that A, B, C influence the swelling index. The positive sign of independent variables (A, B, C) clearly indicated that the swelling index was increase with an increase in polymer concentration.

Drug release

The mechanisms of drug release from HPMC matrix systems include wetting, hydration, and swelling of the polymer, followed by the formation of the gel layer. After the formation of a gel layer, the amount of the drug released from the HPMC polymer matrix decreases, depending on the rate of drug diffusion, the rate of gel layer disruption, and system erosion [24-27]. In general, an increase in polymer viscosity causes HPMC chains to swell more quickly. Pores of high-viscosity HPMC quickly seal and prevent additional liquid entry. Which results slower rate of drug diffusion and release because the turbid gel that results from this resists erosion and dilution [28]. A high-viscosity polymer is considered to have the potential to prevent dosage dumping due to its quick hydration and gel-forming properties. On the other hand, the desired near-zero-order release profile is not usually achieved with a single hydrophilic swellable polymer, and it has been suggested that combinations of these polymers are more likely to achieve the desired release profile [29, 30]. In this study, xanthan gum was chosen to achieve the desired drug release along with HPMC. A number of papers have been published about mixtures of HPMC and Xanthan gum.

Xanthan gum is an anionic polysaccharide. Individual xanthan gum particle hydration leads to extensive swelling, which slows the rate of release. Xanthan gum regulates the release of highly soluble drugs by forming a thick gel structure that delays drug release from the matrix tablet [31-33]. In a xanthan gum matrix, the majority of drugs are transported by Case II diffusion, which is characterized by linear kinetics (zero-order) and a strong diffusion front; it occurs in polymer-penetrant systems where the penetrant significantly swells the polymer.

From the dissolution study, it was observed that with increasing polymer concentration, the time required to drug release 90% of the drug was increased. A greater degree of swelling results from the higher concentration of HPMC. As a result, the drug's diffusional path length is lengthened, which in turn decreases drug release. On the other hand, lowering the HPMC content lowers swelling and gel layer thickness. This permits more rapid medication release rates [15].

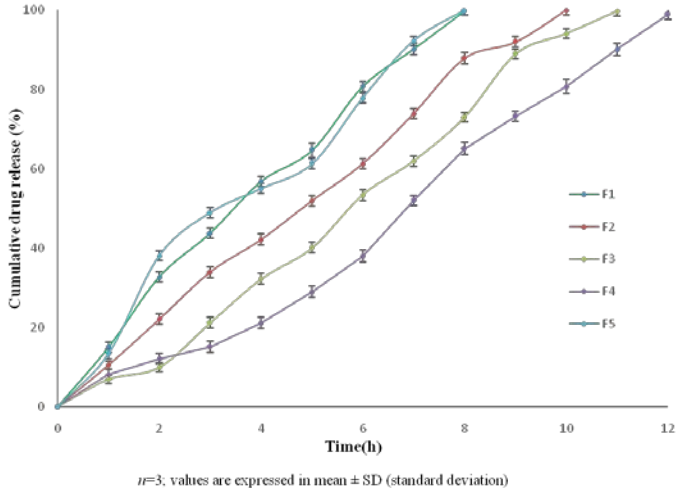

Fig. 9: *In vitro* drug release profile of levofloxacin floating tablets formulation (F1-F5)

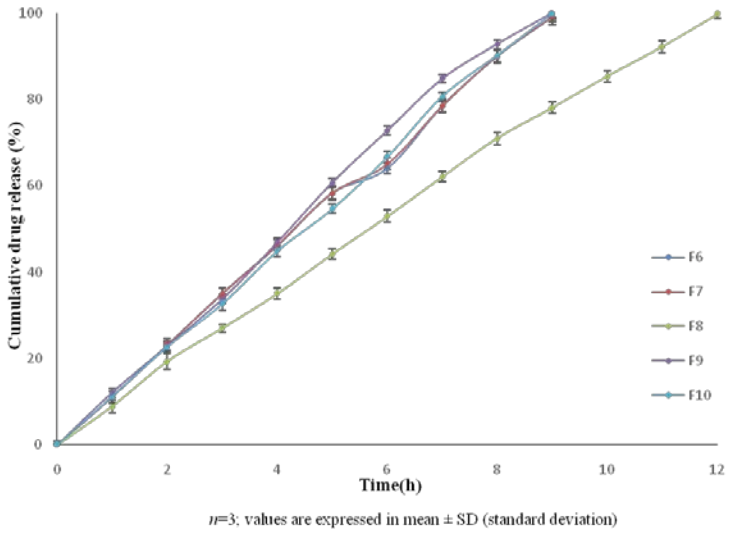

Fig. 9.1: *In vitro* drug release profile of levofloxacin floating tablets formulation (F6-F10)

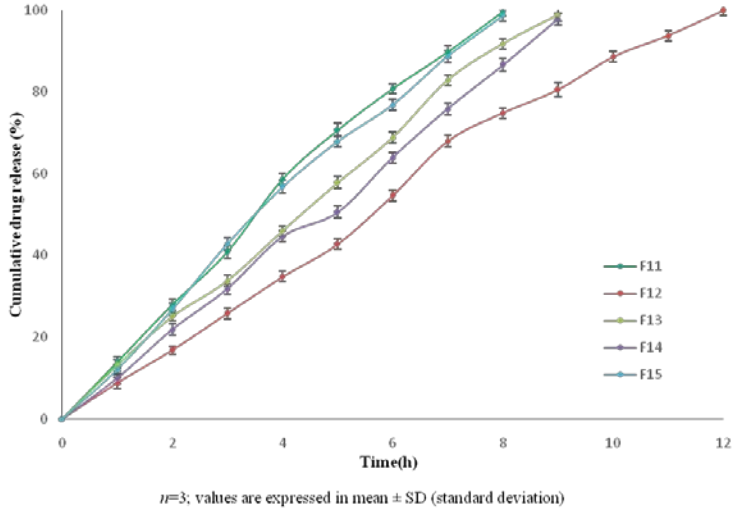

Fig. 9.2: *In vitro* drug release profile of levofloxacin floating tablets formulation (F11-F15)

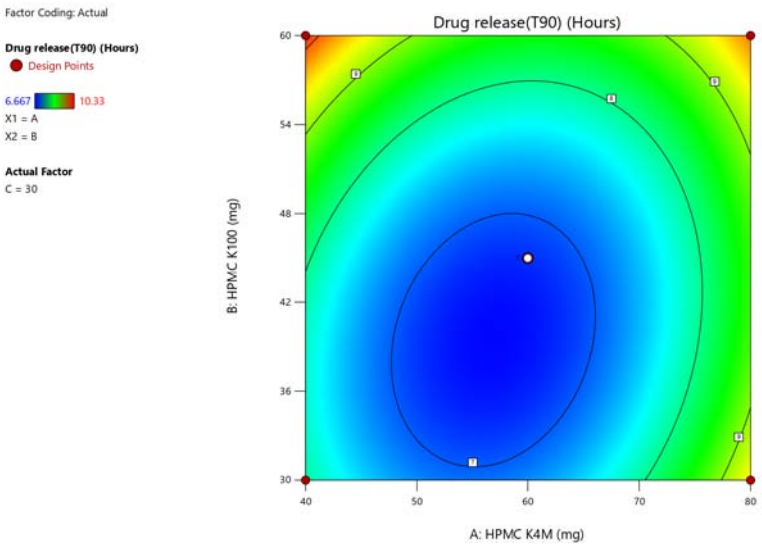

Fig. 10: $T_{90\%}$ contour plot of levofloxacin release from the formulation (HPMC K4M vs HPMC K100M)

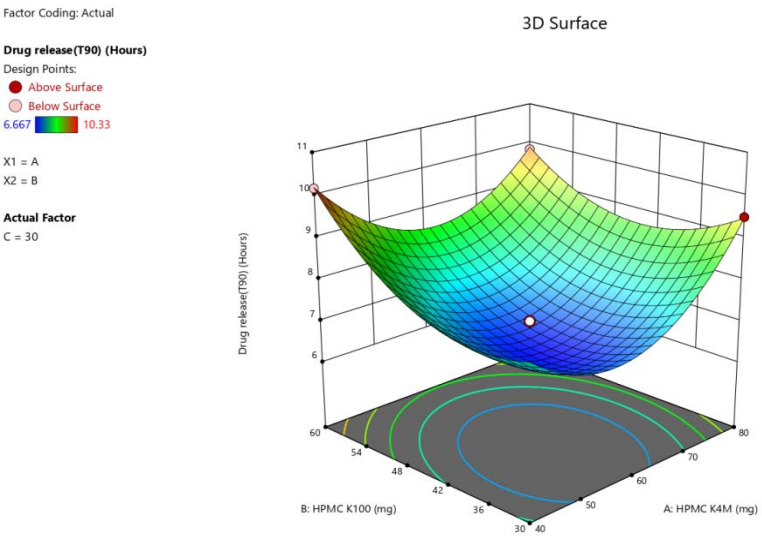

Fig. 10.1: $T_{90\%}$ 3D surface plot of levofloxacin release from the formulation (HPMC K4M vs HPMC K100M)

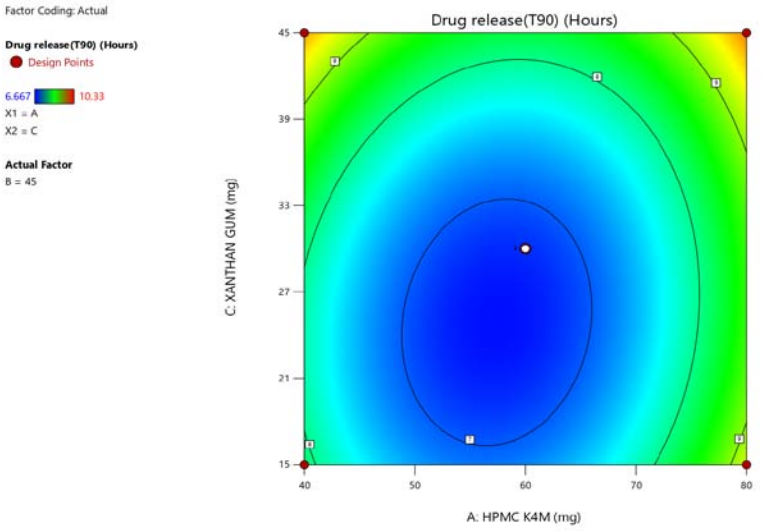

Fig. 11: $T_{90\%}$ contour plot of levofloxacin release from the formulation (HPMC K4M vs Xanthan gum)

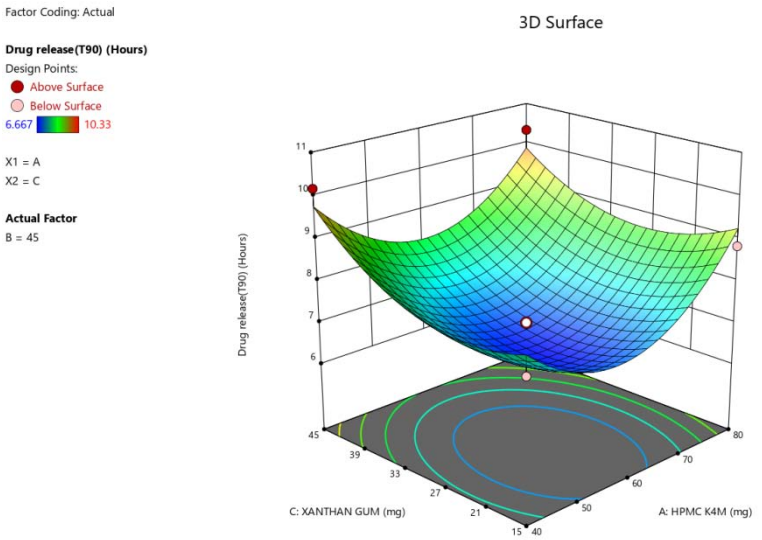

Fig. 11.1: $T_{90\%}$ 3D surface plot of levofloxacin release from the formulation (HPMC K4M vs Xanthan gum)

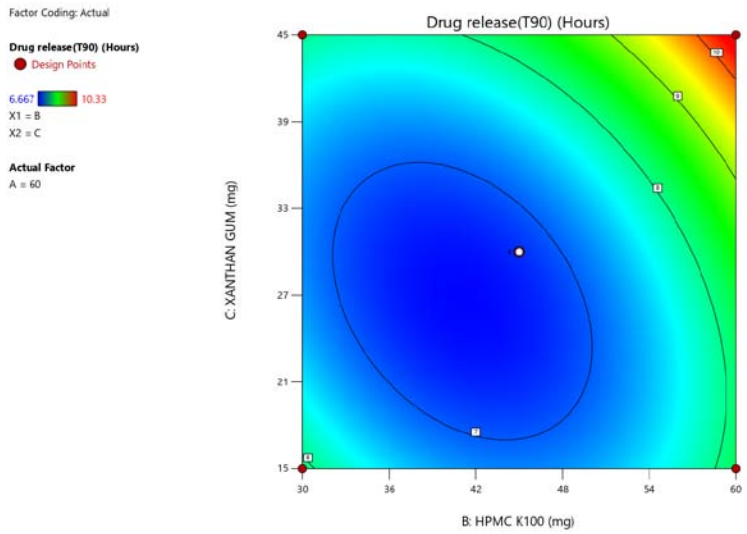

Fig. 12: $T_{90\%}$ contour plot of levofloxacin release from the formulation (HPMC K100M vs Xanthan gum)

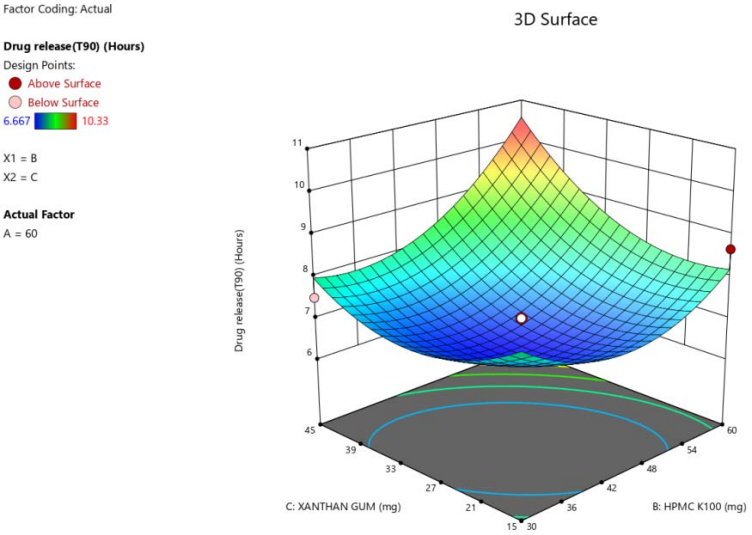

Fig. 12.1: $T_{90\%}$ 3D surface plot of levofloxacin release from the formulation (HPMC K100M vs Xanthan gum)

When compared to xanthan gum and HPMC K100M, the drug release rate from HPMC K4M was higher. It may be related to the rapid hydration of the polymer matrix. It was reported that the gel formation is proportional to the concentration of HPMC polymer and *vice versa*. This gel enhances the path length of drug diffusion. The viscosity of the polymer also impacts the drug diffusion coefficient. HPMC K100M being more hydrophilic than HPMC K4M, hydrates quickly and forms a protective barrier layer immediately, preventing the medium dissolution entry into the tablet matrix and decreasing drug release. Consequently, the drug release rate is decreased [15]. The drug release $T_{90\%}$ was observed 7.0±0.55 h to 10.33±0.289 h. Drug release can also be affected by factors such as the type of polymer and its viscosity, in addition to the concentration of the polymer.

The study revealed that HPMC grade had an effect on drug release. This is because matrices with a higher viscosity grade expand more rapidly. Similarly, xanthan gum concentration in the formulation influences $T_{90\%}$. Higher swelling is produced when xanthan gum particles are hydrated. This leads to well-separated gel particles coming into close contact. The hydrated product's rheology causes the enlarged particles to agglomerate. This creates a continuous viscoelastic matrix that fills the interstices, preserving the tablet's integrity and retarding further penetration of the dissolution media. Our results are in accordance with the previous work of Talukdar *et al.* [30].

$$T_{90\%} = 6.83333 + 0.311125^{*}A + 0.6675^{*}B + 0.562875^{*}C - 0.45925^{*}AB - 0.2515^{*}AC + 0.62575^{*}BC + 1.54158^{*}A^2 + 1.00083^{*}B^2 + 0.875083^{*}C^2$$

$$R^2 = 0.9349; \text{F value} = 7.98; P < 0.05$$

Kinetic studies

Zero-order kinetics, first order, Higuchi equation [34] and Korsmeyer-Peppas models [35] were used to determine the drug release kinetics. Rao KR and Lakshmi KR prepared clopidogrel floating tablets by using three polymers such as xanthan gum, HPMC K15M and HPMC K4M. In their study, they reported similar drug release kinetics. In our study rate of drug, release was found to depend on the type and amount of polymer in the formulation. As the concentration of the polymer went up, it was found that the drug release slowed down [36]. A similar type of drug release pattern was observed in a study conducted by Patel *et al.* [37] and Loh *et al.* [38]. The data on drug release was analysed to determine the type of release mechanism followed. The best match with the highest determination R^2 coefficients was shown by both the Higuchi and first-order models, followed by the zero-order model, which indicates that the drug release mechanism is diffusion. In controlled or sustained release formulations, the three basic rate-controlling mechanisms are diffusion, swelling, and erosion. The majority of the

drug release from the polymeric system occurs via diffusion, which is best characterised by fickian diffusion. However, in the case of formulations that contain swelling polymers, other processes are involved. These processes include the relaxing of polymer chains, the absorption of water, which causes polymers to swell, and the transformation of polymers from an initial glassy state to a rubbery state. As a result of swelling, a significant amount of volume expansion takes place, which results in changing diffusion boundaries. Therefore, in order to investigate the release pattern, the outcomes of the *in vitro* release data were inserted into the equation developed by Korsmeyer and Peppas to characterise the transport mechanism. This equation is a generalisation of the observation that superposes two seemingly independent mechanisms of drug transport. These mechanisms are fickian diffusion and a case II transport, and they describe drug release from a swelling polymer. The value of n provides insight on the mechanism responsible for the release.

The slope of Peppas model was the release parameters "n." In the case of tablets with a cylindrical shape, n values less than 0.45 indicated a classical Fickian diffusion-controlled release, but n values greater than 0.89 indicated a swelling/erosion mechanism. It was established that non-Fickian transport occurred for values of n between 0.45 and 0.89, incorporating both mechanisms. The value of "n" in this case was between 0.45 and 0.89, which showed that the release of levofloxacin was regulated by more than one process. Furthermore, it was controlled by a coupling of swelling, erosion, and diffusion, which was categorised as non-Fickian or anomalous type diffusion.

CONCLUSION

Levofloxacin floating tablet oral drug delivery system was prepared and evaluated in this study. A combination of sodium bicarbonate and citric acid was used to generate gas. The findings showed that the floating characteristics and drug release of the floating tablets were affected by formulation factors such as the concentration of HPMC K4M, HPMC K100M, and Xanthan gum. High viscosity grade and molecular weight polymers slowed down the rate of drug release. Different behaviours were shown when the drug was released from the release layer with different types of polymers. Our results showed that, in comparison to other polymers, HPMC K100M significantly contributed to regulating drug release. HPMC K4M, HPMC K100M and Xanthan gum could be used to effectively change the release rate for a prolonged time up to 12h. In conclusion, the developed gastro-floating tablets can extend levofloxacin duration in the stomach and produce a prolonged release effect. The prepared levofloxacin floating tablet oral drug delivery system appears to be a promising choice for the efficient eradication of *H. pylori.*

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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