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Preparation and In Vitro Evaluation of Levofloxacin-Loaded Floating Tables Using Various Rate-Controlling Agents

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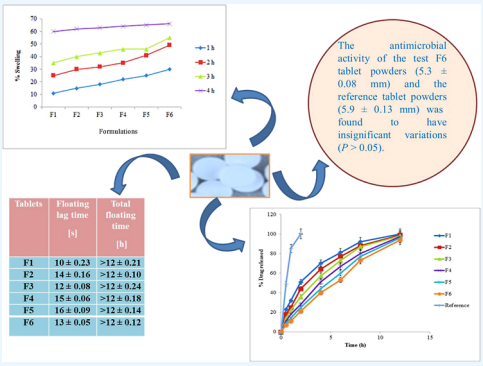
ABSTRACT: Floating tablets are a new approach to extending the time a drug is in the stomach to improve therapy outcomes. Floating tablets were formulated with the drug, the polymers hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), and starch, fillers, and lubricants. The tablets were prepared using the direction compression method. The tablets' physical quality control tests were found to be within acceptable limits. The tablets extended drug release up to 12 h and were uniform in their drug contents. The swelling index of the tablets ranged from 60 ± 0.11 to 66 ± 0.14%, and the tablets were less dense than water. The floating lag time (10 ± 0.23 to 16 ± 0.09 s) and total floating time (>12 h) showed good floating behaviors. The kinetic modeling showed that the drug was released from the tablets by pseudo-diffusion, swelling, erosion, or anomalous non-Fickian diffusion. F6 (starch and CMC) showed higher n values (0.994 ± 0.04), exhibiting pseudo-zero-order drug release kinetics compared to those of other tablets. The dissolution data of the test and reference tables were not similar ($P > 0.05$). In terms of antimicrobial activity, the zones of inhibition of the test F6 tablet powders (5.3 ± 0.08 mm) and the reference tablet powders (5.9 ± 0.13 mm) were found to be significantly similar ($P > 0.05$). The study concluded that these floating tablets can improve the gastric residence time and therapeutic outcomes.



INTRODUCTION

Helicobacter pylorus is known to be widespread throughout the world. *H. pylorus* is the cause of chronic active gastritis, duodenal ulcers, and stomach cancer.[1] Although the bacteria are resistant to many drugs in vitro, they are difficult to eliminate from the human body.[2] Effective eradication of *H. pylorus* requires a longer residence time of drugs in the stomach and the floating system;[3] this is a novel approach to gastric retention. The system[4] floats longer on gastric fluid because its density is lower than that of gastric fluid. Floating systems[4] are divided into effervescent and noneffervescent types. Effervescent floating systems[4] have a gas-generating agent and release the drug over a longer period of time, which was used in the current study. Polymers[5] that form gel easily are highly swellable and can be added to floating systems. The white powder HPMC[6] is a nonionic cellulose ether that has high tensile strength, biodegradability, and remarkable biocompatibility. It is used as a filler and polymer in drug delivery systems. CMC[7,8] is used for various drug delivery applications as matrix-forming agents and diluents because of their affordability, nontoxicity, biodegradability, and compatibility.[9−11] These polymers were included in the current study in the floating tablets of levofloxacin due to their hydrophilic nature.

Levofloxacin[12] is a fluoroquinolone antibiotic, and ofloxacin has levorotatory isomers. Oral bioavailability is 100% and is only slightly affected by food. It is widely distributed in the body; the average volume of distribution is 1.1 L/kg; 24−38% binds to serum plasma proteins (mainly albumin), which does not depend on the concentration of the drug in the serum.[13] The plasma elimination half-life is 6−8 h with normal renal function. About 80% of the drug is excreted unchanged in the urine. Levofloxacin[14] is effective against both Gram-positive and Gram-negative bacteria, including *Helicobacter pylori*. Being a water-soluble drug, it was selected for this study because of its short half-life and its activity against *H. pylori*. It was selected as an addition to floating tablets for site-specific delivery in the stomach.

The levofloxacin floating tablets were prepared using direct compression methods. They were evaluated for various characteristics and aimed to attain a total floating time of 12 h.

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Table 1. Floating Tablet Formulations

ingredients	F1 [mg]	F2 [mg]	F3 [mg]	F4 [mg]	F5 [mg]	F6 [mg]
levofloxacin	250	250	250	250	250	250
HPMC	195			97.5	97.5	
starch		195		97.5		97.5
CMC			195		97.5	97.5
magnesium stearate	9.8	9.8	9.8	9.8	9.8	9.8
talc	11.8	11.8	11.8	11.8	11.8	11.8
sodium bicarbonate	74.2	74.2	74.2	74.2	74.2	74.2
spray-dried lactose	71.2	71.2	71.2	71.2	71.2	7.2
total weight (mg)	612	612	612	612	612	612

MATERIALS AND METHODS

Materials. Levofloxacin was purchased along with Avicel 102, HPMC, starch, CMC, lubricants, and sodium bicarbonate from BDH, England. Hydrochloric acid (HCl) 35% and buffer tablets were purchased from Sigma-Aldrich, USA. The instruments used for the experiments are as follows: Fourier transform infrared spectrophotometer (L1600300 spectrum, Two Lita, Llantrisant, UK), vernier caliper (Erweka, Germany), UV−visible spectrophotometer (UV-1800, Hitachi, Italy), hardness tester, single punch tableting machine, friabilator (Erweka, Germany), and digital electronic balance (ATX224, Shimadzu, Philippines).

Tablet Formulations. Levofloxacin's (drug API) amount (250 mg) was kept constant in the floating tablets of levofloxacin. Different polymers (HPMC, CMC, and starch) were incorporated into the tablets either alone or in combinations, and lubricants (magnesium stearate and talc) and fillers were also added. About 140 tablets were prepared for each type of formulation as pilot lots. Table 1 shows the formulations.

Flow Properties of Formulation Powder Mixtures. The formulation powder mixture's flow properties, such as Hausner's ratios, compressibility indices, and angles of repose, were determined using USP29-NF24[15] standard methods. Angle of repose: funnel and cone assemblies were used to determine the angle of repose. The funnel was fixed with a stand above the Petri dish. The formulation powder mixtures (50 g) were passed through the funnel into a Petri dish to get the heap of powders. The heap height (h) and diameter (d) were determined by a clean ruler. From the diameter, the radius "r" was calculated. The angle of repose (θ) was calculated from eq 1.[15] In order to determine the compressibility index and Hausner's ratio, 16 bulk and tapped densities were to be determined. The formulation powder mixtures (50 g) were individually added to a graduated cylinder (50 mL). Their surfaces were leveled and tapped once to obtain the bulk volume. Then, the cylinder was tapped 100 times to obtain the tapped volume. The values of these volumes were added to eq 2[15] to calculate the bulk density and the tapped density.

$$\text{Angle of repose } (\theta) = \tan^{-1}\frac{h}{r} \tag{1}$$

$$\text{Density } (\rho) = \frac{m}{v} \tag{2}$$

where "v" refers to the bulk or tapped volume and "m" stands for powder mass. The values of bulk (ρ_{bulk}) and tapped densities (ρ_{tapped}) were used in the equations to calculate the compressibility index and Hausner's ratio.[16] Experiments were carried out in triplicate.

$$\text{Hausner's ratio} = \frac{\rho_{tapped}}{\rho_{tapped}} \tag{3}$$

$$\text{Compressibity index } (\%) = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \tag{4}$$

FTIR Analysis. In accordance with standard guidelines,[17] FTIR analysis was performed using the FTIR spectrophotometer (LI600300 spectrum, Two Lita, Llantrisant, UK) to ascertain any potential interactions between the drug and excipients. The samples were separately added to the inlet chamber of the spectrophotometer, and the instrument was run at room temperature, measuring wavenumber 4000−400 cm^{-1}.

Preparation of Tablets. The direct compression method[18] was used for preparing the tablets. The formulation mixtures were passed twice through sieve no. 60 to ensure proper mixing. The mixtures were tableted by using a single punch machine (Erweka, Germany). About 130 tablets were produced in each batch. The hardness was maintained at 5−10 kg/cm^2.

Physical Quality Control Tests. Shape and general appearance:[19] with naked eyes, the tablet's appearance was checked. The shapes of the tablets were examined with a magnifying lens. Diameter and thickness: 10 tablets were randomly picked from each batch of tablets. Their diameter and thickness[20] were measured using clean vernier calipers (Erweka, Germany). Hardness test: for the hardness test, 10 tablets were chosen at random from each batch of tablets. Their hardness was determined by using a hardness tester (Erweka Model TB, Germany). Friability test: to determine their friability, 20 tablets were selected, weighed (W_1), and placed in the friabilator (Erweka, Germany) for 4 min at a speed of 25 rpm. The ultimate weight, W_2, was measured after 100 revolutions. Friability[21] was calculated in percent (%) using eq 5. Weight variation test:[22] for the weight variation test, 20 tablets were selected randomly from each batch of tablets. Each tablet was individually weighed by using a digital electronic balance (Shimadzu, Philippines). The average weight of 20 tablets was calculated. The value of the tests was expressed as the mean ± SD.

$$\text{Friability } (\%) = \frac{W_1 - W_2}{W_1} \times 100 \tag{5}$$

Tablet Density. The tablets were weighed using a digital electronic balance (ATX224, Shimadzu, Philippines), and their

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volumes were determined from the die cavity. Eq 6 was used to calculate density.[23]

$$\text{Density } (\rho) = \frac{\text{Tablet mass}}{\text{Tablet volume}} \quad (6)$$

Swelling and Floating Behaviors. Each type of tablet was randomly chosen and weighed (W_o) using a digital balance. The tablet was added to 25 mL of a 0.1 N HCl solution in a vessel and agitated at 25 rpm at 37 ± 0.5 °C. The tablet was taken from the vessel; water was removed from the surface using filter paper, and it was weighed (W_t). Then the values of the weights were added to eq 7.[24] The USP paddle method[25] was employed to study floating behaviors for 24 h using 0.1 N HCl solutions (900 mL) in a flask of the apparatus. The temperature of the medium was maintained at 37 ± 2 °C with a rotational speed of 50 rpm. The floating lag time of the tablet was noted, and the total floating time was also noted by using a stopwatch.

$$\text{Water uptake} = \frac{(W_t - W_o)}{W_o} \times 100 \quad (7)$$

Tablet's Content Uniformity. In each batch, 20 tablets were randomly taken and crushed into powder, and the equivalent weight of 250 mg of the drug was added to a 100-mL flask with 0.1 N HCl solutions. About 5 mL was taken from this solution and diluted to 100 mL with the same solution. In a similar way, it was diluted several times and filtered. The 5 mL samples were taken with a filter syringe and examined at 293 nm using a spectrophotometer, and the absorbance (abs) was added in eq 8. For reference tablets, a similar process was used. This method was used with slight changes by Samanthula et al.[26]

$$\text{Content uniformity } (\%) = \frac{\text{Sample abs}}{\text{Reference abs}} \times 100 \quad (8)$$

Dissolution Study. In the vessel of USP apparatus type-II,[26,27] 900 mL of a 0.1 N HCl solution was added. The paddle rotation was kept at 100 rpm and a constant temperature of 37 ± 0.5 °C. The tablet was added, and the experiment was continued for 10 h. At regular intervals, 5 mL of samples was taken, and the same amount of medium was added to the flask as the solution. The samples were filtered and examined using a UV−visible spectrophotometer to measure the absorbances of the drug at 294 nm. The drug amount was determined by using the drug standard calibration curve.

Drug Release Kinetics. To determine the drug release mechanisms, drug release data were fitted into the following various kinetic models:

1. Zero-order kinetic model[27]

$$W = K_1 t \quad (9)$$

where K_1 is the rate constant, and the time is shown by t but the unit is concentration/time.

2. 1st-order kinetic model[27]

$$\ln(100 - W) = \ln 100 - K_2 t \quad (10)$$

where Ln 100 is the initial concentration, while K_2 is the 1st-order constant.

3. Hixon Crowell's erosion model[27]

$$(100 - W)^{1/3} = 100^{1/3} - K_3 t \quad (11)$$

where $(100 - W)^{1/3}$ is the initial amount, while K_3 is the model constant and 100 1/3 indicates the level at time t.[27]

4. Higuchi's diffusion model[27]

$$W = K_4 t^{1/2} \quad (12)$$

where K_4 is the model constant.

5. Power law kinetic model[27]

$$\frac{M_t}{M_\infty} = K_5 t^n \quad (13)$$

Dissolution Profile Comparison. For comparison of the drug release profile of the test tablets with reference tablets (Levoflox 250 mg tablets), dissolution data were fitted in the two models: difference factor f_1 and similarity factor f_2 below.[28]

$$\text{Difference factor } (f_1) = \frac{[\sum_n^{t=1}(R_t - R_t)]}{[\sum_n^{t=1} R_t]} \times 100 \quad (14)$$

$$\text{Similarity factor } (f_2) = \frac{[\sum_n^{t=1}(R_t - R_t)]}{[\sum_n^{t=1} R_t]} \times 100 \quad (15)$$

Antimicrobial Activity. The antimicrobial activity[29] was determined by the disc diffusion method. Mueller−Hinton (beef extract, casein's acid hydrolysate, starch, and agar) and Sabouraud (40 g/L dextrose, 10 g/L peptone, and 20 g/L agar) agar media solutions were added into Petri dishes of 90 mm and inoculated with the *H. pylori* strains 39 and solidified. After that, 6 mm cuts were made in the center of the medium and filled with standard powder (ciprofloxacin) and tablet powder. The Petri dishes were incubated for a period of 24 h; zone of inhibition diameters was measured, and experiments were completed in triplicate.

Statistical Tools. One-way of variance (SPPS version 27.0.1) was applied to compare the dissolution profiles of test tablets with reference. The rest of the data were calculated as the mean ± SD in Microsoft Excel.

RESULTS AND DISCUSSION

Flow Properties. The flow properties of all formulation powder mixtures were performed using USP29-NF24 standard methods. The all formulation powder mixtures' Hausner's ratio ranged from 1.11 ± 0.05 to 1.16 ± 0.16. Their angle of repose of the mixtures ranged from 23.7 ± 0.16 to 26.6 ± 0.08°. The compressibility index of all mixtures ranged from 10.2 ± 0.16 to 12.5 ± 0.18%. These flow properties of the mixtures were found within the USP29-NF24's limits[30] of good to excellent flow for angle of repose (25−35°), Hausner's ratio (1.01 ± 0.87 to 1.18 ± 0.01), and compressibility index (1.56 ± 0.14). The different formulation powder mixtures had insignificant variations ($P > 0.05$), which might be due to the presence of lubricants. These results are consistent with the findings of Qin et al.,[31] who evaluated drug (API) powder and various formulations' flow properties and found that their powder mixtures were free-flowing and facilitated the tableting process.[30] These results are given in Table 2.

FTIR Analysis. The drug (API) powder and formulation powder mixtures were analyzed through FTIR analysis to check for any potential interactions between the drug and excipients in the formulation powder mixtures. The drug (API)

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Table 2. Formulation Powder Mixture Flow Properties

formulations	compressibility index [%]	Hausner's ratio	angle of repose [°]
F1	10.2 ± 0.16	1.16 ± 0.16	26.6 ± 0.08
F2	12.4 ± 0.14	1.15 ± 0.12	23.8 ± 0.19
F3	10.6 ± 0.14	1.12 ± 0.05	25.4 ± 0.18
F4	12.5 ± 0.18	1.11 ± 0.09	24.9 ± 0.05
F5	10.5 ± 0.13	1.13 ± 0.01	23.7 ± 0.16
F6	11.8 ± 0.14	1.11 ± 0.05	25.4 ± 0.02

powder functional groups were OH/NH (3681.45 cm^{-1}), C−H stretching asymmetric (2974.43 cm^{-1}), C═O (1724.54 cm^{-1}), C═C stretching (1619.32 cm^{-1}), and C−H bend (1458.37 cm^{-1}). The same functional groups were found in the powder formulation mixtures shown in Table 3, which showed

Table 3. Interpretations of the FTIR Analysis

functional groups	drug (API) powder (cm^{-1})	F1 formulation powder mixture (cm^{-1})	F2 formulation powder mixture (cm^{-1})	F3 formulation powder mixture (cm^{-1})
OH/NH group	3681.45	3679.22	3674.26	3675.36
C−H stretching asymmetric	2974.43	2974.12	2974.31	2973.43
C═O stretching	1724.54	1720.21	1722.46	1723.31
C═C stretching	1619.32	1619.29	1619.62	1619.54
C−H bending	1458.37	1456.48	1440.43	1449.36

negligible changes. Khatri et al. conducted an FTIR study to check the compatibility of the drug and excipients, and they found that there were slight variations in the functional groups of the drug and formulation mixtures, which exhibited negligible interactions, and these confirm the current study results.[32]

Tablet's Swelling Index. In the swelling study, the tablets swelled by 60 ± 0.11 to 66 ± 0.14% of their original size. F1 swelled 60 ± 0.11, F2 62 ± 0.06, F3 63 ± 0.15, F4 64 ± 0.21, F5 65 ± 0.08, and F6 66 ± 0.14% of the original size. The possible reason for swelling might be the hydrophilic nature of polymers; they swell due to the penetration of the solution. Tablets' swelling was also observed by Anusha et al.,[33] who developed tablets using hydrophilic polymers, which swell when the medium penetrates inside the tablets. Results are presented in Figure 1.

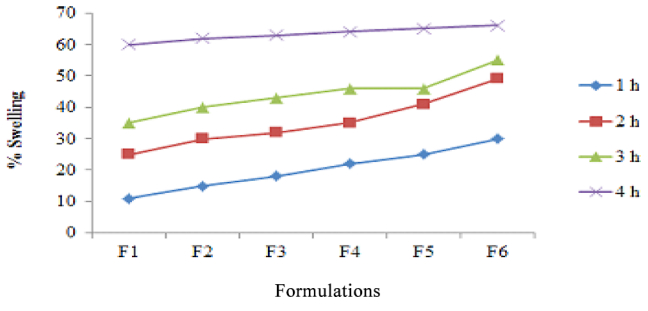

Figure 1. Percent swelling of the tablets.

Floating Behaviors and Densities of Tablets. In the floating behavior study, the floating lag time and total floating time were determined. The floating lag time of the tablets ranged from 10 ± 0.23 to 16 ± 0.09 s, and the total floating time of the tablets was found to be greater than 12 h, indicating good flow behaviors. The densities of all the tablets were calculated and ranged from 0.46 ± 0.12 g/cm^3 to 0.78 ± 0.25 g/cm^3. F1 had significantly ($P < 0.05$) less floating lag time (10 ± 0.23 s) and density (0.46 ± 0.12 g/cm^3) than those of other tablets. The floating tablet's density was less than that of water (1.004 g/cm^3)[34] and showed excellent floating behaviors, which might be due to the addition of a gas-generating material, sodium bicarbonate, and hydrophilic polymers, which might cause its floating to the surface of the medium. These results were similar to the findings of Rabani et al.,[35] who also found floating behaviors of their tablets and suggested that it was due to the addition of gas-generating agents (citric acid and sodium bicarbonate) in the tablets, which could bring the tablets to the surface of the solution. Table 4 presents the results.

Table 4. Floating Parameters of the Floating Tablets

formulations	density of tablets [g/cm^3]	floating lag time [s]	total floating time [h]
F1	0.46 ± 0.12	10 ± 0.23	>12 ± 0.21
F2	0.58 ± 0.05	14 ± 0.16	>12 ± 0.10
F3	0.64 ± 0.02	12 ± 0.08	>12 ± 0.24
F4	0.76 ± 0.19	15 ± 0.06	>12 ± 0.18
F5	0.78 ± 0.25	16 ± 0.09	>12 ± 0.14
F6	0.70 ± 0.08	13 ± 0.05	>12 ± 0.12

Physical Quality Control Tests. The surfaces of the tablets were level, clean, smooth, and elegant in their appearance. The tablet thicknesses ranged from 3.1 ± 0.02 to 3.1 ± 0.09 mm, which was found within the USP limits (2−4 mm).[30] The tablet diameters ranged from 9.0 ± 0.02 to 9.0 ± 0.03 mm, which fell within the USP's limits (4−13 mm).[30] The tablet hardnesses ranged from 8.6 ± 0.06 to 9.3 ± 0.04 kg/cm^2, which was found within the limits of USP (5−10 kg/cm^2).[30] The tablet friabilities ranged from 0.01 ± 0.14 to 0.07 ± 0.18%, which was within USP limits (<1%).[30] The tablet weights ranged from 612.0 ± 0.01 to 612.3 ± 0.06 mg, which was within USP's limits (weight ≥ 324 with 5% variations).[30] These results were found within the USP's limits,[30] indicating that tablets were prepared with constant processing variables. The physical quality of tablets might affect the drug release in the tablet dissolution study. These findings were consistent with the findings of Huang et al.,[36] who prepared tablets, and their tablets' physical quality control tests met the compendial limits, which was due to constant tablet processing parameters. These findings are given in Table 5.

In Vitro Dissolution. The in vitro dissolution studies were performed according to standard procedures[26,27] for 24 h; it was found that the floating tablet extended the drug release rates up to 12 h. It was noted that formulation F1 released 100 ± 0.01% of the drug in 12 h and formulation F2 released 99 ± 0.03% of the drug in 12 h. F3 released 98.0 2 ± 0.26% and F4 released 97.80 ± 0.10% of the drug in 12 h. F5 released 95.81 ± 0.21% and F6 released 93.68 ± 0.14% of the drug in 12 h. F6 (93.68 ± 0.02%) had longer drug release rates than those of other tablets. The reference tablets released 100 ± 0.02% of the drug in 2 h. These tablets extended the drug release rates,

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Table 5. Tablets of Physical Test Quality Control Tests

formulations	thickness (mm)	diameter (mm)	crushing strength (kg/cm^2)	friability (%)	weight (mg)
F1	3.1 ± 0.02	9.0 ± 0.02	9.2 ± 0.01	0.06 ± 0.16	612.0 ± 0.01
F2	3.1 ± 0.08	9.0 ± 0.03	8.9 ± 0.02	0.05 ± 0.03	612.2 ± 0.10
F3	3.1 ± 0.06	9.0 ± 0.02	9.1 ± 0.04	0.06 ± 0.08	612.1 ± 0.02
F4	3.1 ± 0.09	9.0 ± 0.03	8.8 ± 0.07	0.07 ± 0.18	612.3 ± 0.06
F5	3.1 ± 0.05	9.0 ± 0.01	8.6 ± 0.06	0.04 ± 0.17	612.1 ± 0.01
F6	3.1 ± 0.04	9.0 ± 0.05	9.3 ± 0.04	0.02 ± 0.12	612.0 ± 0.03
F7	3.1 ± 0.08	9.0 ± 0.05	8.9 ± 0.01	0.01 ± 0.14	612.1 ± 0.05

which might be due to the presence of hydrophilic polymers. Tablets swell as the medium penetrates inside, and their micropores decrease in size, causing retardation of drug release. These results confirm the findings of Emami et al.,[37] who also used hydrophilic polymers in the tablets, and drug release rates were extended due to swelling of the polymeric network when the medium penetrated into the tablets, which reduced the micropores and extended the drug release rates. Khan et al.[38] found that their floating tablets with hydrophilic polymers (HPMC K100 M and xanthan gum) extended their drug release rates for a longer period of time. These results are displayed in Figure 2.

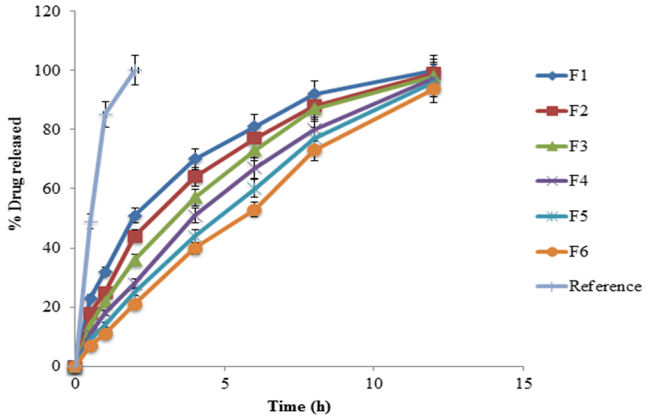

Figure 2. Drug release profiles of floating tablets and reference tablets.

Content Uniformity. The content uniformity test for each batch of tablets was performed. The content of levofloxacin ranged from 99.96 ± 0.13 to 101.3 ± 0.18% in the tablets and was found within the USP29-24[30] limits (90−110%). F1 and F5 showed that the content was significantly ($P < 0.05$) uniformly distributed in the tablet formulations. This might be due to the proper mixing of the drug with excipients, which might distribute the drug throughout the formulation mixtures. Gangane et al.[39] also found that their drug was uniformly dispersed in their tablets, which could be the result of proper mixing of drugs with excipients in their formulations, which confirms the finding of the present study. Table 6 indicates these results.

Drug Release Kinetics. The drug release data of the tablets followed the zero-order kinetic model, as the r^2 values ranged from 0.988 ± 0.41 to 0.997 ± 0.14, indicating that the drug was released by pseudo-zero-order kinetics, which might be due to the addition of polymers in the tablets. These results are similar to those of Shanmugam et al.,[40] who found that their tablets might release the drug with zero-order kinetics. The resultant r^2 values of the 1st-order kinetic model ranged from 0.186 ± 0.06 to 0.432 ± 0.21, showing that the drug was

Table 6. Content Uniformity of the Levofloxacin Tablets

formulations	content uniformity [%]
F1	100.0 ± 0.02
F2	99.98 ± 0.12
F3	99.99 ± 0.14
F4	101.3 ± 0.18
F5	100.6 ± 0.16
F6	99.96 ± 0.13

not released from the tablets by 1st-order kinetics, which might be due to the polymeric nature of the tablets, which might extend drug release rates rather than burst release of the drug. These findings confirm the results of Khan et al.,[41] who found that their drug release data of the floating tablets did not follow the 1st-order models. The Higuchi model's r^2-values ranged from 0.987 ± 0.06 to 0.994 ± 0.19, showing pseudo-diffusion release mechanisms. These results are similar to those of Shanmugam et al. and Khan et al.,[40,41] who also found that their drug could be released by pseudo-diffusion. The r^2-values of Hixon Crowell's kinetic model ranged from 0.985 ± 0.28 to 0.995 ± 0.18, showing that the drug was released by pseudo-swelling and erosion mechanisms. It might be due to the addition of the polymers in tablets, which might control the drug release with swelling or erosion release mechanisms. Shanmugam et al.[40] applied Hixon Crowell's model to their drug release data and found that their drug might be released by pseudo-swelling and erosion mechanisms, which support the findings of the current study. The r^2-values of the power law kinetic model ranged from 0.989 ± 0.02 to 0.995 ± 0.25, showing linearity in the drug release from tablets, and the n-values (exponential amount of drug) ranged from 0.865 ± 0.18 to 0.994 ± 0.04, showing that the drug was released by pseudo-anomalous non-Fickian diffusion. F6 was found to have a higher n-value of 0.994 ± 0.04, which is near 1.0 (the maximum value of n), showing pseudo-zero-order release kinetics. This might be due to the fact that the reference tablets were immediate-release tablets without the addition of rate-controlling polymers. These findings of drug release kinetics or mechanisms are similar to those of Shanmugam et al.,[40−42] who found that their tablets released the drugs by pseudoanomalous non-Fickian diffusion. The reference tablets only followed the ester-order kinetic model with r^2-values of 0.986 ± 0.14 but did not follow the other kinetic models with lower r^2-values shown in Table 7.

Difference and Similarity Factors. The difference factor f_1 values ranged from 18.6 ± 0.31 to 26.8 ± 0.16 and f_2 values ranged from 26.9 ± 0.21 to 40.4 ± 0.02, which was not found within the acceptable[43] limits of f_1 (1−15) and f_2 (50−100). These indicated that the drug release data of the test tablets did not match the reference dissolution profile as the obtained values of f_1 and f_2 were not within the acceptable limits. These

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Table 7. Release Mechanism of the Floating Tablets[a]

formulations	1st-order kinetic model (r^2)	zero-order kinetic model (r^2)	Higuchi's kinetic model (r^2)	Hixon Crowell's kinetic model (r^2)	power law kinetic model (r^2)	n-values	release mechanism
F1	0.321 ± 0.31	0.990 ± 0.28	0.987 ± 0.06	0.985 ± 0.28	0.989 ± 0.08	0.869 ± 0.11	ANFD
F2	0.265 ± 0.18	0.988 ± 0.41	0.989 ± 0.31	0.988 ± 0.10	0.989 ± 0.02	0.865 ± 0.18	ANFD
F3	0.186 ± 0.06	0.989 ± 0.48	0.990 ± 0.11	0.989 ± 0.06	0.990 ± 0.06	0.901 ± 0.26	ANFD
F4	0.432 ± 0.21	0.993 ± 0.16	0.991 ± 0.32	0.992 ± 0.12	0.992 ± 0.18	0.866 ± 0.13	ANFD
F5	0.268 ± 0.12	0.996 ± 0.04	0.992 ± 0.26	0.993 ± 0.26	0.993 ± 0.04	0.993 ± 0.09	ANFD
F6	0.324 ± 0.08	0.997 ± 0.14	0.994 ± 0.19	0.995 ± 0.18	0.995 ± 0.25	0.994 ± 0.04	ANFD
Reference tablets	0.986 ± 0.14	0.123 ± 0.41	0.432 ± 0.07	0.489 ± 0.03	0.436 ± 0.13	0.348 ± 0.02	does not follow

[a]NDFD = anomalous non-Fickian diffusion.

results are listed in Table 8. These findings confirm those of Somasundaram and Azab et al.,[44,45] who found that the drug release profiles of the test tablets did not match those of the reference tablets when applied to f_1 and f_2. One-way analysis was also applied for comparison of test tablet dissolution profiles, and P-values were found to be greater than 0.05, indicating differences in dissolution profiles. F6 is different than the other formulations as the P-value was 0.198.

Table 8. Values of Difference and Similarity Factors

test vs reference	f_1	f_2
F1 vs reference tablets	22.6 ± 0.18	40.4 ± 0.02
F2 vs reference tablets	24.1 ± 0.24	38.2 ± 0.15
F3 vs reference tablets	18.6 ± 0.31	35.4 ± 0.08
F4 vs reference tablets	19.2 ± 0.11	30.2 ± 0.05
F5 vs reference tablets	25.4 ± 0.28	28.1 ± 0.12
F6 vs reference tablets	26.8 ± 0.16	26.9 ± 0.21

Antimicrobial Activity. The antimicrobial activity of the test F6 tablet powders (5.3 ± 0.08 mm) and the reference tablet powders (5.9 ± 0.13 mm) was found to have insignificant variations ($P > 0.05$). The current study's findings support the finding of Somasundaram,[44] who found that levofloxacin-based therapy (74.5 ± 0.01%) was connected with a significant ($P < 0.04$) higher rate of eradication against *H. pylori* than that of clarithromycin-based therapy (62%) in 14 days.

CONCLUSIONS

The levofloxacin floating tablets were prepared by direct compression using the polymers HPMC, CMC, and starch. Physical quality control tests were found within USP29-NF24 official compendial limits. Tablets swelled 60 ± 0.11 to 66 ± 0.14% of their original size, indicating good swelling behavior. The tablets' floating lag time (10 ± 0.23 to 16 ± 0.09 s) and total floating time (>12 h) showed good floating behaviors. The tablets extended the drug release rates up to 12 h. The drug content (99.96 ± 0.13 to 101.3 ± 0.18%) was uniformly found in the tablets. The tablets released the drug by pseudo-diffusion, swelling, erosion, or anomalous non-Fickian diffusion, and F6 exhibited higher n-values (0.994 ± 0.04) indicating pseudo-zero-order kinetics than those of the rest of the tablets. The dissolution patterns of the test and reference tablets were not similar using similarity and difference factors and one-way analysis of variance ($P > 0.05$). The antimicrobial activity of the test F6 tablet powders (5.3 ± 0.08 mm) and the reference tablet powders (5.9 ± 0.13 mm) was found to have insignificant variations ($P > 0.05$). It is concluded from the study that the floating tablets could improve the gastric residence time and patient compliance.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c05419.

Standard calibration curve of levofloxacin (PDF)

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F.Y.S. and K.A.K. designed the work, carried out the experimental work, and evaluated and inferred the data. A.Y.S., A.A., M.A.B., A.A.F., and O.A.M. performed the experiments and analyzed and interpreted the data using software.

Notes

The authors declare no competing financial interest.

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