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Research Article

Controlled Release Bilayer Floating Effervescent and Noneffervescent Tablets Containing Levofloxacin and Famotidine

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The present study is aimed at designing bilayer-floating tablets to improve the drug concentration in the stomach for enhanced therapeutic efficacy. The tablets are comprised of an upper layer of levofloxacin (466.5 mg) and a lower layer of famotidine (133.5 mg). Five formulations (F1-F5) were developed by using hydroxypropyl methylcellulose grades (K4M, K15M, and K100M) along with Carbopol 934. In the case of the effervescent system (F1-F3), sodium bicarbonate was added to impart buoyancy to the tablets; while in the case of noneffervescent formulations (F4 & F5), guar gum and xanthan gum were incorporated to induce flotation and swelling and retard the release of a drug. The precompression characteristics of tablets depict the suitability of all formulation powder for direct compression. The ATR-FTIR analyses have shown that the components of both effervescent and noneffervescent tablets are compatible with each other. The total weight of each tablet was 600 mg, with a weight variation of about ≤10 mg. Both the layers were smooth and flat with a thickness ranging from 3.16 ± 0.04 to 3.54 ± 0.01 mm. The diameters of prepared floating tablets were about 15 mm, optimum for oral administration. After adjusting the tablet's hardness to 6-7 kg/cm^2, its friability was found to be <0.35 percent. The mean drug content of the formulations was above 90%. The floating lag time of all formulations (F2-F5) was below 25 seconds, except F1 which took almost 50 seconds to start floating on the surface of gastric content due to its higher density. The total floating time of effervescent (F1-F3) and noneffervescent formulations was in the range of 15-25 hours, thereby providing sufficient time to complete drug release and absorption in the gastric area. The total floating time of noneffervescent formulations was higher ($p \leq 0.05$) than effervescent formulations due to efficient wettability and swelling characteristics. The release of drugs from both layers of noneffervescent tablets was significantly controlled when compared to the effervescent system, and an anomalous non-Fickian diffusion was found for the drug release. The stability study of the optimized formulation proved the integrity and stability of the developed formulation. Thus, developed formulations are deemed suitable for controlled codelivery of active pharmaceutical ingredients for the effective treatment of *H. pylori*.

1. Introduction

Considering oral administration is the most convenient, cost-effective, flexible formulation, which is easy to store and carry, and has a high patient compliance rate, thus, it is the most promising and desired approach to drug delivery [1, 2]. In oral drug delivery, tablets are particularly preferred due to higher stability, ease of preparation, and sustained drug release [1]. However, developed oral drug delivery systems face various challenges such as low bioavailability due to the heterogeneity of the gastrointestinal system, variation of pH and commensal flora, the gastric retention time of the dosage form, surface area, and enzymatic activity [2]. Conventional drug delivery systems may not be able to overcome issues imposed by the gastrointestinal tract (GIT) such as the incomplete release of drugs, decrease in dose effectiveness, and frequent dose requirement. Therefore, the failure of conventional drug delivery systems to retain drugs in the stomach may lead to the development of gastroretentive drug delivery systems (GRDDS). There are several GRDDS that includes super porous hydrogel, bioadhesive, raft-forming, magnetic, ion-exchange, expandable, and low- and high-density systems [2–4]. The floating systems are the most practical and extensively studied gastroretentive dosage forms, being divided into effervescent and noneffervescent systems. Effervescent systems contain gas-forming agent and/or volatile liquids that contribute to their floatation. Swellable polymers are combined with effervescent substances, either separately or in combination, such as calcium carbonate, sodium bicarbonate, citric acid, and tartaric acid, in a gas-generating floating system. Upon contact of the system with gastric fluids, the gas-generating agent reacts with hydrochloric acid, and CO_2 is generated. CO_2 trapped in a polymer matrix lowers the density and helps in the floatation of the tablet [5, 6]. However, this system is not suitable for patients with achlorhydria since the low excretion of gastric acid in these patients can lead to a higher gastric pH, thus resulting in extended floating lag times [7, 8]. The bilayer noneffervescent floating tablet can be designed by uniform mixing of the drug, relevant excipients, and gel-forming hydrophilic polymer, which hydrates and swells upon contact with the gastric fluid and maintains the bulk density of the tablet at $<1\,g/cm^3$. Thus, the low-density systems float on the gastric fluid and prolong the gastric residence time [2, 9]. These floating systems are useful in the treatment of stomach disorders for drugs that are predominantly absorbed in the acidic medium and unstable in the lower parts of the intestine [10, 11]. A fluoroquinolone, levofloxacin inhibits DNA gyrase and acts as a broad-spectrum antibiotic. It inhibits both gram-positive and gram-negative bacteria with mild effects on anaerobes. In twain, a triple regimen having levofloxacin has been effectively used as second-line therapy for the eradication of *H. pylori* within 10 to 14 days [12–14]. In previous studies, levofloxacin floating microparticles and tablets are effectively used to enhance its gastric residence time [14–16]. Its elimination half-life is from 4 to 7 hours, thereby needing a controlled-release dosage form [17, 18]. Famotidine is an H2 receptor antagonist with a short half-life of 2.5 to 4 hours and low oral bioavailability (40-45%) and so needs sustained release tablets for increasing its gastric residence time for enhanced bioavailability [19, 20]. Other researchers have developed sustained release tablets of famotidine to enhance bioavailability by using Methocel as gel-forming polymer [19, 21]. As levofloxacin and famotidine are used as 2nd line therapy in the treatment of *H. pylori*, the patient has to take a tablet of each of the drugs, which might lead to noncompliance. Here, the present study was aimed at preparing their bilayer-controlled release floating tablets, which might improve compliance and ensure site-specific delivery of the drugs in a single bilayer tablet.

2. Material and Methods

Levofloxacin (purity 99%), Talc and Avecil 102, and Famotidine (purity 100%) were used as model drugs, gifted by Wilson's Pharmaceuticals, Pakistan. Methocel K4, K15, and, K100, Xanthan gum and Carbopol 934, and guar gum (Sigma Aldrich, USA) were used as release retardants. Floating agent sodium bicarbonate and magnesium stearate were used as flow promoters and lubricants (BDH Chemical Limited, Poole, England) was used as an effervescent agent in effervescent system designs. The analytical-grade chemicals were used lacking any additional handling for refinement.

2.1. Preparation of Tablets. The bilayer effervescent and noneffervescent floating controlled release tablets were prepared by direct compression method with composition as mentioned in (Table 1). Initially, levofloxacin was mixed with polymers (Methocel K4, k15, K100, and Carbopol 934 (1 : 1) along with xanthan and guar gum) and sodium carbonate in case of effervescent formulations. Individual formulation powder mix was passed through sieve no:40. Then, a pestle and mortar were used for mixing the powders for 15 minutes. Avecil (102), talc, and magnesium stearate were then added to the mixed powders, and mixing was continued for 5 minutes. Finally, a total weight of 466.5 mg of levofloxacin layer was manually added into the die cavity of tableting machine (Erweka-Apparatebau compression machine type T B 24) to attain the first layer of a tablet. The same procedure was adopted for the famotidine layer where a total weight of 133.5 mg of the formulation was compressed over the levofloxacin layer to get a bilayer tablet of 592 mg, maintaining tablet hardness at 6-7 kg/cm^2 with the help of a hardness tester (Erweka Model TB, Germany), and all the tablets were prepared manually [21–23].

2.2. Precompression Characteristics

2.2.1. Flow Properties of Powder. Estimation of flow properties of powder mix is important in the development of elegant products (matrices). In accordance to the standard procedures mentioned earlier (USP 2007) [24–26], the flow properties were determined. The blended powder was passed through a funnel on a horizontal surface, the specific height and diameter achieved by the powder blend were

Table 1: Formulation of effervescent and noneffervescent floating controlled-release bilayer tablets.

Drugs	Components of formulation (mg)	Effervescent bilayer tablets			Noneffervescent bilayer tablets	
		F1	F2	F3	F4	F5
Levofloxacin Layer (LF)	Levofloxacin	250	250	250	250	250
	Carbopol (934)+Methocel (K4)	78				
	Carbopol (934)+Methocel (K15)		78		78	78
	Carbopol (934)+Methocel (K100)			78		
	Talc	12.5	12.5	12.5	12.5	12.5
	Avecil (102)	42	42	42	42	42
	Sodium bicarbonate	78	78	78		
	Magnesium stearate	6	6	6	6	6
	Xanthan gum				78	
	Guar gum					78
Famotidine Layer (FM)	Famotidine	20	20	20	20	20
	Carbopol (934)+Methocel (K4)	60				
	Carbopol (934)+Methocel (K15)		60		60	60
	Carbopol (934)+Methocel (K100)			60		
	Talc	3.5	3.5	3.5	3.5	3.5
	Avecil (102)	18	18	18	18	18
	Sodium bicarbonate	30	30	30		
	Magnesium stearate	2	2	2	2	2
	Xanthan gum				30	
	Guar gum					30

recorded, and equation (1) was used to determine the angle of repose [27].

$$\theta = \tan^{-1}\frac{h}{r}, \tag{1}$$

where "θ" is the angle of repose, "h" is the heap height, and the heap radius is "r".

The densities of powder were used to get the compressibility index as well as Hausner's ratio [25]. Briefly, in a graduated cylinder, a specified amount of powder was added to get volume ($V1$). The cylinder was gently tapped for a sufficient time. The tapping was continued until a constant volume ($V2$) was noticed. The process was repeated thrice ($n = 3$) for each formulation, and the average was taken for the determination of bulk and tapped density as well as Hausner's ratio and compressibility index.

$$\text{Bulk Density}(\rho) = \frac{m}{V1}, \tag{2}$$

$$\text{Tapped density}\ (\rho) = \frac{m}{V2}, \tag{3}$$

where "m" is the powder mass, "$V1$" is the bulk, and "$V2$" is the tapped volume.

$$\text{Hausner ratio} = \frac{\rho\,\text{tapped}}{\rho\,\text{bulk}} \tag{4}$$

$$\text{Compressibility index}(\%) = \frac{(\rho\,\text{tapped} - \rho\,\text{bulk})}{\rho\,\text{tapped}} \times 100 \tag{5}$$

2.2.2. ATR-FTIR Analysis. The attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR) spectra of pure drugs, polymers, and powder of crushed tablets were obtained by using an ATR-FTIR spectrometer (Spectrum 100, Perkin Elmer, Shelton, CT, USA) using MIRacle ATR accessory (PIKE Technologies, Madison, WI, USA). The samples were scanned from 4000 to 400 cm^{-1}. The resulting spectra were compared for any spectral changes to determine any interface with the drug-excipient to ensure the compatibility of the formulation [28, 29].

2.3. Postcompression Characteristics. The physical characteristics of tablets were assessed, which include appearance, friability, thickness, diameter, hardness, and weight variation [30, 31]. The tablet's appearance was checked with a magnifying glass. A clean Vernier caliper was used to measure the tablets' ($n = 10$) thickness and diameter. A friabilator (Roche Friabilator) was used to determine the friability of 20 tablets [31]. A hardness tester (Erweka Model TB, Germany) was used to get the hardness [30] of 10 tablets. In the weight variation test, the weight of 20 individual tablets was determined using a weighing balance (Mettler Toledo, Germany), and their average weight was calculated [31]. The drug contents of prepared tablets were determined by randomly selecting 10 tablets. The bilayer tablets of levofloxacin and famotidine were crushed separately to get powder

form and then added to a 50 ml of 0.1 N HCl solution. The samples were taken, filtered using a 0.45 μm membrane filter, and analyzed spectrophotometrically (UV-1601, Shimadzu, Japan) for levofloxacin and famotidine content at 294 and 265 nm, respectively, using similarly blank samples with famotidine and levofloxacin as control [16, 32].

2.4. Floating Behavior

2.4.1. Buoyancy Evaluation. The floating property of optimized batches of tablets was visually determined in triplicate. The USP dissolution apparatus-II (paddle method) was used to determine the tablet floating lag time and the total floating time. The flask of apparatus was filled with 900 ml 0.1 N HCl (pH 1.2) solution whose temperature was maintained at 37 ± 0.5 °C), and the experiment was conducted for 24 hours. The floating lag time was noted from the tablet rising to the surface of the medium. The total floating time was noted from the total stay of the tablet on the medium surface [33, 34].

2.4.2. Swelling Behavior. The swelling study of tablets involves the absorption of liquid by excipients, increasing its weight and volume. For this study, tablets from the optimized batch were weighed and retained in a beaker having 0.1 N HCl solution (25 mL). After the fixed time interval (1, 2, 4, 6, and 8 hr), the tablets were removed from the beaker and dabbed with filter paper to remove surface adhered liquid and weighed. The swelling index was determined by equation (6), and the average was calculated as mean ± S.D . [14, 27].

$$\text{Water uptake} = \frac{(W_t\text{-}W_o)}{W_o} \times 100, \tag{6}$$

where the tablet weight at time "t" is the Wt and Wo is the initial weight.

2.4.3. Erosion Study. The erosion study of bilayer tablets was carried out by gravimetric analysis in the USP type-II dissolution apparatus. Tablets were weighed individually (Wo) and placed separately in 900 mL solution of 0.1 N HCl (pH 1.2) in vessels, which run at 100 rpm and 37 ± 0.5 °C. The swelled tablets were taken from the vessels after 8 hours, and the liquid on the tablets' surface was wiped with the help of a filter paper and dried at 60 °C until persistent weight was achieved. The tablets were reweighed (Wr) to calculate erosion mass (RM). The RM (%) was calculated by using equation (7), and the average weight was calculated as mean ± S.D. [28, 29].

$$\text{RM}\,(\%) = \frac{Wr}{Wo} \times 100, \tag{7}$$

where RM (%) represents the erosion mass of the tablet, the initial weight of the dry tablet is "Wo", and the weight of the continuing dried tablet is "Wr" after entering the media at the time.

2.4.4. Tablet Density. The floating density of tablets is a very important parameter that governs the floating of tablets. A tablet can float when its density is less than 1.004 g/cm^3. The density of formulations was determined for each batch according to equation (8) [30, 31].

$$\rho = \frac{m}{v}, \tag{8}$$

where "ρ" is tablet density, "m" represents tablet mass of tablet (g), and "v" is tablet volume (cm^3), which is calculated from the following equation:

$$V = \pi r^2 h, \tag{9}$$

where "π" is 3.14, "r" represents the radius of the tablet in (cm), and "h" represents the crown thickness of the tablet (cm).

2.4.5. Drug Release Behavior. In vitro drug release of a floating bilayer tablet, which contains levofloxacin 250 mg and famotidine 20 mg, was determined in USP dissolution apparatus having 0.1 N HCl (900 ml) at 37 ± 0.5 °C where paddle rotated at speed of 50 rpm for 24 hours. The 5 ml solution was collected at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12, 18, and 24 h and replaced with adding the fresh medium solution (5 ml). A membrane filter of 0.45 μm was used to filter the sample. Then, filtrate was analyzed in spectrophotometer (UV-1601, Shimadzu, Japan) to determine the absorbance of samples at $\lambda_{\max}$ of 294 nm and 265 nm after suitable dilution. The analytical curves were employed to get the percent cumulative release from the drugs separately, and the readings were shown as triplicate results in the form of mean ± S.D. [16, 22, 35].

2.4.6. Drug Release Kinetics. It is important to note that knowledge of the release mechanism and the physicochemical characteristics of the active components are crucial for establishing accuracy in the dissolving test. Numerous kinetic models could be used to explain the kinetic of drug release. Drug release data was analyzed by zero order, first order, and the Higuchi release kinetic equation [36]. Later, the release data was also fitted into the Korsmeyer-Peppas (power law) empirical equation (10) to confirm the mechanism of the release. The maximum correlation coefficient values of the model were reflected to be the finest-suitable one [22]. Microsoft Excel (DD Solver, an add-in program) was used for modeling drug release profiles [33].

$$\frac{Mt}{M\infty} = Kt^n, \tag{10}$$

where $Mt/M\infty$ is the drug release fraction after "t" time. K is the constant of the model. n is the indicative of the drug release mechanism with exponential release amount. $n < 0.45$ means the drug will be released on Fickian diffusion or case I transport [34]. $n \geq 0.45$ means showing a non-Fickian diffusion or anomalous release because of the relaxation and diffusion of the polymer. $n \geq 0.89$ depicts case II transport or zero order kinetics.

Table 2: Flow properties of both effervescent and noneffervescent floating bilayer tablets.

Code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Compressibility index (%)	Angle of repose (degrees)
F1	0.45 ± 0.005	0.52 ± 0.005	1.119 ± 0.009	11.151 ± 0.186	25.33 ± 0.577
F2	0.44 ± 0.006	0.52 ± 0.001	1.173 ± 0.015	15.182 ± 1.168	27.23 ± 0.493
F3	0.44 ± 0.006	0.52 ± 0.015	1.152 ± 0.014	13.291 ± 0.741	29.53 ± 0.458
F4	0.45 ± 0.002	0.51 ± 0.002	1.133 ± 0.011	12.016 ± 0.610	25.47 ± 0.321
F5	0.45 ± 0.005	0.52 ± 0.006	1.153 ± 0.152	13.530 ± 1.107	28.43 ± 0.450

2.4.7. In Vitro Release Profile Comparison. The release of levofloxacin and famotidine from control release bilayer effervescent and noneffervescent floating tablets was compared by applying fit factors ($f1$ for difference and $f2$ for similarity) as mentioned previously [37] to establish the similarity of two release profiles of the effervescent and noneffervescent floating systems. The difference between the two release profiles (the test and the reference levofloxacin tablets) could be achieved if $f1$ values were 0–15, and similarity could be assessed when the $f2$ values were 50–100 [37, 38]. The calculations were performed using the Excel add-in DDSolver [39].

2.5. Stability Study. Physical stability studies of optimized formulations of control release bilayer floating effervescent (F2) and noneffervescent tablets (F5) were carried out according to International Conference on Harmonization (ICH) guidelines [40]. Our optimized batches were sealed in an airtight aluminum package and kept in a humidity chamber. The stability conditions were a temperature of 40 ± 2 °C and an RH of 75 ± 5%. The sample was withdrawn at predetermined time intervals of 0 (initial), 30, 60, and 90 days. Bilayer tablets were evaluated for the different postcompression parameters such as appearance, hardness, weight variation, drug content, floating behavior, total swelling index (%), and erosion mass [41, 42].

2.6. Statistical Analysis. The *in vitro* comparison between dissolution profiles of effervescent (F2) as reference and noneffervescent (F4, F5) as test formulation batches was performed with the help of independent sample paired t-test via SPSS version 17.0 (SPSS Inc., Chicago, USA) to check their similarity and dissimilarity, and $p \leq 0.05$ were considered statistically significant [41, 43].

3. Result and Discussion

3.1. Precompression Characteristics. The relatively lower variation among the bulk and tapped density of different effervescent formulations (F1-F3) resulted in significantly lower Car's index values (11 to 15), depicting its suitability to be compressed directly [21]. Hausner's ratio lay in the range of 1.12-1.17, and the angle of repose is within the range of 25-30° (Table 2), which is within the permissible limits and indicates good flow characteristics. This good flow of powder mix was due to the presence of magnesium stearate being present as flow-promoting agent in the formulation [26, 35, 43, 44]. Good flow is empirical to ensure the formation of tablets with uniform weight and contents. When sodium bicarbonate was replaced by xanthan gum (F4) and guar gum (F5), both the Car's index and Hauser's ratio were slightly decreased. However, no significant difference between the flow properties of the different formulations was observed ($p \leq 0.05$). Thus, all the formulations were optimally prepared by using the direct compression method (Table 2).

3.2. Compatibility of Formulation Components. The ATR-FTIR spectra of levofloxacin have shown spectral bands at 2802, 1702, 1618, 1517, 1439, 1394, 1340, and 1289 cm^{-1} corresponding to alkynes terminal, carboxylic acid, aromatics, nitro, and alkyl halides functional groups in levofloxacin (Figure 1) [15, 45]. The spectral bands of famotidine were found at 3398, 3349, 3104, 1597, 1530, 1426, 1331, and 1276 cm^{-1} corresponding to amines, amides, aromatics, alkyl halides, and alkene groups predominantly involved in therapeutic activity of drug [19, 39]. The ATR-FTIR spectra of selected formulations F2 and F5 in (Figure 1) have shown that there were no potential changes in the spectral bands for the above groups, depicting no potential harmful interaction between the selected drugs and their corresponding formulation components in both effervescent and noneffervescent tablets [41, 46].

3.3. Postcompression Characteristics. The bilayer floating tablets comprised a light yellowish layer of levofloxacin and a whitish layer of famotidine. Both the layers were smooth and flat with a thickness ranging from 3.16 ± 0.04 to 3.54 ± 0.01 mm, being within the acceptable range of 2–4 mm for floating tablets [26, 42]. The diameters of prepared floating tablets were about 15 mm, optimum for oral administration [21, 37, 38]. The hardness of tablets was adjusted to 6-7 kg/cm^2, which was found to be within the range of 5-10 kg/cm^2, resulting in a friability of ≤0.35. The hardness values with friability in the range of 0.22 to 0.35 indicate that floating tablets are of sufficient strength to withstand physical abrasion [47, 48] during storage and transportation. The total weight of tablets was kept at 600 mg, with a weight variation of about ≤10 mg as mentioned in (Table 3) [49]. The mean drug content of the formulations was found to be above 90%, which met the standard pharmacopeia requirements of 90–110% [50].

3.4. Density and Floating Behavior. The density of effervescent floating tablets was found to be below 1.004 g/cm^3, which supports the floating of tablets. In the floating tablets,

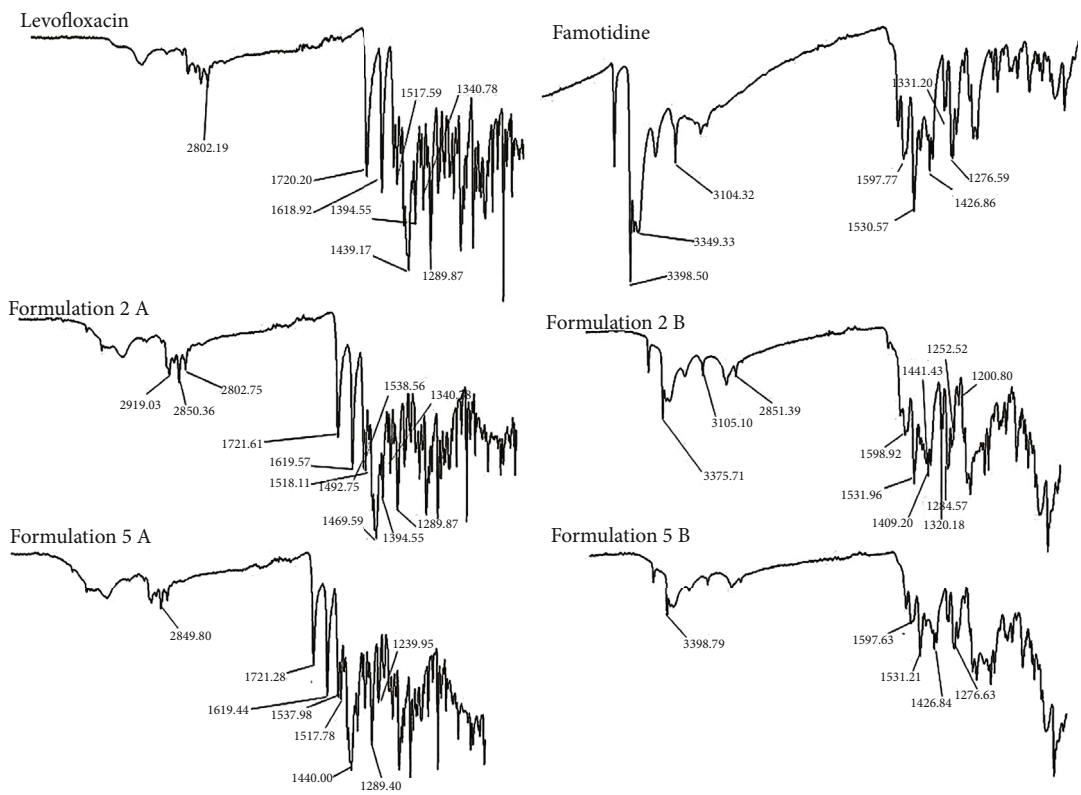


Figure 1: ATR-FTIR spectra of pure drugs and their respective formulations (F2 and F5). Here, 2A and 5A represent the levofloxacin layer of formulations F2 and F5. While 5A and 5B represent the famotidine layer of formulations F2 and F5.

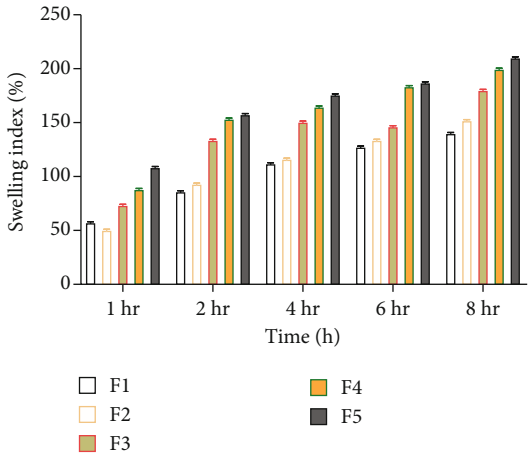
Table 3: Postcompression characteristic of bilayer floating tablets.

Code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Total weight (mg)	Drug content (%)	
						Levofloxacin	Famotidine
F1	3.16 ± 0.04	14.92 ± 0.21	6.54 ± 0.49	0.22 ± 0.05	592.3 ± 4.15	98.48 ± 0.63	99.50 ± 0.66
F2	3.44 ± 0.01	14.99 ± 0.03	6.92 ± 0.11	0.33 ± 0.01	592.9 ± 4.79	100.86 ± 0.96	99.40 ± 0.93
F3	3.44 ± 0.07	14.92 ± 0.17	6.92 ± 0.11	0.33 ± 0.01	593.1 ± 4.22	95.68 ± 0.89	98.77 ± 0.74
F4	3.35 ± 0.03	14.95 ± 0.12	6.16 ± 0.55	0.35 ± 0.01	592.4 ± 3.78	96.84 ± 0.18	96.80 ± 0.95
F5	3.54 ± 0.01	14.97 ± 0.09	6.88 ± 0.11	0.27 ± 0.01	591.5 ± 3.72	99.66 ± 0.58	98.90 ± 0.92

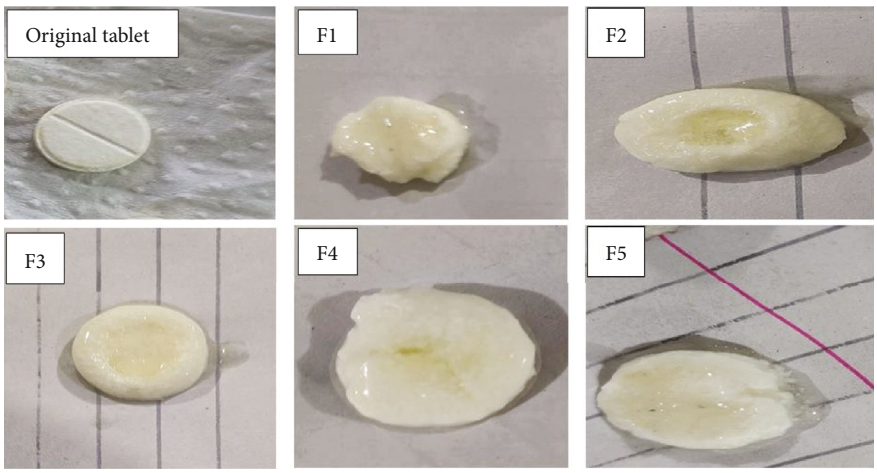
Table 4: The density and floating characteristics of bilayer floating tablets.

Code	Tablet density (g/cm^3)	Floating lag time (seconds)	Total floating time (hours)	Erosion (%) (24 hours)
F1	1.05 ± 0.01	50.33 ± 0.15	20.41 ± 0.52	48.58 ± 3.27
F2	0.98 ± 0.007	14.39 ± 0.15	18.37 ± 0.54	52.03 ± 4.28
F3	0.99 ± 0.007	18.28 ± 0.17	15.40 ± 0.52	51.17 ± 3.15
F4	1.01 ± 0.006	24.44 ± 0.20	22.67 ± 0.57	55.27 ± 5.10
F5	0.96 ± 0.005	18.44 ± 0.20	24.03 ± 0.74	53.56 ± 4.20

hydrophilic gelling polymers (HPMC and Carbopol) swell due to hydration. The $NaHCO_3$ reacted with simulated gastric acid and generates carbon dioxide, which is entrapped by swelled polymer [51–53]. The density of F1 was slightly higher than the density of stomach content due to the lower thickness of the tablets in this formulation (Table 3 vs. Table 4). The density of the noneffervescent formulation (F4) was also found to be higher than F5 due to the lower



(a)



(b)

Figure 2: The percent swelling index (a) and photographs of swelled floating tablets after 8 hours (b).

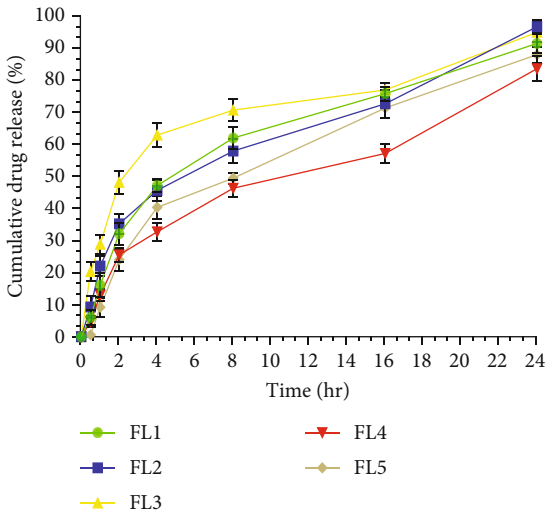


Figure 3: Release profile of levofloxacin from designed bilayer tablets: levofloxacin layer (FL).

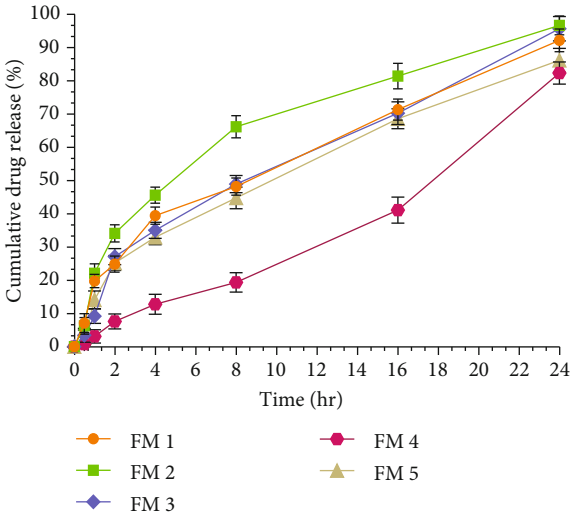


Figure 4: Release profile of famotidine from designed bilayer tablets: famotidine layer (FM).

Table 5: Release kinetics of levofloxacin and famotidine from bilayer floating tablets.

Drugs	Code	Zero order R^2	First order R^2	Higuchi model R^2	Korsmeyer-Peppas model R^2	K (min^{-1})	n	Release mechanism	BFM
Levofloxacin layer (FL)	FL1	0.682	0.963	0.971	0.969	21.6	0.46	Non-Fickian	HUM
	FL2	0.677	0.928	0.978	0.981	22.6	0.45	Non-Fickian	KPM
	FL3	0.199	0.878	0.850	0.959	34.9	0.32	Fickian	KPM
	FL4	0.815	0.934	0.976	0.978	14.5	0.54	Non-Fickian	KPM
	FL5	1.000	0.974	0.968	0.971	14.9	0.57	Non-Fickian	ZO
Famotidine layer (FM)	FM1	0.810	0.956	0.990	0.991	17.1	0.53	Non-Fickian	KPM
	FM2	0.681	0.972	0.977	0.979	22.9	0.46	Non-Fickian	KPM
	FM3	0.882	0.972	0.971	0.983	13.9	0.60	Non-Fickian	KPM
	FM4	0.970	0.910	0.791	0.981	1.31	1.29	Non-Fickian	KPM
	FM5	0.855	0.970	0.982	0.989	14.1	0.57	Non-Fickian	KPM

Note: best fitting model: BFM; zero order: ZO; Higuchi model: HUM; Korsmeyer-Peppas model: KPM.

thickness of the tablets. However, all formulations were able to float in the simulated gastric content due to the presence of sodium bicarbonate and lower density of gelled polymers (guar gum and xanthan gum) that provided sufficient buoyant force for floatation [54–56]. The floating lag time of all formulations (F2-F5) was below 25 seconds, except F1 which took almost 50 seconds to start floating on the surface of gastric content due to its higher density. The total floating time of effervescent (F1-F3) and noneffervescent formulations was in the range of 15-25 hours, thereby providing sufficient time to complete drug release and absorption in the gastric region [8, 18, 43, 57]. The total floating time of noneffervescent formulations was higher ($p \leq 0.05$) than effervescent formulations due to efficient wettability, higher swelling characteristics, and increased higher liquid retention, thereby replacing the air entrapped inside the floating tablets [8, 58, 59]. Generally, hydration and swelling of gelling polymers and the rate of generation of gas are key factors for inducing the floating of the tablets.

Table 6: Dissolution pattern comparisons.

Test vs. reference	Difference factor ($f1$)	Similarity factor ($f2$)
Levofloxacin profile comparisons		
F4 vs. F2	22.5	48.38
F5 vs. F2	16.64	53.93
Famotidine profile comparisons		
F4 vs. F2	52.57	27.75
F5 vs. F2	22.9	46.94

Table 7: Paired t-test results.

Test vs. reference	p value for levofloxacin	p value for famotidine
F4 vs. F2	5.34	3.97
F5 vs. F2	4.41	4.25

3.5. Swelling and Erosion Study. The swelling properties of tablets affect not only buoyancy but also the release of drugs and the adhesion abilities of tablets to the mucous membrane [53, 60]. The swelling of tablets increased gradually with time, and maximum swelling was achieved at the 8th hour [53, 61]. Figure 2 depicts that noneffervescent formulations (F4 & F5) swelled significantly more than effervescent formulations (F1-F3). The higher swelling of the noneffervescent formulation was due to more absorption capacity of gums with respect to other hydrophilic polymers [14, 62]. The hydrophilic tablet begins to swell due to the diffusion of water into the glassy HPMC material. As mentioned earlier, water plasticizes the polymer and lowers its glass transition temperature. When the glass transition temperature of a polymer decreases to ambient temperature, a change from a glassy state to a rubbery state occurs. As the water penetrates further into the tablet, a highly concentrated polymer solution called a gel layer is formed. The solvent continues to penetrate the tablet, and the gel layer and the dimensions of the swollen tablet increase significantly (Figure 3), which not only supports floating but also the release of drugs from designed tablets [63, 64]. The erosion of noneffervescent tablets was higher than effervescent tablets due to the hydrophilic nature of gum that erodes quickly and to a higher degree on contacting dissolution medium. However, the erosion of different formulations does not vary significantly ($p \geq 0.05$). Overall, less than 55% of erosion was observed in 24 hr. This suggests that bilayer floating tablets prolong the release of entrapped ingredients and slowly release them by erosion and diffusion mechanisms. Our data was consistent with previous studies where HPMC was used as a swelling polymer for the development of gastroretentive carrier tablets of alfuzosin hydrochloride and clarithromycin [53, 65].

3.6. Drug Release Behavior. Drug release studies are helpful to assess the reproducibility of drug release, stability, safety, efficacy, and quality of developed formulation. The levofloxacin and famotidine from both effervescent and noneffervescent tablets were released completely within 24 hours (Figures 3 and 4). The release of drugs from polymeric

Table 8: The stability parameters of drug and dosage form in optimized selected formulations.

Parameters	F2	F5	F2	F5	F2	F5
Time (days)	After 30 days		After 60 days		After 90 days	
Appearance	No changes	No change	No change	No change	No change	No change
Hardness (kg/cm^2)	6.81 ± 0.12	6.78 ± 0.11	6.79 ± 0.32	6.49 ± 0.22	6.69 ± 0.23	5.73 ± 0.21
Weight variation (mg)	594 ± 3.22	592.1 ± 3.83	593 ± 3.02	592.1 ± 3.33	591 ± 3.28	590.1 ± 3.13
Drug contents of levofloxacin (%)	95.58 ± 0.89	98.72 ± 0.48	95.49 ± 0.57	98.72 ± 0.48	94.58 ± 0.48	97.93 ± 0.41
Drug content of famotidine (%)	98.57 ± 0.64	97.88 ± 0.88	97.36 ± 0.54	97.38 ± 0.86	97.25 ± 0.49	97.08 ± 0.84
Floating lag time (second)	19.44 ± 0.15	22.40 ± 0.20	19.79 ± 0.13	22.98 ± 0.31	20.54 ± 0.25	24.40 ± 0.41
Total floating time (hours)	15.60 ± 0.82	24.33 ± 0.44	14.94 ± 0.62	24.33 ± 0.44	15.60 ± 0.74	23.91 ± 0.42
Swelling index (8 hours)	151.18 ± 1.18	209.38 ± 2.96	150.08 ± 1.11	207.28 ± 2.88	148.98 ± 1.04	206.97 ± 2.94
Erosion (%) (24 hours)	51.23 ± 3.35	54.11 ± 4.40	51.08 ± 3.23	53.89 ± 4.31	50.40 ± 3.10	52.99 ± 4.30

controlled-release noneffervescent floating bilayer tablets (F4–F5) was comparatively more retarded than effervescent systems (F1 to F3) [14]. The retarded drug release of noneffervescent systems was attributed to the slow dissolution of the polymeric gum matrix during swelling (Figure 2) [66, 67]. The presence of sodium bicarbonate as an effervescent component, in the effervescent tablets, is responsible for developing a large number of pores in the floating tablets. This brings in a relatively rapid release of drugs from the tablet compared to noneffervescent tablets [53]. Afterward, the data was fitted in different equations to elucidate the drug release mechanism. It was found that Korsmeyer-Peppas best describes the release mechanisms as elaborated by R^2 (regression coefficient) value of approximately 1. The n value depicted non-Fickian diffusion from both levofloxacin and famotidine layers, except F3 [22, 68]. The levofloxacin layer of F3 follows the Fickian diffusion due to the higher viscosity of HPMC K100 (Table 5) [69].

3.7. In Vitro Release Profile Comparison. The dissolution profile of the noneffervescent as tested formulations (F4 and F5) and effervescent as reference formulation (F2) was compared separately by applying the difference factor $f1$ and similarity factor $f2$ (Table 6). These results were not within the acceptable limit of $f1$ and $f2$, 1–15 and 50 to 100, respectively [41, 70]. Therefore, the dissolution profile of effervescent and noneffervescent formulations was dissimilar from each other.

3.8. Paired Sample t-Test. The result shows that the dissolution profiles of the noneffervescent formulation were statistically significantly different from the effervescent formulation (Table 7).

3.9. Stability Study. The stability of the drug and dosage form with respect to its properties is important to ensure the therapeutic performance of the developed dosage form during its shelf life. The study evaluated both the effervescent and noneffervescent systems for three months at a controlled temperature of 40 ± 2 °C and relative humidity of 75 ± 5% according to ICH guidelines [19, 41]. There were no significant ($p > 0.05$) changes in either the physicochemical properties of bilayer tablets or the drug content reduced significantly (Table 8).

4. Conclusion

Here, we successfully designed both effervescent and noneffervescent systems for the simultaneous delivery of levofloxacin and famotidine from bilayer tablets. The effervescent system was formulated with sodium bicarbonate in conjunction with Carbopol and three different grades of HPMC. The sodium bicarbonate in the optimized effervescent formulation (F2) was later replaced by guar gum and xanthan gum to design noneffervescent bilayer floating tablets. The formulation components were compatible with each other as indicated by ATR-FTIR analysis. All the formulations achieved optimum physicochemical properties, and both the effervescent and noneffervescent systems floated within less than 25 seconds with a total floating time of 14–24 hours. The drug was completely released from both tablets in 24 hours; however, the noneffervescent systems significantly retarded the drug release rates due to the presence of gums. In the stability study of 90 days, there was an insignificant change in the physicochemical properties of the tablets. It can be concluded that both the effervescent and noneffervescent systems could be an effective strategy for the concurrent delivery of drugs for site-specificity and controlled drug release properties. Thus, the fabricated tablets can be successfully used for their clinical studies.

Data Availability

All the data is presented in this article. However, raw or processed data required to reproduce these findings cannot be shared at this time due to technical or time limitations.

Conflicts of Interest

All authors declare no conflict of interest.

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