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Original Article

Development of a Floating Drug Delivery System for Prolonged Release of Metronidazole in the Stomach for Gastrointestinal Infection

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ABSTRACT

Introduction: Gastroretentive Drug Delivery System like floating tablets out performs traditional dosing forms. When compared to conventional tablets, floating tablets have higher bioavailability, higher drug concentration in the systemic circulation, and lower frequency of dose. Metronidazole floating tablets were formulated using a variety of polymer combinations by the direct compression process. Polyvinyl pyrrolidone (PVP K30), Guar gum, and Xanthum gum are the polymers employed in the composition. **Materials and Methods:** The drug-excipient compatibility was determined by FTIR Spectroscopy and a total of nine formulations of floating tablets have been prepared. Among these, an appropriate formulation was chosen. The angle of repose, Bulk, and tapped density of metronidazole tablet mixes were previously evaluated. Carr's index, Hauser's ratio, physical appearance, hardness, weight fluctuation, friability, floating qualities, and *in-vitro* dissolving testing were used to characterize the tablets. **Results:** The flow properties were found optimum in all the pre-compression parameters and hence suitable for the direct compression method. The evaluation of tablets showed a good floating effect of about 4-7 hr in almost all the formulations. The floating tablets showed drug release of more than 90% after 6 hr and hence gastric retention was achieved. The study findings revealed that formulation 3 was the best, with a floating lag time of less than a minute and more than 7 hr of retention in the gastric pH with optimum floating behavior and drug release in the stomach. **Conclusion:** Hence, the prepared floating system involving a combination of polymers was found to be a reliable tool for gastric retention.

Keywords: Metronidazole, Floating tablet, Polyvinyl pyrrolidone (PVP K30), Guar gum.

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INTRODUCTION

The most common method of medication administration is oral administration. Approximately half of all drugs on the market are delivered orally, which has several benefits, including fewer patient complaints, as well as being easy, inexpensive, and safe to use.[1] However, drawbacks such as a brief stomach retention period, a short half-life, and rapid elimination from the circulatory system are present. As a result, they need repeated doses to achieve the desired therapeutic effect. Oral sustained-controlled-release preparations were developed to overcome this limitation by gradually releasing the medication into the intestinal system while maintaining an efficient drug concentration in systemic circulation for an extended period of time. This decreases the frequency of doses and boosts the drug's bioavailability. This is especially beneficial for medications that are absorbed through the digestive system.[2] These pharmaceutical administration systems have two significant drawbacks: 1) a brief Gastric Retention Time (GRT) and 2) an unpredictably brief Gastric Emptying Time (GET). Both of these variables may contribute to poor drug clearance in the absorption zone of pharmaceutical formulations leading to a decrease in the effectiveness of the supplied dosage.[3] The medicine delivery system must produce a site-specific orally administered controlled-release dosage form in order to achieve a longer stomach retention time. Extended stomach retention may increase medication bioavailability. Drug waste was reduced, and the solubility of medications that are less soluble in high pH conditions has been improved.[4-6] Gastroretentive Drug Administration (GRDD) is a technique for prolonging the time a drug spends in the stomach, allowing for site-specific medication delivery for local or systemic effects in the

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upper part of the gastrointestinal tract. This delivery mechanism has the ability to stay in the digestive system for a long duration, significantly increasing the drug's gastric retention time.[7,8] Drugs with a low absorption rate in the lower GI tract, that are unstable and poorly soluble at alkaline pH, that have a short half-life, and that act locally in the gastrointestinal system.[9-12] Over the last few decades, numerous GRDD techniques have been developed and refined, including high-density systems, low-density systems, super porous hydrogels, magnetic, ion-exchange mucoadhesive, raft-forming, and expendables systems.[11-14] The present research examines many Gastroretentive strategies that have emerged as cutting-edge methodologies in recent years, as well as their future prospects.

MATERIALS AND METHODS

Materials

Metronidazole was obtained from Carbanio, Hydroxypropyl Methylcellulose (HPMC) was obtained from Carbanio, Sodium bicarbonate was obtained from SRL Chemicals, Polyvinyl Pyrrolidone was obtained from SRL Chemicals, Citric acid was obtained from SRL Chemicals, Talc, Magnesium stearate and Guar gum were obtained from fine research Chemicals. All the chemicals are used without further purification.

Methods

Calibration of metronidazole

The absorbance of the series of diluted solutions with 2 µg/mL to 10 µg/mL concentrations will be measured against a blank of 0.1 N HCl/ at 275 nm. UV-visible Spectrophotometry was used to calculate the absorbance of known samples. The calibration graph was created by plotting concentrations on the x-axis and related absorbances on the y-axis. The regression coefficient (R^2) and straight line equation (Y= mx + c) were calculated with the application of the Microsoft Excel statistical function program.

Preformulation Studies

Bulk Density

Bulk density can be determined by taking 25g of the powder into 100mL of the measuring cylinder. The measurement of the drug in the volumetric cylinder is noted. The obtained value represents bulk volume. Bulk density can be determined using the formula bulk density = weight of the powder (g) / Bulk volume (mL).[15]

Tapped Density

Tapped density can be determined by tapping the volumetric cylinder of the drug for 1-2 min and the measurement in the measuring cylinder is noted. The obtained value represents tapped volume. Tapped density was calculated by the formula Tapped density = weight of the powder (g) / tapped volume (mL).[16]

Carr's index

The compressibility index is another name for Carr's index. The compressibility of a powder is related to its relative flow rate, cohesiveness, and particle size. It is a significant number derived from bulk and tapped density. Using the following formula, the compressibility index is determined-Carr's Index (%) = {(Tapped density)-(Bulk density)/ (Tapped density} ×100.[17]

Hauser's ratio

Hausner's ratio is a measurement of a powder's capacity to flow. The provided equation is used to determine Hausner's ratio – Hausner's ratio = Tapped density / Bulk density.[18]

Angle of repose

The angle of repose is the greatest possible angle between the surface of a pile of powder and the horizontal plane. The improper flow is caused by the angle of repose used to measure frictional force. The angle of repose was determined using the funnel stand method. Using the provided equation, the average value is taken, and the angle of repose is determined, "tan θ = h/r; θ = tan-1 (h/r)" [θ = Angle of repose; h = height of the heap; r = radius of the heap].[19]

Fourier transform infrared spectroscopy

The KBr disc method was used to investigate the interaction between excipients and drugs, and the values ranged from 4000 to 400 cm^{-1}. The test samples were examined after being dispersed in Potassium Bromide (KBr) powder. From the FTIR spectrum, the positions of the main functional groups of medicines' FTIR bands are detected and then interpreted.[20,21]

Preparation of metronidazole Floating tablet by direct compression method

A direct compression approach was used to make metronidazole floating tablets. Metronidazole floating tablets contain sodium bicarbonate as a gas-generating agent, as well as polymers such as HPMC, PVP, Xanthan gum, and guar gum. A total of 9 formulations are designed by changing the concentration of PVP, Xanthan gum, and guar gum with the set of 3/3 (Table 1). Except for magnesium stearate and talc, each item was accurately measured and passed through sieve #40 before being thoroughly combined. The powder combination was lubricated using magnesium stearate and talc. To prevent stacking, the lubricated tablet mixture was punched using a multi-tool, 8-station rotating punching machine in a laboratory at a constant speed with a high compression capacity.

Table 1: Formulation design of Effervescence Floating Tablets of Metronidazole.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	200	200	200	200	200	200	200	200	200
HPMC	175	165	155	175	165	155	175	165	155
PVP K30	30	40	50	-	-	-	-	-	-
Guar Gum	-	-	-	30	40	50			
Xanthan Gum	-	-	-	-	-	-	30	40	50
Sodium Bicarbonate	50	50	50	50	50	50	50	50	50
Citric Acid	25	25	25	25	25	25	25	25	25
Magnesium Stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10

S.No	Concentration (µg/ml)	Absorbance
1	2	0.174 ± 0.002
2	4	0.273 ± 0.004
3	6	0.412 ± 0.007
4	8	0.567 ± 0.002
5	10	0.644 ± 0.005

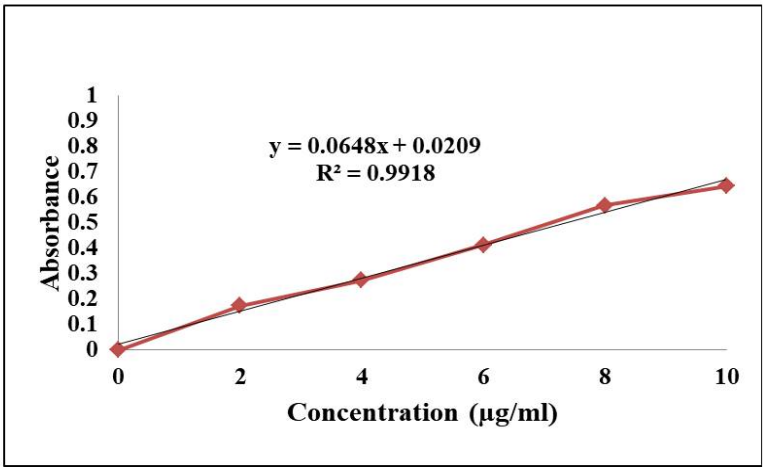

Figure 1: Calibration curve of metronidazole.

Post-Compression Evaluation of Effervescence Floating Tablets of Metronidazole

General appearance of the tablets prepared were checked for uniform color, size, and shape. The surface of the tablets must be free from cracking and chipping. The thickness of the tablet was measured using Vernier caliper. Three tablets were selected at random from each batch and average thickness in mm was reported. The hardness of the tablet is evaluated in order to test the prepared tablet to withstand damage while traveling and storage. Each formulation's six tablets are swallowed and their hardness is measured. Utilizing a Monsanto tablet hardness tester, it is estimated. The unit of measurement is kg/cm^2. The friability of the tablets was evaluated using the Roche friabilator. It was turning at a 25 rpm speed. The friabilator chamber was filled with five pills that had been weighed collectively. Due to the tablets falling freely inside the friabilator's chamber, the tablets were subjected to rolling there. The pills were removed from the friabilator after 100 rotations or 4 min, and the intact tablets were once more weighed collectively. The permitted friability limit is 1.0%. The percent friability was determined using the following formula "F = (W1-W2)/W1 x 100" [W1 = weight of the tablets before the test, W2 = weight of the tablets after the test]. 20 pills were separately weighed to check for weight variation. The total weight of all tablets was used to calculate the average weight. The average weight was contrasted with the individual weights. The weight variation's percentage difference should fall within the permitted range (7.5%).

In vitro buoyancy/ floating study

All of the formulations were subjected to *in-vitro* buoyancy tests. In a 100 mL beaker with 0.1N HCl pH 1.2, the tablets from each formulation that were randomly chosen were retained. Total floating time was calculated as the amount of time the dosage form spent continuously resting on the medium's surface. Floating lag time was the amount of time it took for the tablet to rise to the Surface and Float (TFT).

In vitro dissolution studies and determination of Drug release kinetics

Metronidazole floating tablets were the subject of *in vitro* dissolution tests utilizing USP class II equipment (paddle type). After adding 900mL of 0.1 N HCl pH 1.2 to the dissolution vessel, the medium's temperature was set to 370.5°C. One tablet was put into each dissolution vessel after the paddle's rotating speed was set to 50 rpm. For eight hours, 5mL of the solution was removed from the dissolving vessels every hour, and samples were

replaced with 5mL of brand-new dissolution medium. Using a UV-spectrophotometer, the solution's absorbance at 275 nm was determined. The outcome of the *in-vitro* dissolution research of the formulation, which displays good characteristics, was examined in accordance with multiple kinetics equations to determine the precise mechanism of drug release from the dosage form (Zero order, First order, Higuchi model, and Korsmeyer-Peppas).

RESULTS

Determination of Calibration curve

Figure 1 shows the calibration curve of Metronidazole. A linear curve was obtained.

Pre-formulation Studies

The principle FTIR characteristic peaks of Pure Drug Metronidazole 1369.50 cm^{-1}, 1535.39 cm^{-1}, 1479.45 cm^{-1}, 1155.40 cm^{-1} which represents NO_2 (stretching) Symmetric, NO_2 (stretching) Asymmetric, C=C Aromatic, C-N imidazole groups respectively, and the other excipients HPMC K15M and PVP were retained in the FTIR spectrum of the physical combination of the Metronidazole with every excipient, as shown in Figure 2.

Evaluation of Pre-Compression Parameters

The funnel method was used to calculate the angle of repose for all 9 tablet formulation mixes. The readings were in the 28.7° to 32.9° range, showing that the tablet blends flew well. Table 2 lists the values for the angles of repose for each of the nine formulations. It was discovered that the bulk densities of the tablet blends were within the permitted ranges, allowing for satisfactory flow qualities. The tapped density was likewise determined to be within the permitted ranges for the blends of all nine tablet formulations, similar to the bulk density. This makes it possible to compress tablets effectively using the direct method. All of the formulations' Carr's indices, which range from 6.25% to 14.28%, were discovered to be within acceptable bounds, suggesting excellent to good flow qualities. All of the formulations' Hausner's ratios were determined to be between 1.05 and 1.17, falling within the permitted range and showing that the blend had satisfactory flow characteristics. All the values are given in Table 2.

Evaluation of post-compression parameters

The compressed tablets were white and spherical shaped. The surface of the tablets was smooth, uniform and free from cracking and chipping. The tablets were rigid and evenly compressed similar to the standard dimensions of the marketed tablet formulations. To regulate the release of the highly soluble

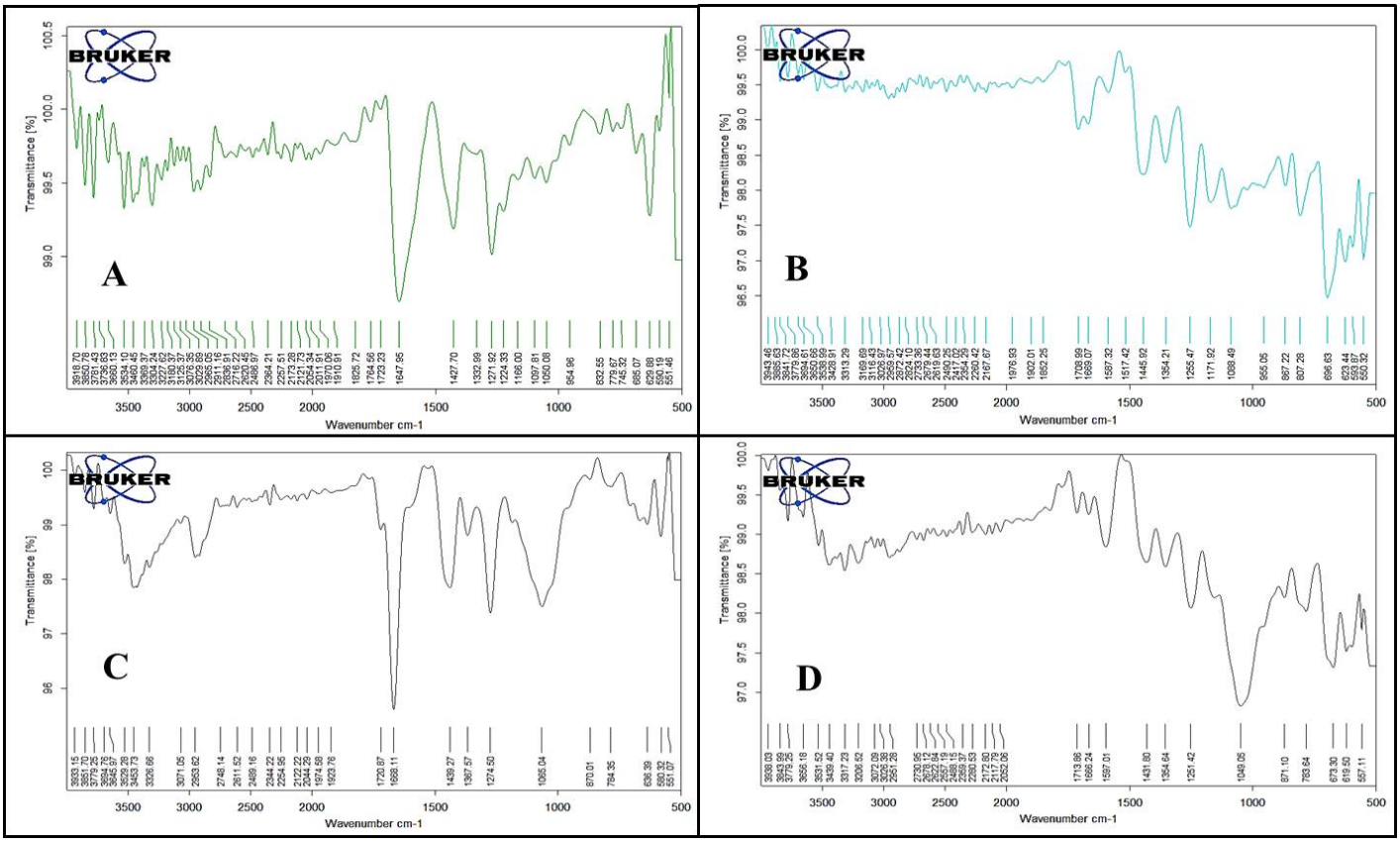

Figure 2: FTIR spectrum A) FTIR spectrum of physical mixture of Metronidazole with HPMC K15M and PVP; B) FTIR spectrum of Metronidazole; C) FTIR spectrum of physical mixture of Metronidazole with HPMC K15M and Guar gum; D) FTIR spectrum of physical mixture of Metronidazole with HPMC K15M and Xanthum gum.

Table 2: Pre-compression evaluation of Effervescence Floating Tablets of Metronidazole.

Formulation code	Angle of Repose (^{0}) (*n*=3)	Bulk density (g/mL) (*n*=3)	Tapped density (g/mL) (*n*=3)	Carr's index (*n*=3)	Hausner's ratio (*n*=3)
F1	29 ± 0.356	0.31 ± 0.03	0.28 ± 0.03	12.5	1.16
F2	30 ± 0.097	0.35 ± 0.05	0.31 ± 0.05	14.28	1.13
F3	30.4 ± 0.235	0.33 ± 0.08	0.30 ± 0.08	8.82	1.05
F4	31.2 ± 0.132	0.31 ± 0.04	0.28 ± 0.04	9.37	1.09
F5	30 ± 0.232	0.35 ± 0.02	0.31 ± 0.02	9.67	1.13
F6	32 ± 0.104	0.33 ± 0.05	0.32 ± 0.05	6.25	1.13
F7	31 ± 0.176	0.36 ± 0.03	0.28 ± 0.03	13.5	1.10
F8	32.6 ± 0.203	0.35 ± 0.02	0.29 ± 0.02	7.8	1.10
F9	30 ± 0.320	0.31 ± 0.04	0.28 ± 0.04	8.82	1.05

*n=3; All the values are expressed in terms of mean ± SD.

Table 3: Post Compassion evaluations of Effervescence Floating Tablets of Metronidazole.

Formulation Code	Hardness (kg/cm^2) [n = 5]*	The average weight of the tablet (mg) [n = 10]*	Friability (%) [n = 5]*	Floating lag time (min)	Floating time (h)
F1	3.32±0.14	497.30±1.36	0.72±0.24	02.40	6.17
F2	3.254±0.16	499.25±1.13	0.69±0.16	01.36	6.05
F3	3.58±0.15	498.20±1.16	0.70±0.12	00.53	7.35
F4	4.59±0.16	497.80±1.15	0.56±0.11	02.15	6.08
F5	4.78±0.14	498.35±1.12	0.64±0.12	04.06	5.43
F6	4.52±0.12	499.05±1.11	0.64±0.09	05.03	5.17
F7	3.46±0.13	499.82±1.09	0.69±0.10	07.04	04.23
F8	4.22±0.15	497.90±1.08	0.71±0.13	07.24	04.45
F9	4.38±0.14	498.32±1.02	0.65±0.13	07.42	04.22

Table 4: *In vitro* release study of Effervescence Floating Tablets of Metronidazole.

Time (hours)	Cumulative percentage drug released (%) [*n*=3]								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	21.18	28.125	14.23	24.65	17.7	7.29	20.83	11.37	6.94
2	35.18	35.22	38.62	42.15	31.69	21.22	24.76	32.62	22.6
3	52.74	45.83	49.251	52.8	63.12	42.17	45.73	50.38	46.34
4	73.86	53.03	56.467	63.5	80.83	63.27	63.35	64.51	59.1
5	95.1	84.57	63.722	77.74	88.22	81.06	81.06	85.22	86.5
6	99.1	98.92	84.9	92.06	95.65	91.23	91.23	90.64	98.44

drug, higher tablet hardness is necessary. Although we are using high-viscosity polymers, tablets with high hardness are essential to delay drug delivery. The tablet formulations exhibit sufficient hardness that falls within the permissible limits and the values are tabulated in Table 3. The weight variation of the prepared tablets was determined. The percentage departure from the mean weight was discovered to be within the permitted range. The percentage deviation of the 500 mg tablet is not more than 5%. All values are present and within acceptable bounds. Formulation 3 was found to have excellent *in-vitro* floating qualities, with a good floating lag time of less than one minute and a total floating time of more than 7 hr (Table 3).

In-vitro dissolution studies and release kinetics

According to the findings of the *in-vitro* release investigation (Figure 3), all formulations were capable of retention in the

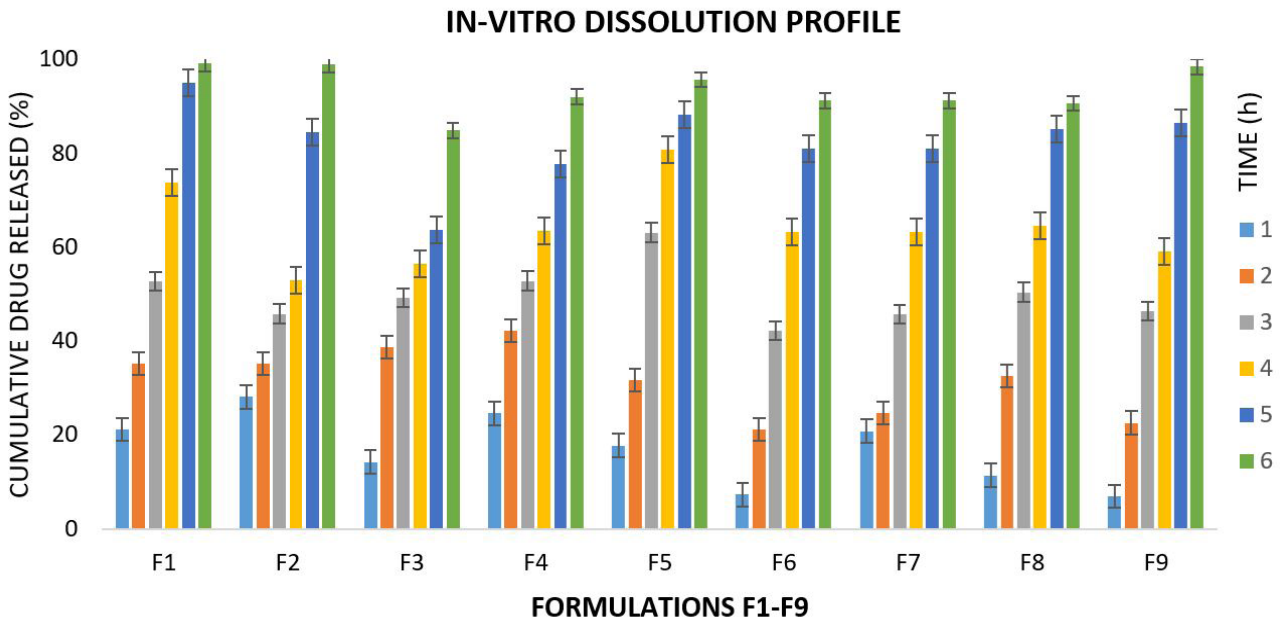

Figure 3: *In vitro* Release of Metronidazole floating tablet in respect of time and cumulative % drug release.

Table 5: *In vitro* release kinetic model studies Metronidazole floating tablet.

Formulation Code	Zero-order	First order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas	Korsmeyer n (Release exponent)	Release Kinetics
F1	0.9806	0.9427	0.9728	0.9441	0.9894	0.99538	Non-Fickian
F2	0.9346	0.981	0.8725	0.8134	0.8951	0.957043	Non-Fickian
F3	0.9346	0.981	0.8725	0.8134	0.8951	0.957343	Non-Fickian
F4	0.9949	0.945	0.984	0.9479	0.9951	0.706126	Non-Fickian
F5	0.9415	0.8646	0.9683	0.9889	0.9696	0.986709	Non-Fickian
F6	0.9908	0.889	0.9882	0.9781	0.9915	0.93202	Non-Fickian
F7	0.9799	0.9549	0.9506	0.9579	0.9383	0.75631	Non-Fickian
F8	0.9845	0.9392	0.9528	0.9471	0.9901	0.67390	Non-Fickian
F9	0.9915	0.883	0.9757	0.919	0.9893	0.92312	Non-Fickian

gastrointestinal fluid by a floating action. Within six hours of dissolving, only the F3 formulation released the lowest percentage of the medication at a constant rate, whereas F1, F2, and F9 released the most (Table 4). The nature of the drug release from floating was determined by fitting the collected dissolution data to several dissolution kinetic models. The regression coefficient values (R^2) derived from the release kinetic models demonstrated that all formulations exhibit zero-order release (R^2 closest to 1) Table 5. This model best represents the release of metronidazole medicines in the stomach and small intestine. The Korsmeyer-Peppas model for the dissolution data offers the release exponent value of the model, from which the sustained release tablet release mechanism may be understood. Thus, the R^2 values and n exponent from the Korsmeyer-Peppas plot are calculated. All nine formulations had n values greater than 0.5, indicating that Non-Fickian diffusion governs the release of the medication. It is also shown as anomalous diffusion.

DISCUSSION

As a result of the drug-excipient compatibility study, the FTIR spectrum of the physical combination matched that of the drug in the spectrum of Metronidazole. Metronidazole is compatible with HPMC K15M and PVP, indicating that there is no physical contact between the medicine and the excipients. Nine different formulations of floating tablets were designed and in order to ensure good flow qualities, pre-compression parameters of the tablet blends, such as angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio were examined and were found to be within the permissible limits. Post-compression evaluation for general appearance, hardness,

weight variation, friability, and floating time of all the nine tablet formulations were assessed. All values were within the acceptable bounds and formulation 3 was found to have excellent *in-vitro* floating qualities, with a good FLT and TFT. To ascertain the drug release and observe the retention of the floating tablets, *in-vitro* dissolving tests were carried out. The dissolving patterns of the formulations were also fitted into various kinetic models to study the nature of drug release and it was found that the formulations were governed by Non-fickian/anomalous diffusion drug release kinetics. The formulations F1, F2, and F3 exhibit better drug release, hardness, low friability, good buoyancy lag time, and total floating time, according to the results.

CONCLUSION

The current work focused on the formulation of Metronidazole floating tablets using various polymer combinations to improve gastric retention of the drug. The tablets were prepared by direct compression method employing PVP K30, Guar gum, and Xanthum gum as polymers, and the floating behavior was studied. Eventually, the prepared effervescent floating tablets containing Metronidazole were found to deliver delayed and complete drug release over 6 hr. The floating tablets of Metronidazole were successfully formulated and based on the obtained results, it can be concluded that the formulation F3 could efficiently release the drug over a prolonged period.

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CONFLICT OF INTEREST

The authors declare that there is to conflict of interest.

ABBREVIATIONS

FLT: Floating Lag Time; **GET:** Gastric emptying time; **GI:** Gastro-intestinal; **GRDD:** Gastroretentive drug delivery; **GRT:** Gastric retention time; **HPMC:** Hydroxy propyl methyl cellulose; **PVP:** Polyvinyl pyrrolidone; **TFT:** Total floating time.

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