



ORIGINAL ARTICLE

Formulation and evaluation of ranitidine floating tablets using different polymer combinations

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Abstract

The current study was designed for preparation of gastro-retentive floating tablet of ranitidine HCl by using polymers ethyl cellulose (EC) and hydroxypropyl methylcellulose and xanthan gum (XG) in an attempt to delay its gastric retention time. The tablets were manufactured by direct compression technique. The outcome of varying concentrations of HPMC, XG and EC on drug release was evaluated. The preparation was augmented on the basis of adequate tablet qualities, total duration of floating, floating lag time and *in-vitro* drug release. The prepared tablets found to have optimal hardness, low friability, consistent weight uniformity and thickness. Dissolution studies and floating lag time results indicated that formulation F5 showed better and controlled release of drug. The optimized formulation F5 containing 18% HPMC 8% ethyl cellulose and 5% xanthan gum showed 69% drug release within 6 hours, floating lag time was about 1 second and total floating time was 10 hours. The release mode of actions were discovered and elucidated with zero, first order, Higuchi release model and Korsmeyer-Peppas release model. FTIR spectroscopy studies showed no interaction between used polymers and drug. Non-effervescent floating delivery of drug could be a favorable method to attain *in-vitro* buoyancy. Current approach may enhance the gastric retention time of Ranitidine HCl up to 10 hours, thereby improving its antiulcer activity, thus its bioavailability.

Keywords

Drug release kinetics
Floating tablets
Gastro retentive drug delivery system
Ranitidine HCl

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Introduction

Gastric emptying for dosage forms is a highly variable process, specifically for those dosage forms that have a stomach stay for more than that of conventionally prepared dosage forms (Hirtz, 1985). Several variables should be considered while designing a controlled release dosage form in order to give optimal absorption and bioavailability profile. For instance, the incapability to bound dosage forms to the

desirable area within GIT. Absorption of drug is proportional to its mucosal contact time with small intestine (Desai & Bolton, 1993). For Controlled release, drugs were designed in such dosage form to drug release at programmed rate for maintaining particular concentration of drug specific time period with minimal side effects (Yeole et al., 2005). The Gastric retentive systems are so formulated in an attempt to retain in GIT for a longer time period ultimately enhances the retention time of the drugs in

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gastric region hence increasing their potential for absorption (Mayavanshi & Gajjar, 2008). Many different approaches are available that protract the gastric retention, including floating drug delivery systems (FDDS) (Oth et al., 1992).

Floating system, a density controlled system, increases the retention time of a drug in GIT. For this we use several approaches like, muco-adhesion, gas generating, high density and low density systems. Floating improves the efficacy of tablet by controlling rate of drug release and reduces dose frequency (Pawar et al., 2011). Floating systems can be either non-effervescent or effervescent floating drug delivery systems. Non-effervescent approach utilizes various polymers in providing the floating drug delivery system. Many different types of the polymers namely ethylcellulose, chitosan, xanthan gum, guar gum and moringa gum etc. have been discovered to form such a drug delivery system (Singh & Kim, 2000).

Hydroxy propyl methyl cellulose is cellulose ether polymer of non-ionic nature. It may be fibrous or in granular powder form which is soluble in cold water and is insoluble in hot water (Higuchi & Hussain, 1978). HPMC has been in use as a tablet binder, as a film coater and also to produce matrix tablets of extended release. It is also used for synthesis of the oral controlled drug delivery system. It has excellent characteristics of compression and has good swelling properties, which helps in the formation of gel layer (external) which further control the release of drug (Desai & Bolton, 1993).

Ethyl Cellulose is water insoluble at low pH and can be used as taste masking agent, for moisture barrier applications and also in controlled release dosage forms (Rekhi & Jambhekar, 1995). Due to the differences of polarity between ethyl group of EC and the oxygen from water, it can take up water. Ethyl cellulose decreases the density of the floating tablets (Agrawal et al., 2003). Xanthan Gum is sensitive to pH and shows biocompatibility and bioadhesiveness. It is capable to create a large boost in viscosity (Rosalam & England, 2006). Unlike other gums, it is very stable under an extensive range of temperatures and pH. It has been extensively investigated as a possible polymeric material in diverse floating drug delivery technology (Barrere et al., 1986).

Ranitidine HCl is an H₂ receptor antagonist of histamine and indicated in gastric ulcer, gastroesophageal reflux, and Zollinger-Ellison syndrome (Dave et al., 2004). The biological half life of drug is 2 to 3 hours, which favors this to form sustained release dosage form. It is strongly basic drug having pKa 8.08, bioavailability of the drug is 60% and protein binding is 10 to 19%. The purpose to delay its stomach release was not only to extend its pharmacological action but also minimize possible side effects (Daly et al., 1981).

Floating non-effervescent tablets of Ranitidine HCl were formulated in this study. Pre-compression parameters such as repose angle, tapped density, bulk density, and compressibility index and after compression parameters such as, thickness, weight variation, friability, hardness, drug content and *in-vitro* drug release were investigated. Dissolution studies were performed in 0.1N HCl solution. By applying the release kinetic models release pattern of drug. Moreover, FTIR was performed to investigate the drug-polymer interaction.

Materials and Methods

Chemicals: Hydroxypropyl methylcellulose, Ethyl cellulose, Xanthan gum, Lactose, Talc (glidant) and Magnesium stearate (lubricant) were purchased by Merck. Moreover, Hydrochloric acid, Potassium hydrogen and sodium hydroxide phosphate were also procured by Merck and the drug Ranitidine HCl was gifted by Akson Pharmaceutical, Mirpur. All chemicals were of analytical grades.

Instruments: UV spectrophotometer, paddle (Apparatus II) dissolution apparatus, disintegration apparatus, analytical weighing balance, Eurweka hardness tester, vernier calipers, roche Friabilator and single punch tablet compression machine.

Method of preparation: Eight preparations of non-effervescent floating tablets of Ranitidine HCl were formulated by using direct compression method using polymers namely Hydroxypropyl methyl cellulose, Ethyl cellulose, Xanthan gum, excipients such as lactose, magnesium stearate and talc. Firstly, all ingredients were weighed accurately on weighing balance and were then passed through sieve no. 40. The drug, HPMC, EC, XG and lactose were mixed properly in a pestle and mortar in an attempt to get a uniform tablet blend. Finally, talc and magnesium stearate were mixed with the so obtained blend. The blend was compressed into round tablet using Rotary tablet punch machine (Mahapatra & Vidyasagar). The different formulations were labeled as F1–F8, the formulae of which are given in table no. 1.

Pre-compression studies: Formulations prepared for compression were subjected for pre-compression parameters to study the flow properties of powders (repose angle, tapped density, bulk density, Hausner's ratio and compressibility index).

Angle of Repose: To measure repose angle of weighed powder, method of fixed funnel was used. Funnel was stationary with the help of a supporting stand such that the tip of the funnel remained at 10cm above the horizontal surface. A circular-dish of known radius (*r*) was positioned on a plane horizontal surface centered beneath funnel tip, having sharp edges, and the diameter of its cone base was denoted as "D". Powder

Table 1: Composition of various formulations.

Ingredients per tablet	F1	F2	F3	F4	F5	F6	F7	F8
Ranitidine HCl (mg)	168	168	168	168	168	168	168	168
HPMC(mg)	54.5	30	30	54.5	54.5	30	54.5	30
Ethyl Cellulose(mg)	40	40	40	40	24.5	24.5	24.5	24.5
Xanthan Gum (mg)	8	8	16	16	16	16	8	8
Lactose(mg)	37	177	147	7	57	197	87	227
Magnesium stearate(mg)	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Talc (mg)	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Total weight (mg)	300	300	300	300	300	300	300	300

was filled in the funnel and the funnel tip was obstructed with thumb which was then immediately removed. Powder was permitted to fall through a funnel over a petri dish till the excess powder slide down at the sides of the petri dish. Vertical height (h) of the heap was obtained. The repose angle was calculated by given formulae (Lachman et al., 1976).

$$\Theta = \tan^{-1} \left(\frac{2H}{D} \right) \quad \text{Eq (1)}$$

Bulk Density: Apparent bulk density was evaluated by torrential drug excipients mixture into a graduated cylinder and computing the weight and volume (Rao et al., 2012).

$$D_b = M/V_b \quad \text{Eq (2)}$$

Whereas, D_b depicts bulk density, M for mass and V_b is bulk volume. The unit of bulk density is g/ml

Tapped Density: To find out the tapped density the graduated cylinder was mechanically tapped containing the powder sample. The initial powder volume was observed, marked at the graduated cylinder and was tapped on to the hard and smooth impervious surface, until the mass or volume changes became constant. The tapped density was determined by following formula (Rao et al., 2012).

$$D_t = M/V_t \quad \text{Eq (3)}$$

Whereas, D_t depicts tapped density, M for mass and V_t is for tapped volume.

Carr's Compressibility Index: It was calculated by importing previously received data of bulk and tapped density into the following equation (Rao et al., 2012).

$$C.I = (D_t - D_b)/D_t \times 100 \quad \text{Eq (4)}$$

Hausner's Ratio: It was calculated by inducing values of bulk and tapped density into the following formula:

$$H.R = D_t / D_b \quad \text{Eq (5)}$$

Post compression studies: Different post formulation tests like thickness, diameter, hardness, weight variation and friability for each batch were conducted

separately. Moreover, *In-vitro* buoyancy test and dissolution were conducted on 8 formulations.

Thickness and diameter: Ten tablets were selected randomly from each formulation. Thickness and diameter were measured by using digital vernier calipers (Patel et al., 2012).

Weight variation: From each batch twenty tablets were selected randomly and their average weights were determined. Percentage weights and their deviations were calculated and were compared with USP specifications (John Wesley et al., 2014).

Hardness test: Ten tablets were nominated randomly and determined tablet hardness from each batch, by using the Eurweka hardness tester. Unit of hardness was Kg/cm^2 (Thulluru et al., 2015).

Friability test: It was performed according to the USP specifications using Roche Friabilator. Tablets weight was less than 650 mg so a random sample of whole tablets corresponding to 6.5grams was de-dusted and then was accurately weighed. After weighing, tablets were de-dusted and placed in a drum of Roche Friability Tester. Drum was rotated for 4 minute at 25 rpm and tablets were removed after 4 minutes, de-dusted and then were accurately weighed. The percentage weight loss was determined by using this equation (Malviya et al., 2010).

$$F = W_{\text{initial}} - W_{\text{final}} / W_{\text{initial}} \times 100 \quad \text{Eq (6)}$$

Percentage loss of tablets less than 1% is considered acceptable according to the USP.

In vitro buoyancy test: *In vitro* buoyancy was attaining by floating lag time (FLT). 3 tablets from each formulation were randomly selected. The tablets were taken in a beaker having 200 ml of 0.1 NHCl (Malviya et al., 2010). The time necessary for the tablet to go up to the surface and then float was floating lag time (FLT). The time stage at which tablets remain buoyant was measured as Total Floating Time (TFT) (Mishra & Rana, 2009).

Content uniformity: The prepared formulation of Ranitidine HCl was weighed and crushed. Powder equivalent to Ranitidine HCl (150mg) was weighed and shaken with 100 ml of 0.1 NHCl in 100ml volumetric flask and filtered with Wattsman filter paper No. II. The aliquot (1ml) was taken and its volume was made with

0.1N HCl upto 100ml having pH 1.2 while absorbance was taken at 313nm using UV spectrophotometer. Content of drug was evaluated by using standard curve of Ranitidine HCl (Sharma et al., 2011; Thulluru et al., 2015).

Preparation of standard curve of Ranitidine HCl: Ranitidine Hydrochloride was dissolved in 0.1 NHCl and volume was made up to 100 ml in volumetric flask. From the stock solutions 5 dilutions (10, 20, 30, 40 and 50 μ g/ml) were prepared. Each solution absorbance was measured at 313 nm using UV spectrophotometer by using reference standard of 0.1N HCl. The standard curve was plotted by applying data in MS Excel format as presented in figure 1.

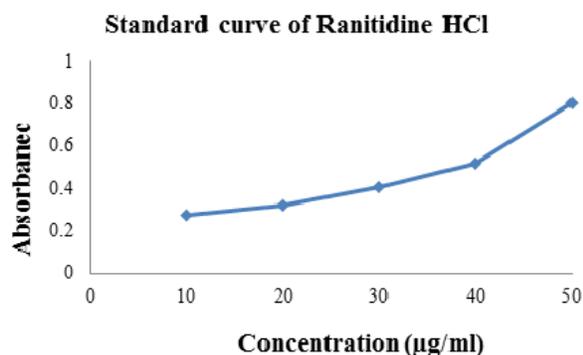


Figure 1: Standard curve of ranitidine HCL.

In vitro dissolution test: The rate of release of Ranitidine from floating tablets was evaluated by paddle method from United States Pharmacopoeia (USP) dissolution apparatus II (paddle method). The dissolution test was performed using 0.1 NHCl (900ml) at 37°C \pm 0.5 for 6 hours at 50rpm. Aliquot equal to 5ml was taken at particular time intervals and the samples were substituted with renewed dissolution medium. The samples were filtered and diluted to a suitable concentration with 0.1 NHCl. These solutions absorbance was measured at 313 nm using a UV spectrophotometer. Cumulative percentage of release of drug was determined using the equation obtained from a standard curve (Szepes et al., 2008).

Analysis of release pattern: Drug release analysis mechanism from a dosage form is significant but

complex procedure and is almost obvious in floating systems cases. The release drug from FDDS was defined by using zero, first order kinetics and Higuchi release model. The mode of action of release of drug from FDDS was studied by using Korsmeyer Peppas equation (Kumar et al., 2013).

FTIR spectroscopic analysis: Fourier transform infrared spectroscopy (FTIR) was performed for pure Ranitidine HCl, HPMC, EC, xanthan gum and sample formulation F5. Samples of floating tablet, pure Ranitidine HCl, HPMC, EC and xanthan gum were rumbled in an agate mortar with pestle. The crumpled material was mixed with potassium bromide (Merck IR spectroscopy grade) in 1:100 ratios and dried at 40°C. Then the mixture was crushed to a 12 mm semitransparent disc by applying 65 kN pressure (by Pressure gauge, Shimadzu) for 2minutes. The FTIR spectrums, over the range of 4000-400 cm^{-1} wavelength were documented using FTIR spectrometer (FTIR 8400 S, Shimadzu) (Saritha et al., 2013).

Results

Pre-compression studies: Formulations prepared for compression were subjected for pre-compression parameters to study the flow properties of powders (repose angle, tapped density, bulk density, Hausner's ratio and compressibility index). Results are described in table 2.

Post compression parameters: Different parameters after compression like thickness, hardness, diameter, weight variation, friability and content uniformity were evaluated. Results are described in table 3.

In vitro buoyancy studies: All the tablet formulations were prepared by non-effervescent approach. *In vitro* buoyancy of tablets was determined in 0.1 NHCl and the results were presented in Table 4.

In vitro dissolution studies: *In vitro* dissolution studies were performed in 0.1 NHCl (pH 1.2) by using USP type II dissolution apparatus (paddle apparatus). Effects of various ingredients and their concentration on drug release were studied and presented in table 5.

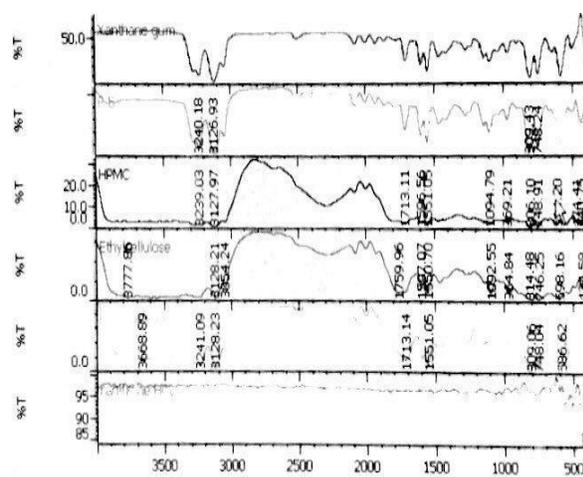
Fourier transform infrared spectroscopy studies: The peaks attained in the spectra of each formulation associates with drug spectrum peaks, given in figure 2.

Table 2: Pre-compression parameters of the blend.

Formulation Code	Angle of repose ($^{\circ}$)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's ratio
F 1	27.65	0.650	0.693	6.20	1.06
F 2	28.63	0.468	0.577	18.98	1.23
F 3	27.12	0.640	0.683	6.30	1.06
F 4	29.64	0.486	0.590	17.60	1.21
F 5	29.89	0.488	0.599	18.53	1.22
F 6	30.25	0.490	0.569	12.5	1.16
F 7	28.65	0.485	0.564	14.0	1.16
F 8	27.28	0.610	0.665	8.27	1.09

Table 3: Post compression parameters of ranitidine HCl floating tablets.

Formulation Code	Thickness (mm)	Diameter (mm)	Hardness (Kgcm ⁻²)	Friability (%)	Weight Variation (mg)	Content uniformity (%)
F1	0.18±0.12	0.33±0.16	4±0.02	0.80±0.03	299 ±0.0	99.5
F2	0.18±0.13	0.33±0.16	4±0.00	0.82±0.02	300±0.0	97.5
F3	0.18±0.12	0.34±0.18	5±1.02	0.44±0.05	300±0.0	99
F4	0.18±0.12	0.33±0.16	4.6±0.06	0.74±0.01	300±0.0	95.4
F5	0.18±0.12	0.33±0.16	5.6±0.05	0.44±0.01	299±0.1	100
F6	0.18±0.12	0.33±0.15	5±0.02	0.42±0.01	300±0.0	91.5
F7	0.18±0.12	0.34±0.16	4.2±0.02	0.80±0.03	299±0.2	93
F8	0.18±0.12	0.33±0.16	3.5±0.02	0.42±0.02	300±0.0	98

**Figure 2: FT-IR spectrum of floating tablet of ranitidine HCl. FT-IR spectra (A) Xanthan Gum (B) F5 (C) HPMC (D) EC (E) Ranitidine HCl.****Table 4: In-vitro buoyancy studies of ranitidine HCl formulations.**

Formulation Code	Floating Lag Time (seconds)	Total Floating Time (hours)
F1	52	8
F2	10	5
F3	14	6
F4	12	9
F5	1	10
F6	3	6
F7	6	4
F8	12	3

Discussion

Powder was evaluated for repose angle value which was found within the range of 27.28-30.25 indicating powder flow for all the eight formulations were excellent. Bulk density for all eight formulations was found to be in the range of 0.46-0.65 while tapped density was in the range of 0.56-0.69. The percent compressibility index for all eight formulations was found to be 6-19. These results indicated that the powder had well to fairly acceptable flow property. The thickness of tablet indicates that, die fill was uniform. Results obtained were within acceptable limits

according to pharmacopoeia. The result obtained was similar to (Patel et al., 2005) studies who prepared floating tablets of Ranitidine HCl. The tablets were manufactured using diverse polymers like HPMC 4 K, Xanthan gum, HPMC 100 K, Moringa gum and Guar gum in different ratios and result of post compression parameters of different formulations were nearly similar to the results being presented in this study. The thickness depended on the size of the punches (8 mm) and the weight of one tablet (300 mg). The weight variation test for all the formulations depicted too low values of standard deviation showing excellent mixing of drug with polymer and excipients. The thickness of tablet of formulation (F2.) was found to be 0.18±0.5 mm and the hardness was found to be 4-5 Kg/cm². It has good mechanical strength. Percentage weight loss of the 10 tablets of each formulation was measured and found to be within the range of 0.42-0.82% which was not acceptable i.e. in between 0.5-1%. These results obtained were comparable to study of (Patel et al., 2005). Studies who prepared floating tablets of Ranitidine HCl. In that study, tablets were prepared using different polymers like HPMC 4 K, HPMC 100 K, Xanthan gum, Guar gum and Moringa gum in different ratios and results of post compression parameters of eight formulations were nearly similar to the present results.

The formulation batch containing higher value of HPMC and xanthan gum and lower value of ethyl cellulose showed higher floating properties, due to its hydrophobicity which in turn decreases its density letting the tablet to float. From the results obtained, it was experimental that the increased concentration of ethyl cellulose augmented the floating properties. Buoyancy of the tablets was provided by ethyl cellulose (EC). The quantity of EC was not constant in all the formulations. It acted as a buoyancy increasing agent, which swelled and increased water uptake capacity of tablet because of hydrophilic properties. The tablets of batch F3 and F4 exhibited buoyancy lag time of 14 and 12 seconds, respectively, and did float for 5 hours and 6 hours. The tablets of batch F7 and F8 showed lag time of 6 and 12 seconds respectively, but the total buoyancy time was 4 and 3 hrs. The tablets F1, F5 and F4 showed high buoyancy time. The results obtained were

comparable to Basha *et al.* (Basha et al., 2013). Studies who prepared matrix floating tablets of Tinidazole and Ofloxacin combination using EC and HPMC and xanthan gum as polymers. Tablets of formulation F9 were float for 10 hours which contained HPMC 15%, EC 8% and xanthan gum 8% which is nearly similar to F5 of present study which also float for 10 hours with HPMC 18%, EC 8% and xanthan gum 6%.

Effects of various ingredients and their concentration on drug release were studied. Where, formulations F1 and F2 showed release of 72% and 80% at the end of 6th hour respectively. The formulation F1 contained higher amounts of HPMC (i.e. 18.1%) as compare to F2 (i.e. 10%). However, the concentrations of EC and XG were same in both the formulations. While F3 showed 79% of release at the end of the 6th hour which is near to F2 having higher concentration of XG (5.33%) whereas in F1 and F2 its concentration was 2.66% while keeping the concentrations of HPMC and EC constant as in F2. Tablets of batch F4 released the drug 60% at the end of 6th hour in controlled manner at maximum levels of HPMC, EC and XG concentration (i.e. 18.1%, 13.33% and 5.33%). Drug release rate and extent are inversely proportional to the thickness of this gel layer, because it takes time for drug molecules to travel across the gel layer and reach the dissolution medium. EC acted as retarding agent and XG also played role in sustained release action thus, prolonging the release rate. The formulation F6 and F7 showed release of 80% and 72% containing a constant concentration of EC (i.e. 8.16%) in both formulations, whereas in F6 the HPMC and XG concentrations were 18.1% and 5.33% on the other hand side, in F7 these polymers concentrations were 18.1% and 2.66%. Formulation F8 contained the minimum concentration of HPMC, EC and XG (i.e. 10%, 8.16% and 2.66%) and the release rate of this batch was 90% at the end of 6th hour that may reflect its least appropriate hardness about 3.5 Kg/cm² (Table 3). It was observed that the amount of polymer/retardant influenced the drug release pattern.

Moreover, from the above results it was noticed that, as the concentration of the polymer (HPMC) is increased in formulation F4, there were decreased in the drug release rates due to the increased diffusion path. Lactose was chosen as a diluent due to its water solubility and hydrophilic nature. It enabled better

matrix hydration, and promote free volume, which may have facilitated the drug release. Therefore, when the dosage form was added to the dissolution medium, the medium penetrates readily into the spaces between chains of the polymer. This formed a gel-like network surrounding the tablet. This hydration property of the hydrophilic polymers such as HPMC and Xanthan gum can cause an abrupt formation of a surface barrier around the non-effervescent floating tablet that eliminates the burst release. Formulation F5 was considered as optimized formulation because it showed 69% of drug release at end of 6th hour and a successfully sustained effect up to 12 hours. Formulations F1, F5 & F4 gave good results, based upon their drug retardation up to 6 hours with continuous buoyancy properties. Combination of polymers was important an attempt to produce an entirely appropriate and successful sustained release dosage form, hindering a bit of demerits of the other polymer.

The release kinetics for the overhead formulations was evaluated by finding the R² value for each kinetic model viz. zero, first order, Higuchi Release Model. Regression co-efficient for zero and first order obtained from HPMC/EC/XG for most of the sample, the values of R² obtained for zero order release rate constants were higher than that of first order. The results of which were same as those obtained in Saritha et al., (2013) who prepared Pioglitazone floating tablets. The rate and mechanism of drug release be contingent on the type of polymer and the polymer concentration. For HPMC as well as XG based formulations, higher polymer concentrations changed the rate from first order to zero order and the mechanism from Fickian to non Fickian diffusion. it was concluded that formulations had the regression value was fitted into zero order release kinetics which was matched with present study (Basha et al., 2013). The n value for Korsmeyer-Peppas model was found to be followed non Fickens diffusion which was also similar to the release mechanism of our study. Non Fickens diffusion referred to combination of both diffusion and erosion controlled.

The study does not show any well-defined interaction between Ranitidine HCl and excipients. No change in peak showed that there was no interaction between drug and polymers. N-H stretching of primary amine, C-H stretching, C-S stretching, C-H deformation

Table 5: *In vitro* dissolution profile of GRFT formulations.

Time (hours)	Cumulative % drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
1	7	11	4	16	15	16	16	22
2	20	16	20	22	30	24	24	32
3	22	25	27	32	35	28	36	38
4	32	47	39	36	45	32	46	46
5	58	58	52	58	55	45	58	60
6	72	80	79	60	69	78	72	90

N-H out of plain bending of pure ranitidine HCl with polymer were almost in the same region of wave number ranging from 400 and 4000. It was observed that there were no changes in the functional groups of drug and polymers, which shows that there were no physical interactions between drug and polymers. Similar results were shown with the study of Patil et al (Patil et al., 2010) studies who prepared floating tablets of ranitidine HCl by using HPMC and EC as polymers.

Conclusion: The novel drug delivery non effervescent-based floating system is an emerging approach for receiving *In-vitro* buoyancy. Gastric retention time of Ranitidine HCl was increases up to 10 hours hence enhancing its antiulcer usefulness.

Conflict of interest: All authors declare no conflict of interest.

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