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FORMULATION AND IN VITRO EVALUATION OF EFFERVESCENT FLOATING TABLET OF COIPROFLOXACIN HYDROCHLORIDE

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ABSTRACT: One of the most fascinating and difficult tasks for researchers is to create floating tablets with the necessary buoyancy, lag time, and control over the drug's release behaviour at the target spot. The goal of the current study is to develop effervescent floating controlled release tablets containing famotidine and clarithromycin for the treatment of peptic ulcers caused by Helicobacter pylori (H. pylori). Five formulations (F1-F5) were created, three of which had bilayered tablets and the other four contained plain tablets. Sodium bicarbonate, HPMC K4M, and hydroxypropyl methylcellulose (HPMC) K100M were used as the swelling and floating agents, respectively, in the direct compression process used to create these tablets. To guarantee the quality of the produced tablets, qualitative tests including thickness, hardness, weight variation, friability, and content consistency were carried out. Every formulation had a floating lag time that varied between 14 and 20 seconds. The HPMC K100M-prepared effervescent floating tablets (F2 & F4) had a total floating duration of less than 7 hours, but the HPMC K4M-prepared tablets (F1, F3, & F5) had a total floating time of more than 12 hours. One possible explanation for this discrepancy in floating behaviour is that the two polymers' compaction and flow characteristics differ. When contrasted to formulations F1, F3, and F4 that use HPMC K4M as swelling and floating polymer, formulations F2 and F4 using HPMC K100M show relatively more prolonged drug release capabilities. This may be explained by HPMC K100M's improved compaction. The produced tablets exhibit diffusion kinetics that are non-Fickian. All things considered, these plain and floating controlled release effervescent bilayer tablets may improve famotidine and clarithromycin's therapeutic effects and compliance when used to treat H. pylori.

KEYWORDS: controlled release, effervescent floating pills, hydroxypropyl methylcellulose, famotidine, and clarithromycin.

1. INTRODUCTION:

The oral route of drug delivery is mostly preferred due to ease of administration, patient compliance, flexibility in formulation and low cost of manufacturing as compared to other routes of drug delivery1 .

The conventional oral dosage forms are mediated by multiple doses to maintain the therapeutic window of the drug, however, such formulation approach did not substantially retard the drug fluctuation plasma levels that attributed to the rapid gastrointestinal transit, hence promoting the premature drug loss2 .This limitation demands for the development of novel drug delivery system that could ensure controlled release properties, reduced side effects and enhanced site specificity. The gastro-retentive delivery system is envisaged to provide an effective and safe therapy with reduced systemic adverse effects, reduced drug dose, reduced treatment duration and

improved patient compliance due to convenience in drug administration compared to that of conventional daily multi-doses3 . Specifically, this approach can be adopted to improve the drug efficacy used in the treatment of upper gastrointestinal tract infections such as peptic ulcer4 . The development of gastric retention system is promoted by decreasing the carrier density (floating systems), improving mucoadhesive properties and designing expandable or modified shape systems5,6. These systems are particularly useful in the treatment of stomach disorders for the drugs that are predominantly absorbed in the acidic medium and unstable in the intestinal or colonic environment. Drugs like clarithromycin and famotidine are reported to be suitable for gastro-retentive delivery system7 . This is ascribed to the demand of high levels of clarithromycin in the stomach to ensure effective eradication of H. pylori regardless of its rapid absorption throughout the gastrointestinal tract. Additionally, the low bioavailability (40%) and short half-life (2.5-4 h) advocate the choice of famotidine in formulating sustained release system8 .

Tablet dosage form is the most convenient drug delivery system by offering various features such as compactness and easy manufacturing, greater flexibility in doses, low cost and convenience of self-administration9 . Controlled release dosage forms is believed to be of added advantage to overcome the daily multi-doses required to maintain the therapeutic levels of drugs10,11 . In oral drug delivery, factors such as pH, gastrointestinal motility, enzymes and ions may influence systemic drug availability12 . These factors affect drug stability, ionization as well solubility, thereby altering absorption levels13. Gastro-retentive systems reveal a positive impact on addressing the above-mentioned obstacles as a carrier that increase drug bioavailability and therapeutic effectiveness after oral administration14,15. The relatively low density of such system allows them to float and prolong the retention time of the drug in the stomach, negating normal gastric emptying duration and rate, which accounts to elevation of the degree of drug absorption, ultimately enhancing the clinical outcome16,17 .

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This study aimed to design and evaluate effervescent floating bilayer-controlled release tablets loaded with

clarithromycin and famotidine by admixing of hydroxypropyl methylcellulose (HPMC)K100M, HPMC K4M and sodium bicarbonate as swelling and floating agents, respectively, mediated by means of direct compression method. The prepared formulations were characterized based on their thickness, hardness, weight variation, friability and uniformity of content to ensure the quality of prepared tablets.

2. MATERIALS AND METHODS:

Materials: Clarithromycin and famotidine were the drugs of choice and gifted by Ferozsons Laboratories Limited (Nowshera, Pakistan). HPMC K4M, HPMC K100M (BDH Chemical limited, Pool England) were used as swelling agents and retardants, respectively. Sodium bicarbonate (Sigma, Germany) was used as gassing agent, magnesium stearate (Sigma, Germany) as release rate retardants and talc (BDH Chemical limited, Pool England) as lubricant. Lactose (Sigma, Germany) was used as release rate accelerator. All the chemicals were of analytical grades and were used without any further purification.

Calibration curves: Famotidine and clarithromycin at 100mg each, were separately dissolved in 0.1N HCl to get 1mg/ml clear solutions21. The stock solution was diluted with 0.1N HCl to get required dilutions. The dilutions along with stock solutions were analysed spectrophotometrically at respective lambda maximum of 210nm and 265nm for clarithromycin and famotidine, respectively. The respective concentrations were plotted against their respective absorbencies and obtained standard curves were used for drug release calculations.

The composition and preparation of effervescent controlled release bilayer tablets: The compositions of both bilayer and plain effervescent floating controlled release tablets are shown in table 1. A total of 120 tablets were prepared as a pilot batch. Both bilayer and plain tablets were prepared by direct compression method. With reference to bilayer tablets, ingredients were mixed with clarithromycin layer for 15 minutes of trituration and passed through sieve number 60. Subsequently, a lubricant was added to the sieved mass and the tablets were attainable by means of direct compression. The same procedure was adopted for famotidine layer made by compressing its formulation over clarithromycin layer. In case of plain tablets, the lubricated materials were directly compressed with tableting machine (Erweka-Apparatebau compression machine type T B 24) and hardness value was kept at 6.6 Kg/cm. All the tablets were prepared manually.

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

Bilayer tablets					Plain tablets	
Drugs	Chemicals	Formula 1	Formula 2	Formula 3	Formulation 4	Formulation 5
Clarithromycin layer	Clarithromycin	250 mg	250 mg	250 mg	250 mg	250 mg
	HPMC K100M	77.5 mg	155 mg	———	165.49 mg	———
	HPMC K4M	77.5 mg	———	155 mg	———	165.49 mg
	Talc	10.8 mg	10.8 mg	10.8 mg	13.4 mg	13.4 mg
	Mg Stearate	5.4 mg	5.4 mg	5.4 mg	6.7 mg	6.7 mg
	Lactose	37.8 mg	37.8 mg	37.8 mg	46.9 mg	46.9 mg
	$NaHCO_3$	81 mg	81 mg	81 mg	167.5 mg	167.5 mg
Famotidine layer	Famotidine	20 mg	20 mg	20 mg	20 mg	20 mg
	HPMC K100M	32.5 mg	65 mg	———		
	HPMC K4M	32.5 mg	———	65 mg		
	Talc	2.6 mg	2.6 mg	2.6 mg		
	Mg Stearate	1.3 mg	1.3 mg	1.3 mg		
	Lactose	9.1 mg	9.1 mg	9.1 mg		
	$NaHCO_3$	32 mg	32 mg	32 mg		

Characterization: Flow characteristics: Flow characteristic like angle of repose, Hausner's ratio as well as compressibility index of the powder mixtures were determined according to standard procedures22–24 .

Drug and excipients compatibility study: In order to determine the possible interactions between drug and excipient, FTIR studies were conducted using Fourier Transform Infrared

Spectrophotometer (LI600300 spectrum Two Lita, Liantrisant, UK) at measuring wave number of 4000-400 cm-1 .
Shape and dimensions of the prepared tablets: Magnifying lens were used to determine the shape of tablets. The thickness and diameter were calculated by using clean and calibrated vernier caliper (Erweka, Germany). Five tablets from each of the formulation were selected randomly and their thicknesses and diameters were calculated individually25. The data were shown as mean ± SD.

Hardness: The hardness of the tablets shows their ability to withstand the mechanical force during handling. The hardness was calculated by using the hardness tester (Erweka Model TB 24 Apparatus, Germany) that expressed in kg/cm2 . Five tablets from each formulation were randomly selected and their hardness was determined26

Weight variation and friability test: Ten tablets were randomly selected from each formulation and were individually weighed using weighing balance (AX120, Shimadzu, Japan). The average weight of the tablets was shown as mean ± SD and evaluated against allowed pharmacopoeia limits25,27 . The friability was determined for each batch of tablets by randomly selected 20 tablets with common laboratory friabilator (Erweka, Germany). This was done in accordance to standard procedure and the results were

Tablet density: The density is an important parameter for floating tablets. Tablets will only float if their density is lower than that of gastric fluid i.e. lesser than 1.004g/cm3 . The density of tablets was calculated by the following equation as shown previously25 .

$$\rho = \frac{m}{v} \quad \ldots\ldots\ldots\ldots\ldots\ldots(1)$$

Where "ρ" is density, "m" is mass of the tablet (g), "v" is volume of the tablet (cm3). The volume can be calculated from equation 2:

$$v = \pi r^2 h \quad \ldots\ldots\ldots\ldots\ldots\ldots(2)$$

Where "r" is the radius of tablet (cm), and "h" is the crown thickness of the tablet (cm).

Swelling study The weight gain or water uptake which referred to the swilling propensity of the tablet was examined according to previous method with small modification29. The tablets were added to the solution of 0.1N HCL and the temperature was kept at 37±0.5ºC with continuous stirring rate at 25rpm. The tablets were withdrawn and re-weighed after removal of surface water using filter paper at specified time intervals. The water uptake/swelling index was determined using the following equation:

$$\text{Water uptake} = \frac{Wt - Wo}{Wo} X\ 100 \ldots\ldots(3)$$

Where Wt is the weight of the tablet at specific time "t" and W0 is initial weight of the tablet at zero time.

Floating behaviour: The floating behaviour was evaluated using USP type II dissolution apparatus (paddle type). The vessels were filled with 900ml of 0.1N HCl, and rotation speed of paddle was kept constant at 50rpm. The temperature was kept at 37±0.5oC, for a duration of 12 hrs. Buoyancy lag time and total floating time of each type of tablet formulation was recorded separately (El-Zahaby et al., 2014).

Drug content and drug release behaviour: The powdered tablets (10 from each batch) and equivalents weights of each drug were placed in 100ml of 0.1N HCl at pH of 1.2 and dissolved at temperatures of 37 ± 0.5oC. The pure drug and powdered tablets mass were suitably diluted before spectrophotometric analysis at 210nm

and 265nm for clarithromycin and famotidine, respectively. The drug release was determined using USP paddle method in 900ml of 0.1N HCl as dissolution medium. The rotation of paddle was maintained at 50 rpm and temperature was kept at 37±0.5oC. The aliquots of 5ml were withdrawn at predetermined time interval,

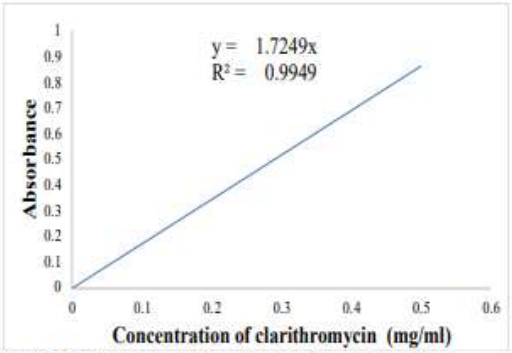


Figure 1: Standard curve of clarithromycin and famotidine

filtered and analysed spectrophotometrically at the respective lambda maximum of the drugs. The percent of drug release was recorded and the readings were shown as triplicate results in the form of mean±SD31 . Drug release mechanism was determined from power law formula (Power Law; $Mt/M\infty = K\ t\ n$) using Microsoft excel 32,33 .

3. RESULTS AND DISCUSSIONS:

Standard calibration curves: Standard curves were constructed and straight lines were obtained indicated direct relationship between concentration and absorbencies as shown in figure 1. The regression equation of clarithromycin standard curve obtained was y = 1.7249 x, and R2 value was at 0.9949. Similarly, the regression equation of famotidine standard curve was y = 25.825 x, and R2 value was at 0.999.

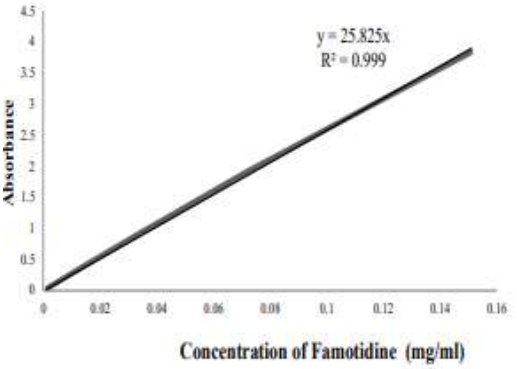


Table 2: Standard (A) and determined (B) values of flow characteristics

A. Standard values			
Flow characteristics	Hausner's ratio	Compressibility index (%)	Angle of repose
Excellent	1.00-1.11	<10	25-30
Good	1.12-1.18	11-15	31-35
Fair	1.19-1.25	16-20	36-40
Possible	1.26-1.34	21-25	41-45
Poor	1.35-1.45	26-31	46-55
Very poor	1.46-1.59	32-37	56-65
Very, very poor	>1.60s	>38	>66

B. Determined values					
Code	Angle of repose	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Compressibility index (%)
F1	27.3 ± 0.05	0.443 ± 0.06	0.50059 ± 0.09	1.140	12.28
F2	27.6 ± 0.08	0.442 ± 0.12	0.49504 ± 0.11	1.147	12.30
F3	27.9 ±0.06	0.439 ± 0.10	0.50405 ±0.12	1.150	13.04
F4	26.6 ± 0.04	0.450 ± 0.11	0.49494 ± 0.9	1.160	13.79
F5	27.7 ± 0.05	0.440 ± 0.09	0.50715 ± 0.14	1.157	13.56

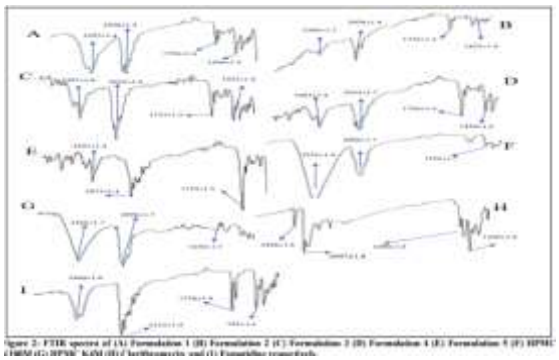
Flow characteristics: In order to formulate elegant product, determination of flow properties is highly essential. Flow characteristics like angle of repose, compressibility index and Hauser's ratio met the standard limits (USP.org: harmonization

2004) as given in table 2. The compressibility index, Hausner's ratio and angle of repose values ranged from 12.30% to 16.70%, 1.12-1.18 and 26.7o -29.4o , respectively for the formulation mixtures indicating good flow properties and their suitability for directcompression as mentioned in previous studies25,34 (Table 2 A and B).

FTIR results: The characteristics peaks of active drugs i.e. famotidine and clarithromycin were not significantly altered in the formulations35 (Figure 2).

The polymers bands of HPMC K100M and HPMC K4M are also in correspondence to previous finding without any change in position or intensity36,37 . Thus, the chemical interactions were negated in the formulation components of prepared tablet formulations.

Physical characteristics: The physical appearance of the controlled release floating tablets was elegant. Thickness of the fiveformulations ranged from 3.55-3.57mm and diameter of all the formulations was found to be in the range of 15.15-15.17mm. The hardness of tablets ranged from 6.5-6.8kg/cm2 . The results showed that all the tablets could withstand the hurdles during handling of tablets, due to acceptable range of hardness i.e. 5-10kg/cm2 25 . The friability characteristic of prepared tablets was ≤ 1.0 % that ensures mechanical stability of the plain and double layered tablets22. The weight of all the tablet formulations were within the acceptable USP limit i.e.± 5 %37,38. The theoretical/calculated weight of the tablet was kept at constant value of 670mg for each of the five formulations. The inter-batch variation of weight was also kept at minimal value. The results of physical tests of the tablets were given in table 3



Swelling index and floating behaviour: The density of the tablets must be lower than that of gastric contents (1.004g/cm3), in order to exhibit floating propensity. All prepared formulations float on the surface of fluid that mimic gastric content, thereby ensuring the suitability of their density. Wateruptake/swelling ratio indicates the amount of water uptake by the polymers used. The swelling occurs as a result of functional network structure and ionization of functional groups. This test was performed for all the formulations for 4 hours, showing that the tablet swells up to 90% of their original size. The swelling of the tablets increased in response to time due to hydrophilicity characteristic of polymers used (HMPC K100M and HPMC K4M). The swelling profile of tablets prepared with HPMC K4M was found to be significantly higher than those floating tablets prepared with HMPC K100M (Student t-test: $p \leq 0.05$; Figure 3; F2 Vs F3; F4 Vs F5). Initially, the outer most layer of polymer swelled and created gel barrier layer. As the outer gel barrier layer was dissolved slowly, new layer swelled up due to water uptake and this process was repeated toward new exposed surfaces. This maintained the integrity of the dosage form and helped to control the drug release profile. Polymer viscosity has direct impact on the swelling ratio, tablet integrity and floating capability. Figure 3 shows the swelling index of the prepared tablets.

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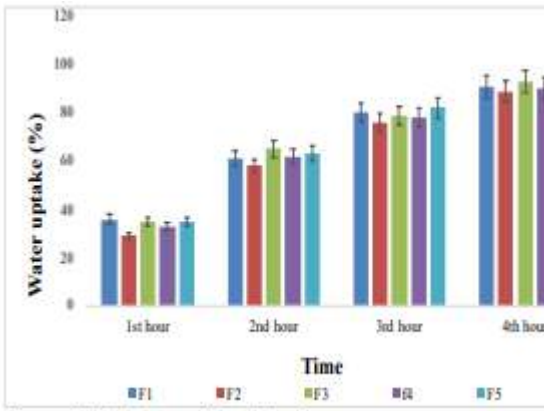


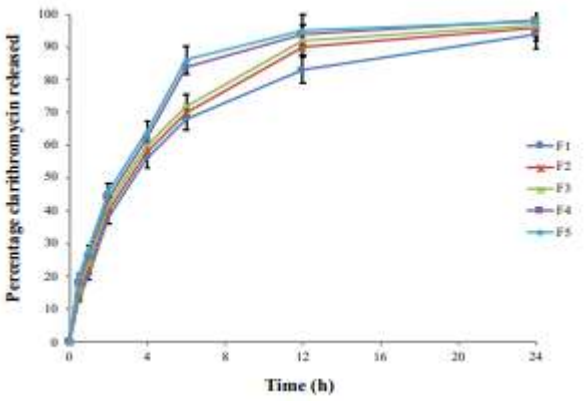
Figure 3: Tablets swelling behaviour

Along with polymers, gas sourcing agent i.e. sodium bicarbonate was also present in all formulations. Due to the presence of sodium bicarbonate, tablets when came in contact with the medium of 0.1 N HCl with pH 1.2 and temperature at 37 ± 0.5oC, they started to float and remained in floating conditions for hours. The total lag and total floating time for different prepared formulations are shown in table 4. Among bilayered floating tablets, F3 with HPMC K4M has significantly prolonged the lag and floating time of greater than 12 h ($p<0.05$). The same trend was observed in plain tablets whereby F5 achieved floating time of greater than 10 h as compared to less than 7 h for F4 prepared with HPMC K100 ($p<0.05$). This can be advocated to the low density and compromised compression characteristics in F3 and F5 as a function of HPMC K4M used as compared to other formulation39–42. The formulations prepared with HPMC K 100M (F) have better compressibility and hence retarded floating behaviour as compared to formulation with polymer HPMC K4M. These results are in accordance with other reported findings that investigated flow properties and compaction of different grades of HPMC. The finding of previous studies has shown that HPMC K100M resulted in better compaction as compared to HPMC K4M while HPMC K4M

Table 4: Tablet floating characteristics

Code	Tablet density (g/cm^3)	Floating lag time (sec)	Total float time (hours)
F1	0.95 ± 0.070	15.9 ± 3.72	> 12
F2	0.97 ± 0.070	20.8 ± 7.66	< 7
F3	0.92 ± 0.069	14.3 ± 3.34	> 12
F4	0.96 ± 0.071	15.75 ± 4.95	< 7
F5	0.93 ± 0.070	18.9 ± 8.5	> 10

The dissolution profile of clarithromycin from bilayered floating tablets depicted sustained release behaviour. The drug release from the tablets was successfully sustained up to 24 h (Figure 4). The release in case of HPMC K100M based formulation (F2) have comparatively more sustained drug release properties as compared to F3 (containing HPMC K4M) as result of better compaction of HPMC K100M. In case of plain tablets, similar effects of HPLC grades on release profile were observed (Figure 4). The effect is more pronounced in case of famotidine release from above formulations (Figure 4). The results demonstrate that drug release rates were prolonged via using mere polymer or in combination42,43. Both the drugs were released by nonFickian diffusion method from the polymeric tablets as indicated by n values greater than 0.5 and less than 1 (Table 5)44,45 .



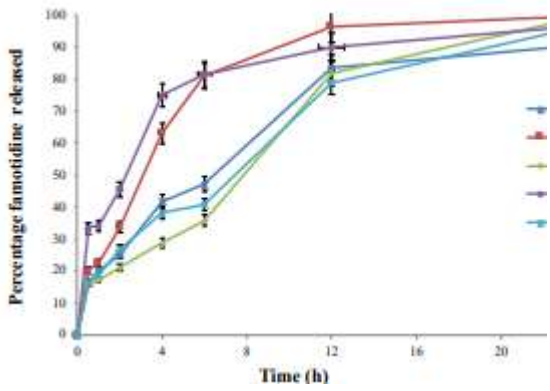


Table 5: Drugs release kinetics for prepared floating tablets

Code	Power law			
	K±SD	R^2	n	Release Mechanism
Clarithromycin				
F1	0.0029±0.0023	0.9865	0.6315	Anomalous non-Fickian Diffusion
F2	0.0021±0.0.0062	0.9786	0.6126	Anomalous non-Fickian Diffusion
F3	0.0021±0.0003	0.9800	0.6221	Anomalous non-Fickian Diffusion
F4	0.0065±0.0.00017	0.9698	0.5101	Anomalous non-Fickian Diffusion
F5	0.0015±0.0016	0.9568	0.5581	Anomalous non-Fickian Diffusion
Famotidine				
F1	0.002±0.005	0.965	0.515	Anomalous non-Fickian Diffusion
F2	0.001±0.0024	0.957	0.510	Anomalous non-Fickian Diffusion
F3	0.006±0.0014	0.962	0.605	Anomalous non-Fickian Diffusion
F4	0.001±0.0028	0.961	0.500	Anomalous non-Fickian Diffusion
F5	0.003±0.008	0.958	0.555	Anomalous non-Fickian Diffusion

4. CONCLUSION:

This study has successfully designed plain and bilayer sustained release floating tablets of clarithromycin and famotidine. The prepared tablets achieved suitable physicochemical properties as per pharmacopeial requirements. The in-vitro studies revealed that all formulations showed sustained release behavior as a function of hydrophilic polymers like HPMC K4M and HPMC K100M. The floating behavior and release profiles of these drugs from designed tablets were significantly influenced by adding gas forming agent like sodium bicarbonate. HPMC K100M possesses better compressibility attribute that reduces water uptake. The release of drug from HPMC K100M as compared to HPMC K4M was significantly retarded.

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