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Research Article

Optimization of Hydrodynamically Balanced Tablets of Clarithromycin: An Approach to Prolong and Increase the Local Action by Gastric Retention

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ABSTRACT

The objective of the present investigation is to formulate gastro retentive floating tablets (GRFT) of clarithromycin for the treatment of *Helicobacter pylori*, to prolong the gastric residence time after oral administration, at a particular site. Controlled release of drug is especially useful for achieving controlled plasma level as well as for improving bioavailability. The effect of formulation variables on floating lag time, t_{50} and t_{90} are also studied. The GRFT contains hydroxypropyl methylcellulose (HPMC) and hydroxyl ethyl cellulose (HEC) as release retarding polymers. The concentration of sodium bicarbonate ($NaHCO_3$) was initially optimized. The tablets were prepared by wet granulation method and evaluated for all their physicochemical properties, *in vitro* buoyancy, drug release and rate order kinetics. From the results, FHM4 was selected as an optimized formulation based on the polymer concentration, 12 hrs drug release, minimal floating lag time and maximum total floating time. The optimized formulation followed first order rate kinetics with erosion mechanism. The optimized formulation was characterized with FTIR studies and no interaction between the drug and the polymers was observed.

INTRODUCTION

Oral controlled release systems are designed, offering a number of advantages including improvement in patient compliance, therapeutic efficacy and safety, decreased side effects and reduced dosing frequency. Majority of the drugs are having site specific absorption in the gastro intestinal tract and parameters like pH dependent solubility, stability and ionization of the drug in different portions of the G.I. tract, influence such absorption [1]. Gastric retention systems are such systems, which increase the gastric retention time of the dosage form at the stomach and upper parts of the small intestine and suitable for the drugs having site-specific absorption from the above sites. The controlled release of the drug from these systems at the preferred absorption site optimizes delivery of the drug, maximizing its therapeutic benefits and reduces side effects by permitting a large portion of the drug to be absorbed before passing through the lower G.I. tract [2].

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Many attempts have been made in recent years to provide a dosage form with a longer gastric retention time and therefore a more efficient absorption. These approaches include floating drug delivery systems, swelling and expanding systems, polymeric bio-adhesive systems; modified-shape systems, high-density systems and other delayed gastric emptying devices. Compared to these approaches, the gastric floating drug delivery system and GRFT developed have provided several advantages, which are established by the encouraging results reported earlier [3]. Furthermore, the buoyancy action provided by the GRFT seems to offer a greater safety for clinical uses than some of the above-mentioned approaches. In fact, no adverse effects due to floating devices have been reported to date [4].

Helicobacter pylori (*H.pylori*) resides mainly in the gastric mucosa or at the interface between the mucous layer and the epithelial cells of the stomach and is considered to be an important etiologic factor in the development of the gastritis, gastric ulcer and gastric carcinoma.

Mehmet Demir *et al,* has described in detail that the antimicrobial resistance in *H.pylori* infection

is an important factor leading to the failure of the therapy. In meta-analytical studies, it has been shown that nearly half of the patients' *H pylori* infection is not eradicated because of antimicrobial resistance [5]. Clarithromycin resistance is less frequent than metronidazole resistance. Hence clarithromycin is selected as drug for the investigation of GRFDDS. Clarithromycin is a broad spectrum antimicrobial which is a macrolide antibiotic widely prescribed in *H.pylori* mediated peptic ulcers, upper respiratory tract infections. As the drug is effective when the plasma fluctuations are minimized, sustained release dosage form of clarithromycin is desirable.

The major reasons for the failure of treatment of *H. pylori* with conventional dosage forms of antibiotics is probably that the residence time of antibiotics in the stomach is short and so effective concentrations of the antimicrobials cannot be achieved in the gastric mucous layer or epithelial cell surfaces where *H. pylori* exists. And many combination therapies were selected for the treatment of *H.pylori* infection such as dual therapy, triple therapy and quadrate therapy which causes more side effects and causes incovenience to the patient and maximum amount of drug quantities will be consumed by the patient which leads to complications of the patients [5].

Margret Chandira *et al* have made an attempt to deliver clarithromycin via oral mucoadhesive drug delivery system to the vicinity of absorption site by prolonging the gastric residence time of the dosage form. For the formulation of oral mucoadhesive tablet various polymers are used like Hydroxyproplyl methylcellulose K15M (HPMC K15M), Hydroxyproplyl methylcellulose K4M (HPMC K4M), Carbopol 974P, as hydrophilic matrix forming and mucoadhesive polymer in varying concentration **[6]**.

Rahul Sutar *et al* have made an attempt to develop and evaluate hydrodynamically balanced matrix tablets of clarithromycin which were prepared by using HPMC K4M, HPMC K15M and Chitosan with $NaHCO_3$ as gas forming agent [7].

Liandong Hu *et al* have developed and validated a method to prepare clarithromycin microcapsules to mask the bitter taste and provide effective treatment, and evaluate the quality of microcapsules in detail, especially the *in vitro* and *in vivo* pharmacokinetics behaviour [8].

Putta Rajesh Kumar *et al* have aimed to develop a gastroretentive tablet that could deliver antibiotic in stomach from the coat tablet for localized action and acid liable anti secretory agent in duodenum from the enteric coated core [9].

Therefore a traditional oral sustained release formulation of clarithromycin may not be useful in the eradication of *H.pylori,* because the organism lives deep inside the gastric mucosa; also the oral bioavailability of clarithromycin is 55%. From literature survey, it was concluded that this drugs has absorption window in the stomach and upper small intestine and there are no reports on the use of floating concept in the formulation of gastric retention systems of clarithromycin which provides site specific release in the stomach, decreases the dosing frequency and also overcomes antibiotic resistance [10].

Based on previously published literature, applications of gastro retentive drug delivery system (GRDDS) may be suitable for the drugs insoluble in intestinal fluids (acid soluble basic drugs), e.g., propranolol, metoprolol, diazepam, clarithromycin [11].

The objective of the present investigation is to develop gastro retentive floating tablets (GRFT) of clarithromycin using statistical optimisation to provide increased residence time in stomach for delivery of antibiotic to treat *H. pylori* induced gastric ulcers. As the drug has its absorption window in stomach and upper small intestine and there are no reports on the use of floating concept in the formulation of gastric retention tablets of clarithromycin. In this study sodium bicarbonate concentration was optimised. The tablets were formulated using sodium carboxymethyl cellulose as swelling agent to reduce the concentration of synthetic polymer and to retard the floating time of the formulation with two different synthetic polymers HPMC K4M and HEC.

MATERIALS AND METHODS

Materials

Clarithromycin is obtained as a gift sample from M/s. Dr. Reddy's Laboratories Ltd., Hyderabad, India. Methanol (HPLC grade), and Hydrochloric acid (ExcellaR grade) were purchased from Qualigens Fine Chemicals, Mumbai, India. Hydroxypropyl methylcellulose and hydroxyethyl cellulose, sodium bicarbonate and microcrystalline cellulose were received as a gift

sample from M/s. Aurbindo Pharma Ltd, Hyderabad, India. Talc and magnesium stearate (S.D. Fine Chemicals Ltd., Mumbai, India) were used as glidant and lubricant, respectively. All other ingredients were of laboratory grade.

Methods

Optimizations of the effect of sodium bicarbonate concentration on floating lag time

The FS1-FS5 formulated tablets were prepared with different concentrations of $NaHCO_3$ with 20%w/w of HPMC K4M. Which were given in the Table 1. These tablets were subjected to floating lag time and results were observed.

Table 1: Formula for optimizations of clarithromycin floating tablets with $NaHCO_3$:

Ingredients (mg)	FS1	FS2	FS3	FS4	FS5
Clarithromycin	250	250	250	250	250
HPMC K4M	120	120	120	120	120
$NaHCO_3$	30	40	50	60	70
NaCMC	30	30	30	30	30
Mg. stearate	6	6	6	6	6
Talc	6	6	6	6	6
MCC	158	148	138	128	118
Total weight	600	600	600	600	600

Preparation of clarithromycin floating matrix tablets

Gastro retentive floating tablets of clarithromycin were prepared in different proportions of polymers as per the formulae given in Table 2. The required quantities of medicament and matrix materials were mixed [4] thoroughly in a glass mortar by following geometric dilution. Isopropyl alcohol (1.5%v/v) solution was added and mixed thoroughly to form dough mass. The wet granules were prepared by passing through sieve number 12 and the wet granules were dried at 60^0C. The dried granules were passed through sieve number 16, and mixed with $NaHCO_3$ and lubricated with magnesium stearate (1%w/w) and talc (1%w/w) by passing through sieve number100 just 4-5 min before compression and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multi-station punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 4-6 kg/sq.cm using 12 mm punches.

Evaluation of the tablets

The floating tablets were evaluated for floating characteristics, *in vitro* dissolution studies and other physico chemical parameters like weight variation, hardness, friability and assay.

Weight variation

According to I.P. twenty tablets were selected at random, weighed individually for the determination of weight variation of tablets. The mean and standard deviation were determined [12].

Hardness test

Five tablets were selected at random and the hardness of each tablet was measured on a Monsanto hardness tester.

Friability test

The friability test was carried out in a Roche Friabilator [12]. Twenty tablets were weighed initially (Xo) and put in a rotating drum. They were subjected to 100 falls of 6 inches height (25 rpm for four minutes). After complete rotations the tablets were dedusted by using a camel hairbrush and weighed (X). The percentage loss in weight or friability (f) was calculated by the formula given in the following equation:

$$F = \left[1 - \frac{X}{X_0}\right] \times 100$$

Estimation of clarithromycin in tablets

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 250mg of medicament was taken into 25 mL volumetric flask and 20 mL of methanol was added [12]. The mixture was shaken thoroughly for about 30 min while heating in a hot water bath to dissolve the clarithromycin. The solution was then made up to volume with methanol. The methanolic solution was subsequently diluted suitably with simulated gastric fluid of pH 1.2 and assayed for clarithromycin at 271 nm. Four samples of tablet powder were analyzed in each case.

Floating characteristics

All the formulated floating tablets were subjected to floating studies and five tablets were used for each batch. The *in vitro* buoyancy was determined by the floating lag time, as per the method described by Meka Srikanth *et al*. [13]. The tablets were placed in a 900 mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as the floating lag time. The duration that the dosage form remained constantly on the surface of medium was determined as the total floating time.

In vitro dissolution studies

The release of clarithromycin from floating tablets was determined by using a Dissolution Tester USP XXIII (LABINDIA, Disso 2000). The dissolution test was performed using 900 mL 0.1N HCl solution at 37 ± 0.5°C and the paddles were rotated at 50 rpm. At the appropriate time intervals, a 5 mL aliquot was withdrawn from the dissolution medium and it was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to suitable concentrations with 0.1 N HCl. The absorbances of the solutions were measured at 271nm for clarithromycin with a UV-Visible double beam spectrophotometer (Elico SL210, India). The cumulative percentage of drug release was calculated using an equation obtained from a standard calibration curve. The dissolution experiments were done in triplicate.

Release kinetics

There are a number of kinetic models available to describe the overall release of drug from the dosage forms. The dissolution profiles of all the batches were fitted to zero order, first order, Higuchi, Hixon-Crowell (erosion) and Korsemeyer-Peppas models to ascertain the kinetic modeling of drug release [14-17]. Mathematical equations of the above models are mentioned in Table 3. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using the Higuchi or erosion equations. The 'n' value was obtained as a slope for different batches of matrix tablets by plotting the log percent of drug dissolved against log time. A value of n = 0.45 indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II transport. Case II generally refers to the erosion of the polymeric chain, and non-Fickian diffusion refers to a combination of both diffusion and erosion mechanism from the controlled drug release tablets.

Table 3: Mathematical models

S.No.	Model	Equation
1.	Zero order	$Q_t = Q_0 + K_0t$
2.	First order	$InQ_t = InQ_o - K_1t$
3.	Higuchi	$Q = K_Ht^{1/2}$
4.	Hixson – Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_st$
5.	Korsmeyer-Peppas	$Q_t/Qo = K_kt^n$

Where: Q_t: amount of drug released in time t, Q_0: initial amount of drug in the tablet, Q_t/Qo: fraction of drug released at times t, K_0; K_1; K_H; K_k; K_s: release rate constants, n: the release exponent indicative of the mechanism of drug release.

Characterization of the optimized formulation

Formulation was optimized based on the drug retarding properties, polymer quantity and buoyancy properties. Optimized formulation was further characterized with Fourier transformation-infrared spectroscopy (FTIR) for interaction studies.

Fourier transformation-infrared spectroscopy (FTIR)

FTIR was used to identify if there is any drug excipient interaction. FTIR studies were performed on drug, polymer and optimized formulation. Samples were analyzed by the potassium bromide pellet method in an IR spectrophotometer (Shimadzu, FTIR 8700) in the region between 3500-500$cm^{-1.}$

RESULTS AND DISCUSSION

3.1. Optimizations of effect of $NaHCO_3$ concentration on floating lag time

The prepared tablets FS1-5 were subjected to floating lag time and it was observed that as the concentration of sodium bicarbonate increased the floating lag time decreased and floating time increased. The results were given in Table 4 & Fig. 1.

Table 4: Effect of sodium bicarbonate on floating lag time:

Formula Code	FS1	FS2	FS3	FS4	FS5
Sodium Bicarbonate (mg)	30	40	50	60	70
Floating Lag Time (sec)	110	90	70	45	35
Floating Time (hrs)	5	7	9	10	>12

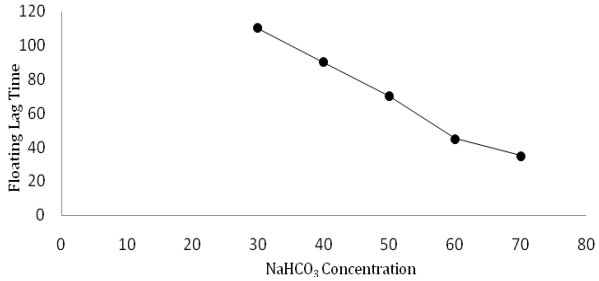

Figure 1: Effect of sodium bicarbonate concentration on floating lag time.

The results of weight uniformity, hardness, friability as well as drug content are presented in Table 5. It was observed that all the formulations of clarithromycin prepared using selected polymers HPMC K4M and HEC complied with compendia standard for uniformity of weight. The hardness for all the formulations was found to be in the range of 4-6 kg/cm^2. The assay of the drug was >98%. The percentage weight loss in the friability test was found to be <0.5%. Thus, all the formulations were found to be of good quality fulfilling all the official requirements.

In vitro buoyancy studies

Formulations were evaluated for *in vitro* buoyancy properties and results are mentioned in Table 5. It was observed that the floating lag times of HPMC K4M and HEC based formulations were in the range of 30-42 sec and 70-130 sec respectively. Total floating time were in the range of 6-14 hrs and 4-12 hrs respectively. Floating lag times were found to be significantly controlled by sodium bicarbonate content. The sodium bicarbonate induces CO_2 generation in the presence of 0.1 N HCl. The gas generated is trapped and protected within the gel formed by hydration of the HPMC and HEC, thus decreasing the density of the tablet below 1 gm/mL, and making it buoyant [18-19]. From the results, it is observed that as the concentration of polymer increased floating lag time decreased and the total floating time increased (at constant sodium bicarbonate ratio (11.66%w/w)). Though both polymers are readily swellable polymers and made the tablets buoyant in less time. HPMC K4M based formulations floated more rapidly than HEC, which may be due to its high swelling property.

In vitro dissolution studies

The results of dissolution studies of formulations FHM1 to FHM5 and FHE1 to FHE5 containing increasing concentrations of HPMC K4M and HEC respectively are shown in Fig. 2 respectively.

In batch FHM1, clarithromycin tablets were prepared using HPMC K4M at 5% of polymer. The tablet failed to float continuously and did not remain intact; moreover, 40% of the drug was released within 1 hour at this low concentration of HPMC K4M. Hence the concentration of polymer was increased to 10% for batch FHM2, which showed matrix integrity, but the release of drug was too rapid. In batches FHM3 to FHM5, the concentration of polymer was increased to 15%, 20% and 25% in order to get the desired floating behaviour as well as retarding properties. In these formulations diluent i.e. microcrystalline cellulose was included to make up the bulk volume of the tablet. Formulation FHM4 gave the best results in terms of floating behaviour (lag time 36-42 Sec, duration >10 hrs), and drug release was in accordance with the USP specification[20]. Formulations FHM3, FHM4 and FHM5 exhibited the complete drug release in 10, 12 and 14 hrs respectively as mentioned in Table 6.

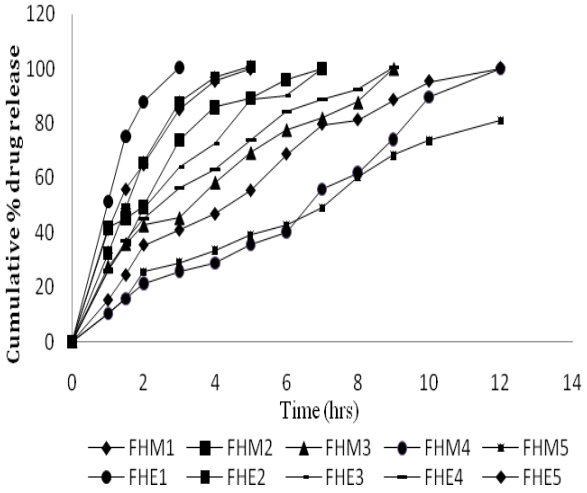

Figure 2: Cumulative% drug release of tablets containing HPMC K4M & HEC in pH 1.2 buffer.

Another polymer HEC, was tried for floating controlled release. In these formulations diluent i.e. microcrystalline cellulose was included to make up the bulk volume of the tablet. The formula FHE1 at 15% polymer showed a burst release pattern, and more than 45% of the drug was released in 1 hr. This may be due to the low concentration of the polymer and high concentration of microcrystalline cellulose. MCC may act as a disintegrant in high concentrations and hence the matrix tablet with high concentration of MCC was disintegrated quickly and lost its integrity. The concentration of HEC was further increased to 20%, 25%, 30% and 35% in order to get the desired release profile. The formulations FHE2, FHE3, FHE4 and FHE5 showed maximum drug release at 6, 8, 10 and 12 hrs respectively. The formulation FHE5 showed excellent buoyancy properties and retarding properties than all other formulations and results are mentioned in Table 7.

From the above results it can be concluded that the drug retardation mainly depends up on the concentration of the polymer as well as swelling property of the polymer. The order of the drug

Table 2: Formula for clarithromycin floating tablets containing HPMC K4M & HEC:

Ingredients (mg)	FHM1	FHM2	FHM3	FHM4	FHM5	FHE1	FHE2	FHE3	FHE4	FHE5
Clarithromycin	250	250	250	250	250	250	250	250	250	250
HPMC K4M	30	60	90	120	150	-	-	-	-	-
HEC	-	-	-	-	-	90	120	150	180	210
$NaHCO_3$	70	70	70	70	70	70	70	70	70	70
NaCMC	30	30	30	30	30	30	30	30	30	30
Mg.stearate	6	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6	6
MCC	208	178	148	118	88	148	118	88	58	28
Total weight	600	600	600	600	600	600	600	600	600	600

Table 5: Physical evaluation of clarithromycin matrix tablets containing HPMC K4M & HEC (n = 3)

Formulation Code	Hardness (Kg/cm^2)	Weight Variation (%)	Friability (%)	Assay Values (%)	Floating Lag Time (sec)	Floating Time (hrs)
FHM1	4-6	0.896±0.05	0.34±0.04	99.84±0.45	30	6
FHM2	4-6	1.08±0.15	0.43±0.12	98.36±0.57	33	8
FHM3	4-6	0.96±0.08	0.48±0.14	98.03±0.90	36	10
FHM4	4-6	0.997±0.12	0.48±0.04	99.62±0.63	38	12
FHM5	4-6	1.027±0.06	0.43±0.08	99.25±0.55	42	14
FHE1	4-6	0.89±0.08	0.42±0.06	98.76±0.46	70	4
FHE2	4-6	0.99±0.15	0.29±0.07	98.62±0.50	78	6
FHE3	4-6	1.02±0.04	0.44±0.08	99.11±0.22	90	8
FHE4	4-6	0.96±0.04	0.38±0.12	98.01±0.91	105	10
FHE5	4-6	0.98±0.06	0.28±0.06	99.85±0.73	130	12

Table 6: Drug release from floating tablets containing HPMC K4M (n=3).

Time (hrs)	FHM1	FHM2	FHM3	FHM4	FHM5
1	41.26±0.51	41.69±0.80	27.55±0.09	10.24±0.39	10.25±1.05
2	55.89±0.24	45.26±0.17	35.83±0.81	15.86±0.82	15.63±0.99
3	64.98±0.33	49.37±0.62	42.67±0.27	21.37±0.17	25.68±0.80
4	85.22±0.42	73.85±0.35	45.35±0.63	25.81±0.69	28.99±0.01
5	95.66±0.15	85.91±0.44	58.39±0.45	28.79±0.85	33.46±0.72
6	100.12±0.6	89.26±0.53	69.25±0.45	35.64±0.47	38.92±0.63
7	-	95.99±0.26	77.68±0.63	40.26±0.63	42.53±0.45
8	-	100±0.71	81.99±0.27	55.82±0.25	48.95±0.34
9	-	-	87.78±0.81	61.99±0.41	60.28±0.52
10	-	-	100.12±0.09	74.26±0.03	68.19±0.16
11	-	-	-	89.67±0.29	73.64±0.97
12	-	-	-	100.11±0.81	80.97±0.88
13	-	-	-	-	96.48±1.01
14	-	-	-	-	100.12±0.76

Table 7: Drug release from floating tablets containing HEC (n = 3)

Time (hrs)	FHE1	FHE2	FHE3	FHE4	FHE5
1	51.26±0.19	32.54±0.16	26.36±0.10	25.86±0.90	15.26±0.38
2	75.26±0.02	48.36±0.52	35.84±0.92	36.72±0.18	24.38±0.92
3	87.85±0.31	65.59±0.34	48.56±0.38	44.88±0.72	35.41±0.10
4	100.48±0.24	87.48±0.43	63.82±0.74	56.28±0.36	40.86±0.91
5	-	96.7±0.52	72.56±0.56	63.11±0.54	46.72±0.28
6	-	100.71±0.16	88.88±0.65	73.87±0.54	55.34±0.73
7	-	-	90.19±0.47	83.99±0.36	68.7±0.46
8	-	-	100.09±0.83	88.45±0.72	79.63±0.55
9	-	-	-	92.35±0.18	81.24±0.64
10	-	-	-	100.29±0.09	88.53±0.37
11	-	-	-	-	95.38±0.82
12	-	-	-	-	100.18±0.19

Table 9: Clarithromycin release characteristics of matrix tablets

Formulation Code	Polymer Concentration (%)	T_{50} (h)	T_{90} (h)	K_0 (mg/h)	K_1 (h^{-1})	'n' in Peppas equation
FHM1	5	1.4	3.4	0.0470	-2.4110	0.8589
FHM2	10	2	6	0.0679	-3.0551	0.7739
FHM3	15	3	8	0.0983	-4.7532	0.5688
FHM4	20	6.5	10	0.1197	-5.7548	0.7273
FHM5	25	7	12.5	0.1487	-16.834	0.8133
FHE1	15	1	2.2	0.0269	-1.3970	0.8990
FHE2	20	1.6	3.2	0.0450	-2.3097	0.9005
FHE3	25	2.2	6	0.0692	-3.5626	0.7127
FHE4	30	2.4	7.6	0.0929	-4.8627	0.6806
FHE5	35	4.4	9.2	0.1145	-6.1487	0.8183

retarding capacity of the polymer and their polymer-concentration was as follows HPMC K4M (25%) > HEC (35%). Even though positive results were obtained by FHE5 formulated with HEC, FHM4 formulated with HPMC K4M was selected as an optimized formulation as the same desired results were obtained with less quantity of the polymer besides its good buoyancy properties.

Release kinetics

HPMC K4M based formulations FHM1 and FHM2 followed first order rate kinetics with higher regression values of 0.9557 and 0.9143 respectively. Formulations FHM3, FHM4 and FHM5 followed zero order rate kinetics with higher regression values of 0.9511, 0.9756 and 0.9721 respectively. HEC based formulations FHE1 and FHE2 followed first order rate kinetics with higher regression values of 0.9225 and 0.9633 respectively. Formulations FHE3, FHE4 and FHE5 followed zero order rate kinetics with higher regression values of 0.9428, 0.9341 and 0.9722 respectively. All the above formulations followed erosion mechanism. From the results it is observed that the rate order kinetics depends upon the concentration of the polymer. As it increases rate order has changed from first order to zero order.

Table 8: Correlation coefficient (r) values in the analysis of release data as per zero, first order, higuchi and erosion equation models.

Formulation Code	Correlation coefficient (r-value)			
	Zero order model	First order model	Higuchi model	Erosion Plot
FHM1	0.8947	0.9557	0.9906	0.9974
FHM2	0.8801	0.9143	0.9820	0.9851
FHM3	0.9511	0.7695	0.9866	0.9880
FHM4	0.9756	0.9123	0.8954	0.9416
FHM5	0.9721	0.9528	0.9415	0.9668
FHE1	0.9098	0.9225	0.9857	0.9924
FHE2	0.9135	0.9633	0.9653	0.9906
FHE3	0.9428	0.8681	0.9801	0.9855
FHE4	0.9341	0.8654	0.9939	0.9941
FHE5	0.9722	0.9634	0.9642	0.9840

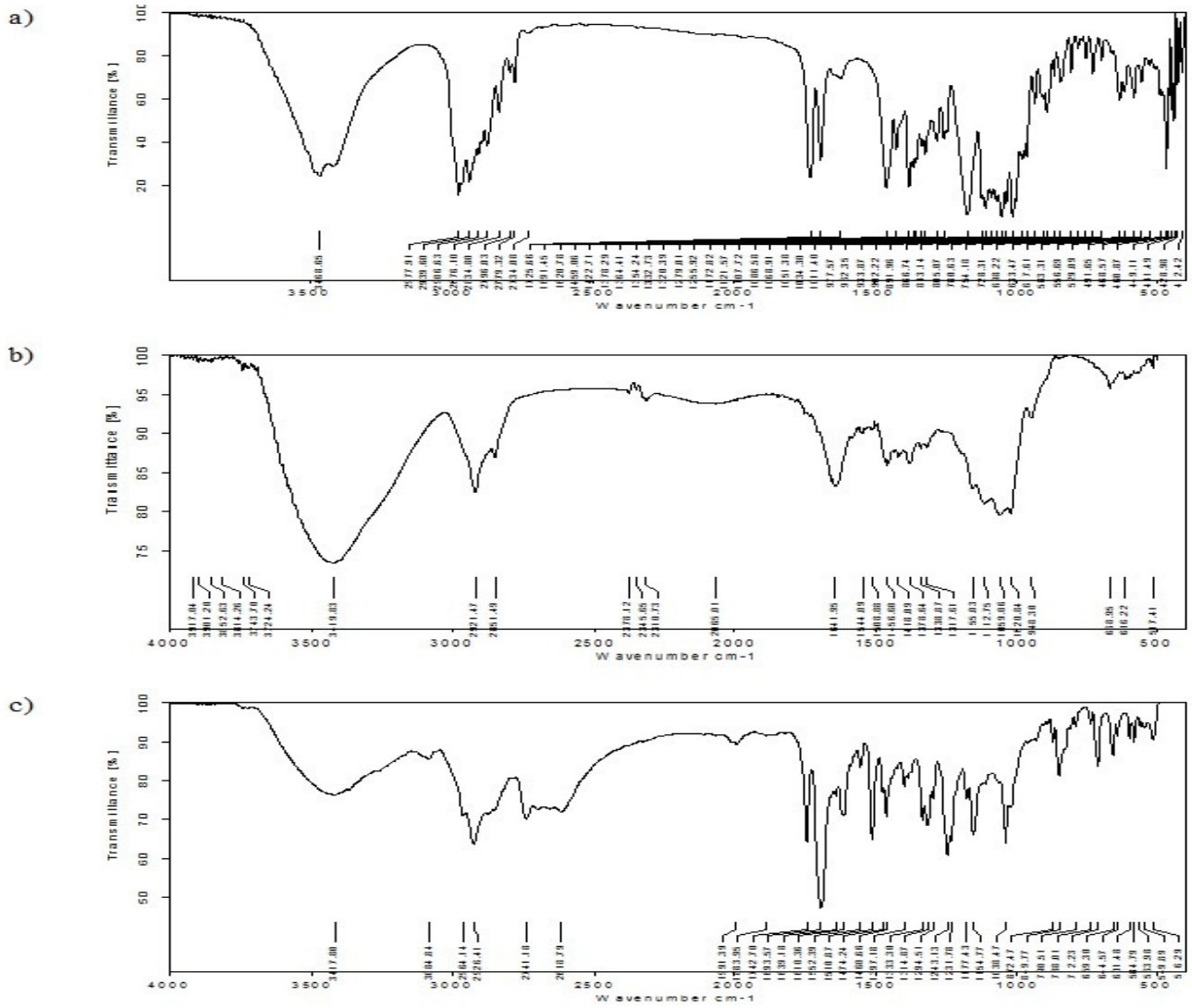

Figure 3. FTIR profiles of a) Clarithromycin b) HPMC K4M c) FHM4

HPMC K4M FHM4 and HEC FHE5 based optimised formulations followed zero order rate kinetics and followed erosion mechanism. From the results it is observed that, as the concentration of polymer increases, the mechanism of drug release changed from diffusion to erosion (Table 8 & 9).

Optimization

Based on the low polymer concentration, buoyancy properties and best dissolution profile, FHM4 was selected as an optimized formulation. HPMC K4M was selected as a suitable polymer for the development of gastric retentive floating tablets of clarithromycin with low polymer concentration.

Fourier transformation-infrared spectroscopy (FTIR)

The FTIR spectra of clarithromycin and HPMC K4M were compared with FTIR spectra of optimized formulation (FHM4). From the spectra as given in Fig. 3 no significant changes were observed in the FTIR profile of pure drug and formulation (FHM4).

The FTIR spectrum of clarithromycin showed characteristic –O–H stretch at 3468 cm^{-1}, aliphatic stretch C-H at 2977.91 cm^{-1}, C=O stretch at 1725 cm^{-1}, C-N stretch at 1691 cm^{-1}, C-H aromatic stretch at 1459.06 cm^{-1}, C-O stretch at 1172.82 cm^{-1} and C-0-C stretch at 1107.72 cm^{-1} (Fig. 3). The FTIR spectrum of HPMC K4M showed the characteristic alcoholic –OH stretch at 3419.83 cm–1, -C-O-C asymmetric stretch at 1112.75 cm–1 and -C-O-C symmetric stretch at 1059.06 cm–1. Optimized HPMC K4M based formulation (FHM4) showed all the characteristic peaks of clarithromycin with minor shifts in its FTIR spectrum. It can be concluded that there was no incompatibility between the drug clarithromycin and polymer.

CONCLUSION

Effervescent based floating drug delivery is a promising approach to achieve *in vitro* buoyancy, by using hydrophilic polymers of cellulose grades, such as HPMC K4M and HEC and sodium bicarbonate as gas generating agent. The results concluded that HPMC K4M and HEC based formulations at 20%w/w polymer concentration for FHM4 and 35%w/w polymer concentration for FHE5 respectively retarded the drug release more effectively than all other formulations. High molecular weight HPMC K4M grade exhibited higher retarding and better buoyancy properties. The optimized formulation gives the best result in terms of the required lag time (38 sec) and floating duration of 12 hrs. The optimized formulation showed no interactions between drug and polymer, when characterized with FTIR studies. Hence, HPMC K15M is a suitable polymer for the development of gastric floating drug delivery systems.

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