RESEARCH ARTICLE

Effect of polymers and excipients on the release kinetics, bioadhesion, and floatability of metronidazole tablet

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Stomach-specific floating tablet of metronidazole based on the buoyancy and bioadhesion concept was prepared with a purpose to retain the drug in stomach for longer duration and helps in releasing the drug in the antrum region of gastric mucosa, a safe heaven for *Helicobacter pylori*. This research work systematically studied the effects of various polymeric blends of bioadhesive polymers namely chitosan and carbopol 971P with low density polymer- methocel K100LV on the desired *in vitro* drug release profile in the stomach, buoyancy, swelling index, and mucoadhesion of tablet formulation. Chitosan and carbopol 971P concentration significantly influence the *in vitro* drug release and bioadhesion strength. An increase in buoyancy was observed with increase in Methocel K100LV concentration in the polymeric blend. The increase in buoyancy and drug release was obtained in the presence of microcrystalline cellulose, sodium bicarbonate, and sodium citrate. The optimum formulation provides desired high drug concentration (~35%) during 1 hour and sustained release up to 12 hours, following the Higuchi model. The mechanism of release of metronidazole from the floating bioadhesive tablets was anomalous diffusion transport. The studies indicated successful formulation of gastroretentive compressed tablet with excellent controlled release, mucoadhesion, and hydrodynamic balance.

***Key words*:** *Bioadhesion displacement force, chitosan, floating tablets, Helicobacter pylori, release kinetics*

INTRODUCTION

Metronidazole, a 5-nitroimidazole derivative is a unique bactericidal antibiotic particularly against obligate anaerobes such as *Bacteroides* and *Clostridium* species, and facultative anaerobes such as *Gardnerella* and *Helicobacter.*[1] Metronidazole is rapidly and completely absorbed after oral administration of conventional tablet dosage forms.[2] The 1-week triple therapy regimen comprising metronidazole with omeprazole and amoxicillin, being low cost, good compliance, and mild adverse effects, may offer a good choice for the treatment of peptic ulcers associated with *H pylori* infection.[3] However, antibiotic resistance particularly with metronidazole (MIC > 8 mg/l) frequently causes failure of eradication of *H. pylori*,[3,4] which may be due to poor drug concentration at the site of action as after absorption to blood circulation results in distribution of drugs throughout the body. Also it increases the chances of antibiotic resistance as well as systemic adverse effects.

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Local administration of drug in the stomach region can limit the adverse effects of systemic administration and better efficacy of medication at the targeted site.[5]

Retaining the drug in stomach for longer duration using the gastroretentive drug delivery systems can help in releasing the drug in the antrum region of gastric mucosa, a safe heaven for *H. pylori*.[6] Several approaches currently in use for gastroretention are floating delivery systems, swelling, and expanding systems, bioadhesive systems, modified shape systems, high density systems, etc.[7,8] The floating system or hydrodynamically balanced systems (HBS) are simple, most approachable systems to provide high gastric residence time and sustained release of drug.[9]

Floating tablets or buoyant systems using swellable polymers such as chitosan (CS), hydroxyl propyl methyl

Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.97118

cellulose (HPMC), polyoxyethylene, carbopols, polycarbophils, guar gum, xanthan gum, etc. have been prepared for various drugs with or without CO_2 generating agent.[9-13] These single unit formulations are associated with drawback of "all or none" system and require sufficiently high stomach fluid to be buoyant. Hence depending on the size, floating tablets may cross over to small intestine during house-keeper waves. [14,15] This serious limitation can be overcome by making the buoyant system which also adheres to the mucous lining of the stomach wall.[16] Among various mucoadhesive polymers, CS offers a great advantage being polycationic in nature and also has some antibacterial activities. However, adhesion failure may occur when overhydration converts the chitosan gel network to slippery mucilage in gastric environment.[17] Therefore, addition of other types of biodegradable polymers in the delivery system may provide control over the swelling of CS and thereby prevent adhesion failure.

In the above context, a floating system with mucoadhesion property was needed to develop for anti-*H. pylori* agents like metronidazole which can increase the efficiency of drug with least systemic side effects. Thus, an attempt was made to prepare a buoyant tablet of chitosan along with low density polymer-HPMC (Methocel K100LV) and release retardant polymer-carbopol 971P (CP), which also have mucoadhesion behavior due an electrostatic type of interaction between polycationic chitosan, mucin glycoproteins, sialic acid, and other anionic moieties present on gastric mucosa.[18] The present research work also investigates the optimum polymeric blend of selected polymers on the desired float lag time, swelling index, bioadhesion force, and drug release kinetics. The effect of diluents and gas generating agents was also evaluated in the systematic approach to develop a floating bioadhesive tablet of metronidazole.

MATERIALS AND METHODS

Materials

Chitosan (CS) (viscosity 200-400 mPas) was purchased from Sigma-Aldrich (USA). Carbopol 971P (CP) and HPMC (Methocel K100LV) was received as a gift sample from Panacea Biotech Ltd., Lalru (Pb.) India. Metronidazole was provided as a gift sample from Siemens Laboratories, Gurgaon (India). Microcrystalline cellulose powder (MCC), magnesium stearate, and talc were provided as a gift sample from Psyco Remedies, Ludhiana (India). Calcium carbonate, sodium bicarbonate, and sodium citrate were purchased from Loba Chemie, Mumbai, India. Simulated gastric fluid (SGF) without pepsin was prepared as per USP 29. Double distilled water was used in all the preparations. All other solvents and chemicals used were of analytical grade.

Methods

Formulation and optimization of metronidazole bioadhesive floating tablet

Different tablet formulations of metronidazole were formulated using varying amounts of the polymers, i.e., CS, Methocel-K100LV, CP, MCC or lactose as inert diluents, calcium carbonate or sodium bicarbonate with or without sodium citrate as a gas generating agent, and talc and magnesium stearate (MS) as glidant and lubricant respectively. Tables 1 and 2 enlist the various compositions employed during the study. Composition of formulations in Table 2 was selected on the basis of optimized formulation from Table 1 (high f2 value for P7).

Prior to use, metronidazole and other excipients were sieved through #60 mesh size (250 mm). Before blending with other ingredients, chitosan was pretreated with 2% w/v acetic acid.[19] All the ingredients were accurately weighed and mixed intimately in a polythene bag for 10 minutes. The blended mixture was compressed into a 510 mg tablet using flat faced round punches (12.8 mm diameter) fitted to a multipunch tablet compression machine (M/s Dhiman Engineering, Nakodar, India) (Batch -100 tablets).

During optimization studies on oral controlled release mucoadhesive floating tablets of metronidazole (P1-P11 and E1-E4), the levels of the following parameters were kept constant in all batches:

a) Tablet breaking force: More than 5 kgf
b) Friability: Less than 1.0%
c) Floating lag time: Not more than 2 minutes
d) Float duration: More than 8 hours
e) % Drug release at 1 hour, 4 hours, 6 hours, 8 hours and 12 hours: ~35%, 60.0%, 70%, 80%, >95% respectively
f) Bioadhesion displacement force using 8 cm^2 mucous membrane: Not less than 8 g.

Table 1: Composition of metronidazole bioadhesive floating tablets for polymer interaction studies

Ingredients	Amount (mg) in various formulations (Coded)										
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Metronidazole	200	200	200	200	200	200	200	200	200	200	200
Chitosan	200	-		100	100	50	50	50	25	25	25
Carbopol 971 P	-	200	-	100	-	100	75	50	75	100	125
Methocel K100LV	-	-	200	-	100	50	75	100	100	75	50
MCC	75	75	75	75	75	75	75	75	75	75	75
Sodium bicarbonate	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5
Talc	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Table 2: Composition of metronidazole bioadhesive floating tablets for excipients interaction studies

Ingredients	Amount (mg) in various formulations (Coded)			
	E1	E 2	E 3	E 4
Metronidazole	200	200	200	200
Chitosan	50	50	50	50
Carbopol 971P	75	75	75	75
Methocel K100LV	75	75	75	75
Lactose	75	75	-	-
MCC	-	-	75	75
Calcium carbonate	22.5	-	22.5	-
Sodium citrate	5	5	5	5
Sodium bicarbonate	-	22.5	-	22.5
Talc	5	5	5	5
Magnesium stearate	2.5	2.5	2.5	2.5

Physical evaluation of tablets

The formulated tablets were evaluated as per IP 2010 for weight variation, tablet dimensions (tablet thickness and diameter using calibrated vernier calipers), Tablet breaking force (by Monsanto hardness tester), friability (by Roche friabilator), content uniformity (dissolved the drug from fine powdered tablets equivalent to 10 mg of metronidazole in 100 mL of methanolic 0.1 N HCl with continuous stirring for 5 minutes, filtered through 0.45 µm Whatman filter paper and the filtrate was analyzed spectrophotometrically for metronidazole content at 277.8 nm using UV-1700 spectrophotometer, Shimadzu, Japan, using a previously determined standard calibration curve equation (Absorbance = 0.0471 × conc. + 0.0187 (R^2 = 0.995)). The experiments were performed in triplicate.

In vitro floatability study

The test was performed by placing the tablet in to glass jar containing 900 ml of 0.1 N HCl of USP29 type II Dissolution test apparatus, maintained at 50 rpm and 37±0.5°C. The time required for the tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time.[20]

Swelling study

Formulated tablets, weighed individually (W_0), were placed separately in beakers containing 50 ml of 0.1 N HCl maintained at 37±0.5°C in an incubator. At regular 2-hour time intervals until 8 hours, the tablets were removed from the beaker, air dried, reweighed (W_t), and the % swelling index was calculated using the following formula:[21]

$$\%\,\text{Swelling Index (SI)} = \left(\frac{Wt - W0}{W0}\right) \times 100 \quad (1)$$

where Wt is the weight of tablet at time t and W0 is the weight of tablet before immersion.

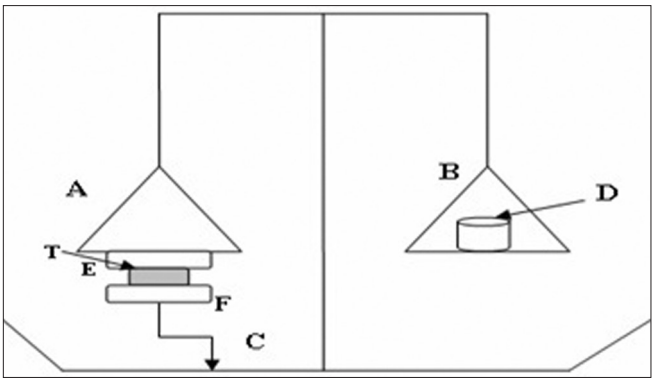

Figure 1: Bioadhesion detachment force measurement balance

Bioadhesion detachment force

The detachment force method using modified balance as shown in Figure 1 was used to assess the tendency of mucoadhesive material to adhere to mucosal membrane. Two sections (area - 2×4 cm^2) of tissue were cut from the the antrum region of pig stomach and fixed onto each glass slide using polyacrylic glue and were stored at 37.0°C for 10 minutes. Next, one glass slide (E) was fixed to the lower portion of left pan (A) of balance and the other glass slide (F) was fixed on a height-adjustable stand (C). Metronidazole floating bioadhesive tablet (T) was added onto the stomach tissue on the slide (F). Then, the height of the stand was adjusted so that the tablet could adhere between the mucosal tissues of both slides. A constant weight (10 g) was placed on the left pan (A) for 2 minutes, after which it was removed and then weight on right pan (B) was adjusted for initial balance and then the weights (D) were increased until the two slides were detached. Bioadhesion detachment force or bioadhesion strength (g) was determined from the minimal weights that detached the two slides. The mucosal membrane was changed for each measurement. Measurements were repeated 3 times for each of the tablet formulations.[22]

Tablet dissolution test studies

Dissolution studies were carried out by USP29 Type-II apparatus (M/s Electrolab India Ltd., Mumbai) at 100 rpm and 37±0.5°C, using 900 mL of 0.1N HCl (pH 1.2) as the dissolution medium on all formulated floating tablets. An aliquot of sample (5 mL) was withdrawn periodically, replaced with equivalent volume of dissolution medium. Samples, filtered through Whatman filter paper (0.45 µm), were analyzed spectrophotometrically at 277.8 nm. Drug release data obtained during *in vitro* dissolution studies were analyzed using different kinetic models as shown in Table 3 and fitted into the Korsmeyer-Peppas model for evaluation of release mechanism from matrices.[23]

Comparison of dissolution profile

To compare the dissolution profile of various formulations

with the theoretical drug release profile, similarity factor (f_2) was calculated by the following formula:

$$f_2 = 50\log\left\{(1+1/N)\sum(R_i - T_i)^2)^{-0.5}\right\}\times 100 \qquad (2)$$

where N is the number of time points, Ri and Ti are dissolution of reference and test products at time i.

The dissolution profiles are considered to be similar when f2 is between 50 and 100.

Accelerated stability studies

The accelerated stability testing was performed on the optimized formulations (P7 and E4) by placing the tablets (packed in aluminum foil) in thermostatically controlled ovens adjusted at different temperatures - 40°C, 50°C, and 60°±0.5°C with relative humidity 75±5% (maintained using a saturated solution of NaCl) and at 25°C with relative humidity 57.6±0.40% (maintained using a saturated solution of NaBr) for a period of 12 weeks. The stored tablets were examined for physical evaluation weekly and analyzed for the drug content, mucoadhesion strength and float lag time after 1, 2, 4, 6, 8, and 12 weeks.[12]

In-vivo gastro-retention studies

The optimized formulation E4 was evaluated for the gastro-retention test using radiological examination of barium sulfate tagged placebo tablets.

a) Preparation of placebo barium sulfate (high density) tablets.
   The radio-opaque tablets of optimized formulation batch E4 were prepared by the earlier mentioned method, replacing metronidazole with sufficient quantity (10 mg) of barium sulfate and diluent. The other parameters of tablets were kept constant.

b) The *in-vivo* gastro-retention study was carried out by administering a placebo floating tablet using a gastric feed tube to the overnight fasted New Zealand Rabbits (2.5-3.0 kg, n=3) and monitoring them through a radiological method (2nd, 4th, and 6th hours).[24]

RESULTS AND DISCUSSION

Physical evaluation and drug content

Tablet weights in various formulations varied between 509.5 and 510.4 mg, tablet diameter between 12.79 and 12.82 mm, and thickness between 2.58 and 2.60 mm as shown in Table 4. The tablets were tested for breaking force and friability from each batch to check their adequacy to withstand the mechanical shocks during their packaging and transport and also for appropriate disintegration and dissolution profiles. The breaking force values for tablets were ranging between 6.58 and 9.32 kgf and the friability values were between 0.25% and 0.89% w/w, indicative of adequate strength to provide good tablet. The assayed content of drug in various formulations varied between 97.6% and 99.6% w/w. The absence of any significant inter- and intrabatch variability in tablet breaking force, friability, and thickness may be related to the random causes rather than the floating composition and hence the effect of polymeric blends on drug release profile will be highly indicative.

In vitro floatability study

From the results of tablet floating studies as shown in Table 5, all formulations except P1, P2, and P4 showed good buoyancy properties, i.e., floating time more than 8 hours due to their low density than GI fluid. With increase in methocel K100LV, buoyancy time of the tablets increased in a linear fashion apparently due to swelling on hydration of the hydrocolloid particles, which increases the bulk volume.[25] With increase

Table 3: Characteristics of release kinetic models

Model	Equation	Parameters	Graph plotted form *in-vitro* release data
Zero order	$C = k_o t$	C = cumulative % drug release k_o = zero order release rate constant	Cumulative % drug release versus time
First order	Log C = Log C_o - Kt	C = log cumulative % of drug remaining to be released Co =Log % of initial drug conc K = first order release rate constant	Log cumulative of % Drug remaining versus Time
Higuchi	$Q = K\sqrt{t}\, t$	Q = cumulative % drug release K = Higuchi rate constant	Cumulative % drug release versus square root of time
Korsmeyer-peppas	$M_t/M_\infty = K t^n$	M_t/M_∞ = fraction of drug released at time t, K = Korsmeyer peppas rate constant, n = value characterize different release mechanisms for cylindrical shaped matrices	Log cumulative % drug release versus Log time Fickian diffusion - n = 0.45 Anomalous (nonFickian) diffusion if 0.45 < n < 0.89 Case-II transport- n = 0.89 Super case-II transport- n >0.89
Hixson-Crowell Cube Root Law	$Q_0 1/3 - Q_t 1/3 = KHC\, t$	Q0 = initial amount of the drug in tablet, Qt = amount of drug remaining to be released in time t, KHC = rate constant for Hixson-Crowell rate equation	Cube root of drug % released in Matrix versus Time

Table 4: Physical characteristics of metronidazole bioadhesive floating tablets

Formulation code	Weight (mg) mean±SD (*n* = 10)	Diameter (mm) mean±SD (*n* = 6)	Thickness (mm) mean±SD (*n* = 6)	Tablet breaking force (kgf) mean±SD (*n* = 6)	Friability (%)
P1	509.8±0.252	12.80±0.007	2.58±0.121	6.58±0.124	0.89
P2	510.4±0.172	12.79±0.004	2.60±0.138	9.32±0.196	0.68
P3	509.6±0.284	12.81±0.010	2.59±0.068	9.04±0.136	0.91
P4	510.1±0.028	12.81±0.007	2.59±0.132	7.94±0.094	0.81
P5	510.2±0.032	12.81±0.009	2.60±0.178	7.92±0.120	0.65
P6	510.1±0.147	12.79±0.008	2.59±0.061	7.16±0.098	0.42
P7	510.3±0.276	12.80±0.005	2.59±0.154	7.24±0.154	0.32
P8	510.2±0.374	12.80±0.006	2.60±0.122	7.47±0.086	0.25
P9	509.3±0.018	12.80±0.012	2.58±0.215	7.28±0.124	0.34
P10	510.2±0.045	12.81±0.004	2.60±0.086	7.12±0.085	0.36
P11	510.2±0.054	12.81±0.012	2.60±0.156	6.86±0.214	0.40
E1	510.7±0.019	12.80±0.002	2.60±0.036	7.01±0.116	0.39
E2	509.9±0.064	12.82±0.002	2.59±0.284	7.10±0.202	0.44
E3	510.2±0.410	12.80±0.010	2.59±0.067	7.32±0.067	0.35
E4	510.5±0.118	12.8±0.007	2.59±0.201	7.04±0.175	0.38

in CP content, however, buoyancy time decreases in a linear trend, probably due to the higher density of CP (1.76 g/cc) than that of methocel K100LV (1.28 g/cc). But it is expected that due to high mucoadhesive nature of CP, the tablet may retain for longer duration in stomach by adhering to gastric mucosa.[26] The presence of sodium citrate along with carbonate as an effervescent agent decreased the floating lag time (FLT). The optimum formulation E4 showed low FLT (0.1 minute). The low density as well as gelling capacity of polymers helps the tablet to float by entrapping the gas in the gel network.

Swelling studies

Results showed the swelling index [Figures 2a and b] of floating tablets containing polymer blends was highest for formulation P11 (284%) and least for E2 (167.3%). Swelling capability of tablets with high Methocel K100LV have shown less swelling initially which may be due poor wetting properties and less viscous nature. However with time methocel showed good swelling capacity due to high hydration properties.[27] Also swelling index of all tablets increased with time because of the increase in hydration rate of polymers with time. On imbibition of more and more water by polymers, gel floating is formed at the outer surface which depends mainly on polymer concentration and viscosity.[28]

Formulation E2 showed lowest swelling index which may be due to poor hydration of floating in the presence of calcium carbonate. The presence of lactose, being more hydrophilic, results in initial fast swelling of floating than MCC containing tablets but after 4 hours, there was no significant difference in swelling index of tables (E1 vs. E3, E2 vs. E4) which may be due to complete imbibition of water into the polymers in both cases. The optimum formulation E4 showed 217.33% swelling index after 8 hours.

Bioadhesion detachment force

All formulations have shown sufficiently high bioadhesion strength (>8 g) except P3 as shown in Table 5. The bioadhesion strength was increased with increase in the amount of either polymer (CS or CP), as reported earlier.[9,11] On contact with hydrated mucous of pig stomach tissue, hydrogels swell rapidly, resulting in increased uncoiling of polymer chains leading to reduced glass transition temperature (tg) of the polymer. The uncoiled polymeric chains interact electrostatically and tend to increase the adhesion and interpenetration with mucin.[12] The formulations with high concentration of CS and CP have shown the maximum value of bioadhesive strength (P1, P2, P4, P11). The highest bioadhesion force of P1 revealed that formulations containing chitosan showed higher mucoadhesion property, due to its surface positive charge which interact electrostatically with anionic groups present in gastric mucin.[26] The optimum formulation P7 and E4 showed high bioadhesion detachment force of 10.23 g and 8.2 g respectively. The decrease in bioadhesive strength may be attributed to the presence of sodium citrate in E4, which results in high CO_2 bubbles on the tablet surface comparatively.

In vitro drug release studies

The *in vitro* drug release studies were performed using 0.1 N HCl as dissolution medium to evaluate the control release profile of bioadhesive floating tablets in gastric environment. For eradication of *H. pylori*, antibiotics must be released near the antrum region of stomach for mucosal penetration in controlled manner. The optimized formulation must release ~35%, 60%, 80%, ~95% drug in 1 hour, 4 hours, 8 hours, and 12 hours respectively as per the theoretical guidelines of USP. Most of earlier works on floating tablets were unable to achieve the above release profile and hence it was decided to optimize formulation based on above drug release profile, based on similarity factor (f2) as statistical tool. Formulation

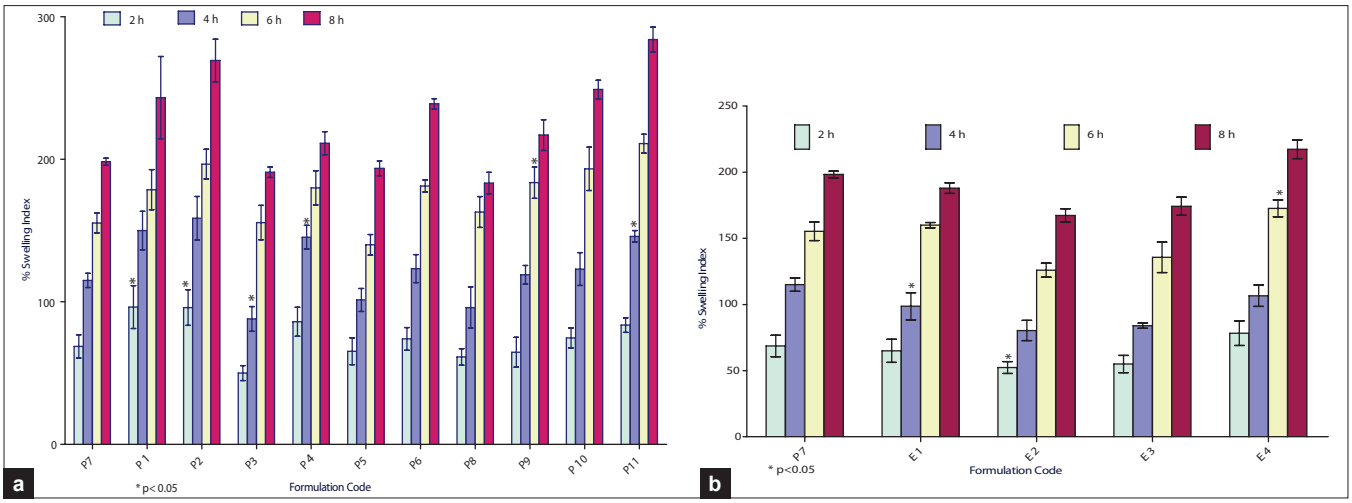

Figure 2: (a) Swelling index profile of metronidazole tablets (P1-P11) at 37°C in 0.1N HCl. Mean value±SD (*n* = 3). (b) Swelling index profile of metronidazole tablets (E1-E4) at 37°C in 0.1N HCl. Mean value±SD (*n* = 3)

Table 5: Evaluation of buoyancy, bio-adhesion and drug content of metronidazole bioadhesive floating tablets (*n*=3)

Formulation code	Drug content (%) mean±SD	Floating lag time (FLT) (minutes) mean±SD	Floating time (hours)	Swelling index At 8 hours (%) mean±SD	Bioadhesion detachment force (g)
P1	99.06±0.12	NF*	NF*	243.33±28.87	15.03±2.12
P2	98.90±0.50	12±0.8	6.4	269.33±15.01	13.33±1.55
P3	97.80±2.12	0	>24	191.00±3.61	6.43±0.60
P4	98.60±1.20	11.2±1.4	~8	211.33±8.08	14.56±1.66
P5	97.56±0.64	0.1±0.02	>24	193.67±5.13	8.26±0.68
P6	99.20±0.21	1.0±0.3	>12	239.00±3.61	10.36±0.96
P7	99.10±0.68	0.1±0.08	~20	198.33±2.52	10.23±0.85
P8	99.10±0.32	0	>24	183.33±7.57	8.73±0.30
P9	98.82±0.74	0	>24	217.00±10.82	8.06±0.98
P10	99.62±0.15	0.1±0.03	>24	249.00±6.56	9.26±1.09
P11	98.75±0.82	0.4±0.06	>12	284.00±8.72	10.6±1.05
E1	99.48±0.22	0.5±0.01	>12	188.00±4.00	8.73±1.00
E2	97.94±1.47	0.3±0.08	>12	167.33±5.03	8.2±0.53
E3	98.46±0.92	0.3±0.04	>12	174.33±6.81	8.5±0.70
E4	98.72±0.98	0.1±0.02	>12	217.33±7.02	8.2±0.70

*NF: No buoyancy observed

P7 have shown high similarity factor value (f2-89.03), which was further studied to observe the effect of lactose versus MCC as diluent and calcium carbonate versus sodium bicarbonate as a gas-generating agent in the presence of sodium citrate on % drug release. The dissolution profile of various floating tablet formulations of metronidazole are tabulated as Table 6 and graphically represented in Figures 3 and 4.

Various important observations from the *in vitro* dissolution profile of tablets are as follows:

Effect of polymers

In the present study, Chitosan, a natural cationic polysaccharide polymer has been selected because of its high mucoadhesion capabilities. Chitosan in the concentration of 200 mg (Formulation P1) has shown high mucoadhesion detachment force, proving its efficacy, but also showed high swelling with gradual erosion leading to fast release of drug in simulated gastric fluid (chitosan has high solubility in acidic environment). The dissolution of drug was complete in 1.3 hour as shown in Figure 3.

To overcome the high erosion, release controller polymers Carbopol 971P (Ionic) and Methocel K100LV (nonionic) were selected (formulation P2 and P3). These polymers have already been successfully used in attaining excellent control release (CR) characteristics along with desired mucoadhesive properties.[12,29,30] Carbopols, the polyacrylates, are more suitable polymer to control the release of drugs in acidic region of GIT.[9] CP971P was found to be the most promising in regulating the drug release profile, followed

Table 6: *In vitro* dissolution rate profile of metronidazole floating tablets (*n*=6)

Formulation code	% Drug release (Q)				
	1 hour	4 hours	8 hours	t50% (hours)	t80% (hours)
P1	89.00	97.80	-	0.4	~1.0
P2	18.00	35.70	54.20	7.0	17.8
P3	20.70	39.60	64.60	4.8	11.9
P4	23.30	44.20	66.20	4.4	10.9
P5	28.20	43.60	74.20	3.8	9.8
P6	21.30	43.60	68.70	4.5	11.1
P7	32.20	57.80	80.20	2.7	7.6
P8	29.80	57.40	78.90	3.2	8.1
P9	28.60	51.00	79.80	3.5	9.1
P10	23.40	41.20	70.60	4.4	11.2
P11	20.70	39.70	67.00	4.9	12.1
E1	32.40	52.20	78.20	3.2	8.8
E2	37.40	58.00	79.10	2.7	7.8
E3	37.60	60.40	80.10	2.7	7.9
E4	34.10	60.20	82.40	2.7	7.5

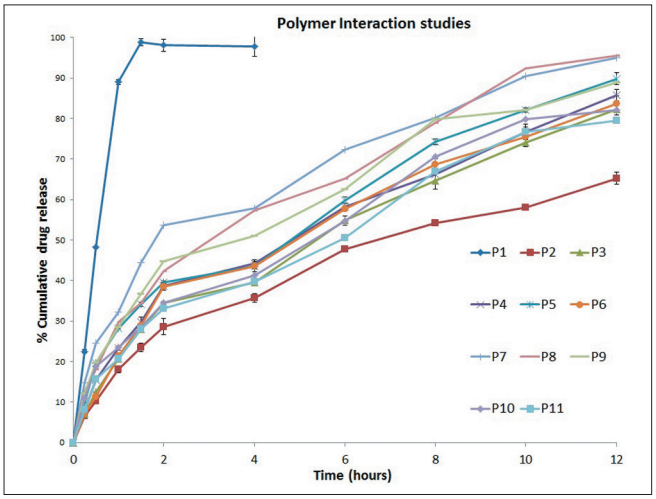

Figure 3: *In vitro* dissolution rate profile of metronidazole tablets (Formulation code P1-P11; effect of polymer)

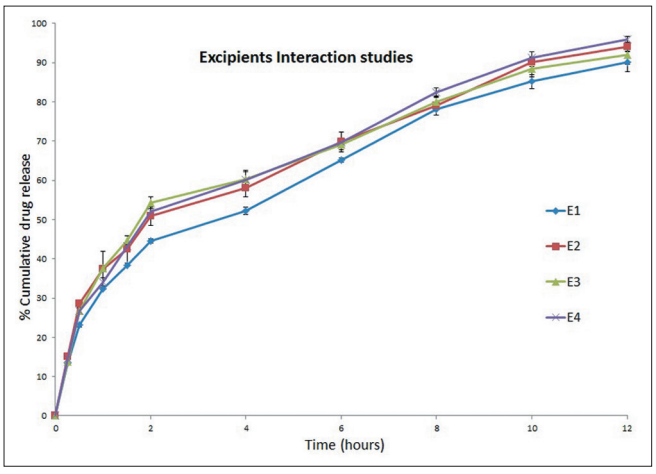

Figure 4: *In vitro* dissolution rate profile of metronidazole tablets (Formulation code E1- E4; effect of excipients)

by methocel K100LV and CS, as revealed by the high values of $t_{80\%}$ (>12 hours). But CP971P(formulation-P2) showed the low buoyancy of floating tablet (less than 6 hours with large float lag time) probably due to higher density of CP (1.76 g/cc). Hence the compressed floating (P3) was formulated with methocel K100LV (density-1.28 g/cc) and was found to be most buoyant with the order of floating time as: methocel K100LV >> CP971P (CS showing no buoyancy). Due to the lowest percentage of the hydrophobic substituent (methoxyl group) and the highest amount of hydrophilic substituent (hydropropoxyl), Methocel K100LV hydrate at faster rate and hence considered to be beneficial in improving the floating properties.[25]

In order to achieve the prerequisite standards for floating bioadhesive tablets, we blended the above three polymers in different proportions from formulation P4-P11. With increase in methocel K100LV and decrease in CP971P (P6-P8), floating tablets showed high buoyancy (>12 hours), low floating lag time (<1.0 minute). With increase in CP971P, more controlled drug release (high $t_{50\%}$ and $t_{80\%}$) was observed. An increase in methocel K100LV in the floating tablet resulted in slow drug release during the first hour, which may be attributed to the polymer's poor wetting, slow swelling due to its low viscosity. However, increased swelling was observed with time, leading to high drug release in 12 hours (82.2% drug release in P3). This may be attributed to reduction in polymer viscosity and hence increased drug diffusion through gel floating of methocel and CP as reported earlier.[30] The concentration range selected in this study for CS, though not influenced much on the buoyancy but high bioadhesion strength and high drug release during 1st hour was observed with increase in CS.

To eradicate *H. pylori,* a high local concentration of drug in gastric mucosa is required in comparison to concentration in systemic circulation. Hence it is desirable to formulate a floating tablet with high total float time (>12 hours), low float lag time (<1 minute), high bioadhesion strength (>8 g). Also drug release profile must be fast during the first hour (>35%) and slow controlled release up to 12 hours. The most optimum polymer blend in this investigation was found with formulation P7 (CS-50 mg, CP-75 mg and Methocel K100LV-75 mg) based on the high similarity factor (f2- 89.03) in comparison to optimized levels for parameters kept constant during the study.

The selected polymeric blend was further studied for effects of diluents and gas-generating agents.

Effect of excipients

In this research, we have compared the effects of water-soluble diluents-MCC and lactose on the swelling index, floatability, and bioadhesion strength of floating tablet as shown in Table 5. The formulation composition E1-E4 consist of same polymeric blend as in formulation P7 but the composition of diluents and gas-generating agents

Table 7: Drug release kinetics of metronidazole tablets

Model		P6	P7*	P8	P9	P10	P11	E1	E2	E3	E4#
Zero order - R^2		0.93	0.87	0.93	0.90	0.95	0.95	0.9	0.87	0.84	0.87
First order - R^2		0.98	0.96	0.95	0.98	0.98	0.98	0.99	0.97	0.98	0.97
Higuchi - R^2		0.99	0.97	0.99	0.99	0.99	0.99	0.99	0.98	0.97	0.98
Kosmeyer- R^2		0.98	0.97	0.99	0.98	0.99	0.98	0.97	0.96	0.97	0.97
peppas	n	0.62	0.45	0.52	0.49	0.50	0.46	0.45	0.45	0.45	0.45
	k	2.97	3.48	3.31	3.31	3.16	3.39	3.52	3.51	3.50	3.50
Hixon-Crowel - R^2		0.82	0.80	0.86	0.83	0.90	0.87	0.84	0.81	0.76	0.81
Similarity factor f2		54.4	89.03	85.28	74.06	55.09	51.04	77.67	88.14	89.02	92.69

*P7 Being more similar to theoretical release profile, the polymer blend of Formulation P5 was selected for further study. #E4 being more close to theoretical release is selected as optimum formulation

were varied. Formulations E1 and E2 comprising lactose as diluent showed initial fast drug release during the first hour in comparison to P7 as shown in Figure 4, which may be due to loosening of the hydrogel structure of floating on fast dissolution of lactose than MCC. On comparison of the release profile of E1-E4, total drug release after 8 hours was significantly same for both diluents. MCC being slightly hydrophobic influences the swelling and erosion properties of the tablets. Formulations E1 and E2 prepared with water soluble lactose showed less swelling index compared with formulations E3 and E4, prepared with MCC, which might be due to the tendency of the MCC to form a tight gel barrier around the hydrophilic polymeric matrix.[9] Hydration and porosity are two essential features for a tablet to remain buoyant on gastric fluid. Carbon dioxide bubbles, obtained after reaction of sodium bicarbonate or calcium carbonate with the acidic dissolution medium, expand the floating volume and produce a reinforcement of the tablet's floatability.[27] Carbon dioxide bubbles show a trend to disappear progressively with time as the hydration of tablet progresses. The presence of citric acid increases the carbon dioxide bubbles and hence decreases the floating lag time in formulation E4 compared to P7. However, the rapid gas formation erodes the matrices surface area, resulting in faster release. In the comparative study between the efficiency of calcium carbonate and sodium bicarbonate in the presence of citric acid on the buoyancy of floating tablets, calcium carbonate provided statistically insignificant decrease in floatability of formulation. However, it has to be considered that the addition of sodium bicarbonate means a reduction in the matrices swelling capability. Moreover, the decrease of the swelling polymer as well as a minor consistency of matrices containing bicarbonate facilitates the floating erosion. It is considered that the gas bubbles dissipating from the inside to the outside of the floating debilitates the floating structure. E4 showed a better drug release profile, more near to the theoretical release profile (f2-92.6) than E2 (f2-88.1) indicating the proficiency of MCC over lactose in controlling the release profile of drug.

Drug release kinetics

The drug release profile of various matix tablets was evaluated for various release kinetic equations as in Table 3 and the characteristic parameters are tabulated as Table 7.

1. The value of *n* (Kosmayer-Peppas model) varies between 0.45 and 0.62, indicating nonFickian (anomalous) release behavior. This can be attributed to highly swelling polymeric blend. The release mechanism from the floating tablets refers to a combination of both diffusion and erosion controlled drug release, which is attributed to the rapid hydration, swelling, and erosion of polymeric blend. Also the presence of methocel K100LV with CP resulted in the reduction of polymer viscosity leading to more diffusion of drug.[26]
2. The table shows a rising trend in the values of *n* as the content of CP971P is increased with highest *n* value (0.56) at the highest levels of CP971P (P11), which may be due to the decrease in relaxation mechanism of matrix.
3. Based on the highest value of R^2 in the release kinetics study, all the formulations followed the Higuchi model of drug release (R^2 between 0.97 and 0.99).

Analysis of similarity factor

The drug release profiles of various floating tablets were evaluated in comparison to theoretical release profile of controlled release products as per USP. As depicted in Table 7, the average similarity factor f2 for formulations P7, P8, E3, E4 were between 85.28 and 92.69, indicating almost analogy of release performance. The finally selected optimum formulation E4 showed the best release kinetics (f2-92.69) due to optimum blend of hydrophilic polymers with balanced viscosity, swelling on hydration. E4 showed 50% drug release in 2 hours and 80% drug release in ~8 hours indicating the high efficacy of gastroretentive formulation with a local effect in stomach.

Accelerated stability studies

The optimized tablets (P7 and E4) on subjected to various temperature and humidity conditions for 12 weeks have shown no changes in color or appearance. The chemical stability results of metronidazole floating tablets demonstrated that the percent drug remaining after storage for a period of 12 weeks was found to be 96%, 93%, 91%, and 90% for formula P7 and 96%, 92%, 90%, and 88.5%for formula E4 at 25°C, 40°C, 50°C, 60°C temperatures, respectively. There was statistically insignificant difference of bioadhesion strength and buoyancy properties in all the tablets during 12 weeks at 25°C and 40°C. Regression analysis of stability data indicated that the decomposition of the drug followed first-order kinetics.

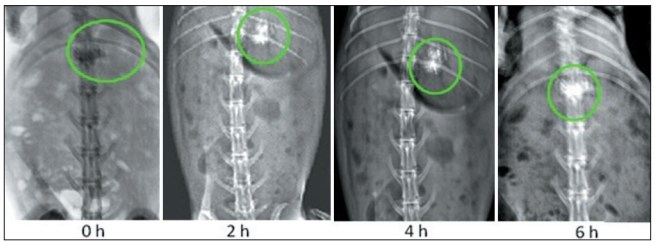

Figure 5: X-ray photographs of New Zealand rabbit's abdomen region after administration of placebo $BaSO_4$ tagged floating, bioadhesive tablets

In vivo gastro-retention study

The digital X-ray obtained for radio-opaque placebo floating tablet in New Zealand rabbits found less buoyancy than *in-vitro* data of floatability studies in SGF. The $BaSO_4$ tagged tablet, similar to formulation E4 was observed in stomach region till 6±1.2 hour as shown in Figure 5. The decrease in gastric retention compared to *in vitro* studies may be due to the presence of the peristaltic movement of the stomach during *in vivo* studies.

CONCLUSION

In present scenario, the antibiotics for eradication are available as conventional film coated tablets or floating tablets or mucoadhesive microspheres which suffered from disadvantages of incomplete therapy and hence there was need to work on a system which can be retained in stomach for longer duration. From this study, we developed an effective delivery which can be retained in stomach for 8 hours by using combination of polymers with both floatability and mucoadhesion. It was concluded that by blending release retardant polymer carbopol 971P with low density polymer methocel K100LV and acid degradable, bioadhesive polymer Chitosan appropriately provide the potential sustained release floating floating tablets for local action in stomach. The study concluded that the increase in concentration of methocel K100LV with decrease in carbopol 971P concentration results in decreased swelling and increased buoyancy but decrease in bioadhesion strength. The presence of chitosan in the blend increased the drug release profile in gastric pH, while carbopol 971P retarded the drug release. The *in vitro* drug release profile of the optimized formulation E4 showed high similarity factor (f2) with the theoretical control release profile. Also it was found that among diluents; MCC helped more in controlling the drug release, decreasing the floating lag time in comparison with lactose and in gas-generating agents sodium bicarbonate in the presence of sodium citrate provide better buoyancy compared to calcium carbonate.

ACKNOWLEDGMENTS

The authors are grateful to Prof. R. S. R. Murthy for kind guidance in the final outcome of this manuscript and Mr. Parveen Garg, Chairman, ISF College of Pharmacy, Moga, for providing facilities and financial assistance during the project.

REFERENCES

1. Löfmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. Clin Infect Dis 2010;50:S16-23.
2. Nasra MA, EL-Massik MA, Naggar VF. Development of metronidazole colon-specific delivery systems. Asian J Pharm Sci 2007;2:18-28.
3. Sun WH, Ou XL, Cao DZ, Yu Q, Yu T, Hu JM, *et al.* Efficacy of omeprazole and amoxicillin with either clarithromycin or metronidazole on eradication of *Helicobacter pylori* in Chinese peptic ulcer patients. World J Gastroenterol 2005;11:2477-81.
4. Glupczynski Y, Megraud F, Lopez-Brea M, Andersen LP. European multicentre survey of *in vitro* antimicrobial resistance in *Helicobacter pylori*. Eur J Clin Microbiol Infect Dis 2001;20:820-3.
5. Patel JK, Patel MM. Stomach Specific Anti-*Helicobacter Pylori* Therapy: Preparation and Evaluation of Amoxicillin-Loaded Chitosan Mucoadhesive Microspheres. Curr Drug Deliv 2007;4:41-50.
6. Singh BN, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63:235-59.
7. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert Opin Drug Deliv 2006;3:217-33.
8. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: A review. Asian J Pharm Clin Res 2010;3:2-10.
9. Trivedi ND, Trivedi UN, Patel MM, Patel JK, Bhandari A. Preparation and evaluation of floating matrix tablet of ranitidine. Am J Drug Discov Dev 2011;1:8-23.
10. Nama M, Rao GC, Veerareddy PR. Formulation and evaluation of gastroretentive dosage forms of clarithromycin. AAPS Pharm Sci Tech 2008;9:231-7.
11. Derle D, Joshi O, Pawar A, Patel J, Perdeshi V. Effect of tablet excipients on mucoadhesive properties of polyoxyethylene and carbopol 971P. Indian J Pharm Sci 2009;1:198-205.
12. Ahmed AA, El-Gazayerly ON, El-Gendy NA, Ali AA. Floating Tablet of Trimetazidine Dihydrochloride: An Approach for Extended Release with Zero-Order Kinetics. AAPS Pharm Sci Tech 2010;11:1058-67.
13. Dalavi VV, Patil JS. Gastroretentive drug delivery system of an antiretroviral agent. Int J Pharm Tech Res 2009;1:1678-84.
14. Timmermans J, Andre JM. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: New data for reconsidering the controversy. J Pharm Sci 1994;83:18-24.
15. Vyas SP, Khar RK. Gastroretentive Systems In: Controlled Drug Delivery: Concepts and Advances. 1st ed. New Delhi: Vallabh Prakashan; 2002. p. 196-217.
16. Chitnis VS, Malshe VS, Lalla JK. Bioadhesive polymers-synthesis, evaluation and application in controlled release tablets. Drug Dev Ind Pharm 1991;17:879-92.
17. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS, Rao YM. Polymers for mucoadhesive drug delivery system: A current status. Drug Dev Ind Pharm 2008;34:1246-66.
18. Deacon MP, McGurk S, Roberts CJ, Williams PM, Tendler SJ, DaviesMC, *et al*. Atomic force microscopy of gastric mucin and chitosan mucoadhesive systems. Biochem J 2000;348:557-63.
19. Patel VF, Patel NM, Yeole PG. Studies on Floating and evaluation of Ranitidine floating tablets. Ind J Pharm Sci 2005;67:703-9.
20. Patel VM, Prajapati BG, Patel HV, Patel KM. Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS Pharm Sci Tech 2007;8:1-12.
21. Kerec M, Bogataj M, Mugerle B, Gaš perlin M, Mrhar A. Mucoadhesion on pig vesical mucosa: Influence of polycarbophil/calcium interactions. Int J Pharm 2002;241:135-43.
22. Jagdale SC, Agavekar AJ, Pandya SV, Kuchekar BS, Chabukswar AR. Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. AAPS Pharm Sci Tech 2009;10:1071-9.
23. Tapia-Albarran M, Villafuerte-Robles L. Assay of amoxicillin sustained release from matrix tablets containing different proportions of Carbopol 971P NF. Int J Pharm 2004;273:121-7.
24. Baumgartner S, Kristel J, Vreer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000;195:125-35.

25. Singh B, Rani A, Babita, Ahuja N, Kapil R. Formulation optimization of hydrodynamically balanced oral controlled release bioadhesive tablets of tramadol hydrochloride. Sci Pharm 2010;78:303-23.
26. Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the release and floating properties of Gastric Floating Drug Delivery System using factorial design. Int J Pharm 2003;253:13-22.
27. Gutiérrez-Sánchez PE, Hernández-León A, Villafuerte-Robles L. Effect of Sodium Bicarbonate on the Properties of Metronidazole Floating Matrix Tablets. Drug Dev Ind Pharm 2008;34:171-80.
28. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. *In vitro* evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int J Pharm 1992;78:43-8.
29. Kavanagh N, Corrigan OI. Swelling and erosion properties of hydroxyl propyl methyl cellulose (Hypromellose) matrices – influence of agitation and dissolution medium composition. Int J Pharm 2004;279:141-52.
30. Longer MA, Ching HS, Robinson JR. Bioadhesive polymers as platform for oral control drug delivery. III. Oral delivery of chlorthiazide using bioadhesive polymer. J Pharm Sci 1985;74:406-10.

How to cite this article: Arora S, Budhiraja RD. Effect of polymers and excipients on the release kinetics, bioadhesion, and floatability of metronidazole tablet. Asian J Pharm 2011;5:215-24.

Source of Support: I. S. F. College of pharmacy, Moga. **Conflict of Interest:** None declared.