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Design and evaluation studies on novel floating tablets for peptic ulcer treatment

Putta Rajesh Kumar*, Hiremath Doddayya, S. Rajendra Reddy

Department of Pharmaceutics, N. E. T. Pharmacy College, Raichur, Karnataka, India.

*Corresponding author: prkrguhs@gmail.com

ABSTRACT:

The aim of this study was to develop enteric coated esomeprazole core tablet followed by compression coating with clarithromycin coat granules to obtain a single unit core in coat floating tablet. The tablets were prepared by investigating various porous carriers, cellulosic polymers and natural gums. Sodium bicarbonate is used as gas generating agent. The enteric coating of core tablet showed significant protection of esomeprazole from gastric acid by acryl EZE and *in vitro* release of drug in simulated intestinal fluid. The rheological and compressional parameters of the core powder and coat granular beds showed their ease of flow and compaction in to tablet. The tablets showed optimum floating parameters with minimum floating lag time. *In vitro* dissolution in modified dissolution apparatus indicated the clarithromycin release in simulated gastric fluid for first 2h and esomeprazole in simulated intestinal fluid for 10h. A zero order drug release was observed for clarithromycin coat and first order drug release for esomeprazole. Porous carriers, HPMC and natural gums as matrix polymers optimization studies indicated their suitability for floating tablet formulations. The dosage forms could be further evaluated for pharmacokinetic studies to study actual drug release *in vivo.*

Key words: Peptic ulcer, Esomeprazole, Super disintegrant, Clarithromycin, Porous carriers.

INTRODUCTION:

Peptic ulcer is an open sore in the lining of the stomach or intestine, much like mouth or skin ulcers. Peptic ulcers are usually caused by acid and pepsin, a digestive stomach enzyme. An ulcer forms when there is an imbalance between aggressive and defensive factors. More than 50% of the world population is believed to be infected by *Helicobacter pylori (H. pylori)* a major pathogenic factor in peptic ulcer and gastric neoplasm. Peptic

ulcer is caused by *H. pylori*, non steroidal anti inflammatory drugs and aspirin. Esomeprazole an S-isomer of omeprazole that acts as proton pump inhibitor used to treat gastric ulcer. It suppresses acid production by inhibiting gastric parietal H^+/K ATPase involved in hydrochloric acid production in the stomach. [1] Clarithromycin is a broad spectrum antimicrobial new generation macrolide active against most Gram positive aerobic cocci and Gram positive bacilli. [2] The activity of clarithromycin is enhanced by its extensive tissue distribution and by formation of the 14-(R)-hydroxyclarithromycin metabolite. Clarithromycin and 14-(R)-hydroxyclarithromycin have a minimum inhibitory concentration of 0.03 and 0.06 µg/ mL for *h. pylori*, respectively. The clarithromycin is reported that it has activity against *h pylori* bacteria that causes peptic ulcer. [3]

The literature was updated for floating dosage forms and some of the relevant recent references related to present study were presented here. Nama M. et al., prepared clarithromycin floating tablets by wet granulation. They observed the mechanism of drug release of from tablets is anomalous diffusion with zero order kinetics. *In vivo* radiographic studies indicated increased gastric residence time of tablet evidenced localized drug action for peptic ulcers. [4] Chandira M. et al., designed famotidine effervescent floating tablets by direct compression technique. They concluded that HPMC K4M, HPMC K100 M and Xanthan gum can be successfully used in formulation of Famotidine sustained release gastro retentive floating drug delivery system using low density polymer. [5] Kumar R. et al., developed famotidine floating drug delivery system using sodium bicarbonate, citric acid, HPMC and carbopol 934P. They found that the mechanism of drug release occurred by diffusion due to polymeric relaxation. The type of polymer affected the drug release rate and mechanism. Polymer swelling is crucial in determining the drug release rate and for flotation. Optimized formulation was stable during storage at 45 °C/75% RH for three months. [6] Prakash K.G. et al formulated Ranitidine HCl floating tablets with isolated chitosan by wet granulation technique. They concluded that the floating formulations were able to delay the gastric emptying of Ranitidine HCl tablets in beagle dogs. This would maximize absorption by allowing the slowly released drug in the stomach to reach the upper small intestine. The floating tablets of Ranitidine HCl also showed better gastric cytoprotection when compared with conventional dosage form due to its extended duration of release and action. [7]

Floating delivery systems when come in contact with stomach fluid, carbon dioxide is generated and entrapped in the hydrocolloid gel leads to an upward drift of the dosage form and maintains it in a floating condition results in localized drug delivery in

stomach. The patients with peptic ulcer and *h. pylori* infection require treatment with anti secretory agent along with antimicrobial agent acts against *h. pylori* that gives more symptomatic relief and patient compliance. Hence the present study is designed to develop a single unit core in coat floating tablet containing esomeprazole core and clarithromycin coat to deliver the drugs simultaneously at different sites in GIT for the effective treatment of *h. pylori* associated peptic ulcer.

The formulated core in coat tablet is intended to deliver clarithromycin in stomach and helps to act against *h pylori* localized in the mucosal lining of stomach. Later, due to the erosion of polymer coat core tablet released, passed through pyloric antrum to duodenum to deliver esomeprazole to suppress excess acid secretion. The esomeprazole core tablets were developed using various super disintegrants along with directly compressible vehicles by direct compression technique. The powder bed was studied for various rheological parameters and compressed tablets were subjected for compression parameters studies. Later these tablets were enteric coated with methacrylic acid copolymer Acryl EZE to protect esomeprazole from gastric acid. The coated tablets were subjected for acid uptake studies. The results were presented in our previously published article. [8] In continuation to this in the present study the developed core formulations were compression coated with clarithromycin coat blends and studied for *in vitro* drug release profiles.

Various clarithromycin formulations was developed by investigating porous carriers, cellulosic polymers and natural gums for preparing its powder blend or granular bed for compression coating over the developed esomeprazole cores to form single unit core in coat floating tablet. The coat formulations were also studied for pre and post compressional characteristics. Further the developed formulations were subjected for various floating parameters followed by *in vitro* dissolution studies in modified dissolution apparatus that mimics open flow through cell assembly.

MATERIALS AND METHODS:

Esomeprazole magnesium trihydrate was gifted by Aurobindo pharma limited, A.P, India. Crospovidone, Sodium starch glycolate, Croscarmellose sodium obtained from Danmed Pharmaceuticals Pvt Ltd, Hyderabad. Lactose DC and Mannitol DC were procured from SD Fine Chemicals Limited, Mumbai. Acryl EZE (Eudragit L 30 D55, Colorcon) was supplied by Medreich Limited, Bangalore. Polypropylene, Calcium silicate, Aerosil purchased for from Sigma Aldrich, Bangalore. Xanthan gum, Guar gum,

HPMC K4M, MCC was purchased from INR Chem and yarrow chemicals, Mumbai. Other solvents and chemicals used in the research were of LR grade.

Porous carriers size reduction:

The Polypropylene pellets were placed in a ball mill (J.T. Jagtiani Instruments, India) containing pebbles that occupied 45% volume. Drum was rotated at optimum speed for 90 min. The size reduced material through impact and attrition was taken out and is subjected for further size reduction in a waring blender (Samurai instruments, India) operated at 12,000 rpm for 20 min. The fine powder obtained was taken and placed over sieve shaker with # 120 sieve and operated for 05 min. Over sized polypropylene particles retained on # 120 sieve were subjected for further size reduction in waring blender. The process continued till all polymer powder passed or undersized through # 120 sieve. The fine powder passed through # 120 sieve is collected in receiving pan was taken out and placed in self sealing polythene bag and then packed in air tight container and labeled as porous polypropylene undersize # 120 until further use. Similarly fine powder of Calcium silicate and Silicon dioxide (Aerosil) was undersized through # 100 followed by # 120 sieve. The fine powder was taken out and placed in self sealing polythene bag and packed in air tight container and labeled as porous Calcium silicate undersize # 120, porous silicon dioxide undersize # 120 until further use.

Various polymers and excipients were studied for their suitability towards formulation of proposed core in coat gastroretentive tablets. Porous carriers like fumed silicon dioxide, calcium silicate and polypropylene, sodium bicarbonate as effervescence agent, matrix forming agents like xanthan gum, guar gum, carbopol and HPMC K4M along with drug and lubricants were subjected for preliminary screening studies by using direct compression and wet granulation techniques for their effect on rheological and post compressional parameters along with significant parameters like floating lag time, duration of floating time for gastroretentive tablets.

Clarithromycin powder blend preparation for compression coating over Esomeprazole magnesium enteric coated core tablets by Direct Compression:

The clarithromycin coat formulation Ingredients of F1, F2, F3 and 1 to 4 were accurately weighed, milled and passed through sieve # 100/ 120 and then thoroughly blended with glidant and lubricant. The powder blends blended was studied for rheological characteristics and further the uniform blend of powder containing Clarithromycin and direct compressible vehicles were then kept ready to be used for

compression coating over esomeprazole core tablets by direct compression through compression coating technique using various core tablets in a 10 station tablet punching machine using 13 mm flat punches at a pressure of 4-6 kg/cm^2. In each batch 300 core in coat tablets were prepared.

Clarithromycin coat granules preparation by wet granulation for compression coating over Esomeprazole magnesium enteric coated core tablets:

The formulation ingredients containing drug, porous carrier, effervescent agent and matrix carrier for a batch 300 tablets were weighed accurately and passed through # 100 mesh sieve and the powder was uniformly blended in a cube mixer. The powder blends of CC1 to CC4 and CT1 to CT3 were wet granulated with water and starch paste (15% w/w) as binder to produce wet mass. The wet mass was passed through mesh # 16, dried in an oven at 40°C for 4 - 5 h, and again passed through mesh # 20. Later, talc and magnesium stearate as required were incorporated and blended. Later for formulations T1 to T3 the powder blends of ingredients were wet granulated with (1.5% w/w) each of guar gum, xanthan gum and HPMC K4M as binder in water to produce wet mass. The wet mass of respective coat formulations was then passed through mesh # 14, dried in an oven at 40°C /30 % RH for 4 h. Later dried coat granules were passed through mesh # 16. Later, talc and magnesium stearate were incorporated as glidant, lubricant and blended thoroughly. The granules were studied for their rheological parameters and used for compression coating over esomeprazole core tablets. [9, 10]

Rheological parameters evaluation of Clarithromycin coat Powder / Granular bed:

Angle of repose (°θ):

Angle of repose of granules was determined by measuring the height and radius of the heap of the powder/granule bed. A cut stem funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the horizontal plane. Powder/granule was placed in the funnel and allowed to flow freely to form a heap. With the help of vernier calipers (Mitutoyo) the height and radius of the heap were measured and noted. ø = tan^{-1} h /r. Where h is height of heap of powder/granule bed. r is radius of heap of powder/granule bed. Average of three repose angles was taken and tabulated. [11]

Bulk density:

Bulk density was determined (Konark instruments, India) by placing a fixed weight of powder/granules blends in a measuring cylinder on bulk density testing unit (Konark

Instruments, India) and the total volume was noted. Bulk density was calculated by using the formula. Bulk density = Total weight of powder or granules **/** Total volume of powder or granules. Average of three densities of powder/granule was taken and tabulated. [11]

Tapped density:

Tapped density was determined in a bulk density testing apparatus (Konark instruments, India) by placing the powder/granules blend in the measuring cylinder and the total volume of powder blend was noted before and after 100 tappings. Tapped density was calculated by using the formula.

Tapped density = Total weight of powder or granules **/** Total volume of powder/ granules after 100 tappings.

Average of three densities of powder/granule was taken. [12]

Carr's Compressibility index:

Compressibility index was determined by placing the powder/granules in a measuring cylinder and the initial volume (V_0) was noted before tapping. After 100 tapping again final volume (V) was noticed. Compressibility index = (1- V/ V_0) x 100. Where V_0 = volume of powder/granules before tapping. V = volume of powder/granules after 100 tappings. Average of three readings was taken. [12]

Method of preparation of Core in coat tablet containing Esomeprazole magnesium trihydrate core and Clarithromycin coat:

PP1D Pilot press loaded with 13 mm dies was cleaned and dried as per standard operating procedure. The punching pressure was adjusted to produce tablets of hardness 4 to 6 kg/ cm^2. Then compression coating was performed with clarithromycin coat powder blend / coat granules over enteric coated esomeprazole magnesium core tablets. Initially 55% w/w of the coat powder blend / coat granules containing Clarithromycin was placed into the die cavity (diameter 13 mm) and then core tablet of esomeprazole (diameter 6 mm) was placed into the same die cavity, by carefully adjusting the core tablet to the centre of the coat blend inside the die cavity. The remaining 45 % w/w of clarithromycin coat powder blend / coat granules were filled over the core tablet so that the core is completely and uniformly surrounded by the coat powder blend / coat granules and were then punched on a 10 station tablet press

(PP1D, Chamunda, India). These tablets were studied for compression characteristics and later *in vitro* dissolution studies were carried out. [13]

Evaluation methods for Esomeprazole magnesium trihydrate core in Clarithromycin coat compressional parameters of compression coated tablets:

Tablet weight variation:

Ten tablets were randomly sampled and accurately weighed on Dhona analytical balance. The tablet weight variation was expressed as mean values ± SD. [14]

Friability test:

Roche Friabilator was used for testing the friability of the tablets. Ten tablets were weighed accurately and placed in the tumbling chamber and rotated at 20 rpm for a period of 5 min. The tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated by using formula given below.

Percent friability = Initial weight of tablets- Final weight of tablets / Initial weight of tablets ×100. [15]

Hardness test:

Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the tester plungers, and the handle was pressed, the force of the fracture was recorded in the recorder guaze. The results were expressed as mean values ± SD. [14]

Diameter test:

The tablets were evaluated for their diameter using a vernier Caliper (Mitutoyo, Japan). Average of three readings were taken and tabulated (n = 3) and their respective SD was computed. [16]

Tablet thickness:

A vernier calipers (Mitutoyo, Japan) was used to determine thickness of randomly selected tablets (n=3). [16]

Determination of drug content:

Coat tablet of clarithromycin was separated from core in coat tablet and crushed into powder in a mortar and 100 mg of powder was taken in a volumetric flask containing

dry ethanol and kept aside with constant shaking for 24 hours on a rotary flask shaker (Konark instruments, Ambala cantonment, Haryana.) to extract total drug present in the tablet. The absorbance of the solution was measured after suitable dilution at 211 nm against dry ethanol as blank (n=3). [16]

Density measurement:

The apparent density was calculated from the volume and mass of the tablet. The volumes V of the tablets were calculated from their height h and radius r using micrometer. Volume of the tablets was calculated by using the following equation. Average of three readings were taken and tabulated (n = 3). $V = \prod x r^2 x h$. [17]

Floating lag time:

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa et al. The tablets were placed in a 100 ml beaker containing 100 ml 0.1 N HCl and the time required for the tablet to rise to the surface and float was determined as floating lag time. Average of three readings was taken and recorded. [18]

Duration of floating time:

A glass beaker containing 100 ml of 0.1N HCl was taken, in which a tablet was placed for observation. The total duration for which a tablet remains floating was recorded as duration of floatation. Average of three readings were taken (n = 3). [19]

***In vitro* dissolution studies through modified flow through dissolution system:**

A modified dissolution apparatus was fabricated from a 100 ml glass beaker, by attaching an S-shaped side arm (glass tube) and capable of holding 70 ml of dissolution medium (simulated gastric fluid/simulated intestinal fluid). The medium was stirred on a magnetic stirrer. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min. The tablet was put in the modified beaker containing 70 ml of dissolution medium and the medium was stirred at 75 rpm. The temperature of the medium was maintained at 37 ± 0.5 ºC. From the burette, simulated gastric fluid pH 3.0 was added at a rate of 2 ml/min. Samples of 1 ml were collected at predetermined time intervals for 2 h. The dissolution was further carried out with the same tablet by replacing the dissolution media with alkaline borate buffer pH 9.0 and study continued for next 10 h and samples of 1 ml were withdrawn periodically and analyzed spectrophotometrically. All the studies were carried out in triplicate (n = 3). The withdrawn samples were analyzed for both the drugs simultaneously at 203.5 nm

for esomeprazole magnesium trihydrate and at 211nm for clarithromycin respectively throughout the study by using U.V. 1700 (Pharmaspec Shimadzu. Japan). [20, 21]

RESULTS AND DISCUSSION:

Treatment of peptic or gastric ulcer requires an antibacterial agent like clarithromycin, a broad spectrum antibacterial agent, which is effective against peptic ulcer causing *h. pylori* bacteria and a gastric acid suppressing drug like esomeprazole magnesium trihydrate, a proton pump inhibitor. Clarithromycin has its absorption window in stomach where as esomeprazole is absorbed well from small intestine because of its instability in stomach. *In lieu* of the previous reports, in the current investigation a novel core in coat gastro retentive tablets were developed by compression coating method. The dosage form containing 20 mg of esomeprazole presented as enteric coated core tablet within coat formulation containing 250 mg clarithromycin dispensed as a single unit. Further the clarithromycin coat tablets were formulated as FDDS or GRDF and esomeprazole core as enteric release tablets. The core tablets were initially punched using 6 mm punches and later coat formulation was manipulated in 13 mm die cavity so as to surround the core tablets completely and then the tablets was punched in a 10 station Pilot press. Porous polymers, gas generating agents and other excipients were studied in preliminary studies for their suitability towards formulation of proposed core in coat gastroretentive tablets.

The developed formulations were studied for the following rheological properties. The angle of repose (°θ) of Clarithromycin coat powder blends of F1, F2, F3 and 1 to 4 was found to be in the range of 24.50 to 31.36. The bulk density of coat formulation powder blend is in between 0.240 to 0.400 and tapped density is from 0.310 to 0.500. Compressibility index of the above directly compressible Clarithromycin coat powder blends were found to be in between 13.17 to 15.10. Rheological parameters evaluation showed the angle of repose (°θ) of Clarithromycin coat granules of formulations CC1 to CC4 and CT1 to CT3 was found to be in the range of 18.96 to 25.96. The bulk density of coat formulation granular blend is in between 0.340 to 0.480 and tapped density is from 0.460 to 0.540. Compressibility index of the above compressible Clarithromycin coat granular blends were found to be in between 09.10 to 15.00. The results were represented in table1. The floating parameters of preliminary coat formulations were given in table 2.

Table 1. Rheological parameters of preliminary Clarithromycin coat formulations

F. code	Angle of repose (Øº)				Bulk density		Tapped density		Compessibility Index		Hardness	
	B.gli	sd	A.gli	sd	BD	sd	TD	sd	(%)	sd	kg/cm2	sd
F1	32.83	0.20	31.36	0.76	0.40	0.01	0.45	0.01	14.12	1.02	4.23	0.20
F2	30.21	0.17	28.98	0.59	0.38	0.01	0.43	0.01	14.31	0.96	4.40	0.10
F3	27.75	0.60	25.83	0.64	0.36	0.01	0.41	0.05	13.17	0.96	4.50	0.17
1	30.16	0.28	26.56	0.07	0.35	0.02	0.41	0.01	14.26	0.32	4.20	0.20
2	29.76	1.57	25.20	0.72	0.38	0.01	0.50	0.04	14.66	0.57	4.60	0.10
3	28.23	0.86	24.50	0.50	0.37	0.01	0.49	0.01	15.00	0.40	4.40	0.17
4	27.10	0.85	25.10	0.90	0.24	0.03	0.31	0.02	15.10	0.36	4.10	0.20
CC1	27.97	0.70	25.96	0.51	0.48	0.01	0.54	0.01	10.63	1.45	4.83	0.15
CC2	25.71	0.83	23.94	0.75	0.47	0.04	0.50	0.02	9.100	1.60	5.30	0.20
CC3	22.28	0.56	23.58	1.31	0.44	0.03	0.51	0.05	13.26	1.13	4.60	0.02
CC4	27.63	0.03	25.70	0.43	0.42	0.01	0.47	0.02	12.00	0.50	4.90	0.36
CT1	22.30	0.08	19.83	0.15	0.41	0.01	0.46	0.02	9.700	0.10	4.60	0.10
CT2	21.33	0.57	18.96	0.05	0.34	0.01	0.47	0.03	14.23	0.05	4.80	0.10
CT3	23.40	0.79	22.00	0.87	0.38	0.01	0.50	0.02	15.00	0.79	4.40	0.10

The angle of repose (°θ) of Clarithromycin granules of T1 to T3 coat formulations was found to be in the range of 21.401 to 26.113. The bulk density of coat formulation granular blend is in between 0.356 to 0.403 and tapped density is from 0.414 to 0.452. Compressibility index of the above compressible Clarithromycin coat granular blends were found to be in between 11.633 to 14.200. The data was represented in table 3. The rheological characteristics of Clarithromycin coat powder blends and granular blends indicated that the powder / granular beds of coat formulations are freely flowable and easily compressible.

Later the compression coated tablets of T1 to T3 formulations showed the floating lag time was in the range of 02 sec to 112 sec. whereas the duration of floating was found to be 02 h to 24 h and core tablet exposed / released in 39 to 124 min. These results showed in table 4 revealed the suitability of the above formulations to explore as core in coat gastroretentive tablets. The core in coat tablets during the investigation initially sanked to bottom of the beaker, hydrated and floated to the surface of 0.1 N HCl gastric fluid with minimum lag time desired for gastroretentive tablets. Further the tablets were continued to float over surface with a prolonged duration of floating which is desirable

for regioselective absorption of Clarithromycin from the dosage form through gastric mucosa. The enteric coated core tablet is released due to coat erosion with in time to deliver esomeprazole in pH 9.0 which simulates intestinal environment. The tablets also showed minimum erosion of particles during floating lag time studies.

Table 2. Floating lag time and duration of floating of preliminary Clarithromycin coat formulations

F code	Tablet Floating lag time and Duration of Floating studies observations
F1	Tablet sank to the bottom, was swollen, later eroded but did not float to the surface.
F2	Tablet sank to the bottom, was swollen, later eroded but did not float to the surface.
F3	Tablet sank to the bottom, was swollen, later eroded but did not float to the surface.
1	Tablet sank to the bottom hydrated but did not float to the surface.
2	Tablet sank to the bottom hydrated but did not float to the surface.
3	Tablet sank to the bottom hydrated but did not float to the surface.
4	Tablet sank to the bottom hydrated, swelled but did not float to the surface.
CC1	Tablet sank to the bottom, was swollen, later eroded with effervescence but did not float to the surface.
CC2	Tablet sank to the bottom, eroded with effervescence but did not float to the surface.
CC3	Tablet sank to the bottom, eroded by effervescence but did not float to the surface.
CC4	Tablet sank to the bottom and eroded but did not float to the surface.
CT1	Tablet sank to the bottom eroded with effervescence but did not float to the surface.
CT2	Tablet sank to the bottom eroded with effervescence but did not float to the surface.
CT3	Tablet sank to the bottom eroded with effervescence but did not float to the surface.

The accuracy studies of Clarithromycin from T1 to T3 coat formulations was 94.93 to 97.50 % and precision of 0.115 to 0.306 shows the drug content uniformity of Clarithromycin in the tablets. The core in coat tablets was studied for various

compressional parameters. The weight variation of C1T1 to C3T3 formulations was found to be uniform and thicknesses (mm) of 4.32 to 4.39 were observed. Similarly diameters of (mm) 13.45 to 13.47 were found to be uniform. The hardness (Kg/cm^2) of the tablets was found to be between 5.63±0.113 to 5.73±0.115, the friability of C1T1 to C3T3 tablets was 0.776 to 0.895 which was found to be minimum. The density (g/cc) of C1T1 to CT33 formulations obtained as 0.963 to 0.981 indicates the suitability of tablets for their floating ability to the surface in 0.1N HCl. The drug content studies of Clarithromycin from C1T1 to C3T3 tablets in dry ethanol released 237.33 to 243.67 mg of drug from tablets containing 250 mg dose shows the uniformity in drug content. Results were represented in table 5. Esomeprazole magnesium trihydrate C_{20} from C1 to C3 was 21.0 to 59.0 min, with slope ranges from 0.0352 to 0.0656 and showed regression values (r^2) of 0.9049 to 0.9323. Clarithromycin C_{20} from T1 to T3 was 15.7 to 21.0 min, with slope ranges from 1.9520 to 1.9906 and showed regression values of 0.9840 to 0.9985. Data showed in table 6.

In vitro release was studied by using modified flow through cell apparatus model in simulated gastric juice for 2 h and continued with the same tablet in simulated intestinal fluid. A constant temperature of 37 ± 0.5°C and 75 rpm for a period of 12 h was maintained during the studies.

Table 3. Rheological parameters of T1 to T3 Clarithromycin coat formulations granules:

F. code	Angle of repose (Øº) ± SD		Bulk Density ± SD	Tapped Density ± SD	Carr's compressibility Index± SD
	Before Adding glidant	After Adding glidant			
T 1	27.467 ±0.462	26.133 ±0.115	0.403 ±0.006	0.452 ±0.006	11.933 ±0.306
T 2	23.733 ±0.416	21.400 ±0.361	0.355 ±0.030	0.556 ±0.001	14.300 ±0.265
T 3	22.613 ±0.180	21.617 ±0.404	0.272 ±0.015	0.304 ±0.008	08.633 ±0.208

Table 4. Floating parameters study of C1T1 to C3T3 core in coat formulations.

Sl.no	Floating Parameter	C1T1	C2T2	C3T3
1	Floating lag time (sec)	02	11	112
2	Duration of floating (h)	24	02	18.25

Table 5. Post compressional parameters of core in coat tablets:

Formulation code	Weight Variation (mg±SD)	Diameter (mm±SD)	Thickness (mm±SD)	Hardness (kg/cm²) ±SD	Friability (%)	Apparent Density (g/cc)	Drug content in dry ethanol (mg±SD)
T1 C1	601.38 ±0.910	13.47 ±0.015	4.35± 0.036	5.73± 0.115	0.895	0.969	237.33 ±0.115
T2 C2	604.60 ±0.759	13.45 ±0.023	4.39± 0.011	5.63± 0.057	0.860	0.963	242.00 ±0.114
T3 C3	602.22 ±0.955	13.46 ±0.020	4.32± 0.010	5.73± 0.115	0.776	0.981	243.67 ±0.200

Table 6. Drug release kinetics of core in coat floating tablets:

F.Code	Core/coat	C_{20} (min)	Slope(m)	Regression (r)
T1	T1	21.0	1.9520	0.9985
C1	C1	59.0	0.0656	0.9323
T2	T2	16.5	1.9906	0.9936
C2	C2	48.0	0.0406	0.9148
T3	T3	15.7	1.9870	0.9840
C3	C3	21.0	0.0352	0.9049

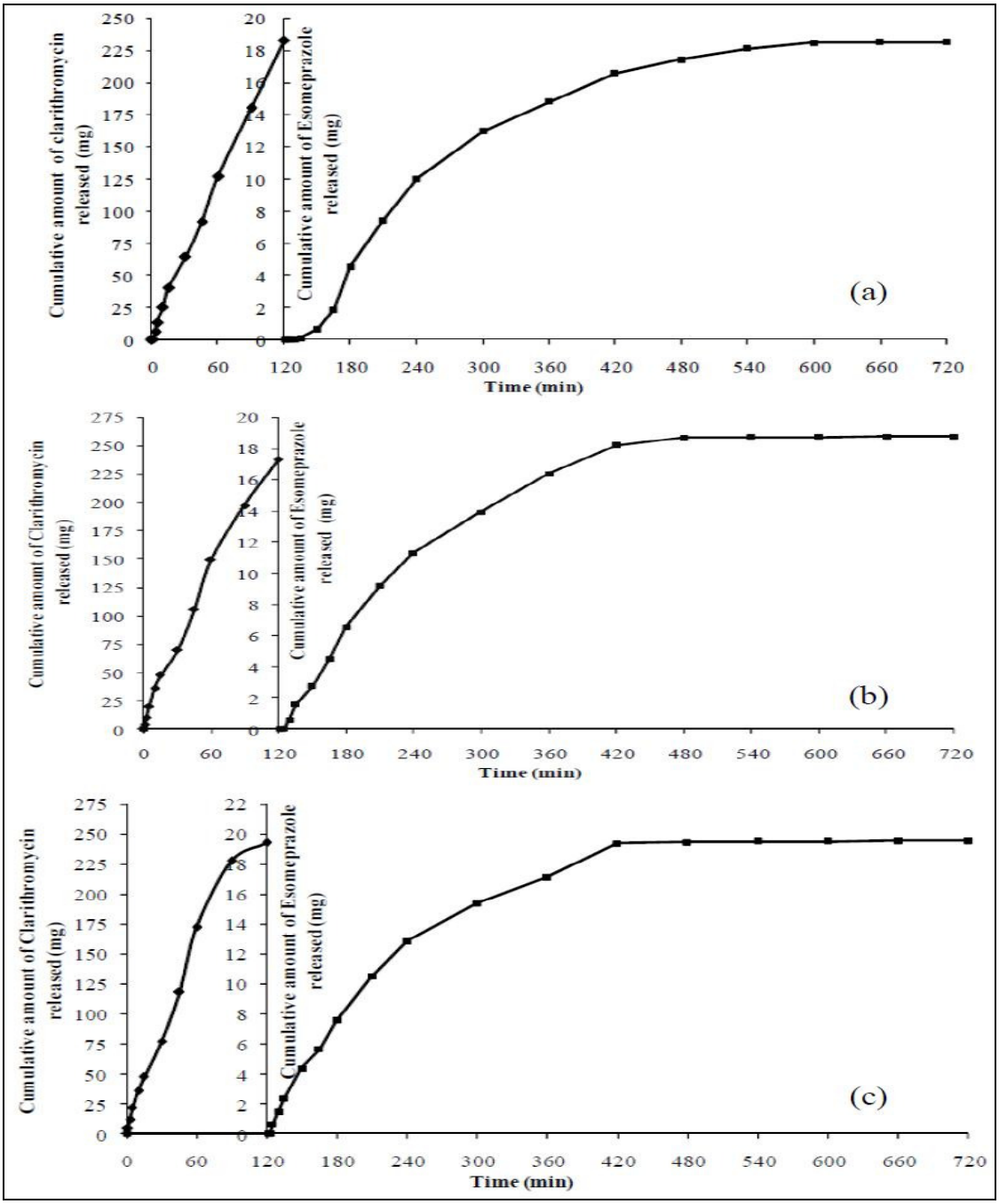

Figure 1. a) Cumulative amount release of clarithromycin from T1 containing guar gum and esomeprazole magnesium trihydrate from C1 containing DC lactose. **b)** Cumulative amount release of clarithromycin from T2 containing xanthan gum and esomeprazole magnesium trihydrate from C2 containing DC lactose. **c)** Cumulative amount release of clarithromycin from T3 containing HPMC K4M and esomeprazole magnesium trihydrate from C3 containing DC lactose.

In vitro dissolution study of T1C1 showed Clarithromycin from T1 coat released 20% of drug in 21 min and 232.96 mg (93.18%) in 120 min from 237.33 mg dose. The release followed zero order kinetics with slope value 1.9520 and correlation coefficient (r) of 0.9985. Esomeprazole from C1 core released 20% of drug in 59 min and 18.527 mg (92.63%) in 600 min from 19.79 mg dose. The release followed first order kinetics with slope value 0.0656 and correlation coefficient (r) of 0.9323. Graphically represented in figure 1 a. *In vitro* dissolution study of T2C2 showed Clarithromycin from T2 coat released 20% of drug in 16.5 min and 238.18 mg (95.27%) in 120 min from 242.0 mg dose. The release followed zero order kinetics with slope value 1.9906 and correlation coefficient (r) of 0.9936. Esomeprazole from C2 core released 20% of drug in 48 min and 18.762 mg (93.18%) in 600 min from 19.84 mg dose. The release followed first order kinetics with slope value 0.0406 and correlation coefficient (r) of 0.9148 as represented in figure 1 b. *In vitro* dissolution study of T3C3 showed Clarithromycin from T3 coat released 20% of drug in 15.7 min and 242.76 mg (99.61%) in 120 min from 243.67 mg dose. The release followed zero order kinetics with slope value 1.9870 and correlation coefficient (r) of 0.9840. Esomeprazole from C3 core released 20% of drug in 21 min and 19.550 mg (98.59%) in 600 min from 19.86 mg dose. The release followed first order kinetics with slope value 0.0352 and correlation coefficient (r) of 0.9049 indicated in figure 1 c.

CONCLUSION:

The enteric coating of esomeprazole magnesium trihydrate tablets with Acryl EZE protects the drug from degradation in gastric environment and it can be successfully delivered to proximal part of small intestine. Drug content estimation studies of Clarithromycin in coat tablet formulations indicated the fair uniformity of Clarithromycin in coat formulations. Studies on rheological characteristics of Clarithromycin coat powder blends and granular blends showed their free flowing nature and ease for compression to tablet. Evaluation of floating lag time, duration of floating showed the suitability of the formulations to formulate core in coat gastroretentive tablets for release of Clarithromycin in gastric pH and esomeprazole in alkaline pH to treat peptic ulcer disease associated with *h. pylori* bacteria. Studies on core in coat tablets of esomeprazole magnesium core and Clarithromycin coat indicated uniform and reproducible compression characteristics. The tablets also showed optimum floating parameters with density < 1. The drug content in all coat formulations was found to be uniform and consistent. The *in vitro* dissolution studies in modified dissolution apparatus simulates open flow through assembly and are suitable to mimic *in vivo* conditions which helps to study actual drug release of Clarithromycin in gastric

and esomeprazole magnesium trihydrate in proximal intestine regions for effective peptic ulcer treatment.

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