*Original Article*

# STUDIES ON CORE IN COAT GASTRORETENTIVE TABLETS USING POROUS CARRIERS WITH CELLULOSIC POLYMERS AND NATURAL GUMS

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## ABSTRACT

The present study was 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. During tablet formulation Studies on rheological characteristics of Clarithromycin coat granular blends showed their free flowing nature and ease for compression to tablet. The compressed tablets exhibited uniform post compressional characteristics. Evaluation of floating parameters indicated results suits for the tablets to formulate core in coat tablets for release of Clarithromycin in gastric pH and esomeprazole in alkaline pH to treat peptic ulcer disease associated with *h pylori* bacteria. The formulations exhibited uniform rheological and post compressional properties. The drug content was found to be uniform and consistent in all formulations. The tablet showed density < 1 facilitated tablets floating ability over 0.1N HCl with minimum floating lag time. *In vitro* release studies showed that T6C6 formulation exhibited better release for both the drugs in simulated gastric and intestinal fluids for 12 h. The study revealed the role of porous carriers, cellulosic polymers and natural gums on drug release profiles of esomeprazole core in clarithromycin coat gastroretentive tablets in duodenal ulcer treatment.

**Key Words:** Floating tablet, porous carrier, xanthan gum, guar gum and duodenal ulcer.

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**Running Title:** Gastroretentive tablets design and *in vitro* evaluation for peptic ulcer.

**Subtitle:** Studies on Core in Coat Gastroretentive tablets using Porous carriers with Cellulosic polymers and Natural gums

## INTRODUCTION

Development of oral controlled release systems formulation of drug in a gel forming polymer such as semi synthetic derivatives of cellulose, it swells in the gastric fluid with a bulk density less than one [1]. Floating drug delivery systems have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from floating system due to

extended gastric residence time leads to better control over fluctuations in plasma drug concentration. Peptic ulcers are defects in gastric or duodenal mucosa extend through muscularis mucosa as indicated in figure 1. An ulcer may develop if there is an alteration in balance between acid amount and mucus defense results in damage of lining in the stomach or duodenum by excess acid.

The patients suffering from peptic ulcers with *h pylori* infection requires medication that addresses immediate symptomatic relief followed by rapid ulcer healing effect. The medications currently available were conventional separate dosage forms and are erratically absorbed in the stomach. Clarithromycin has a $t_{1/2}$ of 3.5±0.5 h with an oral bioavailability of 50% and Esomeprazole has a half life of 1.25±0.25 h and has a bioavailability of 48% when administered orally. Esomeprazole has been clinically successful in a dose 20 mg bid [2-4]. Clarithromycin at a dose of 500 mg bid, has been reported to inhibit *h pylori* in humans [5-6]. Hence treatment of peptic ulcer disease with antibiotic Clarithromycin, along with proton pump inhibitor esomeprazole, would be beneficial and effective. Based on above rationale, this investigation is planned to develop floating type of 'coat' tablets containing clarithromycin, to release antibiotic in stomach and increase its residence time. Further small enteric coated tablets of esomeprazole to release the drug in small intestine, will be developed as a 'core' tablet. The clarithromycin 'coat' surrounds the esomeprazole 'core' so that both the drugs are dispensed as one unit and to release one medicament in stomach and the other in small intestine.

## MATERIALS AND METHODS

### Active pharmaceutical ingredient and Reagents:

Esomeprazole magnesium trihydrate were procured from Aurobindo pharma limited. Croscarmellose sodium, Crospovidone, Sodium starch glycolate gifted by Danmed Pharmaceuticals Pvt Ltd, Hyderabad. Lactose DC and Mannitol DC were procured from SD Fine Chemicals Limited. Eudragit L 30 D55, Colorcon (Acryl EZE) was supplied by Medreich Limited, Bangalore. Clarithromycin obtained from Limited, Bangalore. Polypropylene, Calcium silicate, Aerosil purchased for from Sigma Aldrich, Bangalore. Xanthan gums, Guar gum, HPMC K4M, MCC were purchased from INR chem and yarrow chemicals, Mumbai.

**Formulation of esomeprazole core tablet by direct compression and enteric coating** [7]**:** The esomeprazole core tablets were prepared by direct compression technology. The uniform blend of powder containing esomeprazole and direct compressible vehicles was studied for rheological characteristics. The blend of powder was then compressed to tablets using 6 mm flat punches. To protect esomeprazole from gastric acid and to deliver in duodenum the core tablets were coated with enteric coating polymer, Acryl EZE.

**Preparation of clarithromycin coat granules by wet granulation for compression coating** [8-9]**:** The ingredients with drug, porous carrier, effervescent agent and matrix carrier for a batch 250 tablets were accurately weighed, passed through # 100 sieve and blended uniformly. The powder blends CTP1 to CTP4, D1 and D2 were wet granulated with distilled water and starch paste (15% w/w) as binder. The wet mass obtained was passed through # 16 sieve then dried in an oven at 40°C for 4 h and passed through sieve # 20. Later, talc and magnesium stearate as required were added and blended. The coat granules were studied for flow properties and used for compression coating over esomeprazole cores. Then the powder blends of various batches

formulations 5 to 20 were prepared and are wet granulated with guar gum (1.5% w/w) as binder in water to produce wet mass. Further ingredients of S4 to S10 formulations were wet granulated with (1.5% w/w) each of xanthan gum, guar gum and HPMC K4M as binder in water to produce wet mass. Later for formulations T4 to T6 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 for 4 h. Later the dried coat granules were passed through mesh # 16. Later, talc and magnesium stearate as required were incorporated as glidant and lubricant and blended thoroughly. The granules were studied for their rheological parameters and further used for compression coating over esomeprazole core tablets.

**Preparation of core in Coat tablet** [10]**:** First half of the weight of coat tablets containing clarithromycin granules was placed into the die cavity (13mm) and then enteric coated core tablets of esomeprazole (6 mm) was placed into the same die cavity, the core tablet was adjusted and centered. The remaining half of the coat granules was placed over the core tablet so that the core is completely and uniformly surrounded by the coat granules and was then punched in a 10 station tablet press (PP1D, Chamunda) at 4-6 kg/cm$^2$ hardness. In each batch 300 tablets were manufactured. These tablets were studied for compression characteristics and later, *in vitro* dissolution studies were carried out.

**Evaluation of rheological properties of powder/granular bed** [10]**:** (Prabhakar Reddy Veerareddy., 2010).

**Bulk density** [10]**:** Bulk density was determined (Konark instruments, India) by placing the powder/granules blend in a measuring cylinder and the total volume was noted. The weight of powder/granule bed was determined in a Dhona 200 D electronic balance. Bulk density was calculated by using the formula. Bulk density = Total weight of powder / granules / Total volume of powder / granules. Average of three densities of powder/granule were taken and tabulated. (n=3). Similarly Tappped density was also studied.

**Compressibility index** [10]**:** Compressibility index was determined by placing the powder/granules in a measuring cylinder and the volume ($V_0$) was noted before tapping. After 100 tapping again volume (V) was noticed. Compressibility index = (1- V/ $V_0$) X 100. Where $V_0$ = volume of powder/granules before tapping and V = volume of powder/granules after 100 tappings. (n = 3).

**Angle of repose (°θ)** [10]**:** Angle of repose 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 plane. Powder/granule was placed in the funnel and allowed to flow freely. With the help of vernier calipers (Mitutoyo, Japan) the height and radius of the heap were measured and noted. Average of triplicate reading were noted (n = 3). Tan ø = h /r. where h = height of heap of powder/granule bed and r = radius of heap of powder/granule bed.

**Evaluation of compressional characteristics of the tablets** [11]**:**

**Thickness test** [11]**:** The tablets were evaluated for their thickness using a micrometer (Mitutoyo, Japan). Average of three readings were taken and the results were tabulated (n = 3).

**Diameter test** [11]**:** The tablets were evaluated for their diameter using a micrometer (Mitutoyo, Japan). Average of three readings were taken and tabulated (n = 3).

**Hardness test** [11]**:** The tablets were evaluated for their hardness using Pfizer hardness tester. Average of three reading were taken and tabulated (n = 3).

**Determination of drug content** [12]**:** Ten core tablets of esomeprazole was crushed into powder in a mortar and 100 mg of powder was taken in a volumetric flask containing distilled water and kept aside with constant shaking for 24 hours to extract the total drug present in the tablet. Then the absorbance of the solutions was measured after suitable dilution at 203.5 nm against drug devoid methanol as blank. Averages of triplicate readings were taken. Similarly Coat tablets of Clarithromycin was 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 to extract the total drug present in the tablet. Then the absorbance of the solutions was measured after suitable dilution at 211 nm against drug devoid dry ethanol as blank. Averages of triplicate readings were taken.

**Density measurement** [13]**:** The apparent density of the tablets was calculated from their volumes and masses. 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 $V = \prod x r^2 x h$. Average of three readings were taken and tabulated (n = 3).

**Buoyancy lag time** [14]**:** The buoyancy of tablets was studied at 37 ± 0.5 °C, in 100 ml of 0.1N HCl. A glass beaker containing 100 ml of 0.1N HCl was taken, in which a tablet was placed for observation. The duration of time taken to float the tablet was observed visually. Average of three readings were taken and tabulated (n = 3).

**Duration of floating time** [15]**:** (Pare A et al., 2008). 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 and tabulated (n = 3).

***In vitro*** **dissolution studies** [16]**:** (Mukesh C. Gohel et al., 2006) 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 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 buffer pH 9.0 for 10 h and samples of 1 ml were withdrawn analyzed spectrophotometrically. All the studies were carried out in triplicate, (n = 3).

## RESULTS

**Table 1. Rheological parameters of preliminary Clarithromycin coat formulations.**

| F. Code | Angle of repose (Ø°) | | Bulk density±SD | Tapped density±SD | C.I±SD (%) | Hardness±SD |
|---|---|---|---|---|---|---|
| | Before glidant±SD | After glidant±SD | | | | |
| **Ctp I** | 26.33±0.28 | 25.40±0.36 | 0.43±0.01 | 0.50±0.02 | 14.33±0.05 | 5.03±0.1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | 5 |
| **Ctp II** | 25.50±0.50 | 23.03±0.15 | 0.39±0.02 | 0.48±0.02 | 15.00±0.50 | 4.06±0.11 |
| **Ctp III** | 32.20±0.34 | 29.96±0.40 | 0.33±0.01 | 0.44±0.05 | 13.90±0.36 | 3.80±0.10 |
| **Ctp IV** | 27.63±0.32 | 25.70±0.43 | 0.42±0.06 | 0.47±0.02 | 12.00±0.50 | 3.70±0.10 |
| **D1** | 27.16±0.76 | 25.20±0.20 | 0.40±0.01 | 0.50±0.01 | 14.03±0.55 | 4.03±0.15 |
| **D2** | 26.06±0.70 | 24.80±0.55 | 0.41±0.01 | 0.52±0.01 | 14.73±0.32 | 4.10±0.26 |
| **5** | 25.40±0.55 | 24.66±0.57 | 0.38±0.02 | 0.47±0.04 | 15.03±0.45 | 5.06±0.20 |
| **6** | 28.73±0.46 | 26.33±0.57 | 0.37±0.02 | 0.50±0.02 | 14.00±0.50 | 5.20±0.17 |
| **7** | 26.56±0.81 | 24.70±0.52 | 0.41±0.02 | 0.51±0.02 | 14.50±0.81 | 4.80±0.34 |
| **8** | 25.23±0.28 | 23.60±0.43 | 0.43±0.02 | 0.52±0.02 | 14.50±0.50 | 5.00±0.20 |
| **9** | 26.83±0.28 | 25.03±0.55 | 0.41±0.03 | 0.52±0.03 | 14.10±0.36 | 4.20±0.17 |
| **10** | 25.73±0.64 | 24.06±0.90 | 0.43±0.01 | 0.55±0.05 | 14.20±0.75 | 4.70±0.26 |
| **11** | 26.50±0.50 | 24.66±0.57 | 0.41±0.01 | 0.51±0.06 | 14.03±0.35 | 4.30±0.26 |
| **12** | 26.13±0.80 | 24.93±0.60 | 0.42±0.01 | 0.55±0.04 | 15.00±0.88 | 4.80±0.26 |
| **13** | 28.10±0.96 | 26.16±0.58 | 0.43±0.07 | 0.52±0.02 | 14.43±0.49 | 5.20±0.17 |
| **14** | 26.50±0.50 | 24.76±0.40 | 0.40±0.03 | 0.50±0.01 | 15.03±0.45 | 5.40±0.26 |
| **15** | 28.23±0.86 | 26.50±0.50 | 0.41±0.01 | 0.53±0.01 | 15.06±0.40 | 4.16±0.15 |
| **16** | 27.03±0.55 | 25.43±0.66 | 0.40±0.01 | 0.52±0.02 | 15.06±0.30 | 5.00±0.10 |
| **17** | 26.00±0.50 | 25.03±0.55 | 0.38±0.01 | 0.50±0.06 | 14.06±0.60 | 4.80±0.20 |
| **17C** | 25.96±0.55 | 24.66±0.20 | 0.40±0.01 | 0.50±0.01 | 14.06±0.92 | 5.03±0.15 |
| **18** | 24.46±0.47 | 24.73±0.30 | 0.40±0.08 | 0.50±0.01 | 14.20±0.34 | 5.20±0.20 |
| **19** | 27.00±0.60 | 25.76±0.25 | 0.42±0.01 | 0.52±0.02 | 14.96±0.40 | 5.43±0.15 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **20** | 26.56±0.25 | 24.06±0.11 | 0.42±0.08 | 0.55±0.01 | 14.26±0.41 | 4.83±0.05 |
| **S4** | 26.98±0.15 | 25.30±0.28 | 0.35±0.03 | 0.41±0.05 | 14.20±0.02 | 5.50±0.20 |
| **S5** | 27.34±0.40 | 25.76±0.28 | 0.31±0.02 | 0.35±0.50 | 12.70±0.02 | 5.80±0.10 |
| **S6** | 28.17±0.43 | 26.16±0.64 | 0.38±0.02 | 0.45±0.36 | 14.50±0.02 | 5.60±0.17 |
| **S7** | 27.56±0.55 | 25.80±0.55 | 0.36±0.01 | 0.42±0.02 | 15.01±0.88 | 5.51±0.34 |
| **S8** | 28.00±0.46 | 26.41±0.07 | 0.38±0.08 | 0.43±0.04 | 14.21±0.49 | 5.60±0.20 |
| **S9** | 27.50±0.81 | 25.84±0.72 | 0.40±0.03 | 0.45±0.02 | 12.00±0.45 | 5.20±0.17 |
| **S10** | 26.90±0.28 | 25.50±0.50 | 0.43±0.02 | 0.52±0.02 | 15.00±0.40 | 5.60±0.26 |

**Table 2. Floating parameters of preliminary Clarithromycin coat formulations - I.**

| F code | Tablet Floating lag time and Duration of Floating studies observations |
|---|---|
| Ctp I | Tablet sank to the bottom; swollen mass formed and disintegrated in 6 sec but did not float to the surface. |
| Ctp II | Tablet sank to the bottom , swelled by slight erosion, floating lag time is 38 min and duration of floating was >24 hr. |
| Ctp III | Tablet sank to the bottom hydrated, floating lag time is 3 min and duration of floating is 16 hrs. |
| Ctp IV | Tablet sank to the bottom hydrated and swollen, floating lag time is 10 min, duration of floating is > 24 hrs. |
| D1 | Tablet sank to the bottom hydrated, swelled and eroded but did not float to the surface. |
| D2 | Tablet sank to the bottom hydrated, swelled and eroded but did not float to the surface. |
| 5 | Tablet sank to the bottom swelled and eroded but did not float to the surface. |
| 6 | Tablet floated after 3 sec to surface with effervescence, Core tablet released after 15 min and sank to bottom, coat tablet completely eroded in 22 min |
| 7 | Tablet floating lag time is 5 sec, core tablet released after 5 min and sank to bottom, coat tablet eroded in 17 min. |
| 8 | Tablet floating lag time is 3 sec, core tablet released after 8 min and sank to bottom, coat tablet eroded in 15 min. |
| 9 | Tablet floating lag time is 2 sec, core tablet released after 7 min and sank to bottom, coat tablet eroded in 22 min. |
| 10 | Tablet floating lag time 3 sec, core tablet released after 11 min and sank to bottom, coat tablet eroded in 29 min. |

| | |
|---|---|
| 11 | Tablet floating lag time 2 sec, core tablet released after 8 min and sank to bottom, coat tablet eroded in 23 min. |
| 12 | Tablet floating lag time is 3 sec, erosion of particles with effervescence and sank to bottom, core tablet released after 10.5 min, coat tablet eroded in 28 min. |
| 13 | Tablet sank to the bottom hydrated and swelled but did not float to the surface. |
| 14 | Tablet sank to the bottom hydrated, swelled with simultaneous erosion, about a half of tablet without core floated to surface after 5 min , eroded with simultaneous effervescence and particles sank to bottom, coat tablet eroded in 22 min |
| 15 | Tablet sank to the bottom hydrated and swelled but did not float to the surface. |
| 16 | Tablet sank to the bottom hydrated, swelled with simultaneous erosion due to effervescence about a half of tablet without core floated to surface after 3 min , eroded with effervescence and particles sank to bottom, coat tablet eroded in 15 min |

**Table 3. Floating parameters of preliminary Clarithromycin coat formulations - II.**

| | |
|---|---|
| **17** | Tablet floating lag time is 3 sec with hydration and swelling of tablet, duration of floating is 30 min, after 30 min tablet sank to the bottom and intact for 6 hrs |
| **17C** | Tablet sank to the bottom, swelled and eroded but did not float to the surface. |
| **18** | Tablet sank to the bottom, hydrated, swelled and eroded with effervescence in 5 min, but did not float to the surface. |
| **19** | Tablet sank to the bottom, swelled hydrated with slight erosion of surface, but did not float to the surface. |
| **20** | Tablet sank to the bottom, hydrated swelled and slightly eroded and but did not float to the surface. |
| **S4** | Tablet sank to the bottom, swelled and disintegrated, but did not float to the surface. |
| **S5** | Tablet sank to the bottom, swelled and not disintegrated, but did not float to the surface. |
| **S6** | Tablet floating lag time is 4 sec, duration of floating is 1 h 50 min, core released 1 h 22 min |
| **S7** | Tablet floating lag time is 3 sec, duration of floating 15 min with slight erosion, core released after 9 min. |
| **S8** | Tablet floating lag time is 2 sec, core released after 2min. Effervescence, erosion, tablet eroded in 5 min, but did not float to the surface. |
| **S9** | Tablet floating lag time is 35 min; duration of floating is 55 min and no erosion of tablet. |
| **S10** | Tablet floating lag time is 3 sec, Tablet swelled; core released after 4 min, coat tablet eroded in 7 min, but did not float to the surface. |

**Table 4. Rheological parameters of T4 to T6 Clarithromycin coat formulations granules:**

| F. code | Angle of repose (Ø$^o$) ± SD | | Bulk Density ± SD | Tapped Density ± SD | Carr's compressibility Index± SD |
|---|---|---|---|---|---|
| | Before Adding glidant | After Adding glidant | | | |
| **T 4** | 24.967 ±0.351 | 23.600 ±0.361 | 0.386 ±0.004 | 0.434 ±0.009 | 11.633 ±0.321 |
| **T 5** | 23.867 ±0.321 | 22.767 ±0.208 | 0.527 ±0.002 | 0.623 ±0.005 | 14.767 ±0.208 |
| **T 6** | 27.000 ±0.500 | 26.167 ±0.569 | 0.311 ±0.011 | 0.392 ±0.007 | 14.767 ±0.208 |

**Table 5. Tablet Floating lag time and Duration of Floating studies, core release studies of T4 to T6 core in coat formulations.**

| Parameters | | T4 C4 | T5 C5 | T6 C6 |
|---|---|---|---|---|
| Floating lag time (sec) | | 05 | 20 | 135 |
| Duration of floating (h) | | 24 | 2.25 | 15 |
| Core tablet (min) | Exposed | 90 | -- | 150 |
| | Released | -- | 55 | -- |

**Table 6. Post compressional parameters of core in coat tablets of Esomeprazole magnesium trihydrate and Clarithromycin:**

| Formulation code | Weight Variation (mg±SD) | Diameter (mm±SD) | Thickness (mm±SD) | Hardness (kg/cm$^2$) ±SD | Friability (%) | Apparent Density (g/cc) | DC in dry ethanol (mg±SD) |
|---|---|---|---|---|---|---|---|
| **T4 C4** | 602.37 ±0.882 | 13.45 ±0.010 | 4.28± 0.005 | 5.50± 0.100 | 0.842 | 0.990 | 245.33 ±0.115 |
| **T5 C5** | 604.49 ±0.758 | 13.48 ±0.026 | 4.31± 0.010 | 5.93± 0.156 | 0.800 | 0.986 | 246.67 ±0.306 |
| **T6 C6** | 605.14 ±0.849 | 13.49 ±0.035 | 4.27± 0.005 | 5.86± 0.111 | 0.906 | 0.985 | 248.34 ±0.111 |

**Table 7.** ***In vitro*** **release studies of clarithromycin and esomeprazole magnesium trihydrate from SGF and SIF in modified dissolution apparatus in media SGF pH 3 (2h) and SIF pH 9 (10 h)**.

| Time (min) | T4C4 | | T5C5 | | T6C6 | | |
|---|---|---|---|---|---|---|---|
| | Cum. amt of drug (mg) | % drug release | Cum. amt of drug (mg) | % drug release | Cum. amt of drug (mg) | % drug release | |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | Clarithromycin in SGF |
| 1 | 2.053 | 0.82 | 3.827 | 1.53 | 6.067 | 2.43 | |
| 3 | 10.36 | 4.14 | 14.65 | 5.86 | 18.29 | 7.32 | |
| 5 | 22.86 | 9.15 | 29.12 | 11.65 | 34.34 | 13.74 | |
| 10 | 42.00 | 16.80 | 47.13 | 18.85 | 53.57 | 21.43 | |
| 15 | 67.57 | 27.03 | 79.42 | 31.77 | 91.56 | 36.62 | |
| 30 | 124.5 | 49.80 | 139.1 | 55.66 | 165.1 | 66.04 | |
| 45 | 173.8 | 69.55 | 183.5 | 73.43 | 206.08 | 82.43 | |
| 60 | 197.5 | 79.03 | 208.9 | 83.59 | 224.2 | 89.71 | |
| 90 | 230.8 | 92.33 | 235.4 | 94.19 | 239.7 | 95.91 | |
| 120 | 244.0 | 97.63 | 246.0 | 98.41 | 248.0 | 99.23 | |
| 121 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| 123 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | Esomeprazole Magnesium Trihydrate in SIF |
| 125 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| 130 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| 135 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| 150 | 0.029 | 0.147 | 0.195 | 0.974 | 0.360 | 1.801 | |
| 165 | 0.406 | 2.030 | 0.764 | 3.822 | 1.196 | 5.980 | |
| 180 | 1.709 | 8.543 | 1.804 | 9.021 | 3.144 | 15.71 | |
| 210 | 2.914 | 14.57 | 3.044 | 15.22 | 5.883 | 29.41 | |
| 240 | 4.654 | 23.26 | 5.199 | 25.99 | 7.849 | 39.24 | |
| 300 | 6.618 | 33.08 | 8.157 | 40.78 | 10.50 | 52.51 | |
| 360 | 8.979 | 44.89 | 9.703 | 48.51 | 12.12 | 60.63 | |
| 420 | 10.70 | 53.52 | 11.32 | 56.63 | 13.58 | 67.93 | |
| 480 | 13.33 | 66.65 | 14.01 | 70.08 | 15.11 | 75.58 | |
| 540 | 14.43 | 72.19 | 15.29 | 76.46 | 16.35 | 81.76 | |
| 600 | 15.59 | 77.98 | 16.48 | 82.41 | 17.31 | 86.55 | |
| 660 | 17.00 | 85.00 | 17.92 | 89.62 | 18.78 | 93.93 | |
| 720 | 18.02 | 90.11 | 18.31 | 91.58 | 19.01 | 95.08 | |

**Table 8. Drug release kinetics of core in coat formulations of Esomeprazole magnesium trihydrate and Clarithromycin**

| F.Code | Core/coat | $C_{20}$ (min) | Slope(m) | Regression (r) |
|---|---|---|---|---|
| **T4 C4** | T2 | 11.60 | 1.9725 | 0.9477 |
| | C4 | 100.8 | 0.0563 | 0.9848 |
| **T5 C5** | T5 | 10.60 | 1.9660 | 0.9344 |
| | C5 | 102.4 | 0.0774 | 0.9820 |
| **T6 C6** | T8 | 09.00 | 1.9552 | 0.9057 |
| | C6 | 60.90 | 0.1054 | 0.9665 |

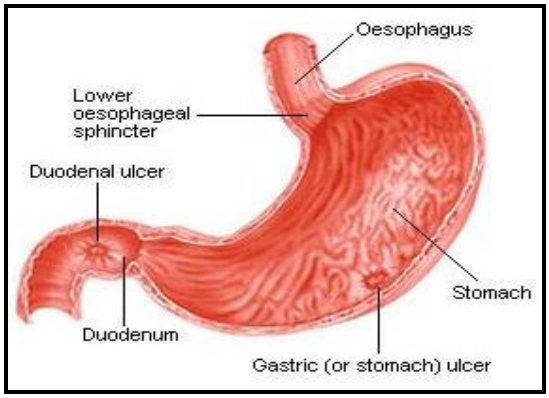


**Figure 1. Incidence of peptic ulcers in human stomach and duodenum by *H. pylori***

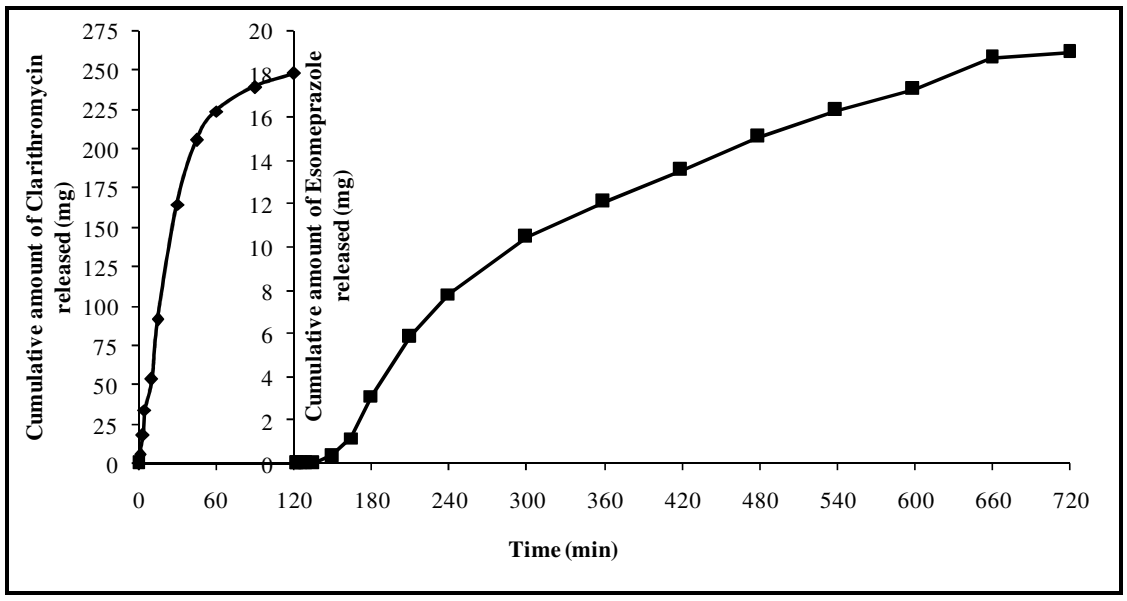


**Figure 2. Dissolution study of T6C6 - Cumulative amount release of clarithromycin from T6 with HPMC K4M and esomeprazole magnesium trihydrate from C6 with Mannogem EZ.**

## 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 and where as esomeprazole is absorbed well from small intestine because of its instability in stomach.

The enteric coated core tablets containing 20 mg of esomeprazole magnesium trihydrate present within coat formulation containing clarithromycin of 250 mg dose was dispensed as a single unit. 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. All the above formulations showed good rheological properties as showed in table 1 but the preliminary formulations after compaction not exhibited desired flow parameters as indicated in table 2 and 3 which might be due to the unsuitable polymer blend for floating ability. Based on these results further formulations were optimized to achieve desired tabletting and floating properties for tablets. Clarithromycin coat powder blends and granules were compression coated over enteric coated esomeprazole cores and the tablets were found to be uniform with respect to their weight variation, thickness and hardness. Evaluation of floating lag time and duration of floating indicated that only a few formulations showed the desired properties of floating lag time in sec, duration of floating, core tablet release after 2 h, all formulations has the hardness of 4 - 6 kg/cm$^2$.

The rheological characteristics of Clarithromycin coat powder and granular blends indicated that they are freely flowable and easily compressible as given in table 4. Later results in table 5 revealed floating parameters and the suitability of formulations as gastroretentive tablets. The tablets showed minimum lag time and extended duration of floating. Tablets showed uniform compression properties. With uniform drug content as represented in table 6. The lactose DC containing core tablets showed lag time of 03 min and Mannitol DC containing core tablets showed lag time of 15 min to release esomeprazole in pH 9.0 this is due to time taken for rupturing and solubilization of Acryl EZE enteric coating over core tablets which is also observed during *in vitro* dissolution studies of core in coat tablets.

The *in vitro* dissolution study data in table 7 indicates that from T4C4 tablet it showed Clarithromycin from T4 coat released 20% of drug in 11.6 min and 244.06 mg (97.63%) in 120 min from 245.33 mg dose. The release followed zero order kinetics with slope value 1.9725 and correlation coefficient (r) of 0.9477. Esomeprazole from C4 core released 20% of drug in 100 min and 18.024 mg (90.11%) in 600 min from 19.73 mg dose. The release followed zero order kinetics with slope value 0.0563 and correlation coefficient (r) of 0.9848 data given in table 8. The *In vitro* dissolution study of T5C5 showed Clarithromycin from T5 coat released 20% of drug in 10.6 min and 246.02 mg (98.14%) in 120 min from 246.67 mg dose. The release followed zero order kinetics with slope value 1.9660 and correlation coefficient (r) of 0.9344. Esomeprazole from C5 core released 20% of drug in 102 min and 18.318 mg (91.58%) in 600 min from 19.94 mg dose. The release followed zero order kinetics with slope value 0.0774 and correlation coefficient (r) of 0.9820.

The *In vitro* dissolution study of T6C6 showed Clarithromycin from T6 coat released 20% of drug in 09.0 min and 248.08 mg (99.23%) in 120 min from 248.34 mg dose. The release followed zero order kinetics with slope value 1.9552 and correlation coefficient (r) of 0.9057. Esomeprazole from C6 core released 20% of drug in 60.9 min and 19.016 mg (95.07%) in 600

min from 19.74 mg dose. The release followed zero order kinetics with slope value 0.1054 and correlation coefficient (r) of 0.9665 indicated in figure 2. The *in vitro* dissolution study of core in coat tablets in modified dissolution apparatus showed that the Clarithromycin was released from coat tablets for the first 2 h in SGF of pH 3.0; later esomeprazole magnesium trihydrate was released from core tablet for the next 10 h in SIF of pH 9.0.

The study explored the use of porous carriers like calcium silicate, polypropylene, aerosol owing to their merely lesser density and compaction ability attained by wet granulation resulted in formulation of novel floating tablets by successful incorporation of porous agents. Later HPMC K4M, xanthan gum and guar gum as matrix carriers were showed swelling up on hydration results in $CO_2$ entrapment in the system pores due to reaction between sodium bicarbonate and gastric acid results in buoyant tablet with desired floating properties and *in vitro* drug release.

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