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RESEARCH ARTICLE

Studies on Novel Pantoprazole and Cefuroxime Axetil Tablets for Site Specific Delivery.

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ABSTRACT

In this study core in coat tablets containing enteric coated Pantaprazole (PP) core and Cefuroxime axetil (CA) floating type coat formulation as single unit prepared by compression coating method. The tablets were evaluated for their various pre-compression, compression characteristics, *in vitro* drug release kinetics and stability studies. The analytical estimation of drugs was found to be accurate and precise. The results of rheological characteristics indicated that, the powder beds of both core formulations of PP are freely flowable and easily compressible. Acryl EZE coating over the core tablets protects PP from GI fluids and helps in release of drug in intestinal pH. These studies on coat granules indicated that, the granule beds of all the coat formulations of CA are easily compressible and that flow increases with the addition of glidants. The release rate of CA from HPMC K4M formulations is majorly by burst effect, since HPMCK4M ($p<0.05$) is relatively more hydrophilic and when swells it forms weaker gel. Also, the release of CA from guar gum and xanthan gum formulations follows zero order release ($p<0.05$). The guar gum when it swells forms thicker gels hence the release rate 'k' is small of the three diluents. Stability studies at 40°C / 75% RH indicated that there is no significant change in CA content for a period of 3 months. Therefore it could be concluded that the combination of PP and CA would be useful for improved ulcer therapy associated with symptomatic relief to the patient.

KEYWORDS: Pantoprazole, Acryl EZE, Cefuroxime axetil, *In vitro* dissolution, Stability studies

INTRODUCTION:

The treatment of peptic ulcer disease involves multi drug regimen which causes patient discomfort. Cefuroxime axetil (CA) and Pantoprazole (PP) are successful agents used in the treatment of peptic ulcer disease, but are available as separate unit dosages. Core in coat type of floating tablets would improve the bioavailability of those drugs whose therapeutic window is in the stomach or proximal part of the small intestine. Such gastroretentive dosages are therapeutically highly beneficial in the treatment of gastric disorders like peptic ulcer disease or peptic cancer. Cefuroxime axetil has broad spectrum of antibacterial activity and previous literature shows it inhibits *H. Pylori*. Pantaprazole is unstable in acidic pH but a valued proton pump inhibitor. Therefore an effort was made in this investigation, to formulate a tablet dosage form containing both of these drugs. Enteric coated core tablets containing pantoprazole and a floating type coat formulation containing Cefuroxime axetil, compressed into a single unit was planned. In this work influence of various excipients on the release of both the drugs were studied. Oral controlled delivery of drugs at the target site helps in better absorption and improved bioavailability. A buoyant tablet is made to float over the surface of the gastric fluids and remain in the stomach for a long time, thereby increasing the gastric retention time (GRT) of drug like Cefuroxime axetil, thereby increased bioavailability and hence therapeutic efficacy is highly improved. Also, it was planned to evaluate such tablets for their various pre-compression and compression characteristics, *in vitro* drug release kinetics and stability of the dosage forms [1-5].

MATERIALS AND METHODS:

PP obtained from CFL Pharmaceuticals Ltd, Panaji, Goa. CA procured from Hetero drugs pvt. Ltd H.P. Microcrystalline cellulose (PH 200), Citric acid, Talc, Magnesium stearate, Starch I.P, Sodium bicarbonate from S.d. Fine chemicals limited, Mumbai. Crospovidone (PVP K30), Sodium carbonate, Lactose (DCL 11), Aerosil, Xanthan gum, Acryl EZE as Complimentary sample from Danmed Pharmaceuticals Pvt Ltd, Hyderabad. Hydroxypropylmethyl cellulose from Rutai, China and Guar gum from Himedia laboratories, Pvt. Ltd, Mumbai.

METHOD OF PREPARATION OF PANTOPRAZOLE POWDER BLEND FOR DIRECT COMPRESSION:

The pantoprazole formulations constituting core of the tablets were prepared by direct compression technology. Ingredients of core 1 were accurately weighed, milled and passed through sieve # 100/ 120 and then thoroughly blended. The powder blended was studied for rheological characteristics like bulk density, compressibility index and angle of repose [6].

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PREPARATION OF CORE IN COAT TABLET CONTAINING PP AND CA:

Core Tablet (mg)		Coat Tablet (mg)						
Ingredients	**Cr 1**	**Ingredients**	**Ct 1**	**Ct 2**	**Ct 3**	**Ct 4**	**Ct 5**	**Ct 6**
Pantoprazole	21.14	Cefuroxime axetil	250	250	250	250	250	250
Sodium carbonate	10.00	Starch paste (10%)	50	50	50	50	50	50
Starch IP	16.47	HPMC K4M	80	-	-	62.5	-	-
Avicel PH 200	48.58	Guar gum	-	80	-	-	62.5	-
Aerosil	1.2	Xanthan gum	-	-	80	-	-	62.5
Talc	1.6	$NaHCO_3$	60	60	60	70	70	70
Mg. sterate % w/w	1.00	Citric acid	45	45	45	52.5	52.5	52.5
Total Weight (mg)	100	Talc % w/w	10	10	10	10	10	10
		Mg. sterate % w/w	5	5	5	5	5	5
		Total Weight (mg)	500	500	500	500	500	500

Table No. 1. Formulations of PP and CA core in coat tablets

PREPARATION OF CORE TABLETS OF PP:

The uniformly blend of powder containing PP and direct compressible Vehicles was then compressed in a 10 station tablet punching machine using 6 mm flat punches at a pressure of 3 kg/cm^2. In each batch 300 core tablets were prepared. The tablets were evaluated for their thickness, hardness, drug content, friability, weight variation, density, disintegration time[7].

COATING OF CORE TABLETS WITH ACRYL EZE:

The core tablets were film coated with an enteric coating polymer, Acryl EZE. First, seal coat was prepared by dissolving HPMC (15cps) in isopropyl alcohol with continuous stirring. Then slowly methylene chloride was added and the solution was filtered by passing through # 200 mesh. 20% w/w of acryl EZE was prepared by dispersing acryl EZE in a beaker containing water and stirred slowly for 20 minutes and passed through # 200 mesh. The tablets were enteric coated in a Kalweka HD coating pan so as to buildup 10% weight. The enteric coated tablets were evaluated for acid resistance of their acryl EZE coat [8].

METHOD OF PREPARATION OF CA GRANULES BY WET GRANULATION:

All the powders were weighed accurately and passed through # 100 mesh sieve and the powder was uniformly blended and was granulated with water and starch paste (10% 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. The granules were studied for all rheological characteristics like bulk density, compressibility index and angle of repose [6].

PREPARATION OF COAT TABLET BLEND OF CA:

After adding lubricants and glidants, half the weight of coat tablets containing CA granules was placed into the die cavity (13mm) and then core tablets of pantoprazole (6 mm) was placed into the same die cavity, the core tablet was manipulated and centered. The remaining half of the coat granules was placed over the PP 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). These tablets were studied for compression characteristics like thickness, hardness, drug content, friability, weight variation, density, disintegration time [7] and later, *in vitro* dissolution studies were carried out.

DETERMINATION OF DRUG CONTENT [9]:

A) Core tablet of PP 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 288 nm against drug devoid distilled water as blank. Averages of triplicate readings were taken. The content of drug was calculated using calibration curve.

b) Coat tablet of CA 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 277nm against drug devoid distilled water as blank.

DENSITY MEASUREMENT [10]:

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 $V = \prod \times r^2 \times h$. Average of three readings were taken and tabulated (n = 3).

DISINTEGRATION TEST [11]:

The disintegration time of tablet was determined by placing one tablet in each of the six tubes of the basket and operated the apparatus, using pH 9.0 buffers solution maintained at 37 $\pm$ 2°C. At the end basket was lifted from the fluid, and tablets were observed. All the tablets disintegrated completely.

BUOYANCY LAG TIME [12]:

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[12]:

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.

***IN VITRO* DISSOLUTION STUDIES: [14]**

A modified dissolution apparatus [15] 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 50 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 8 h and samples of 1 ml were withdrawn and analyzed spectrophotometrically. All the studies were carried out in triplicate, (n = 3).

STABILITY STUDIES OF CORE IN COAT TABLETS [8]:

Stability studies of core in coat tablets were conducted at 40°/75%/RH (ICH guidelines, for region IV) for a period of 90days. At the end of the period, *In vitro* dissolution of core in coat tablets for CA and PP was conducted according to procedure described in the *In vitro* dissolution studies section. Dissolution profiles thus obtained was compared with ambient statistically analyzed by ANOVA, with the dissolution profile of core in coat tablets, under normal conditions.

RESULTS:

Code	Compressibility Index %	Bulk density gm. /cc	Angle of repose (ºθ)	
			Before glidant	After glidant
Cr 1	10.73	0.46	31.35	28.64
Ct 1	9.9	0.60	28.67	26.11
Ct 2	9.1	0.54	28.76	26.50
Ct 3	10.3	0.57	28.5	25.16
Ct 4	9.84	0.59	28.41	26.21
Ct 5	9.26	0.60	28.53	25.50
Ct 6	9.38	0.60	27.75	25.05

Table No. 2. Cefuroxime axetil coat granules rheological parameters evaluation.

Code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Density (gm/cc)	DC (mg)	Flt. lag time(min)	Floatation time (h)
Cr 1	3.10±0.008	06.12±0.007	4.96±0.04	0.97±0.026	20.51	-	-
Ct 1	5.63±0.018	13.11±0.017	5.5±0.05	0.77±0.021	246.50	13.7	2 min
Ct 2	5.54±0.007	13.22±0.022	5.7±0.08	0.79±0.010	247.38	25.13	5.15
Ct 3	5.51±0.001	13.28±0.029	5.7 ±0.08	0.77±0.015	248.10	27.11	4.15
Ct 4	5.62±0.30	13.32±0.036	5.8±0.08	0.75±0.006	247.38	11.15	2 min
Ct 5	5.67±0.009	13.24±0.031	6.0±0.05	0.76±0.015	246.50	24.20	5.15
Ct 6	5.68±0.001	13.22±0.024	5.8±0.08	0.78±0.021	248.10	27.4	4.18

Table No. 3. Compression and floating characteristics of Core in Coat tablets of PP and CA.

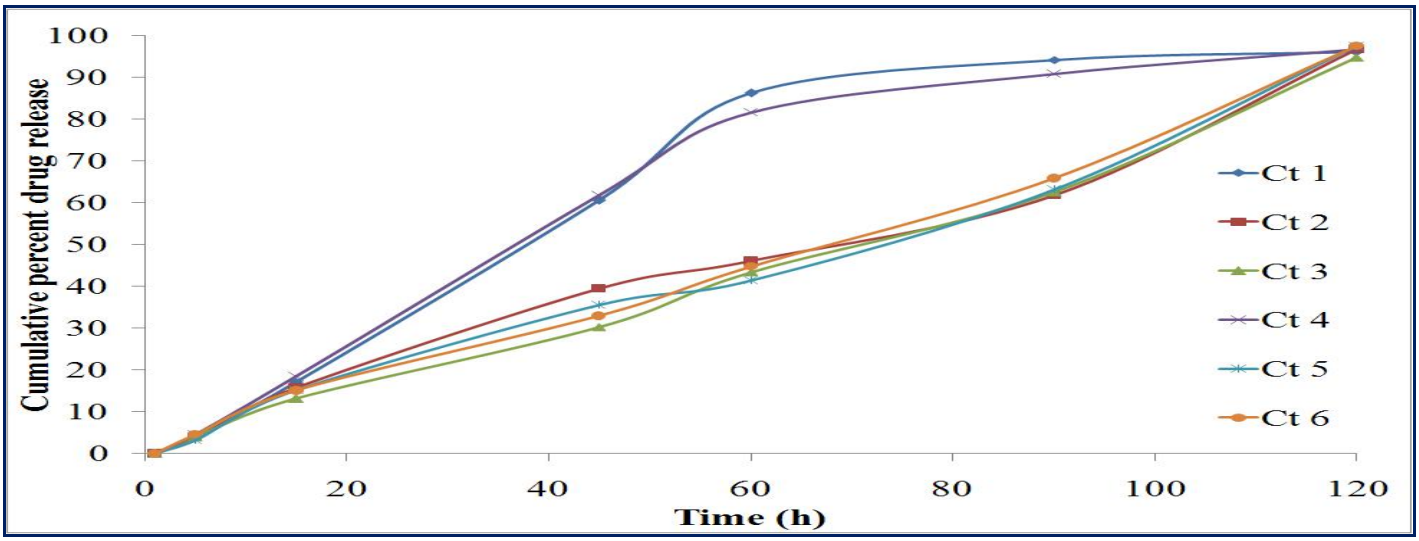

Figure No. 1. *In vitro* drug release of CA from various floating tablet coats in SGF

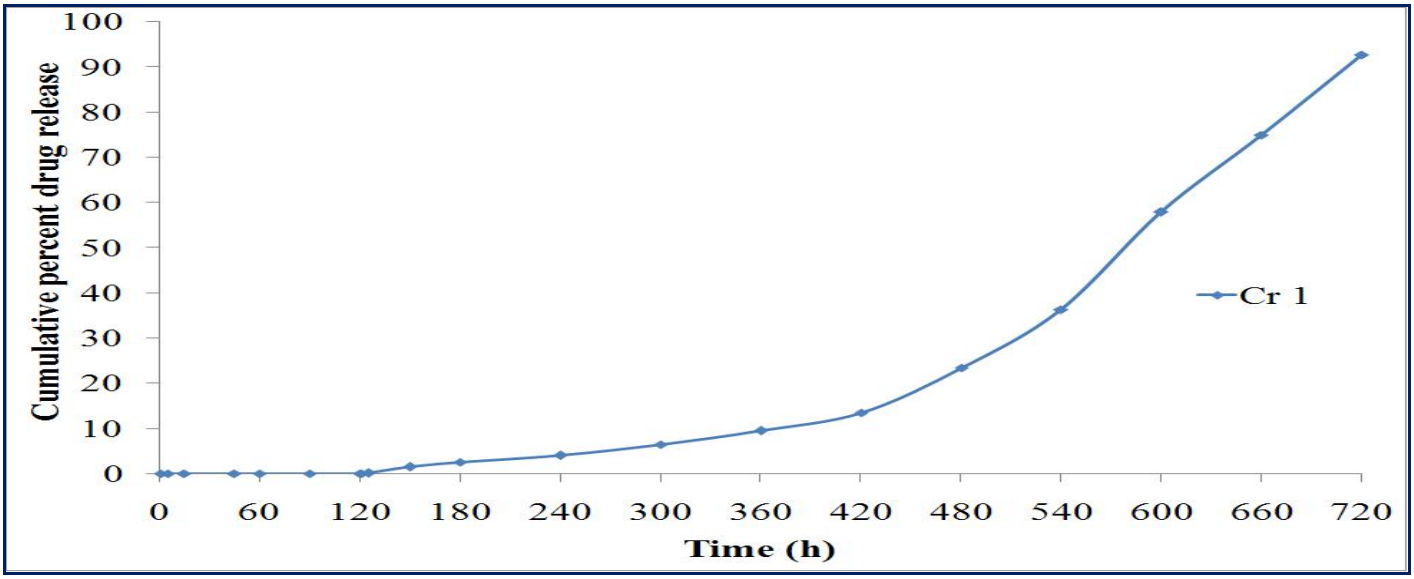

Figure No. 2. *In vitro* drug release of PP from enteric coated core tablet in SIF

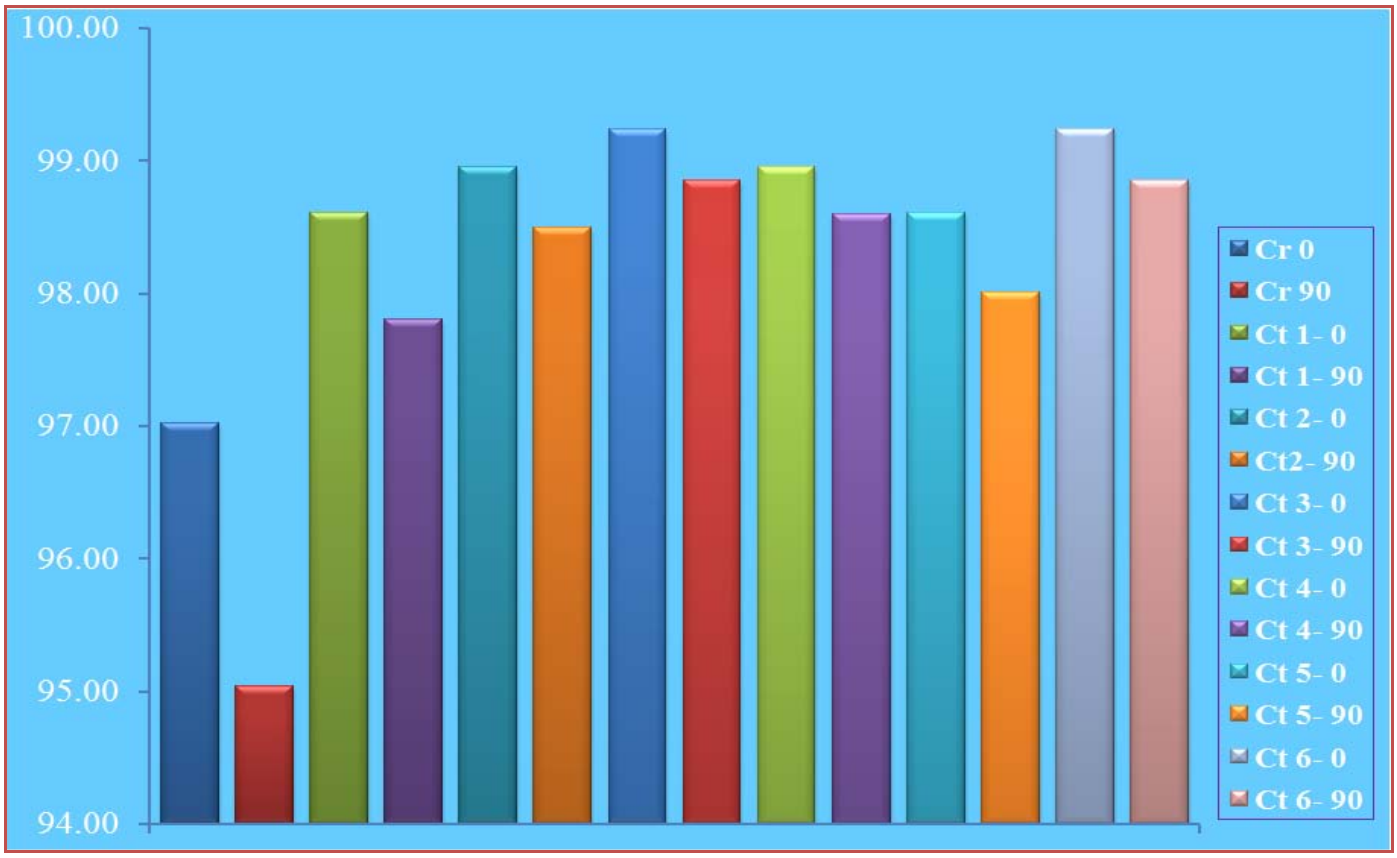

Figure No. 3. Stability studies of PP and CA Core in Coat floating tablets at ambient and 45°C and 75% RH

DISCUSSION:

The absorbance maxima of PP 288 nm obtained during this study corroborates with the literature value. Similarly the value of absorbance maxima of CA 277 nm obtained during this study corroborates with the literature value. Carr's Compressibility index of directly compressible powder bed of PP was found to be 10.73 % which was less than 15 % for core 1 powder bed. Bulk density was found to be 0.46 gm /cc for Cr. The angle of repose (°θ) was found to be 31.35^0. The thickness of compressed core tablets, Cr 1 was found to be uniform, 3.10 ± 0.008 mm. The diameter was also found to be uniform, 6.12 ± 0.007mm. The hardness of tablets Cr 1 was found to be 4.96 ± 0.04 Kg/cm^2. The density was found to be 0.97 ± 0.026 for Cr 1. The core tablets Cr 1 were disintegrated completely within 7 min in simulated intestinal fluid. Drug content of all formulations was found to be 96.98%. *In vitro* results showed that, the release rate of PP from Cr 1 is better due to improved dissolution of the drug from the core tablet. Stability studies at 40°C / 75% RH indicated that the slight amount of PP declines rapidly everyday under the above constraints for a period of 90 days. The Carr's Compressibility index of coat granules containing CA was found to be less than 15 %. The index was observed to be between 9.1 % and 10.3 % for Ct 1 through Ct 6 powder beds respectively. Bulk density was found to be around 0.6 gm/cc respectively for all coat granules. The angle of repose (°θ) was found to be varying between 27.75^0 and 28.76^0 before incorporating glidants. Similar studies conducted showed reduced angle of repose varying between 25.05º and 26.50º. The thickness of the compressed final core in coat tablets (13 mm diameter), were found to be between 5.31 ± 0.015mm and 5.68 ± 0.001 mm. The diameter was also found to be uniform, 13.11 ± 0.017 mm and 13.51 ± 0.025 mm. The hardness of tablets Ct 1 through Ct 12 was found to be varying between 5.5 ± 0.05 Kg/cm^2 and 6.46 ± 0.08 Kg/cm^2. The densities were found to be between 0.75 ± 0.06 and 0.79 ± 0.012 respectively for Ct 1 through Ct 12. Densities of all the tablets formulated were found to be less than 1. Floating lag time was found to be in the range of 13-27 min. The guar gum tablets showed floating duration of 4 h to 5 h and the tablets containing xanthan gum as diluent showed floating duration of 4 h. Drug content of all formulations containing HPMC K4M, guar gum, Xanthan gum as diluent was in the range of 94.72% - 98.80%. It was found that, an amount of 70 mg of sodium bicarbonate and 52.5 mg of citric acid (1:0.75) would be sufficient to make a 600 mg tablet to float on the surface of the fluid. It was found that the release rate (k) of CA from coat

formulations containing HPMC K4M as diluent is significantly higher as compared to other diluents. The release rate of CA from coat tablets containing xanthan gum is second to HPMC formulations. Lastly, CA release from the coat formulations containing guar gum as diluent is lesser of the three in any particular set. Stability studies were conducted according ICH guidelines region IV at 40°C / 75% RH indicates that there is no significant change in drug profiles after a period of 90 days.

CONCLUSIONS:

Multi drug therapy in PUD causes patients to consume two or more number of medications regularly. Also bioavailability of different drugs from different marketed samples might vary owing to formulation and processing variables of different manufactures. In this investigation of two drugs, both proven to be beneficial in the treatment of peptic ulcer disease were dispensed in a single unit as a core in coat tablet. The study has indicated that, gastro retentive floating core in coat tablets of xanthan gum and guar gum are potential oral dosages. Such a dosage form would be effective in the treatment of peptic ulcer disease since it overrides the multi drug therapy. Thus, study of pre compression and compression characteristics, *in vitro* release and stability studies concluded the objectives of the investigation.

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