WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 5, 1433-1444. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF ENTERIC COATED SUSTAINED RELEASE TABLETS OF OMEPRAZOLE FOR DUODENAL ULCER

Dr.M.Sreenivasulu, Srikrishna.T*, Vasanthi.P, Prasanthi.K, Ishrath.Sk, Pavani.M

Department of Pharmaceutics, Narayana Pharmacy College, Nellore-524002. A.P., India.

Article Received on
23 Feb 2015,

Revised on 14 March 2015,
Accepted on 06 April 2015

***Correspondence for Author**
Srikrishna.T
Department of Pharmaceutics, Narayana Pharmacy College, Nellore-524002. A.P., India.

ABSTRACT

The objective of present study was to develop pharmaceutically elegant and stable enteric coated tablet formulation for highly unstable drug in acidic environment using pH dependent polymers. Omeprazole is a specific and non-competitive inhibitor of the enzyme H+ /K+ - ATPase. It is unstable in conditions of low pH and required protection from the effects of gastric acid when given orally so it is formulated in the form of enteric coated dosage forms. The core tablets were prepared by wet granulation method using different concentration of Ethylcellulose as a release retardant, followed by enteric coating with Eudragit L 100.The interaction between the excipients and Omeprazole was studied through FTIR spectroscopy. Various concentrations of polymer was used in the six proposed formulations (F1-F6) for the study of release rate retarded effect at 1%, 2%, 3%, 4%, 5% and 6% of total weight of tablet respectively. Then the tablets were evaluated in terms of their physical parameters (disintegration time, hardness, friability, weight variation), drug content and invitro released studies. All the formulations showed compliance with pharmacopeial standards. The invitro dissolution study were conducted using USP dissolution apparatus-II (paddle method) in 900ml 0.1N HCL for 2 hours and remaining 22 hours performed in 6.8 pH phosphate total period of an buffer at 100rpm for 24 hours. Based on the dissolution data comparisons with innovator product, formulation F5 was as the best formulation.

KEY WORDS: Omeprazole, Enteric coated tablet, Ethylcellulose, Wet Granulation, *in-vitro* dissolution.

INTRODUCTION

A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. Tablet dosage form is one of a most preferred dosage form all over the world. Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits that broadly ranges from facilitating product identification to modifying drug release from the dosage form. After making a good tablet, one must often coat it. Coating may be applied to a wide range of oral solid dosage form, including tablets, capsules, multi particulates and drug crystals.[1]

Enteric Coatings: Oral site-specific drug delivery systems have attracted a great deal of interest recently for the treatment of a variety of bowel diseases and also for improving systemic absorption of drugs, which are unstable in the stomach. However, the micro-environment in the gastrointestinal tract and varying absorption mechanisms generally cause hindrance for the formulation scientist in the development and optimization of oral drug delivery. Delivery of therapeutic agent into the intestinal region could be accomplished by the application of an enteric coating on a solid dosage form. Several approaches have been attempted and reported during the last decade to develop new methodologies for site-specific drug release, including pH sensitive drug release and time controlled drug release. Proton Pump Inhibitors (PPI's) are highly effective in the management of acid related diseases, including duodenal ulcer, gastric ulcer, gastro esophageal reflux disease, erosive esophagitis, hyper secretory syndromes like Zollinger-Ellison, and H.pylori infection. There are currently five different proton pump inhibitors available including Omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. These agents belong to a class of antisecretory drugs and are all substituted benzimidazoles that inhibit the final common pathway of gastric acid secretion. PPIs may also be used in combination with certain antibiotics (e.g. amoxycillin and clarithromycin) when treating H. Pylori infection (a bacterial infection of the stomach), which is thought to be one of the main causes of recurring stomach ulcers. In recent years, omeprazole has been widely used as a gastric acid secretion blocker and selectively inhibits the proton pump in the gastric mucosa. Omeprazole degrades very rapidly in aqueous solutions at low pH values. In aqueous solutions, the rate of degradation proceeds with a half-life of less than 10 min at pH values below 4, 18 h at pH 6.5 and about 300 days at pH 11. Omeprazole degradation is acid-catalysed; with an increase in the pH values, the rate of degradation decreases. In addition, the color of the solution changes immediately to

pale yellow upon the addition of the acid and on heating, the color further changes to dark yellow, then becomes brownish. Preformulation studies have shown that moisture, solvents and acidic substances have deleterious effects on the stability of omeprazole and should be avoided in pharmaceutical formulations. To overcome the stability problems of omeprazole, the best solution seems to be to prepare enteric-coated dosage forms. The preparation must be perfectly coated, since if any drug leaks out of the dosage form in the stomach, it almost immediately degrades.[2]

MATERIALS AND METHODS

Materials used in the experiment were Omeprazole (Lot pharmaceutical co., Ltd., Chennai), Di-basic calcium phosphate (ISP Technologies., Ahmadabad), Eudragit-L100 (ISP Technologies., Ahmadabad), Ethyl cellulose (Dow chemical's., Bangalore), Microcrystalline cellulose (Avicel. Delhi), Magnesium stearate (Nof Corporation., Ahmadabad), Talc (Shengtai Chem Co., Ltd., Chennai), PVP-K 90 (Dow chemical's., Bangalore), Isopropyl alcohol (Shell chemicals, Chennai)

Method of Preparation of Omeprazole Enteric Coated SR Tablets

Omeprazole granules were prepared by wet granulation method. Microcrystaline cellulose, Ethyl cellulose, Dibasic calcium phosphate were weighed and dried and screened through 100 mesh. Then Ethyl cellulose, Dibasic calcium phosphate and half of the amount of Microcrystalline cellulose were mixed with Omeprazole and wet granules were prepared by adding PVP-K90 in Isopropyl alcohol as binding solution and sheared by pestle and formed as dump mass and passed through 12 mesh sieve. Granules were tray dried at 60^{o}C using a hot air oven for 1 hour. Dried granules were screened through 20 sieve. The bulk and tapped densities of the granules were determined and Carr's index was also calculated. Omeprazole SR tablets were ethyl cellulose based hydrophilic matrix system. Dried granules were mixed with remaining half quantity of microcrystalline cellulose, Magnesium stearate and talc. Then they were compressed by using single tablet punching machine. The punched tablets were enteric coated by using Eudragit-L100 solution by using dip method and wet enteric coated tablets were dried by using hot air oven.[3]

CALIBRATION CURVES OF OMEPRAZOLE

100 mg of Omeprazole was taken and dissolved in small amount of acidic buffer i.e, 0.1N HCl and further diluted up to 100 ml with the same buffer. This gives standard solution of Omeprazole (1mg/ml) which can be used for further dilutions. From the standard solution,

samples of different concentrations are prepared, and analyzed spectrophotometrically at 304.8 nm.[4]

100 mg of Omeprazole was taken and dissolved in small amount of phosphate buffer of pH 6.8 and further diluted up to 100 ml with the same buffer. This gives standard solution of Omeprazole (1mg/ml) which can be used for further dilutions. From the standard solution, samples of different concentrations are prepared, and analyzed spectrophotometrically at 304.8 nm.[5]

DRUG-EXCIPIENTS COMPATIBILITY STUDY BY FT-IR

Fourier-transform Infrared (FT-IR) spectra were obtained using an FT -IR spectrometer. The compatibility of Omeprazole with Di-basic calcium phosphate, microcrystalline cellulose, Ethylcellulose, Eudragit L 100, individually and combine in physical mixture were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample:KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press.[6] Forty scans were obtained at a resolution of 4 cm^{-1} , from 4000 to 400 cm^{-1} .

EVALUATION

Pre Compression Studies

Angle of Repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.[7]

$\tan \theta = h/r$

Where, h = height of the heap,

r = Radius of the heap

Pharmacopeial specifications for Angle of Repose

Angle of Repose	Powder Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

Bulk Density and Tapped density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated by using the following formulas.

LBD = weight of the powder / volume of the powder

TBD = weight of the powder / tapped volume of the powder

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [TBD-LBD] / TBD X 100

% Comp.Index	Properties
5-15	Excellent
12-18	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Very very poor

Post Compression Parameters

Weight variation

All prepared tablets were evaluated for weight variation. In this twenty tablets of each batch were used to evaluate weight variation among tablets and standard deviation was calculated.

Friability

Friability testing was done by Friability test apparatus (Lab India Friability Apparatus FT 1020).The percentage friability was then calculated by.

% Friability = [(W1 – W2) / W1] × 100

% Friability of tablets less than 1% is considered acceptable.

Hardness

Hardness of all batches was determined using Tablet hardness tester (Monsanto hardness tester).

Thickness

Thickness was measured by vernier calipers and readings were carried out in triplicate and average value was noted.

Drug content

Transfer an amount of powder (from NLT 20 Tablets) to a suitable volumetric flask to obtain a nominal concentration of 1 mg/ml of Omeprazole. Dissolve in 50% of the flask volume of methanol by shaking for 1 h. Dilute with methanol to volume, and pass through a suitable filter. Sample was analyzed by HPLC method and the chromatographic conditions are column – 3.9mm*15cm packed with phenyl group bonded to porous silica (4 µm), detector.

UV 304.8nm, Flow rate: 1ml/min, injection volume: 20 µl, run time: 6min and the mobile phase composition is methanol and buffer (11:9), Adjust with phosphoric acid to a pH of 5.0. Buffer: 0.5 gm of citric acid monohydrate and 0.4 gm of dibasic sodium phosphate in 1 L of water. The actual content in sample was read by comparison with standard Omeprazole.[8]

Disintegration test

In this process we were using distilled water as medium at 37±2^{o} C at 29-32 cycles per minute; test was completed after 30 minutes.[9]

In vitro Dissolution test

Drug release profile was evaluated in vitro, using a dissolution test apparatus. The USP XIII Type II (paddle type) method (TDT-08L, Electro lab, Mumbai, India.) was selected to perform the dissolution profile of Omeprazole SR Enteric Coated tablets .The dissolution of enteric coated tablet is performed into 0.1 N HCl for 2 hours and then the phosphate buffer pH 6.8 for remaining 22hours.

The temperature was maintained at 37±0.5°C and a constant paddle rotation speed of 100 rpm. Samples (5 ml) were withdrawn at regular intervals and filtered. The samples were analyzed by UV Spectro Photometry.[10, 11]

STABILITY STUDY OF OPTIMIZED FORMULATION

Stability study was done to see the effect of temperature and humidity on tablets. Tablets were evaluated periodically (initial, and after 1 month) for appearance, hardness, friability, drug content and i*n vitro* drug release.[12, 13]

RESULTS AND DISCUSSION

Table 1: Formulations of Omeprazole Enteric coated SR Tablets

S. NO	INGREDIENT	FORMULATIONS (mg/Tablet)					
		F1	F2	F3	F4	F5	F6
1	Omeprazole	40	40	40	40	40	40
2	Di-basic calcium phosphate	87	85	83	81	79	77
3	Ethyl cellulose	2 **(1%)**	4 **(2%)**	6 **(3%)**	8 **(4%)**	10 **(5%)**	12 **(6%)**
4	PVP-k90(3%w/w)	6	6	6	6	6	6
5	Isopropyl alcohol	10	10	10	10	10	10
6	Magnesium stearate	10	10	10	10	10	10
7	Micro crystalline cellulose	50	50	50	50	50	50
8	Talc	5	5	5	5	5	5
Coating							
9	Eudragit-L100	0.5% w/v sol	0.5% w/v sol	0.5% w/v sol	0.5% w/v sol	0.5% w/v sol	0.5% w/v sol

Table 2: Preformulation Characteristics

S.No	Formulations	Angle of Repose (º)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)
1	F1	28.7	.72	0.86	16.27
2	F2	26.4	.78	.89	12.35
3	F3	27.3	0.74	0.86	13.95
4	F4	25.9	0.71	0.87	18.39
5	**F5**	**28.1**	**0.72**	**0.84**	**14.28**
6	F6	26.5	0.73	0.85	14.11

Table 3: Evaluation Parameters

S.No	Formulation	Hardness (kg/cm^2)	Friability	Weight variation (mg)	Disintegration time	Thickness (mm)	Drug Content (%)
1	F1	4.6	0.04	498.16	25min 13sec	5.98	98.70
2	F2	4.8	0.07	499.86	27min 38 sec	5.99	98.25
3	F3	4.2	0.06	497.42	28 min 23 sec	6.0	98.42
4	F4	4.5	0.04	500.11	25 min 42 sec	6.1	97.52
5	**F5**	**4.2**	**0.07**	**497.54**	**28 min 6 sec**	**5.95**	**99.24**
6	F6	4.8	0.05	498.37	26 min 9 sec	5.92	98.63

Table 4: Dissolution Studies

S.No	Dissolution Time(hr)	Percentage Drug Release (%)						
		F1	F2	F3	F4	F5	F6	Innovator
1	1	28.4	23.4	21.9	18.8	**18.4**	11.4	**18.6**
2	2	40.8	39.4	36.5	33.2	**30.6**	27.4	**31.4**
3	4	59.3	57.3	54.1	49.3	**45.2**	40.1	**45.6**
4	8	73.9	72.6	69.4	58.3	**55.4**	52.2	**56.1**
5	12	89.6	87.4	85.8	85.6	**73.9**	75.1	**74.2**
6	24	96.4	95.1	94.6	93.9	**97.6**	82.4	**98.1**

Table 5: Stability Study of Optimized Formulation (F5) at Accelerated (40 ± 2ºC & 75 ± 5% RH) Condition

Test	Initial	After 1month
Appearance	White colour, Capsule shaped biconvex tablet	No change In appearance
Hardness (Kg/cm2)	4.2	4.4
Friability	0.07 %	0.05%
Drug content(%)	99.24	98.99
In vitro drug release (%)	97.6	97.2

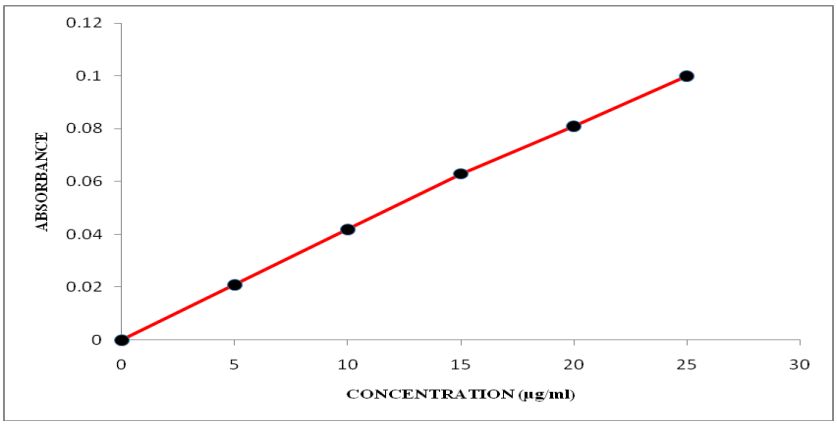

Fig 1(a): Standard curve of Omeprazole in Acidic Buffer

λ_{max} : 304.8nm
Medium : 0.1N HCl

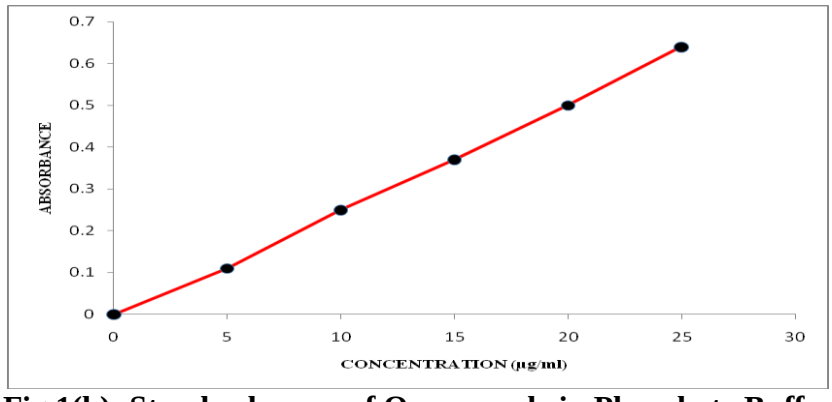

Fig 1(b): Standard curve of Omeprazole in Phosphate Buffer

λ_{max} : 304.8nm
Medium : pH 6.8 Phosphate Buffer

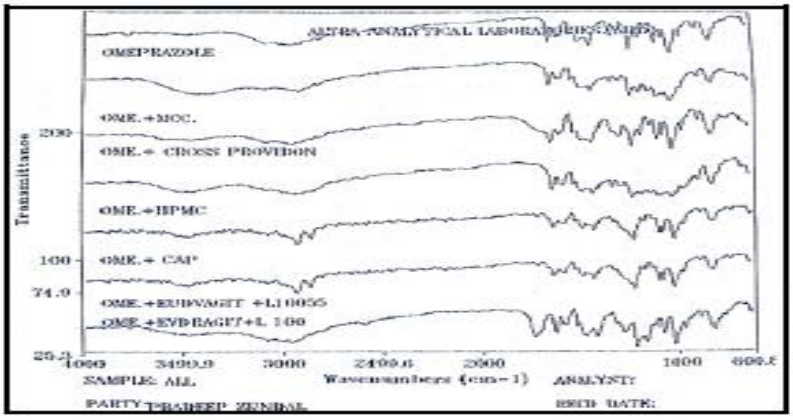

Fig 2: FT-IR spectra of Drug with Excipients

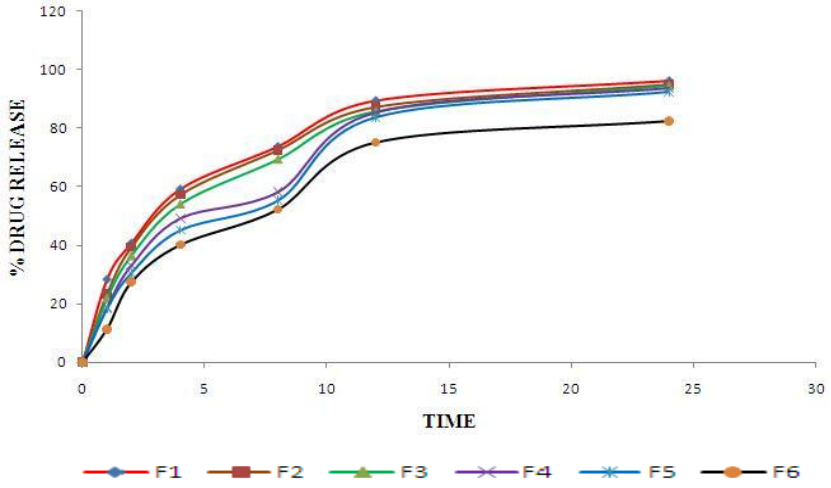

Fig 3: Dissolution Profile of All Formulations

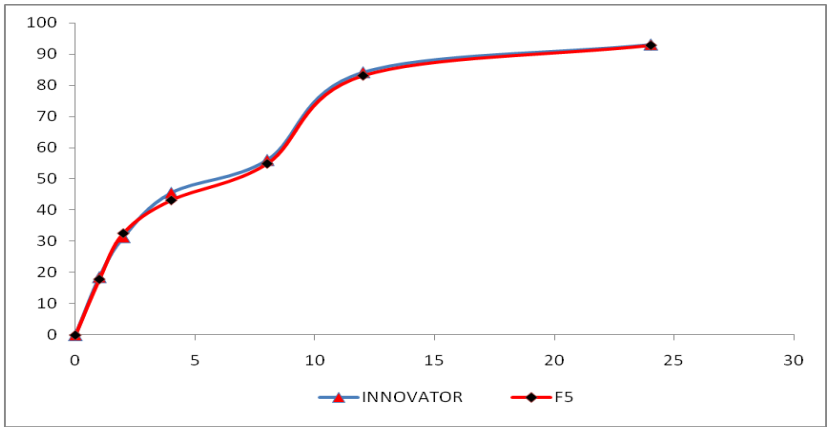

Fig 4: Dissolution Profile of Best Formulation (F5) & Innovator

DISCUSSION

Drug and excipients compatibility study was performed by FT-IR spectrometer. Here the peak of the pure Omeprazole was correlated with drug in presence of the other excipients. In all the FT-IR spectra identical peaks of the Omeprazole could not varied than of its original

peak. So, it can be concluded that the drug is compatible with all the excipients used in the formulation. The FT-IR spectra of the Omeprazole and with other excipients are shown in Fig.2. The granules were prepared by Wet granulation method. Flow properties of granules were estimated by angle of repose. All the formulations showed angle of repose within the range of 25-30^0, indicates that they had good flow property (Table.2). Tapped density of granules was found in range of 0.75 – 0.9gm/ml (Table.2).Bulk density of granules were found to be less than 1gm/ml (Table.2). These values were suitable to punch the granules as compressed tablets. The hardness of the enteric coated sustained release tablets was within the range of 4-5kg/cm^2 (Table.3). The friability results showed that the compressed sustained release tablets can withstand from the shocks (Table.3).The weight variation was within the limit i.e., ±5mg (Table.3).The disintegration time of all the formulations within the limits i.e 30 mins (Table.3). Thickness of all batches was in the range of 5.92– 6.1mm (Table.3). The percentage of drug content for F1 to F5 was found to 97.52% to 99.24% of Omeprazole, it complies with official specifications (90% – 110%). The results were shown in table 3.After 24th hour the percentage drug release from the formulations were 96.4%, 95.1%, 94.6%, 93.9%, 97.6%, 82.4% for the formulations containing Ethylcellulose 1%, 2%, 3%, 4%, 5% and 6% respectively (Table.4). Formulation F5 was identified to be the best as it matches well with the innovator (Fig.4). The results of the stability study for the optimized formulation F5 was given (Table.5). The results of stability indicated that there was no change in the formulation F5 after 1 month accelerated stability study. The prepared formulation of Omeprazole Enteric coated SR release tablet was stable.

CONCLUSION

The excessive liberation of Acetylcholine causes excessive gastric and salivary secretions, which leads to ulcers in the GIT. Omeprazole acts by inhibition of proton pump. It blocks the acetylcholine which works as an anti-ulcer drug. The present work aimed at developing Enteric coated SR Omeprazole tablets by wet granulation. *In vitro* release profile of all formulations showed slow sustained release up to 24hrs.After 24th hour the percentage drug release from the formulations were F1-96.4%, F2-95.1%, F3-94.6%, F4-93.9%, F5-97.6%, F6-82.4% for the formulations containing ethyl cellulose 1%, 2%, 3%, 4%, 5% and 6% respectively. Formulation F5 was identified to be the best as it matches well with the innovator. Accordingly, it can be concluded that the F5 (5%w/w EC) is robust one. The results of stability indicated that there was no change in the formulation F5 after 1 month

accelerated stability study. The prepared formulation (F5) of Omeprazole enteric coated SR tablet was stable.

ACKNOWLEDGEMENT

I am heartly thankful to Dr.M.Sreenivasulu M.Pharm., Ph.D., Principal, Nrayana Pharmacy College, Mr.Vasanth Kumar.PM M.Pharm., (Ph.D), Asso.Prof, Narayana Pharmacy College, Mr.B.Kishore Kumar M.Pharm., Ms.V.Jyothi M.Pharm., for their kind encouragement and support during the research work and thankful to the management of Narayana Pharmacy College, Nellore, A.P., India, for providing all the chemicals and facilities to do this research work.

REFERENCES

1. Chowdary KP, Sundari GB. Design and Evaluation of mucoadhesive controlled release oral tablets of Glipizide. Ind.J.Pharm.Sci, 2003; 65(3): 591–4.
2. Saini M, Jain S, Tiwari AK and Kaur G. Chitosan based buccoadhesive tablets of Pentazocine Hydrochloride: In vitro and in situ kinetics. Ind.J.Pharm.Sci, 2005; 67(5): 743–7.
3. Das S, Bhuyan NR, Chanda R, Bahadur S, Choudhury A and Saha S. Preparation and evaluation of mucoadhesive tablet of omeprazole for oral controlled release. Research Journal of Pharmaceutical Technology, 2008; 5(3): 166–70.
4. Yong CS, Jung JH, Rhee JD, Kook KC and Choi HG. Physicochemical characterization and evaluation of buccal adhesive tablets containing omeprazole. Drug.Dev.Ind.Pharm, 2001; 27(2): 447–55.
5. Remington: The science and practice of pharmacy. B.I publications Pvt.Ltd, Noida, 20 ed., vol.1, 2000; 903-929.
6. Shargel L, Andrew, Applied Biopharmaceutics and pharmacokinetics, 3rd Ed., prentice Hall International Inc, Newyork, 2005; 225-263.
7. Herzig SJ, Howell MD, Ngo LH and Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. Pak.J.Pharm.Sci, 2009; 7(3): 120–128.
8. Madanick RD. Proton pump inhibitor side effects and drug interactions. Clin J Med 2011; 78(6): 39–49.
9. Yang YX, Lewis JD, Epstein S and Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. Int.J.Pharm.Tec.Resch, 2006; 9(6): 947–953.

10. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S and Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. J.Clin.Pharmacol, 2008; 7(9): 319–326.
11. Thomson AB, Sauve MD, Kassam N and Kamitakahara H. Safety of the long-term use of proton pump inhibitors. J.Med.Sci, 2010; 16(4): 323–330.
12. Lau WC, Gurbel PA. The drug-drug interaction between proton pump inhibitors and clopidogrel. Eur.J.Pharm.Sci, 2009; 8(5): 99–105.
13. Kim CK, Jeong EJ, Lee EJ, Shin HJ and Lee WK. Bioequivalence of enteric coated omeprazole products. Resch.J.Bio.Sci, 2003; 23(6): 41–49.