REVIEW OF LITERATURE

- **Ali T. et al. (2009)** reviewed regarding the concerns of long-term PPI use, a literature search was performed to identify pertinent original and review articles. Despite study shortcomings, the collective body of information overwhelmingly suggests an increased risk of infectious complications and nutritional deficiencies. Data regarding any increased risk in gastric or colon malignancy are less convincing. PPIs have revolutionized the management and complications of acid-related disorders with a high margin of safety; however, with the data available, efforts to reduce the dosing of or discontinue the use of PPIs must be reassessed frequently.

- **Dennis L. Avner (2000)** reviewed the pharmacological properties of pantoprazole and summarized the findings from clinical studies of this drug. Due to its unique pharmacokinetic properties, mechanism of action, and reduced potential for producing cytochrome p-450 based drug interaction, report revealed that pantoprazole in both oral and IV formulation was effective for the treatment of GERD over 24 hours and was well tolerated in a variety of patients.

- **Basak et al. (2002)** prepared an enteric coated pancreatin tablets with five different enteric polymers. The tablets were evaluated on the basis of their disintegration time, loss on drying and enzyme activities periodically during a period of 90 days. All tablets but one stored at 45°C and 75% RH failed to meet disintegration test IP. Tablets coated with cellulose acetate phthalate and wincoat polymers failed disintegration test IP even at room temperature. All tablets formulations stored at 45°C and 75% RH failed loss on drying test IP. It was observed that the activities of pancreatic enzymes decreased on storage, but the loss in activity of individual enzymes were found to be different. Acrycoat L100 with polyvinylidene chloride packaging had shown promising results.

- **Brunner et al. (1994)** examined the effectiveness of pantoprazole (40-80 mg) daily in patients (106) with peptic ulceration of the oesophagus, stomach and duodenum, unresponsive to 3 or more months of high-dose treatment with ranitidine. In 96.7% of the patients ulcers healed within 2 to 8 weeks, and in 2.3% of patients the ulcers healed within 12 weeks. After ulcer healing, patients were treated with pantoprazole (40 mg/day) as long-term maintenance therapy. Eighty eight of the 98 patients have been taking pantoprazole for 6 months to 3 years. It was reported that during maintenance therapy, peptic disease was kept in remission in most patients with 40 mg pantoprazole.
Colomé et al., (2007)\textsuperscript{5} pantoprazole loaded microparticles were prepared by spray-drying using a blend of Eudragit S100 and HPMC, which can provide gastroresistance and controlled release. They reported that microparticles presented acceptable drug loading, encapsulation efficiency, surface area, and particle size. The in vivo anti-ulcer evaluation demonstrated that microparticles were effective in protecting stomach against ulceration. Microparticles were successfully tabletted using magnesium stearate. In vitro gastro-resistance study showed that microparticles stabilized pantoprazole in 62.0\% and tablets in 97.5\% and provided a controlled release of the drug.

Comoglu et al., (2008)\textsuperscript{6} made an attempt to prepare different batches of pantoprazole loaded microspheres by emulsion-solvent evaporation technique using two different types of enteric-coating polymers: eudragit S100 and hydroxypropyl methylcellulose phthalate. The microspheres were characterized in terms of their morphology, encapsulation efficiency, and ability of stabilizing pantoprazole in acidic media. They reported that two batches of microspheres were more effective in protecting the drug than other batches in acidic media.

Cronlein et al., (2006)\textsuperscript{7} the development of lansoprazole delayed release dosage forms, testing of the enteric performance is routinely evaluated using the USP dissolution test. This test measures the protection provided due to the enteric coat by exposing the dosage form to an acid media at pH1.2. A multiple dose regimen of proton pump inhibitors (PPIs) results in a decrease in gastric acid secretion with a subsequent elevation in gastric pH. Therefore the enteric coated dosage form may be subjected to a higher pH environment than what is typically tested using USP delayed release dissolution methods. The objective of this study was to investigate the enteric performance of aqueous enteric-coated multiparticulate formulations containing lansoprazole in bio-relevant media which better simulates the gastric environment of a patient on a multiple dose regimen of proton pump inhibitors (PPIs). A secondary objective of this study was to characterize the stability of the finished dosage form under room temperature and accelerated storage conditions.

G Crotts et al.,(2000)\textsuperscript{8} developed an enteric coating formulations and process for tablets primarily composed of a highly water-soluble, organic acid. The purpose of the study was to define coating conditions for the enteric coating of a highly water soluble, acidic tablet core. Acidic tablets containing marker drug were separated into three groups and seal coated. The tablets were coated with five Eudragit L 30 D based enteric formulations containing different
amounts of plasticizer (10-20 parts). During each enteric coating process, a predetermined amount of labeled tablets were removed after attaining 6, 8 and 10 % weight gains. Dissolution results revealed that all enteric coat tablets inhibited drug release for 2 hour in 0.1 N HCl. In contrast it was found that tablets without a seal coat failed the USP disintegration test. In addition seal coated tablets exhibited 1.5 – 5 fold greater drug release at most intermediate sampling time points in phosphate buffer pH 6.8, than tablets without seal coat, suggesting that the dissolution of the latter was delayed by the generation of an acidic environment at the interface of the enteric coat/acidic tablet core.

- **N.M.Davies et al., (1994)** compared the gastric retention of alginate containing tablet formulations; gamma scintigraphy has been used to monitor the gastric residence of tableted alginate preparations. It was found that a new formulation of Gaviscon tablets containing calcium carbonate as an excipient formed a raft which persisted in the stomach for approx. 2 h. in contrast, the raft formed from Gastrocote tablets readily dispersed and emptied with the food contents of the stomach. In vitro experiments illustrated a greater raft breaking strength for the ‘new’ Gaviscon tablets but raft thickness and time of raft formation were similar for both operations. The study suggested that these tablets displayed superior anti-reflux activity and its ability to form a strong persistent raft may be influenced by the ion content of the formulation.

- **Marchetti, F. et al., (2003)** reviewed the available studies concerning the use of proton pump inhibitors in pediatric populations and to point out: indications for use in children, optimal dosage, risk of adverse effects and consequences of the mechanism of action, and drug interactions. We performed a Medline and Embase search of publications printed from January 1980 to December 2002 concerning the use of proton pump inhibitors in children. We consider the available randomised controlled trials and several other uncontrolled studies conducted in the pediatric population, including all available information concerning the pediatric use of proton pump inhibitors. In children as well as in adults, there are clinical conditions (i.e., severe esophagitis or eradication of Helicobacter pylorii) in which proton pump inhibitors offer clear advantages over histamine-2 receptor antagonists. The relatively common use of acid inhibitors (proton pump inhibitors and histamine-2 receptor antagonists) in uncomplicated gastro-esophageal reflux disorders or in the prevention of non-steroidal anti-inflammatory drugs / steroid gastropathy is often unsubstantiated and should be limited to very specific situations. Multicentre randomised controlled studies are needed to better define the efficacy profile, the
optimal dosage with respect to the different indications and the safety profile for chronic therapy of proton pump inhibitors in children.

- **Fan et al., (1996)** made an attempt to perform the *in vitro* and *in vivo* evaluation of multilayer film coatings for omeprazole. The system consists of druglayered with salt, hydroxypropyl methyl cellulose and enteric film-coating layer respectively. A dissolution study was performed in pH 7.4. The multi-layer coated pellets were stable in gastric pH conditions and upper gastrointestinal tract in rats. Salt layer improved the drug stability and its coating levels had little influence on the dissolution profiles. The rate of drug release was significantly delayed by HPMC layer. The drug-layered pellets with multi-layer film coatings not only provided delayed and rapid release of omeprazole, but also could provide a good stable property for omeprazole. It was confirmed that rapid *in vitro* drug release rate resulted in better absorption.

- **Eiji Fukui et al. (2000)** prepared enteric-coated timed release press-coated tablets (ETP tablets) by coating enteric polymer on timed release press coated tablets composed of an outer shell of hydroxypropylcellulose and core tablets containing diltiazem hydrochloride as model drug. The results of the in-vitro dissolution tests in JP 1st fluid (1.2 pH) and JP 2nd fluid (6.8 pH) indicated that these tablets showed both acid resistance and timed release. The gastric emptying time and lag time after gastric emptying were evaluated by determining the time at which PPA and DIL 1st appeared in the plasma were about 4 and 7 hours respectively. This study revealed that ETP tablets seemed to be an effective tool for oral sit-specific delivery including targeting of the colon.

- **Garcia C.V. et al., (2008)** to study the photodegradation of rabeprazole, to determine its kinetics and to elucidate the structures of the main degradation products. UVC-254 nm and metal-halide lamps were used. The analysis of the samples was carried out by HPLC. When the drug was in methanol solution, one main degradation product was formed; the degradation rate followed zero-order kinetics. The 1H and 13C NMR spectroscopic determinations revealed the product was the benzimidazolone. Another isolated product was identified as benzimidazole. The latter was confirmed against an authentic sample. A third photodegradation product was identified as the [4-(3-methoxy-propoxy)-3-methyl-pyridin-2-yl]methanol, by 1H and 13CNMR of the reaction mixture in chloroform-d. When powdered commercial tablets were exposed to UVC irradiation, they showed the same degradation products along with other
unidentified, which appeared as traces; the degradation rate was slower than in solution. The intact tablets were stable after 50 days of exposition to the same light source.

- **Garcia, C. V et al., (2006)** developed and validate a dissolution test for rabeprazole sodium coated tablets using a reverse-phase liquid chromatographic method. After test sink conditions, dissolution medium and stability of the drug, the best conditions were: paddle at 75 rotations per minute (rpm) stirring speed, HCl 0.1M and borate buffer pH 9.0 as dissolution medium for acidic and basic steps, respectively, volume of 900 ml for both. The quantitation method was also adapted and validated. Less than 10% of the label amount was released in the acid step, while more than 95% was achieved over 30 min in the basic one. The dissolution profile for tablets was considered satisfactory. The dissolution test developed was adequate for its purpose and could be applied for quality control of rabeprazole tablets, since there is no official monograph.

- **Marc S.Gordan et al., (1995)** evaluated four different aqueous polymeric dispersions for producing an enteric-coated tablet and were assessed using an uncoated tablet core as a control. The four polymeric dispersions were cellulose acetate phthalate (CAP), cellulose acetate trimellitate, 50:50 CAP/CAT, and methacrylic acid copolymer. Naproxen sodium was the model drug. Polymer pH dissolution profiles showed that CAT dissolved at the most acidic pH, followed by 50:50 CAP/CAT, and then by CAP and methacrylic acid copolymer. It was found that all of the enteric coat formulations performed satisfactorily during initial in-vitro disintegration and dissolution testing.

- **F.C.Hampson et al.,(2005)** conducted study on alginate rafts and their characterization. In their study they tested the in-vitro effectiveness of a range of liquid products in forming rafts that were cohesive, buoyant, voluminous, resistant to reflux and durable under conditions of movement. Products with stronger rafts were found to be more resilient and more resistant to reflux in an in-vitro reflux model. Tested nine products for their formation speed floatation and coherence, raft strengths. They found from their study the factors that have influence on type of alginate rafts formed.

- **Hua et al., (2008)** reported that enteric coated multi-particulate systems may soften and agglomerate on the outer surface when in acidic media, affecting drug release profiles when tested in buffer. In this study the efficacy of fumed silica as an anti-adherent agent on the surface of enteric coated multi-particulates was investigated. Spraying of silicon dioxide dispersion
affected discrete multi-particulate units in acid media and resultant consistent dissolution profiles in buffer media.

- **John M. Imadomi, et al.,(2003)** conducted study to determine whether patients requiring multiple dose single dose PPI for initial symptom resolution could be stepped-down to single dose PPI and whether this intervention affected quality of life. It was concluded from the study that majority of patients rendered asymptomatic on multiple dose PPI might be subsequently stepped-down to single dose without recurrence of reflux-type symptoms. This intervention can decrease management cost without adversely affecting quality of life.

- **Akseli Kivioja, et al.,(2004)** specified in their study the most inexpensive proton pump inhibitor therapy for GERD and examined implications of varying outcome measures like holding time. They reported cost minimizing analysis in three setting with drug having different holding time. Based on holding time it was found that drug with holding time of 11 hours or more in 24 hours period the least expensive drug was lansoprazole.

- **Mandel et al., (2000)** reviewed alginate-raft formulations in the treatment of heartburn and acid reflux. It was reviewed that in the presence of gastric acid, alginates precipitates forming gel. Both in-vitro and in-vivo studies have demonstrated that alginate based rafts can entrap carbon dioxide, as well as antacid contained in the same formulations, rafts can act as a physical barrier to reduce reflux episodes.

- **Marchetti, F .et al., (2003)** reviewed the available studies concerning the use of proton pump inhibitors in pediatric populations and to point out: indications for use in children, optimal dosage, risk of adverse effects and consequences of the mechanism of action, and drug interactions. We performed a Medline and Embase search of publications printed from January 1980 to December 2002 concerning the use of proton pump inhibitors in children. We consider the available randomised controlled trials and several other uncontrolled studies conducted in the pediatric population, including all available information concerning the pediatric use of proton pump inhibitors. In children as well as in adults, there are clinical conditions (i.e., severe esophagitis or eradication of Helicobacter pylorii) in which proton pump inhibitors offer clear advantages over histamine-2 receptor antagonists. The relatively common use of acid inhibitors (proton pump inhibitors and histamine-2 receptor antagonists) in uncomplicated gastro-esophageal reflux disorders or in the prevention of non-steroidal anti-inflammatory drugs/steroid gastropathy is often unsubstantiated and should be limited to very specific situations. Multicentre
randomised controlled studies are needed to better define the efficacy profile, the optimal dosage with respect to the different indications and the safety profile for chronic therapy of proton pump inhibitors in children.

- **Matsuo et al., (1996)** a delayed release tablets of diltiazem was prepared using CM-type Hydroxyl ethyl cellulose of three viscosity grades. The tablets consisted of a core containing 30 mg of diltiazem and an outer shell formed by compressing hydroxyl ethyl cellulose. Diltiazem in the core was released rapidly from the tablets after a lag time of several hours. The lag time to the start of release of diltiazem was more prolonged with an increase in viscosity of CM-type hydroxyl ethyl cellulose. The lag time in vivo for appearance of diltiazem in the blood corresponded well to the lag time in vitro for drug release, but tended to be shortened as compared with the lag time in vivo. They reported that the lag time can be controlled by selecting hydroxyl ethyl cellulose with a proper viscosity and/or by changing the amount of hydroxyl ethyl cellulose forming the outer shell.

- **Pandey et al., (2002)** made an attempt to formulate sustained release capsule containing enteric coated granules of omeprazole. The polymers used for retarding the release are ethyl cellulose and hydroxypropyl methylcellulose. Solvent evaporation technique was followed to prepare sustained release granules. Granules are finally coated with enteric coating of suteric (polyvinyl acetate phthalate). They prepared eight capsule formulations and the formulation found very close to theoretical sustained release according to in vitro study was subjected to stability studies. They reported that product should be stored at room temperature or below ambient temperature.

- **Raffin et al., (2006)** a prepared and characterized of gastro-resistant pantoprazole loaded microparticles. The microparticles were prepared by emulsification/solvent evaporation technique. Furthermore, tablets containing the microparticles were also investigated. The in vivo activity of the pantoprazole-loaded eudragit S100 microparticles was carried out in rats. In vivo anti-ulcer evaluation showed that the microparticles were able to protect rat stomachs against ulcer formation, while the drug aqueous solution did not present activity. Drug dissolution profiles from tablets demonstrated slower release than untabletted microparticles. As regards the acid protection, tablets showed a satisfactory drug protection in acid medium.

- **Ramakrishna, N .et al., (2005)** was developed and validated a simple, sensitive and selective HPLC method with UV detection (284 nm) for quantitation of Rabeprazole in human
plasma, the newest addition to the group of proton-pump inhibitors. Following solid-phase extraction using Waters Oasis™ SPE cartridges, the analyte and internal standard (Pantoprazole) were separated using an isocratic mobile phase of 5 mM ammonium acetate buffer (pH adjusted to 7.4 with sodium hydroxide solution)/acetonitrile/methanol (45/20/35, v/v) on reverse phase Waters symmetry® C18 column. The lower limit of quantitation was 20 ng/mL, with a relative standard deviation of less than 8%. A linear range of 20–1000 ng/mL was established. This HPLC method was validated with between- and within-batch precision of 2.4–7.2% and 2.2–7.3%, respectively. The between- and within-batch bias was −1.7 to 2.6% and −2.6 to 2.1%, respectively. Frequently coadministered drugs did not interfere with the described methodology. Stability of rabeprazole in plasma was excellent, with no evidence of degradation during sample processing (autosampler) and 3 months storage in a freezer. This validated method is sensitive, simple and repeatable enough to be used in pharmacokinetic studies.

- Ravi K.P. et al., (2006) made an attempt to developed spectrophotometry methods for the simultaneous determination of domperidone and pantoprazole from combined tablet dosage forms. The methods involve solving of simultaneous equations and Q-value analysis based on measurement absorptivity at 216, 287 and 290 nm respectively. Linearity lies between 1-15 mcg/ml for domperidone and 0-50 mcg/ml for pantoprazole.

- Reddy G.M. et al., (2007) to detected six impurities in rabeprazole sodium bulk drug substance by a simple isocratic high performance chromatographic method (HPLC) whose area percentage ranged from 0.60 to 1.46%. LC-MS was performed to identify the mass of the impurities. A thorough study was undertaken to characterize these impurities. These impurities were synthesized, subsequently characterized and were co-injected with the sample containing impurities and are found to be matching with the impurities in the sample. Based on their spectral data (IR, NMR and MS), these impurities were characterized as 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl][thio]-1H-benzimidazole (impurity I); 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl] sulfonyl]-1H-benzimidazole (impurity II); 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl-1-oxide] methyl] sulfonyl]-1H-benzimidazole (impurity III); 2-[[4-(3-methoxypropoxy)-3-methyl] pyridin-2-yl]methanesulfinyl]-1-[[4-(3-methoxypropoxy)-3-methyl] pyridin-2-ylmethyl]-1H-benzimidazole (impurity IV); 2-[[4-(3-methoxy-3-methyl-2-pyridinyl] methyl] sulfinyl]-1H-benzimidazole (impurity V); 2-[[4-(3-
methoxypropoxy)-3-methyl-2-pyridine-1-oxide methyl sulfinyl]-1H-benzimidazole (impurity VI).

Rena S. et al., (2007) To developed chemical stability of a proton-pump inhibitor, rabeprazole sodium, was evaluated in simulated intestinal fluid (pH 6.8) containing various Generally Recognized As Safe (GRAS) f-listed excipients, including BrijR 58, Poloxamer 188, Cremophor RH40, Gelucire 44/14 and PEG 6000. After incubation at 37 and 60 .C, the amounts of rabeprazole and its degradation product, thioether-rabeprazole, were quantitated by HPLC analysis. The main degradation product was separated and characterized by LC/MS. The degradation of rabeprazole followed first-order kinetics. In the absence of any excipients, the rate constants (k) obtained at 37 and 60 .C were 0.75 and 2.78 h.1, respectively. In contrast, the addition of excipients improved its stability. Among several excipients tested in this study, BrijR 58 displayed the greatest stabilizing effect. For instance, at 37 and 60 .C, BrijR 58 reduced the k values to 0.22 and 0.53 h.1, respectively. The stabilizing mechanisms of these hydrophilic polymeric excipients with optimal HLB values could be partially explained in terms of their solubilizing efficiency and micellar formation for thioether-rabeprazole. In conclusion, rabeprazole formulations that contain suitable excipients would improve its stability in the intestinal tract, thereby maximizing bioavailability.

Saini V. et al., (2009) studied the pantoprazole is a proton pump inhibitor prodrug used in the treatment of gastric ulcers and gastroesophageal disease. Pantoprazole inhibits gastric acid by blocking the H+/K+- adenosine triphosphate enzyme system (the proton pump) of the gastric parietal cell. It is used to short term treatment of ulceration and erosion of the esophagus. The present study was carried out to determine the special effects of multiple-unit multiparticulate pantoprazole tablet dosage form for anti-ulcer activity. The multiple unit tablet of pantoprazole showed antulcer effects as indicated by a decrease in ulcer index.

Turkoglu M. et al., (2004) to formulated an enteric-coated omeprazole pellets and then compressed the pellets into tablets. The stability of the pellets and those of compressed tablets were evaluated for remaining omeprazole and for degradation products under an accelerated stability protocol. It was found that enteric coated omeprazole pellets could be compressed into quickly disintegrating tablets using microcrystalline cellulose granules as the pressure absorbing matrix. Microcrystalline cellulose matrix showed a strong plastic deformation and all the pellets inside the tablet maintained their integrity with no significant change in their surface properties.
Omeprazole degradation in acid medium was mainly dependent on microcrystalline cellulose concentration. A 90 days accelerated stability test in brown glass bottles with a desiccant showed that all prototype formulations would result in an acceptable stability profile for both remaining omeprazole, and also for the increase of impurity concentrations.

Esther T. Waterhouse et al., (2000) investigated the efficacy of the pectin based anti-reflux formulation. The properties of the new pectin based antireflux agent Aflurax were studied in-vitro and in-vivo. Aflurax had significantly higher in-vitro raft strength than the placebo, which matched the active except for the pectin (4.66±2.10 and 0.22 ±0.04 g, respectively).