ABSTRACT

Esomeprazole was the first discovered single isomeric proton pump inhibitor having bioavailability greater than Omeprazole providing profound inhibition of gastric acid secretion. Esomeprazole is a proton pump inhibitor used in the treatment gastroesophageal reflux disease and zollinger Ellison syndrome. The Plasma concentrations after oral administration of esomeprazole have confirmed that the metabolism of esomeprazole results in increased delivery to the systemic circulation as compared to an equivalent dose of omeprazole. The total body clearance of Esomeprazole was three times lower than Omeprazole (R form). The first pass effect of S isomer was reduced and total clearance was increased resulting in high plasma levels. The crossover study using 15mg dose Esomeprazole and Omeprazole in human volunteers shown that area under the curve for Esomeprazole was almost 4 times to that of Omeprazole. Crossover study using 20mg Esomeprazole, resulted in almost 70 % higher value than Omeprazole when given for 5 days once daily. Esomeprazole gets rapidly converted into sulfonamide at pH 1 which specifically binds to proton pump and inhibits it through inactive covalent bond formation between the reactive sulphur atom of the sulphonamide. The effectiveness of PPI'S in healing erosive eosophagitis confirmed the superiority of 40mg Esomeprazole oral administration daily. Many approaches are taken into account to accomplish this which involves floating tablets, matrix tablets and mucoadhesive tablets.

KEYWORDS: Esomeprazole, gastroesophageal reflux disease, zollinger Ellison syndrome, omeprazole.
Esomeprazole is a proton pump inhibitor widely used to reduce the gastric acid secretion in the stomach that envisages its use in the treatment of peptic ulcer and gastroesophageal reflux disease. It is a drug of choice in heart burn due to acid reflux. Esomeprazole is also used rarely for disease caused by tumour in pancreas known as zollinger Ellison syndrome. They are available as mixed with naproxen which is available as capsules. (vimovo). The lowest available strength in market was 20mg of tablets and capsules.

![Esomeprazole mode of action.](image)

Proton pump inhibitors decreases the secretion of gastric acid. They act by blocking the last enzyme in the system that actively transports acid from the gastric parietal cells into the gastrointestinal lumen i.e. hydrogen– potassium adenosine triphosphatase, also known as the proton pump. Proton pump inhibitors are mainly used to treat the symptoms of gastroesophageal reflux disease and gastritis. Often, they are used only after the therapy with histamine-2 (H2) receptor antagonists, commonly called H2 blockers. The US Food and Drug Administration’s clinical review of esomeprazole indicates that esomeprazole 40 mg is ‘pharmacodynamically thrice that of the s-isomer’ of omeprazole 20 mg. It decreases the amount of acid produced in the stomach and therefore used to treat gastroesophageal reflux disease (GERD), peptic ulcer caused by Helicobacter pylori and to heal erosive esophagitis. As compared to other proton pump inhibitors, esomeprazole confers a statistically significant improvement in healing rates and symptomatic relief in patients with EE. On a comparative study of esomeprazole with other proton pump Inhibitors like omeprazole, lansoprazole and pantoprazole, esomeprazole move rapidly and decreases heart burn sensations. It was found to be more effective than other proton pump inhibitors because of the rapid decrease in heart burn symptoms and acid reflux symptoms in patients with reflux.
esophagitis. The older PPIs (omeprazole, lansoprazole and pantoprazole) have notable limitations. These drugs exhibit substantial inter patient variability and may have significant interactions with other drugs. These first-generation PPIs also do not achieve a rapid and sustained suppression of gastric acid, leading to the development of new acid-pumpantagonists. Lower metabolic clearance of esomeprazole (S-enantiomer of omeprazole) increases its plasma concentrations. Gastric pH studies and therapeutic trials have demonstrated significant advantages of esomeprazole and rabeprazole compared with the older PPIs.

METHODS TO INCREASE GASTRIC RETENTION TIME

Many approaches have been undertaken to improve the retention time of oral dosage form in stomach, e.g. floating tablets, swellable and expansion systems, bioadhesive tablets, high density systems and delayed gastric emptying systems. In this approach, bioadhesive polymers that can adhere to the epithelial surface of gastrointestinal tract are used. Mechanistically, bioadhesion involves the formation of hydrogen and electrostatic bonding at the mucus polymer interface.

FACTORS AFFECTING GASTRIC RETENTION

Gastric retention time (GRT) is affected by several factors including size and shape of dosage forms, density, concomitant intake of food and drugs; such as anticholinergic agents (atropine, propanthelin), prokinetic agents (cisaprich, methoclopramide) and opiates (codeine). Similarly biological factors, which affect gastric emptying, include age, gender, posture, body weight and disease state (Crohn’s disease, diabetes). Bioadhesives is the term that describes the adhesion of a polymer to a biological substrate. The immobilization of drug carrying particles at the mucosal surface would result in:

- A prolonged residence time at the site of action or absorption;
- A localization of the drug delivery system at given target site;
- An increase in the drug concentration gradient due to increased contact of particles with the mucosal surface;
- A direct contact with intestinal cells, which is the step earlier to particle absorption.

Mucoadhesive controlled release devices can improve the effectiveness of a drug by maintaining the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of drug at a
specific site. Mucoadhesion also increases the intimacy and duration of contact between a drug containing polymer and a mucous surface. Anticholinergics, antihistamines and prostaglandin analogues exerted their mechanism of decreasing gastric acid secretion through the receptors on the basolateral membrane of gastric parietal cells. But their actions were compromised due to alternate pathway of activation.\(^1\) Also intersubject variability, acid rebounds and tolerance were also found to be the major demerits of these drugs that lead to decreased patient compliance.\(^2\)

The mechanism involved the direct inhibition of gastric \(\text{H}^+/\text{K}^+\) ATPase present in canaliculus of gastric parietal cells. This was found to be the final common step in the secretion of gastric acid covering all the stimulatory pathways. \(^3\)

**WHY ESOMEPRAZOLE AS COMPARED TO OTHER PPI'S**

Even though Omeprazole proved to be better in controlling the acid secretion compared to previous drugs. It had shown intersubject variability.\(^4\)

Fig 2: Adapted from Katz, et al. Intragastric pH was assessed for 24 hours on day 5 of treatment in 1 double-blind and 3 open-label, randomized, crossover studies. Based on a recent analysis of post hoc studies Nexium 24HR (esomeprazole 20 mg) showed intragastric pH levels maintained at >4 for a significantly greater mean percentage of the 14-hour daytime period than compared with other PPIs available OTC.
This envisages the researchers to develop and introduce a new drug superior than Omeprazole in the effective control of acid secretion. It was the S isomer of Omeprazole that is Esomeprazole, where activity was first screened by Astra Zeneca. Apparently it was difficult to prepare both isomers for in vitro study. Initially, but later both was produced in sufficient quantities to be studied in humans. It was found that the S isomer was approximately four times more effective and potent than R isomer following an oral administration.\(^5\)

**BIOAVAILABILITY**

Higher potential of S isomer Esomeprazole, compared to R isomer, Omeprazole was found because of higher systemic bioavailability. Human liver microsomal study found that Esomeprazole was metabolised to a higher extend than Omeprazole by cut PCYP3A4 and lower extend than Omeprazole by CYP2C19. The total body Clarence of Esomeprazole was three times lower than Omeprazole (R form). The first pass effect of S isomer was reduced and total clearance was increased resulting in high plasma levels. This advantages in metabolism of s isomer resulted in High value of area under the curve than obtained for R isomer for same oral dose.\(^6\)

**Table 1: Percentage bioavailability of PPI’s.**

<table>
<thead>
<tr>
<th>PPI</th>
<th>Percentage Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>90%</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>80%</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>77%</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>52%</td>
</tr>
</tbody>
</table>

The crossover study using 15mg dose Esomeprazole and Omeprazole in human volunteers shown that the area under the curve for Esomeprazole was almost 4 times to that of Omeprazole and resulted in almost 70 % higher value than Omeprazole when given for 5 days once daily.\(^7\) Their enhanced bioavailability of Esomeprazole paved the way to its superior position among the other proton pump inhibitors available in market.

**SPECIFICITY OF ESOMEPRAZOLE**

Esomeprazole is a prodrug that gets converted to its active form in acidic pH. At neutry pH it is lipophilic in nature and cross the biological membranes and circulates in the blood. During gastric acid secretion, the pH drops to one and the drug becomes protonated since the pka value of Esomeprazole is around 4. This helps the drug for its easy penetration into the gastric canaliculus and accumulates. Esomeprazole gets rapidly converted into sulfonamide at
pH 1 which specifically binds to proton pump and inhibits it through inactive covalent bond formation between the reactive sulphur atom of the sulfonamide and the thiol group of 16 enzyme.\textsuperscript{[8]}

![Fig 2: Metabolic products of esomeprazole and omeprazole.](image)

Invivo studies of carbon- 14 radiolabelled Omeprazole using dose of 25 micromol per kg IV Administration revealed the presence of drug primarily in lungs, stomach, kidney and liver after one minute. However after five mins the drug was mainly present in stomach and liver. Finally the radiolabelled drug was found concentrated on parietal cells near the site of proton pump.\textsuperscript{[9]} The fraction of drug present at the site of proton pump that eventually leads to the covalent binding is more relevant factor to be considered than the peak plasma concentration.

**ACID CONTROL OF ESOMEPRAZOLE**

pH greater than 4 was found to be the critical threshold of acid control for the effective treatment of GERD.\textsuperscript{[10]} oral administration of 40 mg Esomeprazole once a day was found to maintain gastric pH greater than 4 upto 24 hours than the duration achieved for other PPI’S when administered in standard doses. This study come to conclusion of using 40mg Esomeprazole once daily dominated in the effectiveness over 20mg and 40mg standard doses.of Omeprazole respectively for GERD.\textsuperscript{[11]}

The study to prove the effectiveness of PPI’S in healing erosive eosophagitis confirmed the superiority of 40mg Esomeprazole oral administration daily. 81.7% healing was achieved
within 4 weeks for Esomeprazole and 84.2% for omeprazole. 93.7% of patients were found to be recovered completely after 8 weeks of using 40mg Esomeprazole once daily.[12]

Table 1: Dosage schedule of Esomeprazole.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td>Esomeprazole 40mg once daily</td>
</tr>
<tr>
<td>Symptomatic GERD</td>
<td>Esomeprazole 20mg once daily</td>
</tr>
<tr>
<td>NSAIDs induced gastropathies</td>
<td>Esomeprazole 20mg / Esomeprazole 40mg 4 weeks</td>
</tr>
<tr>
<td>H. Pylori Eradication</td>
<td>Esomeprazole 40mg, 500mg, 1000mg</td>
</tr>
</tbody>
</table>

Esomeprazole 20mg once daily was also found to be effective in the maintenance therapy of healed eosophagitis and was found to be more effective than lansoprazole 15mg once a day for the maintenance of remission of oesophagitis.[13]

SELECTIVITY AND SAFETY OF ESOMEPRAZOLE

Even though H+/K+ ATPase also exists in large intestine y kidney, the pH of these regions is not sufficient to accumulate and transform Esomeprazole to its active metabolite sulphonamide. It has been found that the ratio of elimination half life to activation half life at pH 5 was the most important factor to find the exposure of acidic tissues to Esomeprazole.[14]

The pka values of all PPIs are around 4 which permits them to accumulate in the gastric parietal cells at pH 1.[15] The maintenance and open label studies of Esomeprazole 40mg once a day suggested that it shows low adverse effects than Omeprazole. The common side effects of Esomeprazole I volved nausea, abdominal discomfort, headache and diarrhoea, but the surveillance studies conducted for Esomeprazole doesn’t show any serious adverse effects compared to Omeprazole.

ADVANTAGES OF ESOMEPRAZOLE

- It is the first discovered single isomeric proton pump inhibitor having bioavailability greater than Omeprazole providing profound inhibition of gastric acid secretion.
- More clinical superiority, efficiency and response predicting than other PPI’s.
- Higher specificity to bind and accumulate at gastric parietal cells.
- No safety issues reported till date and it is free of concern about toxicity.
B. Ashok et al formulated and evaluated Esomeprazole magnesium delayed release tablets each containing 4mg drug. Tablets with appreciable hardness and disintegration time were subjected for enteric coating using HPMC Ptalate. The evaluation results of developed tablets indicated that the application of 8% W/W enteric coating to tablets shown good disintegration time in 0.1N HCL.

**APPROACHES IN THE DEVELOPMENT OF CONTROLLED DRUG DELIVERY SYSTEMS LOADED WITH ESOMEPRAZOLE**

Since the major action is to be exerted on the stomach, it is necessary to enhance the drug resistance time so as to extend the duration of action and site specific delivery of drug. Many approaches are taken into account to accomplish this which involves floating tablets, matrix tablets and mucoadhesive tablets. The duration of drug release is enhanced by the use of controlled polymers that form a mesh like network whose release will follow Higuchi model pattern. The floating tablets formulated using buoyant polymers like chitosan, alginate etc.

The success of controlled drug delivery system is dependent on various physiological activities like short gastric residence time and unpredictable gastric emptying time. Increase in gastric residence time increases the drug solubility in gastric pH. In order to deliver the drugs having narrow therapeutic index and to increase its bioavailability, gastro retentive drug delivery systems were developed which had gained attention in the past decades.

Despite the invention of novel drug delivery techniques, oral route remains to be the preferred route of administration because of low cost therapy, ease of administration and increased patient compliance. From the recent scientific and patient studies, it is evident that oral controlled released dosage forms that are designed to retain in upper GIT for a predicted period of time is the most important topic of interest in both academic and industrial research groups. Certain drugs having narrow absorption window releases the drug in the region preceeding and in close vicinity to the absorption window. The drug released after crossing the absorption window gets eliminated from the body without producing any intrinsic activity. This minimises the time available for drug absorption and its bioavailability. Therefore the aim of oral controlled drug delivery system has faced difficulties related with physiological adversities like short gastric residue time(GRT) and gastric emptying time(GET). Prolonged GRT improves the bioavailability, increase the duration of drug release, reduce the drug waste and improve drug solubility that is less soluble in a high pH environment. This has triggered the attention towards the development
of various gastro retentive drug delivery technologies to deliver narrow absorption window drug with improved bioavailability.\textsuperscript{[16]}

Gastroretentive dosage forms are designed to be retained in the gastric region for prolonged period and release the incorporated drug candidates and thereby enable sustained and prolonged input of the drug to the upper part of the GIT thus ensuring its optimal bioavailability. Thus, they not only prolong the dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms. This application is especially effective in the delivery of sparingly soluble and insoluble drugs. Gastroretentive dosage forms made it possible to treat gastric and duodenal ulcers, esophagitis thereby reducing the risk of gastric carcinoma. Many technological attempts have been made to devise various controlled release gastroretentive drug delivery systems namely, high density (sinking) systems that is retained at the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible or swellable systems which limits the emptying of the dosage forms through the pyloric sphincter of stomach, super porous hydrogel & magnetic systems.

Manivannan Rangasamy et al. formulated and evaluated once daily Esomeprazole controlled release tablet using carbopol as the primary polymer and different grades of hydroxyl propyl methyl cellulose (HPMC) as secondary polymers such as Methocel K4M & Methocel K15 M. The tablets were prepared by direct compression method. Carbopol concentration was kept constant and the amount of Methocel K4 M & Methocel K15 M was varied to develop once daily esomeprazole in nine proposed formulations (FA1-FC3). The dissolution study of the proposed formulations were carried out using USP dissolution apparatus II in the simulated gastric medium (pH 1.3) for first two hours and then in the simulated intestinal medium (pH 6.8) for 24 hours. The formulation FB2 with K4M 20% met with the optimum release rate of esomeprazole for and was considered to be the best formulation among the 9 formulations.. The release kinetics very closely followed Higuchi mechanism and zero order kinetics. Mucoadhesive strength was determined using goat intestine and shows high mucoadhesive strength. Accelerated stability study was performed for optimized formulation FB2 (K4M 20%) which complied with the limit.\textsuperscript{[17]}

Nanne Chandrakanth et al. formulated and evaluated mucoadhesive bilayered buccal devices
of esomeprazole magnesium. The tablets were prepared using carbopol-934, hydroxy propyl methyl cellulose K4M (HPMC K 4M) and hydroxy propyl methyl cellulose E5 (HPMC E5) as bioadhesive polymers to impart mucoadhesion in drug: polymer ratio of 1:1, 1:1.25, 1:1.5 and ethyl cellulose as impermeable backing layer. Different physical parameters such as weight uniformity, hardness, thickness, surface pH, content uniformity, swelling index, ex-vivo mucoadhesion time, ex-vivo mucoadhesion strength, in vitro drug release and in vitro drug permeation were evaluated. The formulation showed controlled release of drug with increased bioavailability. The ex-vivo drug release of formulation containing HPMC E5 and microcrystalline cellulose showed 84.28±0.76 in 7hrs. The drug release pattern was found to be zero order kinetics obeying Peppas and Hixson Crowell release kinetics. The stability of the drug in the tablet was found to be stable in human saliva for 6 hours. Absence of interaction between drug and polymers was confirmed with FTIR studies. The study concluded that mucoadhesive buccal devices of esomeprazole bypasses extensive hepatic first-pass metabolism and thereby improves the bioavailability of esomeprazole.[18]

Patel Deval et al. formulated and evaluated bioadhesive bilayer buccal tablets containing Esomeprazole. The aim was to bypass first pass metabolism, to avoid gastric degradation and to improve its bioavailability and to reduce the dose related side effects. The tablets were prepared by direct compression method using a combination of bioadhesive polymers like POLYOX WSR 303 and HPMC K15M with different concentration. Ethyl cellulose was used as an impermeable backing layer. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, mucoadhesive time, swelling index and in vitro drug release. Maximum percentage of in vitro drug release (92.04%) was obtained from tablets containing POLYOX WSR 303 (30%) and HPMC K15M (20%) in 8 hours with satisfactory bioadhesive strength (20.8 gm). Stability studies indicated that there are no significant changes in drug content and in vitro dissolution, bioadhesive strength and swelling index. The swelling index of tablet increased with increasing amount of HPMC K15M. The formulation consist of esomeprazole (20 mg), HPMC K15M (12 mg), POLYOX WSR 303 (18 mg), Microcrystalline cellulose 102 8.8mg), Magnesium stearate (0.6 mg), talc (0.6 mg) and ethyl cellulose (20mg) was found to be the optimum formulation.[19]

Jagdale Swati C et al. developed Esomeprazole buccal adhesive tablets using direct compression. These were developed using combinations of mucoadhesive polymers like
Carbopol 934P, HPMC K4M and sodium alginate. The physical parameters like weight variation, thickness, hardness, surface PH, content uniformity and swelling index were evaluated. An in-vitro drug permeation study was conducted by egg membrane and ex-vivo studies by goat membrane. The effect of formulation composition on the release pattern of drug was also investigated. Most of the formulations showed the controlled release of esomeprazole based on the grade and polymer ratio. Tablets containing polymers like Carbopol 934P and sodium alginate in the ratio of 1:1(B3) showed the maximum drug release of 94.16% in 8 hours. The swelling index was proportional to sodium alginate content and inversely proportional to Carbopol 934 P content. Formulation B3 showed maximum swelling index after 6 hours. Surface pH of all the formulations was found to be close to the neutral pH. The release mechanisms fit to Peppas’ kinetic model.[20]

CONCLUSION

Esomeprazole in spite of all advantages and specificity over other PPI’s is widely used for the treatment of GERD and zollinger ellison syndrome paved a way towards the development of mucoadhsive, floating and other gastroretentive drug delivery systems. The more Predictable and prolonged suppression of gastric acidity added their advantage over other gastric acid suppressers. The management of gastroesophageal reflux disease and erosive esophagitis in pediatric patients focuses on the delayed-release esomeprazole tablets.

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