Indo Global Journal of Pharmaceutical Sciences, 2012; 2(2): 191-196

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

A Review: Development & Validation of HPLC Method for the Determination of Esomeprazole in Pharmaceuticals

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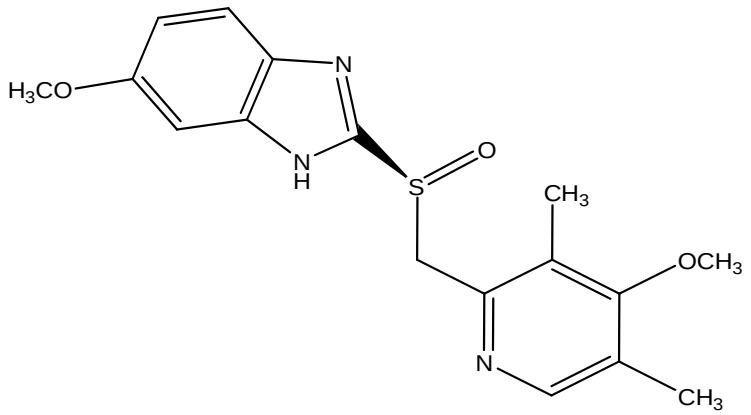
ABSTRACT: Esomeprazole is chemically bis(5methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole-1-yl). It is a gastric proton-pump inhibitor (PPI) used in treatment of gastric-acid related diseases. Simple, selective and accurate high performance liquid chromatographic (HPLC) methods were developed and validated for the analysis of esomeprazole magnesium. The objective of this review is to describe various analytical methods for estimation of Esomeprazole. All methods are validated as per ICH guidelines.

KEYWORDS: Esomeprazole; HPLC; Validation; K^+/H^+ ATPase; S-isomer; Proton Pump Inhibitor.

INTRODUCTION

Esomeprazole is chemically bis(5methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole-1-yl). It is a gastric proton-pump inhibitor (PPI) used in treatment of gastric-acid related diseases.[1] Its molecular formula is $(C_{17}H_{18}N_3O_3S)_2$ Mg x 3 H_2O with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis.[2] Benzimidazole compounds, such as esomeprazole, lansoprazole, pantoprazole and rabeprazole, are gastric parietal cell proton pump inhibitors (PPIs), which are widely used for the treatment of acid-related gastric diseases due to their ability to inhibit acid secretion. *Helicobacter pylori* infection is the main cause of gastritis, gastroduodenal ulcer disease and gastric cancer. Esomeprazole provides better control of intragastric pH than omeprazole, lansoprazole, pantoprazole and rabeprazole. Consequently, esomeprazole produces higher healing rates of erosive oesophagitis and better symptom control than omeprazole in patients with gastro-oesophageal reflux disease. On the other hand, esomeprazole has a higher degree of activity against *H. pylori* than other PPIs as omeprazole the increased antimicrobial activity in vitro of esomeprazole against *H. pylori* could contribute to improving the outcome of the eradication treatment of such an infection

[3]. Esomeprazole is cost effective in treatment of gastric oesophageal reflux diseases [4]. Esomeprazole magnesium was developed as the S-isomer of omeprazole as an attempt to improve its pharmacokinetic properties [5]. It is the first PPI available for clinical use as a single isomer. It demonstrates pharmacological and clinical benefits beyond those seen with the racemic omeprazole [6]. This optical isomer is subject to less first-pass metabolism and lower plasma clearance than omeprazole, thereby offering higher systemic bioavailability [7]. Esomeprazole has higher and more consistent bioavailability than omeprazole [6]. Esomeprazole reduces acid secretion through inhibition of K^+/H^+ ATPase in gastric parietal cells. By inhibiting the functioning of this enzyme, the drug prevents formation of gastric acid. Gastroesophageal Reflux Disease (GERD) is a Condition in which the digestive acid in the stomach comes in contact with the oesophagus (food pipe). The irritation caused by this disorder is known as heartburn. Long term contact between the acid and oesophagus can cause permanent damage to the Oesophagus. Esomeprazole (Nexium) reduces the production of digestives acids, thus minimizing their effect on the oesophagus [8]. Esomeprazole is highly bound (97%) to plasma proteins and primarily metabolized by 2 cytochrome P_{450} (CYP) isozymes, CYP3A4 and CYP2C19, with CYP2C19 being the predominant metabolic pathway [9]. There are stereoselective differences in the metabolism of PPIs by the cytochrome P450 (CYP) isoenzymes 2C19 and 3A4, and this is the basis of the observed pharmacodynamic and clinical efficacy differences between esomeprazole and omeprazole [8-11]. A study in which these enzymes were expressed from cDNAs suggested that CYP2C19 is responsible for 40% and 87% of the total intrinsic clearance of S- and R-omeprazole, respectively, indicating esomeprazole would be cleared more slowly in vivo [7]. Esomeprazole magnesium induced an increase in total antioxidant capacity and Cu/Zn–superoxide dismutase activity in stomach [14].



Structure of Esomeprazole

Proton Pump Inhibitor: Proton pump inhibitors (PPIs) are very effective for the treatment of symptoms and the healing of erosive and ulcerative disease in the spectrum of acid-related disorders (duodenal and gastric ulcer disease and erosive esophagitis). PPIs produce significantly more effective and prolonged acid suppression than H2-receptor antagonists (H2-RAs) and maintain a pH >4 for up to 18–20 h/day. It has been demonstrated that healing in acid-related disorders is directly related to the degree and duration of acid suppression and the length of treatment [15-19].

Pharmacology: It is a prototype member of substituted benzimidazoles. The significant pharmacological action of esomeprazole is dose dependent suppression of gastric acid secretion; without anticholinergic or H2 blocking action. It is a powerful inhibitor of gastric acid: can totally abolish HCl secretion, both resting as well as stimulated by any of the secretagogues, without much effect on pepsin, intrinsic factor, juice volume and gastric motility. The omeprazole is inactive in neutral pH, but at pH below 5 rearranges to

two charged cationic forms (a sulphenic acid and sulphenamide configurations) that react covalently with SH groups of the H^+K^+ATPase enzyme and inactivate it irreversibly, specially two molecules of omeprazole were react with one molecule of enzyme. But unlike omeprazole, esomeprazole claimed to produce better control of intragastric pH than omeprazole in GERD patients [5].

VARIOUS METHODS

Armagan Onal et al (2006) developed and validated a method for routine quality control analysis of esomeprazole magnesium trihydrate in tablets. Separation was achieved isocratically on C_{18} column utilizing a mobile phase of ACN/phosphate buffer (60:40, v/v, pH 7) at flow rate of 1.0 ml/min. with UV detection at 205 nm using lansoprazole as an internal standard. The calibration curve of esomeprazole was linear in the range of 100~1000 µg/ml (r = 0.9992, n = 4). The mean recovery for esomeprazole from tablets ranged between 97.82~98.22% [20].

Patel B. H. et al (2007) described a simple, sensitive, and precise high performance liquid chromatographic method for the analysis of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride, with ultraviolet detection at 210 nm, has been developed, validated, and used for the determination of compounds in commercial pharmaceutical products. The compounds were well separated on a Hypersil BDS C18 reversed-phase column by use of a mobile phase consisting of 0.05 M, 4.70 pH, potassium dihydrogen phosphate buffer - acetonitrile (720:280 *v/v*) at a flow rate of 1.0 mL min^{-1}. The linearity ranges were 400–4,000 ng mL^{-1} for pantoprazole, 200–2,000 ng mL^{-1} for rabeprazole, 400–4,000 ng mL^{-1} for esomeprazole, 300–3,000 ng mL^{-1} for domperidone and 500–5,000 ng mL^{-1} for itopride. Limits of detection (LOD) obtained were: pantoprazole 147.51 ng mL^{-1}, rabeprazole 65.65 ng mL^{-1}, esomeprazole 131.27 ng mL^{-1}, domperidone 98.33 ng mL^{-1} and itopride 162.35 ng mL^{-1}. The study showed that reversed-phase liquid chromatography is sensitive and selective for the determination of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride using single mobile phase [21].

Hultman I. et al (2007) described a LC-MS/MS method was developed for quantitative determination of esomeprazole, and its two main metabolites 5-hydroxyesomeprazole and omeprazole sulphone in 25 _L human, rat or dog plasma. The analytes and their internal standards were extracted from plasma into methyl *tert*-butyl ether - dichloromethane (3:2, v/v). After evaporation and reconstitution of the organic extract the analytes were separated on a reversed phase LC column and measured by atmospheric-pressure positive ionisation MS. The linearity range was 20–20,000 nmol/L for esomeprazole and omeprazole sulphone, and 20–4000 nmol/L for 5-hydroxyesomeprazole. The extraction recoveries ranged between 80 and 105%. The intra- and inter-day imprecision were less than 9.5% with accuracy between 97.7% and 100.1% for all analytes [22].

Kumar Putta Rajesh et al (2010) developed and validated a UV spectrophotometric method for esomeprazole magnesium trihydrate and its physico-chemical characterization. Physico chemical characterization studies showed that EMT has showed a melting point of 177.330 C. The solubility of drug esomeprazole followed the order methanol>ethanol> acetone> buffer pH 9.0 > distilled water. The analytical method developed for the estimation of esomeprazole magnesium trihydrate in bulk fluids showed maximum absorbance λmax of 203.5 nm in methanol between 200 nm and 400 nm. Linearity studies indicated that estimation of esomeprazole magnesium trihydrate between 2.00 µg /ml to 10.00 µg /ml was found to be linear with regression equation of y = 0.1546*X - 0.00414; (r2 = 0.999). Limit of Quantitation of esomeprazole was found to be of1.00 µg/ml. The above analytical parameters indicated that the developed UV Spectrophotometric method of esomeprazole was simple, accurate and reproducible [2].

Zanitti L. et al (2010) described an analytical and semi preparative high-performance liquid chromatography (HPLC) enantioseparation of the proton-pump inhibitor omeprazole (OME) and its potential organic chiral impurities were accomplished on the immobilised-type Chiralpak IA chiral stationary phase (CSP) under both polar organic and normal-phase conditions. The (S)-enantiomers were isolated with a purity of >99% ee and their absolute configuration were empirically assigned by circular dichroism (CD) spectroscopy. A chemo- and enantioselective HPLC method was validated to control the enantiomeric purity of the (S)-enantiomer of OME (ESO), an active ingredient contained in drug products, in the presence of chiral and achiral related substances. The precision, linearity and accuracy of the determination of the (R)-impurity as well as the recovery of ESO from a pharmaceutical preparation were determined. The proposed method uses the mixture methyl tert-butylether (MtBE)–ethyl acetate (EA)–ethanol (EtOH)–diethylamine (DEA) 60:40:5:0.1 (v/v/v/v) as a mobile phase. In these conditions, linearity over the concentration range 0.5–25_g/ml for (R)-enantiomer was obtained. The limits of detection and quantification were 99 and 333 ng/ml, respectively. The intra and inter-day assay precision was less than 2% (RSD %) [1].

Nalwade Santaji Uttam et al (2011) developed a RP-UPLC method for quantitative determination of esomeprazole magnesium and its seven impurities in pharmaceutical dosage forms. Separation has been achieved on an acquity BEH C_{18}, 50 mm × 2.1 mm, 1.7 µm with buffered mobile phase consisting solvent A (0.04 M glycine (pH 9.0) buffer) and solvent B (mixture of ACN and milli Q water in the ratio 90:10 (v/v) ; resp.) delivered at flow rate of 0.2 ml/min and detection wavelength 305 nm. The drug was subjected to stress conditions. The stress samples were assayed against a reference standard and the mass balance was found to be close to 99.1 % [23].

Kumar T. Santhosh et al. (2011) developed and validated a new simple, accurate, rapid and precise isocratic HPLC method for determination of esomeprazole and domperidone in capsule formulation, The method employs waters HPLC system on Thermo RP_8 column (4.6 ×150mm and 3.5 µm) and flow rate of 1 ml/min. with a load of 20 µl. ACN and phosphate buffer was used as mobile phase in the composition of 35:65 at 289 nm. Percent recovery values of esomeprazole and domperidone were found to be within 98-102 % as per ICH guidelines [12].

Jain Deepak kumar et al. (2011) described the simple, precise, sensitive RP-HPLC method which has been validated to determine esomeprazole magnesium trihydrate and naproxen in synthetic mixture form. Chromatographic separation was achieved isocratically on phenomenex luna C_{18} column (5µm, 150 mm × 4.5 mm) and ACN: phosphate buffer (pH 7.0) in the ratio 50: 50 (v/v) as the mobile phase, at a flow rate of 0.5 ml/min. Detection was carried out at 300 nm. The method was linear in the concentration range of 50-250 µg/ml for naproxen and 2-10 µg/ml for esomeprazole with correlation coefficient of 0.9999 and 0.9998 resp. The mean recoveries obtained for naproxen and esomeprazole were 100.01 % and 97.76 % resp. and RSD was less than 2 [24].

Sharma S. et al (2011) developed and validated a method for estimation of esomeprazole and domperidone as bulk and pharmaceutical form. The chromatographic development was carried out on precoated silica gel 60 F_{254} aluminium plates using mixture of ethyl acetate;1,4 dioxane: methanol:25 % ammonia in the ratio of 15:1.5:3:1.5 v/v. The drug was satisfactorily resolved with R_f valve 0.36±0.12 and 0.53±0.52 esomeprazole and domperidone respectively. The accuracy and repeatability of the proposed method was ascertained by evaluating various validation parameters like linearity (200 to 700) ng/spot and 300 to 900 ng/spot esomeprazole and domperidone resp., precision (intra-day RSD 0.143, 0.237 and %), inter-day RSD 0.351 and 0.549 esomeprazole and domperidone resp., accuracy (99.93±0.52) and specificity according to ICH guidelines. The linearity was obtained with correlation coefficients (r^2= 0.9992) and (r^2= 0.9997) for esomeprazole and domperidone respectively. The method was validated as per ICH guidelines [4].

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