Review Article

Analysis of Proton Pump Inhibitors in Bulk and In Different Dosage Forms -A Review

***Mayuri R. Ghadge, Vrushali S. Tambe, Pallavi G. Darade**

Department of Quality Assurance, P. E. S's, Modern College of Pharmacy (For Ladies), Dehu-Alandi Road, Borhadewadi, Moshi, Pune- 412105, Maharashtra, India.

ABSTRACT

Proton-pump inhibitors (PPIs) produce a pronounced and long-lasting effect for the reduction of gastric acid production. They form majority of benzimidazole derivatives, but promising new research indicates the imidazopyridine derivatives may be a more effective means of treatment. Proton pump inhibitors are mainly used to treat symptoms of gastroesophageal reflux disease and gastritis. Often, they are used only after therapy with histamine-2 (H2) receptor antagonists, commonly called H2 blockers, has been unsuccessful for symptoms of reflux. Proton pump inhibitors also are used to treat peptic ulcers (duodenal and gastric) and drug-induced ulcers, such as those associated with nonsteroidal anti-inflammatory drugs; the bacterium that causes ulcers, Helicobacter pylori, is eradicated by treatment with a proton pump inhibitor and antibiotics. Proton pump inhibitors also are used to promote healing of erosive esophagitis. Esophagitis can lead to scarring and narrowing of the esophagus (stricture) or to Barrett esophagus, which is a risk factor for esophageal cancer. Dyspepsia, Peptic ulcer, Gastroesophageal reflux disease (GERD), Laryngopharyngeal reflux. Clinically used PPIs are Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole.etc Due to rapid degradation of these drugs in acidic and aqueous media, it is challenging to develop analytical method where in stability of drug is least hampered. This review entails different methods developed for determination of PPIs like UV-Spectroscopy, liquid Chromatography and LC-MS.

Keywords: HPLC, HPTLC, LC-MS, Proton pump inhibitors, UV-Spectroscopy.

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***Address for correspondence:**
Mayuri R. Ghadge
PES. Modern College of Pharmacy for Ladies, Dehu-Alandi Road, Borhadewadi, Moshi, Pune-412105, Maharashtra, India.
E-mail: mayurighadge77@gmail.com

INTRODUCTION

PPIs are the most potent inhibitors of acid secretion available. They followed and have largely superseded another group of pharmaceuticals with similar effects, but a different mode of action, called H_2-receptor antagonists. The vast majority of these drugs are benzimidazole derivatives, but promising new research indicates the imidazopyridine derivatives may be a more effective means of treatment. High dose of these drugs are used in the treatment of many conditions, such as: Dyspepsia, Peptic ulcer disease, Gastroesophageal reflux disease (GERD), Laryngopharyngeal reflux.

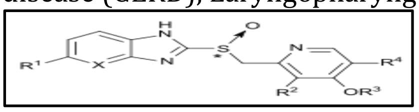

Figure1: General Structure of Proton Pump Inhibitor

Proton pump inhibitors (**Fig. 1**) act by irreversibly blocking the hydrogen/ potassium adenosine triphosphatase enzyme system (The H+/K+ ATPase, or more commonly, the gastric proton pump) of the gastric parietal cells. The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion.

Targeting the terminal step in acid production, as well as the irreversible nature of the inhibition, results in a class of drugs that are significantly more effective than H_2 antagonists and reduce gastric acid secretion by up to 99%. Proton pump inhibitors are mainly used to treat symptoms of gastroesophageal reflux disease and gastritis. Often, they are used only after therapy with histamine-2 (H2) receptor antagonists, commonly called H2 blockers, has been unsuccessful for symptoms of reflux. Proton pump inhibitors also are used to treat peptic ulcers (duodenal and gastric) and drug-induced ulcers, such as those associated with nonsteroidal anti-inflammatory drugs; the bacterium that causes ulcers, Helicobacter pylori, is eradicated by treatment with a proton pump inhibitor and antibiotics. Proton pump inhibitors also are used to promote healing of erosive esophagitis. Esophagitis can lead to scarring and narrowing of the esophagus (stricture) or to Barrett esophagus, which is a risk factor for esophageal cancer.

Clinically used Proton Pump Inhibitors (PPI) are includes Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole. This paper gives an overview of various analytical methods for estimation of proton pump inhibitors. Different methods have been developed for determination of PPI like UV-Spectroscopy, liquid Chromatography, and LC-MS [01].

Reported methods are categorized depending on the following considerations:

1) **Single component PPI**
2) **Multi-drug PPI combination**
3) **Analysis of PPI from combination formulation**

A] Single component PPI

OMEPRAZOLE

Ozaltın et al have developed derivative UV spectroscopic method for determination of Omeprazole in borate buffer (pH 10.0;0.1 M). Second derivative spectra were generated between 200–400 nm. The linearity range was 0.2-40.0 μg/ml [02].

Karljikovic-Rajic et al have developed first-order UV-derivative spectrophotometry method applying zero-crossing for the determination of omeprazole, omeprazole sulphone, pantoprazole sodium salt, and N-methyl pantoprazole in methanol- ammonia 4.0% v/v. The method showed good linearity range 1.16-17.2 μg/ml for omeprazole, 2.15-21.50 μg/ml for omeprazole sulphone, 2.13-21.30 μg/ml for pantoprazole sodium salt and 2.0-2.20 μg/ml for N-methyl pantoprazole. The LOD of omeprazole, omeprazole sulphone, pantoprazole sodium salt and N-methyl pantoprazole were 1.126, 0.76, 0.691 and 0.716 μg/ml respectively [03].

Shimizu et al have developed column-switching high performance liquid chromatographic (HPLC) method for the determination of omeprazole and its two main metabolites, 5-hydroxyomeprazole and omeprazole sulfone, in human plasma. Omeprazole, its two metabolites and lansoprazole as an internal standard were extracted from alkalinized plasma using diethyl ether–dichloromethane (45:55v/v). The extract was injected into a column I (TSK-PW precolumn) for clean-up and column II (Inertsil ODS) for separation. The mobile phase consisted of phosphate buffer–acetonitrile (92:08 v/v, pH 7.0) for clean-up and phosphate buffer–acetonitrile–methanol (65:30:5 v/v/v, pH 6.5) for separation, respectively. UV detection wavelength was 302 nm [04].

Cheng et al have developed HPLC and microdialysis methods for determination as well as studying pharmacokinetic profile of omeprazole in rat blood, brain and bile. Omeprazole and dialysate were separated using a reversed-phase C_{18} microbore column. The mobile phase was comprised of acetonitrile-20 mM monosodium phosphate (pH 7.0) (35:65, v/v) and 0.1 mM 1-octanesulfonic acid, and the flow-rate of the mobile phase was 0.05ml/min. UV detection for omeprazole was done at the wavelength of 300 nm [05].

Yuen et al have developed a HPLC method for the determination of omeprazole in human plasma. Omeprazole and the internal standard, chloramphenicol, were extracted from alkalinized plasma samples using dichloromethane. The mobile phase was 0.05 M Na_2HPO4–ACN (65:35, v/v) adjusted to pH 6.5 at a flow rate of 1.0 ml/min at a detection wavelength of 302 nm. [06]

Toribio et al have developed supercritical fluid chromatographic method for semipreparative enantiomeric separation of omeprazole. Chiralpak AD column was used. The effect of two organic modifiers (ethanol and 2-propanol) was studied [07].

Kanazawa et al have developed Liquid chromatographic and mass spectrometric

(LC-MS) method for determination of omeprazole and its metabolites in human plasma .The analytical column was YMC-Pack Pro C using acetonitrile–50 m*M* ammonium acetate (pH 7.25) (1:4) at a flow-rate of 0.2 ml/min. The drift voltage was 30 V. The sampling aperture was heated at 110^{0}C and Shield temperature was 230^{0}C. In the mass spectrum, the molecular ions of omeprazole, hydroxyomeprazole and omeprazole sulfone were clearly observed as base peaks [08].

Hofmann et al have developed LC-MS method for determination of omeprazole and its metabolites 5-hydroxyomeprazole and omeprazole sulfone in human plasma. Separation was achieved on C_{18} column using a gradient with 10mM ammonium acetate in water (pH 7.25) and acetonitrile [09].

Song et al have developed hydrophilic interaction chromatography with tandem mass spectrometric (HILIC–MS/MS) method for analysis of omeprazole and 5-hydroxy omeprazole in human plasma without use of evaporation and reconstitution steps in 96-well liquid/liquid extraction. Omeprazole, its metabolite 5-hydroxy omeprazole, and internal standard desoxyomeprazole, were extracted from 0.05 ml of human plasma using 0.5 ml of ethyl acetate in a 96-well plate. Betasil silica column was used. Mobile phase with linear gradient elution consists of acetonitrile, water, and formic acid (95:5:0.1 to 73.5:26.5:0.1 in 2 min). The flow rate was 1.5 ml/min with total run time of 2.75 min. The LOQ was 2.5 ng/ml for both analyte [10].

ESOMEPRAZOLE

Bellah et al have developed RP-HPLC method for determination of esomperazole. Separation was achieved from prevail column C_8, with mobile phase consisting of HPLC grade acetonitrile and phosphate buffer solution (35:65) at flow rate 1ml/min with UV detection at 280 nm [11].

Guptha et al have developed RP-HPLC method for assay of esomeprazole in formulation. Isocratic pump elution at a flow rate of 0.8ml/min was employed on symmetry chromosil C_{18} column at 27^{0}C temperature. The mobile phase consisted of methanol: acetinitrile: tetrahydrofuran 60:30:10 (V/V). The UV detection wavelength was 272 nm [12].

Hultman et al have developed a LC-MS/MS method for quantitative determination of esomeprazole, and its two main metabolites 5-hydroxyesomeprazole and omeprazole sulphone in 25 µL human, rat or dog plasma. The separation was performed on a hypersil BDS C_8 column. Mobile phase was made by mixing 250 ml acetonitrile, 1.0ml formic acid, 100 ml 0.1 mol/l ammonium acetate and 645ml water (pH 3.8), and was pumped at a flow rate of 0.75 ml/min. The linearity range was 20-20000 nmol/l for esomeprazole and omeprazole sulphone, and 20-4000 nmol/l for 5-hydroxyesomeprazole [13].

LANSOPRAZOLE

Okram et al have developed extraction-free spectrophotometric method proposed for the determination of lansoprazole (LAN) in bulk and in capsule formulation. The methods are based on the interaction of LAN in dichloromethane (DCM) with acidic sulfonphthalein dyes, namely, bromocresol purple (BCP) in method A and bromothylmol blue (BTB) in method B to form stable, yellow-colored, ion-pair complexes peaking at 400 and 430 nm, respectively. The linear relationship was obtained in range of 0.5-15.0 and 1.25-20.0 µg/ml lansoprazole for method A and method B respectively [14].

Katsuki et al have developed a HPLC assay method for simultaneous determination of lansoprazole enantiomers and its metabolites, 5- hydroxylansoprazole and lansoprazole sulfone in human liver microsomes. Detection wavelength was found to be 285 nm. The mobile phase consisted of a methanol–water (75:25, v/v) at a flow-rate of 0.5 ml/min [15].

Karol et al have developed a HPLC method for the determination of lansoprazole and five of its metabolites in human plasma. Extraction solvent was used diethyl ether-methylene chloride. Separation was obtained using octyldecylsilane column. The mobile phase consisted of 35% aqueous acetonitrile to which 1 ml/1 n-octylamine and N-acetohydroxamic acid (0.005 M) were added (pH-7.0) at flow rate1.0 ml/min .Wavelength of detection was 285 nm [16].

Landes et al have developed a HPLC method for simultaneous determination of lansoprazole and its metabolites in human plasma. Lansoprazole, its metabolites and an internal standard were extracted with tert.-butyl methyl ether. Samples were injected using an automatic injector a loop column, and separation was obtained using a reversed-phase column under isocratic conditions. Wavelength of detection was 285 and 303 nm. The LOQ was 2ng/ml for lansoprazole and 3-5 ng/ml for its metabolites [17].

Muthu Kumar et al have developed a RP-HPLC method for estimation of lansoprazole in tablet dosage form. Mobile phase consisted of disodium hydrogen phosphate buffer of pH 3.0, and acetonitrile in the ratio of 30: 70. The column used was phenomenex luna C8 with flow rate of 1.0 ml / min using UV detection at 285 nm [18].

Reddy et al have developed a HPLC method for the analysis of Lansoprazole. Separation was achieved isocratically on a C_{18} column utilizing a mobile phase of acetonitrile/phosphate buffer (70:30, v/v, pH 7.0) at a flow rate of 0.8 ml/min with UV detection at 260 nm. Linearity range was 0.1-30μg/ml. The LOD was 1.80 ng/ml and LOQ was 5.60 ng/ml [19].

Miura et al have developed a HPLC method for the simultaneous quantitative determination of lansoprazole enantiomers and their metabolites, 5-hydroxylansoprazole enantiomers and lansoprazole sulfone, in human plasma. Chromatographic separation was achieved with a chiral CD-Ph column using a mobile phase of 0.5M $NaClO_4$–acetonitrile–methanol (6:3:1 (v/v/v)).The linearity of this assay was set between 10-1000 ng/ml [20].

Uno et al have developed column-switching HPLC method for the simultaneous determination of lansoprazole, and its major metabolites: 5-hydroxylansoprazole and lansoprazolesulfone in human plasma. The test compounds were extracted from 1ml of plasma using diethyl ether–dichloromethane (7:3, v/v) mixture and the extract was injected into a column I (TSK-PW precolumn) for clean-up and column I (C18 STR ODS-II) for separation. The peak was detected by an UV detector set at a wavelength of 285 nm. The linearity range was 3-5000 ng/ml [21].

Basavaiah et al have developed spectrophotometric and HPLC method for determination of Lansoprazole in bulk and in capsules. Spectrophotometric method was based on formation of charge transfer complex between chloranilic acid as a π acceptor and LPZ as an n-donar in acetonitrile solvent. The absorbance of complex was measured at 520 nm. Beer's law was obeyed for 5-80 μg/ml with an molar absorptivity of $3.45x10^3 Lmol^{-1}cm^{-1}$.The HPLC determination was performed on reverse phase column Hypersil C_{18} using mobile phase consisting of acetonitrile-0.1% phosphoric acid (70:30 v/v) at flow rate 1ml/min with UV detection at 284 nm. The method was linear in the concentration range 6-248 μg/ml. The LOD was 0.62 μg/ml and LOQ was 1.86 μg/ml [22].

Rao et al have developed stability-indicating ultra performance liquid chromatographic method for the estimation of lansoprazole and its Impurities in bulk and pharmaceutical dosage forms. The method was developed using the waters acquity BEH C_{18} column and gradient program with mobile phase A as a pH 7.0 phosphate buffer and methanol in the ratio of 90: 10 (v/v), and mobile phase B as methanol and acetonitrile in the ratio of 50:50 (v/v). Lansoprazole and its impurities were monitored at 285 nm [23].

Pandya et al have developed high performance thin layer chromatographic method for the measurement of lansoprazole in human plasma and its use for pharmacokinetic study has been evaluated. Sample spotted on precoated silica gel 60 F_{254} plates using a Camag Linomat IV autosampler .Chloroform-methanol (15:1, v/v) used as mobile phase. Wavelength of detection was 286nm. Lansoprazole was quantified using a Camag TLC Scanner [24].

Wu et al have developed LC/MS/MS method for quantification of lansoprazole in human plasma by protein precipitation with acetonitrile, lansoprazole and the internal standard bicalutamide were chromatographed on a C18 column with the mobile phase consisted of methanol–water (70:30, v/v, containing 5mM ammonium formate, pH was adjusted to 7.85 by 1% ammonia solution). Detection was performed on a triple quadrupole tandem mass spectrometry by using eletrospray ionization source [25].

Song et al have developed a liquid chromatography coupled with tandem mass spectrometric (LC–MS/MS) method for the simultaneous determination of lansoprazole and its metabolites 5-hydroxy lansoprazole and lansoprazole sulphone. The chromatographic separation was achieved with a mixture of methanol–0.2% ammonium acetate and 0.1% methanoic acid in water (75:25, v/v) as mobile phase on an Inertsil ODS-3 column. Linearity ranges were 10-4000 ng/ml, 5-400 ng/ml and 1-400 ng/ml for lansoprazole, 5-hydroxy lansoprazole and lansoprazolesulphone respectively. The lower limits of quantification were 2.0ng/ml, 2.0 ng/ml, and 0.5 ng/ml for lansoprazole, 5-hydroxy lansoprazole and lansoprazolesulphone respectively [26].

Oliveira et al have developed liquid chromatography–electrospray tandem mass spectrometry for determination of Lansoprazole in human plasma using omeprazole as the internal standard. The analyte and internal standard were extracted from the plasma samples by liquid–liquid extraction using diethyl-ether–dichloromethane (70:30; v/v) and chromatographed on a C_{18} analytical column. The mobile phase consisted of acetonitrile–water (90:10; v/v) 10 m*M* formic acid and The linearity range was 2.5–2000 ng/ ml. Detection was carried out on a micromass triple quadrupole tandem mass spectrometer by Multiple Reaction Monitoring (MRM) [27].

PANTOPRAZOLE

Okram et al have developed a spectrophotometric method for determination of pantoprazole sodium in pharmaceuticals using ferric chloride and two chelating agents. The methods are based on the reduction of ferric chloride by pantoprazole sodiumsesquihydrate in neutral medium and subsequent chelation of iron (II) with 1, 10-phenanthroline (phen) (method A) or 2, 2′-bipyridyl (bipy) (method B).Resulting red colored chromogens measured at 510 and 520 nm, for method A and B, respectively [28].

Ashour et al have developed HPLC method for the analysis of pantoprazole sodium in pharmaceutical dosage forms using lansoprazole as internal standard. The chromatographic separation of pantoprazole and lansoprazole was achieved on a Nucleodur C_8 column using the photodiode array detector at 280 nm. The optimized mobile phase was consisted of a mixture of 0.1 M ammonium acetate solution and methanol (42:58, v/v), pumped at a flow rate 1.0 ml/min. Linearity range was 3.06-1243.0 μg/ml with LOD 0.78 μg/ml [29].

Ramakrishna et al have developed HPLC method for the quantification of pantoprazole in human plasma. Wavelength of UV detection was 290 nm. The analyte and internal standard (zonisamide) were separated using an isocratic mobile phase of 10mM phosphate buffer (pH 6.0)/acetonitrile (61/39, v/v) on reverse phase waters symmetry C_{18} column. LOQ was 20 ng/ml. A linearity range was 20-5000 ng/ml [30].

Cass et al have developed a multidimensional HPLC method for enantiomeric determination of pantoprazole in human plasma. This method was reported the use of multidimensional HPLC by coupling a restricted access media column with a chiral polysaccharide column. The enantiomers from the plasma samples were separated with high resolution on a tris (3,5-dimethoxyphenylcarbamate) of amylose phase after clean-up by a restricted access media of bovine serum albumin octyl column. Flow-rate was 1.0 ml/min for the elution of the plasmatic proteins and acetonitrile-water (35:65 v/v) used for the transfer and analysis of pantoprazole enantiomers, which were detected by UV at 285 nm [31].

Bhaskara et al have developed a sensitive LC/MS/MS method for the determination of pantoprazole sodium (PNT) in human urine. The urine sample was analysed on a C18 column. Interfaced with a triple quadrupole tandem mass spectrometer. Positive electrospray ionization was employed as the ionization source. The mobile phase consisted of acetonitrile–water (90:10, v/v). The linearity range was 1-100 ng/ml and LOQ was 1 ng/ml [32].

Challa et al have developed a bioanalytical LC–MS/MS method for the quantitative estimation of Pantoprazole in human plasma. Pantoprazole D3 (PSD3) was used as internal standard (IS). Chromatographic separation was performed on zorbax SB-C_{18} column with an isocratic mobile phase composed of 10mM ammonium acetate (pH 7.10): acetonitrile (30:70, v/v), pumped at 0.6 ml/min. PS and PSD3 were detected with proton adducts a/z 384.2→200.1 and 387.1→203.1 in multiple reaction monitoring (MRM) positive mode, respectively. The linearity range was 10-3000 ng/ml [33].

Chen et al have developed chiral liquid chromatography–tandem mass spectrometric method for the determination of pantoprazole in dog plasma. After liquid–liquid extraction, a baseline resolution of enantiomers was achieved on an ovomucoid column using the mobile phase of methanol: acetonitrile: 10mM ammonium formate (pH 7) (10.4:2.6:87, v/v/v) at 30°C within 10 min. Stable isotopically labeled (+)-d3-pantoprazole and (−)-d3-pantoprazole were used as internal standards. LOQ was 20 ng/ml [34].

Barreiro et al have developed a chiral–chiral chromatographic ion trap mass spectrometric method for simultaneous quantification of pantoprazole and lansoprazole enantiomers fractions. A restricted access media of bovine serum albumin octyl column was used in the first dimension for the exclusion of the humic substances ,while polysaccharide-based chiral column was used in the second dimension for the enantioseparation of both drugs. LOD was 0.2-0.150 µg/L [35].

Nevin Erk has developed a differential pulse anodic voltammetric method for the determination of pantoprazole in pharmaceutical dosage forms and human plasma using a glassy carbon electrode. The best voltammetric response was reached for a glassy carbon electrode in britton–robinson buffer solution of pH 5.0 with scan rate of 20.0mVs^{-1}and a pulse amplitude of 50.0 mV. For comparative purposes high-performance liquid chromatography with a diode array and UV/VIS detection at 290.0nm determination also was developed [36].

RABERAZOLE

El-Gindy et al have developed spectrophotometric and chromatographic: HPLC, HPTLC method for determination of rabeprazole in presence of its degradation products. High performance liquid chromatographic (HPLC) separation of rabeprazole from its degradation products was performed on a reversed phase, ODS column using a mobile phase of methanol/water (70:30, v/v) and UV detection at 284 nm. HPTLC separation followed by densitometric measurement of the spots at 284 nm. The separation was carried out on Merck HPTLC sheets of silica gel 60 F 254, using acetone/ toluene/methanol (9:9:0.6 v/v) as mobile phase. It was also analysed using first derivative of the ratio spectra (1DD) by measurement of the amplitudes at 310.2 nm [37].

Rao et al have developed liquid chromatographic method for enantioselective separation and determination of R-(+) and S-(−) enantiomers of rabeprazole in drugs and pharmaceuticals using photo diode array (PDA) and polarimetric detectors. Chiralpak AD-H (250mm×4.6 mm) 5 µm column packed with amylose tris(3,5-dimethylphenyl carbamate) as a stationary phase and the mobile phase containing n-hexane:ethanol:2-propanol(75:15:10, v/v/v) was used. Lansoprazole sulphone was used as an internal standard (IS) [38].

Ramakrishna et al have developed a HPLC method for quantification of rabeprazole in human plasma using solid-phase extraction. HPLC method with UV detection (284 nm) was developed. Isocratic mobile phase of 5mM ammonium acetate buffer (pH adjusted to 7.4 with sodium hydroxide solution)/acetonitrile/methanol (45/20/35, v/v) was used on reverse phase Waters symmetry C_{18} column. Linearity range was 20-1000 ng /ml. LOQ was 20 ng/ml [39].

Miura et al have developed a HPLC with solid-phase extraction method for determination of rabeprazole enantiomers and their metabolites rabeprazole-thioether and rabeprazole sulfone, in human plasma. Analytes and the internal standard (omeprazole-thioether) were separated using a mobile phase of 0.5M NaClO4–acetonitrile (6:4, v/v) over a Chiral CD-Ph column [40].

Singh et al have developed HPLC-UV method for the quantitation of rabeprazole in human plasma. The analytical mobile phase was 25.0 mM ammonium acetate buffer (pH adjusted to 7.0 with dilute ammonia solution) and acetonitrile in the ratio 70:30 (v/v) with flow rate of 1.0 ml/min. Pre-treatment mobile phase of 10mM ammonium acetate buffer (pH adjusted to7.0 with dilute ammonia solution) and acetonitrile (95:5v/v) was used at a flow rate of 0.25 ml/min. Separation was carried out on water's symmetry C_{18}. Pre-concentration of samples was performed on "Shim-PackMAYI ODS" column. Wavelength of detection was 290 nm. Zaleplon was used as an internal standard [41].

Uno et al have developed column-switching HPLC with UV detection method for the simultaneous determination of rabeprazole and its active metabolite, rabeprazole thioether in human plasma. Rabeprazole, its thioether metabolite and 5-methyl-2-[{4-(3-methoxypropoxy)-3-methyl pyridin-2-yl} methyl sulfinyl]-1H-benzimidazole, as an internal standard were extracted from 1ml of plasma using diethyl ether dichloromethane (9:1, v/v) mixture. Mobile phase (A) of phosphate buffer (0.05 M, pH 7.0) and acetonitrile (88:12, v/v) and column I (TSK-PW pre column) for cleaning purpose and column II (C_{18} Grand ODS-80TM TS analytical column, 5μm, 250mm×4.6mm I.D.) and mobile phase (B) phosphate buffer (0.05 M, pH 7.0) and acetonitrile (50:50, v/v),was used for separation at flow-rates were 0.8 ml/min for 0–17 min and 1.4 ml/min for 17–25 min for eluent B. Wavelength of detection was 288 nm [42].

Elumalai et al have developed a RP-HPLC method for determination of content uniformity of rabeprazole sodium in its tablets dosage form. The method uses isocratic mobile phase of 0.1M sodium phosphate buffer (pH adjusted to 6.5 with sodium hydroxide solution) and acetonitrile 65:35 compositions on reverse phase RP C_8 column. Wavelength of detection was 285nm [43].

TENATOPRAZOLE

Sugumaran et al have developed a UV-spectrophotometric method for estimation of Tenatoprazole from Pharmaceutical formulation. In 0.1N NaOH, Tenatoprazole showed absorbance maxima at 314nm. Linearity range was 2-12 μg/ml [44].

Kumarswamy et al have developed a RP-HPLC method for the determination of tenatoprazole in pharmaceutical dosage form. Mobile phase consisted of phosphate buffer at pH 2.5: acetonitrile in the ratio 55: 45 v/v on Phenomenax Luna C_{18} column, at a flow rate of 1ml/ min at ambient temperature. The detection was carried out at 314 nm using Shimadzu UV-Visible detector. The linearity range was 2-12 μg/ml. LOD and LOQ were 0.2515 μg/ml and 0.6623 μg/ml resp [45].

Sugumaran et al have developed a RP-HPLC method for the estimation of tenatoprazole in bulk drug and pharmaceutical dosage form. The quantification was carried out using C_{18} column and mobile phase consisting of 10mM phosphate buffer at pH 2.4: acetonitrile (60:40 v/v), at flow rate of 1 ml/min. The separation was performed at ambient temperature. Eluents were monitored by using UV detector at 307 nm [46].

Nirogi et al have developed HPLC method with UV detection at 295 nm in rat plasma for estimation of tenatoprazole. Separation was carried out on a reverse phase C_{18} column using isocratic mobile phase. Linearity range was 20-6000 ng/ml. LOQ was 20 ng/ml [47].

Lin et al have developed a HPLC method with UV detection at 306 nm for determination of tenatoprazole in dog plasma. Tenatoprazole and internal standard pantoprazole were extracted into diethyl ether and separated using an isocratic mobile phase of 10 mm phosphate buffer (pH4.7) acetonitrile (70:30 v/v) on a diamonsil C_{18} column. Linearity range was 0.02-5 μg/ml [48].

Khan et al have developed a bio-analytical HPLC method for estimation of tenatoprazole from human plasma. Plasma samples were precipitated using acetonitrile and chromatographed using HiQ sil C_{18}, column. Detection was done using UV-Visible detector at 307 nm wavelength. Linearity range was 1-5 µg/ml [49].

Dhaneshwar et al have developed a stability-indicating TLC method for the determination of tenatoprazole both as a bulk drug and in formulation. The method uses TLC aluminum plates precoated with Silica Gel $60_{F\text{-}254}$ as the stationary phase and the solvent system of toluene ethyl acetate methanol (6:4:1 v/v/v). Densitometric analysis of tenatoprazole was performed in the absorbance mode at 306 nm. LOD and LOQ were 50 and 100 ng/spot resp [50].

Mahadik et al have studied LC–UV and LC–MS evaluation of stress degradation behaviour of tenatoprazole. Tenatoprazole was subjected to stress conditions of hydrolysis, oxidation, photolysis and neutral decomposition. Separation of drug from degradation products formed under stress conditions was achieved on a chemito ODS-3 column C_{18} using methanol: 0.01 M acetate buffer pH 4.5 adjusted with glacial acetic acid (55:45) as the mobile phase at flow rate of 1 ml/min and wavelength of detection was 306 nm [51].

MULTI-DRUG PPI COMBINATION

Salama et al have developed Spectrophotometric methods for the determination of omeprazole and pantoprazole sodium. The chelates of both drugs with different metal ions in 2:1 ratio were formed. Chelate picked at 455 nm. The procedure retains its accuracy in presence of up to 70% of its degradate, sulfenic acid prepared by degrading the pure drug in borate buffer of pH 8 at 37°C for 5 days. The colored chelates of OMZ in ethanol are determined spectrophotometrically at 411, 339 and 523 nm using iron (III), chromium (III) and cobalt (II), respectively [52].

Wahbi et al have developed Spectrophotometric method for determination of omeprazole, lansoprazole and pantoprazole in pharmaceutical formulations. The compensation method and other chemometric methods i.e. derivative, orthogonal function and difference spectrophotometry have been developed for determination of omeprazole, lansoprazole and pantoprazole in their pharmaceutical preparations [53].

Moustafa et al have developed spectrophotometric methods for the determination of lansoprazole and pantoprazole sodium sesquihydrate. Two methods were based on charge transfer complexation reaction of these drugs, where they act as *n*-donors, with either p acceptor 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and with s acceptor as iodine. A third method was also investigated depending on ternary complex formation with eosin and copper (II). The colored products were quantified spectrophotometrically using absorption bands at 457 nm for DDQ (method A) at 293 and 359 nm for iodine (method B) and at 549 nm using ternary complex formation (method C), for both drugs [54].

Noubaran et al have developed HPLC method for determination of four PPIs, omeprazole, pantoprazole, lansoprazole and rabeprazole in human plasma. Liquid–liquid extraction analytes along with an internal standard were separated using an isocratic mobile phase of phosphate buffer (10 mM)/acetonitrile (53/47, v/v adjusted pH to 7.3 with triethylamine) at flow rate of 1 ml/min on reverse phase ODS-A column at room temperature. The ranges were 20-2500 ng/ml for omeprazole, 20-4000ng/ml for pantoprazole, 20-3000 ng/ml for lansoprazole and 20-1500ng/ml for rabeprazole. LOQ was 20 ng/ml four proton pump inhibitors [55].

Prabu et al have developed UV spectrophotometric method for simultaneous estimation of esomeprazole and domperidone. The method involved solving simultaneous equations based on measurement of absorbance at two wavelengths, 301 nm and 284 nm, λ max of esomeprazole and domperidone respectively. Linearity ranges were 5-20 µg/ml and 8-30 µg/ml for esomeprazole and domperidone respectively [56].

Hishinuma et al have developed a liquid chromatographic/tandem mass spectroscopic method for estimation of lansoprazole and rabeprazole in human serum. Separation was achieved by using a mobile phase of acetonitrile/1mM ammonium formate (140/60, v/v) on a C_{18} analytical column and analyzed in the selected reaction-monitoring (SRM) mode. The linearity range was 0.25-2.5 µg/ml.LOQ was 0.25 ng/ml [57].

Zhang et al have developed a liquid chromatography–tandem mass spectrometric method for estimation of rabeprazole in human plasma using omeprazole as the internal standard. The analyte and internal standard was extracted with n-hexane–dichloromethane–isopropanol (20:10:1, v/v) and chromatographed isocratically on a diamonsil C_{18} analytical column and analysed in selected reaction-monitoring (SRM) mode using an atmospheric pressure chemical ionization source. The linearity range was 2.0-800 ng/ml and LOQ was 2.0 ng/ml [58].

ANAYSIS OF PPI FROM COMBINATION FORMULATION

Patel et al have developed a derivative spectroscopic method for simultaneous determination of domperidone and rabeprazole sodium, in fixed dose combination products. The absorbance values at 253.2 nm and 266.4 nm of first derivative spectrum was used for the estimation of domperidone and rabeprazole sodium, respectively without mutual interference [59].

Birajdar et al have developed a derivative spectrophotometric method for simultaneous estimation of domperidone and rabeprazole sodium in pharmaceutical solid dosage form .UV spectrophotometric Q analysis method used for determination of both drugs in combination in 0.1 N Sodium hydroxide. Wavelength of detection was 291.6 nm (λmax of rabeprazole) and 240 nm isobestic point. Linearity range for rabeprazole 2-12 µg/ml and for domperidone 3-18 µg/ml respectively. The second method involves HPLC separation of rabeprazole and domperidone drugs in reverse phase mode using phenomenx C_{18} column. The wavelength of detection was at 220 nm [60].

Yeung et al have developed a HPLC assay method for simultaneous determination of omeprazole and metronidazole in human plasma and gastric fluid. Wavelength of detection was 254 nm. The mobile phase was a mixture of 0.1M sodium phosphate buffer: methanol: acetonitrile (60:20:20) at pH 7.0. Metronidazole and omeprazole were separated on a C_2-bonded silica gel solid phase extraction column, and eluted with methanol [61].

Kulkarni et al have developed a RP-HPLC method for simultaneous determination of omeprazole and domperidone in solid dosage form. Separation was carried out on a, ODS, C-18 (250× 4.5 mm, 5 micron) column using a mobile phase of acetonitrile: 0.05M ammonium acetate buffer (pH- 4) in the ratio of (85:15). The flow rate and run time were 1 ml/min and 10 min, respectively. Wavelength of detection was set at 280 nm. The linearity ranges were observed 4-12 µg/ml for omeprazole and 8-16 µg/ml for domperidone [62].

Kumar et al have developed RP-HPLC method for simultaneous estimation of naproxen and pantoprazole in pharmaceutical dosage form. Compounds were separated on a hypersil BDS C_{18} reversed-phase column by use of a mobile phase consisting of 0.1 M sodium acetate (pH 8.2), acetonitrile and methanol (70:20:10 v/v) at a flow rate of 1.0 ml/min with detection wavelength at 285 nm. Linearity ranges were 5-70 and 5-40 µg/ml for naproxen and pantoprazole resp [63].

Bageshwar et al have developed stability indicating HPTLC method for simultaneous estimation of pantoprazole sodium and itopride hydrochloride in combined dosage form. The method employed TLC aluminium plates precoated with silicagel 60F $_{254}$ as the stationary phase was used. Mobile phase was consisted of methanol: water: ammonium acetate; 4.0:1.0:0.5(v/v/v). Densitometric analysis of both drugs was carried out at 289nm [64].

CONCLUSION

Proton-pump inhibitors (PPIs) produce a long-lasting effect for the reduction of gastric acid production. This review presents reported chromatographic methods, developed and validated for determination of proton pump inhibitors (Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Tenatoprazole, Esomeprazole). Comparing validation parameters of already reported methods, it can be concluded that different analytical methods like spectrophotometric, TLC, HPTLC can be developed for PPIs showing its simplicity, sensitivity (low LOD and LOQ values), accuracy, precision and specificity and allowing markings in a broad linearity scope.

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