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Proton pump inhibitors: recent developments in analytical methodologies

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Abstract: An extensive survey of the literature published in various analytical and pharmaceutical chemistry-related journals have been conducted, and the instrumental analytical methods that were developed and used for the determination of proton pump inhibitors in bulk drugs, formulations, and biological fluids have been reviewed. This review covers the time period from 1990 to 2011 during which 80 analytical methods, including all types of spectrophotometric and chromatographic techniques were reported. High-performance liquid chromatography (HPLC) with ultra violet (UV) detection was found to be the technique of choice for many workers, and more than 50 methods were based on liquid chromatography (LC) and ultra violet (UV). A critical analysis of the reported data was carried out and the present state of the art of the analytical techniques for the determination of omeprazole, esomeprazole, pantoprazole, rabeprazole, dexrabeprazole, tenatoprazole, lansoprazole, and dexlansoprazole is discussed.

Keywords: analytical methods; chromatography; proton pump inhibitors; spectroscopy.

Introduction

An ulcer is a sore, which means it is an open, painful wound. Peptic ulcers are ulcers that form in the stomach or the upper part of the small intestine, called the duodenum. Peptic ulcers are actually very common. A major causative factor (60% of gastric and up to 90% of duodenal ulcers) is chronic inflammation due to *Helicobacter pylori* that colonizes the antral mucosa. The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis (type B gastritis), resulting in a defect in the regulation of gastrin production by that part of the stomach, and gastrin secretion can either be increased, or as in most cases, decreased, resulting in hypo/achlorhydria. Gastrin stimulates the production of gastric acid by parietal cells, and in *H. pylori* colonization responses to increased gastrin, the increase in acid can contribute to the erosion of the mucosa and therefore an ulcer forms (Figure 1). Another major cause is the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase 1 (*cox-1*), which is essential for the production of these prostaglandins. Proton pump-selective anti-inflammatories (such as celecoxib or rofecoxib) preferentially inhibit the *Proton pump*, which is less essential in the gastric mucosa, and roughly halves the risk of NSAID-related gastric ulceration. As the prevalence of *H. pylori*-caused ulceration declines in the Western world due to increased medical treatment, a greater proportion of ulcers will be due to increasing NSAID use among individuals with pain syndromes and the growth of aging populations that develop arthritis. The incidence of duodenal ulcers dropped significantly during the last 30 years, while the incidence of gastric ulcers has shown a small increase, mainly caused by the widespread use of NSAIDs. The drop in incidence is considered to be a cohort-phenomenon independent of the progress in the treatment of the disease. The cohort phenomenon is probably explained by improved standard of living that has lowered the incidence of *H. pylori* infections. Younger patients with ulcer-like symptoms are often treated with antacids or H2 antagonists. Bismuth compounds may actually reduce or even clear organisms, though the warning labels of some bismuth subsalicylate products indicate that the product should not be used by someone with an ulcer. Patients who are taking nonsteroidal anti-inflammatories (NSAIDs) may also be prescribed a prostaglandin analog (misoprostol)

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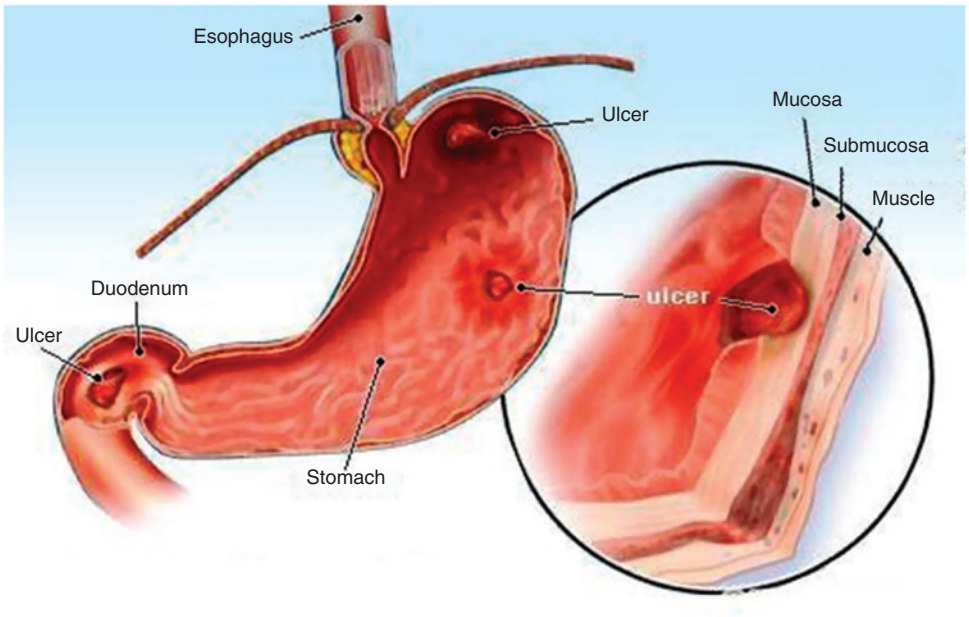


Figure 1: Ulcer formation.

in order to help prevent peptic ulcers, which may be a side effect of the NSAIDs. When *H. pylori* infection is present, the most effective treatments are combinations of two antibiotics (e.g. clarithromycin, amoxicillin, tetracycline, metronidazole) and one proton pump inhibitor (PPI), sometimes together with a bismuth compound. In complicated, treatment-resistant cases, three antibiotics (e.g. amoxicillin+clarithromycin+metronidazole) may be used together with a PPI and sometimes with a bismuth compound. An effective first-line therapy for uncomplicated cases would be amoxicillin+metronidazole+panto prazole (a PPI).

In the absence of *H. pylori*, long-term higher dose PPIs are often used. Treatment of *H. pylori* usually leads to clearing of infection, relief of symptoms, and eventual healing of ulcers. Recurrence of infection can occur and retreatment may be required, if necessary with other antibiotics. Since the widespread use of PPIs in the 1990s, surgical procedures, such as "highly selective vagotomy", for uncomplicated peptic ulcers became obsolete. A perforated peptic ulcer is a surgical emergency and requires surgical repair of the perforation. Most bleeding ulcers require endoscopy urgently to stop bleeding with cautery, injection, or clipping.

Ranitidine provides relief of peptic ulcers, heartburn, indigestion and excess stomach acid and prevention of these symptoms associated with excessive consumption of food and drink. Ranitidine is available over the counter from pharmacies and works by decreasing the amount of acid produced by the stomach, which allows healing of ulcers. Zantac tablets contain ranitidine 150 mg as the active ingredient, which can also be bought generically. Sucralfate (carafate) has also been a successful treatment of peptic ulcers (Majumdar et al. 2011).

Proton pump inhibitors

Inhibition of gastric acid secretion has been the major means of treatment of acid-related diseases, such as peptic ulcers and gastroesophageal reflux disease (GERD). The first medicinal target to be identified was the histamine-2 receptor, the major, but not the only one, activating parietal cell receptor. The second medicinal target was the gastric acid pump, the gastric (H^+, K^+)-ATPase. Since proton transport by the gastric (H^+, K^+)-ATPase is the final step in acid secretion, it was anticipated that drugs of this type would be more effective inhibitor of acid secretion.

Omeprazole was the first clinically useful compound of this class, and it was introduced in 1989. Its structure, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-ridinyl) methylsulfinyl]-*1H*-benzimidazole, is similar to the structures of the other commonly used PPIs, lansoprazole, and pantoprazole, which all have a benzimidazole.

PPIs consist of two heterocyclic moieties. One is a burden moiety, and the other is a benzimidazole or an imidazo-pyridine. The two heterocyclic moieties are linked through a methylenesulfinyl (-CH2SO-) group. Clinically available PPIs are omeprazole, *S*-omeprazole (*S*-enantiomer of omeprazole), lansoprazole, pantoprazole, and rabeprazole. Lansoprazole is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-yl]methylsulfinyl]-*1H*-nzimidazole. Pantoprazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-pyridin-2-yl) methylsulfinyl]-*1H*-benzimidazole. Rabeprazole is 2-[4-(3-methoxypropoxy)-3-methyl-pyridine-2-yl] methylsulfinyl-*1H*-benzimidazole.

The chemistry of PPIs, including omeprazole, lansoprazole, and pantoprazole, led to a new era in the effective therapy of acid peptic diseases. Gastric PPIs are prodrugs that require an acid induced activation. These are weak bases and are converted to the active form by gastric acid before acting on the proton pump. The proposed mode of action involves inhibition of gastric acid secretion into the lumen of the stomach by blockage of (H^+/K^+) ATPase (proton pump) of the parietal cell.

Chemical classification

Alagarsamy (2010) has surveyed most of the available PPIs and proposed an extremely useful classification system based on selectivity, which has been widely adopted. The following classification as shown in Figure 2 has been proposed for the currently known PPIs based on their active functional groups involved in the chemical structures.

PPIs are the recent development of ulcer, and there is a great need to review the analytical work reported so far in the literature. Until today not even a single article of this nature has been appeared in the literature. Our objective is to compile all the published analytical methods with an emphasis on the spectrophotometric and chromatographic conditions of analysis dealing with formulated, unformulated drugs, biological samples including metabolites, enantiomers, stability, and degradation studies. Efforts have been made to collect the literature, and all the analytical procedures have been tabulated in the preceding sections. The present review comprises all analytical methods for the analysis of PPIs in bulk drugs, pharmaceuticals, therapeutic monitoring studies viz., bioavailability and pharmacokinetics published in the last 10 years.

Techniques such as spectrophotometric, fluorimetric, voltametric, thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), capillary electrophoresis (CE) and others have been used for analysis. It could be seen that HPLC followed by spectrophotometric methods have used extensively. Further analysis of

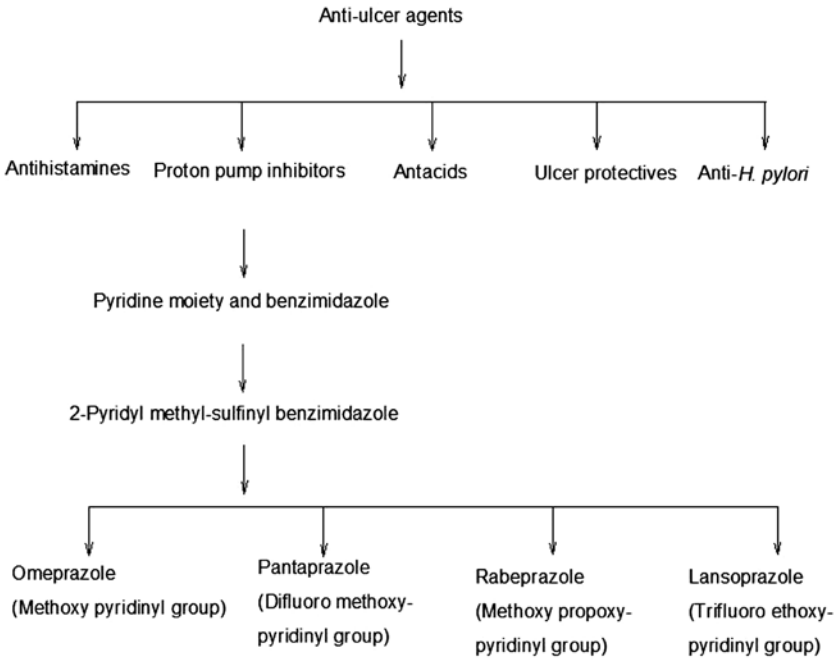


Figure 2: Classification of proton pump inhibitors.

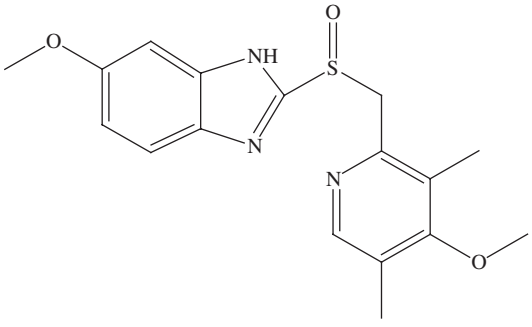
this data has indicated that these techniques are applied mostly for the analysis of bulk drugs, formulations, biological matrices, and stability studies.

Omeprazole

Omeprazole (OPZ), 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1*H*-benzimidazole is a substituted benzimidazole compound and a prototype antisecretory agent, being the first "proton pump inhibitor" widely used for the prophylaxis and treatment of gastroduodenal ulcers and for the treatment of symptomatic gastroesophageal reflux. It acts by interacting with H^+/K^+ ATPase in the secretory membranes of the parietal cells and is very effective in the treatment of Zollinger-Ellison syndrome.

It is a lipophilic, weak base drug with pKa1=4.2 and pKa2=9 and can be degraded unless it is protected against acid conditions. OPZ contains a true coordinated sulfur atom in a pyramidal structure and therefore can exist in two different optically active forms, (S)- and (R)-OPZ. OPZ was first approved as a racemic mixture, but the (S) isomer was recently introduced to the market (Espinosa et al. 2007).

Several HPLC methods with ultraviolet (UV) detection and electrochemical detection, liquid chromatography (LC) coupled with tandem mass spectrometry, spectrophotometry, polarography (Gupta et al. 2008), voltammetry, capillary electrophoresis, and TLC methods have been developed for the determination of OPZ in different samples.



Structure of omeprazole

Spectral method

Rajic et al. (2003) reported first-order UV-derivative spectrophotometry in the analysis of OPZ and pantoprazole sodium salt and corresponding impurities. Sastry et al. (1997) reported spectrophotometric methods for the determination of OPZ in bulk form and pharmaceutical formulations. Kumaraswamy et al. (2010) reported statistical assurance of process validation by analytical method development and validation for OPZ capsules and blend. Bhandage et al. (2009) reported extractive spectrophotometric determination of OPZ in pharmaceutical preparations. Ahmed et al. (2009) reported visible spectrophotometric methods for the estimation of losartan potassium and OPZ in single-component pharmaceutical formulations. Shaghaghi and Jouyban (2008) reported indirect spectrofluorimetric determination of OPZ by its quenching effect on the fluorescence of Tb3+-1,10-phenanthroline complex in the presence of bis (2-ethylhexyl) sulfosuccinate sodium in capsule formulations. The details are given in Table 1(A).

Chromatographic methods

Iuga and Sorine (2009) reported the development of a validated RP-HPLC method for the separation and determination of process-related impurities of OPZ in bulk drugs. Schubert et al. (2003) reported determination of OPZ in bulk and injectable preparations by liquid chromatography. Murakami et al. (2007) reported the development and validation of the RP-HPLC method to quantify OPZ in delayed release tablets. Vyas et al. (2011) reported the development and validation of a stability indicating method for the enantio-selective estimation of OPZ enantiomers in the enteric-coated formulations by HPLC. Sluggett et al. (2001) reported OPZ determination using HPLC with coulometric detection. Yuen et al. (2001) reported improved high-performance liquid chromatography analysis of OPZ in human plasma. Lagerström and Persson (1984) reported the determination of OPZ and metabolites in plasma and urine by liquid chromatography. Kobayashi et al. (1994) reported the development and preliminary application of a high-performance liquid chromatography assay for OPZ metabolism in human liver microsomes. The detailed chromatographic conditions are described in Table 2(A).

Esomeprazole

PPIs are the most potent inhibitors of gastric acid secretion and are effective for treating all gastric acid-related disorders. Esomeprazole (EZ) is indicated for the treatment of gastroesophageal reflux disease in

Table 1: Spectral data of proton pump inhibitors.

Sample matrix	Solvent/reagent	Linearity range (μg/ml)	Detection (nm)	References
(A) OPZ				
API	Methanol/ammonia 4.0% v/v	1.61–17.2	UV 304	Rajic et al. 2003
API and Capsule	0.1 N NaOH	1–10	VIS. 660	Sastry et al. 1997
Capsule	0.1 N NaOH	2–10	UV 302	Kumaraswamy et al. 2010
Capsule	0.05 M HCl	5–30 and 50–250	UV 408 and 508	Bhandage et al. 2009
Capsule	Acidic buffer solutions	10–80	UV 300	Ahmed et al. 2009
Capsule	0.1 N NaOH	0.05–10	UV 345	Shaghaghi and Jouyban 2008
(B) Esomeprazole				
API	Methanol	2–10	UV 203.5	Kumar et al. 2010b
API	Methanol/chloroform (80:20), Using indigo carmine	5–35	VIS. 577 and 617	Sharma and Sharma 2011
API and Tablet	Methanol	4–40	UV 279	Gawande and Chandewar 2010
Tablet	Methanol	5–40	UV 292 and 303	Patil and Kuchekar 2009
Tablet	Methanol/chloroform using sulfosalicylic acid	2–48 and 10–100	UV 365 and 380	Rahman et al. 2008a
Capsule	Bromocresol green in methanol	50–250	VIS. 420	Reddy et al. 2011
(C) Pantoprazole				
Tablet and API	Methanol/water	10–90	UV 457	Moustafa 2000
Tablet	Methanol/water(1:9 v/v)	2.5–80	UV 295 and 303	Suslu et al. 2003
Tablet	Water and $KMnO_4$	2.5–40	UV 350	Basavaiah and Vinay 2010
(D) Rabeprazole				
API	Distilled water	2–10	UV 272.2	Gouda et al. 2010
API	Bromothymole blue in acidic buffer	10–100	UV 354	Patel et al. 2007
API	Acid (0.1 N HCl)	15–75	λex=320 and 274, λem=416 and 311	Osma and Osman 2009
Tablet	$FeCl_3$ and methanol	10–60	VIS. 455	Madhuri et al. 2010
Tablet	Distilled water	14–140 and 7.5–165	UV 320	Rahman et al. 2008b
Tablet	Methanol	2–20	UV 284	Mandhanya et al. 2011
(E) Dexrabeprazole				
API and Tablet	Methanol	6–36	UV 305	Shedpure et al. 2011
(F) Tenatoprazole				
API and Tablet	0.1 N NaOH	2–12	UV 314	Sugumaran et al. 2010
API and Tablet	0.1 M HCl	3–18	UV 314	Kumaraswamy et al. 2011
(G) Lansoprazole				
API and Capsule	Ceric ammonium sulfate, iron, orthophenanthroline, and thiocynate	2.5–30 and 2.5–25	VIS. 510 and 470	Basavaiah et al. 2006
Capsule	Methanol	3–90	UV 281.1	Sudheer et al. 2011
Capsule	0.1 M NaOH	3–25 and 0.5–25	UV 296	Nuran 1999
Capsule	0.01 M NaOH	5.4×10^{-6} to 5.4×10^{-5} M	UV 292	Yeniceli et al. 2004
Capsule and human urine	Dichloromethane, bromocresol purple and bromothymole blue	0.5–15 and 1.25–20	VIS. 400 and 430	Basavaiah and Vinay 2013

API, Active pharmaceutical ingredient.

adults and children, risk reduction of NSAIDs-associated gastric ulcer, *H. pylori* eradication, and control of pathological hypersecretory conditions associated with Zollinger-Ellison syndrome (Vachhani et al. 2009). EZ is bis(5methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H* benzimidazole-1-yl) magnesium trihydrate. The stability of EZ magnesium is a function of pH, it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 h at 25°C and about 8 h at 37°C (www.rxlist.com). EZ has a half-life of 1.25±0.25 h and has bioavailability of 48%

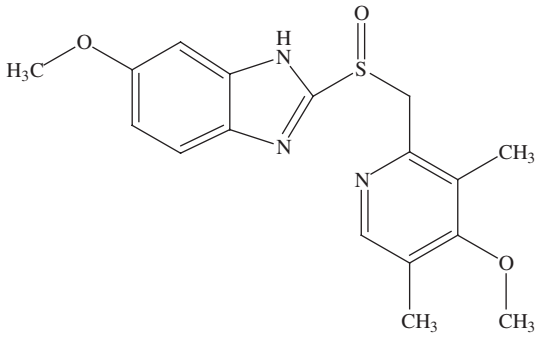
Table 2: Chromatographic data of proton pump inhibitors.

Sample matrix	Column	Mobile phase (v/v)	Detector (nm)	References
(A) OPZ				
API	C18	Acetonitrile/water/triethyl amine 1% (pH 9.5)	UV 280	Iuga and Sorine 2009
API and injectable	C18	Methanol/water (90/10)	UV 301	Schubert et al. 2003
Delayed release Tablet	C18	Phosphate buffer (pH 7.4) and acetonitrile (70/30)	UV 280	Murakami et al. 2007
Enteric-coated Formulation	ODS	Isopropyl alcohol/ethanol (85/15)	UV 301	Vyas et al. 2011
Paste	C8	36%(v/v) Acetonitrile in 0.01 m phosphate buffer (pH 7.6)	+800 mV	Sluggett et al. 2001
Human plasma	C18	0.05 m Na_2HPO4/acetonitrile (65/35) pH 6.5	UV 302	Yuen et al. 2001
Plasma and urine	C18	Acetonitrile/phosphate buffer (20/80 pH 7.5)	UV 302	Lagerström and Persson 1984
Human liver microsomes	C18	Acetonitrile/sodium phosphate (26/74 pH 8.4)	UV 302	Kobayashi et al. 1994
(B) Esomeprazole (EZ)				
API and Tablet	C18	Acetonitrile/phosphate buffer (55/45)	UV 301	Rathi et al. 2010
Tablet	C18	Acetonitrile/phosphate buffer (60:40 pH 7.0)	UV 205	Armagnac 2006
Tablet	Chiralpak IA	Methyl tert butyl ether/ethyl acetate/ethanol/ diethyl amine(60/40/5/0.1)	UV 299	Zanitti et al. 2010
Human plasma	C18	Acetonitrile/water (80/20 pH 7.0)	MS	Sathiyaraj et al. 2010
Human, Rat, Dog Plasma	C8	Acetonitrile/formic acid/ammonium acetate/ water (250/1/100/645)	MS	Hultman et al. 2007
API and Tablet	Silica gel 60F254	Ethyl acetate/ammonia(8/0.8)	UV 301	Gosavi et al. 2010
(C) Pantoprazole				
Tablet and human plasma	C18	Acetonitrile/phosphate buffer (70/30 pH7)	UV 260	Reddy and Reddy 2009a
Human plasma	C18	Phosphate buffer (pH6) and acetonitrile (61/39)	UV 290	Ramakrishna et al. 2005b
Human plasma	C18	Ammonium acetate/acetonitrile (30/70 pH 7.1)	UV 285	Balasekhara et al. 2010
Rat plasma	C18	Water/acetonitrile (55/45) pH 7	UV 290	Mohankandhasamy et al. 2010
Human urine	C18	Acetonitrile/water (90/10)	UV 288	Bhaskara et al. 2011
Injection	Silicagel60 F254	Toluene/ethyl acetate/methanol/acetic acid (7/2/1/0.1)	UV 290	Patel 2011
(D) Rabeprazole				
API	ODS	Methanol/water (70/30)	UV 284	Moustafa 2003
API and Tablet	C18	Methanol/water (65/35)	UV 284	Rao et al. 2008
API and Tablet	Chiralpak AD-H	n-hexane/ethanol/2-propanol (75/15/10)	UV 284	Rao et al. 2006
Tablet	C8	Acetonitrile/sodium phosphate buffer (35/65 pH 6.5)	UV 285	Elumalai et al. 2011
Human plasma	C18	Ammonium acetate/acetonitrile (70/30 pH 7.0)	UV 290	Singh et al. 2004
Human plasma	C18	Ammonium acetate/acetonitrile/methanol (45/20/35 pH 7.4)	UV 284	Ramakrishna et al. 2005a
Human plasma	C18	Phosphate buffer/acetonitrile (88/12 pH 7.0)	UV 288	Shimizu et al. 2005
Human plasma	Chiral CD-PH	0.5 m $NaClO_4$/acetonitrile (60/40)	UV 285	Tada et al. 2006
(E) Dexrabeprazole				
API and Tablet	Chiralpak AD-RH(Amylose)	Water/acetonitrile (50/50)	UV 284	Patil et al. 2011
(F) Tenatoprazole				
API	ODS-3-C_{18}	Methanol/acetate buffer (55/45 pH 4.5)	UV 306	Mahadika et al. 2009
API and Tablet	C_{18}	Acetonitrile/phosphate buffer (40/60 pH 2.4)	UV 307	Sugumaran et al. 2011
API and Tablet	C_{18}	Acetonitrile/phosphate buffer (45/55 pH 2.5)	UV 314	Kumar and Rao 2011
Dog plasma and capsule	C_{18}	Phosphate buffer/acetonitrile (70/30 pH 4.7)	UV 306	Liu et al. 2007
API and Tablet	Silicagel 60F254	Toluene/ethyl acetate/methanol (6/4/1)	UV 314	Dhaneshwar et al. 2008

Table 2: (continued)

Sample matrix	Column	Mobile phase (v/v)	Detector (nm)	References
(G) Lansoprazole				
Tablet	C_{18}	Acetonitrile/phosphate buffer (60/40 pH 7)	UV 230	Reddy et al. 2009
Tablet	C_8	Di hydrogen phosphate/acetonitrile (30/70)	UV 285	Kumar et al. 2010
Capsule	C_{18}	n-hexane/ethanol (8/2)	UV 285	Katsuki et al. 1996
Oral suspension	C_{18}	Acetonitrile/water (40/60)	MS	Brown et al. 2011
Capsule and human plasma	C_{18}	Acetonitrile/triethyl amine/phosphate buffer (60/0.2/39.8 pH 4)	UV 285	Rababah and Momani 2010
Human plasma	C_{18}	Acetonitrile/water (90/10)	MS	Oliveira et al. 2003
Human plasma	Chiral CD-PH	0.5 m $NaClO_4$/acetonitrile/methanol (6/3/1)	UV 285	Miura et al. 2004
Human plasma	Silicagel $60F_{254}$	Chloroform/methanol (15/1)	UV 286	Pandya et al. 1997
Human serum and urine	ODS-120T	Phosphate buffer/ethanol/acetonitrile (20/10/3 pH 7.2)	UV 285 and 303	Aoki et al. 1991
Human liver microsomes	OD-R	Methanol/water (75/25)	UV 285	Katsuki et al. 2001
Capsule	Silicagel $60F_{254}$	Chloroform/methanol/n-hexane (75/25/60)	UV 285	Sherif et al. 2005
(H) Dexlansoprazole				
Human plasma	C_{18}	Ammonia/acetonitrile (20/80)	MS	Bharathi et al. 2011

when administered orally (www.rxlist.com, www.dailymed.nlm.nih.gov). EZ, the *S*-isomer of OPZ, inhibits the gastric parietal H^+/K ATPase irreversibly which involved in hydrochloric acid production in the stomach. It acts as proton pump inhibitor, used to treat gastroesophageal reflux disease (GERD), erosive esophagitis, and gastric ulcer (Mucklow 2002). EZ is combined with the antibiotics clarithromycin and amoxicillin or metronidazole in 7–14 days eradication triple therapy of *H. pylori* infection where the majority of peptic and duodenal ulcers were caused by *H. pylori* (www.en.wikipedia.org).



Structure of Esomeprazole

Spectral method

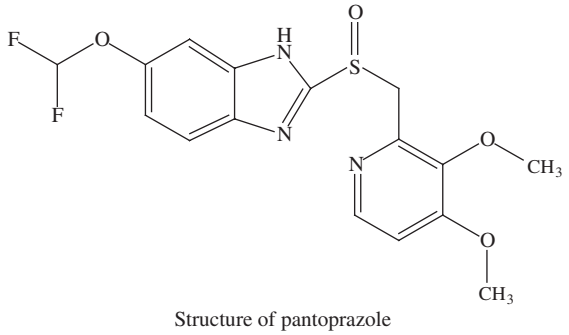
Kumar et al. (2010b) reported physicochemical characterization, UV spectrophotometric method development, and validation studies of EZ magnesium trihydrate. Sharma and Sharma (2011) reported spectrophotometric methods for the estimation of EZ magnesium trihydrate in pharmaceutical formulations using indigo carmine reagent. Gawande and Chandewar (2010) reported spectroscopic estimation of EZ magnesium in solid dosage form. Patil and Kuchekar (2009) reported the development and statistical validation of spectrophotometric method for the estimation of EZ in tablet dosage form. Rahman et al. (2008a) reported spectrophotometric determination of EZ magnesium in commercial tablets using 5-sulfosalicylic acid and *n*-bromosuccinimide. Reddy et al. (2011) reported simple spectrophotometric determination of EZ magnesium in pharmaceutical formulations. The details are given in Table 1(B).

Chromatographic methods

Rathi et al. (2010) reported a RP-HPLC method for the estimation of EZ magnesium in bulk and its pharmaceutical dosage forms. Armagnac (2006) reported the development and validation of a HPLC method for the determination of EZ in tablet. Zanitti et al. (2010) reported direct HPLC enantioseparation of OPZ and its chiral impurities: application to the determination of enantiomeric purity of EZ magnesium trihydrate. Sathiyaraj et al. (2010) reported a bioanalytical method development and validation of esomepraole in human plasma by LC-MS/MS. Hultman et al. (2007) reported the determination of EZ and its two main metabolites in human, rat, and dog plasma by liquid chromatography with TMS. Gosavi et al. (2010) reported the estimation of EZ in bulk and tablet dosage form by the use of planar chromatography. The detailed chromatographic conditions are described in Table 2(B).

Pantoprazole sodium sesquihydrate

Pantoprazole sodium sesquihydrate is chemically known as sodium 5-(difluoromethoxy)-2–{[(3,4-dimethoxy-2-pyridinyl) methyl]sulfinyl}-1 *H*-benzimidazolesesquihydrate. It is used as an anti-ulcerative agent (Budavari 1996) by inhibiting the gastric acid secretion. PNT is frequently used for the cure of erosion and ulceration of the esophagus caused by a gastroesophageal reflux disease. It is pharmaceutically formulated as gastro-resistant tablets containing 40 or 20 mg pantoprazole sodium sesquihydrate. The literature survey reveals a few methods based on HPLC, densitometric HPTLC, LC/MS, derivative UV-spectrophotometry, and difference UV spectrophotometry have been reported for the assay of PSS in commercial dosage forms as well as in bulk and biological fluid.



Structure of pantoprazole

Spectral method

Moustafa (2000) reported spectrophotometric methods for the determination of lansoprazole and PNT. Suslu et al. (2003) reported the determination of pantoprazole in tablet dosage forms by two different spectrophotometric methods. Basavaiah and Vinay (2010) reported sensitive and selective spectrophotometric determination of pantoprazole sodium in pharmaceuticals using permanganate. The details are given in Table 1(C).

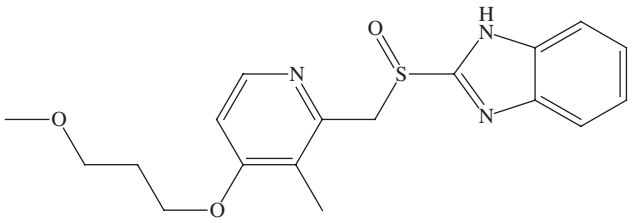
Chromatographic methods

Reddy and Reddy (2009a) reported the development and validation of RP-HPLC for the PNT in pharmaceutical dosage forms and human plasma. Ramakrishna et al. (2005a) have reported a HPLC method for the quantification of pantoprazole in human plasma. Balasekhara et al. (2010) reported the development and validation of a sensitive bioanalytical method for the quantitative estimation of pantoprazole in human plasma samples by LC-MS/MS: application to a bioequivalence study. Mohankandhasamy et al. (2010) reported a HPLC method for the quantification of pantoprazole in rat plasma. Bhaskara et al. (2011) reported sensitive a LC-TMS method for the determination of pantoprazole sodium in human urine. Patel (2011) reported a HPLC method for the estimation of pantoprazole in injection. The detailed chromatographic conditions are described in Table 2(C).

Rabeprazole

Rabeprazole (RB) sodium is chemically 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*-benzimidazole sodium salt, half-life of 1–2 h, and has an oral bioavailability of 52% when administered orally (www.pharmainfo.net). RB belong to a class of antisecretory compounds that do not exhibit anticholinergic or histamine H2-receptor antagonist properties but suppress gastric acid secretion by inhibiting the gastric H^+, K^+ ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within a parietal cell, RB has been characterized as a gastric proton pump inhibitor. RB blocks the final steps of gastric acid secretion (Desai and Samant 2002). It is used in the treatment of active duodenal ulcers and active benign gastric ulcers. It is also used in the treatment of GORD. In combination with appropriate antibacterial therapeutic regimens, it is being used for the eradication of *H. pylori* in patients with peptic ulcer disease (PUD) (www.rxlist.com).

Different analytical methods have been reported for its determination which include HPLC, LC-MS/MS, capillary electrophoresis (CE), derivative spectrometry, and UV-spectrophotometry. These reported methods, such as HPLC, LC-MS/MS, and CE, are sensitive but expensive due to high cost. The main problem associated with these determinations is the laborious cleanup procedure required prior to analysis of the drug. The preparation of the drug sample included liquid-liquid or solid-liquid extraction to isolate and preconcentrate the drug samples. Spectrophotometry is attractive because of its speed and simplicity.



Structure of rabeprazole

Spectral method

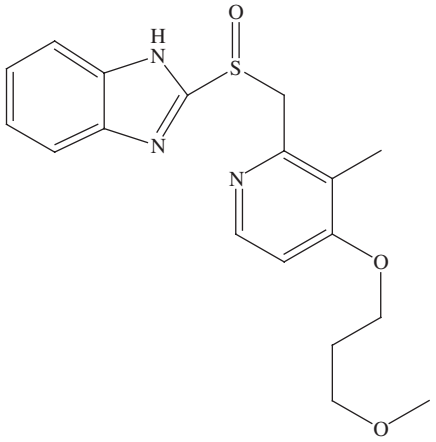
Gouda et al. (2010) reported the physicochemical characterization, UV spectrophotometric analytical method development, and validation studies of RB sodium. Patel et al. (2007) reported a spectrophotometric method for the estimation of RB. Osma and Osman (2009) reported spectrofluorometry, TLC, and column HPLC determination of RB sodium in the presence of its acidic and oxidized degradation products. Madhuri et al. (2010) reported the validation of spectrophotometric determination of RB using ferric chloride ($FeCl_3$). Rahman et al. (2008b) reported the quantitative analysis of RB sodium in commercial dosage forms by spectrophotometry. Mandhanya et al. (2011) reported simultaneously the estimation of paracetamol, aceclofenac, and RB in tablet dosage form using UV spectroscopy. Moustafa (2003) reported spectrophotometric and chromatographic determination of RB in the presence of its degradation products. The details are given in Table 1(D).

Chromatographic methods

Rao et al. (2008) reported the development of a RP-HPLC method for the estimation of RB in pure and tablet dosage form. Rao et al. (2006) reported enantio-specific resolution of RB by LC on amylose-derived chiral stationary phase using photodiode array and polarimetric detectors in series. Elumalai et al. (2011) reported the development and validation of a RP-HPLC method for the determination of content uniformity of RB sodium in its tablets dosage form. Singh et al. (2004) reported a direct injection, column switching–liquid chromatographic technique for the estimation of RB in a bioequivalence study. Ramakrishna et al. (2005a) reported a HPLC method for the quantification of RB in human plasma using solid-phase extraction. Shimizu et al. (2005) reported the determination of RB and its active metabolite, RB thioether in human plasma by column-switching HPLC and its application to pharmacokinetic study. Tada et al. (2006) reported the determination of RB enantiomers and their metabolites by HPLC with solid-phase extraction. Zhang et al. (2004) reported the quantification of RB in human plasma by LC-TMS. Reddy and Reddy (2009b) reported the development and validation of RP-HPLC for the RB sodium in pharmaceutical formulations and human plasma. Hishinum et al. (2008) reported simple quantification of lansoprazole and RB concentrations in human serum by LC-TMS. Bharekar et al. (2011) reported a validated HPTLC method for the simultaneous estimation of rabeprazole sodium, paracetamol, and aceclofenac in bulk drug and formulation. Shirkhedkar and Surana (2009) reported the application of stability-indicating RP-TLC densitometric determination of rabeprazole sodium in bulk and pharmaceutical formulation. The detailed chromatographic conditions are described in Table 2(D).

Dexrabeprazole

Dexrabeprazole (DZ) [(R) (+) rabeprazole] is a novel PPI, which has recently become available in India for the treatment of acid peptic diseases. Experimental and clinical studies have shown superiority the of DZ (at half the recommended RB dose) over RB in terms of favorable pharmacokinetics, better efficacy, and faster healing activity. DZ showed its effectiveness in the treatment of gastro-oesophageal reflux disease and also showed its effectiveness in the treatment of patients with peptic ulcers (gastric/duodenal) (Jain 2009). Owing to the pharmacological difference between these enantiomers, it is very important to develop an enantio-specific LC method for the quality assurance of drug substance and drug product. The separation of enantiomers has become very important in analytical chemistry, especially in the pharmaceutical and biological fields, because some stereoisomer of racemic drugs have very different pharmacokinetics and different pharmacological or toxicological effects (Sahajwalla 2004). It was revealed from the literature survey that the chiral HPLC method for enantiomeric separation of RB by using a Chiralpak AD-H [tris(3,5-dimethylphenylcarbamate) amylose] column in the normal phase mode and the determination of rabeprazole enantiomers and their metabolites by HPLC and solid-phase extraction were reported.



Structure of Dexrabeprazol

Spectral method

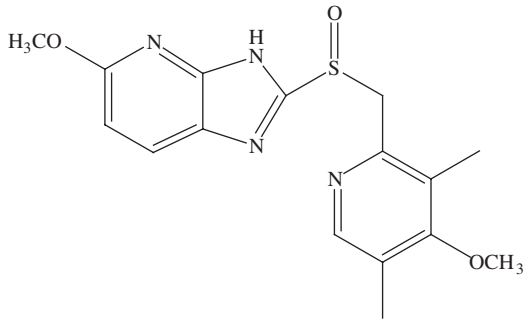
Shedpure et al. (2011) have reported spectrophotometric determination of DZ sodium in bulk and tablet dosage form by first-order derivative spectroscopy and the area under the curve. The details are given in Table 1(E).

Chromatographic methods

Patil et al. (2011) reported a validated chiral LC method for DZ on the reverse-phase amylose-based stationary phase. The detailed chromatographic conditions are described in Table 2(E).

Tenatoprazole

Tenatoprazole (TPZ) is chemically, 3-methoxy-8-[(4-methoxy-3,5-dimethyl-pyridin-2 yl) methyl sulfinyl] 2,7,9-triazabicyclo nona-2,4,8,10-tetraene. It is a prodrug of the (PPI) class, which is converted to the active sulfenamide or sulfenic acid by acid in the secretory canaliculus of the stimulated parietal cell of the stomach. This active species binds to luminally accessible cysteine of the gastric H^+ K^+-ATPase resulting in disulfide formation and acid secretion inhibition (Robinson 2005).



Structure of Tenatoprazole

Spectral method

Sugumaran et al. (2010) reported the UV-spectrophotometric determination of TPZ from its bulk and tablets. Kumaraswamy et al. (2011) reported spectrophotometric determination of tenatoprazole in bulk drug and pharmaceutical dosage form. The details are given in Table 1(F).

Chromatographic methods

Mahadika et al. (2009) reported LC-UV and LC-MS evaluation of stress degradation behavior of TPZ. Sugumaran et al. (2011) reported a RP-HPLC method for the determination of TPZ in pharmaceutical formulations. Kumar and Rao (2011) reported the development and validation of a RP-HPLC method for the estimation of TPZ in bulk and tablet dosage form. Liu et al. (2007) reported HPLC determination and pharmacokinetic study of TPZ in dog plasma after oral administration of enteric-coated capsule. Dhaneshwar et al. (2008) reported the application of a stability-indicating TLC method to the determination of TPZ in pharmaceutical dosage forms. The detailed chromatographic conditions are described in Table 2(F).

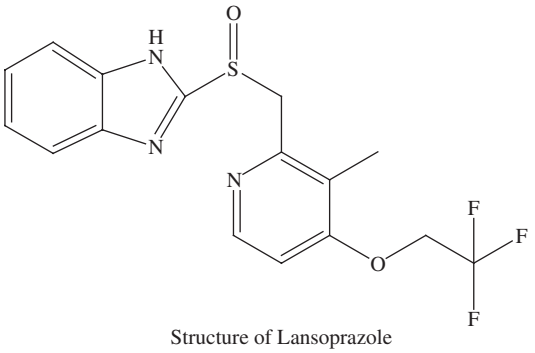
Lansoprazole

Lansoprazole (LZ), chemically known as 2-[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl] methylsulfinyl]-1H-benzimidazole. LZ, a member of the PPI class of gastric acid inhibitory agent, effectively raises intragastric pH and is indicated for the short-term treatment of active erosive reflux esophagitis, gastric ulcer, duodenal ulcer, and nonerosive gasteroesophageal reflux disease. LZ is also indicated as a long-term maintenance therapy in patients with healing reflux esophagitis and healed duodenal ulcer and in the treatment of pathological hypersecretory conditions, such as Zollinger-Ellison syndrome.

As a PPI, LZ is also a necessary component of dual- and tripletherapy regimens for the eradication of *H. pylori* infection. The latest FDA-approved labeling for LZ includes the indication of healing and risk reduction in nonsteroidal anti-inflammatory drug-associated gastric ulcers (Brummer et al. 1997; Tolman et al. 1997; Threlkeld 1998).

The absorption of LZ is rapid, with mean Cmax occurring approximately seven hours after oral dosing and relatively complete with absolute bioavailability over 80%. There is no significant food effect if the drug is given before meals. LZ is 97% bound to plasma proteins. LZ is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (hydroxylatedsulfinyl and sulfone derivatives of LZ). LZ belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H^+, K^+)-ATPase + + enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, LZ has been characterized as a

gastric acid pump inhibitor, in that it blocks the final step of acid production (Fitton and Wiseman 1996; Matheson and Jarvis 2001; Bown 2002).



Structure of Lansoprazole

The literature survey reveals a few methods based on HPLC, densitometric HPTLC, LC/MS-derivative UV-spectrophotometry and difference UV spectrophotometry have been reported for the assay of LZ in commercial dosage forms as well as in bulk and biological fluid.

Spectral method

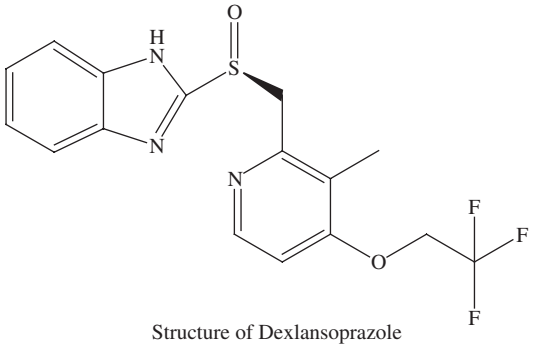
Basavaiah et al. (2006) reported sensitive spectrophotometric determination of LZ in pharmaceuticals using ceric ammonium sulfate based on redox and complex formation reactions. Sudheer et al. (2011) reported a new UV-spectrophotometric method for the determination of LZ in pharmaceutical dosage form and its application to protein binding study. Nuran (1999) reported the determination of LZ in pharmaceutical dosage forms by two different spectroscopic methods. Yeniceli et al. (2004) reported the determination of LZ in pharmaceutical capsules by flow injection analysis using UV detection. Basavaiah and Vinay (2013) reported quantitative determination of LZ in capsules and spiked human urine by spectrophotometry through ion-pair complex formation reaction. The detail is given in Table 1(G).

Chromatographic methods

Reddy et al. (2009) reported the determination of PNT and LZ in individual tablet dosage forms by RP-HPLC using a single mobile phase. Kumar et al. (2010a) reported the development and validation of RP-HPLC method for the estimation of LZ in tablet dosage form. Katsuki et al. (1996) reported the determination of R(+) and S(-) LZ using chiral stationary phase liquid chromatography and their annuity-selective pharmacokinetics in humans. Brown et al. (2011) reported quantification of LZ in oral suspension by a ultra-HPLC hybrid ion-trap time-of-flight mass spectrometry. Rababah and Momani (2010) reported the validation of HPLC and FIA spectrophotometric methods for the determination of LZ in pharmaceutical dosage forms and human plasma. Oliveira et al. (2003) reported LZ quantification in human plasma by liquid chromatography-electrospray tandem mass spectrometry. Miura et al. (2004) reported simultaneous determination of LZ enantiomers and their metabolites in plasma by LC with solid-phase extraction. Pandya et al. (1997) reported a HPLC method for the detection and determination of LZ in human plasma and its use in pharmacokinetic studies. Aoki et al. (1991) reported HPLC determination of LZ and its metabolites in human serum and urine. Katsuki et al. (2001) reported a HPLC assay for the simultaneous determination of LZ enantiomers and metabolites in human liver microsomes. Sherif et al. (2005) reported stability-indicating methods for the determination of lansoprazole. The detailed chromatographic conditions are described in Table 2(G).

Dexlansoprazole

Dexlansoprazole (DL) is chemically 2-[(R)-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2 pyridinyl]methyl]sulfinyl]-1H-benzimidazole. DL is in a group of drugs called PPIs. DL decreases the amount of acid produced in the stomach. DL is used to treat heartburn caused by GERD and to heal erosive esophagitis (damage to the esophagus from stomach acid). DL may also be used for purposes not listed in this medication guide (www.drugs.com).



Structure of Dexlansoprazole

Chromatographic methods

Bharathi et al. (2011) reported the development and validation of a highly sensitive LC-MS/MS method for the

quantitation of DL in a human plasma: application to a human pharmacokinetic study. The detailed chromatographic conditions are described in Table 2(H).

Conclusion

An overview of the current state of the art for analytical methods for the determination of PPIs has been presented. The literature compilation has revealed that a variety of methods are available for PPIs. For drugs, such as tenatoprazole, dexrabeprazole, and dexlansoprazole, only a limited number of methods have been reported. Our analysis of the published data revealed that the HPLC was extensively used for the estimation of PPIs in biological fluids. Most of the workers have used the reversed-phase mode with UV absorbance detection because this provided the best available reliability, repeatability, analysis time, and sensitivity. LC coupled with mass detector (LC-ESI/MS) was used not only to detect most of the metabolites of PPIs in human urine and plasma but also the degradation products of bulk drugs and formulations. Other detectors, such as fluorescence and electrochemical, were also used in the evaluation and control of purity of PPIs. There is a great scope for the development of newer analytical methods for latest drugs such as tenatoprazole.

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