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An overview of the recent developments in analytical methodologies for determination of proton pump inhibitors in bulk drugs, pharmaceuticals and biological matrices.

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Abstract

An extensive survey of the literature published in various analytical and pharmaceutical chemistry related journals has been conducted and the instrumental analytical methods which were developed and used for 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 spectrophotmetric and chromatographic techniques were reported. HPLC with UV detection was found to be the technique of choice for many workers and more than 50 methods were based on LC and UV. A critical analysis of the reported data has been carried out and the present state-of-art of the analytical techniques for determination of omeprazole, esomeprazole, pantoprazole, rabeprazole, dexrabeprazole, tenatoprazole, lansoprazole and dexlansoprazole has been discussed.

Keywords:

Proton pump inhibitors; Pharmaceuticals; Biological fluids; Spectrophotometry; Chromatography

1. Introduction

An ulcer is a sore, which means it's 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 or achlorhydria. Gastrin stimulates the production of gastric acid by parietal cells and in *H. pylori* colonization responses that increase gastrin, the increase in acid can contribute to the erosion of the mucosa and therefore ulcer formation (Figure 1).

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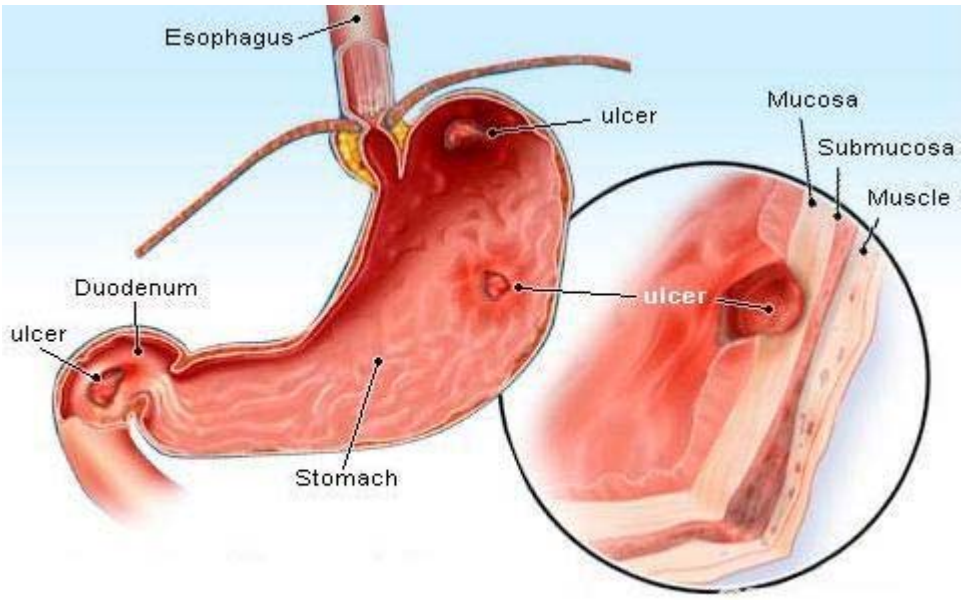


Another major cause is the use of nonsteroidal anti-inflammatories drugs (NSAIDs). The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase 1 (*cox-1*), which is essential for the production of these prostaglandins. PROTON PUMP selective anti-inflammatories (such as celecoxib or rofecoxib) preferentially inhibit *Proton pump*, which is less essential in the gastric mucosa, and roughly halve 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 as well as the growth of aging populations that develop arthritis.

The incidence of duodenal ulcers has 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 treatment of the disease. The cohort-phenomenon is probably explained by improved standards of living which 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 analogue (Misoprostol) 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 2 antibiotics (e.g. Clarithromycin, Amoxicillin, Tetracycline, Metronidazole) and 1 proton pump inhibitor (PPI), sometimes together with a bismuth compound. In complicated, treatment-resistant cases, 3 antibiotics (e.g. amoxicillin + clarithromycin + metronidazole) may be used together with a PPI and sometimes with bismuth compound. An effective first-line therapy for uncomplicated cases would be Amoxicillin+Metronidazole+Pantoprazole (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 PPI's in the 1990s, surgical procedures (like "highly selective vagotomy") for uncomplicated peptic ulcers became obsolete.

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 a pharmacy and works by decreasing the amount of acid the stomach produces allowing 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.[1]

2. Proton pump inhibitors

Inhibition of gastric acid secretion has been the major means of treatment of acid related diseases such as peptic ulcers and gastro-esophageal reflux disease. 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 Proton pump inhibitors, lansoprazole and pantoprazole, which all have a benzimidazole.

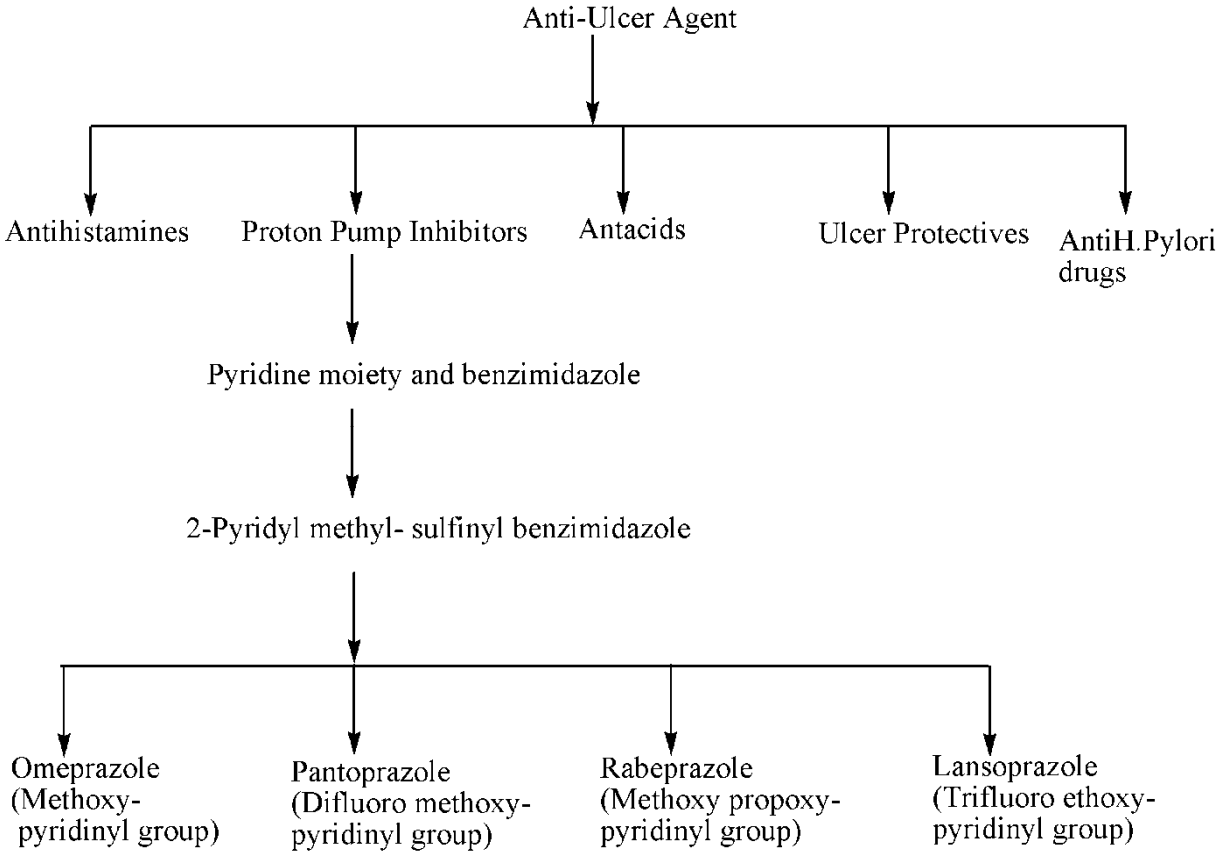
Proton pump inhibitors consist of two heterocyclic moieties. One is a pyridine moiety, and the other is a benzimidazole or an imidazo-pyridine. The two heterocyclic moieties are linked through a methylenesulfinyl (-CH2SO-) group. Clinically available proton pump inhibitors are omeprazole, *S*-omeprazole (*S*-enantiomer of omeprazole), lansoprazole, pantoprazole, and rabeprazole. Lansoprazole is 2-[3-methyl-4- (2,2,2-trifluoroethoxy)-pyridin-2-yl]methylsulfinyl]-*1H*-benzimidazole. 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 proton pump inhibitors Proton pump inhibitors, including omeprazole, lansoprazole and pantoprazole, led to a new era in the effective therapy of acidpeptic diseases. Gastric Proton pump inhibitors are pro-drugs 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.

2.1 Chemical classification

Alagarsamy et al. have surveyed most of the available proton pump inhibitors and proposed an extremely useful classification system based on selectivity, which has been widely adopted. The following classification as shown in Fig.2 has been proposed for the

currently known proton pump inhibitors based on their active functional groups involved in the chemical structures.



Proton pump inhibitors are the recent development of ulcer and there is a great need to review the analytical work reported so far in the literature. Till 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 to 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 proceeding sections. The present review comprises of all analytical methods for the analysis of proton pump inhibitors in bulk drugs, pharmaceuticals, therapeutic monitoring studies viz., bioavailability and pharmacokinetics published in the last 10 years.

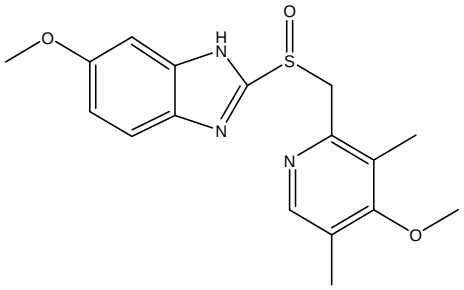
Techniques like spectrophotometric, fluorimetric, voltametric, thin layer chromatography [TLC], high-performance liquid chromatography [HPLC], capillary electrophoresis [CE] and others have been used for analysis. It could be seen that HPLC followed by spectrophotometric methods have used extensively. Further analysis of this data has indicated that these techniques are applied mostly for analysis of bulk drugs, formulations, biological matrices and stability studies.

3. Omeprazole

Omeprazole (OPZ), 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2- pyridinyl)methyl]-sulphinyl]-1H-benzimidazole is a substituted benzimidazole compound and a prototype anti-secretory agent, being the first “proton pump inhibitor” widely used for the prophylaxis and treatment of gastro-duodenal ulcers and for the treatment of symptomatic gastro-oesophageal 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 with pKa1 = 4.2 and pKa2 = 9 and can be degraded unless it is protected against acid conditions. OPZ contains a tricoordinated sulphur atom in a pyramidal structure and therefore can exist in two different optically active forms, (S)- and (R)-omeprazole. OPZ was first approved as a racemic mixture, but the (S) isomer was recently introduced on the market [4].

Several high-performance liquid chromatography (HPLC) methods with ultraviolet detection and electrochemical detection, liquid chromatography coupled with tandem mass spectrometry, spectrophotometry, polarography,voltammetry, capillary electrophoresis and thin-layer chromatography methods have been developed for determination of omeprazole in different samples.



Structure of omeprazole

3.1 Spectral Method

Marinkovic et al. [5] have reported first-order UV-derivative spectrophotometry in the analysis of omeprazole and pantoprazole sodium salt and corresponding impurities. Chilukuri et al.[6] have reported Spectrophotometric methods for the determination of omeprazole in bulk form and pharmaceutical formulations. Bhupendra et al.[7] have reported Statistical assurance of process validation by analytical method development and validation for omeprazole capsules and blend. Kasture et al.[8] have reported Extractive spectrophotometric determination of omeprazole in pharmaceutical preparations. Kalyane et al.[9] have reported Visible spectrophotometric methods for the estimation of losartan potassium and omeprazole in single component pharmaceutical formulations. Shaghaghi et al.[10] have reported indirect Spectrofluorimetric determination of omeprazole by its quenching effect on the fluorescence of Tb^{3+}-1,10-phenanthroline complex in presence of bis (2-ethylhexyl) sulfosuccinate sodium in capsule formulations.The detail are given in Table 1(A).

Table 1. Spectral data of proton pump inhibitors

Sample Matrix	Solvent/Reagent	Linearity Range ($\mu g\ mL^{-1}$)	Detection, (nm)	Ref.
(A) Omeprazole				
API	Methanol-/Ammonia 4.0% v/v	1.61-17.2	UV 304	[5]
API and Capsule	0.1 N NaoH	1-10	VIS. 660	[6]
Capsule	0.1 N NaoH	2- 10	UV 302	[7]
Capsule	0.05M HCl	5 - 30 and 50 - 250	UV 408 and 508	[8]
Capsule	Acidic Buffer Solutions	10-80	UV 400	[9]
Capsule	0.1 N NaoH	0.05-10 .	UV 545	[10]

Table 1 (continued)

Sample Matrix	Solvent/Reagent	Linearity Range (μg mL^{-1})	Detection, (nm)	Ref.
(B) Esomeprazole				
API	Methanol	2-10	UV 203.5	[25]
API	Methanol-Chloroform(80:20), Using indigo carmine	5-35	VIS. 577and 617	[26]
API and Tablet	Methanol	4-40	UV 279	[27]
Tablet	Methanol	5-40	UV 292 and 303	[28]
Tablet	Methanol-Chloroform using Sulpho-Salicylic Acid	2-48 and 10-100	UV 365 and 380	[29]
Capsule	Bromo cresol green in Methanol	50-250	VIS. 420	[30]
(C) Pantoprazole				
Tablet and API	Methanol-Water	10-90	UV 457	[38]
Tablet	Methanol-Water(1:9 v/v)	2.5-80	UV 295 and 303	[39]
Tablet	Water and $KMNO_4$	2.5-40	UV 350	[40]
(D) Rabeprazole				
API	Distilled-Water	2-10	UV 272.2	[50]
API	Bromo Thymole blue in acidic buffer	10-100	UV 454	[51]
API	Acid(0.1N Hcl)	15-75	λ ex =320 and 274, λ em= 416 and 311	[52]
Tablet	Fecl3 and Methanol	10-60	VIS. 455	[53]
Tablet	Distilled-Water	14-140 and 7.5-165	UV 420	[54]
Tablet	Methanol	2-20	UV 284	[55]
(E) Dexrabeprazole				
API and Tablet	Methanol	6-36	UV 305	[71]
(F)Tenatoprazole				
API and Tablet	0.1N NaoH	2-12	UV 314	[74]
API and Tablet	0.1M HCl	3-18	UV 314	[75]
(G)Lansoprazole				
API and Capsule	Ceric ammonium sulphate, iron,orthophenanthroline and thiocynate	2.5-30 and 2.5-25	VIS. 510 and 470	[87]
Capsule	Methanol	3-90	UV 281.1	[88]
Capsule	0.1M NaoH	3-25 and 0.5-25	UV 296	[89]
Capsule	0.01M NaoH	5.4*10-6 to 5.4*10-5M	UV 292	[90]
Capsule and Human Urine	DichloroMethane,Bromo Cresol Purple and Bromo Thymole Blue	0.5-15 and 1.25-20	VIS. 400 and 430	[91]

API=Active pharmaceutical ingredient

3.2 Chromatographic methods

Cristina et al.[11] have reported Development of a validated RP-HPLC method for separation and determination of process-related impurities of omeprazole in bulk drugs. Schubert et al.[12] have reported Determination of omeprazole in bulk and injectable preparations by liquid chromatography. Murakami et al.[13] have reported Development and validation of a RP-HPLC method to quantify omeprazole in delayed release tablets. Samir et al.[14] have reported Development and validation of a stability indicating method for the enantioselective estimation of omeprazole enantiomers in the enteric-coated formulations by HPLC. Gregory et al.[15] have reported Omeprazole determination using HPLC with coulometric detection. Yuen et al.[16] have reported Improved high performance liquid chromatographic analysis of omeprazole in human plasma. Lagerstrem et al.[17] have reported Determination of omeprazole and metabolites in plasma and urine by liquid chromatography. Ishizaki et al.[18] have reported Development and preliminary application of a high performance liquid chromatographic assay for omeprazole metabolism in human liver microsomes.The detailed chromatographic conditions are described in Table 2(A).

Table 2. Chromatographic data of proton pump inhibitors

Sample matrix	Column	Mobile phase (v/v)	Detector (nm)	Ref.
(A) Omeprazole				
API	C_{18}	Acetonitrile/water/triethyl amine 1%(pH 9.5)	UV 280	[11]
API and Injectable	C_{18}	Methanol/water(90/10)	UV 301	[12]
Delayed Release Tablet	C_{18}	Phosphate buffer(pH7.4)and acetonitrile(70/30)	UV 280	[13]
Enteric Coated Formulation	ODS	Isopropyl alcohol/ethanol(85/15)	UV 301	[14]
Paste	C_8	36%(v/v)Acetonitrile in 0.01m phosphate buffer(ph7.6)	+800mV	[15]
Human Plasma	C_{18}	0.05m Na_2HPO_4/ acetonitrile (65/35)pH 6.5	UV 302	[16]
Plasma and Urine	C_{18}	Acetonitrile /phosphate buffer(20/80 pH7.5)	UV 302	[17]
Human Liver Microsomes	C_{18}	Acetonitrile /sodium phosphate (26/74 pH8.4)	UV 302	[18]
(B) Esomeprazole				
APIand Tablet	C_{18}	Acetonitrile / phosphate buffer (55/45)	UV 301	[31]
Tablet	C_{18}	Acetonitrile /phosphate buffer (60:40 pH7.0)	UV 205	[32]
Human Plasma	C18	Phosphate buffer/ acetonitrile(88/12 pH 7.0)	UV 288	[62]
Human Plasma	Chiral CD-PH	0.5mNaclo4 /acetonitrile(60/40)	UV 285	[63]
Human Plasma	C18	Phosphate buffer/ acetonitrile(88/12 pH 7.0)	UV 288	[62]
Human Plasma	Chiral CD-PH	0.5mNaclo4 /acetonitrile(60/40)	UV 285	[63]

Table 2 (Continued)

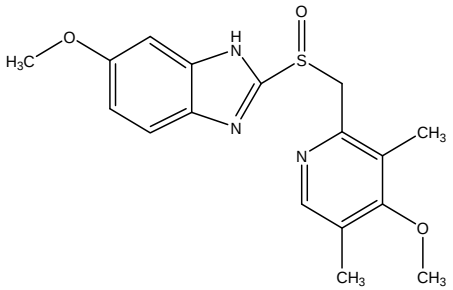
Sample matrix	Column	Mobile phase (v/v)	Detector (nm)	Ref.
Tablet	Chiralpak IA	Methyl tert butyl ether/ ethyl acetate/ethanol/diethyl amine(60/40/5/0.1)	UV 299	[33]
Human Plasma	C_{18}	Acetonitrile:water (80/20 pH 7.0)	MS	[34]
Human,Rat,Dog Plasma	C_8	Acetonitrile/formic acid /ammonium acetate/water(250/1/100/645)	MS	[35]
API and Tablet	Silica gel $60F_{254}$	Ethyl acetate/ammonia(8/0.8)	UV 301	[36]
(C)Pantoprazole				
Tablet and Human Plasma	C_{18}	Acetonitrile /phosphate buffer(70/30 pH7)	UV 260	[41]
Human Plasma	C_{18}	Phosphate buffer(pH6) and acetonitrile(61/39)	UV 290	[42]
Human Plasma	C_{18}	Ammonium acetate/acetonitrile(30/70 pH 7.1)	UV 285	[43]
Rat Plasma	C_{18}	Water/acetonitrile (55/45) pH 7	UV 290	[44]
Human Urine	C_{18}	Acetonitrile/water(90/10)	UV 288	[45]
Injection	Silicagel60 F_{254}	Toluene/ethyl acetate/methanol/acetic acid(7/2/1/0.1)	UV 290	[46]
(D) Rabeprazole				
API	ODS	Methanol/water(70/30)	UV 284	[56]
API and Tablet	C_{18}	Methanol/water(65/35)	UV 284	[57]
API and Tablet	Chiralpak AD-H	n-hexane/ethanol/2-propanol(75/15/10)	UV 284	[58]
Tablet	C_8	Acetonitrile /sodium phosphate buffer (35/65 pH 6.5)	UV 285	[59]
Human Plasma	C_{18}	Ammonium acetate /acetonitrile(70/30 pH 7.0)	UV 290	[60]
Human Plasma	C_{18}	Ammonium acetate /acetonitrile/ methanol (45/20/35 pH 7.4)	UV 284	[61]
Human Plasma	C18	Phosphate buffer/ acetonitrile(88/12 pH 7.0)	UV 288	[62]
Human Plasma	Chiral CD-PH	0.5mNaclo4 /acetonitrile(60/40)	UV 285	[63]
Human Plasma	C18	n-hexane /dichloromethane/isopropanol (20/10/1)	MS	[64]
Human Serum	C18	Acetonitrile/ammonium formate(140/60)	MS	[66]
Human Plasma and Tablet	C18	Phosphate buffer /acetonitrile(30/70 pH7.0)	UV 228	[65]

Table 2 (Continued)

Sample matrix	Column	Mobile phase (v/v)	Detector (nm)	Ref.
API and Tablet	Silicagel $60F_{254}$	Toluene/ethyl acetate /methanol/acetic acid(6/4/0.8/0.4)	UV 256	[67]
API and Tablet	Silicagel $60F_{254}$	Acetonitrile/water(3.5/1.5)	UV 284	[68]
(E)Dexrabeprazole				
API and Tablet	Chiralpak AD-RH(Amylose)	Water/acetonitrile (50/50)	UV 284	[72]
(F)Tenatoprazole				
API	ODS-3-C_{18}	Methanol/acetate buffer (55/45 pH4.5)	UV 306	[76]
API and Tablet	C_{18}	Acetonitrile /phosphate buffer (40/60 pH 2.4)	UV 307	[77]
API and Tablet	C_{18}	Acetonitrile /phosphate buffer (45/55 pH2.5)	UV 314	[78]
Dog Plasma and Capsule	C_{18}	Phosphate buffer /acetonitrile (70/30 pH 4.7)	UV 306	[79]
API and Tablet	Silicagel $60F_{254}$	Toluene/ethyl acetate /methanol(6/4/1)	UV 314	[80]
(G)Lansoprazole				
Tablet	C_{18}	Acetonitrile/phosphate buffer (60/40 pH 7)	UV 230	[92]
Tablet	C_8	Di hydrogen phosphate/acetonitrile(30/70)	UV 285	[93]
Capsule	C18	n-hexane/ethanol (8/2)	UV 285	[94]
Oral Suspension	C18	Acetonitrile/water(40/60)	MS	[95]
Capsule and Human Plasma	C18	Acetonitrile/triethyl amine /phosphate buffer (60/0.2/39.8 pH 4)	UV 285	[96]
Human Plasma	C18	Acetonitrile/water(90/10)	MS	[97]
Human Plasma	Chiral CD-PH	0.5m Naclo4/acetonitrile/methanol (6/3/1)	UV 285	[98]
Human Plasma	Silicagel 60F254	Chloroform/methanol(15/1)	UV 286	[99]
Human Serum and Urine	ODS-120T	Phosphate buffer /ethanol/acetonitrile(20/10/3 pH7.2)	UV 285 and 303	[100]
Human Liver Microsomes	OD-R	Methanol/water(75/25)	UV 285	[101]
Capsule	Silicagel $60F_{254}$	Chloroform/methanol /n-hexane (75/25/60)	UV 285	[102]
(H)Dexlansoprazole				
Human Plasma	C_{18}	Ammonia/acetonitrile(20/80)	MS	[104]

4. Esomeprazole

(PPIs) are the most potent inhibitors of gastric acid secretion and are effective for treating all gastric acid-related disorders. Esomeprazole is indicated for the treatment of gastroesophageal reflux disease in adults and children, risk reduction of NSAIDs associated gastric ulcer, Helicobacter pylori eradication and control of pathological hypersecretory conditions associated with Zollinger-Ellison syndrome [19]. Esomeprazole is bis(5methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole- 1-yl) magnesium trihydrate. The stability of esomeprazole 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 hours at 25° C and about 8 hours at 37° C [20]. Esomeprazole has a half-life of 1.25 ± 0.25 h and has a bioavailability of 48% when administered orally [21,22]. Esomeprazole, the S-isomer of omeprazole, 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 [23]. Esomeprazole is combined with antibiotics clarithromycin and amoxicillin or metronidazole in 7-14 days eradication triple therapy of *Helicobacter pylori* infection where majority of peptic and duodenal ulcers were caused by *H. pylori* [24].



Structure of Esomeprazole

4.1 Spectral Method

Shyale et al.[25] have reported Physico-chemical characterization, UV spectrophotometric method development and validation studies of esomeprazole magnesium trihydrate. Sharma et al.[26] have reported Spectrophotometric methods for the estimation of esomeprazole magnesium trihydrate in pharmaceutical formulations using indigo carmine reagent. Chandewar et al.[27] have reported Spectroscopic estimation of esomeprazole magnesium in solid dosage form. Shamkant et al.[28] have reported Development and statistical validation of spectrophotometric method for estimation of esomeprazole in tablet dosage form. Rahman et al.[29] have reported Spectrophotometric determination of esomeprazole magnesium in commercial tablets using 5-sulfosalicylic acid and n-bromosuccinimide. Reddy et al.[30] have reported Simple spectrophotometric determination of esomeprazole magnesium in pharmaceutical formulations. The detail are given in Table 1(B).

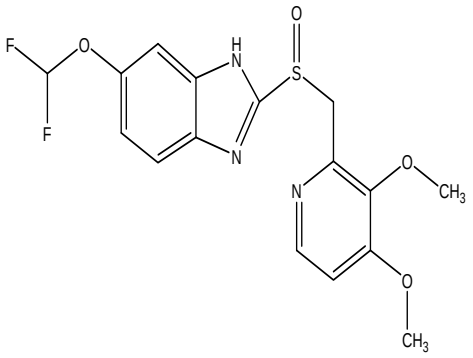
4.2 Chromatographic methods

Kumar Singh et al.[31] have reported RP- HPLC method for the estimation of esomeprazole magnesium in bulk and its pharmaceutical dosage forms .Aysel et al.[32] have reported Development and validation of high performance liquid chromatographic method for the determination of esomeprazole in tablet. Zanitti et al.[33] have reported Direct HPLC enantioseparation of omeprazole and its chiral impurities: application to the determination of enantiomeric purity of esomeprazole magnesium trihydrate. Sathiyaraj et al.[34] have

reported Bioanalytical method development and validation of esomepraole in human plasma by LCMS/MS. Hultman et al.[35] have reported Determination of esomeprazole and its two main metabolites in human, rat and dog plasma by liquid chromatography with tandem mass spectrometry. Gosavi et al.[36] have reported Estimation of esomeprazole in bulk and tablet dosage form by use of planar chromatography. The detailed chromatographic conditions are described in Table 2(B).

5. Pantoprazole sodium sesquihydrate

Pantoprazole sodium sesquihydrate is chemically known as sodium 5-(difluoromethoxy)-2–{[(3,4- dimethoxy-2-pyridinyl) methyl]sulfinyl}-1 H-benzimidazole sesquihydrate . It is used as an antiulcerative agent [37] by inhibiting the gastric acid secretion. Pantoprazole sodium sesquihydrate is immensely used for the cure of erosion and ulceration of 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

5.1 Spectral Method

Moustafa et al.[38] have reported Spectrophotometric methods for the determination of lansoprazole and pantoprazole sodium sesquihydrate. Emine et al.[39] have reported Determination of pantoprazole in tablet dosage forms by two different spectrophotometric methods. Vinay et al.[40] have reported Sensitive and selective spectrophotometric determination of pantoprazole sodium in pharmaceuticals using permanganate. The detail are given in Table 1(C).

5.2 Chromatographic methods

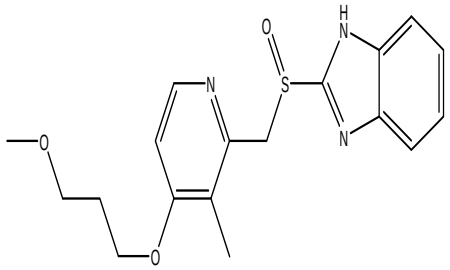
Prasanna et al.[41] have reported Development and validation of RP-HPLC for the pantoprazole sodium sesquihydrate in pharmaceutical dosage forms and human plasma. Ramakrishna et al.[42] have reported High-performance liquid chromatography method for the quantification of pantoprazole in human plasma. Balasekhara et al.[43] have reported Development and validation of a sensitive bioanalytical method for the quantitative estimation of pantoprazole in human plasma samples by LC–MS/MS: application to bioequivalence study. Thiagarajan et al.[44] have reported High - performance liquid chromatography method for the quantification of pantoprazole in rat plasma. Basavaiah et al.[45] have reported Sensitive liquid chromatography–tandem mass spectrometry method for the determination of pantoprazole sodium in human urine. Satish et al.[46] have reported

High performance thin layer chromatographic method for estimation of pantoprazole in injection. The detailed chromatographic conditions are described in Table 2(C).

6. Rabeprazole

Rabeprazole sodium is chemically 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H-Benzimidazole sodium salt. Half-life of 1-2 h and has a oral bioavailability of 52 % when administered orally [47]. Rabeprazole 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 parietal cell, rabeprazole has been characterized as a gastric proton –pump inhibitor. Rabeprazole blocks the final steps of gastric acid secretion [48]. It is used in the treatment of active duodenal ulcer and active benign gastric ulcer. It is also used in the treatment of gastro–oesophageal reflux disease (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) [49].

Different analytical methods have been reported for its determination which include high performance liquid chromatography (HPLC), liquid chromatography coupled with tandem mass spectrometry (LCMS/ 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 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 speed, and simplicity.



Structure of rabeprazole

6.1 Spectral Method

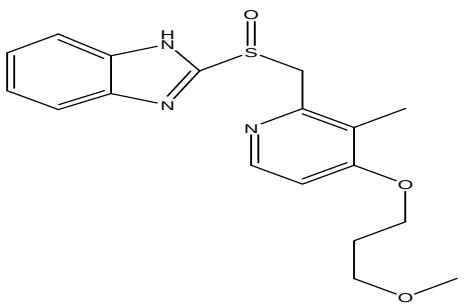
Mallikarjuna et al.[50] have reported Physico-chemical characterization, UV spectrophotometric analytical method development and validation studies of rabeprazole sodium. Desai et al.[51] have reported spectrophotometric method for estimation of rabeprazole. Mohamed et al.[52] have reported Spectrofluorometry, thin layer chromatography, and column high-performance liquid chromatography determination of rabeprazole sodium in the presence of its acidic and oxidized degradation products. Chandrasekhar et al.[53] have reported Validation of spectrophotometric determination of rabeprazole using ferric chloride (Fecl3). Rahman et al.[54] have reported Quantitative analysis of rabeprazole sodium in commercial dosage forms by spectrophotometry. Chaturvedi et al.[55] have reported Simultaneously estimation of paracetamol, aceclofenac and rabeprazole in tablet dosage form using UV spectroscopy. Maher et al.[56] have reported Spectrophotometric and chromatographic determination of rabeprazole in presence of its degradation products. The detail are given in Table 1(D).

6.2 Chromatographic methods

Lakshmana et al.[57] have reported development of RP-HPLC method for the estimation of rabeprazole in pure and tablet dosage form. Nageswara et al.[58] have reported Enantiospecific resolution of rabeprazole by liquid chromatography on amylose-derived chiral stationary phase using photo diode array and polarimetric detectors in series. Gupta et al.[59] have reported Development and validation of RP-HPLC method for determination of content uniformity of rabeprazole sodium in its tablets dosage form. Ruchy et al.[60] have reported Direct injection, column switching–liquid chromatographic technique for the estimation of rabeprazole in bioequivalence study. Ramakrishna et al.[61] have reported High-performance liquid chromatography method for the quantification of rabeprazole in human plasma using solid-phase extraction. Tomonori et al.[62] have reported Determination of rabeprazole and its active metabolite, rabeprazole thioether in human plasma by column-switching high-performance liquid chromatography and its application to pharmacokinetic study. Masatomo et al.[63] have reported Determination of rabeprazole enantiomers and their metabolites by high-performance liquid chromatography with solid-phase extraction. Zhang et al.[64] have reported Quantification of rabeprazole in human plasma by liquid chromatography–tandem mass spectrometry. Prasanna et al.[65] have reported development and validation of RP-HPLC for the rabeprazole sodium in pharmaceutical formulations and human plasma. Takanori et al.[66] have reported Simple quantification of lansoprazole and rabeprazole concentrations in human serum by liquid chromatography/tandem mass spectrometry. Bharekar et al.[67] have reported Validated HPTLC method for simultaneous estimation of rabeprazole sodium, paraetamol and aceclofenac in bulk drug and formulation. Shirkhedkar et al.[68] have reported 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)

7. Dexrabeprazole

Dexrabeprazole [(R) (+) rabeprazole] is a novel proton pump inhibitor, which has recently become available in India for the treatment of acid peptic diseases. Experimental and clinical studies have shown superiority of dexrabeprazole (at half the recommended rabeprazole dose) over rabeprazole in terms of favorable pharmacokinetics, better efficacy and faster healing activity. Dexrabeprazole 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)[69]. Owing to the pharmacological difference between these enantiomers, it is quite important to develop an enantio specific LC method for quality assurance of drug substance and drug product. Separation of enantiomers has become very important in analytical chemistry, especially in the pharmaceutical and biological fields, because some stereoisomer of racemic drugs have quite different pharmacokinetics and different pharmacological or toxicological effects[70].It was revealed from the literature survey, that the chiral high-performance liquid chromatography method for enantiomeric separation of rabeprazole by using Chiralpak AD-H [tris(3,5 dimethylphenyl carbamate) amylose] column in normal phase mode and determination of rabeprazole enantiomers and their metabolites by HPLC and solid phase extraction were reported.



Structure of Dexrabeprazol

7.1 Spectral Method

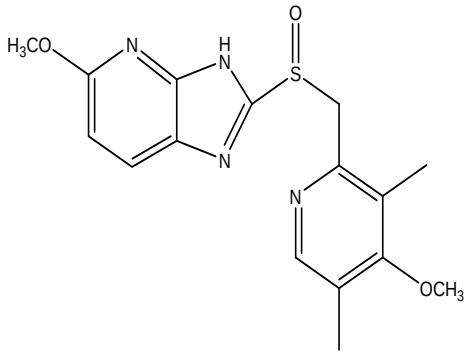
Shedpure, et al.[71] have reported Spectrophotometric determination of dexrabeprazole sodium in bulk &tablet dosage form by first order derivative spectroscopy and area under the curve. The detail are given in Table 1(E).

7.2 Chromatographic methods

Patil et al.[72] have reported Validated chiral LC method for dexrabeprazole on reverse phase amylose based stationary phase. The detailed chromatographic conditions are described in Table 2(E).

8. Tenatoprazole

Tenatoprazole (TPZ) is chemically, 3-methoxy-8- [(4-methoxy-3,5-dimethyl-pyridin-2yl) 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+ -ATP ase resulting in disulfide formation and acid secretion inhibition [73].



Structure of Tenatoprazole

8.1 Spectral Method

Sugumaran et al.[74] have reported The UV- spectrophotometric determination of tenatoprazole from its bulk and tablets. Kumaraswamy et al.[75] have reported Spectrophotometric determination of tenatoprazole in bulk drug and pharmaceutical dosage form. The detail are given in Table 1(F).

8.2 Chromatographic methods

Dhaneshwara, et al.[76] have reported LC–UV and LC–MS evaluation of stress degradation behaviour of tenatoprazole.Sugumaran et al.[77] have reported RP-HPLC method for the determination of Tenatoprazole in pharmaceutical formulations Kumaraswamy et al.[78] have reported Development and validation of RP – HPLC method for the estimation of tenatoprazole in bulk and tablet dosage form. Famei et al.[79] have reported HPLC determination and pharmacokinetic study of tenatoprazole in dog plasma after oral administration of enteric-coated capsule. Dhaneshwar et al.[80] have reported Application of a stability-indicating thin-layer chromatographic method to the determination of tenatoprazole in pharmaceutical dosage forms. The detailed chromatographic conditions are described in Table 2(F).

9. Lansoprazole

Lansoprazole, chemically known as 2-[[3-methyl- 4-(2,2,2-trifluoroethoxy) pyridin-2-yl] methylsulfinyl] -1H-benzimidazole. Lansoprazole, a member of the proton-pump-inhibitor 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. Lansoprazole is also indicated as a long-term maintenance therapy in patients with healed reflux esophagitis and healed duodenal ulcer and in the treatment of pathological hypersecretory conditions, such as Zollinger-Ellison syndrome.

As a proton-pump inhibitor, lansoprazole is also a necessary component of dual- and tripletherapy regimens for the eradication of Helicobacter pylori infection. The latest FDA-approved labeling for lansoprazole includes the indication of healing and risk reduction in nonsteroidal anti-inflammatory drug-associated gastric ulcers [81-83].

The absorption of lansoprazole is rapid, with mean Cmax occurring approximately 1. 7 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. Lansoprazole is 97% bound to plasma proteins. Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivativesnof lansoprazole). Lansoprazole 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, lansoprazole has been characterized as a gastric acidpump inhibitor, in that it blocks the final step of acid production [84-86].

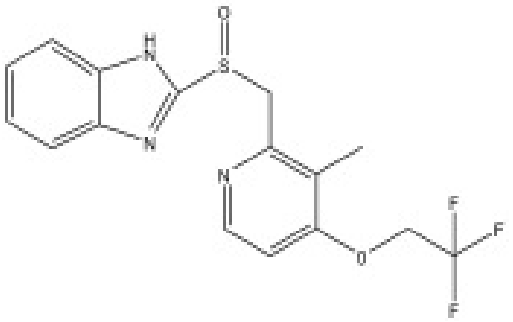


Fig. Structure of Lansoprazole

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 Lansoprazole in commercial dosage forms as well as in bulk and biological fluid.

9.1 Spectral Method

Basavaiah et al.[87] have reported Sensitive spectrophotometric determination of lansoprazole in pharmaceuticals using ceric ammonium sulphate based on redox and complex formation reactions. Sudheer et al.[88] have reported New UV-spectrophotometric method for the determination of lansoprazole in pharmaceutical dosage form and its application to protein binding study. Nuran et al.[89] have reported Determination of lansoprazole in pharmaceutical dosage forms by two different spectroscopic methods. Yeniceli et al.[90] have reported Determination of lansoprazole in pharmaceutical capsules by flow injection analysis using UV-detection. Basavaiah et al.[91] have reported Quantitative determination of

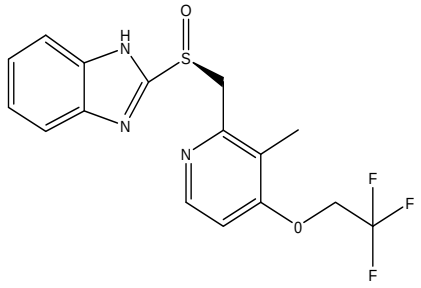
lansoprozole in capsules and spiked human urine by spectrophotometry through ion-pair complex formation reaction. The detail are given in Table 1(G).

9.2 Chromatographic methods

Ramachandran et al[92] have reported Determination of pantoprazole sodium and lansoprazole in individual tablet dosage forms by RP-HPLC using single mobile phase. Muthu Kumar et al.[93] have reported Development and validation Of RP-HPLC method for the estimation of lansoprazole in tablet dosage form. Katsuki et al.[94] have reported Determination Of R(+) and S(-) lansoprazole using chiral stationary phase liquid chromatography and their enantioselactive pharmacokinetics in humans. Nicholas et al.[95] have reported Quantification of lansoprazole in oral suspension by ultra-high-performance liquid chromatography hybrid ion-trap time-of-flight mass spectrometry. Rababah et al.[96] have reported validation of HPLC and FIA spectrophotometric methods for the determination of lansoprazole in pharmaceutical dosage forms and human plasma. Oliveira et al.[97] have reported Lansoprazole quantification in human plasma by liquid chromatography–electrospray tandem mass spectrometry. Masatomo et al.[98] have reported Simultaneous determination of lansoprazole enantiomers and their metabolites in plasma by liquid chromatography with solid-phase extraction. Pandya et al.[99] have reported High-performance thin-layer chromatographic method for the detection and determination of lansoprazole in human plasma and its use in pharmacokinetic studies. Yashiki et al.[100] have reported High-performance liquid chromatographic determination of lansoprazole and its metabolites in human serum and urine. Hisakazu et al.[101] have reported High-performance liquid chromatographic assay for the simultaneous determination of lansoprazole enantiomers and metabolites in human liver microsomes. Zeinab et al.[102] have reported Stability-indicating methods for the determination of lansoprazole. The detailed chromatographic conditions are described in Table 2(G).

10. Dexlansoprazole

Dexlansoprazole is chemically 2-[(R)-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole. Dexlansoprazole is in a group of drugs called proton pump inhibitors. Dexlansoprazole decreases the amount of acid produced in the stomach. Dexlansoprazole is used to treat heartburn caused by gastroesophageal reflux disease (GERD), and to heal erosive esophagitis (damage to the esophagus from stomach acid). Dexlansoprazole may also be used for purposes not listed in this medication guide [103].



Structure of Dexlansoprazole

10.1 Chromatographic methods

Venkateswarulu et al.[104] have reported Development and validation of a highly sensitive LC-MS/MS method for quantitation of dexlansoprazole in human plasma: application to a human pharmacokinetic study. The detailed chromatographic conditions are described in Table 2(H).

11. Conclusion

An overview of the current state-of art analytical methods for determination of Proton Pump inhibitors has been presented. The literature compilation has revealed that a variety of methods are available for Proton Pump inhibitors. For drugs like Tenatoprazole,Dexrabeprazole and Dexlansoprazole only a limited number of methods were reported.Our analysis of the published data revealed that the HPLC was extensively used for estimation of Proton Pump inhibitors in biological fluids. Most of the workers have used the reversed-phase mode with UV absorbance detection because this provided with 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 Proton Pump inhibitors 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 Proton Pump inhibitors. There is a great scope for development of newer analytical methods for latest drugs such as Tenatoprazole.

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