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Review Article

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Analytical method for determination of proton pump inhibitors in bulk and in different dosage forms

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ABSTRACT

Proton pump inhibitor is very effectively used in gastric disorder for reducing acid secretion. They very potent in nature and used only after therapy with histamine-2 (H2) receptor antagonists, known as H2 blockers, have been unsuccessful for symptoms of reflux. PPIs are inactivated by exposure to gastric acid, 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 entitles different methods developed for determination of PPIs like UV-Spectroscopy, liquid Chromatography and LC-MS.

Key words: Proton pump inhibitor (PPI), UV-Spectroscopy, High performance liquid chromatography (HPLC), H2 receptor antagonists, Liquid Chromatography and Mass Spectroscopy (LCMS)

INTRODUCTION

Proton pump inhibitors (PPIs) inhibit the parietal cells in the lining of the stomach from producing too much acid by irreversibly binding to and inhibiting the hydrogenpotassium adenosine triphosphate (H+/K+ ATPase) enzyme system, otherwise known as the “proton pump”[1]

They are most potent inhibitors of acid secretion available that work by reducing the amount of stomach acid made by glands in the lining of your stomach. The most of these drugs are Benzimidazole derivatives, but new research indicates the Imidazopyridine derivatives may be a more effective means of treatment. These drugs are used in the treatment of many conditions, such as: Peptic ulcer disease, Dyspepsia, Laryngopharyngeal reflux, Gastro esophageal reflux disease (GERD). [1]

The proton pump is responsible for secreting H+ ions into the gastric lumen and thus PPIs target on gastric proton pump for inhibiting the acid secretion. Proton pump inhibitors irreversibly block the hydrogen/ potassium adenosine triphosphatase enzyme system (H+/K+ ATPase) of the gastric parietal cells. They are significantly more effective than H2 antagonists and reduce gastric acid secretion by up to 99%.

PPIs are inactivated by exposure to gastric acid, and are generally administered as enteric-coated tablets or capsules that pass through the stomach intact, and are absorbed in the proximal part of the small intestine. [2]

PPIs have a relatively short plasma half-life (approximately 1–2 hours). However, their duration of action is much longer because of their unique mechanism of action. PPIs are lipophilic weak bases that cross the parietal cell membrane, and enter the acidic parietal cell canaliculus. In this acidic environment, the PPI becomes protonated, producing the activated sulphenamide form of the drug that binds covalently with the H+/K+ ATPase enzyme, which results in irreversible inhibition of acid secretion by the proton pump. The parietal cell must then produce new proton pumps or activate resting pumps to resume its acid secretion. [2]

Proton Pump Inhibitors (PPI) includes Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, and 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, HPTLC and LC-MS

Reported methods are categorized depending on the following considerations:
1. Single component PPI analyzed by UV-Spectroscopy methods and Chromatographic method.
2. Analysis of PPI from combination formulation by UV-Spectroscopy methods and Chromatographic method

Table I: Analysis of single component PPIs by UV-spectroscopy methods

Sr. No.	Drug	Method	Description	Ref. No.
1.	**Pantoprazol**e in pharmaceutical dosage forms	Ultraviolet Spectroscopy	**Wavelengths:** 292 nm **Solvent**: water **Linearity range**: 5-70 µg/mL **Correlation coefficient**: 0.9998	3
2.	**Lansoprazole** In Bulk And Pharmaceutical Dosage Forms	Ultraviolet Spectroscopy	**Wavelengths**: 298 nm **Solvent**: 0.01 M Phosphate Buffer of pH 6.8 **Linearity range**: 5-30 µg/ml **Correlation coefficient**: 0.9996 **% Recovery**: 99.8 to 100.2 %	4
3.	**Rabeprazole sodium** tablet	Ultraviolet Spectroscopy	**Wavelengths**:284nm **Solvent**: Methanol **Linearity range**: 4.08- 24.5 µg/ml **Correlation coefficient**: 0.9992	5
4.	**Omeprazole**tablet	Ultraviolet Spectroscopy	**Wavelengths**: 301nm **Solvent:** Methanol **Linearity range:** 5-25µg/ml **Correlation coefficient:** 0.999 **% Recovery ranges :** 101.25%	6
5.	**Ilaprazole** in bulk and pharmaceutical dosage form	UV spectroscopic	**Wavelength:** 307nm **Solvent:** Acetonitrile: ethanol (50:50) **Linearity range**: 2-12µg/ml **Correlation coefficients:** 0.999	7
6.	**Esomeprazole** and **Domperidone**	Ultraviolet Spectroscopy	**Wavelength:** 301 nm λ max of Esomeprazole and 284 nm λ max of Domperidone **Solvent:** methanol **Linearity range:** 5-20 µg/m for Esomeprazole and 8-30 µg/ml for Domperidone.	8
7.	**Rabeprazole Sodium** and **Domperidone** in combined dosage forms	simultaneous equation method by Ultraviolet Spectroscopy	**Wavelengths:** 249 nm for Rabeprazole sodium and 271.5 nm for Domperidone **Solvent:** 0.05 M MethanolicHCl **Linearity range:** 2 to 10 µg/ml for Rabeprazole Sodium and 3 to 15 µg/ml for Domperidone **Correlation coefficient**: 0.9999 for Rabeprazole Sodium and 0.9995 for Domperidone.	9
8.	**Rabeprazole** sodium and **Aceclofenac** capsule	Method-I: simultaneous equation method Method-II: formation of Q-absorbance equation	**Method-I:** **Wavelengths:** 283 nm (λmax of Rabeprazole) and 276 nm (λmax of Aceclofenac). **Solvent:** Methanol **Method-II** **Wavelengths:** 256nm (isoabsorptive point) and 276nm (λmax of Aceclofenac) **Solvent:** Methanol **Linearity range:** 10–60 µg/ml for both methods. **Correlation coefficient**: 0.9981 at 283nm for Rabeprazole sodium and 0.9997 at 276nm for Aceclofenac. **% Recovery ranges:** Method 1: 100.22 for Rabeprazole sodium and 99.96 for Aceclofenac. Method 2: 99.99 for Rabeprazole sodium and 100.05 for Aceclofenac.	10
9.	**Naproxen** And **Esomeprazole**in a Laboratory Mixture	Method 1: Simultaneous Equation Method 2: Absorption Correction Method 3: Absorption Ratio Method 4: Area Under Curve Methods	**Method 1: Simultaneous Equation** **Wavelength:** 232nm for naproxen and 301.5nm for Esomeprazole. **Method 2:Absorption Correction** **Wavelength:** 232nm λmax of naproxen, 239.2nm isoabsorptive point of Naproxen & Esomeprazole. **Method 3: Absorption Ratio** **Wavelength:** 301.5nm **Method 4: Area Under Curve Methods** **Wavelength:** 227-237nm for naproxen and 296.5-	11

			306.5nm for Esomeprazole. **Solvent:** Methanol **Linearity range:** 5µg/ml for naproxen and 4-12µg/ml for Esomeprazole. **% Recovery:** 98.23% for naproxen and 98.87% for Esomeprazole.	
10.	**Omeprazole** and **Cinitapride** in combined dosage	Method-I: simultaneous equation method Method-II: formation of Q-absorbance equation	**Method-I:** **Wavelengths:** 267 nm (λmax of Cinitapride) and 302 nm (λmax of Omeprazole). **Solvent:** Methanol **Method-II** **Wavelengths:** 283 nm (isoabsorptive point) and 267nm (λmax of Cinitapride) **Solvent:** Methanol **Linearity range:** 3-18 µg/ml for both Omeprazole and Cinitapride for both methods. **Correlation coefficient**: 0.999 at 267nm for Cinitapride and 0.997 at 302nm for Omeprazole. **% Recovery ranges :** 99.25 to 102 for both methods	12
11.	**Levosulpiride** and **Esomeprazole** in Capsule Dosage Form	Method-1: simultaneous equations and Method-2: Q-absorbance Ratio method	**Method 1:** **Wavelength:** 234nm λmax for Levosulpiride and 300nm for Esomeprazole **Solvent:** Methanol **Method 2:** **Wavelength:** 234nm λmax for Levosulpiride and 300nm for Esomeprazole and 241 nm is isobestic point **Linearity range:** 1-20 µg/ml at isobestic point.	13
12.	**Granisetron** and **Pantoprazole** in Synthetic Mixture	Derivative Spectroscopy	**Wavelengths:** 248 nm for Granisetron and 291 nm for Pantoprazole. **Solvent:** Methanol **Linearity range:** 2-20µg/ml for Granisetron and over 5-100 µg/ml for Pantoprazole **LOD:** 0.40 µg/ml for Granisetron and 0.62 µg/ml for Pantoprazole **LOQ:** 1.22 µg/ml for Granisetron and 1.89 µg/ml for Pantoprazole	14
13.	**Levosulpiride** and **Rabeprazole** sodium Tablet	Simultaneous equation method, Derivative Spectroscopy	**Wavelength:** 284nm for Rabeprazole sodium and 232 nm for Levosulpiride **Solvent:** methanol **Linearity range:** 1-20 µg/ml for both drugs.	15
14.	**Pantoprazole** and **Levosulpiride** in combined dosage form	Method-1: simultaneous equations and Method-2: Q-absorbance Ratio method	**Method-I:** **Wavelengths:** 287 nm (λmax of Pantoprazole sodium) and 231nm (λmax of Levosulpiride) **Solvent:** Methanol **Method-II** **Wavelengths:** 287 nm (λmax of Pantoprazole sodium) and 231nm (λmax of Levosulpiride) and 248 nm (isoabsorptive point) **Solvent:** Methanol **Linearity range:** 5-30 µg/ml for both methods **Correlation coefficient**: 0.999 for both methods	16
15.	**Esomeprazole** and **Naproxen** in bulk and tablet dosage form	Ultraviolet Spectroscopy	**Wavelengths:** 301.0 nm for Esomeprazole and 262.0 nm for Naproxen **Solvent:** Distilled water **Linearity range:** 5-50 µg/ml for Esomeprazole and 5-50 µg/ml for naproxen	17
16.	**Lansoprazole** and **naproxen** tablet	Ultraviolet Spectroscopy	**Wavelengths:** 284 nm for Lansoprazole and 271 nm for Naproxen. **Solvent:** methanol **Linearity range:**10-35µg/ml for Naproxen and 5-30µg/ml for Lansoprazole **Coefficient correlation**: 0·999 for naproxen and 0·999 for Lansoprazole. **LOD:** 0·04µg/ml for naproxen and 0·5µg/ml for Lansoprazole **LOQ:** 0·15µg/ml for naproxen and 1·7µg/ml for Lansoprazole	18
17.	**Aspirin** and **Lansoprazole** in synthetic mixture	Method 1: Q-Absorption ratio method Method 2: Dual Wavelength Method	**Method 1: Q-Absorption ratio method** **Wavelength:** 299.2 nm isoabsorptive point and 276.6 nm λmax of Aspirin. **Method 2: Dual Wavelength Method** **Wavelength:** Aspirin at the absorbance difference between 272.28 nm and 286.41 nm and Lansoprazole at the absorbance difference between 269.20 nm and 294 nm	19

			Linearity range:33.3-166.6 µg/ml for Aspirin and 5-25µg/ml for Lansoprazole **% Recovery:** 98 to 102%.	
18.	**Omeprazole magnesium** and **Domperidone** from combined solid dosage form	Ultraviolet Spectroscopy	**Wavelengths:** 300 nm for Omeprazole and 287 nm for Domperidone **Solvent:** ethanol **Linearity range:** 4-45µg/ml in both drugs **Correlation coefficient:** 0.99 **% Recovery ranges :** 101.4% for Omeprazole and 104.9% for Domperidone	20
19.	**Itopride Hydrochloride** and **Lansoprazole** in Synthetic Mixture	First order Derivative	**Wavelength:**244.12 nm for Itopride Hydrochloride and 278.12nm for Lansoprazole **Solvent:** methanol **Linearity range:** 5-25µg/ml for both of the drug **Coefficient correlation:** 0.999 for Itopride Hydrochloride and0.996 for Lansoprazole	21
20.	Process-Related Impurities In **Pantoprazole** Bulk Drug And Formulations	Stability Indicating HPLC	**Stationary phase:** Hypersil ODS column **Mobile phase:** 0.01 M phosphate buffer of pH 7 and Acetonitrile as eluent **Flow rate**: 1 ml/min **Detection wavelength**:290 nm **Linearity range:**0.1 to 2 µg/ml **Correlation coefficient:** 0.999 **5.%Recovery**: 97.9-103% **L6.OD:** 0.043-0.047 µg/ml **LO7.Q:**0.13-0.14 µg/ml	22
21.	**Rabeprazole** in Pure and Tablet Dosage Form	RP-HPLC	**Statio8.nary phase:** RP-C18 column (150mm x 4.6 m9m I.D, 5 µm particle size) **Mobile phase:** methanol: water65:35 v/v **Flow rate**: 0.8 ml/min **Wavelength:** 284 nm **Retention time**: 4.41±0.05 **Linearity range:** 0.25-20 µg/ml **Correlation coefficient**: 0.9999 **LOD:** 100 ng/ml	23
22.	**Ilaprazole** and **its metabolites** in human plasma	LC-MS/MS	**Stationary phase:** Thermo HyPURITY C18 column (150×2.1 mm, 5 µm) **Mobile phase:** 10 mmol/L Ammonium formate water-Acetonitrile solution (50:50, *v/v*) **Flow rate**: 0.25 mL/min **Linearity range:** 0.23−2400.00 ng/mL for Ilaprazole, 0.05−105.00 ng/mL for Ilaprazolethiol ether and 0.06−45.00 ng/mL for Ilaprazole sulfone **Lower limit of quantification (LLOQ):** 0.23ng/mL for Ilaprazole, 0.05ng/mL Ilaprazole thiol ether and 0.06ng/mL for Ilaprazole sulfone.	24
23.	**Lansoprazole tablet**	RP-HPLC	**Stationary phase:** Phenomenex Luna C8, (5µ, 250 mm × 4.6 mm id) **Mobile phase:** disodium hydrogen phosphate buffer of pH 3.0, and Acetonitrile (30: 70) **Wavelength:** 285 nm **Flow rate**: 1.0 ml / min **Linearity range:** 40-60 µg/ml **Retention time**: 8.82 min	25
24.	**Pantoprazole** in injection	HPTLC	**Stationary phase:** silica gel 60 F_{254} **Mobile phase:** Tolune :Ethyl Acetate: Methanol: AceticAcid (7:2:1:0.1v/v/v/v) **Wavelength:**290nm **Linearity range:** 50-800 nano/spot **% Recovery ranges:** 98.16-100.5% **LOD:**8.45 ng/spot **LOQ:**25.60 ng/spot	26
25.	**Omeprazole** enantiomers in the enteric coated formulations	NP-HPLC	**Stationary phase:** Chiralcel ODH analytical column (250mm × 4.6mm, 5μm particle size) **Mobile phase:** 85% of n hexane, 8% of methanol and 7% a mixture of isopropylalcohol and ethanol (85:15, v/v). **Flow rate**: 0.75 ml/min **Injection volume**: 5 μl **Wavelength:** 301nm Linearity range: 0.39800μg/ml **Correlation coefficient**: 0.999 for (S) and (R)Omeprazole **% Recovery ranges:** 93.5 to 104 for (R) Omeprazole **LLOD:** (R)Omeprazole 0.39 μg/ml	27

			LLOQ: (R)Omeprazole 0.78 μg/ml	
26.	**Omeprazole**in bulk and capsule dosage forms	RP-HPLC	**Stationary phase:** Novapak C18, (250 x 4.6 mm, 5µ) **Mobile phase:** Phosphate buffer (pH 7.4) : Acetonitrile (60:40, v/v) **Flow rate**: 1.0 ml/min **Injection volume**: 20 µl **Wavelength:** 302 nm. **Retention time:** 7.71 min. Linearity range: 20-60 ppm	28
27.	**Esomeprazole** in Bulk and Pharmaceutical Dosage Form	RP-HPLC	**Stationary phase:** C18 analytical column (250 mm × 4.6 mm i.d., 5.0 µm) **Mobile phase:** Acetonitrile and phosphate buffer (pH 7.4) in ratio of 50:50 v/v **Flow rate**: 1.0 ml/min **Wavelength:** 302nm **Retention time**: 6.5min **Linearity range:** 25-150µg/ml **Correlation coefficient**: 0.9991 **LOD:** 0.015µg/ml **LOQ:** 0.04µg/ml	29
28.	**Omeprazole Enantiomers In The Enteric-Coated Formulations**	Stability Indicating Chiral-HPLC	**Stationary phase:** Chiralcel OD-H analytical column (250mm × 4.6 mm, 5μm particle size) **Mobile phase:** Isopropylalcohol and ethanol (85:15, v/v) **Flow rate**: 0.75 ml/min **Detection wavelength**: 301nm **Linearity range:**0.39-800μg/ml **Correlation coefficient:** 0.999 for (S)- and (R)-omeprazole **%Recovery**: 93.5 to 104 % **LLOD:** 0.39μg/ml **LLOQ:** 0.78 μg/ml	30
29.	**Lansoprazole** and its Impurities in Bulk Drug and Pharmaceutical Dosage Forms	Stability-Indicating UPLC	**Stationary phase:** BEH C18 column **Mobile phase:** **Mobile phase A:** pH 7.0 phosphate buffer and methanol (90: 10 v/v) **Mobile phase B:** methanol and Acetonitrile (50:50 v/v) **Wavelength:** 285 nm **Flow rate**: 0.3 mL/min	31
30.	**Lansoprazole** Tablet	RP-UPLC	**Stationary phase:** Phenomenex Luna C18 (5µm ~25cm ~4.6mm) **Mobile phase:** methanol: water (80:20 v/v) **Wavelength:** 284 nm **Flow rate**: 1.0 mL/min **Linearity range:** 50-30 µg/ml **Retention time**: 3.905 min **Correlation coefficient**: 0·998	32
31.	**Pantoprazole** tablet	RP-HPLC	**Stationary phase:** BDS Thermohypersil Symmetry C8 column(250 x 4.6mm x 5 µ) **Mobile phase:** Methanol: Dipotassium hydrogen phosphate buffer(pH-9) (50:50) **Flow rate**: 1.2ml/min **Wavelength:** 226nm **Retention time:** 4.189min Linearity range:50-150 µg/ml **Correlation coefficient:** 0.999 **LOD:** 0.1958µg/ml **LOQ**: 0.5934µg/ml	33
32.	**Ilaprazole** Pharmaceutical dosage forms	RP-HPLC	**Stationary phase:** Hypersil BDS C18 (4.6 x 250 mm) column **Mobile phase:** Methanol: Water 70:30 pH-3.0 **Flow rate**: 1.0 ml/min **Detection wavelength**: 237 nm **Retention time:** 4.4 minutes **Linearity range:** 5-25 µg/ml	34
33.	**Ilaprazole** And Its Related Compounds In Pharmaceutical Dosage Forms	UPLC	**Stationary phase:** Acquity BEH SHIELD RP18 column (1.7 µm, 2.1 mm × 150 mm) **Mobile phase:** Acetonitrile: Methanol and ammonium acetate buffer (0.05 M; pH 8.5 adjusted with NaOH solution) **Flow rate**: 0.25 mL/min **Detection wavelength**: 305 nm **Linearity range:** 0.05 to 0.60 µg/mL **LOD:** 0.015 to 0.021 µg/mL	35

34.	**Ilaprazole** in bulk drug and tablets	Stability indicating HPLC	**Stationary phase:** Kinetex C-18 100A (5µ, 250×4.6 mm) **Mobile phase:** Acetonitrile: water (50:70v/v) for 1 min then changed to 70:30v/v in next 6 min and finally equilibrated back to initial composition in 14min **Flow rate**: 1.0ml/min **Injection Volume**: 20µl **Detection wavelength**: 305 nm **Linearity range:** 5-15 µg/ mL **LOD:** 0.05µg/ml **LOQ:** 0.14 µg/ mL **%Recovery**: 99.27%	36
35.	**Domperidone** and **Lansoprazole** capsule	HPTLC	**Stationary phase:** pre-coated silica gel plate 60 F_{254} **Mobile phase:** toluene: isopropyl alcohol: chloroform: Acetonitrile (4:3:6:2) **Wavelength:** 254 nm **R_f values:** 0.22 for Domperidone and 0.76 for Lansoprazole	37
36.	**Lansoprazole** and **Domperidone**	RP-HPLC	**Stationary phase:** RP-C18 column **Mobile phase:** Acetonitrile: Methanol (81:19) **Flow rate:** 1 ml/min **Retention time:** 2.8min for Lansoprazole and 1.57 min for Domperidone **Wavelength:** 280 nm **Linearity range:** 8-24µg/ml of Lansoprazole and 8-24µg/ml of Domperidone **Coefficient correlation**: 0.9977 for Lansoprazole and 0.9992 for Domperidone.	38
37.	**Pantoprazole** and **Domperidone** Tablets	RP-HPLC	**Stationary phase:** Hypersil, BDS, C-18 (150×4.6 mm, 5 micron) **Mobile phase:** Potassium dihydrogen phosphate buffer - Acetonitrile (720:280v/v) **Flow rate**: 1.0 ml/min **Wavelength:** 280 nm **Linearity range:** 10-60 µg/ml for Pantoprazole and 5-30 µg/ml for Domperidone	39
38.	**Naproxen** and **Esomeprazole** in pharmaceutical formulations	Stability indicating RP-HPLC	**Stationary phase:** Xterra RP-18 column (150 × 4.6 mm, 5µ) **Mobile phase:** Buffer, Acetonitrile and Methanol in the ratio of (70:20:10) v/v/v **Flow rate**: 1.5 ml/min **Wavelength:** 305 nm **Linearity range:** 100.28 to 902.520 µg per ml for Naproxen and 9.6 to 45.6 µg per ml for Esomeprazole.	40
39.	**Esomeprazole** and **Naproxen** in Binary Combination	RP-HPLC	**Stationary phase:** Phenomanex, Luna C18 column (5 µm, 150mm × 4.60mm) **Mobile phase:**Acetonitrile: phosphate buffer (pH 7.0) Acetonitrile: phosphate buffer (pH 7.0). **Flow rate**: 0.5 ml/min **Wavelength:** 300 nm **Retention time:** 2.67 ±0.014min for Esomeprazole and 5.65 ±0.09 min for Naproxen.	41
40.	**Rabeprazole Sodium** and **Aceclofenac** in Bulk Drug and Formulation	HPTLC	**Stationary Phase:** Precoated silica gel 60F254 aluminum plate. **Mobile Phase:** Toluene: Ethyl Acetate: Methanol: Acetic Acid 6: 4: 1: 0.2 (v/v/v/v) **Wavelength**: 279nm **Linearity range:** 100 to 200 ng/spot for Rabeprazole sodium and 1000 to 2000 ng/spot for Aceclofenac **Correlation Coefficient:** 0.997 for Rabeprazole sodium and 0.998 for Aceclofenac **% Recovery:** 99.12 % for Rabeprazole sodium and 99.99 % for Aceclofenac.	42
41.	**Rabeprazole sodium** and **Aceclofenac** in tablet	RP-HPLC	**Stationary Phase:** Pursuit C-18 column (250 mm x 4.6 mm i.d., 5 µm) **Mobile Phase:** methanol: Acetonitrile: water (60: 10: 30 v/v/v) **Flow Rate:** 1 ml/min **Wavelength**: 280 nm **Retention Time:** 5.611 min for Rabeprazole Sodium. And 2.102 min for Aceclofenac. **Linearity range:** 1-10 µg/ml for Rabeprazole Sodium and 3-15 µg/ml for Aceclofenac. **LOD:** 0.091µg/ml for Rabeprazole sodium and	43

			0.043µg/ml for Aceclofenac.	
42.	**Esomeprazole** Magnesium and **Domperidone** in Combined Dosage	RP-HPLC	**Stationary phase:** Hyper chrome C-18 (4.6´150 mm, 5µ particle size) **Mobile phase:** Acetonitrile: phosphate buffer (pH 5.0) (60:40 (v/v)) **Flow rate**: 1.0 ml/min **Wavelength:**290 nm **Retention time:** 3.91 min for Esomeprazole Magnesium and 2.92min Domperidone **Linearity range:** 10-50 µg/ml for Esomeprazole Magnesium and 5-25 µg/ml for Domperidone **Coefficient correlation:** 0.999 for both the drugs. **%Recovery:** 99.38% for Esomeprazole Magnesium and 96.26% for Domperidone	**44**
43.	**Aspirin** and **Esomeprazole Magnesium** Tablet	RP-HPLC	**Stationary phase:** Hyper Chrom ODS-BP C18 column (200 mm × 4.6 mm; 5.0 $\mu\mu$m) **Mobile phase:**Acetonitrile: Methanol: 0.05 M phosphate buffer at pH 3 (25 : 25 : 50, v/v) **Flow rate:**1 mL/min **Wavelength:** 230 nm **Retention time:** 4.29 min for aspirin and 6.09 min for Esomeprazole magnesium **Linearity range:**10–70 μg/mL for aspirin and 10–30 μg/mL for Esomeprazole magnesium **Coefficient correlation:** 0.9986 for aspirin and 0.9973 for Esomeprazole magnesium **%Recovery**: 99.80–100.57% for aspirin and 99.70–100.83% for Esomeprazole magnesium.	**45**
44.	**Levosulpiride** and **Esomeprazole** Capsule	RP-HPLC	**Stationary phase:**C-18 (5µm, 250×4.6 mm) HPLC column **Mobile phase:** Methanol: Buffer (pH 3) (65:35% *v/v*) **Flow rate**: 1.0 ml/min **Wavelength:** 260 nm. **Retention time:** Levosulpiride at 2.7 min and Esomeprazole at 5.7 min. Linearity range: 5 to 30 µg mL-1 for Esomeprazole and 10 to 60 µg/ mL for Levosulpiride. **Coefficient correlation:**0.9995 for Esomeprazole and 0.9993 for Levosulpiride.	**46**
45	**Levosulpirid**e and **Rabeprazole sodium** Tablet	UV and RP-HPLC	**Method I: Simultaneous equation method** **Wavelength:** 232 nm (λmax of Levosulpiride) and 284 nm (λmax of Rabeprazole Sodium) **Solvent:** Methanol **Method II: 1st order derivative method** **Wavelength:** 247 nm for Levosulpiride and 291.60 nm for Rabeprazole Sodium **Solvent:** Methanol **Method III:RP-HPLC method** **Stationary phase:** Phenomenexluna ODS C18 (250mm X 4.6 mm i.d., 5 µm particle size) **Mobile phase:** Acetonitrile: 50 mM phosphate buffer pH 5 (55:45 v/v.) **Flow rate**:1.0 ml/min, **Injection volume:** 20µl **Detection wavelength**: 288 nm **Retention time:** Levosulpiride 2.31±0.1min and Rabeprazole Sodium 3.85 ±0.1min, **Linearity range:** 5-30 µg/ml for Levosulpiride and 2-12 µg/ml for Rabeprazole Sodium	**47**
46.	**Lafutidine** And **Rabeprazole Sodium** tablet	RP-HPLC	**Stationary Phase:** Thermo Hypersil, C18 column, 250 mm × 4.6 mm **Mobile Phase:** Acetonitrile**:**0.02M Potassium dihydrogen orthophosphate pH 7.2 (50:50 v/v) **Flow Rate:** 1.5ml/min **Wavelength**: 215 nm **Retention Time:** 2.99 min for Rabeprazole Sodium and 8.13 min for Lafutidine. **Linearity range:** 40-120 µg/ml for Lafutidine and 80-240 µg/ml for Rabeprazole Sodium.	**48**
47.	**Pantoprazole** sodium and **Itopride hydrochloride** in its bulk dosage forms	RP-HPLC	**Stationary phase:** c18 column (150mm× 4.6mm ,5mm) **Mobile phase:** Acetonitrile : Phosphate buffer (40:60) **Flow rate**: 1ml/min **Wavelength:** 207nm	**49**

			Retention time: for Pantoprazole sodium 3.52min and for Itopride Hydrochloride 2.51 min **Linearity range:** 2.6-13 mg/ml for Pantoprazole sodium and 10-60 mg/ml Itopride **Correlation coefficient:** 0.999 **Resolution** :5.314min	
48.	**Omeprazole** and **Ketoprofen** in a Developed Tablet Formulation	HPTLC	**Stationary phase:**coated with silica gel $60F_{254}$ **Mobile phase:** chloroform: methanol 9:1 (v/v) **Wavelength:** 283 nm **Resolution:** Rf value 0.45± 0.02 for OME and 0.32± 0.02 for KET **Linearity range:** 30-120 ng/ band for OME and 150-600 ng/ band for KET **Correlation coefficient:** 0.999 for both OME and KET **% Recovery ranges :** 98.9-100.8%	**50**
49.	**Rabeprazole, Pantoprazole,** and **Itopride**	RP-HPLC	**Stationary phase:** Phenomenex C18 (Luna) column (250 mm ×4.6 mm, dp ¼ 5 mm) with C18 guard column (4 mm ×3 mm ×5 mm) **Mobile phase:** 10 mM Potassium dihydrogen orthophosphate (adjusted to pH 6.8): Acetonitrile (70:30 v/v) **Flow rate**: 1.0 mL/min **Wavelength:** 288 nm **Retention time:** 5.35min Rabeprazole, 7.92min Pantoprazole, and 11.16min Itopride. **Linearity range**: 2.5-25µg/ml for Rabeprazole, 1-30µg/ml for Pantoprazole and 3-35µg/ml for Itopride **Correlation coefficient:** 0.994 for Rabeprazole, 0.978 for Pantoprazole, and 0.991 and Itopride. **LOD**: 1µg/ml for Rabeprazole, 0.3 for Pantoprazole, and 1 µg/ml for Itopride **LOQ:** 2.5µg/ml for Rabeprazole, 1µg/ml for Pantoprazole, and 3 mg/ml for Itopride.	**51**
50.	**Clopidogrel, Pantoprazole** and **Rosuvastatin** in human plasma	RP-UFLC	**Stationary phase:** Phenomenex C8 (250 × 4.6 mm, 5µm) **Mobile phase:** Phosphate buffer (pH-2.5) and Acetonitrile (45: 55 v/v) **Flow rate**: 1.2 mL/min **Injector volume:** 20 µl **Wavelength:** 254nm for Clopidogrel, 243nm for Pantoprazole and 220nm for Rosuvastatin **Retention time:** 2.566min for Clopidogrel, 5.002min for Pantoprazole and 9.301min for Rosuvastatin **Linearity range:** 5 to 50µg/mL of Clopidogrel, Pantoprazole &Rosuvastatin.	**52**
51.	**Rabeprazole Sodium** And **Mosapride Citrate** In Bulk And Formulation	Stability Indicating RP-HPLC	**Stationary Phase:** Thermo Inert Silca, C_{18} (250 X 4.6 Mm I. D., 5 M) **Mobile Phase:** Methanol: Buffer (Ammonium Acetate Ph 6.5): Acetonitrile (50:20:30 %) **Flow Rate:** 1.0 ml/min **Wavelength:** 245 nm **Retention Time:** 2.951 min For Rabeprazole Sodium and 4.195 min For Mosapride Citrate **Correlation Coefficient:** 0.999 For both of the drug **% Recovery:** 97-103 % For Rabeprazole Sodium and 98-102 %, For Mosapride Citrate	**53**
52.	**Rabeprazole Sodium** and **Lafutidine** in Bulk and Pharmaceutical dosage	RP-UPLC	**Stationary Phase:** Phenomanex, C18 column, 150 × 2.5 mm **Mobile Phase:** Acetonitrile: buffer (0.01 M Potassium di-hydrogen orthophosphate) pH 6.8 (60:40% v/v) **Flow Rate:** 1.2ml/min **Wavelength:** 215 nm **Retention Time:** 3.1min for Rabeprazole Sodium and 5.8min for Lafutidine **Linearity range:** 40-120µg/ml, for Lafutidine and 80-240µg/ml for Rabeprazole Sodium	**54**
53.	**Levosulpiride** and **Rabeprazole** sodium Tablet	Stability indicating RP-HPLC	**Stationary phase:** Hypersil BDS C18 250mm × 4.6mm ×5/m **Mobile phase:** Buffer: Acetonitrile (72:28) **Flow rate**: 1.5ml/min **Wavelength:** 282nm **Retention time:** Levosulpiride 2.23 min and Rabeprazole sodium 7.27min	**55**
54.	**Levosulpiride** and **Esomeprazole**	HPTLC	**Stationary phase:** Precoated aluminum plates with	**56**

	Capsule		silica gel 60 F254 **Mobile phase:** ethyl acetate: methanol: ammonia (9: 1: 0.5, v/v/v) **Wavelength:** 216 nm. **Retardation factor (*Rf*):** 0.30 ± 0.02 for Levosulpiride and 0.64 ± 0.02 for Esomeprazole. **Linearity range:** 100-1000 ng band-1 for both Levosulpiride and Esomeprazole	
55.	**Lansoprazole** and **Metronidazole** in Pharmaceutical Dosage Form	RP-HPLC	**Stationary phase:** Phenomanex C18 column (25 cm × 4.6 mm i.d., 5 µ) **Mobile phase:** Acetonitrile ,water and Triethanol amine (40:60:1 v/v) **Flow rate:** 1.0 ml/min injection volume was 20 µl **Retention time:** 14min for Lansoprazole and 10.13 min Metronidazole **Wavelength:** 290 nm. **Linearity range:** 5-25 µg/ml for Metronidazole and 2-10 µg/ml for Lansoprazole	**57**
56.	**Domperidone** And **Ilaprazole** capsule	Chemo metrics assisted RP-HPLC for the simultaneous estimation	**Stationary phase:** Phenomenex C18 column (150 X 4.6 mm i.d, 5µ particle size) **Mobile phase:**64.89% of Acetonitrile and 35.11 % of Ammonium acetate buffer (14.18mM) **Flow rate**: 1.2 mL/min **Detection wavelength**: 286nm **Retention time:**1.661min for Domperidone and 2.420min for Ilaprazole **Linearity range:** 30-90µg/ml for Domperidone and 10-30 µg/ml for Ilaprazole **Correlation coefficient:** 0.9997 for Domperidone and 0.9995 for Ilaprazole. **LOD:** 58.12ng/ml for Domperidone and 101.68 ng/mL for Ilaprazole **LOQ:** 479.16ng/mL for Domperidone and 308.12ng/mL for Ilaprazole.	58
57.	**Ilaprazole** and **Domperidone** in their Combined Dosage Form	RP-HPLC	**Stationary phase:** Inertsil C-18 column, (5 µm, 250mm x 4.6mm i.d) LC-20 AT **Mobile phase:** Phosphate Buffer (pH 3): Methanol (40:60 v/v) **Flow rate:**1.0 ml/min **Retention time:** 4.21min for Ilaprazole and 6.4min for Domperidone **Resolution:** 9.636 **Linearity range:** 5 – 15 µg/ml for Ilaprazole and 15 - 45 µg/ml for Domperidone **Correlation coefficient:** 0.999 for both of the drug **Detection wavelength:** 229 nm isobestic point of Ilaprazole and Domperidone **LOD:** 0.347µg/ml for Ilaprazole and 1.04µg/ml for Domperidone. **LOQ:** 1.05µg/ml for Ilaprazole and3.16µg/ml for Domperidone.	59
58.	**Lansoprazole** and**PaliperidonePalmitate** in Bulk Drugs	RP-HPLC	**Stationary phase:** Agilent TC 1120 RP 18 column **Mobile phase:** Methanol : Acetonitrile (60:40 v/v) **Flow rate:** 1.5 mL/min **Retention time:** 2.2 min for Lansoprazole and 5.76 min for Paliperidone Palmitate **Wavelength:** 285 nm. **Linearity range:** 30-70 ppm for Lansoprazole and 120-280 ppm for Paliperidone Palmitate **Coefficient correlation**: 0.997±0.257 for Lansoprazole and 0.998±0.359 for Paliperidone Palmitate.	60
59.	**Aspirin** and **Lansoprazole**	RP–HPLC	**Stationary phase:** Phenomenax-luna C18 (250 x 4.6mm, 5 µm) **Mobile phase:** Acetonitrile : Tris buffer : Methanol (30:40:30 % v/v/v) **Flow rate:** 1.2 ml/min **Wavelength:** 280 nm **Linearity range:** 13.2 – 66.0 µg/ml for Aspirin and 2 - 10 µg/ml for Lansoprazole.	61

CONCLUSION

This review represents the reported spectrophotometric and chromatographic methods; developed and validated for determination of proton pump inhibitors According to the literature review I concluded that for Proton pump inhibitor (Pantoprazole, Lansoprazole, Omeprazole, Rabeprazole, Esomeprazole and Ilaprazole) in single component and its combination with other drug spectroscopy and chromatography method available. This all methods found to be simple, accurate, economic, precise, and reproducible in nature. Comparing various validation parameters of already reported methods, it can be concluded that different analytical methods like spectrophotometric, HPTLC and HPLC can be developed for PPIs showing its simplicity, sensitivity (low LOD and LOQ values) linearity and accuracy. Most of the workers have used the reversed-phase HPLC and UV absorbance detection because this provided with best available reliability, repeatability, analysis time and sensitivity. Most common combination of PPIs is with Levosulpiride and Domperidone. There is a great scope for development of newer analytical methods for latest drugs such as Ilaprazole

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