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Spectrophotometric and Chromatographic Methods for Anti-Ulcer Drugs: A Review

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ABSTRACT: In this review, we introduced most of the reported spectrophotometric and chromatographic analytical methods developed with analytical equipment such as UV-visible spectrophotometers, high-performance liquid chromatography, reversed-phase high-performance liquid chromatography, and ultra-high-performance liquid chromatography. And which was developed to describe certain anti-ulcer drugs such as H2 antihistamines, proton pump inhibitors, prostaglandin analogues, and Ulcer protective. Development of spectrophotometric and chromatographic methods and their evaluation of pure forms, pharmaceutical compounds, human plasma, and other biological fluids. Validation parameters mainly addressed flow rate, wavelength, linearity, LOD, and LOQ.

KEYWORDS: Anti-ulcer drugs, Analytical equipment, H2 antihistamines, Proton pump inhibitors, Prostaglandin analogues, Ulcer protective.

I. INTRODUCTION:

Peptic ulcers are local erosions of the mucous membranes of the stomach and duodenum. The pain associated with ulcers is caused by irritation of exposed surfaces caused by stomach acids. The most commonly used anti-ulcer agents are H2-antihistamines, proton pump inhibitors, prostaglandin analogs, and ulcer protectives. This review sheds light on all reported methods developed for the determination of pure forms of antiulcer drugs, pharmaceutical compounds, human plasma, and other biological fluids (e.g., chromatography and spectrophotometry).

TABLE 1: Classification of anti-ulcer agents

CATEGORY	DRUGS
H2 Anti histamines	Cimetidine Ranitidine Famotidine
Proton pump inhibitors	Omeprazole Esomeprazole Pantoprazole Lansoprazole Rabeprazole
Prostaglandin analogue	Misoprostol
Ulcer protective	Sucralfate

II. H2 ANTI HISTAMINES:

The selective histamine type 2 receptor antagonists/blockers (H2 blockers) are widely used in the treatment of acid-peptic disease, including duodenal and gastric ulcers, gastroesophageal reflux disease and common heartburn. The four H2 blockers in current use are available by prescription as well as over-the-counter, and are some of the most widely used drugs in medicine.

The H2 receptor blockers act by binding to histamine type 2 receptors on the basolateral (antiluminal) surface of gastric parietal cells, interfering with pathways of gastric acid production and secretion. The selectivity of H2 blockers is of key importance, as they have little or no effect on the histamine type 1 receptors, which are blocked by typical antihistamines that are used to treat allergic reactions and have little effect on gastric acid production. The selective H2 blockers are less potent in inhibiting acid production than the proton pump inhibitors (which block the common, final step in acid secretion) but, nevertheless, suppress 24hour gastric acid secretion by about 70%. The effect of H2 blockers is largely on basal and nocturnal acid secretion, which is important in peptic ulcer healing. The selective H2 blockers were first developed in the early 1990s by Sir James Black, who subsequently received the Nobel Prize for his work developing selective

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receptor antagonists for clinical use (including the beta blockers as well as the H2 blockers). The initial H2 blocker approved for use in the United States was cimetidine (1977), which was followed by ranitidine (1983), and famotidine (1986). All three of these agents are available by prescription and as over-the-counter oral formulations. Intravenous and intramuscular forms are available for cimetidine, ranitidine and famotidine. [1]

Mechanism of action:

H2 antagonists inhibit gastric acid secretion elicited by histamine and other H2 agonists in a dose dependent, competitive manner; the degree of inhibition parallels the concentration of the drug in plasma over a wide range. The H2 antagonists also inhibit acid secretion elicited by gastrin and, to a lesser extent, by muscarinic agonists. Importantly, these drugs inhibit basal (fasting) and nocturnal acid secretion and that stimulated by food, sham feeding, fundic distention, and various pharmacological agents; this property reflects the vital role of histamine in mediating the effects of diverse stimuli. [2]

Ranitidine hydrochloride:

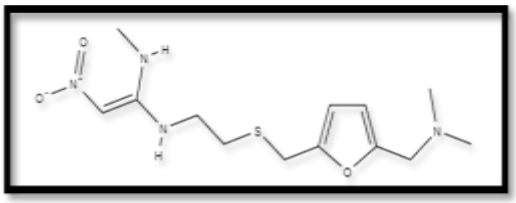

FIGURE 1: Structure of Ranitidine

IUPAC Name: (E)-1-N'-[2-[[5-[(dimethylamino)methyl]furan-2-yl]methylsulfanyl]ethyl]-1-N-methyl-2-nitroethene 1,1-diamine [3]

Spectrophotometric methods:

Basavaiah K et al. described the determination of ranitidine hydrochloride as an oximetic reagent with potassium bromate and acid dyes, methyl orange, indigo carmine, and methane yellow. With a direct titrometer (Method A), the drug is titrated directly with bromate in an acidic medium and in the presence of an excess of bromide, using methyl orange as an indicator. In back titrimetry (method B), the drug is treated with a measured excess of bromate in the presence of bromide and acid, and the unreacted bromine is determined iodometrically. Both spectrophotometric methods are based on the oxidation of ranitidine hydrochloride with a known excess of bromate in an acidic medium or in the presence of an excess of bromide and measuring the absorbance at 610 or 530 nm. [4]

Darwish I et al. described a sensitive spectrophotometric method for the determination of H2-receptor antagonists using a fully developed and validated ranitidine hydrochloride. The method was based on the reaction of these drugs with NBS and subsequent measurement of the excess of N-bromosuccinimide (NBS) upon its reaction with p-aminophenol to give a violet-colored product (λmax at 552 nm), and corresponding drug concentrations were observed with a good correlation coefficient (0.9988–0.9998) in the concentration range of 4–20 mg ml^{-1}. The limits of detection for ranitidine were 0.74 mg ml^{-1}. [5]

Another method described by Darwish et al. A spectrophotometric method was developed and validated for the determination of H2-receptor antagonists: ranitidine hydrochloride. The method was based on oxidizing these drugs with cerium (IV) in the presence of perchloric acid and then measuring the excess of Ce (IV) through this reaction. with p-dimethylaminobenzaldehyde to give a red product (λmax at 464 nm) with good correlation coefficients (0.9990-0.9994) in the concentration range of 1–20 g ml^{-1}. [6]

Walash M.I. et al. described a kinetic spectrophotometric method based on the catalytic effect of ranitidine on the reaction between sodium azide and iodine in aqueous solution. The calibration curve was linear between 4 and 24 μg/ml. The drug was determined by measuring the decrease in iodine absorbance at 348 nm using the fixed time. The decrease in absorption 1 minute after the onset of the reaction was related to drug concentration. The detection limit of the method was 0.76 g/ml. The proposed method was successfully used in the determination of the drug in pharmaceutical preparations, with an average yield of 99.83 to 101.16%. [7]

Khalil MM et al. A sensitive spectrophotometric method is proposed for the determination of ranitidine hydrochloride drug in pure form and dosage forms. The method was based on the formation of ranitidine hydrochloride ion pairs with various dyes such as methyl orange (MO), bromocresolviol (BCP), eriochromicyanin R (ECR), and alizarin red S (ARS). The resulting ion pairs were measured spectrophotometrically at 408, 420, 330, and 326 nm using BCP, MO, ECR, and ARS reagents, respectively. These results were also confirmed with percentage yields of 99.78-

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100.52%, 99.86-101.12%, 99.82-100.31%, and 100.18-101.25% for reagents BCP, MO, ECR, and ARS. [8]

Chromatographic methods:

HPLC method:

Oh C et al. Chromatographic methods have been widely used for the determination of ranitidine in its pure form, in pharmaceutical preparations, or in biological fluids. These methods include the HPLC method for the determination of ranitidine in commercial products. An Inertsilr ODS-2 column was used, and the mobile phase was 0.04 M aqueous sodium dihydrogen phosphate, acetonitrile, methanol, and triethylamine (345:20:35:0.7, v/v/v/v). The detection wavelength was set to 230 nm. [9]

Kokoletsi M X et al. An HPLC method was developed for the simultaneous determination of ranitidine in oral liquids. Chromatographic separation was performed by HPLC using a mixture of 0.5 M ammonium acetate, acetonitrile, and methanol as the mobile phase, a Nucleosil C18 column, and UV detection at 254 nm.[10]

RP-HPLC method:

Sharma N Reported A stability-indicating RP-HPLC method was developed for the determination of ranitidine in the presence of its impurities, forced degradation products, and placebos such as saccharide and paraben. Chromatographic separation was achieved on an ACE C18 column using a gradient mixture of two solvents. The first solvent is a mixture of phosphate buffer (pH 6.5) and acetonitrile (98:2, v/v). The second is a mixture of water and acetonitrile (5:95, v/v). Ultraviolet detection was performed at 230 nm. [11]

Tatar Ulu S et al. An RP-HPLC method for the determination of ranitidine in human plasma with fluorescence detection was described. The method was based on the reaction of ranitidine with 4-fluoro-7-nitrobenzo-2-oxa-1,3-diazole (NBD-F), resulting in the formation of a yellow fluorescent channel. The separation was carried out on a C18 column using methanolic water (60:40, v/v) as the mobile phase. Fluorescence detection was used with excitation and emission at 458 and 521 nm, respectively. [12]

HPTLC method:

Novakovic J. described that there are HPTLC methods used for the determination of ranitidine HCl in pharmaceutical preparations. Separation was performed on silica-precoated plates using a U.S.P. XXIII mobile phase: toluene:methanol:diethylamine (9:1:1, v/v/v). Samples were automatically placed on the HPTLC plate. Quantification was performed densitometrically by in situ UV absorption at 320 nm. [13]

Kelani MK et al. A HPTLC method for the determination of ranitidine in the presence of its sulfoxide derivatives. The latter method involved quantitative densitometric evaluation of a mixture of the drug and its derivatives after separation by high-pressure thin-layer chromatography on silica gel plates using ethyl acetate:methanol:20% ammonia (10:2:2, v/v/). (v) as a mobile phase. [14]

GC method:

Majidano S A et al. Capillary gas chromatography (GC) was developed for the determination of ranitidine drug formulation after pre-column derivatization with methylglyoxal (MGo). GC was performed using an HP-5 column (30 m 9 x 0.32 mm) at an initial column temperature of 90 C for 2 min, followed by heating at 25 C min^{-1} to 265 C. The flow of nitrogen was 2.5 ml min-1, with a distribution ratio of 10:1. A linear calibration curve was obtained between 50 and 1000 ng ml^{-1}, and the limit of detection (LOD) was 17–25 ng ml^{-1}. Derivatization, GC elution, and separation were reproducible with a relative standard deviation of ± 4.6% for retention time and peak height/peak area. [15]

Cimetidine hydrochloride:

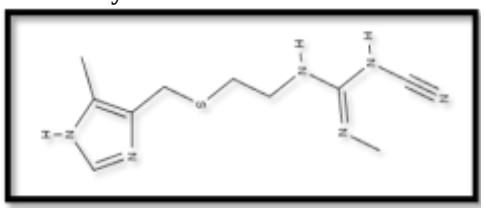

FIGURE 2: Structure of Cimetidine

IUPAC Name: 1-cyano-2-methyl-3-[2-[(5-methyl-1H-imidazol-4-yl)methylsulfanyl]ethyl]guanidine [16]

Spectrophotometric methods:

Darwish I. et al. described a spectrophotometric method for the determination of H2-receptor antagonists: cimetidine, which was fully developed and validated. The method was based on the reaction of these drugs with NBS and subsequent measurement of the excess of N-bromosuccinimide upon its reaction with p-

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aminophenol to give a violet-colored product (λmax at 552 nm) with good correlation coefficients (0.9988–0.9998) in the concentration range of 8–30 mg ml1. The detection limits for cimetidine were 1.22 mg ml^{-1}. The percentage yield varied from 98.5 ± 0.9 to 102.4±0.8% without the intervention of common excipients. [5]

Another method by Darwish I et al. was developed and validated for the determination of H2 receptor antagonists. described method, the spectrophotometric method: cimetidine. The method was based on the oxidation of these drugs with cerium (IV) in the presence of perchloric acid and the subsequent measurement. Excess Ce(IV) upon its reaction with p-dimethylaminobenzaldehyde to give a red product (max at 464 nm) with a good correlation coefficient (0.9990-0.9994) in the concentration range of 1–20 g ml^{-1}. [6]

Soledad Garcia M et al. described two sensitive and rapid spectrophotometric methods using batch and flow injection methods for the determination of cimetidine. The methods are based on the formation of a green complex between this drug and Cu (II) in acetoacetate medium at pH 5.9. Calibration curves obtained from absorbance measurements at 330 nm are linear between 2.5106/1.0103 and 5106/2.0103 M with detection limits of 9.5107 and 2.1106 for batch and flow injection methods. [17]

Kelani K.M and others described a spectrophotometric method for a complex reaction using cobalt II.

A colorless complex was developed with a maximum at 319 nm in a 1:1 ratio and a log stability constant of 5.49.

The percentage yield was 99.84 ± 0.858 in the concentration range 10–60 μgml^{-1}.[18]

Chromatographic methods:

HPLC method:

Diane A.I. et al. described an HPLC-UV method for the determination of cimetidine in human urine. All calibration curves showed good linear regression (r 2 > 0.9960) over the test ranges. The method showed good accuracy, with daily variations ranging from 0.2 to 13.6 percent and 0.2 to 12.1 percent. [19]

Mary T. Kelly et al., A new method for the determination of cimetidine in human plasma is described. Drug and internal standard (ranitidine) were separated on a Nucleosil C8 (25 x 4.6 mm) column using acetonitrile phosphate buffer, pH 6.2 (25:75, v/v) mobile phase containing heptanesulfonic acid. The mobile phase was delivered at a flow rate of 0.9 ml/min; detection was by UV absorption at 228 nm; and concentrations were calculated from peak areas. Drugs were extracted from alkaline plasma into ethyl acetate by a salting-out method involving the addition of 100 ml of saturated K2CO3 solution to each 250 μl aliquot of plasma. The method was validated in two separate studies with concentrations of 50–3000 ng/ml and 100–7000 ng/ml. Average intra- and inter-assay coefficients of variation were less than 6% in both studies, and yields ranged from 71% to 81%. [20]

HPLC-MS method:

Tabosa et al. described bioanalytical methods for bioequivalence studies that require high sensitivity and speed due to large sample volumes and low plasma concentrations of drugs. The aim of this study was to develop and validate high-performance liquid chromatography coupled with sequential mass spectrometry (HPLC-MS/MS) for the quantification of cimetidine in human plasma and its application in bioequivalence studies. Cimetidine and the internal standard ranitidine were extracted from plasma by liquid-liquid extraction. After extraction, samples were analyzed by HPLC-MS/MS. Chromatographic separation was performed on a C18 column, and the mobile phase consisted of acetonitrile and 10 mM ammonium acetate buffer supplemented with 5% isopropyl alcohol and 0.1% formic acid. The yield of cimetidine was 67.14% in the linear range of 25–6000 ng ml^{-1}. [21]

RP-HPLC method:

Marina Kontou et al. described a selective RP-HPLC method using a monolithic column developed for the simultaneous determination of the histamine H2 receptor antagonist cimetidine in the presence of sulfadimethoxine as an internal standard. Separation was performed on a Chromolith Performance RP-18 column (100 mm x 4.6 mm ID) with an isocratic mobile phase consisting of 0.05 mol/L acetate buffer (pH adjusted to 6.5 with triethylamine)/ methanol/ acetonitrile (85:10). The wavelength was set to 230 nm. Linearity was obtained at concentrations between 0.2 and 50 μg/ml, and detection limits were between 0.07 and 0.17 μg/ml. [22]

Tahira Iqbal et al. An RP-HPLC method developed for the determination of cimetidine in human plasma and urine. Plasma samples were basified, then liquid extracted with water-saturated

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ethyl acetate, and then evaporated under nitrogen. The extracts were recovered in the mobile phase and injected into a C18 reverse phase column; UV detection was set at 228 nm. Urine samples were diluted with an internal standard/mobile phase mixture (1:9) before injection. The lower limit of quantification in plasma and urine was 100 ng/ml and 10 ng/ml, respectively. [23]

GC method:

Majidano S.A. et al. described a capillary gas chromatography (GC) method developed for the determination of a pharmaceutical formulation of ranitidine after pre-column derivatization with methylglyoxal (MGo). GC was performed on an HP-5 column (30 m 9 x 0.32 mm) at an initial column temperature of 90°C for 2 min, followed by heating at 25 C min^{-1} to 265 C. The nitrogen flow rate was 2.5 mL min^{-1} with a split ratio of 10:1. A linear calibration curve was obtained between 50 and 1000 ng ml-1, and the limit of detection (LOD) was 17–25 ng ml^{-1}. Derivatization, GC elution, and separation were reproducible within 4.6% of the relative standard deviation of retention time and peak height/peak area. [15]

Famotidine Hydrochloride:

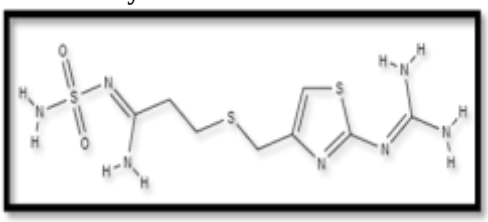

FIGURE 3: Structure of Famotidine

IUPAC Name: 3-[[2-(diaminomethylideneamino)-1,3-thiazol-4-yl] methylsulfanyl]-N' sulfamoyl propanimidamide [24]

Spectrophotometric methods:

Amin A. S. et al. reported three simple, accurate, sensitive, and selective spectrophotometric methods (A, B, and C) for the determination of famotidine in total samples, dosage forms, and in the presence of its oxidative metabolites. The first method A is based on oxidizing the drug with N-bromosuccinimide (NBS) and determining the unreacted NBS by measuring the decrease in absorption of amaranth dye (AM) at the appropriate maximum value (521 nm). Methods B and C involve adding excess cerium sulfate and determining unreacted Ce(IV) by reducing the red color of chromotrope 2R (C2R) to 528 nm in method B or by reducing the orange-pink color of rhodamine 6G (Rh6G) to 526 nm in method C. For more accurate results, Ringbom's optimal concentration ranges were 0.2–2.2 mg ml^{-1} for method A and 0.2–2.0 mg ml^{-1} for methods B and C. [25]

Darwish I et al. described a spectrophotometric method for the determination of H2-receptor antagonists: famotidine, which was fully developed and validated. The method was based on the reaction of these drugs with NBS and the subsequent measurement of the excess of N-bromosuccinimide upon its reaction with p-aminophenol to give a violet-colored product (λmax at 552 nm) with good correlation coefficients (0.9988–0.9998).. Detection limits for famotidine were 1.01 mL^{-1} [5].

Another method described by Darwish I et al. a spectrophotometric method, has been developed and validated for the determination of H2-receptor antagonists: famotidine The method was based on oxidizing these drugs with cerium (IV) in the presence of perchloric acid and then measuring the excess of Ce (IV) upon its reaction with pdimethylaminobenzaldehyde to give a red product (max at 464 nm) with a good correlation coefficient (0.9990-0.9994) in the concentration range of 1–20 g ml^{-1}. The limits of detection and quantification were 0.18–0.60 and 0.54–1.53 g ml^{-1}, respectively. [6]

Chromatographic methods:

HPLC method:

Ho C. et al. Chromatographic methods have been widely used for the determination of famotidine in pure form, dosage forms, or biological fluids. These methods include the HPLC method for the determination of ranitidine in commercial products. An Inertsilr ODS-2 column was used, and the mobile phase was 0.04 M aqueous sodium dihydrogen phosphate, acetonitrile, methanol, and triethylamine (345:20:35:0.7, v/v/v/v). The detection wavelength was set to 230 nm. [9]

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RP-HPLC method:

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developed for the simultaneous determination of the histamine H2 receptor antagonist cimetidine in the presence of sulfadimethoxine as an internal standard. Separation was performed on a Chromolith Performance RP-18 column (100 mm x 4.6 mm ID) with an isocratic mobile phase consisting of 0.05 mol/L acetate buffer (pH adjusted to 6.5 with triethylamine)/methanol/acetonitrile (85:10:5, v/v/v). The wavelength was set to 230 nm. Linearity was obtained at concentrations between 0.2 and 50 µg/ml, and the limits of detection were between 0.07 and 0.17 µg/ml. [22]

N. Helali et al. described a rapid reversed-phase high-performance liquid chromatography method developed for the determination of famotidine (FMT) and its impurities in pharmaceutical preparations. We separated on a Supelcosil LC18 column with an isocratic mobile phase of 13:87 (v/v) acetonitrile in 0.1 M dihydrogen phosphate buffer containing 0.2% triethylamine (pH 3.0). The flow rate of the mobile phase was 1 ml min-1, and the detection wavelength was 265 nm. The response was linearly dependent on concentration from 1 to 80 µg ml-1 (regression coefficient, R 2, 0.9981 to 0.9999). The limits of detection concentrations ranged from 0.08 to 0.14 µg ml^{-1}. [26]

HPTLC method:

Novakovic J. Reported that there are HPTLC methods used for the determination of famotidine in pharmaceutical formulations. Separation was performed on silica-precoated plates using a U.S.P. XXIII mobile phase: toluene:methanol:diethylamine (9:1:1, v/v/v). Samples were automatically placed on the HPTLC plate. Quantification was performed densitometrically by in situ UV absorption at 320 nm. [13]

Kelani MK et al. A HPTLC method for the determination of famotidine in the presence of its sulfoxide derivatives .The latter method involved quantitative densitometric evaluation of a mixture of the drug and its derivatives after separation by high-pressure thin-layer chromatography on silica gel plates using ethyl acetate:methanol:20%:ammonia (10:2:2, v/v/v) as a mobile phase. [14]

GC method:

Majidano S.A. et al. Described a capillary gas chromatography (GC) was developed for the determination of a pharmaceutical formulation of famotidine after pre-column derivatization with methylglyoxal (MGo). GC was performed on an HP-5 column (30 m 9 x 0.32 mm id) at an initial column temperature of 90 C for 2 min, followed by heating at 25 C min-1 to 265 C. The nitrogen flow rate was 2.5 mL min^{-1} with a split ratio of 10:1. A linear calibration curve was obtained between 50 and 1000 ng $ml^{-1,}$ and the limit of detection (LOD) was 17–25 ng ml^{-1}. Derivatization, GC elution, and separation were reproducible with a relative standard deviation of ± 4.6% for retention time and peak height/peak area. [15]

TABLE 2: Spectrophotometric method validation parameters range for H2 Anti histamines

Parameter	Ranitidine	Cimetidine	Famotidine
wavelength(nm)	610-326	464-552	464-521
Linearity(µg/ml)	1-20	5-30	1.5-22
Correlation coefficient	Near to 1 – Good	Near to 1 – Good	Near to 1 – Good
LOD(µg/ml)	0.07-0.74	0.51-2.832	0.31-1.01
LOQ(µg/ml)	0.21-2.25	1.13-20.60	0.95-3.06

TABLE 3: Chromatographic method validation parameters range for H2 Anti histamines

Parameter	Ranitidine	Cimetidine	Famotidine
Flow rate(ml/min)	1-2	1-2	1-2
Linearity(µg/ml)	2-20	5-50	2-20
Correlation coefficient	Near to 1	Near to 1	Near to 1
LOD(µg/ml)	0.02-0.549	0.02-1.44	0.01-0.552
LOQ(µg/ml)	0.45-1.664	0.6-4.36	0.5-1.674

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III. PROTON PUMP INHIBITORS:

Stomach acid is natural, a valuable chemical contributor to orderly digestion. But in excess or in the wrong place, it's a menace, inflaming and irritating the esophagus, typically causing heartburn and sometimes contributing to the development of ulcers in the stomach and the duodenum, the first part of the small intestine.

People have dealt with stomach acid–related woes in a variety of ways, proven and otherwise, for eons, but it wasn't until the mid-1970s and the introduction of cimetidine (Tagamet) that a treatment targeted the production of stomach acid itself. Cimetidine was a huge commercial success; by some accounts, it was the first blockbuster drug. Other drugs in the same class, known as H2 blockers, quickly followed suit.

Now the proton-pump inhibitor drugs (PPIs) have eclipsed the H2 blockers as the most commonly prescribed agents to reduce stomach acid. PPIs include lansoprazole, omeprazole, pantoprazole, rabeprazole, and esomeprazole. They are prescribed to both prevent and treat ulcers in the duodenum (where most ulcers develop) and the stomach. They also counter the various problems that occur when stomach acid escapes into the esophagus, which if it happens on a regular basis is a condition called gastroesophageal reflux disease (GERD). In most head-to-head trials, the PPIs have proved to be superior to the H2 blockers. [27]

Mechanism of action:

Ultimately, PPIs function to decrease acid secretion in the stomach. The proximal small bowel absorbs these drugs, and once in circulation, affect the parietal cells of the stomach. The parietal cells contain the H+/K+ ATPase enzyme, the proton pump, that PPIs block. This enzyme serves as the final step of acid secretion into the stomach. Interestingly, PPIs are prodrugs activated only after undergoing an acid-catalyzed cleavage in the acidic secretory canaliculi of the parietal cells. Hepatic P450 enzymes degrade PPIs. While there are slight variations in the exact P450 enzymes that are dominant in the degradation of the variety of PPIs, most dominantly degrade by the action of CYP2C19. Understanding the metabolism of PPIs allows us to understand why some PPIs work better for some individuals than others. For example, those of Asian ethnicity tend to have increased bioavailability of PPIs and thus should be managed initially with lower dosages. Furthermore, as we age, the bioavailability of PPIs increases, and thus dosages in the elderly should also be closely monitored and adjusted accordingly. While other drugs can reduce acid secretion in the stomach, PPIs represent the most potent drugs for acid reduction. [28]

Omeprazole:

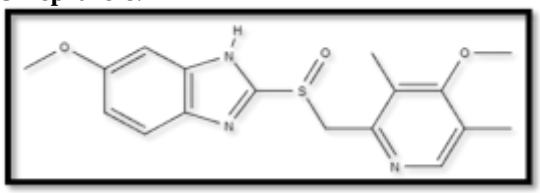

FIGURE 4: Structure of omeprazole

IUPAC Name: 6-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole [29]

Spectrophotometric methods:

Elbermawi et al. reported the use of the nitrosation reaction in a spectroscopic method for the determination of bulk and capsule formulations of omeprazole. Then, the standard and test solutions were dissolved in methanol, then 0.5 mL of 10% (w/v) sodium nitrite and 1 mL of 0.1% HNO3 were added, and then 2 mL of 0.1 M NaOH were added and diluted with distilled water to get the resultant yellow color measured at 390 nm. Absorption between 20 and 110 µg/ml is proportional to the concentration of omeprazole. The LOD and LOQ values of the proposed method were found to be 5.21 and 15.79 µg/ml, respectively. The average recovery was estimated to be 100.22 percent. [30]

Bhandage et al. reported the extractive spectrophotometric determination of omeprazole using acidic ion-binding dyes in aqueous media (pH 7.0 and 6.0, respectively), i.e., bromophenol blue and orange G. Chloroform was used to extract the chromogen from the ion pair formed, measured at 408 nm and 508 nm, respectively. A stock solution was prepared in 0.05 M HCl. The formed ion pair sample obeyed Beer's law from 5–30 µg/ml to 50–250 µg/ml with a R2 of 0.998, and the purity of omeprazole obtained was 98.1 ± 0.9 and 99.7 ± 0.3 in 408 nm and 503 nm, respectively. [31]

Kalyankar et al. reported a method for the co-estimation of diclofenac potassium and omeprazole magnesium in bulk and tablet form using UV spectroscopy. Methanol was used to prepare both standard and test solutions. The simultaneous equation method (Method I) for the measurement of diclofenac potassium and omeprazole magnesium at 282.2 and 301.8 nm and

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the area under the curve method (Method II), which selects the wavelength intervals for diclofenac potassium and 301.8 nm for diclofenac potassium. 300 nm to 305 nm Both diclofenac potassium and omeprazole magnesium methods were found to be linear between 5 and 30 µg/ml and 1 and 6 µg/ml, respectively, with a correlation coefficient of 0.999. Method I, i.e., 0.6249 and 1.8936, and Method II, i.e., 0.6176 and 1.8716, found LOD and LOQ for omeprazole, respectively. The percentage of test results for methods I and II was 99.17% and 99.51%, respectively. [32]

Sanjana et al. reported a UV spectrometric method for the simultaneous determination of omeprazole and aspirin. Standard omeprazole, aspirin, and test solutions were prepared in ethanol. The methods used are (A) zero fold and (B) area under the curve (AUC), where the two wavelength ranges for omeprazole and aspirin were 292.0–312.0 nm and 266.0–286.0 nm, respectively. The method was linear in concentration, between 20 and 100 µg/ml, and R2 is 0.9994. The LODs of methods A and B were 1.6115 and 4.8835 µg/ml, respectively, and the LOQs of methods A and B were 1.7402 and 5.2735 µg/ml, respectively. Recovery studies for both methods have found 99–100%. [33]

Chromatographic methods:

HPLC method:

Chaudhry et al. described a simple HPLC method for the in vitro determination of omeprazole. This study is based on the use of acetonitrile:phosphate buffer 6.8 (65:35) as the mobile phase with a flow rate of 1 ml/min. A Shimadzu CLC ODS-C-18 (150 x 6.0 mm) column was used and detected at 300 nm. Standard and test solutions were prepared with AR-grade ethanol. RT was observed after 6.8 minutes. Linearity was observed at concentrations from 4 to 36 mg/mL and the percent yield was 99.92 ± 0.4%. [34]

Yuen et al. described an improved HPLC method for the determination of omeprazole in human plasma. Product and IS were analyzed using dichloromethane from alkalized plasma samples. The pH of the mobile phase was adjusted to 6.5 with 0.05 M Na2HPO4-acetonitrile (65:35, v:v) using a Crestpak C18 column (150 mm, 4.6 mmmm, and mm). To perform the analysis, the flow rate was 1.0 mL/min, and the detection wavelength was set at 302 nm. 2.5 ng/ml LOD and 5 ng/ml LOQ, the method was accurate and sensitive. The calibration curve was linear from 5 to 1280 ng/ml conc. area. The average recovery rate for the extraction procedure was 96 percent. [35]

RP-HPLC method:

Ali et al. published an RP-HPLC method for the determination of omeprazole capsules. The separation was performed with a mobile phase of acetonitrile and phosphate buffer pH 7.4 (60:40 v/v) at a flow rate of 0.5 mL/min. The run time was 10 min at 302 nm for UV detection by ZORBAX XDB, C-18 column (150 x 64.6 mm, 5 m). Standard and test solutions were prepared in methanol. The proposed method showed a recovery of 100.95% and a linear range of 25–175%, with an R2 of 0.998, peaking at 5.4 min. The LOD and LOQ were recorded as 2.44 mg/kg and 7.33 mg/kg, respectively. [36]

Hammami et al. described a method for the determination of omeprazole in human plasma using lansoprazole as an internal standard using RP-HPLC. The method uses 0.05 M dibasic sodium phosphate, pH 7.0, and acetonitrile (60:40, v:v) with a flow rate of 1.0 mL/min. An Atlantis d C18 column (4.5 x 150 mm, 5µm) was used and detected at 302 nm with a PDA detector. The column temperature was maintained at room temperature, and the test room temperature was 8 °C. RT was 4.4 minutes, and drive time was 9 minutes. The standard solution was prepared in methanol and then diluted with human plasma, or mobile phase. IS was added to the sample solution, then extracted with tert-butyl methyl ether and redissolved using the mobile phase. The method was linear at concentrations from 0.01 to 1.20 µg/ml, and R2 was 0.9992. The recovery for OPZ and IS was 91 percent. The estimated LOD and LOQ values were 0.005 and 0.01 µg/ml, respectively. [37]

UPLC method:

Rao et al. reported a stability-indicating method for the simultaneous evaluation and dissolution experiments of domperidone and omeprazole. The study was performed using a UPLC BEH C18 column (5 mm, 2.1 mm, 1.7 µm) maintained at 50 °C. Phosphate buffer (pH 5.0, 0.05 M): acetonitrile (68:32%) as the mobile phase with a flow rate of 0.4 ml/min and a run time of 2 minutes. Eluted compounds were detected at 285 nm with a 2 L injection volume. The standard and test solutions were prepared with NaOH in methanol, and the RT was 0.9 min. The FD analysis produced impurities with RT times of 1.2 to 2.7 minutes. Linearity was investigated at a

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concentration of 50–150% and an R2 value of 0.999. Recovery was found to be 100%. [38]

Jadhav et al. reported a new UPLC-TOF stability-indicating method for the determination of omeprazole and related substances in pharmaceutical dosage forms. The pH of ammonium acetate buffer, column oven temperature, and acetonitrile composition in mobile phase B were identified as critical method parameters (CMP). Two levels and three variables were selected. Additives and drugs were selected as the levels. Separation was achieved using an Acquity BEH Guard RP18 (100 x 2.1 mm, 1.7 µm) column maintained at 40 °C. Mobile phase A was buffer:acetonitrile (950:50%), and mobile phase B was acetonitrile:methanol (65:35%) in gradient mode. The injection volume was 6 L, and the flow rate was 0.6 ml/min. UV detection was performed at 305 nm. The method was extended to MS, operated in positive ESI mode with a capillary voltage of 2.4 KV and source and desolvation temperatures of 120 and 350 °C, respectively. [39]

Brinda et al. reported a UPLC method for the determination of omeprazole. The method consisted of a 40:60 (v/v) mixture of buffer pH 7.0 and methanol as the socratic mobile phase. Hypersil GOLD (50 4.6 mm, 3 L column) at 25 °C was used. The flow rate was 1 ml/min, and UV detection was at 305 nm. RT was found in 1.2 minutes. The method was found to be linear between 25 and 100%, and R2 was 0.999. The recovery results were 99–103%, and the analysis results were 99.19%. [40]

Esomeprazole:

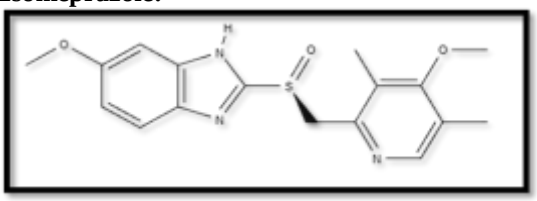

FIGURE 5: Structure of Esomeprazole

IUPAC Name: 6-methoxy-2-[(S)-(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole [41]

Spectrophotometric methods:

Kumar et al. reported a UV spectroscopic method for the estimation and physicochemical characterization of esomeprazole-Mg trihydrate. Standard and sample preparation were performed in methanol, and analytical evaluation was performed at 203.5 nm. Linearity was performed between 2.0 and 10.0 µg/ml, where the R2 value was found to be 0.999. The LOQ value was found to be 1.0 µg/ml. [42]

Mandil et al. described a spectroscopic method for the estimation of esomeprazole-Mg trihydrate in a dosage form. In the present method, the formation of a charge transfer complex between chloranilic acid (CAA) as a p-acceptor and esomeprazole as an n-donor occurred iin amethanol-acetonitrile medium. Absorbance is obtained between 521 and 525 nm. The sample was prepared in a mixture of methanol and acetonitrile. The beer law was followed with a concentration range of 1.250-150.00 µg/ml and an R2 value of 0.999. The LOD and LOQ were found to be 0.156 µg/ml and 0.473 µg/ml, respectively. The percentage was found to be between 98 and 100.12%. [43]

Magesh et al. reported a spectroscopic method for the estimation of esomeprazole using a hydrotropic dissolution technique. 10 M urea was used for the hydrotropic dissolution of esomeprazole, and a wavelength of 301 nm was used for evaluation. Beer's law was observed between 10 and 50 µg/ml, and the R2 value was found to be 0.998. The percentage was found to be 99.86 percent. [44]

Yoganandaswamy and Reddy reported a method for the spectroscopic determination of esomeprazole using Tropaeoline-OO. This method was based on the reaction with tropaeolin-OO dye under acidic conditions, with λmax at 410 nm. Linear analysis was performed between 50 and 250 µg/ml. [45]

Mohan Raj et al. reported a UV method for the determination of esomeprazole in tablet dosage form. The maximum absorption of esomeprazole was at 275 nm. A stock solution was prepared in dimethylformamide and further diluted 50:50 (v/v) with DMF and distilled water. Beer's law was followed between 10 and 50 µg/ml with an R2 value of 0.998. The percentage was found to be between 97% and 99%. [46]

Chromatographic methods:

HPLC method:

Jain et al. described an HPLC method for the estimation of esomeprazole in bulk and pharmaceutical dosage forms. The method involves elution achieved with a Thermo C18 analytical column (250 mm, 4.6 mm, and 5.0 µm). A mobile phase of 50:50% methanol and acetonitrile were used at a flow rate of 1.0 mL/min. UV detection was performed at 300 nm to obtain an RT of 6.8

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min. The method was linear in the concentration range of 5–25 µg/ml, and the R2 was 0.999. The LOD and LOQ obtained were 0.100 and 0.314 µg/ml, respectively. The average recovery rate was found to be 99.78%. [47]

Anisuzzaman Sharif Md. et al. described a method for the determination of esomeprazole by HPLC. Separation was performed on a Prevacil C8 column (150 x 4.6 mm, 5 µm), and detection was performed at 280 nm. The mobile phase contained a mixture of ACN and phosphate buffer at pH 7.6 (35:65%) with a flow rate of 1.0 ml/min. The accuracy of the proposed method was up to 99.12%. Linearity was examined between 10 and 150% with an R2 value of 1. [48]

RP-HPLC method:

Chacko et al. reported an RP-HPLC method for the determination of esomeprazole in enteric-coated tablets. The mobile phase was a mixture of acetonitrile and phosphate buffer, pH 6.8 (60:40%), with a flow rate of 1.0 ml/min. Separation was performed using a Zorbax SB C18 column (250 x 4.6 mm, 5 µm) and detection at 280 nm. It turned out that the percentage is 100.13%. Linearity was performed between 100 and 300 ppm with an R2 value of 0.999. [49]

Khalil et al. developed an RP-HPLC method for the estimation of esomeprazole in bulk and pharmaceutical dosage forms. Separation was performed on a C18 column (250 x 4.6 mm, 5 µm) using acetonitrile:phosphate buffer, pH 7.4 (50:50%) as the mobile phase. The flow rate was 1.0 mL/min, and detection was at 302 nm. The RT was 6.5 minutes. The method was linear over 25–150 µg/ml with an R2 value of 0.999. Recovery was found to be between 99 and 100.5%. The LOD and LOQ were found to be 0.015 and 0.04 µg/ml, respectively. [50]

UPLC method:

Malisetty and Rambabu reported a stability-indicating UPLC method for the simultaneous determination of aspirin and esomeprazole in a combination tablet. Separation was achieved using an Agilent Zorbax XDB column (50 x 4.6 mm, 1.8 mm) and UV detection at 210 nm. Gradient elution was performed with a flow rate of 0.7 mL/min using mobile phase A with 0.2% phosphoric acid and mobile phase B consisting of MeOH:ACN (50:50%). The RT was 2.4 minutes with esomeprazole and 2.8 minutes with aspirin. A mixture of ACN and 0.1 N NaOH (50:50%) was used as a diluent. Sample FD was performed, showing more degradation under acid hydrolysis (1 N HCl) and minimal degradation under other stress conditions. The impurity peaks were well separated from the main peaks, which lasted for 2.5–5 min. Linearity was performed between 5 and 15 µg/ml with an R2 value of 0.999. It turned out that the percentage is 99.1–100.6%. The LOD and LOQ values were found to be 1.4 and 4.4 µg/mL, respectively. [51]

Nalwade et al. reported a UPLC method for the evaluation of esomeprazole and its excipients in pharmaceutical dosage forms. Chromatographic separation was achieved on an Acquity BEH C18 column (50 mmm,2.1 mm, and 1.7 mm). In gradient mode, 0.05 M glycine buffer pH 9.0 as MP A and an ACN:Milli-Q aqueous mixture (90:10%) as MP B were used. The flow rate was 0.21 mL/min, and detection was at 305 nm. esomeprazole RT was found to be 9.13 minutes. The LOD and LOQ were found to be 0.02 and 0.06 µg/ml, respectively. In the linearity study, the R2 value was found to be 0.999. The recovery rate was 98–100.5%. [52]

Pantoprazole:

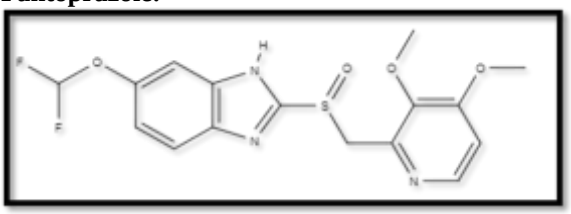

FIGURE 6: Structure of Pantoprazole

IUPAC Name: 6-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-1H-benzimidazole [53]

Spectrophotometric methods:

Basavaiah et al. reported two methodological approaches based on redox and complex reactions for the determination of pantoprazole sodium in drugs using N-bromosuccinimide (NBS) by UV spectrometry. Methods for the estimation of PPZ by adding a known excess of NBS to the HCl medium are followed by the estimation of the unreacted oxidant using two reaction strategies involving treatment with iron (II) and thiocyanate (method A) or thirone (method B). The standard solution was prepared with water. The NBS solution was prepared using heat to dissolve 1.8 g in water, and the amount of water was adjusted to one liter and standardized. NBS specifically used concentration

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followed by the addition of ferrous ammonium sulfate (FAS) and thiocinate, followed by absorbance at 470 nm, to prepare the samples for method A. Specifically, the concentration was applied to NBS, then FAS and throne in Method B, and the absorbance was measured at 670 nm. The absorption showed a linear decrease with pantoprazole concentration, where Beer's rule of Method A and Method B followed in the range of 0.25–3.5–15 µg/ml, and R2 was 0.997–0.996. The LODs of methods A and B were found to be 0.05 and 0.17 µg/ml, respectively. The LOQs of Method A and Method B were found to be 0.15 and 0.52 µg/ml, respectively. The increased yield of pure pantoprazole was found to be 97.2–102.5%, and assay results were 99–101%. [54]

Kumar et al. described a method for the determination of pantoprazole in pharmaceutical formulations using UV spectrophotometry. Water was used as a solvent to prepare the standard and test solutions. Absorption maxima were found at 292 nm. Linearity was studied from 5 to 70 mg/ml, and R2 was 0.9998. The proportion of pantoprazole tablets was found to be 99%. [55]

Basavaiah et al. published a method for the determination of pantoprazole using ccerium (IV) sulfate as an oxidimetric reagent. The approach is based on the oxidation of PSS with a calculated excess of Ce (IV) sulfate using different reaction schemes after measuring the unreacted oxidant. Spectrophotometry involved the reduction of unreacted Ce(IV) sulfate with a fixed amount of Fe(II) and the resulting Fe(III) complex with thiocyanate to test for absorbance at 470 nm. [56]

Salama et al. described a spectroscopic method for the determination of pantoprazole sodium by the formation of its metal chelate. This reaction resulted in the formation of an orange chelate, which was measured at 455 nm. Linearity was observed between 30 and 300 µg/ml with an R2 of 1.00. The percentage accuracy was 100.6%, and the analysis results were 97.2–100.3%. The LOD and LOQ were found to be 3.65 and 12.67 µg/ml, respectively. [57]

Chromatographic methods:

RP-HPLC methods:

Ashour and Omar reported that they used the RP-HPLC method for the estimation of pantoprazole in pharmaceutical dosage form. Separation was performed by PDA detection at 280 nm on a Nucleodur C8 column (250 x 4.6 mm, particle size 5 µm). The mobile phase consisted of a solution of 0.1 M ammonium acetate and methanol (42:58, v/v) with a flow rate of 1.0 mL/min. Linearity with an R2 of 0.999 was examined between 3.06 and 1243.0 µg/ml. The LOD and LOQ values were 0.78 µg/mL and 2.60 µg/mL, respectively, while the recovery ranged from 99.07% to 103.95%. [58]

Prakash et al. described a one-step RP-HPLC process with a mobile acetonitrile:phosphate buffer (pH 7.0, 60:40 v/v) and a flow rate of 1.0 mL/min. An Inertsil C18 column (51, 150 mm, 4.6 mm) and a UV detector at 230 nm were used for separation. Pantoprazole sodium retention time was 2.017 minutes. In the mobile phase, the standard solution and the test solution were prepared in a mixture of acetonitrile and methanol. The procedure was linear, R2 was 0.999, LOQ values were 8.20 ng/mL, and the assay yield was 99.99%. [59]

Basavaiah et al. described a method for the quantification of pantoprazole in medicines using RP-HPLC with an RP column (Inertsil ODS 5 L; 150 ± 4.6 mm) at 35 °C. The mobile phase consisted of pH 7.3 buffer and ACN (70:30%) with a flow rate of 0.6 mL/min. UV detection was performed at 289 nm. The mobile phase was used as a diluent in the preparation of the standard and test solutions. The RT was approximately 7.33 minutes. A linear correlation between mean peak area and pantoprazole concentration was observed between 25 and 200 µg/ml with an R2 of 0.999. The method recorded a LOD of 6.0 µg/ml and a LOQ of 20.0 µg/ml. The results of the analysis were found to be 98–101 percent. [60]

Ognjenka Rahic et al. Separation was achieved at 30 °C on a C8 column (250 x 4.6 mm, 5 L). And as the mobile phase, a mixture of phosphate buffer pH 3.0 and acetonitrile (70:30 v/v) with a flow rate of 2 ml/min UV detection was performed at 290 nm, and RT was 4.7 min. Standard and sample solutions were prepared with NaOH:acetonitrile (50:50). Linearity was between 50 and 150%, with an R2 value of 0.999 and a recovery of up to 99%. [61]

Lansoprazole:

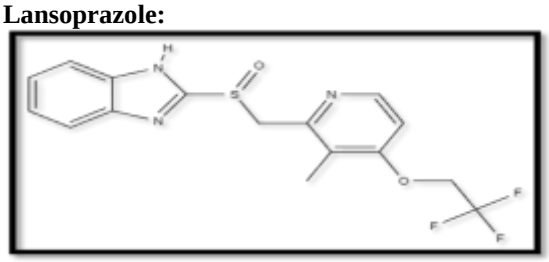

FIGURE 7: Structure of Lansoprazole

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IUPAC Name: 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-1H-benzimidazole [62]

Spectrophotometric method:

Basavaiah et al. described a method using a mixture of bromate bromide based on redox and complex reactions by a spectrophotometric method for the evaluation of Lansoprazole in pharmaceuticals. This study presents two determination methods for tablets and capsules where lansoprazole is oxidized with bromine produced in situ and then unreacted bromine is determined. In two different reaction methods, the remaining bromine was treated with an excess of iron (II) in the first method, and the resulting iron (III) was mixed with thiocyanate and analysed at 470 nm. Another approach involved treating the unreacted bromine with an excess of iron (II) and treating the residual iron (II) at a lower pH with orthophenanthroline and counting at 510 nm. In both methods, the amount of bromine reacting correlates with the amount of lansoprazole present. The reagent and sample solutions were prepared in distilled water, but only the standard stock solution was prepared in HCl and diluted in water to prepare the required concentration. The linearity of the conducted method was in the conc range, i.e., 0.5–4 µg/ml in the first approach and 0.5–6 µg/ml in the second approach, with the same R2 of 0.998. The LOD values of the first and second approaches were 0.07 and 0.095 µg/ml, respectively. The LOQ values of the first and second approaches were 0.21 and 0.36 µg/ml, respectively. The recovery rate was 97–102%. [63]

Sudheer et al. reported a simple and sensitive approach for the evaluation of lansoprazole in pharmaceuticals. In this method, the analysis was performed by grinding the sample capsule. The standard and the test solution were prepared in methanol, and the measurement was performed at a wavelength of λmax 281.1 nm. In the range of 3 and 90 µg/ml, Beer's law was followed with an R2 of 0.9999. The percentage study showed results up to 98–99 percent, and the test results matched the 30 mg (RSD 0.62%) claim on the label. The LOD and LOQ were 0.75 and 2.5 µg/ml of lansoprazole in dichloromethane (DCM), respectively, with acid sulfonphthalein dyes, namely bromocresol purple (BCP) in the first approach and bromothymol blue (BTB) in the second approach, used for stable formulation. yellow-colored ion pair conjugates that showed maximum absorption at 400 and 430 nm, respectively. The first approach used 1 ml of 0.2 P, and the second approach used 1 ml of 0.1% BTB. DCM was used to prepare the standard and all test solutions. A linear relationship was obtained for the concentration between 0.5 and 15.0 µg/ml in the first approach and 1.25 and 20 µg/ml in the second approach, with a regression coefficient of 0.998. The LOD values of the first and second methods were 0.12 and 0.40 µg/ml, respectively. The LOQ values of the first and second approaches were 0.35 and 1.23 µg/ml, respectively. The percentage was 96–105% in the first approach and 95–105% in the second approach. Capsule test results find values for the first and second approaches that match the label claim and percentages up to 99–102%. [64]

Rahman et al developed a simple kinetic spectrometric method based on the oxidation of lansoprazole with basic potassium permanganate. The reaction was then analyzed spectrophotometrically for the increase in absorbance due to the formation of potassium permanganate at 610 nm (method A) and the decrease in absorbance at 530 nm due to the loss of potassium permanganate (method B). The standard solution was mixed with 0.5 mL of 0.10 M NaOH and then diluted with water. The sample solution was dissolved in 50 mL of methanol, then filtered, and 0.5 mL of 0.1 M NaOH was added, followed by 25 mL of water. The recovery values for both methods were found to be 100%. For methods A and B, the calibration curves were linear, ranging from 5–150–5–70 µg/ml, with R2 values of 0.996–0.995. [65]

Chromatographic methods:

HPLC method:

Tang et al. published an HPLC stability indicator process for the evaluation of Lansoprazole enteric capsules and related excipients. It contained a flow rate of 1.2 ml/min, 6.8 phosphate buffer, and acetonitrile with a mobile phase ratio of 65:35%. UV detection was performed for the analyte at 285 nm using a Dikma Technologies Diamonsil C18 column maintained at 25 °C. The RT was approximately 13.5 minutes. Sample and standard solutions were prepared in the mobile phase. The drug and its sample solution were subjected to forced degradation (FD), where impurities E, D, A, B, and C were eluted in approximately 3.0, 3.7, 5.0, 17.5, and 19.5 minutes, respectively. Greater degradation was observed upon acid hydrolysis (0.5 M HCl), up to 16–17%. The linear range was 0.5–1.5 mg/mL, and the R2 was 0.9999. [66]

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RP-HPLC method:

Sundar et al. described an RP-HPLC method for the determination of lansoprazole in human plasma. The isolation process works by separating liquids using 70:30 volume percent t-butyl methyl ether and dichloromethane. Lansoprazole was eluted using a Phenomenex C18 column (5 µm, 150 mm, 4.6 mm). A mixture of 50:50 volume percent methanol and 10 mM mixed phosphate buffer (pH 3) was used as the mobile phase with a flow rate of 1.2 ml/min. The detection wavelength was 285 nm, and the retention time was 6.8 minutes. The standard solution was prepared in methanol, and the sample was prepared in filtered, drug-free human K2EDTA plasma. The method followed Beer's law between 50.25 and 2999.93 ng/mL with an R2 value of 0.998. The overall recovery for human spike samples was 58.97%, while the LOD and LOQ were within acceptable limits. [67]

Patel et al. reported an RP-HPLC method for the simultaneous estimation of lansoprazole and domperidone in capsule formulation. Elution was performed on an RP-C18 column (2.27 µm, 250 mm, 4.6 mm) at a column temperature of 25 °C. Acetonitrile:methanol (81:19%) was used as the mobile phase with a flow rate of 1 mL/min, and PDA detection was performed at 280 nm with a retention time of 2.8 min. A standard and sample were prepared in the mobile phase. Linearity was observed between 8 and 24 µg/ml, and R2 was 0.997. The LOD and LOQ of the proposed methods were found to be 0.03 and 0.09 µg/ml, respectively. The yield was 99–104%, and the analysis results were up to 100%. [68]

Rajkumar et al. (2010) reported a method for the estimation of Lansoprazole in tablet dosage form using RP-HPLC containing a mobile phase, viz., pH 3.0 disodium hydrogen phosphate buffer and acetonitrile in a ratio of 30:70. The flow rate was set at 1.0 mL/min. A Phenomenex Luna C8 column (5 µm, 250 mm 4.6 mm) was used, and a wavelength of 285 nm was used for UV detection. The sample volume was 10 L, and it took 8.82 minutes to separate. A standard and sample were prepared in the mobile phase. Linearity was obtained at a concentration between 40 and 60 µg/ml and an R2 value of 0.9992. The LOD and LOQ values of the proposed method were found to be 0.03 and 0.09 µg/ml, respectively. The percent yield was 98.74%, and test results were as high as 100.06% of the 30 mg label claim. [69]

Rajput and Fanse reported an RP-HPLC method for the combined determination of lansoprazole and aspirin in bulk and dosage forms. For separation, 10 mM phosphate buffer pH 3:acetonitrile (55:45) was used aas the obile phase with a flow rate of 1 ml/min. A ChromasilC-18 column (dimensions: 250 mm, 4.6 mm, 5 µm) was used. The RT was 6.1 minutes long, with a detection wavelength of 284 nm. Standard and sample solutions were prepared in acetonitrile. A linear relationship was achieved at concentrations of 10–60 µg/ml with an R2 value of 0.999. The LOD and LOQ values were found to be 0.9156 and 2.775 µg/ml, respectively. The values for average percent yield and average percent determination were 100.5% and 99.5%, respectively. [70]

Rabeprazole:

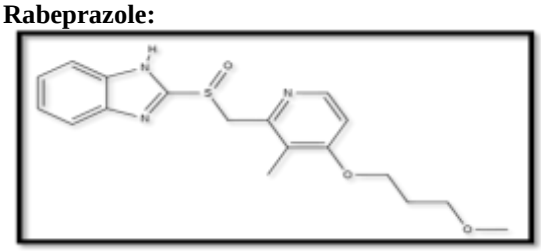

FIGURE 8: Structure of Rabeprazole

IUPAC Name: 2-[[4-(3-methoxypropoxy)-3 methylpyridin-2-yl]methylsulfinyl]-1H-benzimidazole
[71]

Spectrophotometric Methods:

Pandey et al. reported a spectrometric method for the determination of rabeprazole sodium in tablets. Batches of standard stock solution, test solution, and calibration curve were prepared in 20% (v/v) aqueous methanol, and the quantification wavelength was 284 nm. Linearity was observed between 4.08 and 24.5 mg/ml, and R2 was 0.999. Percentage yields were found to be between 97 and 101%, with assay results as high as 100.45%. [72]

Rahman et al. described two spectrophotometric methods. Method A used the reaction of 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH) at 470 nm in acetic acid medium in the presence of ammonium cerium (IV) nitrate as a reddish-brown material. Method B required the reaction of rabeprazole sodium with 1-chloro-2,4-dinitrobenzene (CDNB) in dimethyl sulfoxide (DMSO) at 45 °C to form a yellow Meisenheimer complex with an absorption maximum at 420 nm. A linear study was performed at a concentration of 14–140 and 7.5–165 µg/ml with R2 0.999. The recovery rate was 100%. The

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LOQs for method A and method B were found to be 4.176 and 2.273 mg/mL, respectively. [73]

Sawant et al. reported two spectrophotometric methods for the simultaneous estimation of aceclofenac and rabeprazole. Method 1 was based on a simultaneous equation for the estimation of rabeprazole sodium and aceclofenac at wavelengths of 283 and 276 nm. Standard and test solutions were prepared in methanol. Linearity was achieved with an R2 value of 0.998 between 10 and 60 g/ml. 100.22 and 99.99% were found to calculate the percentage of rabeprazole sodium. The LOD and LOQ of Method were found to be 0.194 and 0.832 mg/mL, respectively. [74]

Chromatographic methods:

RP-HPLC method:

Ranjan et al. (2016) reported a method for the estimation of rabeprazole sodium with 284 nm UV detection using RP-HPLC. Elution was performed with mobile phase pH 5.5 buffer and mobile phase methanol (30:70) at a flow rate of 0.9 ml/min. A C18 column (X Terra 4.6, probably 150 mm, 3.5 µm) was used for separation at room temperature. Standard and test solutions are prepared in the mobile phase. Linearity led to an R2 value of 1.0 between 20 and 60 µg/ml. The determination and recovery rates were 99.5% and 99.8%, respectively. The LOD and LOQ were recorded as 2.96 and 10.1 µg/ml, respectively. [75]

Khokra et al. reported a combined method for the estimation of aceclofenac and rabeprazole sodium using RP-HPLC using MeOH:ACN:water (60:10:30 v/v/v) as the mobile phase. The flow rate was 1.0 mL/min in a column (250 mm, 4.6 mm, and 5 µm) at ambient temperature. UV detection was performed at 280 nm for 5.6 minutes at room temperature. Standard and test solutions were prepared in methanol. Linearity was tested between 1 and 10 µg/ml, and R2 was 0.999. Rabeprazole sodium recoveries were up to 100.7–101.5%, and assay results were up to 101%. The LOD and LOQ were found to be 0.091 and 0.305 µg/ml, respectively. [76]

Battu and Reddy reported an RP-HPLC procedure for the determination of rabeprazole in human plasma using an Inertsil C18 column (5 µm, 150 mm, 4.6 mm). The system used a mobile phase of acetonitrile in phosphate buffer at pH 7.0 (70:30, v/v) with a flow rate of 0.8 mL/min. UV detection at 228 nm at room temperature takes 2.44 min. The standard solution was prepared with methanol. The process was 99.15–101.85 curates, and the linearity range was 0.1–30 µg/ml with an R2 of 0.999. The LOD and LOQ in serum are 1.80 ng/mL and 5.70 ng/mL, respectively. [77]

Saikira et al. described a method for the combined determination of rabeprazole and diclofenac in a tablet formulation by RP-HPLC based on isocratic elution with a mobile phase of water and acetonitrile (50:50% v/v) with a flow rate of 1.0 mL/min. A Phenomenex C-18 column (240 x 4.6 mm, 5 µm) was used. UV detection was performed at 278 nm, and RT was 2.6 min. Standard and sample solutions were prepared in HPLC water. The linearity range was 5–30 µg/ml, and the R2 was 0.999. The test results correspond to the claim on the label in percentages up to 100%. The LOD and LOQ were found to be 0.40 and 1.23 µg/ml, respectively. [78]

Ekambaram et al. described the method using RP-HPLC. Elution was performed on a Phenomenex C18 (Luna) column (250 x 4.6 mm, 5 µm) at 45 °C with a C18 column guard (4 mm x 3 mm, 5 µm). The mobile phase was 10 M potassium dihydrogen orthophosphate buffer (pH 6.8):ACN (70:30 v/v) at a flow rate of 1.0 ml/min. Standard and test solutions are prepared in the mobile phase. The RT was found to be 5.35 minutes in 288 with UV detection. The LOD and LOQ were found to be 1 and 2.5 µg/ml, respectively. A recovery rate of up to 102% was observed. Linearity was observed in the concentration range between 2.5 and 5 µg/ml with an R2 of 0.994. [79]

TABLE 4: Spectrophotometric method validation parameters range for proton pump inhibitors

Parameters	Omeprazole	Esomeprazole	Pantoprazole	Lansoprazole	Rabeprazole
wavelength(nm)	300-508	203.5-525	292-670	470-610	276-283
Linearity(µg/ml)	1-6	2-50	3-300	5-50	4.08-25
Correlation coefficient	Near to 1	Near to 1	Near to 1	Near to 1	Near to 1
LOD(µg/ml)	0.617-5.21	0.02-0.156	0.15-3.65	0.07-0.75	0.194-0.832

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LOQ(µg/ml)	1.87-15.79	0.473-1	0.52-12.67	0.21-1.23	0.742-1.48

TABLE 5: Chromatographic method validation parameters range for proton pump inhibitors

Parameters	Omeprazole	Esomeprazole	Pantoprazole	Lansoprazole	Rabeprazole
Flow rate(ml/min)	0.4-1	0.7-1	0.6-2	1-1.2	0.8-1
Linearity(µg/ml)	50-250	5-25	25-200	10-60	1-10
Correlation coefficient	Near to 1	Near to 1	Near to 1	Near to 1	Near to 1
LOD(µg/ml)	0.02-3.041	0.015-1.4	0.78-6	0.03-0.9156	0.091-2.82
LOQ(µg/ml)	0.05-10.37	0.04-4.44	2.60-20	0.09-2.775	0.305-10.1

IV. PROSTAGLANDIN ANALOGUES:

Prostaglandin E1 and E2 analogues are an attractive new class of drugs that reduce acid secretion and increase mucosal protection. They have the same biological effect as natural prostaglandins in the gastric mucosa, but they are more stable and have a longer action due to changes in their chemical structure. Although several prostaglandin analogues are currently being tested clinically in peptic ulcer disease, the majority of work has been done with prostaglandin analogue E1.

Mechanism of action:

Misoprostol is a synthetic prostaglandin E1 analog that stimulates prostaglandin E1 receptors on parie-tal cells in the stomach to reduce gastric acid secretion. Mucus and bicarbonate secretion are also in-creased along with thickening of the mucosal bilayer so the mucosa can generate new cells.

Misoprostol binds to smooth muscle cells in the uterine lining to increase the strength and frequency of contractions as well as degrade collagen and reduce cervical tone. [80]

Misoprostol:

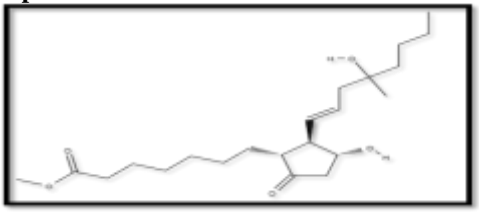

FIGURE 9: Structure of Misoprostol

IUPAC Name: methyl 7-[(1R,2R,3R)-3-hydroxy-2-[(E)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate [81]

Spectrophotometric Methods:

Arunima Aravind et al. A UV spectrophotometric method for the determination of misoprostol in bulk and pharmaceutical forms was developed and validated. Distilled water is used as a solvent because misoprostol dissolves in it. Misoprostol was dissolved in distilled water and scanned in the UV range (200–400 nm). The max (absorption maximum) of the drug was found to be 208 nm. The law of beer is valid at concentrations of 1–5 g/ml. Accuracy, precision, linearity, robustness, LOD, and LOQ were confirmed in the proposed approach. Linearity between 1 and 5 g/ml was achieved with a correlation coefficient of 0.9980, 2.0924 g/ml, and 6.3406 g/ml. [82]

Anusha Gandhi et al. reported that an ELICO Double beam SL-120/UV spectrophotometer is used for validation and method development according to certain specifications. The maximum wavelength of misoprostol is 281 nm. The correlation coefficient of the drug is less than 1. The limits of detection and determination of misoprostol were found to be 0.656 µg/ml and 1.988 µg/ml. [83]

Chromatographic methods:

Manikya Rao T. et al. A selective HPLC method with an ultraviolet detector for the determination of misoprostol 0.1 mg tablets by an in vitro dissolution study was described. After a limited dissolution time, misoprostol in aliquots of the dissolution medium was derivatized with

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methanolic potassium hydroxide. This method involves the conversion of misoprostol to a derivative with maximum absorption at 285 nm. Chromatographic separation was performed using a reversed phase Thermo MOS Hypersil (150 x 4.6 mm, 5 µm) column. The mobile phase consisted of 50 volumes of buffer and 50 volumes of methanol; the buffer consisted of 10 ml of triethylamine in 1000 ml of water; pH was adjusted to 6.0 with 0.05 orthophosphoric acid; a simple ultraviolet detector was used as a detector; and the wavelength was 285 nm. [84]

Komal Nishikant Khillare and others Reported determination of diclofenac sodium and misoprostol in the formula. This method is based on the HPLC separation of two drugs on a Thermo Hypersil BDS-C18 (250 mm × 4.6 mm, 2.5 µm) from Agilent under isocratic conditions and a simple mobile phase containing methanol: 0.05% OPA water pH 2.7 (70: 30) at a flow rate of 0.7 mL/min using UV detection at 235 nm. This method was used for formulation without the intervention of formulation excipients. Data from linear regression analysis of the calibration curves showed a good linear relationship in the diclofenac sodium concentration range of 50–100 µg/ml and misoprostol concentration range of 200-400 µg/ml. The method has been validated for accuracy, robustness, and recovery. The limit of detection (LOD) and limit of quantification (LOQ) were 0.26 µg/ml and 0.78 µg/ml for diclofenac sodium and 1.87 µg/ml and 5.6 µg/ml for misoprostol, respectively. [85]

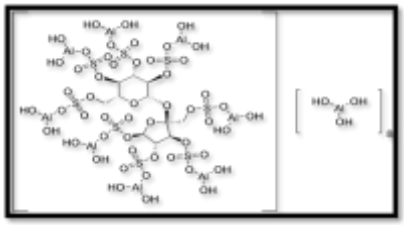
V. ULCER PROTECTIVE:

The ulcer protective agent is defined as having been shown to accelerate ulcer healing without appreciable acid inhibition. Despite an apparently different mode of action, the healing rates are similar to those of commonly used acid inhibitors.

Mechanism of action:

The mechanism of ulcer protection is that it dissociates in the acid environment of the stomach into its anionic form, which binds to the ulcer base. This creates a protective barrier to pepsin and bile and inhibits the diffusion of gastric acid. [86]

Sucralfate:



Chemical name: Hexadeca-µ hydroxytetracosahydroxy[µ8 [1,3,4,6-tetra-O-sulfo-β-Dfructofuranosyl-α-D-glucopyranoside tetrakis(hydrogen sulfato)8-)]]hexadecaaluminum [87]

Spectrophotometric method:

Sreedhar et al. Quantitative determination of sucralfate by spectrophotometric method the λmax of sucralfate was found to be 281 nm, and the calibration curve gives R2 = 0.9999 at 0.1 NHCL at 281 nm. [88]

Chromatographic method:

RP-HPLC method:

Sujitha Parimala S. reported a reliable RP-HPLC chromatographic method developed for the quantitative determination of sucralfate and oxetacin. Chromatography was performed using the reversed phase technique on a C18 column with the mobile phase consisting of acetonitrile and phosphate buffer (pH 8.9) in a ratio of 30:70 v/v with a flow rate of 1 ml/min and a maximum wavelength of 282 nm. This method proved to be specific and accurate, with an average sucralfate yield of 99.60%. The linearity of the proposed method was investigated in the range of 500–1500 µg/ml sucralfate with a 20-minute run time (sucralfate retention time 3.5 minutes). The concentrations of sucralfate and oxetacain were determined, and the average determination was 99.93% and 100.2%, respectively. [89]

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TABLE 6: Spectrophotometric method validation parameters range for prostaglandin analogue and ulcer protective

Parameter	Misoprostol	Sucralfate
wavelength(nm)	200-400	281
Linearity(µg/ml)	1-10	5-25
Correlation coefficient	Near to 1	Near to 1
LOD(µg/ml)	0.656-22.6924	----
LOQ(µg/ml)	1.988-6.3406	----

TABLE 7: Chromatographic method validation parameters range for prostaglandin analogue and ulcer protective

Parameter	Misoprostol	Sucralfate
Flowrate(ml/min)	00.7-1.5	1
Linearity(µg/ml)	2-10	10-30
Correlation coefficient	Near to 1	Near to 1
LOD(µg/ml)	1.87	0.2141
LOQ(µg/ml)	5.6	0.643

VI. CONCLUSION

The most frequently used spectrophotometric and chromatographic analytical techniques have been reported in this literature review. These techniques have been developed using analytical tools like UV-visible spectrophotometers, high-performance liquid chromatography, reversed-phase high-performance liquid chromatography, and ultra-high-performance liquid chromatography. Furthermore, it was created to characterise certain antiulcer drugs. They are including H2 antihistamines, proton pump inhibitors, prostaglandin analogues, and ulcer protection in their pure form, pharmaceutical chemicals, human plasma, and other biological fluids.

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