INTRODUCTION

Medical Importance and clinical usage of H2 receptor blockers

For a number of stomach conditions, H2 receptor blockers or H2 receptor antagonists (H2RAs) are frequently utilized as gastric acid-suppressing drugs. They are FDA-approved for short-term use in the treatment of duodenal or stomach ulcers, uncomplicated gastroesophageal reflux disease (GERD), mild to moderate heartburn or indigestion, and gastric hypersecretion. In addition, H2RAs can be used off-label to avoid stress ulcers, esophagitis, gastritis, gastrointestinal hemorrhage, and urticaria. Sometimes H2RAs are used with other drugs to get rid of Helicobacter pylori. H2RAs have also been shown to be safe for usage in children and adolescents who sometimes or mildly experience heartburn symptoms that don’t get better with dietary or lifestyle changes. The severity of gastric disease, the dosage schedule, and the length of therapy are all important factors that affect how well H2RAs work overall. This activity discusses the indications, contraindications, and use of H2 blockers and demonstrates the role of the interprofessional team in promoting their safety. Overall therapeutic success of H2RAs is substantially impacted by gastrointestinal illness, the dose schedule, and the duration of therapy. This activity discusses the indications, contraindications, and use of H2 blockers and demonstrates the role of the interprofessional team in promoting their safety.1.

Mechanism of action

H2RAs decrease stomach acid secretion by reducing the binding and activity of the endogenous ligand histamine by reversibly connecting to histamine H2 receptors present in gastric parietal cells. H2 blockers are hence competitive foes. After a meal, gastrin often stimulates enterochromaffin-like cells to produce histamine. Stomach acid is then released as a result of histamine’s attachment to histamine H2 receptors on gastric parietal cells. An increase in stomach acid secretion results from the activation of protein kinase A (PKA), which phosphorylates proteins involved in the migration of H+/K+ ATPase transporters to the plasma membrane among other things. The activation of adenylyl cyclase, which raises intracellular cAMP levels, results in an increase in stomach acid secretion. Parietal cells release more acid due to the growth of H+/K+ ATPase transporters in the plasma membrane. By inhibiting the histamine receptor and consequently histamine-stimulated parietal cell acid production, H2RAs reduce both stimulated and basal histamine-induced stomach acid secretion. Given that their duration of action, which ranges from 4 to 10 hours, starts roughly 60 minutes after injection, H2RAs are effective for treating occasional symptoms on-demand. All H2RAs are equally effective at reducing the production of stomach acid.1.
Adverse effects of H2 receptor blockers

Antagonists of the H2 receptor are often well-tolerated. Headache, weariness, drowsiness, fatigue, abdominal pain, constipation, or diarrhea are examples of mild side effects. H2RA use has been linked to central nervous system side effects such as delirium, confusion, hallucinations, or slurred speech in individuals with renal impairment, hepatic impairment, or who are over 50. Although famotidine has also had comparable effects, cimetidine is typically thought to be the most common source of these symptoms.

Drug interactions with H2 receptor antagonists may occur. As a result of the therapeutic increase in gastric pH, the absorption of drugs requiring an acidic environment for dissolution may become altered. Cimetidine is a potent cytochrome P450 (CYP450) enzyme inhibitor and should be avoided with other medications metabolized by CYP450 enzymes such as theophylline, selective serotonin reuptake inhibitors, or warfarin. Prolonged, high doses of cimetidine have also been linked to gynecomastia, reduced sperm count, and impotence in men and galactorrhea in women.

Modern analytical approaches for the assessment of medicines such as cimetidine, ranitidine, famotidine, and nizatidine are reviewed which are observed to be more appropriate simultaneously. A reversed phase HPLC method for the determination of cimetidine is presented. The method is based on D-value measurement at 216 nm, whilst the latter depends on charge-transfer complexation with dichlorophenolindophenol (DCPIP).

High-performance liquid chromatography methods for CIM

S.J. Soldin et al. (1979) described a micro, rapid, and microchemical procedure for the analysis of CIM in serum or plasma. A high-performance liquid chromatograph series 2/2 (Perkin-Elmer Corp., Norwalk, Conn. 06856) and a 4 mm x 30 cm μ-Bondapak C18 column mounted in a temperature-control block were used. The mobile phase was a 91/9 mixture of A/B (Reagent A – 10 mM phosphate buffer pH 3.0; Reagent B is acetonitrile). 220 nm was selected as the wavelength of detection. The percentage of analytical recovery of CIM and its related impurities was determined using a spectrophotometric method (the LOD was found to be 100 µg/l). Two sensitive and fast spectrophotometric methods using batch and flow-injection procedures for the determination of cimetidine (CIM) are proposed. The methods are based on the formation of a green complex between this drug and Cu (II) in an acetic/acetate medium of pH 5.9. The FI system comprised a Gilson HP4 peristaltic pump with silicone flow tubes of 1.0 mm i.d., (Workington, OH, USA), an Omnifit injection valve (NY, USA), a Hitachi Model 561 recorder were used. By two different reaction approaches, cimetidine was treated with HCl in the first method and the resulting HCl was mixed with and analyzed at 216 nm. The second approach included treating the cimetidine with methanol and the methanol at a lower pH with DCPIP which is calculated at 640 nm.

M. Soledad Garcia et al. (2003) Two sensitive and fast spectrophotometric methods using batch and flow-injection procedures for the determination of cimetidine (CIM) are proposed. The methods are based on the formation of a green complex between this drug and Cu (II) in an acetic/acetate medium of pH 5.9. The FI system comprised a Gilson HP4 peristaltic pump with silicone flow tubes of 1.0 mm i.d., (Workington, OH, USA), an Omnifit injection valve (NY, USA), a Hitachi Model 561 recorder were used. By two different reaction approaches, cimetidine was treated with HCl in the first method and the resulting HCl was mixed with and analyzed at 216 nm. The second approach included treating the cimetidine with methanol and the methanol at a lower pH with DCPIP which is calculated at 640 nm.

UV visible spectroscopic methods for CIM

The following UV spectroscopic methods for the estimation of cimetidine are reviewed which are observed to be more robust and precise.
0.003 M sodium L-pentanesulphonate, and the other by using 0.025 M sodium acetate (pH 3.50) containing 0.003 M sodium L-pentanesulphonate plus 20% (v/v) of acetonitrile. The elution of the compounds was carried out at room temperature with a flow rate of 1.0 ml/min. The volume injected was 5-50 µl.

E. Jantratid et al. (2007) demonstrated the analysis of cimetidine in human plasma with HPLC using a simplified sample preparation by protein precipitation with perchloric acid. A Waters Spherisorb® 55 ODs2 (4.6 × 250 mm, i.d.; 5 µm) analytical column connected with a guard column was used. The mobile phase consisted of 11% acetonitrile and 0.2% triethylamine, q.s. to volume with 0.05 M KH2PO4. The flow rate was set at 0.9 ml/min, resulting in a run time of 10 min per sample. The injection volume was 100 µl. A detection wavelength of 228 nm was used. The lower limit of quantification (LOQ) of the method was established at 0.1 µg/ml.

**Ranitidine**

Since its introduction to the market in 1981, ranitidine (N-[2-[5-dimethylamino-methyl]-2-furanil-methylthioethyl] N'-methyl-nitro-1,1-diaminoethane) (Figure 2) has been widely used to treat duodenal and gastric ulcers, reflux esophagitis, and dyspepsia. It is a histamine H2-receptor antagonist with a furan ring structure as opposed to cimetidine, which has an imidazole ring. This substituted aminoalkyl furan derivative is sold in a variety of dosage forms, including tablets, syrups, and injection solutions, and is more effective than cimetidine as an inhibitor of gastric acid secretion.

![Figure 2: Structure of Ranitidine](image)

So, for the quantitative estimation of ranitidine, various analytical methods are reported by using several chromatographic techniques such as HPLC, supercritical fluid chromatography and capillary electrophoresis, GC-MS; spectrophotometric methods using UV Spectrophotometer; and hyphenated techniques like flow-injection method, HS-SPME-GC-MS, polarographic, voltammetric and potentiometric sensors.

**Analytical methods for Ranitidine**

The following methods like spectrophotometry, HPLC, UPLC, HPTLC, and other hyphenated techniques are reviewed here which are more robust and precise.

T. Perez-Ruiz et al. (2001) carried out the spectrophotometric determination of trace amounts of ranitidine by liquid-liquid extraction using bromothymol blue with a flow system. A Perkin-Elmer (Norwalk, CA, USA) 5000 SE spectrophotometer was used for recording spectra. The absorbance of the organic phase was measured at 420 nm. The carrier was an acetate or 20 mM ammonium bicarbonate gradients at a flow rate of 0.45 ml/min and a temperature of 50°C. The column eluent was monitored by UV detection at 230 nm. The UPLC separations were performed on a Waters ACQUITY UPLC™ System using 2.1 × 100 mm 1.7-µm ACQUITY BEH C18, C8, C6, phenyl, and C18 Shield columns with a 1.0-µl injection. The columns were eluted using various gradient profiles with combinations of methanol or ACN with 20 mM ammonium acetate or 20 mM ammonium bicarbonate gradients at a flow rate of 0.45 ml/min and a temperature of 50°C. The column eluent was monitored by UV detection at 230 nm and positive ion electrospray MS. The ranitidine impurity solution was injected into a 2.16100-mm ACQUITY BEH C18 column, the column was eluted with a 5–90% ammonium acetate pH 5 (20 mM) over 6 min at a flow rate of 0.45 ml/min. This resulted in a retention time of 1.5 min for the ranitidine active standard.

P.A. Raymundo-Pereira et al. (2013) described the preparation and electrochemical characterization of a carbon paste electrode modified with the N, N-ethylelen-bis(salicylideneiminato)oxoranium (IV) complex ([VO (salen)]+ as well as its application for ranitidine determination. The electrochemical behavior of the modified electrode for the electroreduction of ranitidine was investigated using cyclic voltammetry, and analytical curves were obtained for ranitidine using linear sweep voltammetry (LSV) under optimized conditions. All voltammetric measurements were carried out in a 20-m1 thermostatted glass cell at 25 °C, with a three-electrode configuration: a modified carbon paste electrode as the working electrode, an Ag/AgCl (3 mol 1⁻¹ KCl) as a reference and a platinum auxiliary electrode. Cyclic voltammetric and linear sweep voltammetry (LSV) measurements were performed with an Autolab/PSTAT-30 (Eco Chemie) potentiostat/galvanostat. The best voltammetric response was obtained for an electrode composition of 20% (m/m) [VO (salen)] in the past, 0.10 mol 1⁻¹ of KCl solution (pH 5.5 adjusted with HCl) as supporting electrolyte, and a scan rate of 25 mV/s. A sensitive linear voltammetric response for ranitidine was obtained in the concentration range from 9.9 × 10⁻5 to 1.0 × 10⁻3 mol 1⁻¹, with a detection limit of 6.6 × 10⁻6 mol l⁻¹ using linear sweep voltammetry.

Y.M. Alshehri, T.S. Alghamdi, and F.S. Aldawsarie et al. (2020) assessed the usefulness of solid-phase microextraction (SPME)
as a method of extraction and introduction into the GC. When using headspace (HS) and liquid injection modes in GC for NDMA analysis in ranitidine, higher NDMA levels were detected compared to using LC–MS/MS. The results obtained using HS-SPME-GC–MS provided a good match with those achieved using LC–MS/MS. NDMA was analyzed by Shimadzu GC–MS/MS model TQ8050 (Kyoto, Japan). The column was DB WAX (Santa Clara, United States) with dimensions of 0.5 m, 30 m, and a diameter of 0.25 mm. The lowest detected NDMA concentration was 1 g/l at a Signal to Noise (S/N) ratio of 3, while the LOQ was 5 g/l at (S/N) $> 10^{12}$.

High-performance liquid chromatography methods for Ranitidine

G.W. Milhaly, O. H. Drummer, A. Marshall, R.A. Smallwood, and W. J. Louis et al. (1980) described an assay for the determination of a new H2 receptor antagonist, ranitidine, and its dimethyl metabolite in human plasma and urine. Assays were carried out using a constant-flow high-pressure liquid chromatograph consisting of a solvent delivery system, a universalinjector, and a variable-wavelength UV absorbance detector operated at 330 nm. The stainless-steel column (Waters Associates µBondapak C18) was obtained prepacked (30 cm x 3.9 mm i.d.). Injection volumes of 50 µl were used. The mobile phase was methanol dibasic ammonium phosphate (pH 8.7 mM) (75:25), and the flow rate was maintained at 1.1 ml/min at a back-pressure of 1500 psi. The retention times of the N-oxide metabolite, the S-oxide metabolite, ranitidine, dimethyl ranitidine, and V were 3.3, 3.8, 4.4, 5.3, and 6.1 min, respectively.

L.G. Hare et al (2001) described a sensitive HPLC method for the determination of ranitidine in small-volume (0.5 ml) pediatric plasma samples. Chromatographic separation was achieved by RP-HPLC with isocratic elution using a µBondapak C18 column (300 x 3.9 mm, 10 µm) fitted with a Waters µBondapak C18 (3.9-20 mm, 10 µm) guard column and a phosphate buffer (10 mM, pH 3.75)-acetonitrile (87:13 v/v) mobile phase with UV detection at 313 nm. The injection volume was 40 µL. The mobile phase was delivered at a flow rate of 1 ml/min. The HPLC system exhibited linearity in the range 8–800 ng ml⁻¹. The limits of detection and quantitation obtained were 2 ng ml⁻¹ and 8 ng ml⁻¹, respectively, and ranitidine extraction recoveries from plasma ranged from 92.30 to 103.88%.

M.J. Nozal et al (2001) described a liquid chromatographic method for the determination of the residues of ranitidine hydrochloride on various surfaces employed in drug manufacture is described. Cotton swabs, moistened with a methanol–water (1:1, v/v) mixture were used to remove any residues of drugs from glass, vinyl, and stainless-steel surfaces, and gave recoveries of 85%, 78%, and 90%, respectively. The chromatographic separation was carried out on a Luna, 5 µm, 250 x 4.6 mm, C18 column. Residues were determined by HPLC on a C18 column at 25°C with methanol–ammonium acetate (40:60 v/v) pH 6.7 as the mobile phase, flow rate was 1 ml/min, and the oven temperature 25°C. The injection volume was 25 µl and the detection was at 320 nm. The method was validated over a concentration range of 20–10000 ng/ml and had a detection limit of 2 ng/ml.

Sevgi Tatar Ulu, Muzafer Tuncel, et al. (2012) described a novel pre-column derivatization RP-HPLC method with fluorescence detection for the determination of ranitidine in human plasma. The separation was achieved on a C18 column using methanol–water (60:40, v/v) mobile phase. Fluorescence detection was used at the excitation and emission of 458 and 521 nm, respectively. The flow rate was 1.2 ml/min. Ranitidine and lisinopril appeared at 3.24 and 2.25 min, respectively. Intra- and inter-day precisions of the assays were in the range of 0.01 – 0.44%. The assay was linear over the concentration range of 50–2000 ng/ml. The mean recovery was determined to be 96.40± 0.02%.

Famotidine

Histamine H2-receptor antagonist famotidine has been used extensively to treat peptic ulcers. The gastrointestinal tract readily absorbs famotidine, however, it does so inefficiently, with peak plasma concentrations occurring around two hours after oral treatment. Famotidine is mostly eliminated unchanged in the urine, with a minor amount of it being converted to famotidine oxide in the liver. A sensitive approach is needed to measure plasma famotidine concentrations in clinical research since the therapeutic doses of famotidine that are advised to patients are low (40 mg daily), and these dosages yield very low therapeutic concentrations in plasma (20-150 ng/ml) after a 40 mg oral dose. The structure is shown in (Figure 3)²³.

![Figure 3: Structure of Famotidine](image_url)

**Figure 3: Structure of Famotidine**

Analytical methods for Famotidine

The following methods like spectrophotometry, HPLC, RPLC, potentiometry, spectrofluorimetric, and other hyphenated techniques are reviewed here which are more robust and precise.

Zarghi et al. (2005) developed a rapid and sensitive HPLC method using a monolithic column for the quantification of famotidine in plasma. The assay enables the measurement of famotidine for therapeutic drug monitoring with a minimum detectable limit of 5 ng ml⁻¹. The separation was carried out in reversed-phase conditions using a Chromolith Performance (RP-18e, 100 mm x 4.6 mm) column with an isotropic mobile phase consisting of 0.03 M disodium hydrogen phosphate buffer–acetonitrile (93.7, v/v) adjusted to pH 6.5. The wavelength was set at 267 nm. The calibration curve was linear over the concentration range of 20–400 ng/ml. The limit of quantification was 15 ng/ml for famotidine.

M.A. Campanero et al. (2001) presented a simple and rapid chromatographic procedure using a specific analytical detection method (ESI tandem mass spectrophotometric detection) in combination with a fast and efficient sample work-up procedure, protein precipitation. The apparatus used for the HPLC analysis was a Model 1100 series LC. Separation was carried out at 50°C on a reversed-phase, 250 x 4 mm base stable C18 column packed with 5 µm silica reversed-phase particles (Tracer-kromasil 100). Mobile phases were: (A) methanol–1% formic acid (24:76, v/v); (B) methanol–17 mM ammonium acetate with 1% acetic acid (24:76, v/v). Separation was achieved by isotropic solvent elution at a flow rate of 1 ml/min. Each analysis required 5 min. The calibration curve of famotidine in the range 1–200 ng/ml was linear with a correlation coefficient of 0.9992 (n=6), and detection limit of a signal-to-noise ratio of 3 was ~0.2 ng/ml. The within- and between-day variations in the famotidine analysis were 5.2 (n=6) and 6.7% (n=18), respectively.

M.M. Ayad et al. (2002) described two new potentiometric methods for the determination of famotidine in pure form and in its pharmaceutical tablet form are developed. In the first method, the construction of plasticized poly (vinyl chloride) (PVC) matrix-type famotidine ion-selective membrane electrode and their use in the potentiometric determination of
famotidine in pharmaceutical preparations are described. It is based on the use of the ion-associate species, formed by famotidine cation and tetraphenylborate (TPB) counterion. Jenway 3010 pH/mV meter with double junction platinum electrode, Jenway 3010 pH/mV meter, with famotidine–tetraphenylborate (TPB)–poly (vinyl chloride) (PVC) membrane electrode in conjunction with double junction Ag/AgCl electrode (Orion 90-02), containing 10% w/v potassium nitrate in the outer compartment were used. In the second method, the conditions for the oxidimetric titration of famotidine have been studied. The method depends on using lead (IV) acetate for oxidation of the thioether contained in famotidine. The titration takes place in the presence of catalytic quantities of potassium bromide (KBr). Direct potentiometric determination of 1.75×10⁻² M famotidine solution showed an average recovery of 100.51% with a mean standard deviation of 1.26%²⁰.

M. I. Walsah, A. El-Brashy, N. El-Enany & M. E. Kamel et al. (2009) developed a simple, economic, selective, and stability-indicating spectrofluorimetric method for the determination of famotidine; is based on its reaction with 9, 10-phenanthroquinone in alkaline medium to give a highly fluorescent derivative measured at 560 nm after excitation at 283 nm. The fluorescence spectra and measurements were recorded using a Perkin Elmer LS 45 Luminescence Spectrometer equipped with a 150 W Xenon arc lamp. A 1 cm quartz cell was used. The fluorescence intensity-concentration plot was rectilinear over the concentration range of 50–600 ng/ml with a minimum quantification limit (LOQ) of 13.0 ng/ml and a minimum detection limit (LOD) of 4.3 ng/ml. The mean % recovery (n=4) was found to be 99.94±0.24, and 105.13±0.64 for spiked and real human plasma, respectively²⁰.

R. El-Shaheny, M.O. Radwan, F. Belal et al. (2020) inspected the competence of hydrophilic interaction liquid chromatography (HILIC) and reversed-phase liquid chromatography (RPLC) modes, employing two new stationary phases: triazole and Penta bromobenzoyl-bonded silica (PBr), respectively for separation of two polar basic analytes: famotidine (FAM) and its acidic degradant famotidine (FON). LC separation was finally selected for analytical applications was ACN: 0.01 M ammonium acetate buffer (25:75, v/v), pH 6.3 at a flow rate of 1 ml/min using the RP column. Hence, the RPLC method was adopted and validated adhering to the FDA guidelines showing excellent linearity for FAM (1.0–20.0 µg/ml) with a detection limit of 0.14 µg/ml.²⁰

So, for the quantitative estimation of nizatidine, various analytical methods are reported by using several chromatographic techniques such as HPLC, and HILIC methods.

Analytical Methods of Nizatidine

M. B. Çakar and S. T. Ulu et al. (2013) developed a sensitive HPLC method for the determination of nizatidine in human plasma. Nizatidine was derivatized by 4-fluoro-7-nitrobenzofurazan (NBD-F). Fluorescence intensity was measured on an RF-1501 spectrometer from Shimadzu (Kyoto, Japan). Chromatographic separation was performed on an Inertsil C₁₈ column (150 mm × 4.6 mm, 5 µm) using isocratic elution by a mobile phase consisting of methanol/water (55:45) at a flow rate of 1.2 ml/min. Amlodipine was used as the internal standard (IS). The fluorescence detector was used and operated at 461 nm (excitation) and 517 nm (emission), respectively. The calibration curve was linear over the range of 50–2000 ng/ml. LOD and LOQ values for Niz were found to be 10.2 and 34.2 ng/ml. The recovery was found to be 98.18%²².

F.A. El-Yazbi et al. (2003) described four simple and accurate methods for the determination of nizatidine (NZ) in pharmaceutical preparations. The first method is based on the formation of an ion-pair complex between the drug and either bromocresol purple or picric acid with subsequent measurement of the developed colors at 411 and 400 nm, respectively. The second method depends on the condensation of mixed anhydrides of citric acid/acetic anhydride, with the tertiary amino group of the drug, where the developed color is measured spectrophotometrically at 545 nm. The oxidation of nizatidine by N-bromosuccinimide was utilized as a basis for the titrimetric method for its assay in capsules. The last method depends on the oxidation of nizatidine by ammonium cerium IV sulfate in the presence of perchloric acid with subsequent measurement of the absorbance at 314 nm. The spectrophotometric determinations were performed using a Perkin - Elmer lambda EZ 201. The detection limits varied from 0.44 to 0.70 µg/ml. The calibration graphs were linear over the concentration range of 5–15 µg/ml⁻¹²⁵.

D.W. Shang et al. (2015) developed and validated an HPLC method coupled with triple quadrupole mass spectrometry for the analysis of nizatidine in human plasma and urine. The biological samples were precipitated with methanol before separation on an Agilent Eclipse Plus C₁₈ column (100mm×46mm, 5µm) with a mixture of methanol and water (95:5, plus 5 mM ammonium formate) as the mobile phase at 0.5 ml/min. The injection volume was 1µL and the total LC run time was 2.7 min. Detection was performed using multiple reaction monitoring modes via electrospray ionization (ESI) at m/z 332.1→155.1 (for nizatidine) and m/z 335.1→155.1 (for [2H₃]-nizatidine, the internal standard). The linear response range was 5–2000 ng/ml and 0.5–80 ng/ml for human plasma and urine, with the lower limits of quantification of 5 ng/ml and 0.5µg/ml respectively. In human plasma, absolute recovery was found to be in the range of 87.06–89.50% for nizatidine, whilst in urine the recovery was 94.21–99.87% for nizatidine²⁴.

Rania El-Shaheny, Mohamed Radwan, Koji Yamada, Mahmoud El-Maghraby et al. (2019) optimized and validated a hydrophilic interaction liquid chromatography (HILIC) method according to FDA guidance by monitoring the nitrosatibility of NZ. A Hitachi HPLC instrument (Tokyo, Japan) composed of a 655A-11 liquid chromatograph, L-4000H UV detector (a high sensitivity series), D-2500 chromato-integrator, LC-organizer, and a Rheodyne injector valve with a 50 ml sample loop was used. The flow rate of the mobile phase was 1 ml/min and the UV-detection was at 325 nm.

Nizatidine

Nizatidine, also known as N-(2-[(2-[(dimethylamino)methyl] thiazol-4-yl])-N-methyl-2-nitrothenene-1,1-diamine, as shown in figure 4, is a histamine H₂ receptor inhibitor that is particularly effective in stomach parietal cells. It is utilized as a continuing treatment for ulcers as well as an active duodenal ulcer treatment²².

Figure 4: Structure of Nizatidine
nm A Cosmosil HILIC® column and a mobile phase composed of acetonitrile: 0.04 M acetate buffer pH 6.0 (92:8, v/v) were used for the separation of NZ and its N-nitroso derivative (NZ-N0) within 6 min with LODs of 0.02 and 0.1 mg/ml, respectively25.

Common methods for estimation of H2 Receptor blockers

There are some common methods reported for the estimation of H2 receptor blockers, the methods involving the use of UV Visible Spectrophotometer, HPLC, HPTLC, electrophoresis, etc. The methods reviewed are discussed below, involving simultaneous estimation or individual formulation by the same method.

T. Pérez-Ruiz et al. (2002) developed a simple and sensitive capillary electrophoresis method using UV detection for the direct determination of ranitidine (RAN) and famotidine (FAM) in serum, urine and pharmaceutical formulations. A buffer consisting of 60 mM phosphate buffer adjusted to pH 6.5 was found to provide a very efficient and stable electrophoretic system for the analysis of both drugs. Separations were performed on a P/ACE 5500 automated CE system (Beckman Instruments, Palo Alto, CA) equipped with a diode array detector. Fused silica capillaries (Beckman) of length 75 µm, od375 µm and lengths 57 cm were used. The samples were introduced using a 10 s low pressure injection (0.5 psi) and the separation was carried out for 8 min at 10 kV and 25°C and absorbance was monitored at 228 nm. Calibration graphs were obtained by injecting standard solutions of the analytes in the concentration range 0.5–50 µg ml⁻¹. The detection limits obtained were 0.008 mg ml⁻¹ for RAN and 0.16 mg ml⁻¹ for FAM26.

Y.H. Tang et al. (2007) developed a new sensitive flow-injection chemiluminescence (FI-CL) method, validated and applied for the determination of three kinds of H2-receptor antagonists: cimetidine (CIM), ranitidine (RAN) hydrochloride and famotidine (FAM) based on the chemiluminescence (CL) intensity generated from the potassium ferricyanide [K3Fe(CN)6]-rhodamine 6G system in a sodium hydroxide (NaOH) medium. The CL signal was measured using a photomultiplier tube. Under the optimum conditions, the linear range for the determination was 1.0 × 10⁻⁶–7.0 × 10⁻⁴ g/ml for CIM, 1.0 × 10⁻⁵–5.0 × 10⁻⁴ g/ml for RAN hydrochloride, and 5.0 × 10⁻⁵–7.0 × 10⁻⁴ g/ml for FAM. The detection limit was 8.56 × 10⁻⁶ g/ml for CIM, 8.69 × 10⁻⁶ g/ml for RAN hydrochloride, and 2.35 × 10⁻⁵ g/ml for FAM (S: N = 3)27.

I.A. Darwish et al. (2008) developed a simple, accurate, and sensitive spectrophotometric method for the determination of H2-receptor antagonists: CIM, FAM, RAN, and NZ has been fully developed and validated. The method was based on the reaction of these drugs with NBS and subsequent measurement of the excess N-bromosuccinimide by its reaction with p-aminophenol to give a violet-colored product (max at 552 nm). UV-1601 PC (Shimadzu, Japan) and Lambda-3 B (Perkin-Elmer, USA) ultraviolet-visible spectrophotometers with matched 1-cm quartz cells were used for all measurements. Limits of detection were 1.22, 1.01, 1.08, and 0.74 mg ml⁻¹ for CIM, FAM, RAN, and NZ, respectively28.

J.J. Berzas Nevado et al. (2013) report a previously optimized method based on non-aqueous capillary electrophoresis (NACE) using UV detection for the separation and simultaneous determination of CIM, RAN, ROX, NZ, and FAM in human urine. Tests were performed on a Beckman (Fullerton, CA, USA) P/ACE System MDQ capillary electrophoresis system equipped with a diode-array detector and controlled via Beckman capillary electrophoresis software. Separations were done in a 31 cm (21 cm from inlet to detector) × 75 cm i.d. fused silica capillary accommodated in a cartridge that was thermostated at 25°C. The detection window was 800 µm × 100 µm. Separation is performed at 25°C and at a separation voltage of 15 kV. Methanol containing 10 mM ammonium acetate and 0.2% acetic acid was used as background electrolyte and detection at 214 nm. These conditions allow the five analytes to be separated within 4 min. Detection limits were evaluated on the basis of baseline noise and were established between 8 and 15 µg l⁻¹ for NACE and between 16 and 162 µg l⁻¹ for HPLC. Finally, the proposed methods were successfully applied to the screening determination of the analytes in human urine, with recoveries between 97 and 105%, being able the use as pharmacokinetic data in clinical urine samples29.

Elshabouey et al. (2015) developed a simple, efficient, and reliable ion-pair chromatography (IPC) method and validated for the determination of some H2 receptor antagonists including RAN, NIZ and FAM. The use of IPC separations provided improved peak resolution with good peak shape in a short analysis time and augmented method selectivity compared with the frequently used RP-C18 methods. A Young Lin Auto-Chro-3000 HPLC system (Younglin, Korea) was used in this study. The studied drugs were separated isocratically as mobile phases, using Kromasil C18 (250 × 4.6 mm, 5 µm) column (Alzeneobel, Japan), and were maintained at ambient temperature (25°C). A simple isocratic mode with a mobile phase containing acetonitrile and 20 mM acetate buffer (50: 50, v/v) containing 20 mM sodium dodecyl sulfate was used for separation. The flow rate was set at 1.0 ml min⁻¹, and the eluent was monitored by a UV detector at 280 nm FAM and 320 nm for NIZ and RAN. The limits of detections and quantitations were 0.008–0.011 and 0.025–0.033 µg ml⁻¹, respectively. The linearity range for the plasma calibration curve was 0.1–100 mg ml⁻¹ with a correlation coefficient of 0.998920.

S. Ahmed et al. (2017) developed a comparative force degradation high-performance thin layer chromatography (HPTLC) method and validated it for some H2-receptor antagonists - RAN, NIZ, and FAM. Full separation of the drugs from their degradation products was successfully achieved on an HPTLC-precoured silica gel plate. The sample was spotted as a band with 4mm width using a Camag 100 µl sample syringe on HPTLC silica gel precoated aluminum plate 60 F-254 plates, (10 cm × 10 cm with 250 μm thickness) by a sample applicator Camag Linomat V (Switzerland). The mobile phase consisted of acetonitrile (ACN): acetate buffer pH 5.8 (60:40, v/v) for RAN and (70:30, v/v) for FAM. The limits of detection and limits quantitation range were 5.47–9.37 and 16.30–31.26 ng/band, respectively, for all investigated drugs. The recovery percentage ranged from 98.3 to 101.6%31.

CONCLUSION

Cimetidine, ranitidine, famotidine, and nizatidine are the most common H2 receptor blockers. They significantly lower gastric acid and are used to treat uncomplicated gastroesophageal reflux disease (GERD), gastric or duodenal ulcers, gastric hyperssecretion, and mild to infrequent heartburn or indigestion. H2RAs can also be used off-label for preventing esophagitis, gastritis, gastrointestinal hemorrhage, ulcetaria, and stress ulcers. This study discusses many hyphenated techniques, such as LC-MS/MS detection, as well as quantitative estimation approaches using UV visible spectrophotometry, HPLC, and human plasma or fluids as the matrix. The contaminants and the primary drug can be
distinguished and measured using the reported stability-indicating methods. To get the needed method optimization, several methods were created utilizing DoE or QbD methodologies. The majority of techniques are found to be quick, easy to repeat, economical, and simple. Their suitability for analysis usage is established by the results of their validation parameters, particularly linearity, recovery, accuracy, LOD, and LOQ. All HPLC techniques use reverse phase chromatography with UV detection, and many spectrophotometric techniques work via reagent reaction or colour development. The principal hyphenated approaches were the LCMS/MS and UPLC-MS/MS procedures, which are mostly used for stability indicating and impurity profiling analyses. Future thoughts on the necessary adaptation to new trends for advancements in modern H2 analytical methods.

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CONFLICT OF INTEREST

The author declared no conflict of interest.

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