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Review Article

Overview of Analytical Methods for the Determination of H2 Receptor Blockers: A Review

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Abstract

Overview of various analytical methods for estimating anti-histaminic (H2 Receptor blockers) drugs, particularly for determining their concentration percentage (assay) by analytical methods developed on analytical instruments i.e., UV visible Spectrophotometer, High-Performance Liquid Chromatography, and Hyphenated techniques. The review includes a literature survey of H_2 receptor blocker drugs namely cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid, Pepcid AC), and nizatidine (Axid). The examined literature survey addressed chromatographic (HPLC) and UV visible spectrophotometric methods with LC-MS/MS methods used in pure forms, pharmaceutical formulations, human plasma, and other biological fluids for their estimation. In the case of validation parameters, mostly Linearity, Recovery study, LOD, and LOQ were considered and mentioned. This review helps researchers to get detailed information regarding various analytical methods of development and validation for H2 receptor antagonists.

Keywords: H2 Receptor blockers, HPLC, Analytical methods, ranitidine, famotidine, nizatidine.

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. The 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 adenylate 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 sides 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 H_2 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[1].

Modern analytical approaches for the assessment of medicines such as cimetidine, ranitidine, famotidine, and nizatidine are presented in the current review. For the mentioned medications, several chromatographic procedures, hyphenated techniques, UV visible spectrophotometric methods, simultaneous estimation methods, and stability-indicating approaches are presented. The chromatographic procedures that are most frequently reported are HPLC, UPLC, and HPTLC techniques. For the estimation of H2 receptor blockers, the extension to chromatographic techniques and hyphenated techniques like LC-MS/MS and UPLC-MS are also reported. Stability indicating and impurity profiling approaches are developed and used for H2 receptor blocker analysis mostly using hyphenated procedures. For the creation and optimization of some procedures, the design of experiments and QbD methodologies are used.

Cimetidine (Tagamet)

The medication cimetidine (N"-cyano-N-methyl-N'-[2-[[(5-methyl-1H imidazol4yl)methyl] Thio]ethyl]guanidine) inhibits acid secretion induced by histamine by acting antagonistically on the parietal cell H2-receptor[2]. In the treatment of duodenal and gastric peptic ulcers and hypersecretory illnesses (such as Zollinger-Ellison syndrome and systemic Masto cytosis), cimetidine is frequently used as an H2-receptor antagonist. The medication has a substituted imidazole structural makeup (Figure 1), functions as a weak base, and has a high-water solubility[3].

So, for the quantitative estimation of cimetidine in formulation or blood plasma various analytical methods are reported by using UV Spectrophotometer, HPLC, and LC-MS.

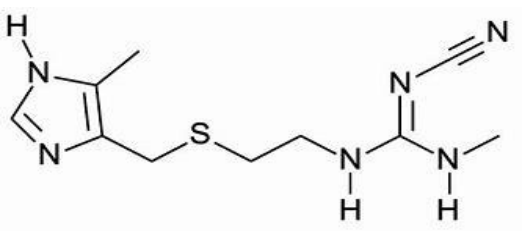

Figure 1: Structure of Cimetidine

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.

Mona M. Bedair et al. (1991) proposed a method by which cimetidine has been determined in the presence of its acid-induced degradation products like ampoules and tablets using a second derivative (D_2-) spectrophotometric method (the method I) or a colorimetric method (method II). The former is based on D-value measurement at 216 nm, whilst the latter depends on charge-transfer complexation with dichlorophenolindophenol (DCPIP). Perkin-Elmer Model 550s UV-vis spectrophotometer with fixed slit width 2 nm and 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[4].

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., (Worthington, OH, USA), an Omnifit injection valve (NY, USA), a Hellma 18 µl flow cell (Jamaica, NY, USA) and a Pyc-Unicam spectrophotometer (Cambridge, UK) as the detector. The calibration graphs resulting from measuring the absorbance at 330 nm are linear over the ranges 2.5 x 10^{-6} to 1.0 x 10^{-3} and 5 x 10^{-6} to 2.0 x 10^{-3} M with detection limits of 9.5 x $10^{-7}$and 2.1 x 10^{-6} for batch and flow-injection methods, respectively[5].

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 C_{18} column mounted in a temperature-control block were used. The mobile phase used 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 analysis. The percentage of analytical recovery of CIM and internal standard (β-hydroxypropyl-theophylline) was 65 and 99%, respectively. The LOD was found to be 100 µ/l[2].

Qisui Lin, Gary L. Lansmeyer, and Frank C. Larson et al. (1985) developed an HPLC method for the simultaneous determination of cimetidine and its major metabolite, cimetidine sulfoxide. These compounds and the internal standard, ornidazole, were extracted from 0.5 ml of serum using a solid phase Bond Elut ~ C_{18} analytical column with detection at 229 nm. The mobile phase was prepared in 1000-ml batches by combining 120 ml acetonitrile, 880 mL 0.02-mol/l acetic acid, and 0.15 ml of dimethylamine. Absolute recoveries were 94 to 103%, 93 to 104%, and 95 to 105% for cimetidine, cimetidine sulfoxide, and ornidazole, respectively. The minimum detection limit for cimetidine was 0.1 mg/l and for cimetidine, sulfoxide was 0.05 mg/l when the concentrating step was used. Cimetidine and cimetidine sulfoxide demonstrated linearity up to 10 mg/l and 7.5 mg/l respectively, with a between-run precision of less than a 5% coefficient of variation for both compounds[3].

P. Betto, E. Ciranni-Signoretti, and R. Di Fava et al. (1991) developed an HPLC method in order to assay cimetidine and its related impurities simultaneously. A reversed-phase system and diode-array detector were used. Analytical HPLC was performed using an LKB Model 2249 gradient pump and the column used was a µBondapak C_{18} (10 µm) (30 cm x 3.9 mm I.D.). The mobile phase was prepared in two ways- one by using 0.025 M sodium acetate, adjusted to pH 3.50, containing

0.003 M sodium I-pentanesulphonate, and the other by using 0.025 M sodium acetate (pH 3.50) containing 0.003 M sodium I-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[6].

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®S5 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 (LLOQ) of the method was established at 0.1 µg/ml[7].

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[8].

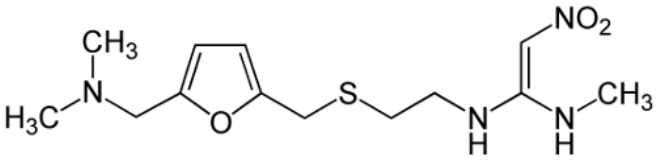

Figure 2: Structure of Ranitidine

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) 550 SE spectrophotometer was used for recording spectra. The absorbance of the organic phase was measured at 420 nm. The carrier was an acetate buffer of pH 5 (0.2 mol l^{-1}) and the reagent stream was a 1×10^{-4} mol l^{-1} bromothymol blue solution. The volume of the sample to be injected was selected as 300 µl. The calibration graph was found to be linear between 1.0×10^{-5} and 1.0×10^{-4} mol l^{-1} (3.51–35.1 mol l^{-1}). The detection limit was 5.68×10^{-6} mol l^{-1}. The sampling rate was 40 samples per hour. The reproducibility of the method was studied by analyzing, on five different days, ten identical solutions of ranitidine (8.0×10^{-5} mol ml^{-1})[8].

SnezanaAgatonovic-Kustrin, Ian G. Tucker, and David Schmierer et al. (1999) developed a new, simple, sensitive, and rapid method to analyze the polymorphic purity of crystalline ranitidine-HCL as a bulk drug from a tablet formulation. For analysis of the samples, a dynamic alignment FT-IR spectrophotometer, extended range KBr beam splitter, DTGS detector, and mid-IR ceramic source (Bio-Rad FTS 175C, Bio-Rad Laboratories, Cambridge, USA) fitted with a diffuse reflectance accessory was used. Diffuse reflectance infrared Fourier transform (DRIFT) spectroscopy was combined with Artificial Neural Networks (ANNs) as a data modeling tool. For the tablet formulation, ANN was trained with 173 (average reflectances) with 35 input data, and five output neurons (sensitivity greater than 1%) one for each tablet ingredient. Better results were obtained for the network trained with 173 inputs[9].

M. D. Jones et al. (2006) have combined the application of sub-2-µm stationary phases and high mobile linear velocities with orthogonal acceleration Q-TOF MS for the impurity structural characterization analysis of small-molecule pharmaceutics. A pharmaceutical drug substance was forcefully degraded and used to test the proof of concept of developing an impurity profile method by ultra-performance liquid chromatography (UPLC). The HPLC was performed on a Waters®XTerra® C_{18} MS 3.96150 mm 5-µm column (Waters Corporation, MA, USA) and Waters Alliance® 2695XE. A 5-µl injection of the sample was made into the column. The column was operated with a flow rate of 1 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 2.16100 mm 1.7-µm ACQUITY BEH C_{18}, C_8, phenyl, and C_{18} 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 C_{18} 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 1.6 min for the ranitidine active standard[10].

P.A. Raymundo-Pereira et al. (2013) described the preparation and electrochemical characterization of a carbon paste electrode modified with the N, N-ethylene-bis(salicyllideneiminato)oxovanadium (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-ml thermostated glass cell at 25 °C, with a three-electrode configuration: a modified carbon paste electrode as the working electrode, an Ag/AgCl (3 mol l^{-1} KCl) as a reference and a platinum auxiliary electrode. Cyclic voltammetric and linear sweep voltammetry (LSV) measurements were performed with an Autolab/PGSTAT-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 l^{-1} of KCl solution (pH 5.5 adjusted with HCl) as supporting electrolyte, and a scan rate of 25 mV/s. A sensitive linear voltametric response for ranitidine was obtained in the concentration range from 9.9 × 10−5 to 1.0 × 10−3 mol l^{-1}, with a detection limit of 6.6×10^{-5} mol l^{-1} using linear sweep voltammetry[11].

Y.M. Alshehri, T.S. Alghamdi, and F.S. Aldawsariet 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 universal injector, and a variable-wavelength UV absorbance detector operated at 330 nm. The stainless-steel column (Waters Associates µBondapak C_{18}) 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[13].

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 C_{18} column (300 x 3.9 mm, 10 µm) fitted with a Waters µBondapak C_{18} (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^{-1}. 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%[14].

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, C_{18} column. Residues were determined by HPLC on a C_{18} 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 ml 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[15].

Sevgi Tatar Ulu, Muzaffer 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 C_{18} 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%[16].

Famotidine

Histamine H2-receptor antagonist famotidine has been used extensively to treat peptic ulcers. The gastrointestinal tract easily 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)[17].

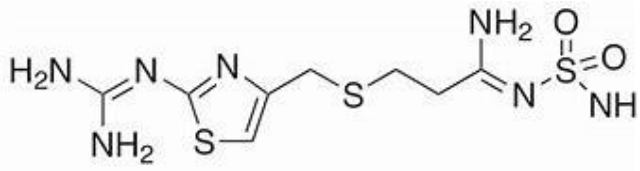

Figure 3: Structure of Famotidine

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 × 4.6 mm) column with an isocratic 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[17].

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 C_{18} column packed with 5 µm silica reversed-phase particles (Tracer-kromasil 100). Mobile phases were: (A) methanol–1% formic acid (24:76, v/v); and (B) methanol–50 mM ammonium acetate with 1% acetic acid (24:76, v/v). Separation was achieved by isocratic 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[18].

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%[19].

M. I. Walash, 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-phenanthraquinone 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, respectively[20].

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 bromobenzyl-bonded silica (PBr), respectively for separation of two polar basic analytes: famotidine (FAM) and its acidic degradant famotidine (FON). LC separation was performed with a Hitachi HPLC setup (Tokyo, Japan) consisting of a 655A-11 liquid chromatograph, and a Rheodyne injector valve with a 50 µl sample loop. Cosmosil®HILIC packed column (250 mm × 4.6 mm ID, 5 m particle size) and Cosmosil®PBr packed column (150 mm × 4.6 mm ID, 5 m particle size). UV detection was carried out at 267 nm for simultaneous sensitive detection of FAM and FON. The optimum mobile phase 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[21].

Nizatidine

Nizatidine, also known as N-(2-[(2-[(dimethylamino)methyl] thiazol-4yl)-N-methyl-2-nitroethene-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 treatment[22].

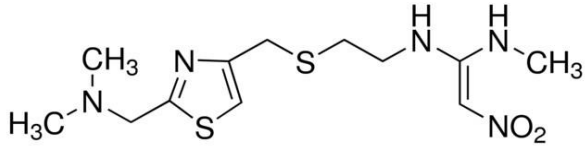

Figure 4: Structure of Nizatidine

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 spectro-fluorimeter from Shimadzu (Kyoto, Japan). Chromatographic separation was performed on an Inertsil C_{18} 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 (NIZ) 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 0.78 µg/ml. The calibration graphs were linear over the concentration range of 5-15 µg/ml[23].

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 C_{18} column (100mm×46mm, 5µm) with a mixture of methanol and water (95:5, plus 5mM 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 nizatidine[24].

Rania El-Shaheny, Mohamed Radwan, Koji Yamada, Mahmoud El-Maghrabey et al. (2019) optimized and validated a hydrophilic interaction liquid chromatography (HILIC) method according to FDA guidance by monitoring the nitrosatability 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 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-NO) within 6 min with LODs of 0.02 and 0.1 mg/ml, respectively[25].

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. Pe´rez-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 i.d 75 µm, o.d375 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 0.088 mg $ml^{-1}$for RAN and 0.16 mg $m1^{-1}$ for FAM[26].

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^{-9}–7.0×10^{-5}g/ml for CIM, 1.0×10^{-9}–5.0×10^{-5}g/ml for RAN hydrochloride, and 5.0×10^{-9}–7.0×10^{-5}g/ml for FAM\. The detection limit was 8.56×10^{-10} g/ml for CIM, 8.69×10^{-10} g/ml for RAN hydrochloride, and 2.35×10^{-9} 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, NIZ, and RAN 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 (*l*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, NIZ, and RAN, respectively[28].

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, NIZ, 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 thermostat 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 samples[29].

Elshaboury 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-C_{18} methods. A Young Lin Autochro-3000 HPLC system (Younglin, Korea) was used in this study. The studied drugs were separated isocratically on Kromasil C_{18} (250 × 4.6 mm, 5 µmi.d.) column (AkzoNobel, 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 effluent 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 µg ml^{-1} with a correlation coefficient of 0.9989[30].

S. Ahmed et al. (2017) developed a comparative force degradation high-performance thin layer chromatography (HPTLC) method was developed 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-precoated 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 CamagLinomat 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 NIZ, while for FAM it consisted of ACN:5M ammonium hydroxide (80:20, v/v). Densitometric measurements were carried out using a Camag TLC Scanner III in the absorbance mode at 320nm for RAN and NIZ, and 280nm 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 hypersecretion, and mild to infrequent heartburn or indigestion. H2RAs can also be used off-label for preventing esophagitis, gastritis, gastrointestinal hemorrhage, urticaria, 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.

REFERENCES

1. Nugent CC, Falkson SR, Terrell JM. H2 Blockers. InStatPearls [Internet] 2022 Feb 13. StatPearls Publishing.

2. Soldin SJ, Fingold DR, Fenje PC, Mahon WA. High-performance liquid chromatographic analysis of cimetidine in serum. Therapeutic Drug Monitoring. 1979 Jan 1;1(3):371-9. https://doi.org/10.1097/00007691-197901030-00010 PMid:555580

3. Lin Q, Lensmeyer GL, Larson FC. Quantitation of cimetidine and cimetidine sulfoxide in serum by solid-phase extraction and solvent-recycled liquid chromatography. Journal of analytical toxicology. 1985 Jul 1;9(4):161-6. https://doi.org/10.1093/jat/9.4.161 PMid:4033072

4. Bedair MM, Elsayed MA, Korany MA, Fahmy OT. Spectrophotometric determination of cimetidine in the presence of its acid-induced degradation products. Journal of pharmaceutical and biomedical analysis. 1991 Jan 1;9(4):291-6. https://doi.org/10.1016/0731-7085(91)80196-G PMid:1911980

5. Garcia MS, Albero MI, Sánchez-Pedreño C, Abuherba MS. Spectrophotometric determination of cimetidine in pharmaceuticals and urine using batch and flow-injection methods. Journal of pharmaceutical and biomedical analysis. 2003 Aug 8;32(4-5):1003-10. https://doi.org/10.1016/S0731-7085(03)00202-4 PMid:12899987

6. Betto P, Ciranni-Signoretti E, Di Fava R. Determination of cimetidine and related impurities in pharmaceutical formulations by high-performance liquid chromatography. Journal of Chromatography A. 1991 Nov 8;586(1):149-52. https://doi.org/10.1016/0021-9673(91)80033-D PMid:1806550

7. Jantratid E, Prakongpan S, Foley JP, Dressman JB. Convenient and rapid determination of cimetidine in human plasma using perchloric acid-mediated plasma protein precipitation and high-performance liquid chromatography. Biomedical Chromatography. 2007 Sep;21(9):949-57. https://doi.org/10.1002/bmc.838 PMid:17474142

8. Pérez-Ruiz T, Martínez-Lozano C, Tomás V, Sanz A, Sahuquillo E. Flow-injection extraction-spectrophotometric method for the determination of ranitidine in pharmaceutical preparations. Journal of Pharmaceutical and biomedical analysis. 2001 Nov 1;26(4):609-15. https://doi.org/10.1016/S0731-7085(01)00489-7 PMid:11516913

9. Agatonovic-Kustrin S, Tucker IG, Schmierer D. Solid state assay of ranitidine HCl as a bulk drug and as active ingredient in tablets using DRIFT spectroscopy with artificial neural networks. Pharmaceutical research. 1999 Sep; 16:1477-82. https://doi.org/10.1023/A:1018975730945 PMid:10496668

10. Jones MD, Plumb RS. The application of sub-2-μm particle liquid chromatography-operated high mobile linear velocities coupled to orthogonal accelerated time-of-flight mass spectrometry for the analysis of ranitidine and its impurities. Journal of separation science. 2006 Nov;29(16):2409-20. https://doi.org/10.1002/jssc.200600118 PMid:17154121

11. Raymundo-Pereira PA, Teixeira MF, Fatibello-Filho O, Dockal ER, Bonifacio VG, Marcolino-Junior LH. Electrochemical sensor for ranitidine determination based on carbon paste electrode modified with oxovanadium (IV) salen complex. Materials Science and Engineering: C. 2013 Oct 1;33(7):4081-5. https://doi.org/10.1016/j.msec.2013.05.051 PMid:23910317

12. Alshehri YM, Alghamdi TS, Aldawsari FS. HS-SPME-GC-MS as an alternative method for NDMA analysis in ranitidine products. Journal of pharmaceutical and biomedical analysis. 2020 Nov 30; 191:113582. https://doi.org/10.1016/j.jpba.2020.113582 PMid:32889348

13. Mihaly GW, Drummer OH, Marshall A, Smallwood RA, Louis WJ. High-pressure liquid chromatographic determination of ranitidine, a new H2-receptor antagonist, in plasma and urine. Journal of Pharmaceutical Sciences. 1980 Oct 1;69(10):1155-7. https://doi.org/10.1002/jps.2600691008 PMid:6252316

14. Hare LG, Millership JS, Collier PS, McElnay JC, Carson DJ, Shields MS. The use of polymeric solid phase extraction and HPLC analysis for the determination of ranitidine in routine plasma samples obtained from paediatric patients. Journal of Pharmacy and Pharmacology. 2001 Sep;53(9):1265-72. https://doi.org/10.1211/0022357011776559 PMid:11578109

15. Hare LG, Millership JS, Collier PS, McElnay JC, Carson DJ, Shields MS. The use of polymeric solid phase extraction and HPLC analysis for the determination of ranitidine in routine plasma samples obtained from paediatric patients. Journal of Pharmacy and Pharmacology. 2001 Sep;53(9):1265-72. https://doi.org/10.1211/0022357011776559 PMid:11578109

16. Tatar Ulu S, Tuncel M. A sensitive and rapid determination of ranitidine in human plasma by HPLC with fluorescence detection and its application for a pharmacokinetic study. Journal of chromatographic science. 2012 Apr 1;50(4):301-6. https://doi.org/10.1093/chromsci/bms003 PMid:22345389

17. Zarghi A, Shafaati A, Foroutan SM, Khoddam A. Development of a rapid HPLC method for determination of famotidine in human plasma using a monolithic column. Journal of pharmaceutical and biomedical analysis. 2005 Sep 15;39(3-4):677-80. https://doi.org/10.1016/j.jpba.2005.03.029 PMid:15894447

18. Campanero MA, Bueno I, Arangoa MA, Escolar M, Quetglas EG, Lopez-Ocariz A, Azanza JR. Improved selectivity in detection of polar basic drugs by liquid chromatography-electrospray ionization mass spectrometry: Illustration using an assay method for the determination of famotidine in human plasma. Journal of Chromatography B: Biomedical Sciences and Applications. 2001 Nov 5;763(1-2):21-33. https://doi.org/10.1016/S0378-4347(01)00355-3 PMid:11710580

19. Ayad MM, Shalaby A, Abdellatef HE, Elsaid HM. Potentiometric determination of famotidine in pharmaceutical formulations. Journal of pharmaceutical and biomedical analysis. 2002 Jun 20;29(1-2):247-54. https://doi.org/10.1016/S0731-7085(02)00024-9 PMid:12062684

20. Walash MI, El-Brashy A, El-Enany N, Kamel ME. Spectrofluorimetric determination of famotidine in pharmaceutical preparations and biological fluids. Application to stability studies. Journal of fluorescence. 2009 Mar;19:333-44. https://doi.org/10.1007/s10895-008-0421-3 PMid:18956234

21. El-Shaheny R, Radwan MO, Belal F, Yamada K. Pentabromobenzyl-RP versus triazole-HILIC columns for separation of the polar basic analyte's famotidine and famotidine: LC method development combined with in silico tools to follow the potential consequences of famotidine gastric instability. Journal of Pharmaceutical and Biomedical Analysis. 2020 Jul 15; 186:113305. https://doi.org/10.1016/j.jpba.2020.113305 PMid:32353682

22. Çakar MB, Ulu ST. HPLC fluorescence method for the determination of nizatidine in human plasma and its application to pharmacokinetic study. Luminescence. 2014 Jun;29(4):357-61. https://doi.org/10.1002/bio.2552 PMid:23836529

23. El-Yazbi FA, Gazy AA, Mahgoub H, El-Sayed MA, Youssef RM. Spectrophotometric and titrimetric determination of nizatidine in capsules. Journal of pharmaceutical and biomedical analysis. 2003 Apr 1;31(5):1027-34. https://doi.org/10.1016/S0731-7085(02)00699-4 PMid:12684116

24. Shang DW, Wang ZZ, Ni XJ, Zhang M, Hu JQ, Qiu C, Wen YG. Development and validation of a sensitive LC-MS/MS assay for the quantification of nizatidine in human plasma and urine and its application to pharmacokinetic study. Journal of Chromatography B. 2015 Aug 15; 998:80-7. https://doi.org/10.1016/j.jchromb.2015.06.026 PMid:26197435

25. El-Shaheny R, Radwan M, Yamada K, El-Maghrabey M. Estimation of nizatidine gastric nitrosatability and product toxicity via an integrated approach combining HILIC, in silico toxicology, and molecular docking. journal of food and drug analysis. 2019 Oct 1;27(4):915-25. https://doi.org/10.1016/j.jfda.2019.08.001 PMid:31590763 PMCid:PMC9306978

26. Pérez-Ruiz T, Martınez-Lozano C, Tomas V, Bravo E, Galera R. Direct determination of ranitidine and famotidine by CE in serum, urine and pharmaceutical formulations. Journal of pharmaceutical and biomedical analysis. 2002 Nov 7;30(4):1055-61. https://doi.org/10.1016/S0731-7085(02)00444-2 PMid:12408896

27. Tang YH, Wang NN, Xiong XY, Xiong FM, Sun SJ. A new sensitive flow-injection chemiluminescence method for the determination of H2-receptor antagonists. Luminescence: The journal of biological and chemical luminescence. 2007 Jul;22(4):343-8. https://doi.org/10.1002/bio.969 PMid:17471472

28. DARWISH IA, HUSSEIN SA, MAHMOUD AM, HASSAN AI. Osjetljivaspektrofotometrijskametoda za određivanjeantagonista H2-receptora uzuporabu N-bromsukcinimidai p-aminofenola. Acta Pharmaceutica. 2008 Mar 1;58(1):87-97. https://doi.org/10.2478/v10007-007-0047-z PMid:18337210

29. Nevado JJ, Peñalvo GC, Dorado RM, Robledo VR. Comparative validations of non-aqueous capillary electrophoresis and high-performance liquid chromatography methods for the simultaneous determination of histamine H2 receptor antagonists in human urine. Journal of Chromatography B. 2013 Mar 15; 921:56-63. https://doi.org/10.1016/j.jchromb.2013.01.020 PMid:23485449

30. Elshaboury SR, Mohamed NA, Ahmed S, Farrag S. An efficient ion-pair liquid chromatographic method for the determination of some H2 receptor antagonists. Journal of chromatographic science. 2016 Mar 1;54(3):419-28. https://doi.org/10.1093/chromsci/bmv159 PMid:26538490

31. Ahmed S, Elshaboury SR, Mohamed NA, Farrag S. Development of a validated comparative stability-indicating assay method for some H2-receptor antagonists. Journal of chromatographic science. 2017 Sep 1;55(8):818-31. https://doi.org/10.1093/chromsci/bmx042 PMid:28486578