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REVIEW

Instrumental analysis of some anti-ulcer drugs in different matrices

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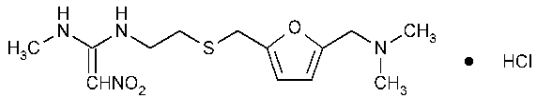
Abstract: In this literature review, we will introduce most reported methods that have been developed for determination of certain anti-ulcer drugs such as Ranitidine hydrochloride, Famotidine, Omeprazole, Pantoprazole sodium, Tinidazole and Doxycycline hyclate in their pure form, combined form with other drugs, combined form with degradation products, and in biological samples.

Keywords: Ranitidine hydrochloride, Famotidine, Omeprazole, Pantoprazole sodium, Tinidazole, Doxycycline hyclate

1 Introduction

Peptic ulcers are localized erosions of the mucous membranes of the stomach and duodenum. The pain associated with ulcers is caused by irritation of exposed surfaces by the stomach acids. Anti-ulcer therapy has been a huge money spinner for the pharmaceutical industry with drugs such as Cimetidine, Ranitidine (H_2-receptor antagonists) and Omeprazole (proton pump inhibitor). None of these drugs were available until the 1960s, however, and it is perhaps hard for us now to appreciate how dangerous ulcers could be before that. In the early 1960s, the conventional treatment was to try to neutralize gastric acid in the stomach by administering antacids. These were bases, such as sodium bicarbonate or calcium carbonate. The dose levels required for neutralization were large and caused unpleasant side effects. Relief was only temporary. The first effective anti-ulcer agents were the H_2 histamine antagonists which appeared in 1960s. These were followed in 1980s by the proton pump inhibitors (PPIs). The discovery of *H. pylori* then led to the use of antibacterial agents in ani-ulcer therapy. The current approach for treating ulcers caused by *H. pylori* is to use combination of drugs, which includes a PPI, and two antimicrobials, such as Tinidazole and Doxycycline.[1] As such, This literature review will shed the light about all reported methods that have been developed for determination of drugs used for peptic ulcer such as Ranitidine hydrochloride, Famotidine, Omeprazole, Pantoprazole sodium, Tinidazole and Doxycycline hyclate in their pure form, combined form with other drugs, combined form with degradation products, and in biological samples such as liquid chromatography, spectrophotometry, spectroflourimetry, electrophoresis, *etc*.

2 Ranitidine hydrochloride



Chemical name:
N-[2-[[[5-[(Dimethylamino) methyl]-2-furanyl] methyl] thio] ethyl]-*N*'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride.[2]

Molecular formula: $C_{13}H_{22}N_4O_3S.HCl$

Molecular weight: 350.87

Physical properties:

Appearance: Off- white to pale yellow crystalline powder

Solubility: Freely soluble in water and sparingly soluble in alcohol

Melting point: About 70°C

Pharmacological action:

Ranitidine is a histamine H_2-receptor antagonist and inhibits the actions of histamine mediated by H_2-receptors such as gastric acid secretion and pepsin output. It is used where inhibition of gastric acid secretion may be beneficial as in peptic ulcer disease including stress ulceration, gastroesophageal reflux disease and selected cases

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of persistent dyspepsia.[3]

Methods of determination:

Ranitidine hydrochloride is official in B.P. 2011[4] where it was determined by titration and the end point was determined potentiometrically, and in U.S.P. XXXII[2] using HPLC method.

Spectrophotometric methods:

Perez-Ruiz *et al.*,[5] described a spectrophotometric method for determination of trace amounts of ranitidine through liquid-liquid extraction using bromothymol blue.

Spectrophotometric stability indicating method was developed for quantitative determination of ranitidine hydrochloride in the presence of its oxidative derivatives in both raw material and in pharmaceutical formulations. Hydrogen peroxide was used to enhance the formation of S-oxide compounds (oxidative derivatives). Direct zero order, first derivative and the second derivative of the ratio spectra had been carried out for the determination of the drug.[6]

Spectrophotometric method was developed for determination of ranitidine through its oxidation by a known excess of bromate in acid medium and in the presence of excess bromide followed by estimation of surplus oxidant by reacting with either indigo carmine or metanil yellow and measuring the absorbance at λ_{max} 610 or 530 nm.[7]

Potassium iodate and 2,7-dichlorofluorescein were used for spectrophotometric determination of ranitidine. The absorbance of the coloured solution was measured at λ_{max} 520 nm.[8]

Another spectrophotometric method was developed depending on addition of fixed amount of perchloric acid-crystal violet mixture to different amounts of ranitidine and measuring the absorbance spectrophotometrically at λ_{max} 570 nm.[9]

Two spectrophotometric methods were developed for determination of ranitidine HCl. The first method was a kinetic spectrophotometric method based on the catalytic effect of ranitidine on the reaction between sodium azide and iodine and measuring the decrease in iodine absorbance at λ_{max} max 348 nm. In the second method; complexes were formed between (o-phenanthroline) iron (II) and tris (bipyridyl) iron (II) measuring the absorbances at λ_{max} 512 nm.[10]

Potassium dichromate was used as oxidimetric reagent in spectrophotometric determination of ranitidine in pharmaceuticals.[11]

N-bromosuccinimide (NBS) was used as an analytical reagent for the determination of ranitidine HCl. The method involved the reaction of ranitidine HCl with NBS and then the excess NBS was estimated by its reaction with p-aminophenol to give a violet colored product that was measured at λ_{max} 552 nm.[12]

Another sensitive spectrophotometric method was described for the determination of ranitidine HCl in pharmaceuticals. This method was based on the formation of red colored condensation product with p-dimethylaminobenzaldehyde followed by measurement of absorbance at λ_{max} 503 nm.[13]

Ceric ammonium sulphate and two dyes; malachite green and crystal violet were used for spectrophotometrically determination of ranitidine HCl at λ_{max} 615 and 582 nm respectively.[14]

Ranitidine gives colored ion-pair complexes with bromocresol purple, methyl orange, eriochrome cyanine and alizaraine red S with maximum absorption peaks at λ_{max} 408, 420, 330 and 326 nm respectively.[15]

Spectroflourimetric methods:

Spectrofluorimetric method was adopted for the analysis of ranitidine depending on its reaction with 1,4- Benzoquinone reagent at pH 5.6. The resulting condensation product exhibited fluorescence at λ_{em} 665 nm when excited atλ_{exc} 290 nm.[16]

Ulu S and Cakar M,[17] developed a sensitive spectrofluorimetric method for the determination of ranitidine hydrochloride. This method was based on derivatization of ranitidine with 4-fluoro-7-nitrofurazan (NBD-F). The method was linear over the range of 40-1200 ng/ml.

Chromatographic methods:

Chromatographic methods have been widely applied for determination of ranitidine in pure form, in pharmaceutical formulations or in biological fluids. These methods include HPLC method for the determination of ranitidine in commercial products. As a column of Inertsil® ODS-2 was used and 0.04 M aqueous sodium dihydrogen phosphate: acetonitrile: methanol: triethylamine at a proportion of (345: 20: 35: 0.7, v/v/v/v) was the selected mobile phase. The detection wavelength was set at 230 nm.[18]

Also, there are HPTLC methods which were used for determination of ranitidine HCl in pharmaceutical preparations. The separation was performed on silica precoated plates using the U.S.P. XXIII mobile phase; toluene: methanol: diethylamine (9: 1: 1, v/v/v). The samples were applied on a HPTLC plate automatically. Quantification was done by densitometry at in situ UV absorption at 320 nm.[19] Another HPTLC method was described for the determination of ranitidine in the presence of its sulfoxide derivatives. The latter method involved quantitative densitometric evaluation of mixture of the drug and its derivatives after separation by high-performance

thin-layer chromatography on silica gel plates with ethyl acetate: methanol: 20% ammonia (10 : 2 : 2, v/v/v) as the mobile phase.[20]

Ranitidine was assayed in plasma samples by HPLC using a Lichrocrat Lichrospher® RP-select B column. The mobile phase consisted of 0.2% triethylamine, 0.04 M phosphate buffer (pH 6.8) and 14% acetonitrile.[21]

Simultaneous determination of ranitidine and metronidazole in human plasma was presented. The plasma protein was precipitated by perchloric acid. The resultant supernatant was analyzed on Shimpak C_{18} column using phosphate buffer (pH 3.5): acetonitrile (90:10, v/v) as a mobile phase and detection wavelength at 315 nm.[22]

HPLC method was developed for the simultaneous determination of ranitidine, methylparaben and Propylparaben as preservatives in oral liquids. The chromatographic separation was achieved by HPLC using a mixture of 0.5 M ammonium acetate, acetonitrile and methanol as the mobile phase, a Nucleosil C_{18} column and UV detection at 254 nm.[23]

Simultaneous determination of ranitidine was performed by Arayn *et al.*,[24] on a Purospher Star RP_{18} endcapped column using a mobile phase of methanol: water: triethylamine (20: 80: 0.05, v/v/v) whose pH was adjusted to 3.0 with phosphoric acid (85%). The detection was set at 229 nm.

Stability-indicating RP-HPLC method was developed for the determination of ranitidine in the presence of its impurities, forced degradation products and placebo substances such as saccharide and parabens. Chromatographic separation was achieved on ACE C_{18} column using gradient mixture of two solvents. The first solvent is mixture of phosphate buffer (pH 6.5) and acetonitrile (98: 2, v/v). The second one is mixture of water and acetonotrile (5: 95, v/v). Ultraviolet detection was performed at 230 nm.[25]

Another RP-HPLC method with fluorescence detection was described for the determination of ranitidine in human plasma. The method was based on the reaction of ranitidine with 4-fluoro-7-nitrobenzo-2-oxa-1, 3-diazole (NBD-F) forming a yellow colored fluorescent duct. The separation was achieved on C_{18} column using methanol-water (60: 40, v/v) as a mobile phase. Fluorescence detection was used at the excitation and emission of 458 and 521 nm, respectively.[26]

Gas chromatography method was developed for the determination of ranitidine in pharmaceutical preparations and serum using methylglyoxal as derivatizing agent.[27]

Miscellaneous methods:

Stability-indicating spectrodensitometric method was applied for the determination of ranitidine HCl using linear and non-linear regression.[28]

A simple capillary zone electrophoresis method was described for the simultaneous determination of ranitidine.[29]

Issa *et al.*,[30] presented ion-selective electrodes for potentiometric determination of ranitidine HCl applying batch and flow injection analysis techniques.

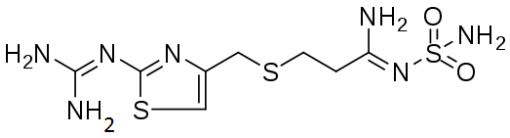
Based on the chemiluminescence intensity generated from the potassium ferricyanide $[K_{(3)}Fe(CN)_{(6)}]$-rhodamine 6G system in sodium hydroxide medium, a flow-injection chemiluminescence (FI-CL) method had been developed, validated and applied for the determination of ranitidine HCl.[31]

Ranitidine HCl was determined potentiometrically through construction of ion-selective electrodes. Two types of electrodes: carbon paste and screen printed electrodes were constructed based on the ion-pair formation during potentiometric titration of ranitidine with tetraphenyl borate.[32]

Chang *et al.*,[33] developed a selective fluorescence quenching method for the determination of ranitidine in tablets and biological fluids.

A sensitive potentiometric method was described for the determination of ranitidine using modified carbon paste and insitu carbon paste electrodes.[34]

3 Famotidine



Chemical name:
N'-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl] methyl]thio]- Propanimidamide

Molecular formula: $C_8H_{15}N_7O_2S_3$

Molecular weight: 337.45

Physical properties:

Appearance: White to pale yellow crystalline powder

Solubility: Freely soluble in glacial acetic acid, slightly soluble in methanol and very slightly soluble in water

Melting point: About 163°C

Pharmacological action:

Famotidine is a histamine H_2-receptor antagonist that inhibits the actions of histamine mediated by H_2-receptors such as gastric acid secretion and pepsin output. It is used in treatment of peptic ulcer disease including stress ulceration, gastroesophageal reflux disease and selected cases of persistent dyspepsia.[3]

Methods of determination:

Famotidine is official and can be determined in both B.P. 2011[4] and U.S.P. XXXII[2] by non aqueous titration and the end point is determined potentiometrically.

Spectrophotometric methods:

Charge transfer complexes were formed between famotidine and chloranilic acid[35] and 7, 7, 8, 8-tetracyanoquinodimethane;[36] measured spectrophotometrically at λ_{max} 525 nm and 840 nm, respectively.

Amin *et al.*,[37] described three methods for the spectrophotometric determination of famotidine. The first method was based on oxidation of the drug by N-bromosuccinimide (NBS) and determination of the unreacted NBS by measuring the decrease in absorbance of Amaranth dye at λ_{max} 521 nm. The other two methods involved addition of excess cerric sulphate and determination of unreacted Ce (IV) by decrease the red color of chromotrope 2R at λ_{max} 528 nm or decrease the orange pink color of rhodamine 6 G at λ_{max} 526 nm.

A ternary complex was formed with famotidine, eosin and Cu (II) which was measured at λ_{max} 548 nm.[38]

Another spectrophotometric method was developed for the determination of famotidine. The method was based on the interaction of ninhydrin with famotidine resulting in a blue colored product measured at λ_{max} 590 nm.[39]

Ayad *et al.*,[40] developed two spectrophotometric methods for the determination of famotidine. The methods were based on the oxidation of the drug with iron (III) in acidic medium. The liberated iron (II) reacted with 1,10- phenanthroline (method A) and the ferroin complex was measured at λ_{max} 510 nm. Method B was based on the reaction of the liberated Fe (II) with 2,2- bipyridyl to form a stable colored complex with λ_{max} at 520 nm.

Palladium (II) chloride was used to form a complex with famotidine which measured spectrophotometrically at λ_{max} 345 nm.[41]

A kinetic spectophotometric method for the determination of famotidine was described. The method was based on the oxidation of the drug with alkaline potassium permanganate and measuring the rate of change of absorbance at λ_{max} 610 nm.[42]

Reddy *et al.*,[43] described a bromination method for famotidine using excess bromine in acidic medium. The developed yellow color was measured spectrophotometrically at λ_{max} 350 nm.

Also famotidine was oxidized by cerium (IV) in presence of perchloric acid and subsequent measurement of excess Ce (IV) by its reaction with p- dimethylaminocinnamaldehyde to give a red colored product measured at λ_{max} 464 nm.[44]

Ion-pair complexes were formed between famotidine and four sulphonphthalein dyes; bromothymol blue, bromophenol blue, bromocresol purple and bromocresol green in dioxane or acetone medium. Complexes were measured at λ_{max} max 410 nm.[45]

Simultaneous spectrophotometric method was developed for the determination of famotidine and domperidone in combined tablet dosage form through using ratio spectra derivative and area under curve method.[46]

Araujo *et al.*,[47] developed two methods for the determination of famotidine in pharmaceutical preparations. The first method was based on the hydrolysis of famotidine with sodium hydroxide, assisted with microwave radiation. The produced sulphide was allowed to interact with N, N- diethyl-p-phenylendiamine oxalate and Fe (III) and measuring the blue colored product at λ_{max} 671 nm. The second method was based upon formation of ternary complex between the drug, lead (II) and eosin in presence of methylcellulose as a surfactant and measuring the absorbance at λ_{max} 541 nm.

Spectrofluorimetric methods:

Spectrofluorimetric method was adopted for the analysis of famotidine depending on its reaction with 1,4 Benzoquinone reagent at pH 5.2. The resulting condensation product exhibited fluorescence at λ_{em} 665 nm when excited with λ_{exc} 290 nm.[16]

Famotidine was determined spectrofluorimetrically in pharmaceutical preparations and biological fluids through ternary complex formation with some lanthanide ions. The relative fluorescence intensity of complexes measured at λ_{em} 580 nm after excitation with λ_{exc} 290 nm.[48]

A stability indicating spectrofluorimetric method was developed for the determination of famotidine. It was based on the reaction of famotidine with 9, 10-phenanthraquinone in alkaline medium to give a highly fluorescent derivative measured at λ_{em} 560 nm after excitation with λ_{exc} 283 nm.[49]

Chromatographic methods:

HPLC method was developed for the determination of famotidine in commercial products depending on using Inertsil ODS-2 column and mobile phase consisting of phosphate: acetonitrile: methanol: triethylamine (345: 20: 35: 0.7, v/v/v/v). Detection wavelength was set at 230 nm.[18] Another HPLC method was described for estimation of famotidine in human plasma and urine using C_{18} reversed phase column and water- saturated ethyl acetate as a mobile phase. Detection was carried out at wavelength 267 nm.[50]

Zhong *et al.*,[51] developed a normal phase chromatography method coupled with tandem mass spectrometry for the determination of famotidine in human plasma and urine. The chromatographic separation was accomplished

by using BDS Hypersil silica column with a mobile phase of acetonitrile-water containing trifluoroacetic acid.

HPTLC method was described for the determination of famotidine in presence of its sulfoxide derivatives. The method involved quantitative densitometric evaluation of mixture of the drug and its derivatives after separation by high-performance thin-layer chromatography on silica gel plates with ethyl acetate: isopropanol: 20% ammonia (9 : 5 : 4, v/v/v) as a mobile phase.[20]

RP-HPLC analysis of famotidine in human plasma was reported after solid phase extraction.[52] Another RP-HPLC methods were developed for the determination of famotidine in pharmaceutical products.[25,53,54]

A quantitative method using silica gel high performance thin layer chromatography (HPTLC) plates with fluorescent indicator, automated sample application, and ultraviolet (UV) absorption videodensitometry was developed for the determination of famotidine tablets.[55]

Reddy *et al.*,[56] developed a stability-indicating liquid chromatographic method for the simultaneous determination of ibuprofen and famotidine in combined pharmaceutical dosage form (tablets).The separation was achieved on Acquity UPLC C_{18} column with gradient elution. The mobile phase A was a mixture of acetate buffer (pH 5.5) and methanol (85: 15, v/v) while the proportion was (25: 75, v/v) for the mobile phase B. The detection wavelength was 260 nm.

Miscellaneous methods:

A simple capillary zone electrophoresis method was described for the simultaneous determination of famotidine.[29]

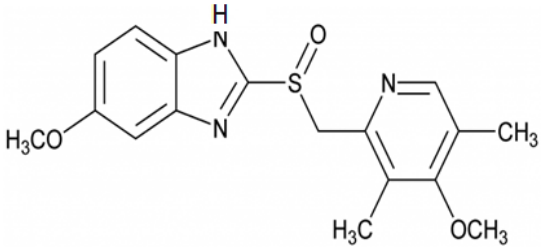
Two potentiometric methods were developed for the determination of famotidine in pure form and in its tablet form. The first method was based on construction of plasticised ploy (vinyl chloride) matrix type famotidine ion-selective membrane electrode. In the second one, lead acetate was used for oxidation of thioether contained in famotidine. The titration was made in presence of catalytic quantities of potassium bromide.[57]

A flow injection kinetic spectrophotometric method was described for the determination of famotidine in pharmaceutical preparations. The method was based on a kinetic investigation of the oxidation reaction of the drug in alkaline potassium permanganate.[58]

Moreover, a flow-injection chemiluminescence (FI-CL) method based on the chemiluminescence intensity generated from the potassium ferricyanide $[K_{(3)}Fe(CN)_{(6)}]$-rhodamine 6 G system in sodium hydroxide medium; was developed, validated and applied for the determination of famotidine.[31]

Electrochemical behavior of famotidine had been studied at composite polymer membrane working electrode. Cyclic voltammetric method was developed for the determination of drug in pharmaceutical formulation.[59]

4 Omeprazole



Chemical name:
5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl] benzimidazole

Molecular formula: $C_{17}H_{19}N_3O_3S$

Molecular weight: 345.42

Physical properties:

Appearance: White to off-white crystalline powder

Solubility: Very slightly soluble in water, soluble in alcohol and dichloromethane

Melting point: 156°C

Pharmacological action:

Omeprazole is a proton pump inhibitor, used in treatment of peptic ulcer disease and NSAID-associated ulceration, in gastro-esophageal reflux disease and the Zollinger-Ellison syndrome.[3]

Methods of determination:

Omeprazole is official in B.P. 2011[4] where it was determined by titration with standard solution of alkali hydroxide and determining the end-point potentiometrically and in U.S.P. XXXII[2] using HPLC method.

Spectrophotometric methods:

Two stability-indicating spectrophotometric methods were described for the determination of omeprazole in the presence of its degradation products. The first method depended on use of first, second and third derivative spectrophotometry at 290, 320, 311 nm, respectively. The second method was based on applying the charge transfer technique with chloranil and measuring the complex at λ_{max} 377 nm.[60]

The compensation method and other chemometric methods (derivative, orthogonal function and difference spectrophotometry) had been applied to the direct determination of omeprazole in pharmaceutical preparations.[61]

Spectrophotometric procedures for the determination of omeprazole were developed. The procedures were based on the formation of chelates of the drug with different

metal ions. The colored chelates of omeprazole in ethanol were determined at λ_{max} 411, 339 and 523 nm using iron (III), chromium (III) and cobalt (II), respectively.[62]

Karljikovic *et al.*,[63] applied the first order UV-spectrophotometry using zero-crossing method for the determination of omeprazole and omeprazole sulphone.

Omeprazole was reacted with iron (III) and subsequent reacted with ferricyanide which yielded a prussion blue product with maximum absorption at λ_{max} 720 nm.[64]

Two spectrophotometric methods were developed for the determination of losartan potassium and omeprazole in single component pharmaceutical dosage forms. The methods were based on the formation of ion-pair complexes of the drug with bromocresol purple and bromophenol blue in acidic buffer solutions followed by their extraction in chloroform.[65]

Extractive spectrophotometric determination of omeprazole was developed using acidic dyes; bromophenol blue and orange G as ion-pairing agents in aqueous medium (pH 7 and 6, respectively). The ion pair chromogen formed, which was extracted with chloroform, was measured quantitatively at λ_{max} 408 nm and 508 nm, respectively.[66]

Mahmoud, A. M,[67] developed a kinetic spectrophotometric method for determination of omeprazole. The method was based on charge-transfer complex, formed between iodine and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Two spectophotometric methods were developed for the simultaneous estimation of omeprazole and cinitapride in combined dosage form through simultaneous equation method and absorbance ratio method.[68]

Comparative study of spectrophotometric methods manipulating ratio spectra was developed for the determination of ternary complex of omeprazole, tinidazole and clarithromycin.[69]

Spectrophotometric method based on nucleophilic substitution reaction was developed for the determination of omeprazole. The method was based on the reaction of omeprazole with sodium 1,2-naphthoquinone-4-sulphonate in alkaline medium and the absorbance was measured at λ_{max} 453 nm.[70]

Spectrofluorimetric methods:

Indirect spectrofluorimetric determination of omeprazole by its quenching effect on the fluorescence of Tb^{3+}-1, 10 -phenanthroline complex in presence of bis (2-ethylhexyl) sulfosuccinate sodium in capsule formulations was reported. The mixture was measured at λ_{em} 545 nm using an excitation wavelength of λ_{exc} 300 nm.[71]

Chromatographic methods:

Different chromatographic techniques have been applied for the analysis of omeprazole. Omeprazole was determined by HPLC with coulometric detection using a porous carbon electrode.[72]

RP-HPLC method was developed for the quantitative determination of omeprazole in the presence of its acid-induced degradation products. The chromatographic analysis was achieved by using Nova-Pak C_{18} column and 0.05 M potassium dihydrogen phosphate: methanol: acetonitrile (50: 30: 20, v/v/v) as a mobile phase. The detection was carried out at wavelength 208 nm.[73]

Another RP-HPLC method was developed for quantification of omeprazole in delayed release tablets. The analysis was carried out using a RP-C_{18} column with UV detection at 280 nm. The mobile phase consisted of phosphate buffer (pH 7.4): acetonitrile (70:30, v/v).[74]

Raval *et al.*,[75] developed a HPTLC method for the determination of ondansetron in combination with omeprazole in solid dosage form. The method involved separation of components by TLC on a precoated silica gel using a mixture of dichloromethane: methanol (9: 1, v/v) as a mobile phase. Detection of spots was carried out at 309 nm. Moreover Dedania *et al.*,[76] developed a RP-HPLC method for the simultaneous estimation of omeprazole and ondansetron in combined tablet dosage form. Chromatographic separation was achieved on RP-C_{18} column. The mobile phase was a combination of methanol: acetonitrile (90: 10, v/v). The detection was carried at 218 nm.

RP-HPLC methods were described for determination of omeprazole in human plasma. Chromatographic separation was performed using gradient elution, on Zorbax C_{18} column. The mobile phase A was 22.0 mM phosphate (pH 6), while the mobile phase B was composed of phosphate: acetonitrile: methanol (10: 80: 10, v/v/v) detection wavelength was set at 302 nm.[77]

Another RP-HPLC method was developed for determination of omeprazole in human serum. As the mobile phase consisted of a mixture of 0.2 M potassium dihydrogen phosphate buffer (pH 7.2) and acetonitrile (70: 30, v/v), pumped through C_{18} column at room temperature. Peaks were monitored by UV absorbance at 302 nm.[78]

Omeprazole and its derivatives were determined in liquid culture medium through HPLC method using a monolithic column for application in biotransformation studies with fungi. The separation was achieved using a monolithic Chromolith Fast gradient RP C_{18} endcapped column, using a mobile phase consisting of 0.15% (v/v) trifluoroacetic acid (TFA) in water (solvent A) and 0.15% (v/v) TFA in acetonitrile (solvent B), under gradient elution and detection at 220 nm.[79]

RP-HPLC methods were developed for the determi-

nation of ternary mixture of omeprazole, tinidazole and either clarithromycin or doxycycline. The analysis was performed on a C_{18} column through a gradient elution system using acetonitrile: methanol: water adjusted to pH 6.6. Drugs were detected at 277 nm.[80] Another method was developed for determination of the cited ternary complex which was based on using a C_{18} column with a mobile phase consisting of methanol and 0.06 M sodium dihydrogen phosphate (65 : 35, v/v) adjusted to pH 4.5. The UV detector was operated at 260 nm.[81]

Miscellaneous methods:

The electrochemical oxidation of omeprazole was studied either at a carbon paste electrode[82] or on glassy carbon electrode[83] by cyclic differential-pulse voltammetry.

A differential pulse polarographic study at the static mercury drop electrode was developed for the determination of omeprazole and its degradation products.[84]

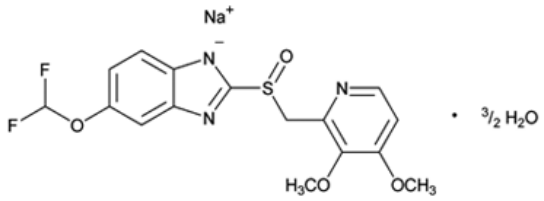
A capillary zone electrophoresis method was developed for the separation of omeprazole enantiomers.[85]

Omeprazole and its metabolites were determined in human plasma using automated solid phase extraction and micellar electrokinetic capillary electrophoresis.[86]

Flow injection chemiluminescence system was used for the determination of omeprazole. It was based on the chemiluminescence reaction of sodium hydrosulfite with Ce (IV) in the nitric acid solution.[87]

Fiqueiras *et al.*,[88] investigated the effect of L-arginine and cyclodextrins on omeprazole stability and solubility.

5 Pantoprazole sodium



Chemical name:
5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl) methyl] sulfinyl] benzimidazole, sodium salt, sesquihydrate

Molecular formula: $C_{16}H_{14}F_2N_3NaO_4S.\ 1.5H_2O$
Molecular weight: 432.37
Physical properties:
Appearance: White to off-white crystalline powder
Solubility: Freely soluble in water
Melting point: About 140°C

Pharmacological action:

Pantoprazole is a proton pump inhibitor, used as an anti-ulcerative agent by inhibiting the gastric acid secretion. It is immensely used for the cure of erosion and ulceration of esophagus caused by a gastroesophagal reflux disease.[3]

Methods of determination:

Pantoprazole is official in B.P. 2011[4] and determined by non-aqueos titration and determining the end point potentiometrically, and in U.S.P. XXXII[2] and determined by HPLC.

Spectrophotometric methods:

Moustafa A. A,[89] described three procedures for the assay of pantoprazole in tablets. Two were based on charge transfere complex formation reaction using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and iodine as π-acceptor and σ-acceptor, respectively. The third method was based on the formation of a ternary complex, involving Cu (II) and eosin as reagents.

The compensation method and other chemometric methods (derivative, orthogonal function and difference spectrophotometry) have been applied to the direct determination of pantoprazole in pharmaceutical preparations.[61]

Spectrophotometric method was described for the determination of pantoprazole. This method was based on the formation of an ethanol-soluble colored chelate with iron (III).[62]

The first order UV-derivative spectrophotometry; applying zero-crossing method was developed for the determination of pantoprazole and its corresponding impurities.[63]

Pantoprazole was reacted with iron (III) and subsequent reacted with ferricyanide which yielded a prussion blue product with maximum absorption at λ_{max} 720 nm.[64]

Known excess of N-bromosuccinamide (NBS) added to pantoprazole in acid medium, followed by determination of unreacted oxidant by reacting with a fixed amount of either methyl orange and measuring absorbance at λ_{max} 520 nm or indigo carmine at λ_{max} 610 nm.[90]

Known excess of permanganate was added to pantoprazole in acid medium, followed by the measurement of the residual permanganate spectrophotometrically at λ_{max} 545 nm. The amount of permanganate reacted corresponds to pantoprazole content.[91]

Furthermore, another spectrophotometric method was described for the determination of pantoprazole. This method was based on the reduction of ferric chloride by pantoprazole and subsequent chelation of iron (II) with 1,10-phenanthroline or 2,2‘-bipyridyl. The resulting red colored products were measured at λ_{max} 510 or 520 nm, respectively.[92]

Chromatographic methods:

A multidimensional HPLC method was developed for

the enantiometric determination pantoprazole in human plasma. This method was based on using a multidimensional HPLC by coupling a RAM column with a chiral polysaccharide column to the analysis of pantoprazole in human plasma by direct injection. The enantiomers from the plasma samples were separated with high resolution on a tris(3,5-dimethoxyphenylcarbamate) of amylose phase after clean-up by a RAM BSA octyl column. Water was used as solvent for the first 5 min for the elution of the plasmatic proteins and then acetonitrile-water (35: 65, v/v) for the transfer and analysis of pantoprazole enantiomers, which were detected by UV at 285 nm.[93]

Another HPLC method was described for the determination of pantoprazole; using Hypersil C_{18} column, potassium dihydrogen phosphate (pH 4.7): acetonitrile (720: 280, v/v) as a mobile phase.[94]

RP-HPLC method was developed for the determination of pantoprazole in commercial products, using Intersil C_{18} column, acetonitrile: phosphate (60: 40, v/v) as a mobile phase and detection was carried out at 230 nm.[95]

Another RP-HPLC method was described for simultaneous separation and quantification of pantoprazole and its impurities in pharmaceutical preparations. The separation was accomplished on a Zorbax Eclipse XDB C_{18} column using a gradient elution with mobile phase A [buffer: acetonitrile (70: 30, v/v)], and mobile phase B [buffer: acetonitrile (30: 70, v/v)]. The buffer was 0.01 M ammonium acetate solution with addition of 1 ml triethylamine/L of the solution, adjusted to pH 4.5 with orthophosphoric acid. The eluate was monitored at 290 nm.[96]

Stability-indicating TLC and HPLC methods were presented for simultaneous determination of mosapride and pantoprazole in pharmaceutical dosage form and plasma samples. The TLC method employed aluminum TLC plates precoated with silica gel as the stationary phase and ethyl acetate: methanol: toluene (4: 1: 2, v/v/v) as the mobile phase to give compact spots for mosapride (Rf 0.73) and pantoprazole (Rf 0.45) separated from their degradation products; the chromatogram was scanned at 276 nm. The HPLC method utilized a C_{18} column and a mobile phase consisting of acetonitrile: methanol: 20 mM ammonium acetate (4:2:4, v/v/v) for the separation of mosapride and pantoprazole from their degradation products. Quantitation was achieved with UV detection at 280 nm.[97]

Furthermore, a reversed phase liquid chromatographic method was developed for the determination of cinitapride and pantoprazole sodium in their marketed formulation. A reversed phase C_{18} column with mobile phase consisting of acetonitrile: water: triethylamine (80: 20: 0.05, v/v/v) were used. The detection was set at 260 nm.[98]

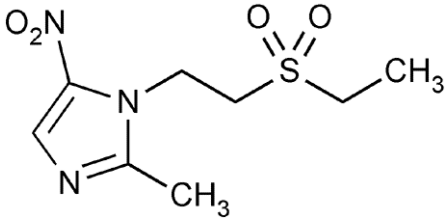
Another stability-indicating HPLC method was reported for the determination of impurities in pantoprazole in bulk drug and in formulations. Resolution of drug, its potential impurities and degradation products were achieved on a Hypersil ODS column utilizing a gradient with 0.01 M phosphate buffer of pH 7 and acetonitrile as eluent, at the detection wavelength of 290 nm.[99]

Miscellaneous methods:

Differential pulse anodic voltammetric method was described for the determination of pantoprazole in dosage forms and human plasma using glassy carbon electrode. The best voltammetric response was reached for a glassy carbon electrode in Britton-Robinson buffer solution of pH 5.0.[100]

A flow injection biamperometric method was developed for the determination of pantoprazole (PTZ) in pharmaceutical tablets. The reversible redox couples Fe^{3+}/Fe^{2+}, $Fe(CN)_6{}^{(3-)}/Fe(CN)6^{(4-)}$, Ce^{4+}/Ce^{3+}, $NO_3{}^{(-)}NO_3{}^{(+)}$, and I_2/I^- were tested as indicating redox systems for biamperometric determination of PTZ in a flow-injection assembly with optimized flow parameters. The best results were obtained using $N0_3{}^{(-)}NO_3{}^{(+)}$, which showed to be a selective and sensitive biamperometric indicating system for PTZ even in the presence of excipients and antioxidants that typically are found in pharmaceutical formulations.[101]

6 Tinidazole



Chemical name:
1-(2-ethyl-sulphonyl ethyl)-2-methyl-5-nitroimidazole
Molecular formula: $C_8H_{13}N_3O_4S$
Molecular weight: 247.28
Physical properties:
Appearance: White to pale yellow crystalline powder
Solubility: Soluble in methanol and insoluble in water
Melting point: About 128°C

Pharmacological action:

Tinidazole is 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa. It is used to eradicate H. pylori in peptic ulcer disease with other antimicrobials and proton pump inhibitor.[3]

Methods of Determination:

Tinidazole is official in B.P. 2011[4] and U.S.P. XXXII[2] where it was determined in both pharmacopeias by non aqueous titration using perchloric acid and the end point was determined potentiometrically.

Spectrophotometric methods:

Reduced form of tinidazole as n-electron donor forms a charge-transfer complex with chloranilic acid as π-electron acceptor with an absorption band at λ_{max} 520 nm.[102]

Ion-pair complex was formed between tinidazole and alizarin red S producing which can be measured at λ_{max} 420 nm.[103]

Based on the reduction of the nitro group of tinidazole by 10% Pd-C and formic acid, the resulting amine was subjected to a condensation reaction with sodium 1,2-naphthaquinone-4-sulfonate to give a red schiff's base measured at λ_{max} 510 nm.[104]

Two spectrophotometric methods were presented for estimation of tinidazole. The first one was based on that reduced drug interacted with 3-methylbenzothiazolin-2-one hydrazone in presence of copper sulphate and acidic pyridine producing yellowish orange colour with λ_{max} 490 nm. The second method was based on reaction of the reduced drug with N-(1-naphthyl) ethylenediamine dihydrochloride yielding pink product with λ_{max} 505 nm.[105]

Diazodized tinidazole reacted with p-dimethylaminobenzaldehyde forming greenish yellow solution which measured spectrophotometrically at λ_{max} 404 nm.[106]

Direct UV-visible spectrophotometric and differential spectrophotometric methods were described for the determination of tinidazole in pure and dosage forms.[107]

Difference spectroscopic method was developed for the simultaneous determination of binary mixtures of norfloxacin and tinidazole without prior separation.[108]

Alhemiary N and Saleh M,[109] described two spectrophotometic methods for the assay of reduced tinidazole. The first method was based on Schiff's base reaction using ethylvanillin and measuring the absorbance of yellow color at λ_{max} 470 nm. Whereas the second method was based on oxidative coupling reaction using promethazine HCl and hypochlorite oxidation agent in alkaline medium, forming red color at λ_{max} 525 nm.

A colored complex was formed between tinidazole and copper (II) acetate, extracted with chloroform and measured spectrophotometrically.[110]

Chromatographic methods:

Mahmoud M. Sebaiy *et al.*,[111–114] introduced four miscellaneous HPLC methods for determination of tinidazole in combination with different drug classes.

RP-HPLC method was developed for the simultaneous determination of tinidazole. The separation was carried out using a mobile phase consisting of acetonitrile: methanol: 0.2 M potassium dihydrogen phosphate (pH 5) in the ratio of 2: 3: 2. The column used was SS Wakosil-II C_{18} and UV detection was set at 282 nm.[115] Another HPLC method was described based on using SS Wakosil-II C_{18} column with mobile phase composition of acetonitrile: phosphate buffer (pH 5) (3: 1, v/v) and UV detection at 295 nm.[116]

Stability-indicating method was described for the determination of ciprofloxacin and tinidazole using RP-UPLC method. The sample was analyzed by reverse phase Purospher Star C_{18} column as stationary phase and phosphate buffer: acetonitrile (80: 20, v/v) as a mobile phase and pH 3.0 was adjusted by ortho-phosporic acid. Quantification was achieved of ciprofloxacin HCl at 278 nm and of tinidazole at 317 nm.[117]

Isocratic RP-HPLC method was developed for the determination of amoxicillin, tinidazole and omeprazole in combined dosage forms. The three compounds were monitored at 230 nm using an isocratic mode on Inertsil ODS C_{18} column and a mobile phase consisting of methanol: acetonitrile: water in a ratio of (49: 49: 2, v/v/v).[118]

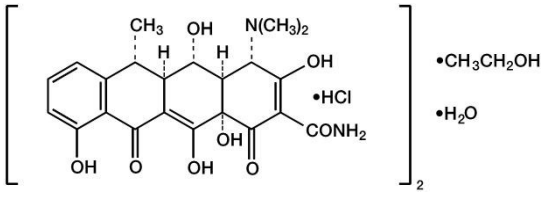
Miscellaneous methods:

Resonance light scattering technique was used to determine tinidazole by using tetraphenylboron sodium (TPB). Tinidazole was found to bind $B(C_6H_5)_4^-$ anion and transformed to tinidazole-TPB aggregate which displayed intense resonance scattering light.[119]

Capillary electrophoresis with UV photo-diode array detection technique was described for the analysis of tinidazole and norfloxacin in pharmaceuticals. This method utilized 32.5 mmol/L phosphate electrolyte at pH 2.5, voltage 25 kv and column temperature 25°C with detection at wavelength 301 nm.[120]

A multisyringe flow injection analysis method for the determination of tinidazole in pharmaceutical preparations was developed. Tinidazole concentrations were determined by spectrophotometric detection at λ_{max} 374 nm using a light emitting diode.[121]

7 Doxycycline hyclate



Chemical name:
4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride

Molecular formula: $(C_{22}H_{24}N_2O_8.HCl)_2$ C_2H_6O, H_2O

Molecular weight: 1025.89

Physical properties:

Appearance: Yellow crystalline powder

Solubility: Soluble in water and in methanol

Pharmacological action:

Doxycycline is a tetracycline derivative which is bacteriostatic with a broad spectrum of antimicrobial activity including many aerobic and anaerobic Gram-positive and Gram-negative pathogenic bacteria and some protozoa. It is used in triple therapy along with tinidazole and proton pump inhibitor in the treatment of peptic ulcer.[3]

Methods of determination:

Doxycycline hyclate is official in B.P. 2011[4] and U.S.P. XXXII[2] and it was determined in both pharmacopeias by liquid chromatography method.

Spectrophotometric methods:

A spectrophotometric method was described for the determination of doxycycline. The method was based on the formation of blue colored chromogen measured at λ_{max} 770 nm due to reduction of tungstate and/or molybdate in Folin-Ciocalteu reagent by doxycycline in alkaline medium.[122]

Rufino *et al.*,[123] described a simple spectrophotometric method for the determination of doxycycline. The method was based on the reaction between the drug and chloramine T in alkaline medium; producing red color with maximum absorbance at λ_{max} 525 nm.

Yellow ion pair complexes were formed between doxycycline and bromocresol green and methyl orange in Britton-Robinson buffer of pH 3 and 2.2, respectively; measuring the complexes at λ_{max} 424 nm and 480 nm. Moreover, Formation of charge transfer complexes were reported between doxycycline and tetracyanoethylene and 7,7,8,8-tetracyanoquinodimethane.[124]

Spectrofluorimetric methods:

Li-Wei *et al.*,[125] described a spectrofluorimetric method for the determination of trace doxycycline with diethyl-O-β-cyclodextrin doxycycline- Eu^{3+} system.

Another spectrofluorimetric assessment of doxycycline hydrochloride in tablets and serum sample was developed. The method was based on the enhancement of luminescence intensity of the optical sensor Sm^{3+} ion.[126]

Chromatographic methods:

Several HPLC methods were developed for the determination of doxycycline in human plasma, serum and biological tissues.[127–129]

HPLC method was developed for the separation of doxycycline and its degradation products. The separation was achieved by using Phenomenex Luna C_8 column, and a mobile phase consisting of acetonitrile: water: perchloric acid (26: 74: 0.25, v/v/v) adjusted to pH 2.5 with 5 M sodium hydroxide and ultraviolet detection at 350 nm.[130]

Another HPLC method was developed for estimation of doxycycline in bulk, tablets and capsules after storage in different temperature for testing thermostability of doxycycline. The samples were eluted from a Bondapak C_8 column with a mobile phase of acetonitrile: water: tetrahydrofuran (29.5: 70: 0.5, v/v/v), adjusted to pH 2.5 with 1.0 M HCl. The detection by UV was at 350 nm. The stability of doxycycline in bulk and in pharmaceuticals was checked over 90 days. Doxycycline showed thermo-degradation after exposure to high temperature; tablets were more stable than capsules.[131]

Mitic *et al.*,[132] developed HPLC method for quantification of doxycyline in pharmaceutical samples; using Lichrosorb RP-C_8 column and mixture of methanol: acentonitrile: 0.01 M aqueous solution of oxalic acid (2: 3: 5, v/v/v) as a mobile phase.

Liquid chromatography-mass spectrometric method was described and validated for the quantification of doxycycline in human plasma. The liquid chromatographic separations were carried out by using Cadenza C_{18} column. The mobile phase was composed of 0.04% trifluoroacetic acid in (methanol: acetonitrile: water (47.5: 47.5: 5, v/v/v). Mass spectrometer was used for detection.[133]

Miscellaneous methods:

The polarographic behavior of doxycycline was studied in phosphate buffer at different pH (2-9).[134] Flow-injection spectrophotometric and liquid chromatographic methods were used for the determination of doxycyline in biological fluids and pharmaceutical preparations. In spectrophotometric method, zirconyl chloride formed a yellow complex with doxycycline in acidic medium measured at λ_{max} 390 nm. Where in HPLC method, reversed phase C18 column was used. The mobile phase composed of 29.5% acetonitrile, 70% of 0.1 M oxalate buffer (pH 2.5) and 0.5% triethylamine.[135]

Flow-injection spectrophotometric method was developed for the determination of doxycycline in pharmaceutical formulations with chloramine T as oxidizing agent.[136]

The utility of carbon paste electrode was demonstrated

for the determination of doxycycline hydrochloride modified with doxycycline-tetraphenyl borate ion-pair.[137]

Electrochemical behavior of doxycycline was investigated by the differential pulse voltammetric method.

8 Conclusion

This literature review represents an up to date survey about all reported methods that have been developed for determination of Ranitidine hydrochloride, Famotidine, Omeprazole, Pantoprazole sodium, Tinidazole and Doxycycline hyclate in their pure form, combined form with other drugs, combined form with degradation products, and in biological samples such as liquid chromatography, spectrophotometry, spectroflourimetry, electrophoresis, *etc*.

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