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HPLC Analyses of H-2 Receptor Antagonist Products (Ranitidine, Cimetidine and Famotidine)

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In this research, the purity of the standard active ingredients of the tablets (ranitidine, cimetidine and famotidine) imported from abroad and the purity percentage of the active ingredients in each of the H-2 receptor antagonist tablets manufactured by several pharmaceutical companies of Iran were investigated and determined by HPLC technique. The analyses were made by using a 30 cm Finepak sil C_{8-5} column. A 20 µL solution from each individual sample and the standard solution were injected separately onto the column of an HPLC instrument which was equipped with ECW2000 software. The results obtained in this research have shown that with the exception of cimetidine tablets manufactured by Lorestan pharmaceutical company, all other tablets used in this research and manufactured in Iran can satisfy the needs of patients. Also, the imported standard powders were 100 % pure.

Key Words: Ranitidine, Cimetidine, Famotidine, H-2 Receptor antagonist, Histamine H_2-Blocker.

INTRODUCTION

Antiulcer drugs are a class of drugs, exclusive of the antibacterial agents, used to treat ulcers in the stomach and the upper part of the small intestine. Recurrent gastric and duodenal ulcers are caused by Helicobacter pylori infections and are treated with combination treatments that incorporate antibiotic therapy with gastric acid suppression. The primary class of drugs used for gastric acid suppression are the proton pump inhibitors (omeprazole, lansoprazole, pantoprazole and rabeprazole). The H-2 receptor blocking agents, cimetidine (**I**)[1,2], famotidine (**II**)[1,2], nizatidine (**III**) and ranitidine (**IV**)[2-4] have been used for this purpose, but are now more widely used for maintenance therapy after treatment with the proton pump inhibitors[5]. Histamine H-2 receptor antagonists, often shortened to H_2 antagonists also known as H-2 blockers are drugs that prevent or block the

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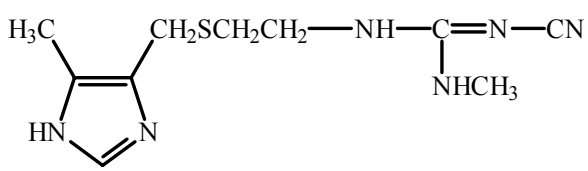
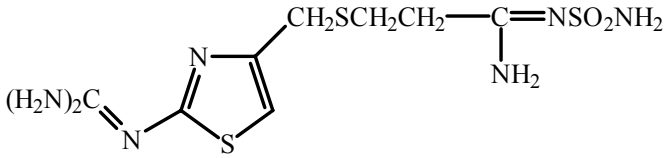


$C_{10}H_{16}N_6S$; mw = 252.3

Cimetidine: N-Cyano-N'-methyl-N"-{2-{[(5-methyl-1H-imidazol-4-yl)methyl]thio}ethyl}guanidine

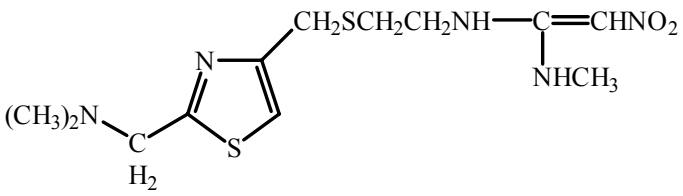
(**I**)



$C_8H_{15}N_7O_2S_3$; mw = 337.4

Famotidine: N'- (aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propanimidamide

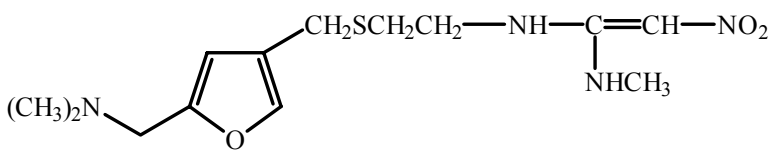
(**II**)



$C_{12}H_{21}N_5O_2S_2$, mw = 331.47

Nizatidine: N-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine

(**III**)



$C_{13}H_{22}N_4O_3S$; mw = 314.4

Ranitidine: N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine

(**IV**)

production of gastric (stomach) acid. These drugs are used to heal ulcers and relieve the symptoms and pain associated with gastroesophageal reflux disease (GERD) (heartburn). There is a pump in the stomach that releases hydrochloric acid when stimulated by histamine. H-2 blockers prevent histamine from stimulating this pump, thereby reducing the amount of acid that is released into the stomach[6]. Therefore, these drugs block the action of histamine on parietal cells in the stomach, decreasing acid production by these cells and are used to treat duodenal ulcers and prevent their return. They are also used to treat gastric ulcers and for some conditions, such as Zollinger-Ellison disease, in which the stomach produces too much acid. In over-the-counter (OTC) strengths, these medicines are used to relieve and/or prevent heartburn, acid indigestion and sour stomach. These drugs are used in the treatment of dyspepsia, since the advent of the more effective proton pump inhibitors[6]. H-2 antagonists are clinically used in the treatment of acid-related gastrointestinal conditions. Specifically, these indications may include: (i) peptic ulcer disease (PUD), (ii) gastroesophageal reflux disease (GERD) (heartburn), (iii) dyspepsia (iv) stress ulcer prophylaxis (raniditine)[7]. Cimetidine, famotidine and ranitidine are the examples of this group, also commonly referred to as H-2 blockers. These drugs are rapidly absorbed reaching peak plasma concentrations within 1-3 h. Ranitidine is widely distributed throughout the body. H-2 blockers are primarily metabolized in the liver. Famotidine and ranitidine are excreted in the urine as metabolites and unchanged drug, while cimetidine is eliminated in feces. The elimination half-life for all the three drugs is *ca.* 2.2 h in dogs. Because cimetidine may inhibit the hepatic microsomal enzyme system, ingestion of an H-2 blocker may result in reduced metabolism of certain drugs, including β-blockers, calcium channel blockers, diazepam, metronidazole and theophylline[8].

Famotidine is a guanidinothiazole derivative, ranitidine contains an aminomethylfuran ring and cimetidine has an imidazole ring. Data from the literature indicate that because of its chemical structure, famotidine has a much greater potency and affinity for the H-2 receptor and a notable lack of drug-drug interactions when compared with ranitidine and cimetidine. As a result, famotidine should be considered the H-2 receptor antagonist of choice for critically ill patients who require gastric-acid suppression and at the same time are being treated with other drugs that depend on the cytochrome P-450 mixed-function oxidase system for their metabolism and/or on renal tubular mechanisms for their excretion[9].

EXPERIMENTAL

All the chemicals used were purchased from Merck Company. Cimetidine, famotidine and ranitidine tablets (200, 150 and 20 mg, respectively) were all purchased from domestic pharmaceutical markets in Iran.

Cimetidine, famotidine and ranitidine standard powders were donated by Chimidarou Pharmaceutical Company of Iran. High performance liquid chromatography analyses were performed on a HPLC (Jasco, Japan, with Liquid Pump 880-PU; UV-Visible detector (870-UV); the instrument was equipped with an Interface (from Knauer company of Germany) and software program ECW2000 version2.05. Millipore membranes (0.45) made in Germany, were used.

Preparation of the standard solution of ranitidine: 150 mg of the ranitidine standard powder was weighed precisely and transferred into a 10 mL volumetric flask. After dissolving in 5 mL methanol, the volume was made exactly to 10 mL by adding more methanol solvent. Then, 1 mL of this solution (15 mg/mL) was transferred into another 100 mL volumetric flask and made the volume by adding more methanol solvent. Therefore, solution with concentration of 0.15 mg/mL (150 µg/mL) was obtained which was used for injection into the HPLC instrument.

Preparation of the sample solution of ranitidine: 150 mg ranitidine tablet was powdered in a porcelain mortar and pestle and transferred into a 10 mL volumetric flask then, 5 mL methanol solvent was added to dissolve it. The volume was made exactly to 10 mL by adding more methanol solvent and filtred through Teflon filter discs. Then, 1 mL of this solution (15 mg/mL) was transferred into another 100 mL volumetric flask and made the volume by adding more methanol solvent. Therefore, solution with concentration of 0.15 mg/mL (150 µg/mL) was obtained which was used for injection into the HPLC instrument.

Preparation of the standard solution of cimetidine: 200 mg of the cimetidine standard powder was weighed precisely and transferred into a 10 mL volumetric flask. After dissolving in 5 mL methanol, the volume was made exactly to 10 mL by adding more methanol solvent. Then, 1 mL of this solution (20 mg/mL) was transferred into another 100 mL volumetric flask and made the volume by adding more methanol solvent. Therefore, solution with concentration of 0.20 mg/mL (200 µg/mL) was obtained which was used for injection into the HPLC instrument.

Preparation of the sample solution of cimetidine: 200 mg cimetidine tablet was powdered in a porcelain mortar and pestle and transferred into a 10 mL volumetric flask then, 5 mL methanol solvent was added to dissolve it. The volume was made exactly to 10 mL by adding more methanol solvent and filtred through teflon filter discs. Then, 1 mL of this solution (0.20 mg/mL) (200 µg/mL) was transferred into another 100 mL volumetric flask and made the volume by adding more methanol solvent. Therefore, solution with concentration of 0.20 mg/mL (200 µg/mL) was obtained which was used for injection into the HPLC instrument.

Preparation of the standard solution of famotidine: 20 mg of the famotidine standard powder was weighed precisely and transferred into a 10 mL volumetric flask. After dissolving in 5 mL glacial acetic acid, the volume was made exactly to 10 mL by adding more glacial acetic acid. Then, 1 mL of this solution (2 mg/mL) was transferred into another 10 mL volumetric flask and made the volume by adding more glacial acetic acid. Therefore, solution with concentration of 0.20 mg/mL (200 µg/mL) was obtained which was used for injection into the HPLC instrument.

Preparation of the sample solution of famotidine: 20 mg famotidine tablet was powdered in a porcelain mortar and pestle and transferred into a 10 mL volumetric flask then, 5 mL glacial acetic acid was added to dissolve it. The volume was made exactly to 10 mL by adding more glacial acetic acid and filtred through teflon filter disc. Then, 1 mL of this solution (2 mg/mL) was transferred into another 10 mL volumetric flask and made the volume by adding more glacial acetic acid. Therefore, solution with concentration of 0.20 mg/mL (200 µg/mL) was obtained which was used for injection into the HPLC instrument.

HPLC optimum conditions used for the analysis of ranitidine standard powder and tablets: Stationary phase: Jasco, Japan, FinePak SIL C8-5 column with 30 cm length and i.d. 4.6 mm; Mobile phase: methanol; Flow rate: 1 mL/min; Column temperature: Room temperature; λ_{max} = 229 nm; AUFS = 0.01; Injected volume: 10 µL; Concentrations of ranitidine standard powder and tablets used: 150 µg/mL.

HPLC optimum conditions used for the analysis of cimetidine standard powder and tablets: Stationary phase: JASCO, Japan, FinePak SIL C8-5 column with 30 cm length and i.d. 4.6 mm; Mobile Phase: methanol Flow rate: 1 mL/min; Column temperature: Room temperature; λ_{max} = 227 nm; AUFS = 0.01; Injected volume: 10 µL; Concentrations of ranitidine standard powder and tablets used: 200 µg/mL.

HPLC optimum conditions used for the analysis of famotidine standard powder and tablets: Stationary phase: Jasco, Japan, FinePak SIL C8-5 column with 30 cm length and i.d. 4.6 mm; Mobile phase: acetonitrile; Flow rate: 2 mL/min; Column temperature: Room temperature; λ_{max} = 267 nm; AUFS = 0.01; Injected volume: 10 µL; Concentrations of famotidine standard powder and tablets used:200 µg/mL.

The purity percentages of ranitidine, cimetidine and famotidine standard powder and tablets manufactured by several Iranian pharmaceutical companies are given in Table-1.

RESULTS AND DISCUSSION

Iran is a country that imports a large amount of different types of medicines and their active ingredients from various countries annually and spends a huge sum of hard currency to purchase them. Since these medicines and

TABLE-1
COMPARISON OF PURITY (%) OF RANITIDINE PRODUCTS

Manufacturer	Ranitidine	Cimetidine	Famotidine
Imported standard powder	100.0000	100.0000	100.0000
Chimidarou	99.8487	99.9932	100.0000
Irandarou	98.5548	97.2234	–
Lorestan	99.4080	94.9211	–
Poursina	–	–	100.0000
Shafa	–	–	100.0000

their active ingredients are purchased from different countries, obviously their qualities would be different from one another. On the other hand, the efficacy of a drug depends largely upon the purity of the active ingredient (the standard) and other additives (excipiants). Of these drugs, H-2 receptor antagonists are important medicines which are used widely[7]. Based upon these facts, the following objectives were followed: (i) investigating and determining the purity of the standard active ingredients imported from abroad, (ii) investigating and determining the purity percentage of the active ingredients in each of the H-2 receptor antagonist tablets (ranitidine, cimetidine and famotidine) manufactured by several pharmaceutical companies of Iran (Chimidarou, Lorestan, Irandarou, Shafa and Poursina) and (iii) qualitative and quantitative comparisons of these tablets.

To achieve the above mentioned objectives, isocratic reversed phase high performance liquid chromatography (HPLC) which is a rapid and precise technique was used[10]. Solutions of ranitidine and cimetidine in methanol and solution of famotidine in glacial acetic acid were made, respectively and diluted to the proper concentrations suitable for HPLC analysis (0.15 mg/mL for ranitidine, 0.20 mg/mL for cimetidine and 0.20 mg/mL for famotidine) and filtred each through teflon filtre discs. For the HPLC analyses of ranitidine and cimetidine, methanol was used as the mobile phase, whereas acetonitrile was used as the mobile phase for the HPLC analysis of famotidine. The analyses were made by using a 30 cm Finepak sil $C_{8\text{-}5}$ column. A 20 µL solution from each individual sample and the standard solution were injected separately onto the column of an HPLC instrument which was equipped with ECW2000 software of Knauer company of Germany. λ_{max} of each drug was obtained from its UV-Vis spectrum. The chromatograms and the results obtained have shown the following results: (i) the purity percentages of ranitidine tablets manufactured by Chimidarou, Lorestan and Irandarou, as well as the imported standard powder were more than 98.5 % (Table-1). The least purity was from Irandarou pharmaceutical company, (ii) the purity percentages of cimetidine

tablets manufactured by Chimidarou, Lorestan and Irandarou pharmaceutical companies, as well as the imported standard powder were more than 94.92 % (Table-1). The least purity was from Lorestan pharmaceutical company and (iii) the purity percentages of famotidine tablets manufactured by Chimidarou, Shafa and Poursina Pharmaceutical Companies, as well as the imported standard powder were 100 % (Table-1).

Therefore, with the exception of cimetidine tablets manufactured by Lorestan pharmaceutical company, all of the other tablets used in this research and manufactured in Iran have the standard limits acceptable by the internationally well known Pharmacopoeia such as USP and can satisfy the needs of patients quite well. Also, the imported standard powders were 100 % pure.

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