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# REVIEW ON HPLC-UV METHOD TO DETERMINE CIMETIDINE, RANITIDINE, FAMOTIDINE AND NIZATIDINE IN URINE

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**ABSTRACT**
*A validated, uncomplicated, and widely applicable HPLC-UV technique for quantifying cimetidine, famotidine, nizatidine, and ranitidine in human urine is elucidated. This represents the inaugural singular HPLC method documented for scrutinizing all four H2 antagonists in human biological specimens. Furthermore, this technique was employed for assessing ranitidine and its byproducts in human urine. All calibration plots exhibited strong linear correlation (r 2 > 0.9960) across the experimental ranges. The methodology demonstrated commendable precision and accuracy, manifesting overall intra- and inter-day fluctuations of 0.2–13.6% and 0.2–12.1%, respectively. The separation of ranitidine and its metabolites through this analysis notably enhanced resolution, precision, and accuracy in comparison to prior methodologies. Subsequently, the analysis was effectively implemented in a human volunteer investigation utilizing ranitidine as the prototype compound.*

**KEY WORD -** *such as H2 antagonists, High performance liquid chromatography, Bioavailability, Metabolism, Ranitidine, Famotidine, Cimetidine, and Nizatidine are commonly utilized in research studies within the field of pharmacology.*

## INTRODUCTION

Histamine (H2) antagonists, including ranitidine, cimetidine, nizatidine, and famotidine, represent established pharmacological agents utilized in the management of gastro-esophageal reflux disease as well as gastric and duodenal ulceration. (1)

All four aforementioned H2 antagonists fall under the category of class III drugs, which are characterized by high solubility and low permeability as per the Biopharmaceutics Classification System (BCS) (2-4). The BCS classification system, established by Amidon et al. in 1995, serves as a tool for exempting the necessity of in vivo bioequivalence evaluations for new or reformulated generic immediate-release pharmaceutical products. At present, the BCS is exclusively applicable to class I oral immediate-release formulations, demonstrating high solubility and high permeability, that exhibit prompt in vitro dissolution following recommended testing protocols. (6-9) However, for class III compounds like the H2 antagonists, such exemption is not feasible, and in vivo bioavailability investigations become obligatory.

It is, therefore, essential that straightforward and dependable techniques are accessible for the examination of these compounds in biological fluids. Several HPLC-UV methodologies have been devised for the evaluation of the individual H2 antagonists in biological specimens such as urine or urine and plasma; cimetidine [9–11], famotidine [12–15], ranitidine [16], nizatidine [17,18]. More intricate or advanced liquid chromatography approaches have also been documented for the specific assessment of H2 antagonists in urine, including HPLC–MS [19–21], paired-ion HPLC-UV [22–23] post-column fluorescence derivatization [24], HPLC-TLC [25] and supercritical chromatography [26]. The majority of these techniques necessitate either solid-phase or liquid-phase extraction procedures which are time-intensive. Furthermore, these methodologies are solely capable of scrutinizing one of the four H2 antagonists. Two research groups have outlined procedures for the quantification of all four H2 antagonists in tablet formulations [27,28]. Nevertheless, there has been no documentation of a singular universal assay competent in scrutinizing all four H2 antagonists in biological samples such as human urine. Analysis from urine serves as a highly valuable approach in ascertaining the bioavailability of these medications in human subjects. Urine presents itself as a more conveniently obtainable biological matrix in comparison to plasma, is simpler to acquire, and is less invasive.

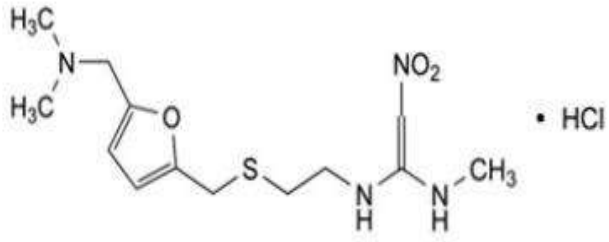
### 3. Drugs

### 3.1 Ranitidine

Ranitidine is a medication used to decrease stomach acid production. It was commonly used to treat conditions like peptic ulcer disease, gastroesophageal reflux disease, and Zollinger-Ellison syndrome

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- Ranitidine works by blocking histamine, which reduces the amount of acid released by the stomach.
- It can be taken orally or administered intravenously
- . Common side effects include headaches and pain/burning at the injection site, while serious side effects may include cancer, liver problems, slow heart rate, pneumonia, and an increased risk of Clostridium difficile colitis




**Structure 3.1 : Ranitidine Hydrochloride**

- Ranitidine is a small molecule drug with the chemical formula C13H22N4O3S

**Mechanism of action**

The mechanism of action involves the hormone gastrin, secreted by stomach lining cells post-meal, stimulating histamine release. Subsequently, histamine binds to histamine H2 receptors, inducing gastric acid secretion. Ranitidine operates by reversible binding to these receptors on gastric parietal cells, reducing gastric acid secretion. This action inhibits histamine binding to the receptor, thereby decreasing gastric acid production. Relief from gastric-acid symptoms may manifest within 60 minutes post a single dose, with effects lasting between 4 to 10 hours, offering rapid and efficient symptomatic alleviation.
Structure of ranitidine (19)

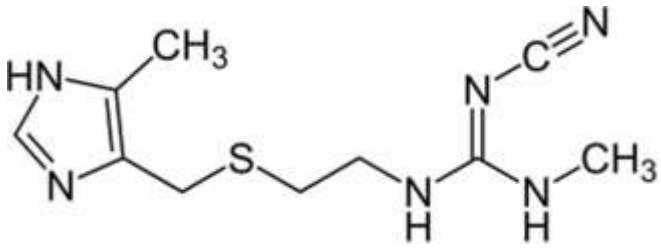
**Uses**

Ranitidine is a pharmaceutical agent that functions to diminish the production of gastric acid within the stomach. Its historical application encompassed the management of dyspepsia, pyrosis, and gastroesophageal reflux, including gastro-oesophageal reflux disease (GORD), a condition characterized by recurrent episodes of acid reflux. Additionally, it was employed in the prophylaxis and treatment of peptic ulcers. (18)

**3.2 Cimetidine**

Histamine H2-receptor antagonist

- Use – Treatment of heartburn and peptic ulcer
- Branded name – Tegamet




**Structure 3.2 : cimetidine**

- Cimetidine, with the chemical formula C10H16N6S

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**Mechanism of action**

The H2-receptor antagonist cimetidine functions by competitively inhibiting histamine's ability to activate the H2-receptors situated on the gastric parietal cells, which play a pivotal role in the secretion of hydrochloric acid and the intrinsic factor. This action leads to a decrease in the amount of gastric acid produced in response to various stimuli such as histamine, food, caffeine, and insulin. (16)

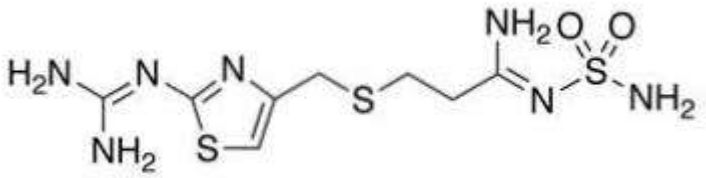
**Uses**

Cimetidine is employed for the treatment of gastric and intestinal ulcers, as well as for the prevention of their recurrence post-healing. Furthermore, this pharmaceutical agent is utilized in the management of specific gastrointestinal issues in the stomach and esophagus, including conditions induced by excessive gastric acid secretion such as Zollinger-Ellison syndrome and erosive esophagitis, or the retrograde movement of stomach acid into the esophagus (acid reflux disease/GERD). Alleviating the surplus stomach acid production can ameliorate symptoms like abdominal discomfort, heartburn, dysphagia, cough, and insomnia. (17)

**3.3 Famotidine**

Histamine H2 receptor antagonist medication that decreases stomach acid production.

- Brand name - Pepcid
- Used - to treat peptic ulcer disease, gastroesophageal reflux disease, and Zollinger-Ellison syndrome.
- Route of administration - Taken by mouth or by injection into a vein.



**Structure 3.3** : **Famotidine**

- Molecular formula is C8H15N7O2S3, with a molecular weight of 337.445 Da

**Mechanism of action**

The mechanism of action involves histamine functioning as a local hormone to stimulate acid output by parietal cells through a paracrine pathway. Adjacent to the parietal cells are neuroendocrine cells known as enterochromaffin-like (ECL) cells, which control the basal secretion of histamine. Additionally, histamine release is induced by acetylcholine and gastrin, a peptide hormone. Gastrin (G) cells secrete gastrin, which acts on CCK2 receptors located on ECL cells, triggering the release of histamine from these cells. Subsequently, histamine interacts with H2 receptors present on the basolateral membrane of parietal cells, resulting in elevated intracellular cAMP levels and activation of proton pumps on parietal cells. The proton pumps then release more protons into the stomach, consequently increasing acid secretion. In conditions characterized by acid hypersecretion like ulcers, the regulation of acid secretion is impaired. Famotidine operates on H2 receptors and inhibits the effects of histamine.

**Uses**

a. Famotidine is employed for the treatment of gastric and intestinal ulcers, as well as for the prevention of ulcer recurrence in the intestines following healing.
b. It relieves symptoms such as cough that doesn't go away, stomach pain, heartburn, and difficulty swallowing. (8)

**4. High performance liquid chromatography**

High-performance liquid chromatography, also known as High pressure liquid chromatography (HPLC), represents a distinct variant of column chromatography commonly applied in the fields of biochemistry and analysis for the purpose of segregating, characterizing, and quantifying bioactive compounds. HPLC predominantly relies on a column containing packing material (referred to as the stationary phase), a pump responsible for propelling the mobile phase(s) through the column, and a detector that indicates the retention times of

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the various molecules. The duration of retention is subject to fluctuations based on the interactions among the stationary phase, the molecules under examination, and the solvent(s) that are employed. The introduction of the specimen slated for analysis occurs in minute quantities into the flow of the mobile phase and is impeded by specific chemical or physical interactions with the stationary phase. The extent of hindrance is contingent upon the characteristics of the substance being analyzed as well as the composition of both the stationary and mobile phases.

The amount of retardation depends on the nature of the analyte and composition of both stationary and mobile phase. The degree of retardation is contingent upon the characteristics of the substance being analyzed and the makeup of both the stationary and mobile phases. The moment at which a particular substance emerges (exits the column) is termed the retention time. Typical solvents employed encompass any miscible blends of water or organic fluids (with methanol and acetonitrile being the most prevalent). Separation is achieved by altering the composition of the mobile phase throughout the analysis, a process referred to as gradient elution. This gradient segregates the mixtures of substances based on their interaction with the current mobile phase. The selection of solvents, additives, and gradient is influenced by the properties of the stationary phase and the substance being analyzed.

**HPLC**

**4.1 Types of HPLC**

1. Normal phase column
2. Reverse phase column
3. Ion exchange column
4. Size Exclusion column (4)



**4.2 Instrumentation**

**A. The pump**

- The pump is located at the upstream end of the liquid chromatography system, where it initiates the movement of eluent from the reservoir of solvent into the system.
- The generation of high pressure is a fundamental necessity for pumps, in addition to the requirement of maintaining a consistent pressure under all conditions and controlling a reproducible flow rate.

**Types** : reciprocating piston pump
Syringe pump
Constant pressure pump

**B. Injector**

- An injector is placed next to the pump.
- One of the most straightforward approaches involves utilizing a syringe for the introduction of the sample into the eluent flow.
- A prevalent injection technique relies on the utilization of sampling loops.

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- Moreover, a commonly employed strategy involves the application of an auto sampler (auto-injector) system, enabling multiple injections at predetermined intervals.

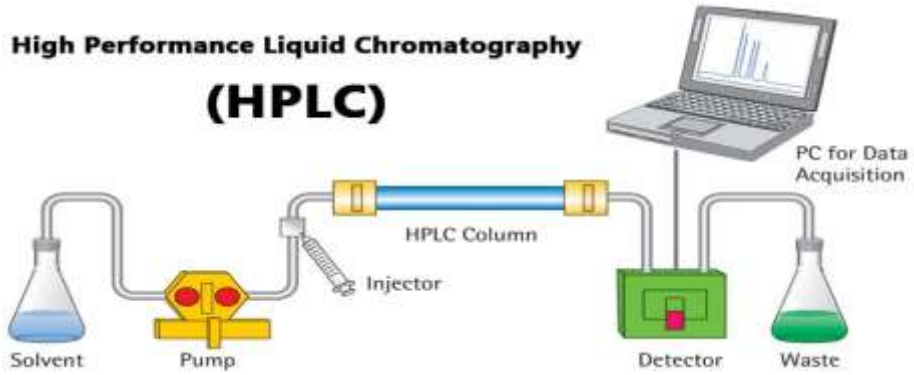
**C. Column**

- The separation is performed inside the column.
- The contemporary columns are frequently fabricated within a stainless steel enclosure, as opposed to glass columns.
- Silica or polymer gels are commonly utilized as the packing material in contrast to calcium carbonate.
- The mobile phase employed in liquid chromatography ranges from acidic to alkaline solvents.
- The majority of column enclosures are constructed from stainless steel due to its resilience towards a wide array of solvents

**Types**: Guard column
Analytical column

**D. Detector**

- Separation of analytes is performed inside the column, whereas a detector is used to observe the obtained separation.
- The composition of the eluent is consistent when no analyte is present. While the presence of analyte changes the composition of the eluent. What detector does is to measure these differences.
- This difference is monitored as a form of an electronic signal. There are different types of detectors available.




**E. Recorder**

- The alteration in the eluent identified by a sensor manifest as an electronic indication, hence remaining imperceptible to the naked eye.
- In ancient times, the pen (paper)-chart recorder enjoyed widespread usage. In the contemporary era, a computer-based data processor (integrator) has become increasingly prevalent.
- There are various types of data processors; from a simple system consisting of the in-built printer and word processor while those with software that are specifically designed for an LC system which not only data acquisition but features like peak-fitting, baseline correction, automatic concentration calculation, molecular weight determination, etc.

**F. Degasser**

- When gas is detected within the eluent, it is identified as interference resulting in an erratic baseline.
- The degasser employs a specific polymer membrane tubing for the elimination of gases.
- The polymer tube's surface features numerous minute pores that facilitate the passage of air while obstructing the flow of liquid through said pores. (5)

**4.3 Application of HPLC**

HPLC has become a staple technique for separating, identifying and quantifying different components in a mixture. Those three tasks lend themselves to a number of applications…

**1.Pharmaceutical development**

One of the primary applications of High-Performance Liquid Chromatography (HPLC) lies in the production stages of pharmaceutical goods. The utilization of HPLC serves as a dependable and accurate means to evaluate the level of purity in the end product.

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Consequently, it plays a crucial role in assisting pharmaceutical manufacturers in the formulation of exceptionally pure products. Nonetheless, its extensive cost implications often render it as a secondary option in the large-scale manufacturing of drugs.

**2. Medical Diagnosis**

High-Performance Liquid Chromatography (HPLC) is utilized for the purpose of isolating components from mixtures, making it suitable for the examination of nutrients in blood and various medical samples. Despite its higher cost in comparison to other methods, HPLC is capable of providing significantly more accurate outcomes when assessing factors such as vitamin D insufficiency. Instead of directly measuring the levels of vitamin D, HPLC can be applied to determine the concentration of 5-hydroxyvitamin D [25(OH)D] – a metabolite linked to the synthesis of vitamin D.

**3. Medical Research**

In addition to determining the levels of nutrients for diagnostic purposes, High Performance Liquid Chromatography (HPLC) is frequently employed in the examination of biological specimens obtained from individuals already diagnosed with certain conditions. For instance, by pinpointing particular metabolites in individuals afflicted with conditions such as Parkinson's disease or cardiovascular ailments, researchers can leverage them as biomarkers to facilitate early detection in prospective patients.

**4. Food production**

Over the past few decades, use of chemicals in agriculture and food production has become far more common. In many cases, this can be problematic, with chemical residues remaining on products and posing health risks to consumers. Thankfully, HPLC can also be used to identify and quantify pesticides along with preservatives and artificial flavorings and colourants.

**5. Legal**

Similar to the above, HPLC is also used for the detection of drug traces in urine. Usually used in tandem with mass spectrometry, the technique can be applied to detect everything from doping agents, metabolites and conjugates to opioids, cocaine, LSD, cannabis and ketamine. When drug traces are detected, the HPLC findings can be used as evidence in police charges as well as sporting disqualifications. Because it can be used to check for metabolites – produced by a reaction to the substance – the method is useful for modern drugs which are designed specifically to disappear within the body. (6)

**5.Experimental**

**5.1 Chemical and reagents**

Ranitidine hydrochloride was acquired from Zhongnuo Pharmaceutical Co., Ltd. Based in Shijiahzuang, China. The metabolites of ranitidine, namely ranitidine N-oxide, desmethyl ranitidine, and ranitidine S-oxide, were procured from GlaxoSmithKline located in Harlow, UK. Cimetidine, nizatidine, and famotidine were obtained from Sigma-Aldrich in the UK.

High-Performance Liquid Chromatography (HPLC) grade acetonitrile and water were sourced from Fisher Scientific in Loughborough, UK. Water utilized for the preparation of samples was obtained from an Elga Purelab option purification system. Sodium acetate from Sigma-Aldrich and glacial acetic acid from VWR International in Poole, UK were of analytical-reagent grade. Blank urine samples were provided by laboratory personnel.

**5.2 Preparation and chromatographic condition**

The configuration of the HPLC system included a high-performance LC (HPLC) system from Hewlett–Packard 1050 Series, which was furnished with a UV detector set at 230 nm to determine the four parent H2 antagonists. Ranitidine and its metabolites were separately analyzed at a wavelength of 320 nm. The collection of chromatographic data was executed through PC/Chrom software (H&A Scientific Co., UK). Utilizing a Phenomenex Luna SCX column (250 mm × 4.6 mm I.D.) filled with 5 m strong cation-exchange resin (VWR International) at 50 ◦C facilitated the successful separation of all molecules. The analysis was conducted with a mobile phase comprising acetonitrile:0.1 M sodium acetate buffer acidified with glacial acetic acid (pH 5.0; 0.1 M) in a ratio of 20:80, v/v. The entire analysis procedure was completed within 15 minutes at a flow rate of 2.0 ml/min.

**5.3 Preparation of standard solutions, quality control Samples and volunteer samples**

i. H2 antagonists—cimetidine, famotidine, And ranitidine

A solution of standard for each drug was individually concocted within the mobile phase and urine, after which it was introduced into the HPLC column to ascertain the distinct retention times of the molecules. Subsequently, a concentrated solution containing 500 g/ml

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of each standard as a free base was formulated in diluted blank urine (human urine diluted in a 50:50 proportion with a solution of 20:80 acetonitrile:water). Working standard solutions were then created through gradual dilutions of the concentrated solution with urine across the spectrum of 0–500 g/ml. Finally, a 10 µl volume from each solution was injected into the chromatographic system.

ii. Ranitidine and its Metabolites

A solution of stock comprising 500 g/ml of ranitidine and 50 g/ml of each metabolite of ranitidine (ranitidine N-oxide, ranitidine S-oxide, and desmethyl ranitidine) was formulated utilizing undiluted human urine mixed in a 50:50 proportion with a solution composed of 20:80 acetonitrile:water (referred to as control urine). Various standards covering the range of 0–500 g/ml for ranitidine and 0–50 g/ml for each metabolite were generated through successive dilution utilizing the control urine. In the context of the human trial, each sample provided by the volunteers was similarly diluted in a 50:50 ratio with a solution of 20:80 acetonitrile:water. A 10 µl aliquot from each solution was introduced into the chromatographic system under specified conditions.

iii. Method validation

Quality control standards ranging from low to high concentrations of the molecules were meticulously formulated in control urine for the purpose of assessing the precision and accuracy of the methodology. Distinct standards pertaining to low concentrations were specifically concocted to explore the thresholds of detection and quantification

iv. Linearity

The method's linearity was assessed across a range of concentrations, specifically from 0.5 to 500 g/ml for cimetidine, famotidine, nizatidine, and ranitidine, and from 0.1 to 50 g/ml for the metabolites of ranitidine.

v. Accuracy, precision and reproducibility

The evaluation of accuracy, precision, and reproducibility is crucial in scientific assays. This evaluation was conducted by assessing the intra- and inter-day coefficient of variation. Furthermore, the quality control samples underwent scrutiny for accuracy and precision through the analysis of five determinations for each quality control concentration at three distinct time points. Additionally, the inter-day variation was examined across three different concentrations on four separate non-consecutive days.

vi. Sensitivity

The determination of sensitivity Involved establishing the limit of detection (LOD) as the minimum analyte concentration yielding a signal at least double the baseline noise level. Furthermore, the determination of the limit of quantification (LOQ) was based on identifying the lowest analyte concentration that could be accurately measured with a precision of 20% and an accuracy falling within the range of 80-120%.

**6.Voluntary study**

**6.1 Sample collection**

Blank urine was obtained from healthy donors who did not have ranitidine in their system and was stored at -20°C. Control human urine samples were created by combining blank samples from donors in a 50:50 ratio with a solution of 20:80 acetonitrile: water.

Six individuals volunteered to take part in the research, having provided written consent after being informed. These participants were non-smokers, self-reported as healthy, and had no prior history of gastrointestinal illnesses. The research procedure was authorized by The Joint UCL/UCLH Committees on the Ethics of Human Research. The study was carried out following the Helsinki guidelines on research ethics (1965) and its subsequent amendments

The volunteers reported to the study centre after an overnight Fast and each received a single dose of 168 mg ranitidineHydrochloride (equivalent to 150 mg ranitidine) in 150 ml water.

A standardised sandwich lunch was provided 4 h post-dose. Cumulative urine samples were collected from each volunteer And involved the collection and measurement of bladder output Over the following time periods: 0 (pre-dose), 0–2, 2–4, 4–6, 6–12 and 12–24 h. For each collection period, 20 ml aliquot was Retained and stored at −20 ◦C.

**6.2 Analysis of Urine Sample**

Prior to the examination of volunteer specimens, an investigation was carried out on the stability of ranitidine and its metabolites in urine under various storage conditions. Duplicate spiked samples containing two different concentrations of ranitidine (267 and 80 µg/ml) were prepared. These spiked samples underwent analysis following diverse storage conditions: immediately upon placement on the auto sampler, after intervals of 4, 9, and 24 hours, following one, two, and three freeze/thaw cycles, as well as after 3 months of storage at -20 °C. Moreover, the stability of the metabolites of ranitidine was assessed after three freeze/thaw cycles and 48 hours of room temperature exposure at concentrations of 9 and 30 µg/ml.

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The urine aliquots obtained from v"lunt'ers were thawed at room temperature, and a mixture of 0.65 ml containing 20:80 acetonitrile:water was added to each sample in duplicates. Subsequently, after brief vortex-mixing, a 10 µl aliquot of each solution was injected into the HPLC column. (7)

**7. conclusion**

The method described in the HPLC-UV study is a straightforward, versatile, convenient, and replicable technique that can be utilized for the determination and quantification of any of the four H2 receptor antagonists. The study effectively examined ranitidine and its metabolites in the urine of healthy human volunteers post-administration of ranitidine. This technique proves valuable for bioavailability investigations and holds promise for exploring drug interactions in clinical pharmacology trials.

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