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Analytical Method: Determination of famotidine drug using chemiluminescence method

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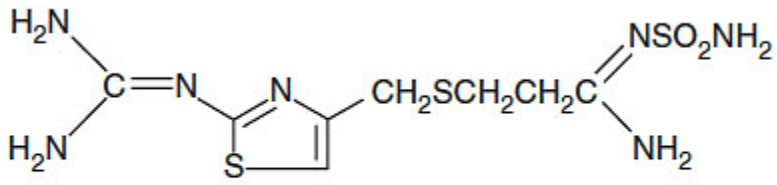
ABSTRACT

This study involved the development of a novel, cost-effective, fast, and highly sensitive analytical technique for quantifying minimal amounts of the drug famotidine through chemiluminescence. The method is centred around the measurement of energy emitted as a result of the interaction between the drug and Luminol in an alkaline solution; this interaction generates an electronically excited intermediate state, releasing a portion of the system's energy as photons. The method was sensitive for the analysis of famotidine. The linear calibration curve (LR) is obtained in the range 2-12 mg mL^{-1}, with a high correlation coefficient (R^2) of 0.9929. The molecular absorption coefficient (ε) was calculated at 2621×10^4 L mol^{-1} cm^{-1}. The method displayed excellent sensitivity with a Sandell's sensitivity of 1.287×10^{-5} mg cm^{-2}, the detection limit (LOD) was found to be 0.0314 mg mL^{-1}, and the limit of quantification (LOQ) was 0.0952 mg mL^{-1}. This study found that recovery was obtained at 104 - 96.5 %, and the relative standard deviation (RSD%) was below 1.981%. The results showed that the proposed technique has efficient recovery for measuring famotidine in pharmaceutical preparations.



$C_8H_{15}N_7O_2S_3$ M.W. 337.45

Scheme 1. The chemical formula of famotidine

1. Introduction

Famotidine is a crystalline substance with a white to light yellow appearance. It is almost insoluble in ethanol and has a high solubility in glacial acetic acid, a mild solubility in methanol, and an extremely slight solubility in water. The active component in famotidine injection acts as a histamine H2 receptor antagonist and has the chemical name [1-Amino-3-[2-[(diaminomethylene)amino]-4-thiazolyl]-methyl] thio] propylidene] sulfamide [1]. Famotidine is commonly known by its generic name, which is "Famotidine" (pronounced fam OH ti deen), and it is available under the trade name "Pepcid." (Scheme1) [2,3].

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Famotidine is used as a treatment for gastrointestinal ulcers and the regulation of acid secretion in the digestive system. Its therapeutic applications extend to addressing the Zollinger-Ellison syndrome, a condition characterized by excessive gastrin secretion, leading to heightened acid production and ulcer development. Functioning as a histamine-2 receptor inhibitor, famotidine effectively diminishes the concentration and volume of gastric acids [3-5]. This medication finds utility in various gastric hyperplasia cases, including Zollinger-Ellison syndrome, active gastric ulcers, gastroesophageal reflux, and esophagitis resulting from reflux. Additionally, famotidine is employed for the treatment of active duodenal ulcers, gastric ulcers, heartburn, acid indigestion, and sour stomach. Administration of the drug can be accomplished through oral ingestion or intravenous injection[6]. Chemiluminescence is the phenomenon of a substance emitting light spontaneously, without the involvement of heat; hence, it is often referred to as "cold light" [7]. This term encompasses all processes wherein materials can convert various forms of energy into visible light [8]. In simpler terms, it encompasses any process that releases energy in the form of visible light [9]. Chemiluminescence is the generation of light produced as a consequence of a chemical reaction. Occasionally referred to as "chemiluminescence," this phenomenon doesn't exclusively involve the emission of light; there may also be a concurrent release of heat, rendering the reaction exothermic. In the process, two chemicals undergo a reaction, forming an excited (high-energy) intermediate. This intermediate subsequently breaks down, releasing a portion of its energy in the form of light photons as it returns to its ground state[10]. When the emission of light arises from a chemical reaction occurring within a living organism, the term used is "bioluminescence." In this context, the light produced is a result of a chemical reaction taking place in vivo[11,12]. The accurate detection of ranitidine and famotidine hydrochloride in pharmaceutical formulations has been made possible by the development, validation, and application of a fast and extremely sensitive high-performance liquid chromatographic (HPLC) method [13]. Four distinct medication classes can be analyzed using a unique capillary gas chromatography (GC) method: metformin, ranitidine, cimetidine, and fumarate. Methylglyoxal (MGo) is a prerequisite for this analytical technique, which improves the precision and effectiveness of the inspection procedure [14]. A technique for identifying cimetidine, famotidine, and ranitidine hydrochloride was developed that is distinguished by its selectivity, precision, and accuracy. This method, which combines scanning densitometry with high-performance thin-layer chromatography (HPTLC), can be used for both pure and dose forms [15, 16]. The detection of famotidine plasma concentrations has been made possible by the development of a fast and accurate high-performance liquid chromatography (HPLC) technology that uses a monolithic column. Additionally, famotidine and ibuprofen have been simultaneously determined in composition using a validated reverse-phase HPLC[17]. A comprehensive comparison analysis was carried out to assess the pharmacological determination of diclofenac sodium utilizing two distinct analytical methods: high-performance liquid chromatography (HPLC) and flow-injection chemiluminescence[18]. The Flow Injection Chemiluminescence (FI-CL) method was used to determine the presence of famotidine, Diclofenac sodium (Voltaren), and Ethambutol HCl as active components and in pharmaceutical formulations [19]. Three H2-receptor antagonists have been identified using a novel, very sensitive liquid-injection chemiluminescence technique that has been designed, tested, and used: cimetidine, ranitidine hydrochloride, and famotidine. This technique is dependent on light intensity. This technique exhibits encouraging promise for precise and trustworthy screening of these medicinal substances [20]. Three newly created UV spectrophotometric techniques that make it easier, more affordable, sensitive, and accurate to determine the presence of famotidine in tablet and bulk drug formulations are described. These techniques offer useful methodological benefits for the quantitative pharmacokinetic analysis of famotidine [21]. Alamgir introduced a novel high-performance liquid chromatography (HPLC) technique in 2017 [22]. This approach, which is intended for the quantification of metformin, famotidine, and ranitidine, involves the pre-derivatization of columns using benzoin. Additional research also concentrated on the pharmacological determination of ranitidine-HCl through the use of active chemiluminescence, flow injection, spectrophotometric, and kinetic techniques. These analytical methods add to the vast array of accurate and thorough instruments for chemical analysis that are now accessible[23]. Ranitidine and famotidine levels in serum, urine, and pharmaceutical formulations can be directly determined using the capillary electrophoresis CE technique [24]. For the measurement of captopril, a novel flow-injection Chemiluminescence (FI-CL) approach without the need for a Chemiluminescence reagent has been

developed. This technique takes advantage of the fact that captopril increases chemiluminescence, which is mostly obtained from the system diperiodatoargentate (III)-sulfuric acid. This creative method provides a special and practical option for the accurate measurement of captopril in analytical applications [25, 26]. Penicillin antibiotics in medications and human urine can now be found using a flow-injection chemiluminescence approach. By making use of the luminol-Ag (III) complex system, this technique offers a sensitive and effective way to analyze penicillin antibiotics in a variety of matrices [27]. A technique that combines flow-injection chemiluminescence (FI-CL) and microdialysis has been developed to ascertain the binding characteristics of a medication that interacts with a protein. This novel method offers insights into the kinetics of drug-protein interaction by using the binding of the antibiotic tetracycline hydrochloride to bovine serum albumin as a model system [28]. A chemiluminescence technique that is both quick and effective has been created to measure and examine the pharmacokinetics of paclitaxel in rat plasma. Paclitaxel levels may be quickly and efficiently analyzed with this technology, which advances our knowledge of the drug's pharmacokinetics in biological materials[29]. The development of quick and reliable techniques for wastewater analysis is becoming more and more important due to the toxicological effects of several pollutants that are frequently found in wastewater from a variety of sources, including industrial and urban sources. Because of its great sensitivity, the chemiluminescence technique is used in wastewater analysis to identify and measure various contaminants. This method supports efforts to analyze and protect the environment by enabling sensitive and effective monitoring of water quality[30, 31]. Several nanomaterial-assisted chemiluminescence systems have been developed to increase sensitivity and expand their analytical uses. An overview of recent developments in electrochemiluminescence that make use of nanotechnology is provided, with a focus on analytical applications. This is important because it demonstrates the growing contribution of nanotechnology to the advancement of analytical techniques and includes applications in immunoassays, DNA analysis, and other biological analyses [32]. The primary goals of the present study are to use the chemiluminescence approach to estimate tiny amounts of famotidine and to establish an analytical method that is sensitive, quick, and inexpensive for detecting famotidine in pharmaceutical preparations. This method aims to measure the energy emitted during the chemiluminescent reaction between famotidine and Luminol, establish a calibration curve with a high correlation coefficient, determine the molecular absorption coefficient, assess Sandell's sensitivity, establish the detection limit, evaluate the quantum-limited sensitivity, and determine the recovery rate while maintaining precision with a relative standard deviation not exceeding 1.981%. Furthermore, this developed method is intended for successful application in pharmaceutical analysis.

2. Material and Methods

2.1. Instruments

Chemiluminescence measurements are performed Lumat LB 9507. Tube Luminometer, Firmware Version 5.03 (Berthold Technologies GmbH & Co.KG, Germany), and using 5ml Glass test tube.

2.2. Reagents

Sodium carbonate (Na_2CO_3), which has a CAS number of 497-19-8 and is sourced from the USA, was purchased from Honeywell Fluka to be used as reagents in this investigation. An essential part of our experimental setup, famotidine, was obtained from Sammarra Drugs in Iraq (SDI). The hydrogen peroxide (CAS number: 7722-84-1) is necessary for oxidative processes, was acquired from Sigma-Aldrich® and originated in Germany. Furthermore, Laminol, a crucial stabilizing agent, was purchased from BDH and acquired from the UK with a CAS number of 521-31-3. Each reagent underwent stringent quality control procedures to guarantee the precision and dependability of our experimental findings.

2.3. Solutions

1.060 g of pure material (Sodium Carbonate1.0×10^{-1}M) was dissolved in a particular amount of distilled water to create a solution. In a volumetric flask, the solution was then added to distilled water until it reached a final volume of 100 mL. To create this solution, 0.01 g of the medication famotidine (100 mg mL^{-1}) was dissolved in distilled water, and the volume was then completed in a volumetric flask at 100 mL. The process involves dissolving 0.1771 g of Luminol 1.0×10^{-3}M) in a specific volume of a 1.0×10^{-1} molar sodium carbonate solution. The solution is then adjusted to a total volume of 100 mL in a volumetric flask until the pH reaches 10.5. The preparation of this solution involved diluting 4.572 ml of hydrogen peroxide (1.0 M) in a volume of distilled water and then filling a volumetric flask to the full 100 mL with distilled water(DW). To prepare the solution of the pharmaceutical composition at 100 mg mL^{-1}

concentration, a tablet equivalent to one pill, weighing 0.1495 g was taken. It contained 20 mL of dissolved famotidine. This solution was filtered and then adjusted to a total volume of 100 mL in a volumetric flask, resulting in a concentration of 200 mg mL^{-1}. Subsequently, 50 mL of the prepared solution was transferred to a 100 mL container and topped up to the mark with DW, yielding a concentration of 100 mg mL^{-1}. Additional concentrations were created by further dilution.

2.4. General Procedure

To develop a new and rapid analytical method for the first time to determine the famotidine drug using the chemiluminescence technique based on the chemical reaction between Luminol and the drug in the presence of the hydrogen peroxide solution as a catalyst to produce an intermediate state of electronic excitement Initial experiments were carried out for the reaction by taking 500 µL of the drug and adding 50 µL of Hydrogen Peroxide 1.0 M concentration and 50 µL of reagent. The concentration of Luminol was 1.0×10^{-3} M. After mixing, the chemiluminescence intensity (Relative Light Units (RLU)) of the product was measured. It is necessary to determine the limits of quantification (LOQ) and the limits of detection (LOD; sometimes known as the detection limit, or DL) in the context of purity tests carried out during method validation. The calibration curve, also referred to as the calibration curve procedure in the literature, is frequently the basis for this decision. The formula for the computation is DL = 3.3x σ / S, where σ is the response standard deviation and S is the calibration curve's slope. Several techniques can be used to calculate the standard deviation.

3. Results and discussion

For the inaugural development of a novel and expeditious analytical method, the determination of the famotidine drug was undertaken using the chemiluminescence technique (Fig.1). This method relies on the chemical interaction between Luminol and the drug in the presence of hydrogen peroxide solution as a catalyst, resulting in the formation of an electronically excited intermediate state. Initial experiments involved taking 500 µL of the drug and supplementing it with 50 µL of a 1.0 M concentration of hydrogen peroxide, along with an additional 50 µL of a specific reagent. The concentration of Luminol in the mixture was maintained at 1.0×10^{-3} M. Following thorough mixing, the chemiluminescence intensity of the resultant product was then measured.

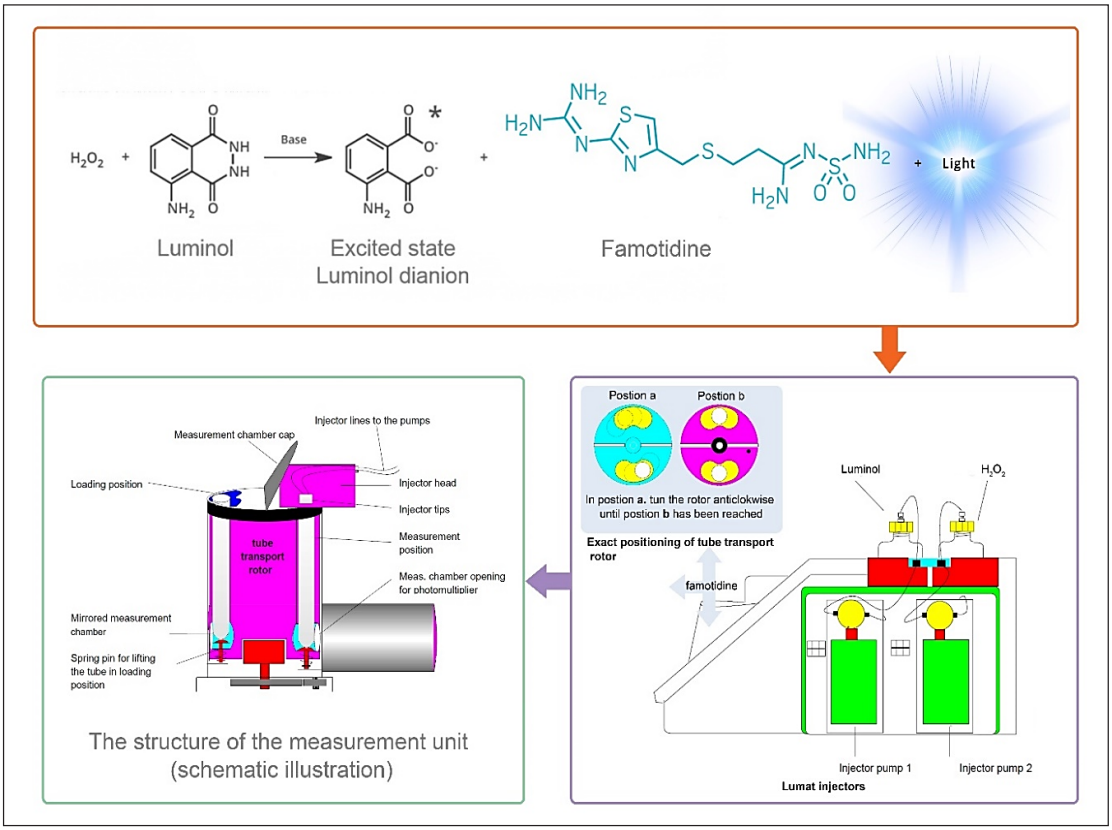

Fig. 1. Schematic of the chemiluminescence unit

3.1. Optimization of the Experimental Conditions

A study was executed for various factors affecting the chemiluminescence intensity of the produced complex to reach the best conditions for the reaction between the drug and the luminol in an alkaline medium and hydrogen peroxide.

3.2. Delay last injection measure

An experiment was carried out to determine the optimal time for injecting hydrogen peroxide at a concentration of 1.0 M into the Luminol at a concentration of 1.0×10^{-3} M several times, between 1-35 seconds. The results showed that the optimal time at which the highest luminescence intensity happened was one second, as shown in Figure 2.

3.3. Effect of Hydrogen Peroxide Volume

A study was executed to fix the best volume of hydrogen peroxide at a concentration of 1.0 M by injecting increased volumes between 50 and 300 µL and keeping other conditions constant. The results explained that the best volume is 250 µL, which is dependent on the best volume for sodium hydroxide in subsequent experiments, as shown in Figure 3.

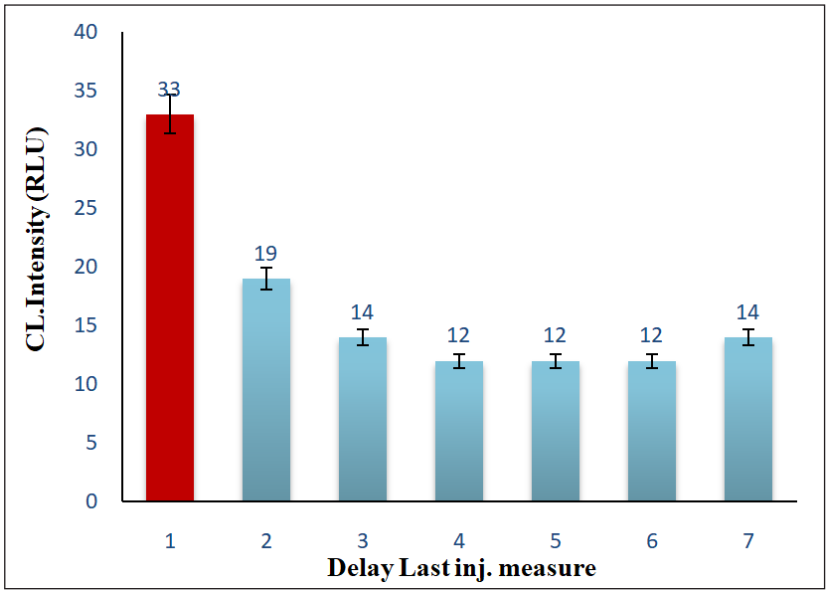

Fig. 2. Effect of injection time on the hydrogen peroxide intensity (RLU) of the chemiluminescence

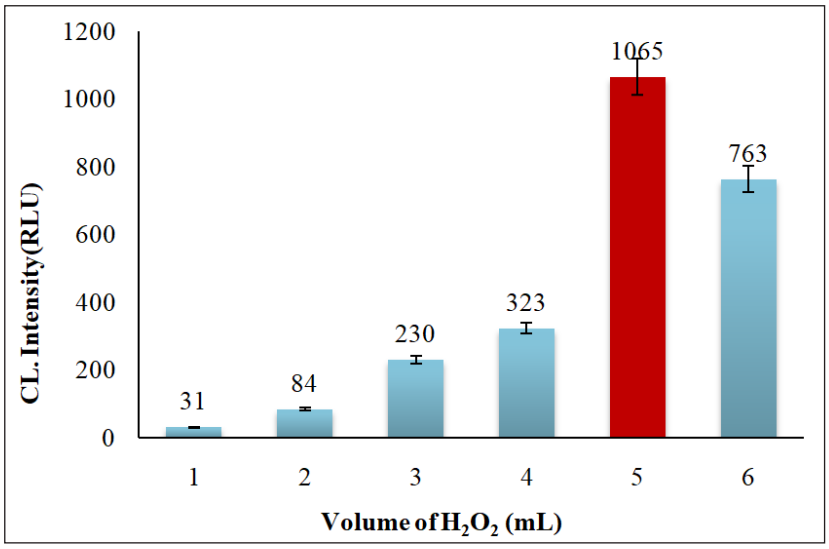

Fig. 3. Effect of hydrogen peroxide on the intensity (RLU) of the chemiluminescence

3.4. Effect of the Luminol volume

A study was conducted to know the optimal volume, which gives the highest chemiluminescence intensity, at a reaction of 500 µL from the famotidine drug (8.0 mg mL^{-1}) concentration and 250 µL from 1.0 M hydrogen peroxide and increased volumes from the Luminol solution between 50-300 µL 1×10^{-3} M. After mixing, the chemical intensity of the solution was measured. The result was that the optimal volume for the reagent that gives the highest luminescence intensity as a reaction product is 100 µL, as shown in Figure 4.

3.5. Effect of measurement time

A study was conducted to determine the optimal time, which gives the highest intensity of luminescence when 500 µL of Famotidine drug and 250 µL of Hydrogen Peroxide 1.0 M, 100 µL of Luminol 1.0×10^{-3} M and measuring the chemiluminescence intensity of the solution in different times ranged from 1-35 second. The results showed that the optimal time to give the highest intensity of the chemiluminescence of the reaction product is 20 seconds, as shown in Figure 5.

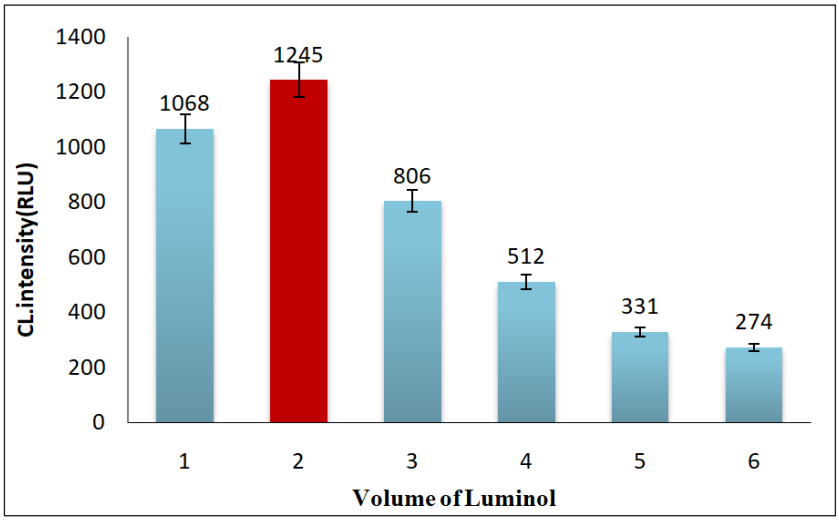

Fig. 4. Effect of the Luminol volume on the intensity (RLU) of the luminescence

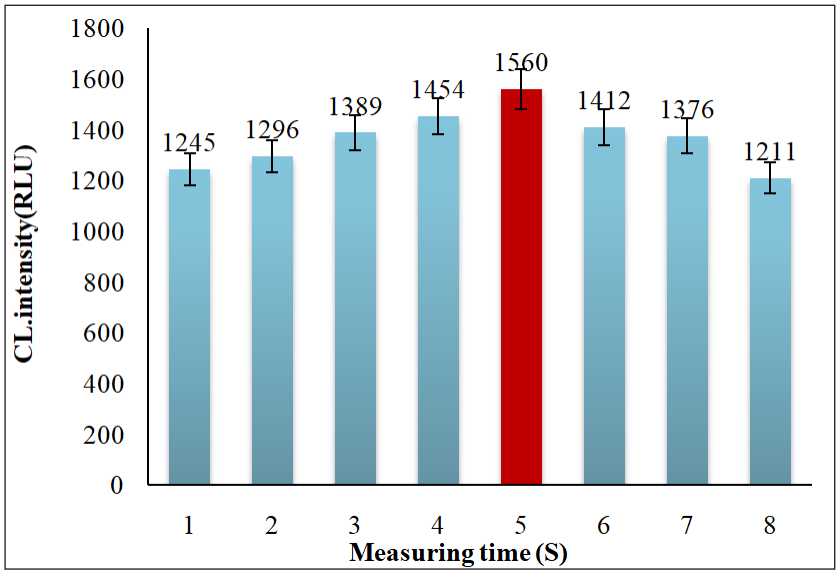

Fig. 5. Effect of the Luminol volume on the intensity (RLU) of the luminescence

3.6. Sequence added

A study was carried out to determine the optimal sequence for the addition of the Luminol reagent and sodium hydroxide, which gives the highest intensity (RLU) of luminescence when 500 µL of famotidine with a concentration of 8 mgml^{-1}, 250 µL of hydrogen peroxide 1.0 M, and 100 µL of Luminol of 1.0×10^{-3} M. The results showed that the optimal sequence that gives the highest intensity of the luminescence of the reaction product is the addition of hydrogen peroxide to the luminol reagent. Results were obtained in Table 1.

3.7. Procedure and Construction of Calibration Curve

After adjusting the optimal conditions for the reaction by the single variable method, by changing one of the conditions and keeping the other condition constant, the calibration curve was prepared by taking a set of concentrations between 1 - 16 mg mL^{-1}, by drawing increasing volumes of 0.1 -1.6 ml of the famotidine drug 100 mg mL^{-1} concentration in a 10 ml volumetric flask and then completing the volume to the mark with distilled water. Then 500 µL was taken from each concentration and placed in a test tube and setting equipment to the best volume of the Luminol reagent is 100 µL of 1.0 × 10^{-3} M and the best volume of 250 µL hydrogen peroxide 1.0 M. The intensity (RLU) of the chemiluminescence was measured at a rate of six readings per concentration. It was found that the concentrations that give Linear ranged 2 - 12 mg mL^{-1} of famotidine drug solution and that the correlation coefficient value was 0.9969, the straight-line equation y = 77.7× + 998.27, the detection limit (LOD) was found to be 0.0314 mg mL^{-1}and the limit of quantification (LOQ) was 0.0952 mg mL^{-1}, the molecular absorption factor was 2621×104 l /mol, and the sandal sensitivity was 1.287 × 10^{-5} mg cm^{-2}, as shown in Figure 6.

Table 1. Effect of Sequence of Addition

Order of Addition	CL. intensity (RLU)
H_2O_2 → Luminol (1 → 2) + Famotidine	1567
Luminol → H_2O_2 (2→1) + Famotidine	1215

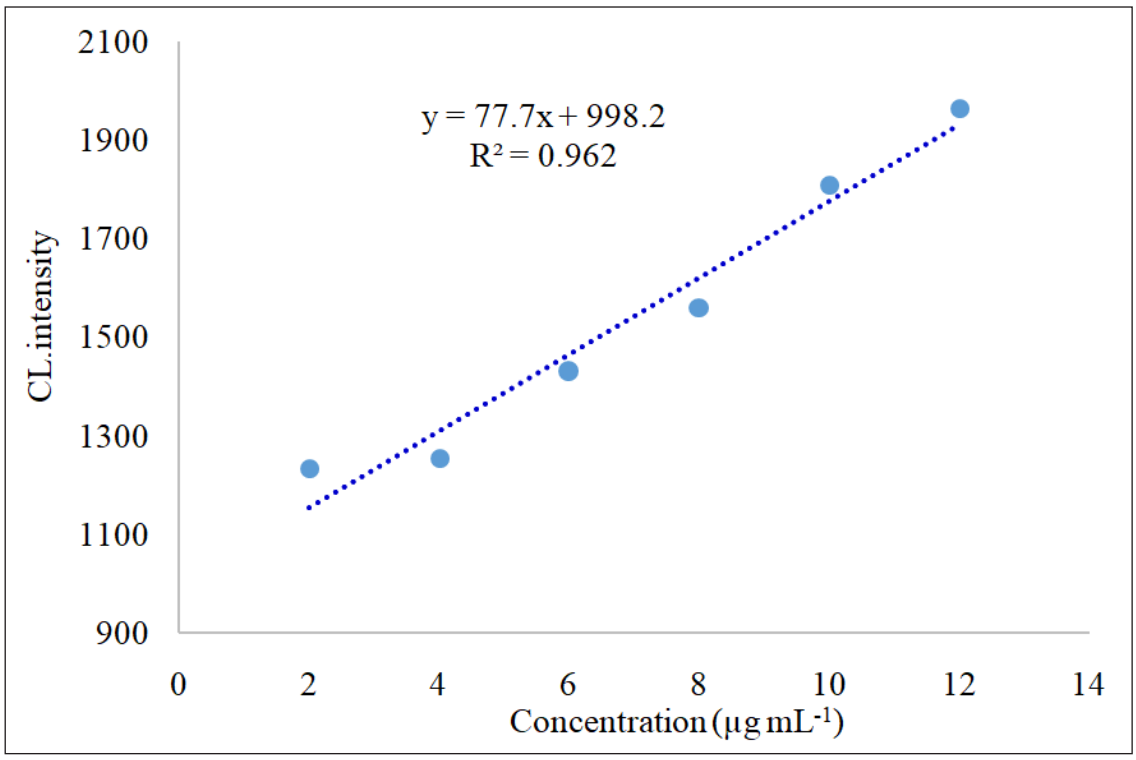

Fig. 6. Calibration curve of Famotidine

3.8. Accuracy and Precision

After studying and determining optimum conditions for the reaction of the luminescence, to estimate the famotidine drug, conduct six experiments for each measurement process carried out for all concentrations of the calibration curve for the drug and find the rate of readings. Used REC% and relative standard deviation RSD% to express the accuracy of the results, where the results showed that the method had high accuracy and compatibility, as shown in Table 2.

3.9. Application of the Method

The method was applied to pharmaceutical compositions, such as 20 mg of famotidine tablets produced by SDI Iraq, where the method was directly applied.

3.10. Direct Method

The direct method was applied to the above pharmaceutical composition with three different concentrations (4, 8, and 10 mg mL^{-1}) of the pharmaceutical product and was treated with the same steps as in the preparation of the calibration curve. The intensity of the luminescence of the above concentrations was measured by six readings per concentration, RE%, and the relative standard deviation of RSD% was calculated as in Table 3.

The chemiluminescence method for famotidine analysis is compared with other analytical methods and estimates, as detailed in Table 4. The table provides insight into the efficiency and operating time of the chemiluminescence method compared to other methods. Also, the organic compounds may be determined by other techniques such as gas chromatography and UV-Vis spectroscopy in water samples[35-38].

4. Conclusion

In this work we successfully concentration of famotidine was measured by a novel, and quick, chemiluminescence-based analytical method. It does

Table 2. Accuracy and Precision of luminescence method for famotidine determination

Sample (µg mL^{-1})	CL. intensity (RLU)	Found* (µg mL^{-1})	R(%)	RSD(%)
2.0	1190	2.076± 0.08	103.82	1.965
4.0	1256	3.976± 0.17	99.40	1.178
6.0	1430	5.799± 0.24	96.65	0.891
8.0	1560	8.320± 0.36	104.00	1.935
10.0	1809	10.386± 0.44	103.86	1.987
12.0	1964	12.295± 0.57	102.45	1.211

* Mean of three determinations ± confidence interval (P = 0.95, n = 8)
R: Recovery

Table 3. Direct Method for determination of famotidine tablets(20 mg)

Drug	Taken (µg mL^{-1})	CL. intensity (RLU)	Found* (µg mL^{-1})	R%	Average of R%	RSD%
Famotidine Tablets	4	1284	3.921± 0.14	98.025	98.913	0.098
	8	1605	7.874± 0.28	98.425	---	1.781
	10	1780	10.029± 0.44	100.29	---	1.209

* Mean of three determinations ± confidence interval (P = 0.95, n = 8)
R: *Recovery*

Table 4. Evaluation of Famotidine Comparatively Using Chemiluminescence and Additional Analytical Techniques.

Parameters	Electrogenerated chemiluminescence (ECL) [33]	Flow-injection chemiluminescence (FT-CL) [34]	Chemiluminescence (CL)
Leaner range	1.0×10^{-9} – 1.0×10^{-6} g mL^{-1}	5.0×10^{-5} – 7.0×10^{-5} g mL^{-1}	2.0 – 12 mg mL^{-1}
Electro-oxidation		Rhodanium-6G	Luminol
Slope	4.4	4.5	77.7
Detection limit LOD	1.0×10^{-10} g mL^{-1}	2.035×10^{-9} g mL^{-1}	0.0314 mg mL^{-1}
Detection quantum LOQ	----	----	0.0952
RSD%	----	2.87	1.981
Correlation coefficient (r)	0.9990	0.990	0.9993

not require heating or extraction. The technique showed good, sample and sensitivity, The LOD was found to be 0.0314 mg ml^{-1}, and the LOQ was 0.0952 mg ml^{-1} with a correlation value of 0.9929. and it was found that the concentrations that give Linear ranged from 2 - 12 mg mL^{-1}. The method has been successfully applied to estimate micro concentrations in pharmaceutical preparations containing famotidine.

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