

Alternative Method with Amperometric Detection for Ranitidine Determination

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An alternative, simple, and reliable FIA amperometric method for ranitidine quantification was developed. A working glassy carbon electrode and a Ag|AgCl|NaCl (3 M) reference electrode were used. The determination is based on the electrochemical oxidation of ranitidine at 1.2 V in phosphate buffer solution (pH 7.2). The determination of ranitidine in the range of 1×10^{-6} to 2×10^{-5} M was possible with a sampling frequency of 120 h^{-1} . The method was validated and satisfactorily applied to the determination of ranitidine in pharmaceutical formulations with a low limit of detection (6×10^{-7} M) and a quantitative recovery with no interferences from excipients. The results compare favorably with those obtained by the liquid chromatographic method of the U.S. Pharmacopoeia.

Introduction

Ranitidine, *N*-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-*N'*-methyl-2-nitro-1,1'-ethylenediamine (Scheme 1), is a histamine H₂ receptor antagonist which inhibits gastric acid secretion and is prescribed for the treatment of peptic ulcers with a recommended dose of 150 mg twice daily and 300 mg once daily. One of the important factors in healing of peptic ulcers is lowering the acid concentration in the stomach and thereby shifting the pH to neutral values.¹

Different analytical techniques have been employed for the quantitative analysis of ranitidine. The reference method given by the U.S. Pharmacopoeia uses liquid chromatography with UV detection.² Other different methods reported in the literature include titrimetry,³ colorimetry,^{4,5} spectrophotometry,⁶ near-infrared diffuse reflectance spectroscopy,⁷ reflectrometry,⁸ and X-ray powder diffractometry.^{9,10}

Several separation techniques such as HPLC^{11–31} and capillary electrophoresis^{32–34} have also been used for the determination of ranitidine and its degradation products or related compounds in different samples.

There is a constant search for simple, reliable, automated and semiautomated analysis for the rapid quantification of substances of therapeutic interest in pharmaceutical samples. High-performance liquid chromatographic methods, while having the advantage of requiring minimal sample preparation, are relatively slow and expensive and require filtration, degassing, and expensive grades of reagents, eluents, and equipment. On the other hand, flow injection (FI) methodology provides a means of automating and speeding up the handling of reagents in routine analysis with good selectivity and sensitivity. However, only a few flow injection methods for the determination of ranitidine had been described in the literature in association with chemiluminescence³⁵ and spectrophotometric^{36,37} and potentiometric^{36,38,39} detection.

Electrochemical detection offers additional advantages such as a better limit of quantification, the possibility to make the sample smaller and simpler, and the use of less expensive components. Electrochemical detection can also be used for quantification of different analytes due to the variety of materials and processes that can be used for the detection.⁴⁰ As far as we know, there is not a paper describing the use of amperometric

detection with an FI system for ranitidine quantification. In the present study the development, validation, and application of a simple and specific FI amperometric method for ranitidine estimation in different commercial pharmaceutical presentations are described. The results were compared with those of the official method reported in the literature.²

Experimental Section

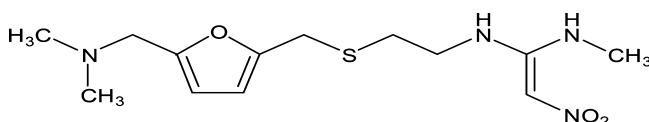
Materials and Reagents. Stock solutions of 2×10^{-2} M ranitidine (Parafarm) were prepared in phosphate buffer of pH 7.0 by dissolving an accurate weight in purified water. Aqueous standard solutions were prepared by diluting the stock solution with phosphate buffer. Water was purified in a Milli-Q system (Millipore). All other reagents were of analytical grade.

All buffer solutions, 0.05 and 0.01 M acetate buffer (J. T. Baker) and 0.05 M phosphate buffer (Cicarelli), were prepared by weighing the appropriate amounts of the drugs in pure water every day.

Sample Preparation. Ten tablets of commercial presentations (Ranital, Vannier, and Lazar) were weighed and crushed to a fine powder in an agate mortar. Accurately weighed quantities of this powder containing approximately 10 mg of ranitidine were transferred to a 250 mL volumetric flask and completed with phosphate buffer that gives a final concentration of approximately 1×10^{-4} M. This solution was further diluted to fit the linear concentration range. Each determination was carried out six times, and the drug was determined by the simple calibration method. Three pharmaceutical presentations from different laboratories were analyzed, Ranital, Vannier, and Lazar; two of them nominally contain 150 mg of the drug, and the other contains 300 mg. No additional sample pretreatment was required.

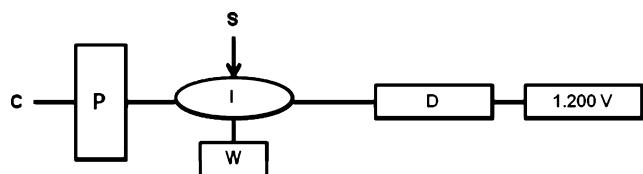
Apparatus. Cyclic voltammetry (CV) experiments were performed in an Autolab PGSTAT 30 (Ecochemie) electrochemical analyzer coupled to a personal computer. Ag|AgCl|3 M NaCl and Pt were used as reference and auxiliary electrodes, respectively. A glassy carbon disk (3 mm diameter MF-2012

Scheme 1. Structure of Ranitidine



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Scheme 2. Schematic Diagram of the Flow System for Ranitidine Determination^a



^a Key: C, carrier solution; P, peristaltic pump; I, manual injector; S, sample or reference solution; W, waste; D, electrochemical flow cell.

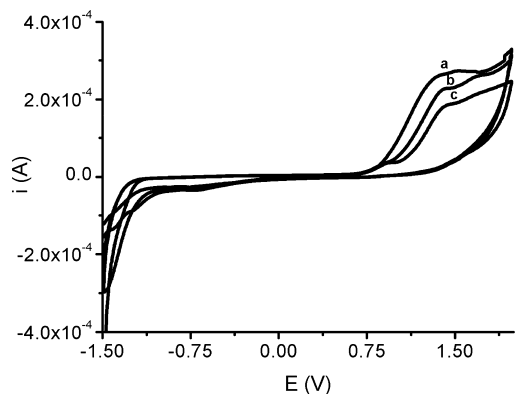


Figure 1. Cyclic voltammograms for ranitidine at 5.0×10^{-3} M in phosphate solution (a) and acetate buffer solutions with different concentrations, 0.05 M (b) and 0.01 M (c).

BAS) was used as a working electrode. The glassy carbon electrode was mechanically polished with alumina ($0.05 \mu\text{m}$) before each experiment.

Amperometric experiments were performed with a Bioanalytical System (BAS) model LC-4C amperometric detector in connection with a personal computer and a homemade program, O3TecADQ. The working glassy carbon electrode (BAS MF-1000), the reference electrode (Ag/AgCl/3 M NaCl, BAS MF-2021), and an auxiliary stainless steel electrode were all housed in a thin layer flow cell cabinet (BAS CC-5). The flow assembly, depicted in Scheme 2, was provided with a Rheodyne 7125 injection valve and a Gilson Minipuls 3 peristaltic pump as a propulsion system. The connections were made of PTFE tubing (0.5 mm), and phosphate buffer solution, 0.05 M (pH 7.2), was used as the carrier solution. All the results are the average of at least five injections, and all experiments were carried out at room temperature.

Results and Discussion

Electrochemical Behavior. Cyclic voltammograms were obtained in different buffer solutions to select the appropriate medium. Acetate and phosphate buffer solutions at different concentrations were analyzed (Figure 1). As can be observed, during the positive scan an anodic current peak is obtained in all the solutions analyzed. However, during the negative scan only a very small reduction peak is observed at ca. -0.75 V for both buffer solutions, indicating that the oxidation process is mainly irreversible. The anodic peak can be attributed to the amino group oxidation, as the potential value corresponds to the potential range for the oxidation of different anilines (0.8 – 1.2 V depending on the degree of substitution).^{41–43} The potential peak value depends on the buffer composition; for acetate buffer solutions the current peak is defined at 1.40 V, while for phosphate buffer it is defined at 1.35 V. For that reason, phosphate buffer solutions were chosen as the working electrolyte.

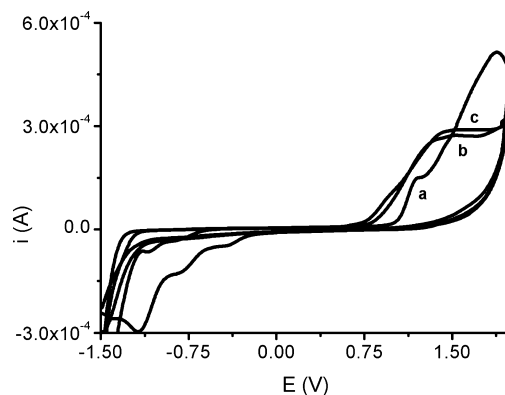


Figure 2. Cyclic voltammograms for ranitidine at 5.0×10^{-3} M in phosphate buffer solutions at different pH values: 2.48 (a), 7.12 (b), 9.45 (c).

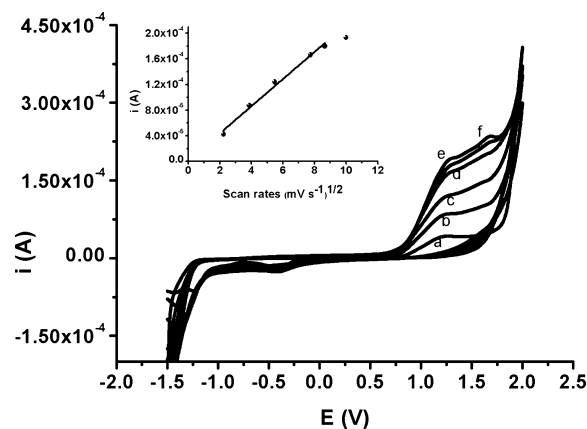


Figure 3. Cyclic voltammograms of 1.0×10^{-3} M ranitidine on a GCE with different scan rates of 5 (a), 15 (b), 30 (c), 60 (d), 75 (e), and 100 (f) mV s^{-1} in phosphate buffer with pH 7.2. Inset: dependence of the current against the square root of the scan rate.

The effect of the buffer pH was also analyzed, and cyclic voltammograms in phosphate buffer solutions at different pH values (2.48, 7.12, and 9.45) were obtained (Figure 2). As previously described, an anodic current peak is obtained during the positive scan. The anodic current peak is defined at 1.46 V for pH 9.45 and 1.35 V for pH 7.12, and the peak shifts to 1.22 V for acid pH values, while the current peak values are significantly lower for acid pH values. Phosphate buffer pH 7.12 was chosen as the optimum supporting electrolyte due to current peak values being higher than those for pH 2.48 and similar to those obtained for pH 9.45, in concordance with the peak potential results. Besides, pH 7.12 is close to the biological fluid pH, which may be interesting for clinical applications. In addition, phosphate buffer showed higher current signals than acetate buffer.

The effect of the potential scan rate on the voltammetric response for 5×10^{-3} M ranitidine oxidation on a glassy carbon electrode was investigated in the 5 – 100 mV s^{-1} range (Figure 3). A linear dependence of $i_{p,a} - v^{1/2}$ was obtained for scan rates lower than 100 mV s^{-1} , indicating that in this scan rate range the ranitidine oxidation process follows a diffusion-controlled mechanism.

Flow Injection Amperometric Detection. Flow parameters were optimized prior to electrode calibration to obtain the highest current signal without compromising the baseline. A single-stream system was used to ensure the sample and carrier mixing.

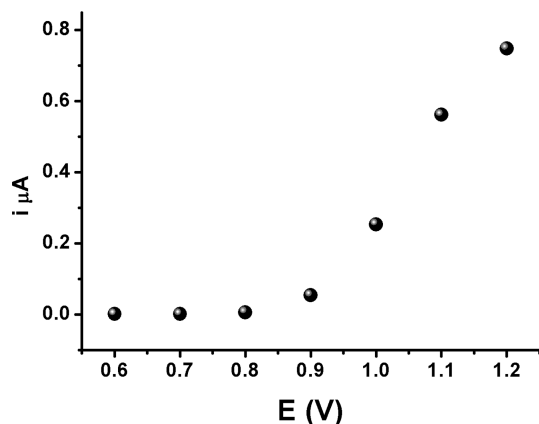


Figure 4. Hydrodynamic voltammogram for ranitidine at 1.0×10^{-5} M in phosphate buffer, 0.05 M (pH 7.00), at a 1.00 mL min^{-1} flow rate and with a $20 \mu\text{L}$ injection volume.

Figure 4 shows the hydrodynamic voltammogram at 1.00 mL min^{-1} ($20 \mu\text{L}$ of ranitidine, 1.00×10^{-5} M); the applied potential was analyzed between 0.60 and 1.20 V. As can be observed, there is a constant current increase for potential values higher than 0.9 V. However, a current plateau is never reached; for that reason, a detection potential of 1.20 V vs Ag/AgCl/3 M NaCl was chosen, as this potential value shows a significant current prior to oxygen evolution.

Another optimized parameter was the carrier stream flow rate. Both the peak height and width depend on this parameter, because sample dispersion during the passage from the injection point to the detector depends on the time taken by the process. This effect was examined for a ranitidine concentration of 2.00×10^{-5} M and a detection potential of 1.20 V by varying the flow rate from 0.50 to 1.50 mL min^{-1} (not shown). A flow rate of 1.00 mL min^{-1} was chosen as optimum, due to the fact that this value presents the best compromise between the peak height and width.

Using the working conditions of 1.20 V and a flow rate of 1.00 mL min^{-1} , the current reaches the baseline value in about 30 s after injection; this allows a maximum sampling frequency of 120 h^{-1} . Under these conditions, the current signal was stable with successive sample injections, indicating an excellent analytical performance.

Validation. The present method was validated by determining several parameters usually recommended by different guidelines: specificity, accuracy, precision or repeatability, intermediate precision, linearity, range, and robustness.

Calibration Range, Linearity, and Limits of Detection.

Using the optimum experimental conditions, the linearity was evaluated by linear regression analysis, which was calculated by the least-squares regression method.⁴⁴ Calibration curves for ranitidine were linear over the 1.0×10^{-6} to 2.0×10^{-5} M concentration range. The detection limit (LOD) was measured as the lowest amount of the analyte that may be detected to produce a response which is significantly different from that of a blank. The limit of detection was calculated on the basis of the standard deviation of the response (δ) and the slope (S) of the calibration curve at the levels approaching the limits according to the equation $\text{LOD} = 3.3(\delta/S)^{45}$, the LOD being 6×10^{-7} M.

Typically, the regression equation for the calibration curve obtained by performing independent analysis with polished working electrodes and five standard solutions was found to be

$$i_p (\mu\text{A}) = (0.02 \pm 0.01) + [(7.1 \pm 0.3) \times 10^4][C_{\text{ranitidine}} (\text{M})]$$

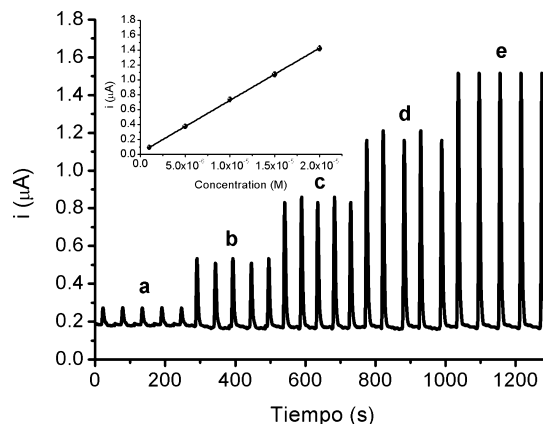


Figure 5. Transient current signals obtained in quintuplicate for ranitidine solutions: 0.1 (a), 0.5 (b), 1.0 (c), 1.5 (d), and 2.0 (e) $\times 10^{-5}$ M (applied potential 1.200 V, in phosphate buffer solution (pH 7.2)). The inset shows a calibration curve for ranitidine.

Table 1. Analysis of Samples of Known Concentration

theoretical concn (M)	experimental concn (M)	CV ^a (%)	<i>p</i>
5×10^{-6}	5.1×10^{-6}	6	0.5198
1×10^{-5}	1.04×10^{-5}	3	0.1472
1.5×10^{-5}	1.51×10^{-5}	1	0.3836

^a CV = coefficient of variation.

Table 2. Recovery Values Obtained from Standard Additions of the Analyte to Real Samples

sample	added amt (mg/tablet)	recovery \pm SD ^a (%)
Ranital ^b	66.4	105 \pm 3
	99.6	102 \pm 1
	132.7	95 \pm 6
Vannier ^c	72.8	105.1 \pm 0.1
	109.2	103.1 \pm 0.6
	145.6	100 \pm 6
Lazar ^d	132.9	111 \pm 3
	199.4	106 \pm 4
	265.8	101 \pm 2

^a Mean values and standard deviation of three determinations.

^b Ranital laboratory. ^c Vannier laboratory. ^d Lazar laboratory.

the correlation coefficient being 0.9999. All the results are the average of at least five injections. A typical calibration experiment is shown in Figure 5; at the inset a calibration curve is included.

Precision and Accuracy. The precision of the assay was investigated with respect to both repeatability and reproducibility.

Repeatability was determined by injecting standard solution at three levels of concentration, 5.00×10^{-6} , 1.00×10^{-5} , and 1.50×10^{-5} M (six replicates each). In Table 1 the obtained results, expressed in terms of the coefficient of variation (CV, %), for five successive ranitidine records are shown. Interday precision was assessed by injecting the same three concentrations over three consecutive days. As can be observed, CV values of less than 6% were obtained, indicating that the repeatability of the proposed method is acceptable.

Accuracy was determined by analyzing a known sample, comparing the measured value with the true value, and determining the percentages of recovery at three levels of concentration in two different situations. Recovery data obtained were within the 95–106% range (Table 2). Applying the *t* test, the experimental mean was not significantly different from the true value with 95% confidence ($p > 0.05$) (Table 1).

Ruggedness. The ruggedness of the method was established by comparison of the intra- and interday assay results for

Table 3. Comparison of the Slopes

sample	slope of standard addition method calibration	slope of the proposed method compared	<i>p</i>
Ranitral	6.8×10^4	6.9×10^4	0.5042
Vannier	7.6×10^4	7.4×10^4	0.5248
Lazar	6.4×10^4	6.5×10^4	0.5132

Table 4. Determination of Ranitidine in Three Pharmaceutical Formulations

sample	amt (mg/tablet)			<i>p</i>
	labeled	found, FIA method	found, official method	
Ranitral	150	156.8	155.6	0.1586
Vannier	150	146.8	148.5	0.2893
Lazar	300	300.7	300.8	0.9138

ranitidine undertaken by two analysts. The CV values for intra- and interday assays of ranitidine in the cited formulations performed in the same laboratory by the two analysts did not exceed 2.5%, thus indicating the method complies with the requirements.

Specificity. Matrix interference can introduce systematic errors on the analytical determination. The relative systematic errors can be detected by applying the standard addition calibration method to different real samples.⁴⁶ Thus, a comparison between the slopes of the standard addition calibration lines and a standard calibration line was carried out. If the matrix does not interfere, both lines must have the same slope. Slope comparison was performed by applying the *t* test. Table 3 shows the calibration slope lines obtained with the proposed method and with the standard addition method applied to different pharmaceutical samples. As can be observed, the slopes were not significantly different with 95% confidence ($p > 0.05$).

Applications to Real Samples. The proposed amperometric procedure was successfully applied for the determination of ranitidine in pharmaceutical formulations without interference from excipients on the basis of the average of six replicates. The obtained results were statistically compared with those obtained by the official method.² Values of the calculated *t* and theoretical *t* are also included in Table 4. No significant differences were noticed between the two methods regarding accuracy and precision as revealed by the *t* value, 2.45,⁴⁶ demonstrating that the proposed method is as accurate and precise as the reference spectrophotometric method.

Comparison of the Sensitivity of the Proposed Method and Other Previously Reported Methods. As already discussed before, different approaches have been reported for ranitidine quantification. Some of them correspond to batch techniques, mainly spectroscopic,^{4-6,8} having detection limits comparable with that of our method. However, most of the literature deals with methods that include a separation technique such as HPLC or capillary electrophoresis,^{15-20,22-24,26,28-31,33,34} in these cases depending on the detector used, lower detection limits can be obtained, but a specific instrument is required. Finally, in Table 5 a comparison of the results obtained by FIA with different detectors is presented. As can be observed, the detection limit of the proposed method is in the same range as those of other FIA systems. The only exception is when fast cyclic voltammetry³⁸ is used as the detector. Again, this technique cannot be performed in a simple way. Therefore, it

Table 5. Comparison of the Detection Limit of the Proposed Method with Those of the Other FIA Methods Reported

detector	reported detection limit	ref
chemiluminescence	6×10^{-7} M	35
spectrophotometry	1×10^{-5} M	37
potentiometry	1×10^{-6} M	36, 38
cyclic voltammetry	25 $\mu\text{g mL}^{-1}$ (about 8×10^{-11} M)	39
amperometry	6×10^{-7} M	proposed method

can be concluded that the proposed method is similar to or even better than most of the other FIA systems.

Conclusions

Flow injection analysis with amperometric detection is a valuable technique for the determination of ranitidine with good accuracy and precision. The electrochemical response shows a linear relationship with concentration (1×10^{-6} and 2×10^{-5} M). The proposed method is fast and not expensive, was successfully applied to the quantification in pharmaceuticals, and compares favorably with the official method.

The electrochemical behavior of ranitidine at a glassy carbon electrode in different buffer solutions was analyzed. A fully validated simple, fast, sensitive, and precise amperometric FI procedure was described for ranitidine quantification in bulk form and in pharmaceutical formulations. The procedure is simple, sensitive, and precise and could be used in trace analysis laboratories.

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Literature Cited

- (1) Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th ed.; McGraw-Hill: New York, 1996.
- (2) *United States Pharmacopoeia Convention*, 23rd ed.; USP: Rockville, MD, 1995.
- (3) Basavaiah, K.; Nagegowda, P. Determination of ranitidine hydrochloride in pharmaceutical preparations by titrimetry and visible spectrophotometry using bromate and acid dyes. *Il Farmaco* **2004**, *59*, 147.
- (4) Amin, A. S.; Ahmed, I. S.; Dessouki, H. A.; Gouda, E. A. Utility of oxidation/reduction reaction for the determination of ranitidine hydrochloride in pure form, in dosage forms and in the presence of its oxidative degradates. *Spectrochim. Acta, Part A* **2003**, *59*, 695.
- (5) Darwish, I. A.; Hussein, S. A.; Mahmoud, A. M.; Hassan, A. I. Spectrophotometric determination of H₂-receptor antagonists via their oxidation with cerium(IV). *Spectrochim. Acta, Part A* **2008**, *69*, 33.
- (6) Hassan, E. M.; Belal, F. Kinetic spectrophotometric determination of nizatidine and ranitidine in pharmaceutical preparations. *J. Pharm. Biomed. Anal.* **2002**, *27*, 31.
- (7) Rosa, S. S.; Barata, P. A.; Martins, J. M.; Menezes, J. C. Development and validation of a method for active drug identification and content determination of ranitidine in pharmaceutical products using near-infrared reflectance spectroscopy: A parametric release approach. *Talanta* **2008**, *75*, 725.
- (8) L. Spazzapam Lima, L.; LosWeinert, P.; Cavalcante Lemos, S.; Sequinel, R.; Redigolo Pezza, H.; Pezzav, L. An environmentally friendly reflectometric method for ranitidine determination in pharmaceuticals and human urine. *Spectrochim. Acta, Part A* **2009**, *71*, 1999.
- (9) Agatonovic-Kustrin, S.; Wu, V.; Rades, T.; Saville, D.; Tucker, I. G. Ranitidine hydrochloride X-ray assay using a neural network. *J. Pharm. Biomed. Anal.* **2000**, *22*, 985.
- (10) Agatonovic-Kustrin, S.; Rades, T.; Wu, V.; Saville, D.; Tucker, I. G. Determination of polymorphic forms of ranitidine-HCl by DRIFTS and XRPD. *J. Pharm. Biomed. Anal.* **2001**, *25*, 741.

- (11) Mody, V. D.; Satia, M. C.; Gandhi, T. P.; Modi, I. A.; Modi, R. I.; Chakravarthy, B. K. Sensitive high-performance thin-layer chromatography method for detection and determination of ranitidine in plasma samples. *J. Chromatogr., B* **1996**, *676*, 175.
- (12) López-Callul, C.; García-Capdevila, L.; Arroyo, C.; Bonal, J. Simple and robust high-performance liquid chromatographic method for the determination of ranitidine in microvolumes of human serum. *J. Chromatogr., B* **1997**, *693*, 228.
- (13) Farthing, D.; Brouwer, K. L. R.; Fakhry, I.; Sica, D. Solid-phase extraction and determination of ranitidine in human plasma by a high-performance liquid chromatographic method utilizing midbore chromatography. *J. Chromatogr., B* **1997**, *688*, 350.
- (14) Wong, C. F.; Peh, K. K.; Yuen, K. H. Simple high-performance liquid chromatographic method for the determination of ranitidine in human plasma. *J. Chromatogr., B* **1998**, *718*, 205–210.
- (15) Novakovic, J. High-performance thin-layer chromatography for the determination of ranitidine hydrochloride and famotidine in pharmaceuticals. *J. Chromatogr., A* **1999**, *846*, 193.
- (16) Khedr, A. Sensitive determination of ranitidine in rabbit plasma by HPLC with fluorescence detection. *J. Chromatogr., B* **2008**, *862*, 175.
- (17) Ahmadiani, A.; Amini, H. Rapid determination of ranitidine in human plasma by high-performance liquid chromatography without solvent extraction. *J. Chromatogr., B* **2001**, *751*, 291–296.
- (18) Munro, J. S.; Walker, T. A. Ranitidine hydrochloride: development of an isocratic stability indicating high-performance liquid chromatographic separation. *J. Chromatogr., A* **2001**, *914*, 13.
- (19) Nozal, M. J.; Bernal, J. L.; Toribio, L.; Martín, M. T.; Diez, F. J. Validation of a liquid chromatographic method for the determination of ranitidine hydrochloride residues on surfaces in the manufacture of pharmaceuticals. *J. Chromatogr., A* **2001**, *919*, 87.
- (20) Shah, S. A.; Rathod, I. S.; Savale, S. S.; Patel, B. D. Development of a sensitive high-performance thin-layer chromatography method for estimation of ranitidine in urine and its application for bioequivalence decision for ranitidine tablet formulations. *J. Chromatogr., B* **2002**, *767*, 83.
- (21) Vehabovic, M.; Hadzovic, S.; Stambolic, F.; Hadzic, A.; Vranjes, E.; Haracic, E. Stability of ranitidine in injectable solutions. *Int. J. Pharm.* **2003**, *256*, 109.
- (22) Flores Pérez, C.; Juárez Olgúina, H.; Flores Pérez, J.; Toledo López, A.; Lares Asseff, I.; Alvarez García, C. Reliable method for the determination of ranitidine by liquid chromatography using a microvolume of plasma. *J. Chromatogr., B* **2003**, *795*, 141.
- (23) Hare, L. G.; Mitchel, D. S.; Millership, J. S.; Collier, P. S.; Elnay, J. C.; Shields, M. D.; Carson, D. J.; Fair, R. Liquid chromatographic determination including simultaneous “on-cartridge” separation of ranitidine cisapride drug combinations from pediatric plasma samples using an automated solid-phase extraction procedure. *J. Chromatogr., B* **2004**, *806*, 263.
- (24) Zendelovska, D.; Stafilov, T. Development of an HPLC method for the determination of ranitidine and cimetidine in human plasma following SPE. *J. Pharm. Biomed. Anal.* **2003**, *33*, 165.
- (25) Castiglioni, S.; Bagnati, R.; Calamari, D.; Fanelli, R.; Zuccato, E. A multiresidue analytical method using solid-phase extraction and high-pressure liquid chromatography tandem mass spectrometry to measure pharmaceuticals of different therapeutic classes in urban wastewaters. *J. Chromatogr., A* **2005**, *1092*, 206.
- (26) Gomes do Nascimento, T.; de Jesus Oliveira, E.; Oliveira Macedo, R. Simultaneous determination of ranitidine and metronidazole in human plasma using high performance liquid chromatography with diode array detection. *J. Pharm. Biomed. Anal.* **2005**, *37*, 777.
- (27) Kokoletsi, M. X.; Kafkala, S.; Tsiaganis, M. A novel gradient HPLC method for simultaneous determination of ranitidine, methylparaben and propylparaben in oral liquid pharmaceutical formulation. *J. Pharm. Biomed. Anal.* **2005**, *38*, 763.
- (28) Li, W.; Tan, F.; Zhao, K. Simultaneous determination of amoxicillin and ranitidine in rat plasma by high-performance liquid chromatography. *J. Pharm. Biomed. Anal.* **2006**, *41*, 594.
- (29) Ashiru, D. A. I.; Patel, R.; Basit, A. W. Simple and universal HPLC-UV method to determine cimetidine, ranitidine, famotidine and nizatidine in urine: Application to the analysis of ranitidine and its metabolites in human volunteers. *J. Chromatogr., B* **2007**, *860*, 235.
- (30) Zhang, Y.; Mehrotra, N.; Budha, N. R.; Christensen, M. L.; Meibohm, B. A tandem mass spectrometry assay for the simultaneous determination of acetaminophen, caffeine, phenytoin, ranitidine, and theophylline in small volume pediatric plasma specimens. *Clin. Chim. Acta* **2008**, *398*, 105.
- (31) Kataoka, H.; Lord, H. L.; Pawliszyn, J. Automated in-tube solid-phase microextraction-liquid chromatography-electrospray ionization mass spectrometry for the determination of ranitidine. *J. Chromatogr., B* **1999**, *731*, 353.
- (32) Kelly, M. A.; Altria, K. D.; Grace, C.; Clark, B. J. Optimisation, validation and application of a capillary electrophoresis method for the determination of ranitidine hydrochloride and related substances. *J. Chromatogr., A* **1998**, *798*, 297.
- (33) Pérez-Ruiz, T.; Martínez-Lozano, C.; Tomás, V.; Bravo, E.; Galera, R. Direct determination of ranitidine and famotidine by CE in serum, urine and pharmaceutical formulations. *J. Pharm. Biomed. Anal.* **2002**, *30*, 1055–1061.
- (34) Gao, Y.; Tian, Y.; Sunb, X.; Yin, X. B.; Xiang, Q.; Mac, G.; Wang, E. Determination of ranitidine in urine by capillary electrophoresis-electrochemiluminescent detection. *J. Chromatogr., B* **2006**, *832*, 236.
- (35) Barnett, N. W.; Hindson, B. J.; Lewis, S. W. Determination of ranitidine and salbutamol by flow injection analysis with chemiluminescence. *Anal. Chim. Acta* **1999**, *384*, 151.
- (36) Hassan, S. S. M.; Mahmoud, W. H.; Othman, A. H. M. Determination of ranitidine in pharmaceutical preparations using manual and flow injection potentiometry and spectrophotometry. *Anal. Chim. Acta* **1996**, *332*, 39.
- (37) Pérez-Ruiz, T.; Martínez-Lozano, C.; Tomás, V.; Sanz, A.; Sahuquillo, E. Flow-injection extraction-spectrophotometric method for the determination of ranitidine in pharmaceutical preparations. *J. Pharm. Biomed. Anal.* **2001**, *26*, 609.
- (38) Issa, Y. M.; Badawy, S. S.; Mutair, A. A. Ion-selective electrodes for potentiometric determination of ranitidine hydrochloride, applying batch and flow injection analysis techniques. *Anal. Sci.* **2005**, *21*, 1443.
- (39) Norouzi, P.; Ganjali, M. R.; Daneshgar, P. A novel method for fast determination of ranitidine in its pharmaceutical formulations by fast continuous cyclic voltammetry. *J. Pharmacol. Toxicol. Methods* **2007**, *55*, 289.
- (40) Matysik, F. M. End-column electrochemical detection for capillary electrophoresis. *Electroanalysis* **2000**, *12*, 1349.
- (41) Altinoz, S.; Ozer, D.; Temizer, A.; Bayraktar, Y. Determination of ranitidine in a biological material by using differential pulse adsorptive stripping voltammetry. *Anal. Lett.* **1992**, *25*, 111.
- (42) Richter, P.; Inés Toral, M.; Muñoz Vargas, F. Polarographic behaviour and determination of ranitidine in pharmaceutical formulations. *Analyst* **1994**, *119*, 1371.
- (43) Kádár, M.; Nagy, Z.; Karancsi, T.; Farsang, G. The electrochemical oxidation of 4-bromoaniline, 2,4-dibromoaniline, 2,4,6-tribromoaniline and 4-iodoaniline in acetonitrile solution. *Electrochim. Acta* **2001**, *46*, 3405.
- (44) Miller, J. C.; Miller, J. N. *Estadística y Quimiometría para Química Analítica*, 4th ed.; Pearson Educación: Madrid, Spain, 2002.
- (45) Validation of analytical procedures: methodology. *ICH Harmonised Tripartite Guideline*; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Geneva, Switzerland, 1996.
- (46) Massart, D. L.; Vandeginste, B. G. M.; Buydens, L. M. C.; De Jong, S.; Lewi, P. J.; Smeyers-Verbeke, J. *Handbook of Chemometrics and Qualimetrics, Part A*; Elsevier: Amsterdam, 1997.

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