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QUANTIFICATION OF RANITIDINE HYDROCHLORIDE IN THE PRESENCE OF ITS DECOMPOSITION PRODUCT BY SPECTROPHOTOMETRIC METHODS. APPLICATION FOR KINETIC STUDY

ANETA SOKÓŁ, JOANNA KARPIŃSKA*, RENATA TALECKA and BARBARA STARCZEWSKA

Institute of Chemistry, University of Bialystok, Hurtowa 1, 15-399 Białystok, Poland

Abstract: Three spectrophotometric methods, based on a spectral analysis, are proposed for quantification of ranitidine hydrochloride (RHCl) in the presence of its decomposition product (R-ox) without isolation from the matrix. One of them is a zero-crossing derivative-spectrophotometry. A value of the first derivative at 332 nm generated by the Savitzky-Golay algorithm ($\Delta\lambda$ = 22 nm and the first polynomial degree) allows for quantification of RHCl in the concentration range 0.5–35.1 μg/mL. The second proposed spectrophotometric procedure, called Vierordt method, utilizes an additivity of the absorbance. The assay of studied compound was realized by the direct reading of absorbance at 312 nm and 202 nm for ranitidine hydrochloride and its decomposition product, respectively. The quantitative results were obtained by resolving of an appropriate system of equations. The third method is based on the bivariate calibration algorithm. The absorbance values were measured at optimum wavelengths found by Kaiser method at 228 nm and 202 nm and used for the quantification of RHCl in the presence of its decomposition product. The Beer's law was obeyed in the concentration range 0.5–35.1 μg/mL for RHCl. The discussion of applicability of all elaborated methods is presented. The proposed methods were applied for assay of ranitidine hydrochloride contents in its preparation Ranigast and for investigation of kinetics of its reaction with hydrogen peroxide.

Keywords: ranitidine hydrochloride, derivative spectrophotometry, Vierordt method, bivariate calibration algorithm

An application of a spectral analysis for estimation of ranitidine hydrochloride (RHCl) stability in aqueous solutions under oxidative conditions is proposed in this paper. For this purpose three methods, based on measurements of absorbance: derivative spectrophotometry, Vierordt's method and the bivariate calibration method are used. The goal of the presented work is the verification and the comparison of the analytical usefulness of proposed procedures and application for determination of ranitidine hydrochloride in the presence of its oxidation product in their binary mixture and use for the investigation of kinetics of ranitidine decomposition.

Ranitidine, N-{2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]thio]ethyl}-N^1-methyl-2-nitro-1,1-ethenediamine hydrochloride, represents histamine (H_2) receptors antagonists (1). It is commonly used for the treatment of gastric diseases connected with an excessive secretion of an acid in a stomach e.g., stomach and duodenal ulcers (2–4). This compound is chemically stable. It undergoes protonation in aqueous solutions with generation of different ionic forms depending on the pH of the solution (5). RHCl undergoes degradation in the presence of oxidation agents (6, 7) with production of mainly N- and S-oxides and desmethyl ranitidine (8). It is believed that under influence of high temperature and mild oxidative agent, only the S-oxide is generated (7). The rate of decomposition process depends on the presence of metal ions, suspended particles and oxygen (9, 10). RHCl is liable to photodegradation (11). It was stated that ranitidine underwent the degradation in a direct photolysis with a half-life of 35 min under noon summertime sunlight at 45° latitude (11).

Due to its pharmaceutical importance and a common use, several methods have been proposed for RHCl determination in bulk, pharmaceuticals and in clinical samples. Its assay in bulk or in phar-

* Corresponding author: e-mail: joasia@uwb.edu.pl

maceuticals was realized by titrimetry (11, 12), UV-Vis spectrophotometry (6, 7, 12–17), IR spectrometry (18, 19), atomic absorption spectrometry (19) and chemiluminometric method (20). The voltammetric behavior of RHCl was utilized for its determination using a mercury coated platinum microelectrode and a hanging mercury drop electrode (21). The resolution of RHCl and its metabolites was achieved by the use of capillary zone electrophoresis (22, 23), RP-HPLC with UV (24–27) and fluorescence detectors (28), LC-MS (29–33) and TLC techniques (34, 35). Recently, a new method applying diffuse reflectance spectroscopy was proposed for ranitidine determination (36).

Procedures described in this work were used for the direct quantification of ranitidine in the presence of its oxidation product for the first time. The obtained results are discussed in relation to their applicability for the quantification of ranitidine in the presence of its decomposition products and applied for an estimation of a rate of RHCl decomposition under oxidative conditions.

EXPERIMENTAL

Chemicals and reagents

Ranitidine hydrochloride (RHCl) was purchased from Sigma-Aldrich (USA). Stock solution (3.5 mg/mL) was prepared from the pure product by dissolving an appropriate weight in 50 mL of MilliQ water with addition of 1 mL 0.4 mol/L NaOH. Working solution (3.5–35.1 μg/mL) were freshly prepared every day by an appropriate dilution of the stock solution in MilliQ water.

Ranitidine decomposition product (R-ox) solution was prepared using the following procedure (7): 0.1 g of RHCl was dissolved in bidistilled water and then 1.0 mL of 12% H_2O_2 was added. The solution was thermostated at 90°C in water bath for 45 min and then diluted in 100 mL calibrated flask to the mark with bidistilled water. The stock solution was diluted quantitatively to obtain degraded samples of required concentrations.

HPLC-grade acetonitrile (Merck, Germany), potassium dihydrogen phosphate, analytical grade (POCh, Poland), 1-hexasulfonic acid, sodium salt, analytical grade (Sigma-Aldrich (USA).

Apparatus

Spectrophotometer U-2800A Hitachi was used for the acquisition and storage of spectra. The following working conditions of the spectrophotometer were applied: the scan speed 1200 nm/min and the spectral bandwidth (1.5 nm).

The chromatographic system, (Thermo Separation) consisted of the 3D detector Spectra System UV 3000, the low-gradient pump P2000, the vacuum membrane degasser SCM Thermo Separation and the Rheodyne loop injector (20 μL), was used. ChromQuest Chromatography Data System software version for Windows NT was used for the acquisition and storage of data. The measurements at 240 nm were done using reversed-phase analytical column, Supelcosil™ LC-8, 150 × 4 mm (5 μm) (Supelco, USA) and mobile phase included acetonitrile and buffer (pH = 2.5) comprised of 0.05 mol/L potassium dihydrogen phosphate and 0.4% sodium salt of 1-hexasulfonic acid 17 : 83 (37). The flow rate was set at 1.0 mL/min.

All calculations and transformations were done by Computer Pentium P120, 16 MB RAM equipped with Excel spreadsheet.

ANALYTICAL PROCEDURES

Calibration curve for assay of ranitidine hydrochloride by derivative method

Individual solutions of RHCl at concentrations in the range from 0.5 to 35.1 μg/mL were prepared in 25-mL calibrated flasks by an appropriate dilution of the stock solution with redistilled water. The absorption spectra were recorded in the wavelength range 200–400 nm. The redistilled water was used as a blank. The first-derivative spectra were generated by the Savitzky-Golay (38) procedure ($\Delta\lambda$ = 22 nm and the first polynomial degree) using the calculation spreadsheet. The measurement of derivative values was made by "peak-to-base line" technique at λ = 332 nm for a construction of a calibration graph for ranitidine.

Simultaneous determination of ranitidine and its oxidation product by Vierordt's method

The individual solutions of ranitidine and ranitidine oxide at concentrations 17.5 μg/mL and 12.5 μg/mL, respectively, were prepared and their absorption spectra were recorded in the wavelength range 190–400 nm *vs*. redistilled water as a blank. The spectra were used for estimation of absorbance coefficients at analytical wavelengths. Next, the mixture of RHCl at the concentration 17.5 μg/mL and R-ox at the concentration 12.5 μg/mL was prepared and its spectrum was recorded *vs*. water as a blank. Values of absorbance were read at 312 nm for quantification of ranitidine and at 202 nm for assay of its oxidation product. The quantification of compounds in mixtures and verification of the method were realized by resolving a system of equations.

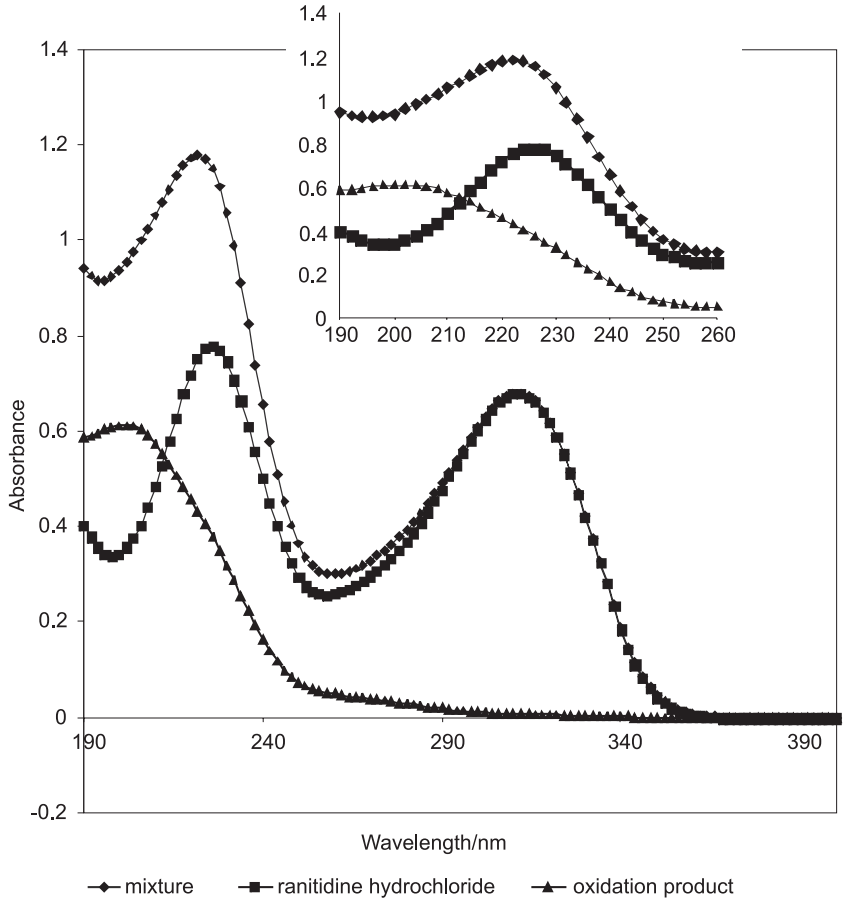

Figure 1. Zero-order spectra of ranitidine hydrochloride (17.5 ppm), oxidation product (12.5 ppm) and their mixture; small picture – the spectra in the wavelength range 190–260 nm

Calibration graphs for bivariate calibration procedure

The individual series of solutions containing RHCl in the concentration range 0.5–35.1 μg/mL and R-oxide in the concentration range 0.5–17.5 μg/mL were prepared for bivariate calibration. Spectra of the obtained solutions were registered in the range 190–250 nm. Absorbance values were measured at optimum wavelengths found by Kaiser method (39) at 228 nm and 202 nm and used for quantification of both compounds.

Calibration graph for chromatographic determination of RHCl

A HPLC procedure (37) was used as comparative method. For this purpose, a series of solutions containing RHCl in the concentration range 0.5–35 μg/mL were prepared and subjected to chromatographic analysis. The retention time of RHCl was 5.71 min. The relationship of picks areas *vs.* concentration was used for calibration and quantification of assayed compound. The concentrations of RHCl were calculated using the following equation of calibration graph: $y = 32623x - 49143$ ($r = 0.998$) where: x = concentration (μg/mL), y = peak area.

Sample preparation

Assays in coated tablets Ranigast produced by Polpharma, Poland

Five tablets, each containing 150 mg of ranitidine, were washed out in the distilled water to remove a colored envelope. Next, they were dried, weighed and finely powdered. A portion, equivalent to about 150 mg of RHCl, was accurately weighed and diluted with small amount of redistilled water. The powder was completely disintegrated on a mechanical shaker and the solution was filtered and transferred into a 500 mL calibrated flask. The filtrate was filled up to the volume with redistilled water with addition of 5 mL of 0.4 mol/L NaOH. For spectral analysis, an appropriate aliquot of tablets solution was transferred into the 25-mL cali-

brated flask and diluted with redistilled water to the mark. The spectra of solutions were recorded and concentration of compounds was assayed according to the procedures given in the calibration section.

RESULTS AND DISCUSSION

Derivative spectrophotometric method

Derivative spectrophotometry is the method which utilized a transformation of a function describing an absorbance spectrum into a derivative function (38). The obtained result is called a derivative spectrum. This operation leads to the separation of overlapped bands, enhances narrow bands and removes broad ones. The use of the derivative spectra has resulted in an amplification of selectivity and sensitivity of an assay.

At the beginning, the spectra of the studied compounds were recorded as it is seen in Fig. 1. The spectrum of the aqueous solution of ranitidine strongly overlaps the spectrum of its oxidation product. Ranitidine solution exhibits maxima at 226 and 312 nm, whereas its oxidation product only at 202 nm. In order to separate overlapped signals, the derivatization of the spectra was done. This mathematical operation was conducted by the Savitzky-

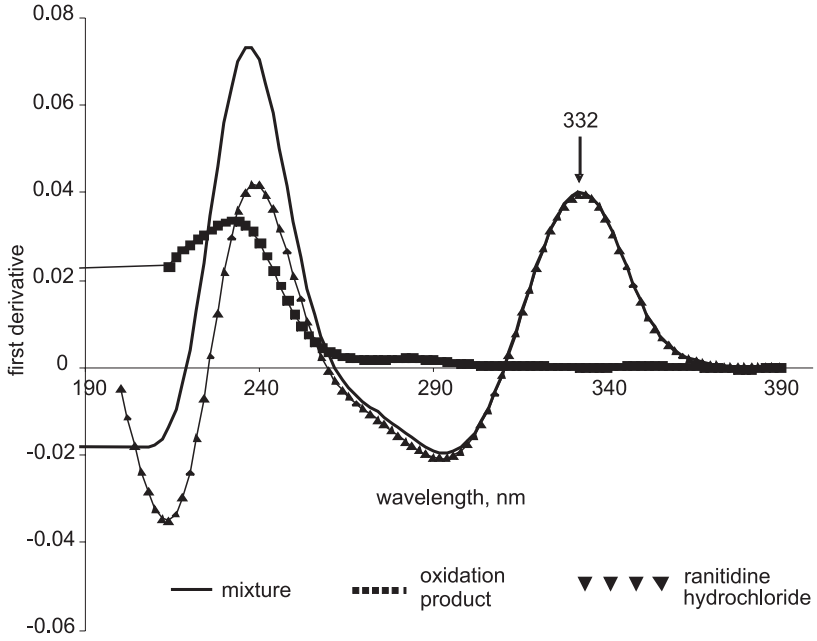

Figure 2. First-derivative spectra of ranitidine hydrochloride (17.5 ppm), oxidation product (12.5 ppm) and their mixture (first polynomial degree, 11-points experimental window, $\Delta\lambda$ = 22 nm)

Table 1. Analytical properties of elaborated derivative spectrophotometric method.

	RHCl	R-ox
Quantification range (mg/mL)	0.5 – 35	0.5 – 25
Equation of calibration curve x = concentration (µg/mL)	$y = (2.6\ x + 0.6)\times10^{-3}$	$y = (2.0\ x + 3.0)\times10^{-4}$
Correlation coefficient	0.9996	0.9832
RSD (%)	0.7% (for 10 µg/mL)	0.25% (for 5 µg/mL)
Limit of detection (taken as $s_L = a + 3s_{y/x}$)	0.001 µg/mL	0.56 µg/mL

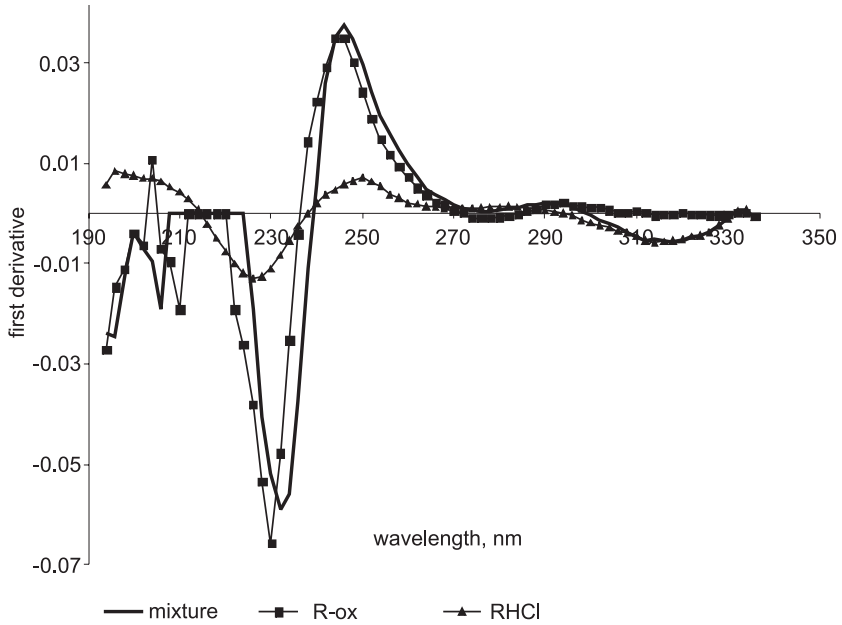

Figure 3. First-derivative spectra of ranitidine hydrochloride (17.5 ppm), oxidation product (12.5 ppm) and their mixture generated with the use of second polynomial degree, 5-points experimental window ($\Delta\lambda$ = 10 nm)

Golay algorithm (38). The application of this approach demands an optimization of such parameters like derivative order, polynomial degree and width of derivatization windows. For this purpose, the zero-order spectra of individual solutions of RHCl and R-ox at the concentrations of 17.5 μg/mL and 12.5 μg/mL, respectively, and their mixture were recorded and next, derivative spectra were generated. The choice of the abovementioned parameters was done taking into account the obtained selectivity and accuracy of determination. After careful analysis, it was stated that the first derivative spectra obtained by the use of first polynomial degree and 22 nm derivatization windows allows the direct determination of RHCl at the presence of R-ox (Fig. 2). The values of the first derivative read at 332 nm were used for the quantification of RHCl. Next, derivative spectra were analyzed for determination of decomposition product. As it is seen in Figure 3, the first derivative spectra generated with the second polynomial degree and 10 nm derivatization windows appeared to be appropriate for the direct quantification of R-ox in the presence of its parent compound. Values of the first derivative read at 238 nm were used for a construction of a calibration graph for the determination of R-ox. The statistical evaluation of the elaborated derivative spectrophotometric method is presented in Table 1.
After selection of mathematical parameters for generation of derivative spectra, the selectivity of the elaborated derivative method was examined. For this purpose, the series of two component solutions at various concentrations were prepared and their spectra were recorded in the wavelength range 190–400 nm. The appropriate derivative spectra were generated and used for the quantification of ranitidine or its oxidation product while the second compound was considered as an interference. The experiments showed that the derivatization enhances the selectivity in the ratio to RHCl. This compound can be assayed at the presence of wide range of the concentrations of its oxidation product (Table 2). However, the presence of RHCl interfered strongly with the determination of R-ox. Quantitative results of R-ox quantification were heavily biased by errors. The obtained values of its recovery were very poor. Taking obtained results into account, it was stated that derivatization almost completely removed the spectral influences of the presence of R-ox while it was impossible in the case of the oxidation product. Derivatization causes fast zeroing of its spectrum. The application of variety derivatization parameters did not improve the selectivity in the ratio to R-ox determination.

Vierordt's method

This method utilizes an additivity of the absorbance. An assay by Vierordt's method does not require construction of the calibration graph. It is based on resolution of a system of equations:

Table 2. Results of ranitidine determination in binary mixtures by derivative method.

Composition of artificial mixture			Concentration of RHCl assayed µg/mL (n = 5)	Recovery of RHCl %
Concentration of RHCl taken µg/mL (n = 5)	Concentration of R-ox µg/mL (n = 5)	Level of RHCl degradation %		
7	5.0	41.7	6.96	99.4
7	7.5	51.7	7.03	100.4
7	10.0	58.8	6.92	98.9
7	12.5	64.1	6.92	98.9
7	15.0	68.2	6.96	99.4
7	17.5	71.4	7.11	101.6

Table 3. Results of RHCl and R-ox determination in binary mixtures by Vierordt's method.

Composition of artificial mixture			C_{RHCl} assayed µg/mL	Recovery of RHCl %	Concentration of R-ox assayed µg/mL	Recovery of R-ox %
Concentration of RHCl taken µg/mL	Concentration of R-ox taken µg/mL	Level of RHCl degradation %				
7	7.5	51.7	7.28	104	8.83	117.7
7	10	58.8	6.87	98.1	9.72	97.2
7	12.5	64.1	6.87	98.1	12.14	97.1
7	15	68.2	6.62	94.6	13.3	88.7
7	17.5	71.4	7.05	100.7	17.21	98.3
3.5	7.5	68.2	3.51	100.3	8.09	107.9
17.5	7.5	30	16.95	96.91	7.53	100.4
24.5	7.5	23.4	25.63	104.6	7.61	101.5
35.1	7.5	17.6	36.8	104.8	9.73	129.7

$A_{M1} = \alpha_1 C_1 + \beta_1 C_2$ for λ_1 and $A_{M2} = \alpha_2 C_1 + \beta_2 C_2$ for λ_2 where: A_{M1} and A_{M2} represent values of mixture absorbance measured at λ_1 and λ_2, C_1 and C_2 are the concentrations of studied compounds and α_1, α_2 (compound 1), β_1, β_2 (compound 2) are values of absorption coefficients of individual solutions of compound 1 and 2 at analytical wavelengths (λ_1 and λ_2). λ_1 and λ_2 should fulfil the following requirements: absorbance of compound 1 at λ_1 should be maximal while absorbance of the second constituent exhibits its minimum. At the second selected value of λ_2, the spectrum of compound 2 should possess maximum while the absorbance of compound 1 could be neglected. After careful analysis of RHCl and R-ox spectra, the following analytical wavelengths were selected: 312 nm for determination of ranitidine and 202 nm for its oxidation product. The determined values of α_1, α_2 for ranitidine were 0.435 (at 312 nm) and 0.0221 (at 202 nm). As the absorbance of R-ox at 312 nm is equal zero, only the value of the coefficient at 202 nm was determined. It is 0.0509. The concentrations of the components were computed using the following equations:

$$C_R = \frac{A_{M1}}{\alpha_1} \text{ and } C_{R\text{-}ox} = \frac{A_{M2} - \alpha_2 C_R}{\beta_2}$$

Next, the series of binary mixtures at various concentrations were prepared and the content of each compound was assayed for estimation of the selectivity of the elaborated method. The obtained results are assembled in Table 3. Its analysis shows that recovery of ranitidine is almost 100% even at high percent of degradation. The determination of R-ox is much more susceptible to the presence of its parent compound. The recovery of R-ox varied from 88.7% up to 129% .

Bivariate calibration method

The bivariate calibration method is based on the law of absorbance additivity. The used mathematic

algorithm applied data obtained from calibration graphs recorded at optimal analytical wavelength. The selection of optimum wavelengths was done by the Kaiser method (39) considering the wavelength range 190–250 nm. For this purpose, the series of one component solutions were prepared and calibration graphs were recorded for each compound. The detailed description of selection of appropriate wavelengths was given in our previous work (40). Based on an analysis of a sensitivity matrix (39, 40) the wavelengths at 202 and 228 nm were chosen for simultaneous determination of ranitidine and its oxidation product as they provided the highest sensitivity for each compound (Fig. 1). At the selected wavelengths, the absorbance of one-component solutions were registered and used for the construction of calibration graphs for one-component calibration. Calibration graphs for RHCl obeyed Beer law in the concentration range 1.0–35 μg/mL, while for R-ox in the concentration range 1.0–15 μg/mL. The obtained regression equations were:

$y_{228} = 0.044x + 0.0111$ (RHCl) and $y_{228} = 0.0289x + 0.0114$ (R-ox)

$y_{202} = 0.0483x + 0.0245$ (RHCl) and $y_{202} = 0.01203x + 0.0104$ (R-ox)

The concentrations of the studied compounds in their binary mixtures were calculated using the following equations:

Table 4. Results of determination in binary mixtures RHCl and R-ox by bivariate calibration method.

Composition of artificial mixture			C_{RHCl} assayed μg/mL	Recovery of RHCl %	Concentration of R-ox assayed μg/mL	Recovery of R-ox %
Concentration of RHCl taken μg/mL	Concentration of R-ox taken μg/mL	Level of RHCl degradation %				
7	5	41.7	6.97	99.6	4.52	90.4
7	7.5	51.7	6.76	96.6	6.64	88.5
7	10	58.8	6.78	96.9	9.24	92.4
7	12.5	64.1	6.59	94.1	12.05	96.4
7	15	68.2	6.52	93.1	14.65	97.7
7	7.5	51.7	6.61	94.4	7.59	101.2
10.5	7.5	41.7	10.01	95.3	7.36	98.1
17.5	7.5	30.0	17.08	97.6	7.34	97.9
24.5	7.5	23.4	25.13	102.6	7.84	104.5

Table 5. Results of RHCl determination in Ranigast tablets (n = 3).

Quantity (mg) of RHCl in coated tablets Ranigast	HPLC method	Derivative spectrophotometry	Vierordt method	Bivariate calibration method
150	151.7	152.8	151.6	149.9
SD	3.2	5.2	2.9	4.3
$(SD)^2$	10.1	27.1	8.5	18.6
RSD (n = 3) (p = 0.05)	2.1	3.4	1.9	2.9
Confidence limit of the mean (p = 0.05)	± 1.5	± 2.5	± 1.3	± 2.0
F-test/critical value $F_{0.05(3.3)}$ = 9.28 (p = 0.05)	–	0.37	1.20	0.54
Relative error*, %		+0.07	–0.1	–1.2

*versus HPLC method

Table 6. Kinetic data of the reaction studied.

Method	Standard solutions (10.5 μg/mL of RHCl)		River water (10.5 μg ml^{-1} of RHCl)	
	k (s^{-1})	$t_{1/2}$/min	k (s^{-1})	$t_{1/2}$/min
Derivative spectrophotometry	0.0225	30	0.0109	63
Vierordt method	0.0201	35	0.0099	70
Bivariate calibration method	0.0205	33	0.0126	55
Average	0.0210	32.7	0.0111	62.7

$$C_{Rox} = \frac{0.0289(A_{202} - 0.0574) + 0.044(0.0574 - A_{228}}{- 0.00154}$$

$$C_{RHCl} = \frac{A_{202} - 0.0579 - 0.0203C_{Rox}}{0.044}$$

Then, the selectivity of the bivariate calibration method was determined. For this purpose the binary mixtures of the studied compounds were prepared and the concentration of one component was assayed while the second was considered as the interferent. The results are presented in Table 4. The analysis of obtained results revealed that bivariate calibration method allowed to obtain an excellent recovery of RHCl in the presence of the wide concentration range of its degradation product. It was observed, similarly as in the case of Vierordt method, that the results of quantification of R-ox are strongly influenced by concentration of both compounds in the mixture. The recovery of the degradation product differed from 88.5% up to 105%.

Determination of ranitidine in pharmaceutical "Ranigast"

The elaborated methods were applied for the determination of ranitidine in its commercial product "Ranigast". In parallel, the same samples were assayed by HPLC method. The results are presented in Table 5. Additionally, the analysis of variances was done. Because the obtained values of F-test were smaller than theoretical ones, it proved that all elaborated methods give precise results. The obtained values of an error show that the elaborated spectrophotometric methods are suitable for the fast and simple quantification of ranitidine hydrochloride in its pharmaceuticals.

Kinetics study

The proposed methods were applied for investigations of oxidation process of ranitidine in the presence of hydrogen peroxide. For this purpose the following procedure was used: a portion of 3 mL of working solution at concentration 35 μg/mL was placed into a 10-mL calibrated test tube. Next, 11 μL of 12% solution of hydrogen peroxide were added and the mixture was filled with bidistilled water to the mark. The solution was thermostated in a water bath at 90°C. Spectra of the reaction mixture were recorded in every 10 min and used for quantification of a current contents of ranitidine by elaborated spectrophotometric method. The obtained data were applied for estimation of kinetics of the reaction studied. The same series of experiments was done using river water as a solvent. The linearity of relationship between log C (C = current concentration of RHCl in solution) and time showed the first order of reaction. The rate constants and half time of reaction were calculated using the elaborated methods. The obtained results are gathered in Table 6. The rate constants and half times of reaction determined by proposed spectrophotometric methods show good conformity between each other and with published one (11). Surprisingly, the observed rate of reaction in river water medium was slower and half time of ranitidine decomposition was longer. Presumably, this phenomenon was caused by the presence of compounds naturally occurred in river such as humic acids, organic matter and metal ions, especially Fe(II) ion, which suppressed the rate of decay. Probably, these compounds caused higher consumption of used portion of hydrogen peroxide, so the oxidative decomposition of RHCl was slower.

Conclusions

In this paper, three spectrophotometric methods were proposed for the fast examination of mixture which contained ranitidine hydrochloride and its oxidation product. The applicability of each method was checked and discussed. The practical

application was verified by the determination of ranitidine content in its pharmaceutical "Ranigast". The methods were used for estimation of kinetics of ranitidine oxidation. The statistical analysis proved that the elaborated spectrophotometric methods give reliable, precise and accurate results. They can be used for the quantification of both studied compounds as well as for investigation of kinetics of oxidative transformation of RHCl.

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