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SPECTROPHOTOMETRIC METHODS FOR QUANTITATIVE DETERMINATION OF SOTALOL IN TABLETS

Olena Maletska, Svitlana Vasyuk

The aim *of the work. To develop a method for spectrophotometric determination of sotalol with diazonium salts. Establish optimal conditions for the quantitative determination of sotalol in drugs. Validate the developed methodology.*

Materials and methods. *Reagents and solvents used in the study were: diazole red 2J (obtained from NVF "Sinbias"), tablets "Sotalol Sandoz" 40 mg (Salyutas Pharma GmbH, series JZ1188), "Sotalol Sandoz" 80 mg (Salyutas Pharma GmbH, series KA0464) and "Sotalol Sandoz" 160 mg (Salyutas Pharma GmbH, series JY3504), methanol (LAB-SCAN, Ireland, batch No. 5120/13), sodium carbonate (Sinbias) and purified water were also used.*
Analytical equipment: spectrophotometer "SPECORD-200" (Analytic Jena AG, Germany), scales laboratory electronic RADWAG XA 210.4Y, bath ultrasonic Sonorex Digitec DT100H, laboratory glassware of class A.
All studies were conducted in the experimental pharmaceutical research department of the scientific medical laboratory center (SMLC) of the Zaporizhzhia State Medical University.

Results and discussion. *The technique of spectrophotometric determination of the quantitative content of sotalol based on its reaction with red diazole in water-methanol medium has been developed. The stoichiometric ratios of the reactive components as 1:1 were obtained by the methods of continuous changes and the saturation method. Validation of the developed on such indicators as linearity, precision, correctness and robustness is carried out. Based on these data, the developed method is correct and could be used in the quality control departments of chemical and pharmaceutical companies.*

Conclusions*. A method of quantitative spectrophotometric determination of sotalol in the tablet dosage form "Sotalol Sandoz" 40 mg, "Sotalol Sandoz" 80 mg and "Sotalol Sandoz" 160 mg of industrial production was developed, validation characteristics were investigated: linearity, precision, correctness, range of application and robustness*

Keywords*: Sotalol, diazonium salts, spectrophotometry, validation, quantitative determination, β-blocker, pharmaceutical analysis, colour reagent, substance, dosage forms*

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1. Introduction

Sotalol, which is a non-selective blocker of β-adrenoceptors, has a pronounced antiarrhythmic effect, reduces heart rate, reduces the automaticity of the sinus node, increases the tone of the smooth muscles of the bronchi, blood vessels [1]. Due to the widespread use of sotalol hydrochloride, the question arises of the analysis of the drug at all stages of the life cycle and in biological fluids.

Sotalol hydrochloride in the substance is determined by acid-base titration using formic acid and acetic anhydride as solvents and perchloric acid as titrant. According to the British Pharmacopoeia, the end point of titration is determined potentiometrically [2].

The US Pharmacopoeia recommends determining sotalol hydrochloride in a substance by HPLC, quantitative determination of hydrochloride is carried out by titration with argetum nitrate, in tablets - by HPLC [3].

Instrumental methods of analysis are mainly used to determine sotalol hydrochloride [4]. Sotalol is most often determined in tablets and biological fluids by HPLC [5] and UHPLC [6, 7]. Spectrophotometric detection is more often used [8, 9]. Rapid HPLC determination of sotalol and its degradation products under the action of stress factors has been proposed [10]. Hossein Heli and co-authors determined sotalol amperometrically [11]. Conductometric titration with a solution of argentum nitrate sotalol hydrochloride in the substance and drugs is described [12]. Fawzia A. Ibrahim and co-authors proposed a sensitive method of spectrofluorimetric determination of sotalol in dosage forms and plasma by its own fluorescence [13]. Another spectrofluorimetric technique is based on quenching the fluorescence intensity of the palmate complex with cucurbituril with sotalol [14]. To determine sotalol in tablets, both direct spectrophotometry in the UV region is used [15] and after reaction with bromocresol purple [16]. Simultaneous determination of sotalol, oxyprenolol and labetol by the method of derivative spectrophotometry in model mixtures and biological fluids is

described [17]. Vislous O. O. and co-authors proposed an extraction-photometric method for the determination of β-blockers. Sotalol in phosphate buffer medium with a pH of 7.5 forms an ionic associate with methyl orange in a ratio of 1:1, which is extracted with chloroform. The resulting product has two absorption maxima at 268 and 425 nm [18].

However, despite the advantages of these methods, some of them are not sensitive, selective or require high-cost equipment.

Therefore, the aim of our work was to develop a highly sensitive, easy to perform, economical and validated spectrophotometric method for the quantitative determination of sotalol hydrochloride in dosage forms based on the reaction with diazole red 2J.

2. Research planning (methodology)

The research methodology is presented in Fig. 1.

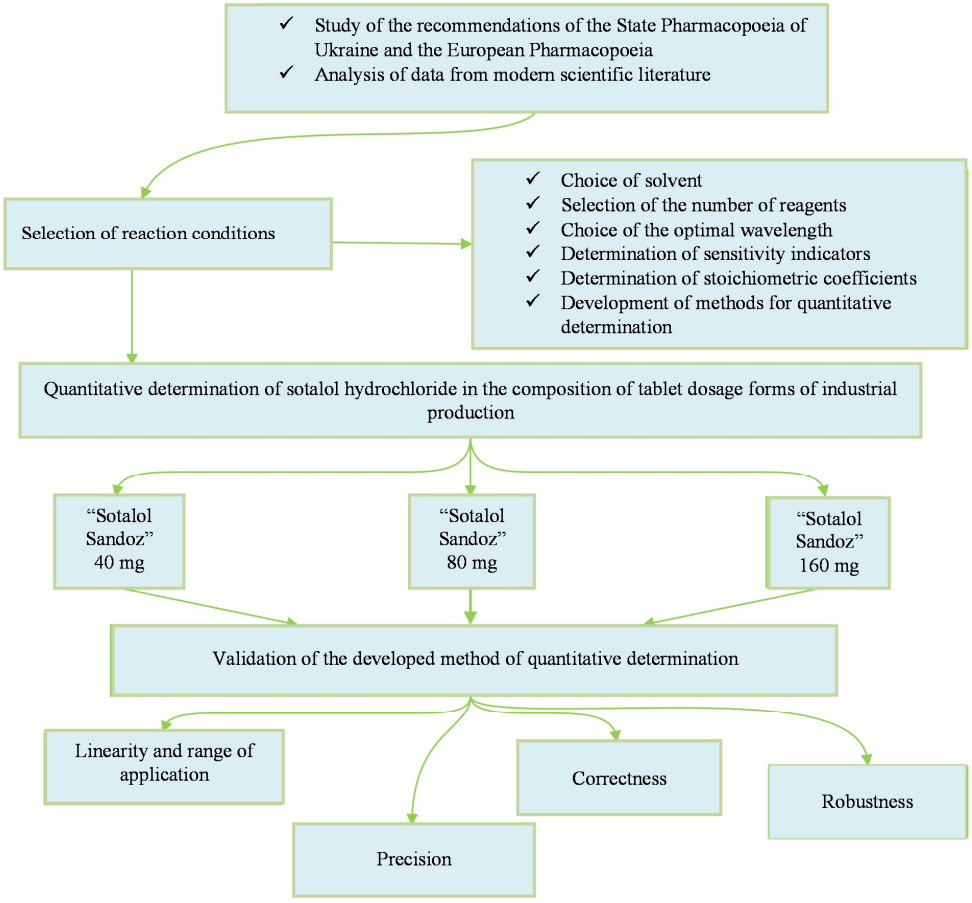

Fig. 1. Methodology of research of quantitative determination of sotalol hydrochloride in dosage forms of industrial production

3. Materials and methods

The study was conducted based on the Department of Experimental Pharmaceutical Research of the Scientific Medical Laboratory Center (SMLC) of Zaporizhzhia State Medical University during 2020–2021.

Sotalol Sandoz 40 mg tablets (Salutas Pharma GmbH, series JZ1188), Sotalol Sandoz 80 mg tablets (Salutas Pharma GmbH, series KA0464) and Sotalol Sandoz 160 mg tablets (Salutas Pharma GmbH, series JY3504) were used for the study.

As a colour reagent was used diazole red 2J (NVF "Sinbias").

All solvents used in the experiment were classified as "p.a." and "c.p.", namely: acetone, methanol, ethanol, isopropanol, water.

Modern equipment was used for the analysis. The optical density of the investigated solutions was measured on a spectrophotometer "SPECORD-200" (Analytic Jena AG, Germany). Samples for the experiment were taken on laboratory electronic scales RADWAG XA 210.4Y, for dissolution of substances used ultrasonic bath Sonorex Digitec DT100H. Class A measuring utensils were used to perform the dilutions.

Statistical processing and determination of validation characteristics were performed in accordance with the requirements of the SPhU. Graphs were built using the program "Sigma Plot 14.0", for spectrum processing used software package WinASPECT 2.2.1.0.

4. Research results

4. 1. General method for determining sotalol

Preparation of sotalol comparison solution: 0.03000 g of sotalol substance is dissolved in methanol and made up to 100.00 ml with a solvent in a volumetric flask and mixed.

Preparation of the compensating solution: to a volumetric flask of 10.00 ml transfer 1.00 ml of 0.2 % solution of diazole red 2J in methanol, add 0.20 ml of 0.1 % aqueous sodium carbonate solution, incubated for 15 min, add 2.00 ml of methanol, make up to the mark with purified water and mix.

An aliquot of sotalol (0.03 g) is placed in a 10.00 ml volumetric flask, 1.00 ml of 0.2 % colour reagent solution, 0.20 ml of 0.1 % aqueous sodium carbonate solution are added, incubated for 15 minutes, 2.00 ml of methanol, make up to the mark with purified water and mix. The absorption of the resulting solution is measured against the background of the compensating solution at a wavelength of 380 nm.

4. 2. Determination of sotalol in tablets

Transfer a precise portion of the thoroughly ground tablet mass (about 0.045 g) dissolved in methanol to a 100.00 ml volumetric flask. The same solvent is brought to the mark and kept in an ultrasonic bath for 2 minutes. The

resulting solution is filtered through a paper filter ("Blue Ribbon"), the first and last portions of the filtrate are discarded. From the filtrate take 1.00 ml of solution, transfer to a volumetric flask of 10.00 ml, add 1.00 ml of 0.2 % solution of diazole red 2J in methanol, 0.20 ml of 0.1 % aqueous sodium carbonate solution, keep 15 min, add 2.00 ml of methanol, make up to the mark with purified water and mix. The absorption of coloured solutions is measured against the background of the compensating solution at an analytical wavelength of 380 nm. In parallel, conduct an experiment with 1.00 ml of sotalol comparison solution. Calculate the content of the active substance according to the generally accepted formula.

During the development of the method, factors that may affect the rate and completeness of the reactions were studied: the number of reagents, the reaction time and the stability of the stained solutions over time.

The solvent was chosen considering the solubility of the test substance and colour reagent. The amount of reagent was chosen according to the maximum value of absorption.

During the experiment it was found that the reaction takes place in aqueous methanol medium at room temperature using 0.2 % solution of diazole red 2J as a colour reagent in the presence of 0.1 % aqueous sodium carbonate solution to form a coloured reaction product with maximum absorption at 380 nm (Fig. 2).

The amount of reagent required for the completeness of the reaction was determined experimentally by the maximum amount of absorption. For this purpose, 1.00 ml of the solution of the investigated drug substance and 0.50; 1.00; 1.50; 2.00 and 2.50 ml of reagent were transferred to 10.00 ml volumetric flasks;. The absorption of the investigated solutions was measured against the background of compensatory solutions at the selected wavelength.

To determine the stability of the coloured reaction product over time, the absorption of the resulting solution was measured under optimal conditions for 60 min with an interval of 5 min. It was found that the test solutions are stable for at least 60 minutes. As an example, we give a graph of the dependence of the absorption of the reaction products of sotalol with diazole red 2J on time (Fig. 3).

Stoichiometric coefficients between sotalol and diazole red 2J were determined by the method of continuous changes (by the method of isomolar series) and by the method of saturation (by the method of molar ratios).

The method of isomolar series is based on determining the ratios of isomolar concentrations of reactants, which corresponds to the maximum yield of compounds formed because of the reaction. To do this, prepare solutions of the reagent and test drug substance of the same molar concentration (0.001 M) and mixed them in the antibate ratio (1/9 to 9/1), while the total volume of the solution remains unchanged. The reaction was carried out according to the developed method. Based on the obtained data, a graph of the dependence of the amount of absorption on the ratio of the volumes of the components of the isomolar series was constructed (Fig. 4).

The method of molar ratios determines the dependence of the absorption on the concentration of one of the components of the reaction mixture at a constant concentration of the other component and vice versa. The inflection point on the saturation curve is equal to the stoichiometric coefficient of the component whose concentration varied (Fig. 5).

As could be seen from Fig. 4, 5, the obtained stoichiometric coefficients of the reacting components of the reaction of the interaction of sotalol with diazole red 2J unambiguously agree with each other and are 1: 1.

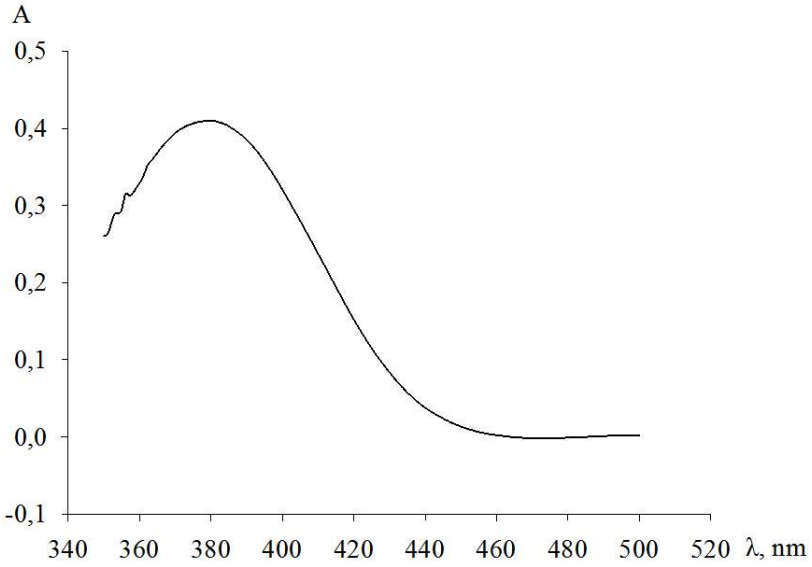

Fig. 2. The spectrum of absorption of the reaction product of sotalol with diazole red 2J

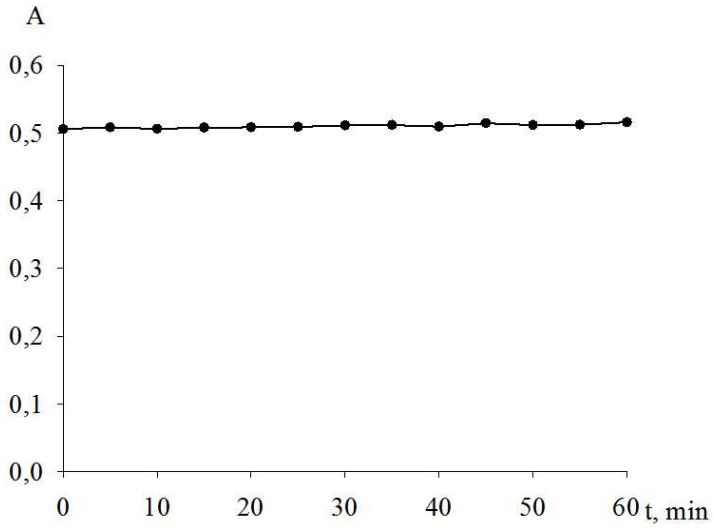

Fig. 3. Graph of the dependence of the absorption of the reaction product of sotalol with diazole red 2J in aqueous methanol solution depending on time

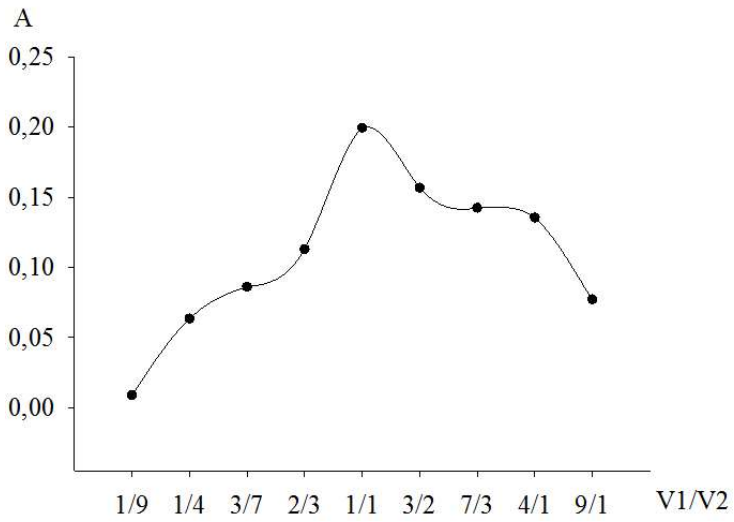

Fig. 4. Graph of the dependence of the amount of absorption on the composition of the isomolar solution: V1 – 0.001 M sotalol solution; V2 – 0.001 M solution diazole red 2J) at 380 nm

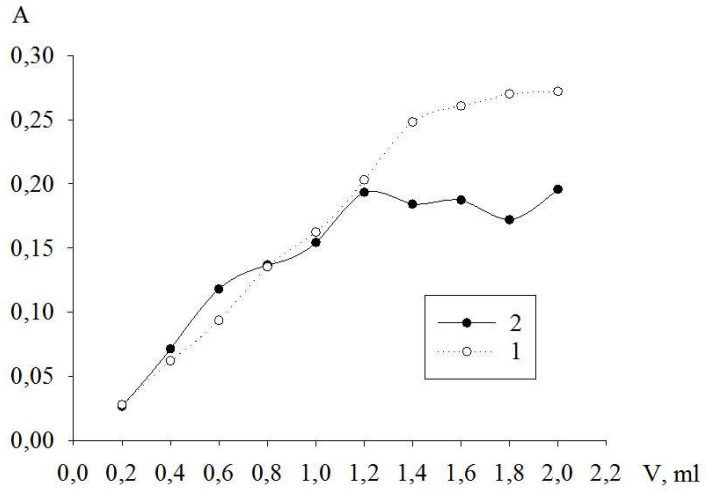

Fig. 5. Saturation curves: 1 – sotalol solution at a constant concentration of reagent (1.00 ml of 0.001 M solution), 2 – diazole red 2J at a constant concentration of sotalol (1.00 ml of 0.001 M solution)

4. 3. Determination of validation characteristics

According to the requirements of the European Pharmacopoeia, a sotalol tablet should contain from 95 to 105 % of the active ingredient.

The developed methodology may be acceptable for the determination of Quantitative Content, Homogeneity of Content and Dissolution, so the critical values for the parameters of linearity, precision and accuracy were determined in accordance with the requirements of the State Pharmacopoeia of Ukraine. The maximum uncertainty of the analysis is 5 % (V, %) [19, 20].

4. 4. Linearity and range of application

The linear dependence of the optical density on the concentration of the test substance is in the range of 1.8–4.0 ml/100 ml. Solutions with a known concentration were prepared by diluting a standard 0.030 % sotalol solution and measuring the absorbance at 380 nm. Based on the obtained results, a graph of the dependence of absorption on the concentration of sotalol in normalized coordinates was constructed (Fig. 6).

The linear dependence parameters were calculated using least squares regression analysis. The obtained values are given in Table 1.

Table 1

Numerical indicators of linear dependence

Indicator	Value	Criteria	Conclusion
$b\pm(s_b)$	0.9995±(0.0028)	–	–
$a\pm(s_a)$	0.1713±(0.2780)	$a\leq\Delta a=t(95\ \%;7)\cdot s_a=$ $=0.5267$	Corresponds
$s_{x,0}(\%)$	0.3383	$\leq\Delta_{As}(\%)/t(95\ \%;7)=$ $=0.5278$	Corresponds
r	0.9999	≥0.9995	Corresponds

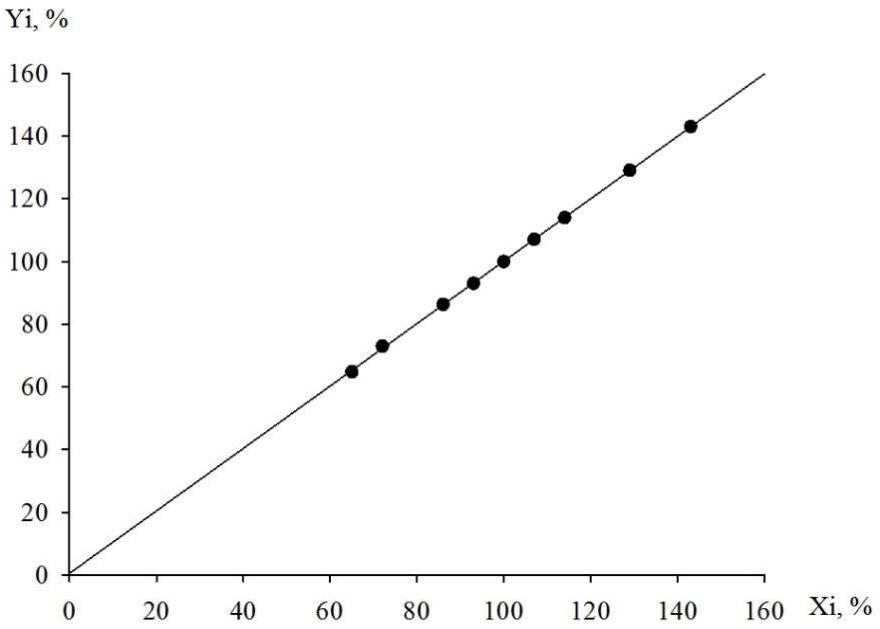

Fig. 6. Graph of the dependence of absorption on the concentration of sotalol

The calculated numerical indicators indicate that all SPhU requirements for linear dependence parameters are met. The range of application of the technique is 65–143 %.

4. 5. Precision

Precision was determined at the level of convergence. According to the SPhU, nine determinations were performed for each dosage form, covering a range of applications (three concentrations/three determinations for each). The absorbance of the reference solution was measured in parallel. The content of sotalol in the dosage forms was calculated according to the conventional formula. According to the obtained results, metrological characteristics were calculated (Table 2). In all cases, the one-sided confidence interval Δ_ % does not exceed the maximum allowable uncertainty of the analysis max Δ_*AS*, so the method is accurate at the level of convergence.

Table 2

Determination of the precision of the results of quantitative determination of sotalol in tablets

Dosage form	$\overline{Z}$ % (n=9)	$S_{z\%}$	maxΔ_{AS}	$\Delta_{\%}$	Conclusion
"Sotalol Sandoz" 40 mg	99.74	0.28	1.60	0.52	Corresponds
"Sotalol Sandoz" 80 mg	100.00	0.36	1.60	0.67	Corresponds
"Sotalol Sandoz" 160 mg	100.38	0.46	1.60	0.85	Corresponds

4. 6. Correctness

Correctness was established by the method of additives. To do this, different amounts of sotalol comparison solution were added to three equal samples of the dosage form and analyzed three times. As could be seen from the data in Table 3, the calculated criteria of practical insignificance for dosage forms do not exceed the maximum allowable uncertainty of the analysis.

Table 3

Determining the correctness of the results of quantitative determination of sotalol in tablets

Dosage form	$\overline{Z}$ % (n=9)	$S_{z\%}$	$\Delta_{\%}$	δ ($\overline{Z}$ – 100)	δ≤$\Delta_{\%}$/3	δ≤0.32·maxΔ_{AS}	Conclusion
"Sotalol Sandoz" 40 mg	99.75	0.50	0.93	0.25	0.31	0.51	Corresponds/Corresponds
"Sotalol Sandoz" 80 mg	99.68	0.72	1.34	0.32	0.45	0.51	Corresponds/Corresponds
"Sotalol Sandoz" 160 mg	100.23	0.26	0.48	0.23	0.16	0.51	Does not Corresponds/Corresponds

4. 7. Robustness

Evaluation of robustness, namely the stability of the analyzed solutions over time and the amount of added reagents, was performed at the stage of development of the method.

In the study of stability, the optical density of the investigated drug solutions and the comparison solution was measured every 15 min for one hour. In the Table 4 there are data for the comparison solution of sotalol (A_0), tablets "Sotalol Sandoz" 40 mg (A_1), "Sotalol Sandoz" 80 mg (A_2) and "Sotalol Sandoz" 160 mg (A_3).

The calculated relative standard deviation (*RSDt* %) and confidence interval (Δ*t* %) do not exceed the allowable systematic error (max δ):

$$\Delta_t(\%) = 2.13 \times RSD_t \le 0.32 \times \max \Delta_{As} = \max \delta,$$

that is, the analyzed solutions are stable during the studied time interval.

Table 4

Stability of the studied sotalol solutions over time

t, min	0	15	30	45	60	Average	RSD_t %	Δ_t %	max δ, %
A_0	0.5133	0.5144	0.5147	0.5149	0.5152	0.5145	0.136	0.29	0.32
A_1	0.5173	0.5152	0.5163	0.5153	0.5175	0.5163	0.194	0.41	0.51
A_2	0.5148	0.5131	0.5134	0.5152	0.5123	0.5137	0.233	0.49	
A_3	0.5118	0.5124	0.5115	0.5129	0.5132	0.5124	0.137	0.29	

5. Discussion of research results

The developed method is more selective in comparison with the method of determination of sotalol by direct spectrophotometry in the UV region [15], because in the UV region it absorbs a significant amount of API. Compared with the extraction-photometric method for the determination of β-blockers [18], the proposed method reduces the analysis time, as no extraction is required, and it could considered as more "green".

The proposed method of quantitative determination of sotalol hydrochloride is characterized by linearity, accuracy, and convergence of results, resistant to minor changes in the reaction conditions within ±10 %. The reliability of the method indicated that minor changes in the method and environment would not affect the effectiveness of the procedure. Approbation of the analytical method of quantitative determination, carried out on three commercial drugs, confirms the reproducibility of the method and the correctness of the results.

Study limitations. The proposed method cannot be used to determine sotalol in the presence of other β-adrenoceptor blockers.

Prospects for further research. The article describes the main stages of quantitative determination of sotalol hydrochloride in dosage forms of industrial production. The next stage of research is planned to isolate and study the reaction products.

6. Conclusions

A sensitive, economical spectrophotometric method for the quantitative determination of sotalol in the composition of tablet dosage forms "Sotalol Sandoz" 40, 80 and 160 mg based on the reaction with diazole red 2J, which was validated according to the standardized validation procedure by the standard method.

It is proved that according to such validation characteristics as linearity, precision, correctness, and robustness the developed technique is reproducible and meets the requirements of SPhU.

Conflict of interests

The authors declare that they have no conflicts of interest.

Financing

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References

1. Sotalol Sandoz. Available at: https://compendium.com.ua/info/173560/sotalol-sandoz-sup-sup-/

2. British Pharmacopeia (2013). London: Her Majesty's Stationery Office.

3. United States Pharmacopeia (2008). Rockville: USP Convention Inc., 3577.

4. Vislous, O. O., Bevz, N. Yu., Heorhiiants, V. A. (2015). The review of identification and assay methods of β-blockers. ScienceRise, 10 (4 (15)), 56–70. doi: http://doi.org/10.15587/2313-8416.2015.52357

5. Saleem, K., Ali, I., Kulsum, U., Aboul-Enein, H. Y. (2013). Recent Developments in HPLC Analysis of β-Blockers in Biological Samples. Journal of Chromatographic Science, 51 (8), 807–818. doi: http://doi.org/10.1093/chromsci/bmt030

6. Baranowska, I., Magiera, S., Baranowski, J. (2011). UHPLC Method for the Simultaneous Determination of -Blockers, Isoflavones, and Flavonoids in Human Urine. Journal of Chromatographic Science, 49 (10), 764–773. doi: http://doi.org/10.1093/chrsci/49.10.764

7. Azzi, M., Ravier, S., Elkak, A., Coulomb, B., Boudenne, J.-L. (2021). Fast UHPLC-MS/MS for the Simultaneous Determination of Azithromycin, Erythromycin, Fluoxetine and Sotalol in Surface Water Samples. Applied Sciences, 11 (18), 8316. doi: http://doi.org/10.3390/app11188316

8. Matysova, L., Zahalkova, O., Klovrzova, S., Sklubalova, Z., Solich, P., Zahalka, L. (2015). Development of a Gradient HPLC Method for the Simultaneous Determination of Sotalol and Sorbate in Oral Liquid Preparations Using Solid Core Stationary Phase. Journal of Analytical Methods in Chemistry, 2015, 1–6. doi: http://doi.org/10.1155/2015/806736

9. Ali, I., Kulsum, U., Saleem, K., Nagae, N., Gaitonde, V. (2015). Novel SPE-HPLC Method for Analyses of β-Blockers in Human Plasma Using New Generation Phenyl-Ethyl Column. American Journal of Advanced Drug Delivery, 3, 32–51.

10. Abdelmonem, A. A., Ragab, G. H., Hashem, H. A., Bahgat, E. A. (2016). A fast stability-indicating HPLC method for determination of sotalol hydrochloride in bulk powder and in dosage form. Main Group Chemistry, 15 (3), 209–219. doi: http://doi.org/10.3233/mgc-150200

11. Heli, H., Zare, S. N., Sattarahmady, N., Karimian, K. (2013). Electrooxidation Behavior and Amperometric Determination of Sotalol on a Graphene Oxide Nanosheets-modified Glassy Carbon Electrode. Current Pharmaceutical Analysis, 9 (3), 291–298. doi: http://doi.org/10.2174/1573412911309030007

12. Ayad, M. M., Abdellatef, H. E., Hosny, M. M., Sharaf, Y. A. (2012). Conductometric titration method for determination of naftidrofuryl oxalate, propafenone HCl and sotalol HCl using silver nitrate. European Journal of Chemistry, 3 (3), 332–336. doi: http://doi.org/10.5155/eurjchem.3.3.332-336.637

13. Ibrahim, F. A., El-Brashy, A. M., El-Awady, M. I., Abdallah, N. A. (2019). Development of a validated spectrofluorimetric method for assay of sotalol hydrochloride in tablets and human plasma: application for stability-indicating studies. Open Chemistry, 17 (1), 64–74. doi: http://doi.org/10.1515/chem-2019-0008

14. Zhang, H.-M., Yang, J.-Y., Du, L.-M., Li, C.-F., Wu, H. (2011). Determination of sotalol by fluorescence quenching method. Analytical Methods, 3 (5), 1156–1162. doi: http://doi.org/10.1039/c0ay00728e

15. Vislous, O., Bevz, N., Palchik, S., Zhivora, N. (2015). UV-spectrophotometric assay sotalol hydrochloride in bulk and tablet formulation. Aktualni pytannia stvorennia novykh likarskykh zasobiv. Kharkiv: NFaU, 172.

16. Zhuk, Iu., Vasiuk, S. (2016). Spektrofotometrichne viznachennia sotalolu v tabletkakh. Farmatcevtichnii zhurnal, 1, 49–55.

17. Stolarczyk, M., Apola, A., Maålanka, A., Kwiecie, A. (2017). Determination of sotalol, oxprenolol and labetalol in binary mixtures and in spiked human serum by derivative spectrophotometric method. Acta Poloniae Pharmaceutica Ñ Drug Research, 74 (1), 93–102.

18. Vislous, O., Bevz, N., Georgiyants, V., Kryvanych, O. (2016). Development of the extraction-photometric method for quantitative determination of beta-blockers. BeProgress2 in international conference of pharmacy students. Lublin, 2.

19. Derzhavna Farmakopeia Ukraïni (2015). Kharkiv: Derzhavne pidpriємstvo «Naukovo-ekspertnii farmakopeinii tcentr», 1128.

20. Hryzodub, A. (2016). Standartyzovani protsedury validatsii metodyky kontroliu yakosti likarskykh zasobiv. Kharkiv: Derzhavne pidpryiemstvo «Ukrainskyi naukovyi farmakopeinyi tsentr yakosti likarskykh zasobiv», 43–68.

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