UDC 615.074:543.422.3:615.225.2:615.453.6]-092.4
DOI: 10.15587/2519-4852.2023.277461

DEVELOPMENT OF THE SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF ROSUVASTATIN IN TABLETS BY USING BROMOPHENOL BLUE

Liudmyla Halka, Tetyana Kucher, Liubomyr Kryskiw, Marjan Piponski, Iryna Furdela, Tetyana Uglyar, Olha Poliak, Liliya Logoyda

The aim *of the work was to develop a spectrophotometric method for the determination of rosuvastatin in tablets based on the reaction with BPB in compliance with the principles of «green» chemistry.*

Material and methods. *Analytical equipment: two-beam UV-visible spectrophotometer Shimadzu model – UV 1800 (Japan), software UV-Probe 2.62, electronic laboratory balance RAD WAG AS 200/C. The following APIs, dosage forms, reagents and solvents were used in work: pharmacopoeial standard sample (CRS) of rosuvastatin calcium (Sigma-Aldrich, (≥ 98 %, HPLC)), BPB (Sigma-Aldrich, (≥98 %, HPLC)), "Rosuvastatin" tablets 10 mg, 15 mg, 20 mg, methanol (Honeywell, (≥99.9 %, GC)), ethanol (Honeywell, (≥99.9 %, GC)), chloroform (Honeywell, (≥99.9 %, GC)), acetonitrile (Honeywell, (≥99.9 %, GC)), and ethyl acetate (Honeywell, (≥99.7 %, GC)).*

Results and discussion. *A spectrophotometric method for determining rosuvastatin by reaction with BPB in an acetonitrile solution using the absorption maximum at a wavelength of 595 nm has been developed. Stoichiometric ratios of reactive components were established, which were 1:1. The developed method for the quantitative determination of rosuvastatin was validated following the requirements of the SPhU. The analytical method was linear in the 7.99–23.97 μmol/L concentration range. The LOD and LOQ values were calculated to be 0.77 μmol/L and 2.36 μmol/L. According to the «greenness» pictogram of the analytical method using the AGREE method, the score was 0.77, indicating that the proposed spectrophotometric method for determining rosuvastatin was developed in compliance with the principles of «green» chemistry.*

Conclusions. *An eco-friendly spectrophotometric method has been developed to quantitatively determine rosuvastatin in tablets based on the reaction with BPB. The appropriate sulfophthalein dye (BPB) and its concentration (4.00×10^{-4}), the optimal eco-friendly solvent (acetonitrile), and the appropriate wavelength (595 nm) were chosen, and the sensitivity of the reaction was calculated. The analytical method was validated, and its possibility for use in the pharmaceutical analysis was shown*

Keywords: *bromophenol blue, rosuvastatin, spectrophotometry, validation, quantitative determination, tablets*

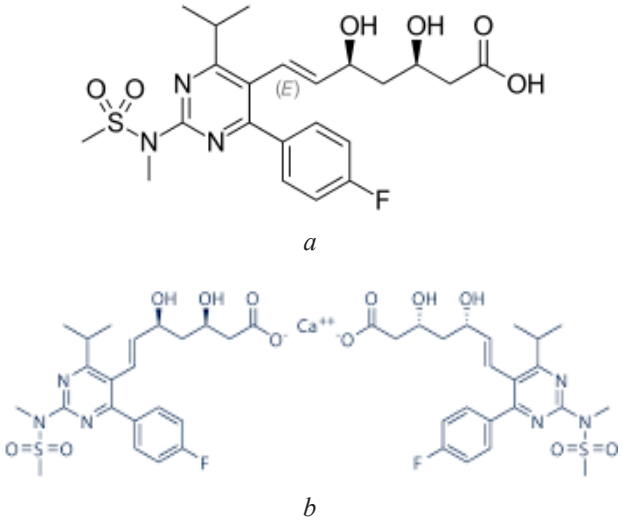
How to cite:
Halka, L., Kucher, T., Kryskiw, L., Piponski, M., Furdela, I., Uglyar, T., Poliak, O., Logoyda, L. (2023). Development of the spectrophotometric method for the determination of rosuvastatin in tablets by using bromophenol blue. ScienceRise: Pharmaceutical Science, 2 (42), 11–19. doi: http://doi.org/10.15587/2519-4852.2023.277461

1. Introduction

Statins are used in medical practice for the prevention and treatment of hypercholesterolemia. Rosuvastatin is one of the most powerful statins available in the pharmaceutical market. Rosuvastatin was first introduced to the pharmaceutical market about 10 years ago. During that time, its effectiveness and safety have been carefully evaluated in a wide variety of patient cohorts in many clinical studies [1]. Rosuvastatin (Fig. 1), bis[(3R,5S,6E)-7-[4-(4-fluorophenyl)-2-(N-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5yl]-3,5-dihydroxyhept-6-enoate], – sparingly soluble in water (17.96 mg/mL), Log *P*=0.13 [2].

Differently from other statins, adding a stable polar methane sulfonamide group in the structure of rosuvastatin confers relatively low lipophilicity [3, 4]. The European Pharmacopoeia (Ph. Eur.) has a monograph on rosuvastatin calcium and tablets [5]. Ph. Eur. regulates the quantitative determination of rosuvastatin in tablets by HPLC. Brazilian scientists conducted a thorough review of literature sources on the development of analytical methods for the analysis of rosuvastatin in dosage forms and biological fluids [6]. Many spectrophotometric [7–23] and chromatographic methods [24–41] are described in the scientific literature. Nowadays, chromatographic techniques are undoubtedly the most modern in terms of specificity, correctness and precision. However, there are laboratories that do not have expensive equipment, and for them, spectrophotometric methods of analysis are more accessible. Spectrophotometric methods are often used as alternatives in implementing quality control of medicines. The scientific literature describes a number of spectrophotometric methods for determining rosuvastatin in dosage forms by its own absorption [24–42]. Considering the advantages of using

sulfophthalein dyes in pharmaceutical analysis, the spectrophotometric method for determining rosuvastatin by reaction with bromocresol green, developed by Syrian scientists, deserves attention [13]. However, the proposed technique involves the use of chloroform as a solvent, which does not confirm the principles of «green» chemistry. Taking into account the facts described above, we became interested in developing spectrophotometric methods for determining rosuvastatin by reaction with sulfophthalein dyes in compliance with the principles of «green» chemistry. The chemistry of sulfophthalein dyes and the development of spectrophotometric methods for determining APIs in dosage forms based on interaction with sulfophthalein dyes is interesting and not easy, as it requires the use of certain approaches to the research methodology. At the preliminary research stage, we tested many sulfophthalein dyes and the results obtained when using bromophenol blue (BPB) were interesting. Therefore, **the aim of our work** was to develop a spectrophotometric method for the determination of rosuvastatin in tablets based on the reaction with BPB in compliance with the principles of «green» chemistry.



a

b

Fig. 1. Chemical structure: *a* – rosuvastatin; *b* – rosuvastatin calcium

2. Planning of the research

Methodology of research of development and validation of the spectrophotometric methods for the determination of rosavastatin in tablets in compliance with the principles of «green» chemistry includes:

1. Analysis of the monograph of Ph. Eur. 11 edition and scientific articles.

2. Study of reaction conditions between rosuvastatin calcium and BPB (choice of sulfophthalein dye, solvent, optimal volume and concentration of reagent, optimal wavelength, stability, detection of stoichiometric coefficients).

3. Validation of the spectrophotometric method for determination of rosuvastatin in tablets.

4. Evaluation of the greenness profile assessment of the proposed method.

3. Materials and methods

All research was conducted in the Department of Pharmaceutical Chemistry, I. Horbachevsky Ternopil National Medical University, Maidan Voli 1, 46001 Ternopil, Ukraine (2022 year).

Objects of study, solvents and equipment.

Analytical equipment: two-beam UV-visible spectrophotometer Shimadzu model -UV 1800 (Japan), software UV-Probe 2.62, electronic laboratory balance RAD WAG AS 200/C (Poland).

The following APIs, dosage forms, reagents and solvents were used in work: pharmacopoeial standard sample (CRS) of rosuvastatin calcium (Sigma-Aldrich, (≥98 %, HPLC)), BPB (Sigma-Aldrich, (≥98 %, HPLC)), "Rosuvastatin" tablets 10 mg, 15 mg, 20 mg, methanol (Honeywell, (≥99.9 %, GC)), ethanol (Honeywell, (≥99.9 %, GC)), chloroform (Honeywell, (≥99.9 %, GC)), acetonitrile (Honeywell, (≥99.9 %, GC)), and ethyl acetate (Honeywell, (≥99.7 %, GC)).

Proposed procedure for the determination of rosuvastatin calcium with BPB.

20.00 mg of CRS rosuvastatin calcium was transferred into a 50.00 mL volumetric flask with 35 mL acetonitrile. The mixture was shaken and diluted to volume with acetonitrile. Aliquot 0.50 mL was added to 0.5 mL of 4.0×10^{-4} M BPB in acetonitrile. The volume of 10.00 mL was made up to the mark by adding acetonitrile. The absorbance of the resulting solution was measured against the background of the compensating solution (a solution containing all components except the analyte) at a wavelength of 595 nm.

Procedure for tablets for the determination of rosuvastatin calcium with BPB.

Twenty tablets were accurately weighed and powdered. A quantity of powder containing 20.00 mg of rosuvastatin calcium was transferred into a 50.00 mL volumetric flask with 35 mL acetonitrile. The mixture was shaken for 15 minutes, diluted to volume with acetonitrile, and then filtered. Aliquot 0.50 mL was added to 0.5 mL of 4.0×10^{-4} M BPB in acetonitrile. The volume of 10.00 mL was made up to the mark by adding acetonitrile. The absorbance of the resulting solution was measured against the background of the compensating solution (a solution containing all components except the analyte) at a wavelength of 595 nm.

4. Research results

4. 1. Selection of reaction conditions

As mentioned above, the scientific literature describes the development of one spectrophotometric method for determining rosuvastatin in tablets by reaction with bromocresol green through ion-pair complex formation at the wavelength of the absorbance maximum at 416 nm in a chloroform medium [13]. However, using chloroform as a solvent makes it impossible to use the proposed analytical method as eco-friendly. Taking into account the described fact, we set ourselves the task of developing an environmentally safe spectrophotometric method for the determination of rosuvastatin

in tablets by reaction with sulfophthalein dyes. We tested such sulfophthalein dyes as BPB, bromocresol green, bromocresol purple, and others. Each of the above sulfophthalein dyes gave positive results in the experiment. For further work, we chose BPB as a promising reagent for developing a spectrophotometric method for determining rosuvastatin in tablets. In the acetonitrile solution, the band of the monoanionic form of BPB predominates. In the presence of rosuvastatin, the acid-base balance of the dye shifts towards the doubly deionized form since rosuvastatin forms a more stable ionic associates with this form of the dye (Fig. 2). rosuvastatin forms complexes with BPB with an absorbance maximum at a wavelength of 595 nm (Fig. 2). In the process of experimental studies, it was established that the optimal concentration of BPB is 4.00×10^{-4} M.

We selected optimal conditions for the reaction in order to form a coloured product of the reaction with maximum stability and sensitivity. The maximum absorbance was observed in the acetonitrile solution with BPB, which we chose for further research (Fig. 3).

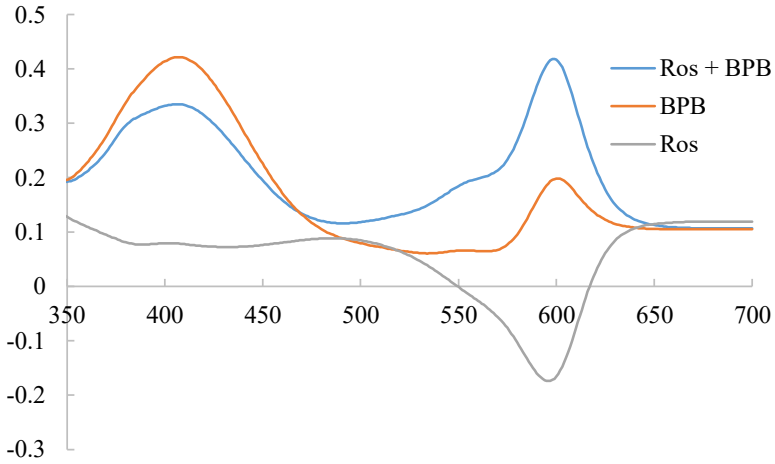


Fig. 2. The spectra of absorbance of the reaction product of rosuvastatin calcium with BPB in acetonitrile medium

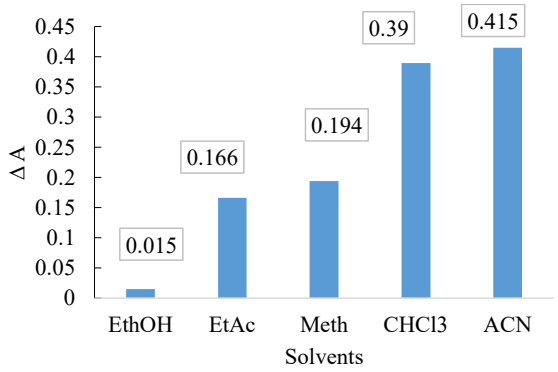


Fig. 3. Effect of solvents on the formation of rosuvastatin calcium-BPB complex

An important aspect in the development of the spectrophotometric method is the study of stability since the research data will also affect the robustness of the analytical method. We have studied the stability of solutions over time. It was established that the obtained solutions were stable for 45 minutes (Fig. 4).

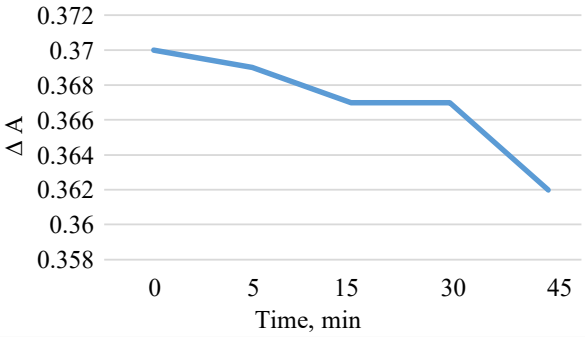


Fig. 4. Graph of the dependence of the absorbance of the reaction product of rosuvastatin calcium with BPB in acetonitrile solution depending on time

The stoichiometric coefficients of the reacting components between rosuvastatin calcium and BPB were determined by continuous changes (Job's method) and the saturation method (the method of molar ratios). Fig. 5 illustrates the study of the stoichiometric coefficients of the reacting components by the method of continuous changes. At the same time, Fig. 6 shows the study results of the stoichiometric coefficients of the reacting components by the method of molar ratios. As seen from Fig. 5, 6, the stoichiometric coefficients of the reacting components between rosuvastatin calcium and BPB correspond 1: 1.

As shown in Fig. 7, the optimal volume of 4.0×10^{-4} M solution BPB is 0.5 mL.

The sensitivity of the reaction between rosuvastatin calcium and BPB was calculated. The molar absorption (ε) was 1.37×10^{4}, the specific absorption (a) was 0.14, and the Sendel coefficient (Ws) was 0.073. The sensitivity parameters indicate a high sensitivity of the reaction between rosuvastatin calcium and BPB.

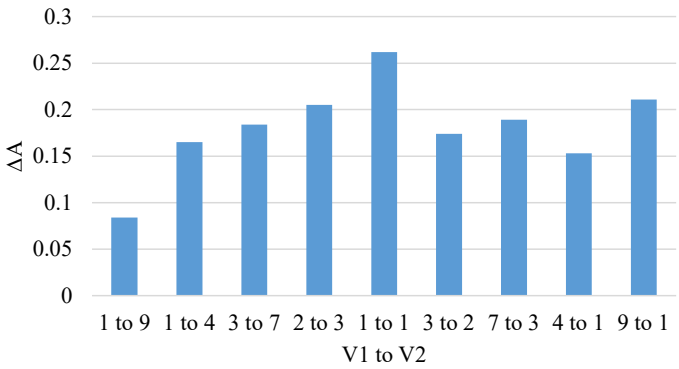


Fig. 5. Graph of the dependence of the amount of absorbance on the composition of the isomolar solution: V1 – 4.0×10^{-4} M rosuvastatin calcium solution; V2 – 4.0×10^{-4} M solution BPB at 595 nm

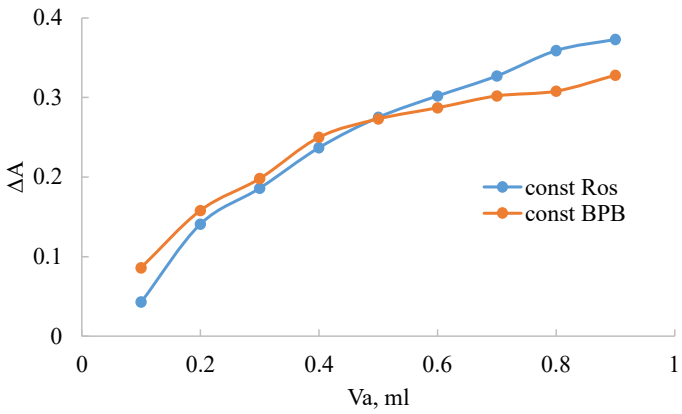


Fig. 6. Saturation curves: rosuvastatin calcium solution at a constant concentration of reagent (0.50 mL of 4.0×10^{-4} M solution), BPB solution at a constant concentration of rosuvastatin calcium (0.50 mL of 4.0×10^{-4} M solution)

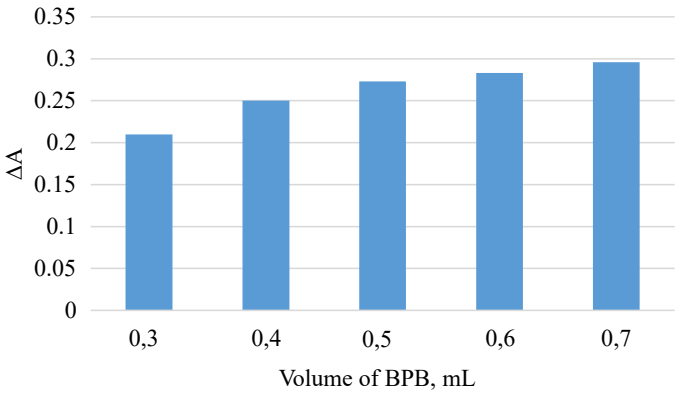


Fig. 7. Graph of the dependence of the absorbance of the reaction product of rosuvastatin calcium with BPB in acetonitrile solution depending on the amount of reagent

4. 2. Determination of validation characteristics

The proposed spectrophotometric method for the determination of rosuvastatin calcium in tablets by reaction with BPB has been validated in accordance with the requirements of SPhU for the following indicators: specificity, linearity, range of application, accuracy, precision and robustness.

4. 2. 1. Specificity

The results of studying the specificity of the spectrophotometric method are presented in Table 1. The absorbance of auxiliary substances is insignificant (the found value of δ noise is 0.37 %) and does not exceed the acceptance criterion (Table 1).

Table 1

The results of the study of the specificity

The absorbance of placebo (A placebo)	The absorbance of the compensating solution (A_{st})	Value δ noise, %	Criteria
0.001	0.273	0.37	≥ 0.5 %

4. 2. 2. Linearity

The study of the linearity of the analytical method was carried out on model solutions by the method of least squares in accordance with the requirements of the SPhU. The results of the linearity study are given in Table 2 and Fig. 8.

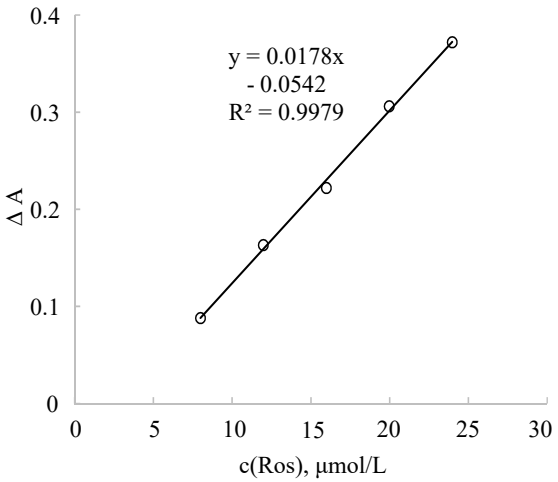


Fig. 8. Graph of dependence of absorbance on the concentration of rosuvastatin calcium, obtained under the conditions of the linearity study

Table 2

The results of the linearity study

Indicator	Value	Criteria	Conclusion
$b\pm(S_b)$	0.0178±(0.0091)	–	–
$a\pm(S_a)$	–0.0542±(0.0042)	>2.6	Corresponds
R^2	0.9979	>0.9961	Corresponds
LOD (μmol/L)	0.77	–	–
LOQ (μmol/L)	2.36	–	–
Beer's law limits (μmol/L)	7.99–23.97	–	–

Analyzing Fig. 8 and Table 2, it can be concluded that a linear dependence is observed in the range of concentrations 7.99–23.97 μmol/L. The LOD and LOQ values were calculated to be 0.77 μmol/L and 2.36 μmol/L.

4. 2. 3. Accuracy and precision

The accuracy and precision study of the spectrophotometric method for the determination of rosuvastatin in tablets by reaction with BPB was carried out on model solutions. The results of the accuracy and precision study are given in Table 3.

The systematic error of the method (0.16 %) was statistically and practically insignificant, i.e. spectrophotometric method was characterized by sufficient accuracy in the whole range of analyzed concentrations.

The study of intra-laboratory precision was carried out on six samples of the same series of tablets, by different analysts, on different days, using flasks of different volumes, by estimating the value of the relative confidence interval, which should be less than the maximum permissible uncertainty of the analysis results: $\Delta z \leq 1.6$ (at B=5 %) (Table 4).

The intra-laboratory precision of the analysis results is confirmed by the fact that the value of the relative confidence interval for six parallel determinations of one series of drugs meets the acceptance criterion (≤1.6 %) (Table 4).

Table 3

The results of the accuracy and precision study

Model solution	Content, %		The ratio of found to add, $Z_i=(Y_i/X_i)\cdot 100$ %
	Added, $X_i=(C_i/C_{ri})$ 100 %	Found, $Y_i=(A_i/A_{ri})$ 100 %	
M_1	70.11	70.02	99.87
M_2	80.09	80.05	99.95
M_3	90.32	90.11	99.77
M_4	94.91	95.63	100.76
M_5	99.99	100.18	100.19
M_6	104.95	104.82	99.88
M_7	110.52	110.89	100.33
M_8	120.16	120.72	100.47
M_9	130.42	130.29	99.90
The average value, Z, %			100.16
Standard deviation, S_z, %			0.39
Relative confidence interval $\Delta z=t(95\ \%, 8)\cdot S_z=2.3060\ S_z$, %			0.90
The critical value for the convergence of results $\Delta z \leq \max\Delta_{As}=1.6$ %			Corresponds (0.90<1.6)
Systematic error $\delta=-\lvert Z100\rvert$, %			0.16
The criterion of uncertainty of systematic error $\delta \leq \max\ \delta$ %			Corresponds(0.16<0.51)
General conclusion			Correct

Table 4

Results of intra-laboratory precision study

No. solution	Value Z_i, %		
	1 experiment	2 experiment	3 experiment
1	100.05	99.87	99.91
2	100.01	100.06	100.23
3	99.95	100.01	99.98
4	99.98	100.12	99.90
5	100.12	100.02	100.03
6	99.92	99.95	100.11
Average Z (%)	100.01	100.01	100.03
RSD_X, %	0.07	0.09	0.13
Relative standard deviation, RSDZ (%)	0.10		
Relative confidence interval, $\Delta\overline{Z}$	0.07≤1.6		
The critical value of the convergence of results, ΔAs, %	1.6		

4. 2. 4. Robustness

The study of robustness was carried out during the development of the analytical method. The stability of solutions over time and the amount of added reagent (BPB) was established.

A study of the robustness of the analytical method showed that the analyzed solutions were stable for 45 min (Fig. 4), and fluctuations in the amount of added BPB within ±10 % did not significantly affect the absorbance (Table 5).

Table 5

Effect of the amount of added reagent on absorbance

Amount of BPB, mL	% BPB	A
0.45	90	0.261
0.50	100	0.273
0.55	110	0.278

4. 3. Application to tablet analysis

After performing the validation procedure of the analytical method, which was carried out on model solutions, we applied the analytical method for the determination of rosuvastatin calcium in tablets. The results of the quantitative determination of rosuvastatin calcium in tablets are presented in Table 6.

Table 6

The results of quantitative determination of rosuvastatin calcium in tablets

Drug	Found, g	Metrological characteristics
Tablets Rosuvastatin 20 mg	0.0204	$\overline{m}=0.0208$ g
	0.0209	$S=1.58\times10^{-4}$
	0.0205	$t=2.57$
	0.0211	$\Delta x=4.06\times10^{-4}$
	0.0206	RDS=1.86
	0.0214	ε=1.95 %
Tablets Rosuvastatin 15 mg	0.0151	$\overline{m}=0.0151$ g
	0.0150	$S=2.24\times10^{-5}$
	0.0151	$t=2.57$
	0.0150	$\Delta x=5.75\times10^{-5}$
	0.0150	RDS=0.36
	0.0151	ε=0.38 %
Tablets Rosuvastatin 10 mg	0.0101	$\overline{m}=0.0101$ g
	0.0100	$S=4.28\times10^{-5}$
	0.0102	$t=2.57$
	0.0101	$\Delta x=1.10\times10^{-4}$
	0.0099	RDS=1.04
	0.0100	ε=1.10 %

4. 4. Assessment of the impact of the analytical method on the environment

As mentioned above, one of the main tasks was to develop an environmentally safe spectrophotometric method for the determination of rosuvastatin in tablets by reaction with BPB. Assessment of the «greenness» of the spectrophotometric method was performed using AGREE tool (Analytical GREEnness), GAPI (Green Analytical Procedure Index) and analytical eco-scale. A pictogram of the analytical method using AGREE tool is illustrated in Fig. 9. Pictogram of the analytical method using the GAPI tool is illustrated in Fig. 10. The score of the analytical method using AGREE tool was 0.77 (Fig. 9). The score of the analytical eco-scale was 90 (Table 7).

Table 7

Analytical eco-scale for assessing the «greenness» of the proposed analytical method

Parameters	Penalty points
Reagents	–
BPB	1
Acetonitrile	3
Energy	1
Waste	5
Total number of penalty points	10
Ball of analytical eco-scale	90
Conclusion	Excellent «green» analysis

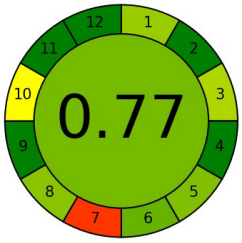


Fig. 9. Pictogram of an analytical method using AGREE tool

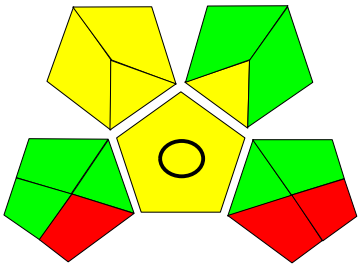


Fig. 10. Pictogram of an analytical method using GAPI tool

As can be seen from Table 7 and Fig. 9, 10, the spectrophotometric method for the determination of rosuvastatin in tablets based on the reaction with BPB was eco-friendly.

5. Discussion of research results

The scientific literature describes the development of one spectrophotometric method for the determination of rosuvastatin in tablets by reaction with bromocresol green [13]. Scientists have proposed a scheme for the interaction of rosuvastatin with bromocresol green with the ion-pair complex formation, and the optimal conditions for the reaction have been investigated. Comparative optimum conditions for spectrophotometric determination are presented in Table 8.

Table 8

Comparative optimum conditions for spectrophotometric methods for the determination of rosuvastatin in tablets

Parameters	[23]	Developed method
Reagent	bromocresol green	bromophenol blue
Solvent	chloroform	acetonitrile
Wavelength, nm	416	595
The molar absorptivity of complex (ε)	1.92×10^4	1.37×10^4
Working concentration of reagent, mol/L	1×10^{-4}	4×10^{-4}

As we can see from Table 8, our proposed method does not require the use of a toxic solvent and, accordingly, is developed in accordance with the principles of «green chemistry», which is an advantage of the method. The molar absorptivity is high (1.37×10^4), which indicates the sensitivity of the reaction. The stoichiometric ratios of the reactive components as 1:1 were obtained by the methods of continuous changes and the saturation method. The developed analytical method was validated in accordance with the requirements of the SPhU. The linearity regression equation was $y=0.0178x-0.0542$, and the obtained correlation coefficient was $R^2=0.9979$ (Table 2, Fig. 8). The linear relationship was found between absorbance at λmax and concentration of rosuvastatin in the range 7.99–23.97 μmol/L. The LOD and LOQ values were calculated to be 0.77 μmol/L and 2.36 μmol/L. The results of studying the accuracy and precision of the analytical method showed compliance with the acceptance criteria (Tables 3, 4). The results of studying the robustness of the analytical method indicate that the change in the amount of added reagent (BPB) does not affect the results of the analysis (Table 5), and the solutions are stable for 45 minutes (Fig. 4). We conducted the study of the «greenness» of the developed analytical method. Taking into account the obtained score of the eco-scale (Table 7) and the AGREE and GAPI tools (Fig. 9, 10), the results show that the spectrophotometric method of the determination of rosuvastatin in tablets by reaction with BPB is «green» and eco-friendly.

Study limitations. The developed spectrophotometric method can not be used to determine rosuvastatin in the presence of other statins.

Prospects for further research. This article describes the main stages of the spectrophotometric method development of rosuvastatin in tablets based on the reaction with BPB. The next stage of research is planned to develop and validate the spectrophotometric method for the determination of rosuvastatin in tablets based on the reaction with other sulfophthalein dyes.

6. Conclusion

An eco-friendly spectrophotometric method has been developed for the quantitative determination of rosuvastatin in tablets based on the reaction with BPB. The ap-

propriate sulfophthalein dye (BPB) and its concentration (4.00×10^{-4}), the optimal volume of reagent (0.5 mL), the optimal eco-friendly solvent (acetonitrile), the appropriate wavelength (595 nm) were chosen, and the sensitivity of the reaction were calculated. 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 analytical method was carried out and its possibility for use in the pharmaceutical analysis was shown.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

Funding

The study was performed without financial support.

Data availability

Data will be provided upon reasonable request.

Acknowledgement

The authors would like to thank all the brave defenders of Ukraine who made the finalization of this article possible.

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Received date 28.12.2023
Accepted date 18.04.2023
Published date 30.04.2023

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