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DEVELOPMENT OF THE SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF METOPROLOL TARTRATE IN TABLETS BY USING BROMOCRESOL GREEN

Mariana Horyn, Tetyana Kucher, Liubomyr Kryskiw, Olha Poliak, Nadiya Zarivna, Kateryna Peleshok, Liliya Logoyda

The aim of the work *was to develop and validate a spectrophotometric method for determining metoprolol tartrate in tablets based on the reaction with bromocresol green (BCG).*
Material and methods*. Analytical equipment: two-beam UV-visible spectrophotometer Shimadzu model UV 1800 (Japan), software UV-Probe 2.62, laboratory electronic balance RAD WAG AS 200/C, pH-meter И-160МИ. The following APIs, dosage forms, reagents and solvents were used in the work: pharmacopoeial standard sample (CRS) of metoprolol tartrate (Sigma-Aldrich, (≥98 %, HPLC)), BCG (Sigma-Aldrich, (≥98 %, HPLC)), "Metoprolol" tablets 50 mg (Kyivmedpreparat, series 0035415), "Metoprolol" 100 mg (Farmak, series 30421), 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 was developed for determining metoprolol tartrate by reaction with BCG in a methanol solution using the absorption maximum at a wavelength of 624 nm. Stoichiometric ratios of reactive components were established, which were 1:1. The developed method for the quantitative determination of metoprolol tartrate was validated following the requirements of the SPhU. The analytical method was linear in the concentration range of 5.47–38.30 μg/mL. The limit of detection and quantification were 0.41 μg/mL and 1.24 μg/mL, respectively. According to the «greenness» pictogram of the analytical method using the AGREE method, the score was 0.79, which indicates that the proposed spectrophotometric method for the determination of metoprolol was developed in compliance with the principles of «green» chemistry.*
Conclusions. *A spectrophotometric method for determining metoprolol tartrate in tablets based on the reaction with BCG in compliance with the principles of «green» chemistry has been developed and validated. Furthermore, the developed method for the quantitative determination of metoprolol tartrate was validated following the requirements of the SPhU. In summary, the developed method has a low negative impact on the environment and can be applied for routine pharmaceutical analysis.*
Keywords*: bromocresol green, metoprolol, spectrophotometry, validation, quantitative determination, tablets*

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1. Introduction

Metoprolol tartrate, bis [(2RS)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl) amino]propan-2-ol] (2R, 3R)-2,3-dihydroxybutanedioate, – water-soluble molecule (0.402 mg/mL), c*ardio-selective beta*-1-*blocker which* has significant advantages in the severity of the antihypertensive effect and the reduced number of side effects compared to non-selective drugs [1, 2]. The European Pharmacopoeia (EP) has a monograph on metoprolol tartrate [3]. The method of determination of metoprolol in the substance presented in the EP makes it impossible to quantify metoprolol in tablets. Several analytical methods have been reported for the determination of metoprolol, including spectrophotometry [4–8], high-performance liquid chromatography (HPLC) [9–15] and LC-MS [16–18]. Laboratories with a limited budget quite often use spectrophotometric methods. A comparison between the proposed and existing spectrophotometric methods are presented in Table 1. As can be seen from comparative Table 1, scientists have developed spectrophotometric methods for the determination of metoprolol in drugs using such reagents as copper(II) chloride [4], bromothymol blue or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone [5], 2,3-dichloro-1,4-naphthoquinone [6], potassium permanganate [8]. However, they require the use of toxic solvents or long sample preparation. There was only one published analytical method for the spectrophotometric determination of metoprolol tartrate in dosage forms using 2,3-dichloro-1,4-naphthoquinone in dimethylformamide medium that has been developed by

Ukrainian scientists [6]. However, as solved, dimethylformamide was used in this analytical method, which did not meet the principles of «green» analytical chemistry.

Table 1

Comparison between the proposed spectrophotometric method and the existing spectrophotometric methods

No.	Drug	Reagent	Medium	λmax, nm	Concentration range, LOD/LOQ, μg/mL	Reference
1	Tablets	Copper(II) chloride	pH 6.0 (Britton-Robinson buffer solution)	675	8.5–70 μg/mL, LOD – 5.56 μg/mL, LOQ – 7.11 μg/mL	[4]
2	In bulk drugs and in tablets and capsules	Bromothymol blue (BTB) or 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)	pH 3.4 (buffer)	413 (BPB method) or 457 (DDQ method)	0.0– 40.0 μg mL^{-1} in BPB method (LOD – 0.363 μg mL^{-1}, LOQ – 1.10 μg mL^{-1}) and 5.0–25.0 μg.mL^{-1} in DDQ method (LOD – 0.746 μg mL^{-1}, LOQ – 2.286 μg mL^{-1})	[5]
3	In pure and dosage forms	2,3- dichloro-1,4-naphthoquinone	Dimethylformamide	493	18.00–28.00 mg/100 mL, –	[6]
4	In bulk and tablet formulation	–	pH 6.8 (buffer)	223 (Method I) and 226 Method II (Derivative)	5–25 μg/mL LOD – 0.0498 μg/mL and LOQ – 0.232 (Method I), LOD – 0.765 μg/mL and LOQ – 0.280 (Method II)	[7]
5	Pharmaceutical formulations	Potassium permanganate	Alkaline	610	10.0-60.0 μg/10 mL, LOQ – 0.04 μg/mL and 0.10 μg/mL.	[8]

There is, therefore, a need for simple and eco-friendly spectrophotometric methods for the determination of metoprolol tartrate in tablets for pharmaceutical analysis purposes. Sulfophthalein dyes are widely used in the pharmaceutical analysis as reagents in the development of spectrophotometric methods of determination of APIs in medicinal products. It is known from the literature that sulfophthalein dyes are characterized by prototropic tautomerism in solutions [19–23]. Based on these data, it was assumed that the result of the reactions of sulfophthalein dyes with the test substances is a change in coloured tautomeric forms of reagents. Metoprolol exhibits basic properties and shifts the ionic balance in the studied solutions. Sulfophthalein dyes change their tautomeric forms in proportion to the solution's pH change. Sulfophthalein dyes dissociate in the first step with the formation of the quinoid form of yellow colour, which causes a faint yellow colour of such solutions. When substances with basic properties are added to this solution, they lead to further dissociation of sulfophthalein in the first stage and increase in the intensity of the yellow colour of the solution (λmax=407 nm). As the concentration of the weak base increases, the dissociation of sulfophthalein begins in the second step due to a shift in the ionic equilibrium of the solution, which leads to the formation of another tautomeric form of sulfophthalein dye, coloured blue. The presence of two forms of reagent in the solution, yellow and blue, leads to a green tint of the solution due to the mixing of colours. Thus, based on the results of the experiments, for further development of the spectrophotometric method for the quantitative determination of metoprolol by reaction with BCG, the absorbance wavelength was 624 nm.

Therefore, **the aim of our work** was to develop a spectrophotometric method for the determination of metoprolol tartrate in tablets based on the reaction with bromocresol green (BCG) in compliance with the principles of «green» chemistry.

2. Planning of the research

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

1. Study of the monograph of the State Pharmacopoeia of Ukraine (SPhU) and EP, analysis of articles in the scientific literature;

2. Selection of reaction conditions between metoprolol tartrate and BCG (choice of solvent, optimal wavelength, detection of stoichiometric coefficients);

3. Development and validation of the spectrophotometric method for determination of metoprolol tartrate in tablets;

4. Study the developed method's greenness profile assessment (eco-scale, analytical GREEnness).

3. Materials and methods

Objects of study, solvents and equipment.

Analytical equipment: two-beam UV-visible spectrophotometer Shimadzu model -UV 1800 (Japan), software UV-Probe 2.62, laboratory electronic balance RAD WAG AS 200/C, pH-meter I-160MI.

The following APIs, dosage forms, reagents and solvents were used in the work: pharmacopoeial standard sample (CRS) of metoprolol tartrate (Sigma-Aldrich, (≥98 %, HPLC)), BCG (Sigma-Aldrich, (≥98 %, HPLC)), "Metoprolol" tablets 50 mg (Kyivmedpreparat, series 0035415), "Metoprolol" 100 mg (Farmak, series

30421), 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 metoprolol tartrate with BCG.

5.48 mg of CRS metoprolol tartrate was transferred into a 50.00 mL volumetric flask with 35 mL methanol. The mixture was shaken and diluted to volume with methanol. Aliquot 1.00 mL was added to 1.0 mL of 1.6×10^{-4} M methanol of BCG. The volume of 10.00 mL was made up to the mark by adding methanol. 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 624 nm.

Procedure for tablets for the determination of metoprolol tartrate with BCG.

Twenty tablets were accurately weighed and powdered. A powder containing 5.48 mg of metoprolol tartrate was transferred into a 50.00 mL volumetric flask with 35 mL methanol. The mixture was shaken for 15 min, diluted to volume with ethyl acetate and then filtered. Aliquot 1.00 mL was added to 1.0 mL of 1.6×10^{-4} M methanol solution of BCG. The volume of 10.00 mL was made up to the mark by adding methanol. 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 624 nm.

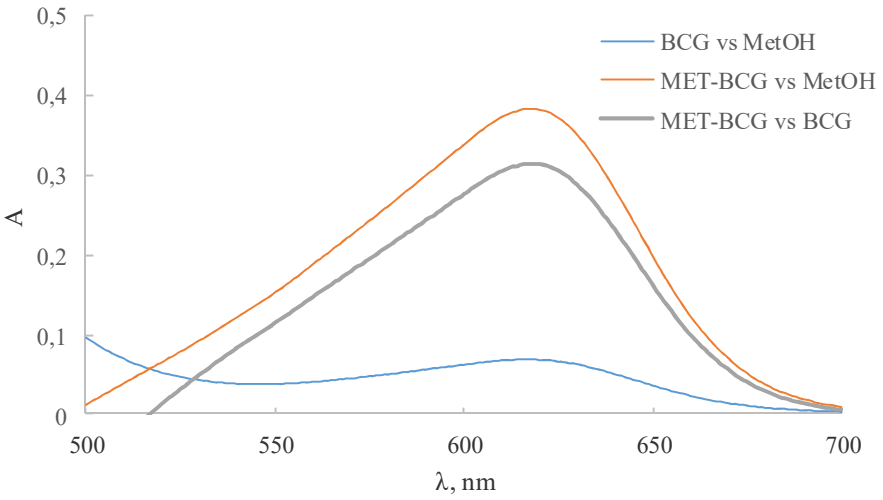

Fig. 1. Absorbance spectra of the reaction product of metoprolol tartrate from BCG against methanol (red), against BCG (grey) and BCG against methanol (blue)

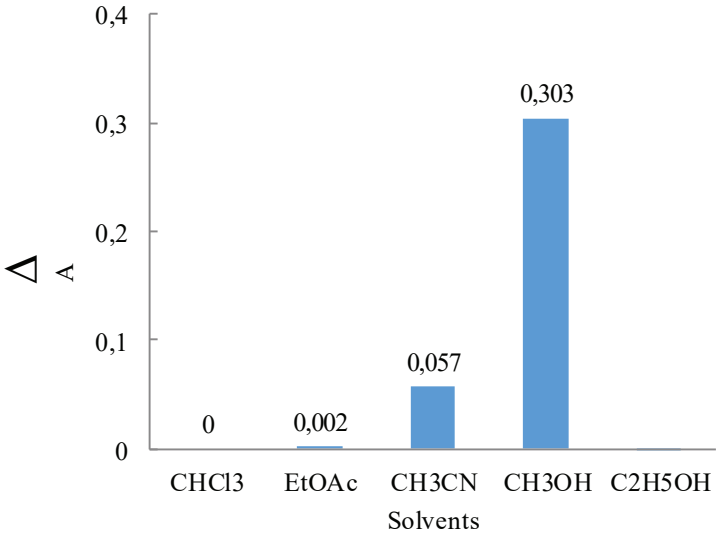

Fig. 2. Effect of solvents on the formation of the metoprolol-BCG complex (1.6×10^{-4} M solutions at 624 nm)

4. Results

4. 1. Selection of reaction conditions

The main purpose of this study was to develop an analytical method for determining metoprolol tartrate in tablets using the principles of «green» chemistry. We conducted preliminary studies on selecting the optimal sulfophthalein dye and found that BCG can be used as a reagent for the spectrometric determination of metoprolol. Metoprolol forms non-extractive ion-pair complexes with BCG with λmax at 624 nm. The spectra of absorbance of the reaction product of metoprolol tartrate with BCG are presented in Fig. 1.

The selection of reaction conditions between metoprolol tartrate and BCG (choice of solvent, optimal wavelength, detection of stoichiometric coefficients) is very important in spectrophotometric method development. However, in order to choose the optimal solvent, it was tested different organic solvents. Therefore, in subsequent experiments to select the optimal conditions for the reaction, the choice was stopped on methanol (Fig. 2).

The study of the influence of the BCG concentration on the absorbance at 624 nm at a constant concentration of metoprolol showed that at concentrations of BCG above 1.6×10^{-4} M, the dependence levels off. Therefore, the concentration 1.6×10^{-4} M was optimal.

An important aspect of the development of spectrophotometric methods is the study of the stability of solutions over time. If the solutions are not stable, it is necessary to stabilize them; for example, use buffer solutions to stabilize the pH, which will have a negative impact on the calculation of the principles of «green» chemistry. However, it was found that the tested solutions were stable for 45 minutes.

The molar absorption (ε) was 2.59×10^{4}, the specific absorption (*a*) was 3.78×10^{-2}, and the Sendel coefficient (*Ws*) was 0.026. Sensitivity parameters, such as apparent molar absorptivity and Sandell's sensitivity values, are indicative of the method's high sensitivity.

Stoichiometric coefficients between metoprolol tartrate and BCG were determined by continuous varia-

tions (or Job's method) and by the method of saturation (by the method of molar ratios). The graph of the dependence of the amount of absorbance on the ratio of the volumes of the components of the isomolar series is presented in Fig. 3.

The inflexion point on the saturation curve corresponds to the ratio of the concentrations of the reacting compounds. It is equal to the stoichiometric coefficient of the component whose concentration varied (Fig. 4).

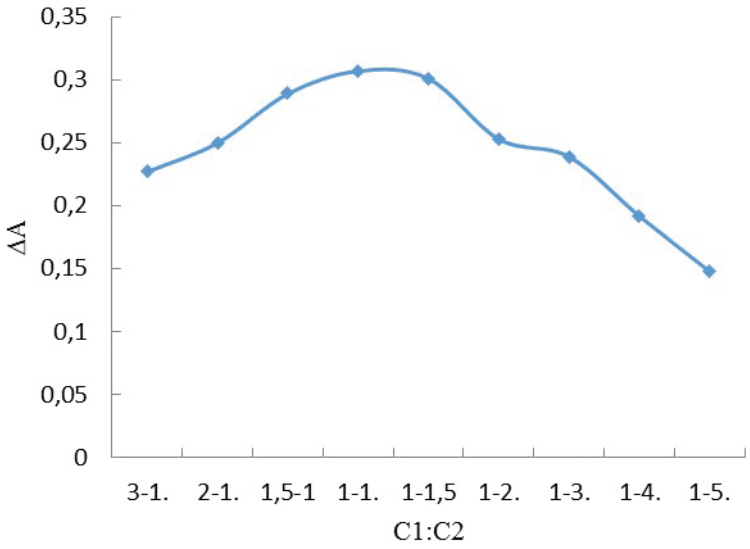

Fig. 3. Graph of the dependence of the amount of absorbance on the composition of the isomolar solution: C_1 – 1.6×10^{-4} M metoprolol tartrate solution; C_2 – 1.6×10^{-4} M solution BCG) at 624 nm

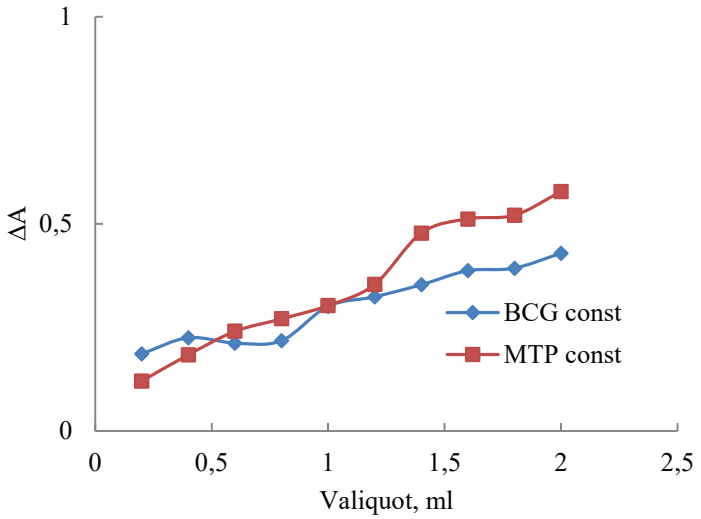

Fig. 4. Saturation curves: metoprolol tartrate solution at a constant concentration of reagent (1.00 mL of 1.6×10^{-4} M solution), BCG solution at a constant concentration of metoprolol tartrate (1.00 mL of 1.6×10^{-4} M solution)

According to the data obtained in Fig. 3, 4, the stoichiometric ratio of the reactive components of the reaction of the interaction of metoprolol tartrate with BCG corresponds 1:1.

4. 2. Determination of validation characteristics

The proposed spectrophotometric method was validated following the requirements of SPhU [24] for the following indicators: specificity, linearity, range of application, robustness, accuracy and precision.

4. 2. 1. Specificity

In order to confirm the specificity of the analytical method, a solution of auxiliary substances («placebo») was prepared. The influence of impurities on the results of the quantitative determination of metoprolol tartrate was not carried out since, in the performance of this work commercial produced tablets were used, which did not contain an unacceptable amount of impurities (the quality certificates of the manufacturers confirmed this fact).

The data presented in Table 2 indicates that the absorbance of auxiliary substances and impurities is insignificant (the found value of δnoise is 0.33 %) and does not exceed the acceptance criterion.

Table 2

The results of the study of the specificity

The absorbance of placebo (A placebo)	The absorbance of a solution of impurities (A impurities)	The absorbance of the compensating solution (Ast)	Value δnoise, %	Criteria
0.001	–	0.301	0.33	≥0.5 %

4. 2. 2. Linearity and range of application

Determination of linearity was performed over the range of applications of the method using model solutions. The obtained results were statistically processed by the method of least squares following the requirements of the SPhU. Analytical parameters are given in Table 3.

Table 3

Analytical parameters

Indicator	Value	Criteria	Conclusion
$b\pm(S_b)$	0.025± ±(0.0128)	–	
$a\pm(Sa)$	0.0112± ±(0.0031)	$\lvert a\rvert\leq\Delta a=$ $=t(2.77)\cdot Sa=$ $=0.0086$	Corresponds
R^2	0.9979	>0.9951	Corresponds
LOD, μg/mL	0.41	–	
LOQ, μg/mL	1.24	–	
Beer'sBeer's law limits (μg/mL)	5.47–38.30	–	

The parameters of the linear dependence of the analytical method (Table 3) met the requirements of the SPhU in the entire range of applications of the method. Furthermore, the high value of the correlation coefficient

R^2=0.9979 also satisfies the requirements of the acceptance criterion (R^2>0.9951) and confirms the linearity of the analytical method.

4. 2. 3. Robustness

The study of the robustness of the analytical method was performed at the stage of development of a spectrophotometric method for determining metoprolol tartrate by reaction with BCG during the establishment of optimal reaction conditions between metoprolol tartrate and BCG (stability of solutions over time, the amount of BCG added). As a result, it was established that the analyzed solutions are stable for 45 minutes (provided the cuvette is tightly closed during absorbance measurement) (Fig. 5), and fluctuations in the amount of the added reagent (BCG solution) within ±10 % do not significantly affect the value of the absorbance (Table 4).

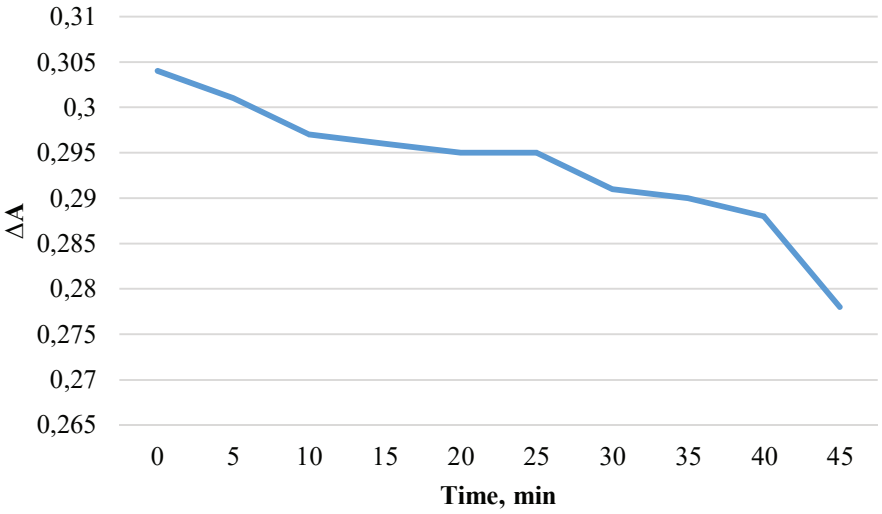

Fig. 5. Graph of the stability of solutions over time

Table 4

Effect of the amount of added BCG solution on the absorbance

The volume of 1.6×10^{-4} M BCG solution, mL	% BGC	Δ*A*
0.90	90.00	0.297
0.95	95.00	0.298
1.00	100.00	0.302
1.05	105.00	0.303
1.10	110.00	0.307

4. 2. 4. Accuracy and precision

The accuracy and precision of the analytical method were checked by preparing model solutions with a precisely known concentration of the drug with a content of 70–130 % of the nominal. The obtained results of the calculations are shown in Table 5.

Obtained results presented in Table 5 show that the spectrophotometric method for determining metoprolol is characterized by sufficient precision (convergence) since the found value of the relative confidence interval of the value Δ*z* (0.16) is less than the critical value for the convergence of results (1.6 %).

The criterion of the insignificance of the systematic error of the method is fulfilled – the systematic error of the method (0.06) is practically insignificant; that is, the analysis method is characterized by sufficient accuracy in the entire range of concentrations from 70 to 130 %.

Table 5

The results of the analysis of model mixtures and their statistical processing for the quantitative determination

Model solutions	Content, %		The ratio of found to add, $Z_i=(Y_i/X_i)\cdot100$ %
	Added, $X_i=(C_i/C_{rs})$ 100 %	Found, $Y_i=(A_i/A_{rs})$ 100 %	
M_1	70.01	70.07	100.09
M_2	80.04	79.99	99.94
M_3	89.95	89.99	100.04
M_4	95.05	95.11	100.06
M_5	100.01	100.09	100.08
M_6	104.93	105.01	100.08
M_7	110.01	110.12	100.10
M_8	120.11	120.27	100.13
M_9	129.97	130.05	100.06
The average value, *Z*, %			100.06
Standard deviation, S_z, %			0.07
Relative confidence interval $\Delta z=t(95\ \%,8)\cdot S_z=2.3060\ S_z$, %			0.16
The critical value for the convergence of results $\Delta z\leq\max\Delta_{As}$=1.6 %			Corresponds (0.16<1.6)
Systematic error $\delta=\lvert Z-100\rvert$, %			0.06
The criterion of the uncertainty of systematic error δ≤max δ, %			Corresponds (0.06<0.51)
General conclusion			Correct

The study of intra-laboratory precision was carried out on six samples of the same series of the drug, by different analysts, on different days (three days), 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 6).

Table 6

Results of intra-laboratory precision study

No. solution	Value Z_i, %		
	1 experiment	2 experiment	3 experiment
1	100.12	99.95	100.01
2	100.03	100.14	100.19
3	99.90	99.87	100.08
4	100.09	100.08	99.81
5	99.88	100.05	100.16
6	100.16	100.02	100.06
Average Z (%)	100.03	100.02	100.06
RSD_x, %	0.12	0.10	0.14
Relative standard deviation, RSD_z (%)	0.12		
Relative confidence interval, Δ_z	0.10≤1.6		
The critical value of the convergence of results, Δ_{4s}, %	1.6		

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 6).

The results of the quantitative determination of metoprolol tartrate in tablets are presented in Table 7.

Table 7

The results of quantitative determination of metoprolol tartrate in tablets

Drug	Found, g	Metrological characteristics
Tablets Metoprolol 0.05 g	0.0504	$\bar{m}$ = 0.0501 g
	0.0505	S=3.6×10^{-4}
	0.0501	t=2.57
	0.0495	Δx=3.78×10^{-4}
	0.0501	RDS=0.72
	0.0499	ε=0.75 %
Tablets Metoprolol 0.1 g	0.1004	$\bar{m}$ = 0.1003 g
	0.1010	S=6.11×10^{-4}
	0.0995	t=2.57
	0.0997	Δx=6.42×10^{-4}
	0.1009	RDS=0.61
	0.1002	ε=0.64 %

4. 3. Assessment of the impact of analytical methods on the environment

As mentioned above, an important aspect is developing analytical methods in compliance with the principles of «green» chemistry. Therefore, the «greenness» of the analytical method was assessed using AGREE tool (Analytical GREEnness) and analytical eco-scale. The score of the analytical eco-scale was 90 (Table 8). The pictogram of the analytical method using AGREE tool is presented in Fig. 6. According to the «greenness» pictogram of the analytical method using the AGREE method, the score was 0.79 and indicated that the proposed spectrophotometric method for the determination of metoprolol was developed in compliance with the principles of «green» chemistry.

Table 8

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

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

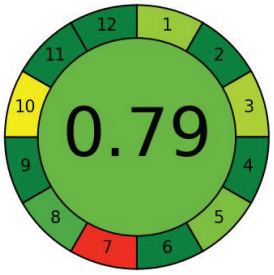

Fig. 6. Pictogram of an analytical method using AGREE tool

5. Discussion of research results

We considered the possibility of applying the differential spectrophotometry method to determine metoprolol tartrate by reaction with BCG using the maximum absorbance of the reaction product at a wavelength of 624 nm. Maximum absorbance of metoprolol tartrate was observed in a methanol solution (Fig. 2). The reaction between metoprolol tartrate and BCG was highly sensitive: the molar absorption coefficient was 2.59×10^4. Continuous changes and the saturation method obtained the stoichiometric ratios of the reactive components as 1:1. The developed method of quantitative determination of metoprolol tartrate was validated. The analytical method was linear in the concentration range of 5.47–38.30 μg/mL. The limit of detection (LOD) and quantification (LOQ) were 0.41 μg/mL and 1.24 μg/mL, respectively. A robustness study showed that the analyzed solutions were stable for 45 min, and fluctuations in the amount of added BCG within ±10 % did not significantly affect the absorbance. Therefore, the proposed analytical method has a low negative impact on the environment and can be applied for the purposes of routine pharmaceutical analysis. As seen from Fig. 6, operation 7 is highlighted in red, indicating analytical wastes that should be avoided or reduced during the development

of the analytical method by reducing the amount of metoprolol tartrate and the volume of methanol. In this case, the amount of tablet powder can be reduced and transferred to a 25.00 mL volumetric flask instead of 50.00 mL, which is not critical as the overall AGREE scale was 0.79. However, such changes in sample preparation may adversely affect the calculation of the uncertainty of sample preparation.

Only one spectrophotometric method for determining metoprolol by reaction with 2,3-dichloro-1,4-naphthoquinone was developed by Ukrainian scientists [6]. In the described article, the sample preparation was not simple, requiring heating. As a result, the molar absorptivity was lower, the calibration range was unexpectedly narrow from 18 to 28 mg/100 mL, and dimethylformamide used as a solvent was not suitable, as it was toxic. Therefore, the method cannot correspond to «green» chemistry principles. In the spectrophotometric method for the determination of metoprolol in tablets developed by us, it was proposed to use BCG as a reagent, the solvent was methanol, without heating (liberates the principles of «green» chemistry), the range of application of the method was 5.47–38.30 μg/mL.

Study limitations. The proposed analytical method can not be used to determine metoprolol tartrate in medicines' presence of other antihypertensive APIs.

Prospects for further research. The presented paper describes the main stages of the spectrophotometric method development of metoprolol tartrate in tablets based on the reaction with BCG. The next stage of research is planned to develop and validate the spectrophotometric method for determining metoprolol tartrate in tablets based on the reaction with BPB (bromophenol blue).

6. Conclusions

A spectrophotometric method was developed for determining metoprolol tartrate by reaction with BCG in a methanol solution using the absorption maximum at a wavelength of 624 nm. Stoichiometric ratios of reactive components were established, which were 1:1. The developed method for the quantitative determination of metoprolol tartrate has been validated following the requirements of the SPhU. The analytical method was linear in the concentration range of 5.47–38.30 μg/mL. LOD and LOQ were 0.41 μg/mL and 1.24 μg/mL, respectively. In summary, the developed method has a low negative impact on the environment and can be applied for routine pharmaceutical analysis.

Conflict of interests

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

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