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

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The aim *of the work was to develop a simple, economical and eco-friendly spectrophotometric method for determining metoprolol tartrate in tablets based on the reaction with bromophenol blue (BPB).*

Material and methods*. A double–beam Shimadzu UV-Visible spectrophotometer, with a spectral bandwidth of 1 nm wavelength accuracy ±0.5 nm, Model –UV 1800 (Japan), Software UV-Probe 2.62, and a pair of 1 cm matched quartz cells, was used to measure the absorbance of the resulting solution. All the chemicals were used in analytical reagent grade. Pharmacopeial standard samples of metoprolol tartrate and bromophenol blue (BPB) were provided by Sigma-Aldrich (≥98 %, HPLC). The used dosage forms of metoprolol tartrate are tablets of Metoprolol 50 mg and 100 mg.*

Results and discussion. *The method of spectrophotometric determination of the quantitative content of metoprolol tartrate based on its reaction with BPB in a methanol solution 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. The developed method of quantitative determination of metoprolol tartrate was validated. The linearity regression equation was y=0.0373x+0.0038, and the obtained correlation coefficient was R^2=0.9984. A linear relationship was found between absorbance at λmax and concentration of metoprolol tartrate in the range of 9.56-15.02 μg/mL. The LOD and LOQ values were calculated to be 0.81 μg/mL and 2.67 μg/mL.*

Conclusions. *A simple, economical and eco-friendly spectrophotometric method has been developed for the quantitative determination of metoprolol tartrate in tablets based on the reaction with BPB. The developed method of quantitative determination of metoprolol tartrate was validated in accordance with the requirements of SPhU. We suggest our work with offered detailed and successful solutions for the mentioned aim with less sophisticated equipment for QC lab for routine manufacturing control*

Keywords: *bromophenol blue, metoprolol tartrate, spectrophotometry, validation, pharmaceutical analysis*

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1. Introduction

Blockers of beta-adrenergic receptors or beta-blockers are a group of drugs whose main property is the ability to block beta-adrenergic receptors reversibly. Beta-blockers are one of the main groups of drugs used in cardiology. They are prescribed for both primary and secondary prevention of cardiovascular diseases. These drugs are used for treating coronary heart disease, arterial hypertension, and chronic heart failure, and as antiarrhythmic drugs. Metoprolol belongs to the most famous drugs of this class and has been used in clinical practice for more than a quarter of a century [1, 2]. Chemically, metoprolol tartrate is bis [(2RS)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl) amino]propan-2-ol] (2R, 3R)-2,3-dihydroxybutanedioate. It is a water-soluble molecule with log*P*=1.8, pKa (strongest acidic)=14.09, and pKa (strongest basic)=9.67 [2, 3]. By surveying the literature review of metoprolol, it was found that numerous methods have been reported for detecting metoprolol alone in bulk or its pharmaceutical formulation or biological fluids, including spectrophotometric [4–9] and chromatographic [10–20] methods. Only one published analytical method for determining metoprolol and meldonium in human plasma was developed by our scientific group [20]. However, they have certain disadvantages and make it impossible to use these methods in laboratories with no HPLC equipment or require toxic solvents, which is negative from the point of view of the principles of «green» chemistry. 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]. There is a need for simple, economical and eco-friendly spectrophotometric methods for the determination of metoprolol tartrate in tablets with less sophisticated equipment and budgets.

The aim of our work was to develop a simple, economical and eco-friendly spectrophotometric method for the determination of metoprolol tartrate in tablets based on the reaction with bromophenol blue (BPB).

2. Planning of the research

Metoprolol tartrate was chosen for the experimental confirmation of the theoretical approach proposed by us in the work, based on statistical data and analytical reviews, which reflects a clear understanding of the issue of pharmaceutical analysis using the spectrophotometric method; a spectrophotometric method for the determination of metoprolol tartrate in tablets based on the reaction with BPB was developed, and its validation was carried out.

Methodology of research of development of simple, economical and eco-friendly spectrophotometric methods for the determination of metoprolol tartrate in tablets based on the reaction with BPB includes:

1. Study of the recommendations of the State Pharmacopoeia of Ukraine (SPhU) and EP, analysis of data from scientific literature.

2. The study of the conditions for reaction metoprolol tartrate and BPB (choice of solvent, optimal wavelength, detection of stoichiometric coefficients) and its optimization for further use in the development of spectrophotometric methods.

3. The application of the proposed spectrophotometric method for determining metoprolol tartrate by using BPB to analyse tablets.

4. Validation of the spectrophotometric method for determination of metoprolol tartrate in tablets (specificity, linearity and range of application, accuracy, precision, robustness).

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

3. Materials and methods

Objects of study, solvents and equipment.

A double–beam Shimadzu UV-Visible spectrophotometer, with a spectral bandwidth of 1 nm wavelength accuracy ±0.5 nm, Model –UV 1800 (Japan), Software UV-Probe 2.62, and a pair of 1 cm matched quartz cells, was used to measure the absorbance of the resulting solution.

Other used instruments: Analytical Balance RAD WAG AS 200/C (Poland).

All the chemicals were used of analytical reagent grade. Pharmacopeial standard samples (CRS) of metoprolol tartrate and BPB were purchased from MERCK, Sigma-Aldrich (Switzerland) (≥98 % (HPLC)).

The used dosage forms of metoprolol tartrate: tablets of Metoprolol 50, 100 mg.

Proposed procedure for the determination of metoprolol tartrate with BPB.

6.83 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 2.0×10^{-4} M methanol of BPB. 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 at a wavelength of 595 nm.

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

Twenty tablets were accurately weighed and powdered. A quantity of powder containing 6.83 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 methanol and then filtered. Aliquot 1.00 mL was added to 1.0 mL of 2.0×10^{-4} M methanol solution of BPB. 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 at a wavelength of 595 nm.

Validation of the analytical method was carried out following the requirements of SPhU according to such parameters as specificity, linearity, range of application, accuracy, precision and robustness [21, 22].

4. Research results

4. 1. Selection of reaction conditions

In choosing the optimal reagent for the spectrophotometric method development, we tested dyes (bromocresol green, BPB, bromothymol blue, bromocresol purple, thymol blue, cresol red, methylene blue, methyl red). For various reasons, bromocresol purple, thymol blue, cresol red, methylene blue, and methyl red were not taken into account as reagents, because they gave a negative result (unstable complexes were formed, the completeness of complex formation was insufficient, calibration curves were non-linear). Therefore, we chose bromocresol green and BPB as reagents to develop spectrophotometric methods. The formation of ionic associates between basic substances and centres with excess electron density is a popular approach used in pharmaceutical analysis. These reactions are simple and rapid, take place at room temperature, and the colouration of sulfophthalein dyes and ion associates is highly intense. Previously, our scientific group had already developed a spectrophotometric method for determining metoprolol in tablets based on the reaction with bromocresol green [23].

Metoprolol forms complexes with BPB with an absorbance maximum at a wavelength of 595 nm (Fig. 1). The first stage of our research was the study of the conditions for this reaction (choice of solvent, optimal wavelength, detection of stoichiometric coefficients) and its optimization for further use in the development of spectrophotometric methods.

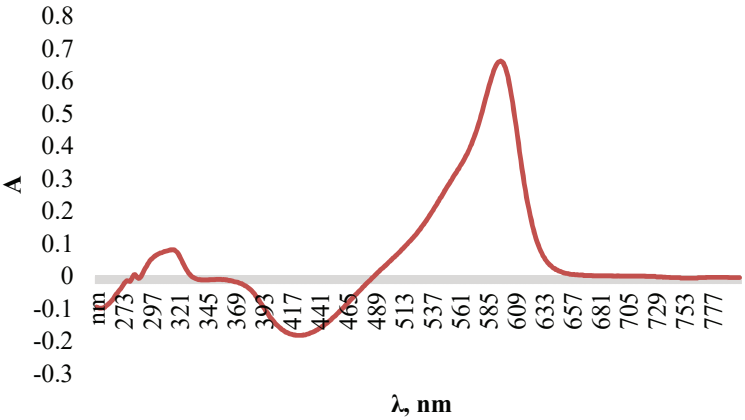

Fig. 1. The spectrum of absorbance of the reaction product of metoprolol tartrate with BPB in a methanol medium

As shown in Fig. 1, the highest absorbance value was observed when using the analytical wavelength of 595 nm, so this analytical wavelength was chosen for our further research. Choosing the optimal solvent is an important stage in the development of spectrophotometric methods. Therefore, we tested various solvents (methanol, ethanol, acetonitrile, ethyl acetate, chloroform) to choose the optimal one. As shown in Fig. 2, methanol gave the highest optical density in the absorbance maximum, so we chose it for our further studies.

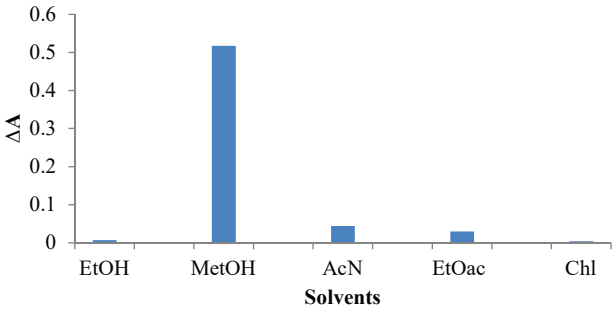

Fig. 2. Effect of solvents on the formation of metoprolol-BPB complex

We studied the stability of the obtained solutions. If the solutions were not stable, further development of the spectrophotometric technique was impossible. However, as we can see from Fig. 3, solutions were stable for 30 min.

Stoichiometric coefficients between metoprolol tartrate and BPB 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 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. 4 (method of continuous changes). Saturation curves are illustrated in Fig. 5 (method of saturation). As seen from Fig. 4, 5, the obtained stoichiometric coefficients of the reacting components of the interaction of metoprolol tartrate with BPB corresponds 1:1.

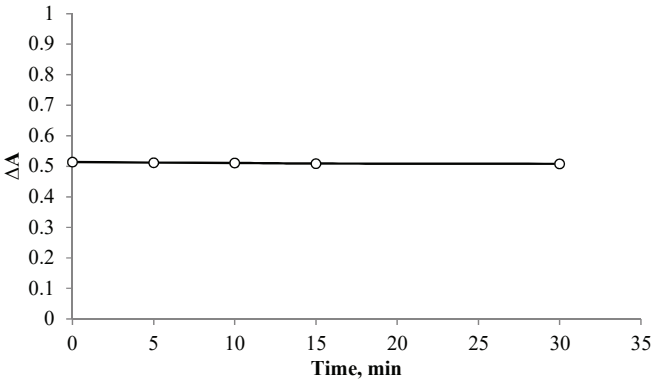

Fig. 3. Graph of the dependence of the absorbance of the reaction product of metoprolol tartrate with BPB in methanol solution depending on time

We calculated the sensitivity of the reaction between metoprolol tartrate and BPB. The molar absorption (ε) was 2.38×10^4, the specific absorption (a) was 3.48×10^{-2}, and the Sendel coefficient (Ws) was 0.029. Sensitivity parameters, such as apparent molar absorptivity and Sandell's sensitivity values, are indicative of the method's high sensitivity.

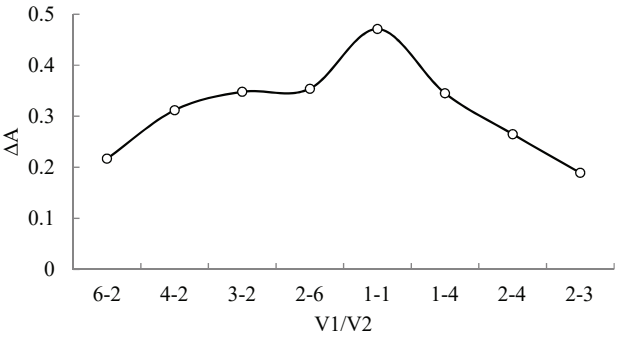

Fig. 4. Graph of the dependence of the amount of absorbance on the composition of the isomolar solution: V1 – 2.0×10^{-4} M metoprolol tartrate solution; V2 – 2.0×10^{-4} M solution BPB at 595 nm

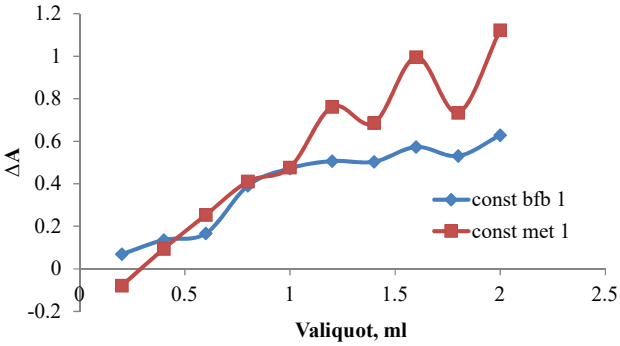

Fig. 5. Saturation curves: metoprolol tartrate solution at a constant concentration of reagent (1.00 mL of 2×10^{-4} M solution), BPB solution at a constant concentration of metoprolol tartrate (1.00 mL of 2×10^{-4} M solution)

4. 2. Determination of validation characteristics

The proposed spectrophotometric method for determining metoprolol tartrate in tablets by reaction with BPB was validated following the requirements of SPhU for the following indicators: linearity, range of application, accuracy, precision and robustness [21, 22].

4. 2. 1. Specificity

To confirm the specificity of the spectrophotometric method of determining metoprolol in tablets by reaction with BPB, a solution of auxiliary substances («placebo») was prepared. The results of studying the specificity of the analytical method are presented in Table 1. According to the results obtained in Table 1, it follows that the absorbance of auxiliary substances is insignificant (the found value of δnoise is 0.39 %) and does not exceed the acceptance criterion.

Table 1

The results of the study of the specificity

The absorbance of placebo (A placebo)	The absorbance of the compensating solution (Ast)	Value δnoise, %	Criteria
0.002	0.510	0.39	≥0.5 %

4. 2. 2. Linearity

Determination of linearity was performed over the range of applications of the method using model solutions. The results of calculations of the linear regression equation are given in Table 2.

Table 2

The results of calculations of the linear regression equation (p=95 %; n=5)

Indicator	Value	Criteria	Conclusion
$b\pm(S_b)$	0.0373± ±(0.0086)	–	–
a±(S_a)	0.0038± ±(0.0092)	$\|a\|\leq\Delta a=t(2.77)\cdot S_a=$ =0.0255	Corresponds
R^2	0.9984	>0.9979	Corresponds
LOD (μg/mL)	0.81	–	Corresponds
LOQ (μg/mL)	2.47	–	Corresponds
Beer's law limits (μg/mL)	9.56–15.02	–	Corresponds

A linear relationship was found between absorbance at λmax and concentration of metoprolol tartrate in the range of 9.56–15.02 μg/mL. The LOD and LOQ values were calculated to be 0.81 μg/mL and 2.47 μg/mL.

4. 2. 3. Accuracy and precision

To determine the accuracy and precision of the analytical method, mixtures with a well-known content of metoprolol tartrate were prepared, which covered the range of applications of the analytical method. The results of the accuracy and precision of quantitative determination of metoprolol tartrate in tablets are given in Table 3.

Table 3

Determination of the accuracy and precision of the results of quantitative determination of metoprolol tartrate in tablets

Model solutions	Content, %		The ratio of found to add, $Z_i=(Y_i/X_i)\cdot 100$ %
	Added, $X_i=(C_i/C_{rs})$ 100 %	Found, $Y_i=(A_i/A_{rs})$ 100 %	
M_1	70.02	70.05	100.04
M_2	80.01	79.98	99.96
M_3	89.55	89.59	100.04
M_4	96.05	96.11	100.06
M_5	99.99	100.06	100.08
M_6	104.92	105.00	100.08
M_7	111.01	111.12	100.10
M_8	122.22	122.31	100.07
M_9	129.95	130.03	100.06
The average value, Z, %			100.05
Standard deviation, S_z, %			0.06
Relative confidence interval $\Delta z=t(95\ \%,8)\cdot S_z=2.3060\ S_z$, %			0.14
The critical value for the convergence of results $\Delta z\leq\max\Delta_{As}=1.6$ %			Corresponds (0.14<1.6)
Systematic error $\delta=\|Z-100\|$, %			0.05
The criterion of the uncertainty of systematic error $\delta\leq\max\delta$ %			Corresponds (0.05<0.51)
General conclusion			Correct

The criterion of the insignificance of systematic error of the spectrophotometric method was fulfilled – systematic error of the method (0.05 %) 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 6 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).

Table 4

Results of intra-laboratory precision study

No. solution	Value Z_i, %		
	1 experiment	2 experiment	3 experiment
1	100.15	100.10	100.08
2	100.07	100.04	100.11
3	99.98	100.19	99.92
4	99.95	99.92	99.97
5	99.92	100.08	100.05
6	99.99	100.01	100.09
Average Z (%)	100.01	100.06	100.04
RSD_x, %	0.09	0.09	0.08
Relative standard deviation, RSD_Z (%)	0.09		
Relative confidence interval, $\Delta_{\bar{Z}}$	0.06≤1.6		
The critical value of the convergence of results, Δ_{As}, %	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 4).

4. 2. 4. Robustness

The study of the robustness of the spectrophotometric method for the determination of metoprolol tartrate in tablets by reaction with BPB was carried out during the development of the analytical method when optimal conditions of reaction between metoprolol tartrate and BCG were established (stability of solutions over time, the amount of added BPB).

Table 5

Determination of the robustness of the analytical method

Amount of BPB, mL	% BPB	A
0.90	90	0.468
0.95	95	0.469
1.00	100	0.471
1.05	105	0.472
1.10	110	0.474

A study of the robustness of the analytical method showed that the analyzed solutions were stable for 30 min (Fig. 3), and fluctuations in the amount of added

BPB within ±10 % did not significantly affect the absorbance (Table 5).

4. 3. Application to tablet analysis

The next stage of our research was the application of the proposed spectrophotometric method for the determination of metoprolol tartrate by using BPB for the analysis of tablets. The results of the quantitative determination of metoprolol tartrate in tablets are presented in Table 6.

Table 6

The results of quantitative determination of metoprolol tartrate in tablets

Drug	Found, g	Metrological characteristics
Tablets Metoprolol 0.05 g	0.0503	$\bar{m}$ = 0.0501 g
	0.0506	S=4.18×10^{-4}
	0.0502	t=2.57
	0.0494	Δx=3.39×10^{-4}
	0.0501	RDS=0.83
	0.0498	ε=0.87 %
Tablets Metoprolol 0.1 g	0.1005	$\bar{m}$ = 0.1003 g
	0.1008	S=6.07×10^{-4}
	0.0994	t=2.57
	0.0998	Δx=6.37×10^{-4}
	0.1010	RDS=0.6
	0.1003	ε=0.63 %

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

Given that many of the analytical methods for determining metoprolol in dosage forms presented in the literature were not «green», we set the goal of developing an analytical method for determining metoprolol in tablets that would correspond to the principles of «green» chemistry. Therefore, the «greenness» of the analytical method was assessed using AGREE tool (Analytical GREEnness) and analytical eco-scale. A pictogram of the analytical method using AGREE tool is presented in Fig. 6. The score of the analytical eco-scale was 90 (Table 7).

Table 7

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

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

As can be seen from Table 7 and Fig. 6, the developed spectrophotometric method for determining metoprolol tartrate in tablets based on the reaction with BPB was eco-friendly.

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

5. Discussion of research results

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 complex, requiring heating. 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 and, therefore, the method cannot correspond to GAC principles.

In our research, we apply the differential spectrophotometry method to determine metoprolol tartrate by reaction with BPB. Maximum absorbance of metoprolol tartrate was observed in a solution of methanol at a wavelength of 595 nm. (Fig. 2). The reaction between metoprolol tartrate and BPB was highly sensitive: the molar absorption coefficient was 2.38×10^4. The stoichiometric ratios of the reactive components as 1:1 were obtained by continuous changes and the saturation method. The developed method of quantitative determination of metoprolol tartrate was validated. The linearity regression equation was y=0.0373x+0.0038, and the obtained correlation coefficient was R^2=0.9984. A linear relationship was found between absorbance at λmax and concentration of metoprolol tartrate in the range of 9.56–15.02 μg/mL. The LOD and LOQ values were calculated to be 0.81 μg/mL and 2.67 μg/mL. The criterion of the insignificance of systematic error of the spectrophotometric method was fulfilled – systematic error of the method (0.05 %) was statistically and practically insignificant, i.e. analytical method was characterized by sufficient accuracy in the whole range of analyzed concentrations. A study of robustness showed that the analyzed solutions were stable for 30 min (Fig. 3). Fluctuations in the amount of added BPB within ±10 % did not significantly affect the absorbance (Table 5). As can be 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.

Summarizing the above, we developed two spectrophotometric methods for determining metoprolol in tablets by reactions with bromocresol green [23] and BPB. Comparative characteristics of both developed methods are presented in Table 8.

Table 8

Comparison between two developed spectrophotometric methods for the determination of metoprolol in tablets

No.	Drug	Reagent	Solvent	λmax, nm	Concentration range, LOD/LOQ, μg/mL	AGREE scale, score of eco-scale	Reference
1	Tablets	Bromocresol green	methanol	624	5.47–38.30, LOD – 0.41, LOQ – 1.24	0.79, 90	[23]
2	Tablets	Bromophenol blue	methanol	595	9.56 – 15.0, LOD – 0.81, LOQ – 2.67	0.79, 90	Developed method

Study limitations. The developed spectrophotometric method can not be used to determine metoprolol tartrate in the presence of other antihypertensive APIs in medicines.

Prospects for further research. This article describes the main stages of the spectrophotometric method development of metoprolol tartrate in tablets based on the reaction with BPB. 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 bromothymol blue.

6. Conclusion

A simple, economical and eco-friendly spectrophotometric method has been developed for the quantitative determination of metoprolol tartrate in tablets based on the reaction with BPB. Selection of reaction conditions between metoprolol tartrate and BCG (choice of solvent, optimal wavelength, detection of stoichiometric coefficients) was performed. The developed method of quantitative determination of metoprolol tartrate was validated following the requirements of SPhU. A linear relationship was found between absorbance at λmax and concentration of metoprolol tartrate in the range of 9.56–15.02 μg/mL. The LOD and LOQ values were calculated to be 0.81 μg/mL and 2.67 μg/mL. We can suggest our work with offered detailed and successful solutions for the mentioned aim with less sophisticated equipment for QC lab for routine manufacturing control.

Conflict of interest

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

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