UDC 615.073/.074:543.422.3:615.225:615.453.6]-092.4
DOI: 10.15587/2519-4852.2024.302635

TWO MASTERFUL ALTERNATIVE SPECTROPHOTOMETRIC METHODS FOR THE DETERMINATION OF RAMIPRIL IN TABLETS

Kateryna Typlynska, Mariana Horyn, Tetyana Kucher, Liubomyr Kryskiw, Liliya Logoyda

The aim of the work *was to develop two simple, rapid, economic, alternative spectrophotometric methods for the determination of ramipril in tablets based on the reaction with sulfonephthalein dyes (bromphenol blue (BPB) and cresol red (CR)).*

Materials and methods. *Analytical instrumentation: Shimadzu UV-1800 double beam UV-VIS spectrophotometer (Japan) with attached UV-Probe ver. 2.62 software, RAD WAG AS 200/C precise analytical balance (Poland). Ramipril (purity ≥98 % (HPLC)) was purchased from AARTI Industries Limited (India). Ramipril tablets 5 mg and 10 mg were purchased from a local pharmacy.*

Results and discussion. *Two spectrophotometric methods for the determination of ramipril in tablets have been developed. We have tested various sulfophthalein dyes (BPB, bromocresol green, bromthymol blue, thymol blue, CR) in order to choose the optimal for the method development. According to the results of the experimental studies, we chose BPB and CR as reagents, and the solvent was acetonitrile for both methods. The optimal conditions for the quantitative determination of ramipril in tablets by using BPB were established: dye concentration – 2.35×10^{-4} mol/L, volume of BPB solution – 1.0 ml, without heating, wavelength – 598 nm, reaction time – 5 min, temperature of the solution – 25 °C. The optimal conditions for the quantitative determination of ramipril in tablets by using CR were established: dye concentration – 1.33×10^{-4} mol/L, volume of CR solution – 1.0 ml, without heating, wavelength – 395 nm, reaction time – 5 min, temperature of the solution – 25 °C. The spectrophotometric method by using BPB was linear in the concentration range of 1.99–5.96 μg/mL, LOD – 0.20 μg/mL, LOQ – 0.60 μg/mL. The spectrophotometric method using CR was linear in the concentration range of 0.42–5.44 μg/mL, LOD – 0.10 μg/mL, and LOQ – 0.36 μg/mL. The results of the study on robustness, accuracy, and precision were within the acceptance criteria. The results of studying the «greenness» of both methods indicate an excellent «green» analysis.*

Conclusions. *Developed methods can be used as an alternative method for the routine analysis of ramipril tablets*

Keywords: *ramipril, spectrophotometry, validation, quantitative determination, tablets*

How to cite:
Typlynska, K., Horyn, M., Kucher, T., Kryskiw, L., Logoyda, L. (2024). Two masterful alternative spectrophotometric methods for the determination of ramipril in tablets. ScienceRise: Pharmaceutical Science, 2 (48), 44–52. doi: http://doi.org/10.15587/2519-4852.2024.302635

1. Introduction

Hypertension is one of the most common diseases of the 21st century, which affects the quality of life of patients and is characterized by high mortality [1].

One of the most effective and proven groups is angiotensin-converting enzyme (ACE) inhibitors [2]. Ramipril (Fig. 1), (2*S*,3*aS*,6*aS*)-1-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-3,3*a*,4,5,6,6*a*-hexahydro-2*H*-cyclopenta[b]pyrrole-2-carboxylic acid, is a prodrug and nonsulfhydryl ACE inhibitor with antihypertensive activity [2]. It is metabolized to ramiprilat in the liver and kidneys.

Nowadays, chromatographic methods are the undisputed leaders in the analysis of dosage forms. The analysis of dosage forms of ramipril is no exception, where liquid chromatography techniques (HPLC) are widely used for the purposes of routine pharmaceutical analysis [3–21]. European Pharmacopoeia (Ph. Eur.) monograph on ramipril [3] and US Pharmacopoeia (USP) [22] prescribes the HPLC method for the determination of ramipril in tablets. Ph. Eur. monograph on ramipril [3] prescribes the alkalimetric titration for the determination of ramipril as an active substance. Our scientific group has developed HPLC methods for the quality control of tablets «Ramipril» according to the indicators of «Quantitative determination», «Impurities», and «Dissolution» [21].

However, there are laboratories that do not have expensive equipment (for example, chromatographs) and cannot analyze ramipril tablets by HPLC.

For such laboratories, spectrophotometric methods of the analysis can be an alternative. Spectrophotometric methods for the determination of ramipril in dosage forms are described in the scientific literature; however, the described approaches are somewhat outdated, which is related to the year of publication of the scientific research data [23–26]. Spectrophotometric methods for the determination of ramipril in recent years are based on UV spectrophotometric determination [27–30]. Therefore, the aim of our work was to develop a two simple, rapid, economic, alternative spectrophotometric methods for the determination of ramipril in tablets

based on the reaction with sulfonephthalein dye (bromphenol blue (BPB) and cresol red (CR)).

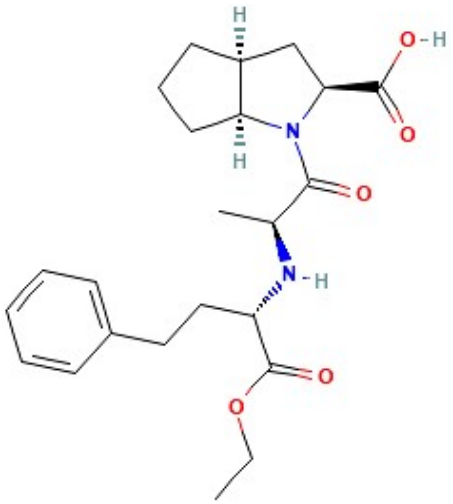


Fig. 1. The chemical structure of ramipril [2]

2. Planning of the research

Methodology of the research of simple, rapid, economic, alternative spectrophotometric methods for the determination of ramipril in tablets based on the reaction with sulfonephthalein dye includes:

1. Analysis of the scientific literature, Ph. Eur. and USP monographs.

2. Selection of reaction conditions between ramipril and dye (choice of reagent, its concentration and amount, optimal solvent and wavelength, detection of stoichiometric coefficients).

3. Development and validation of the spectrophotometric method for determination of ramipril in tablets based on the reaction with sulfonephthalein dye (BPB and CR).

4. Greenness profile assessment of the proposed spectrophotometric method (AGREE and GAPI).

3. Materials and methods

Objects of study, solvents and equipment.

Analytical instrumentation: Shimadzu UV-1800 double beam UV-VIS spectrophotometer (Japan) with attached UV-Probe ver. 2.62 software, RAD WAG AS 200/C precise analytical balance (Poland).

Ramipril (purity ≥98 % (HPLC)) was purchased from AARTI Industries Limited (India). All the chemicals were used of analytical reagent grade. Reagents (BPB and CR) were purchased from MERCK, Sigma-Aldrich (Switzerland) (≥98 % (HPLC)). Ramipril tablets 5 mg, 10 mg were purchased from a local pharmacy.

Proposed procedure for the determination of ramipril with BPB.

Twenty tablets were accurately weighed and crushed. A quantity of powder containing 25.00 mg of ramipril was transferred into a 25.00 mL volumetric flask, dissolved in 15.0 mL of acetonitrile, adjusted with acetonitrile to label, kept in an ultrasound bath for 2 min and filtered. Aliquot 2.5 mL was transferred into a 25.00 mL volumetric flask, dissolved in 15.0 mL of acetonitrile, adjusted with acetonitrile to label, and mixed. Aliquot 0.4 mL was added to 1.0 mL 2.35×10^{-4} M solution of BPB in acetonitrile. The volume of 10.00 mL was made up to the mark by adding acetonitrile and mixing. The absorbance of the resulting solution was measured against the background of the compensating solution at a wavelength of 598 nm. To study linearity, aliquots 0.2–0.6 mL were taken.

Proposed procedure for the determination of ramipril with CR.

Twenty tablets were accurately weighed and crushed. A quantity of powder containing 2.00 mg of ramipril was transferred into a 50.00 mL volumetric flask, dissolved in 20.0 mL of acetonitrile, adjusted with acetonitrile to label, and kept in an ultrasound bath for 2 min and filtered. Aliquot 0.7 mL was added to 1.0 mL of 1.33×10^{-4} M solution of CR in acetonitrile. The volume of 10.00 mL was made up to the mark by adding acetonitrile and mixing. The absorbance of the resulting solution was measured against the background of the compensating solution at a wavelength of 395 nm. To study linearity, aliquots 0.1–1.3 mL were taken.

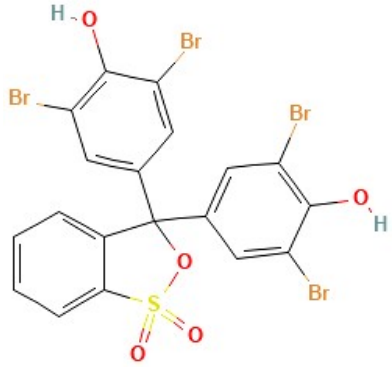
4. Results

4. 1. Selection of reaction conditions

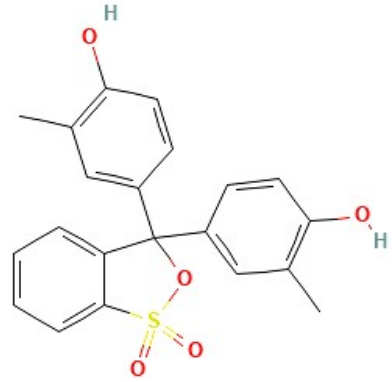
Ramipril is sparingly soluble in water and freely soluble in methanol, pKa1 – 3.74 (caboxylic acid); pKa2 – 5.15 (secondary amine), Log P – 2.9 [2, 3]. Molecular weight is 416.5 g/mol. Considering the available functional groups (Fig. 1), ramipril is not a difficult substance for the development of spectrophotometric methods. Our scientific group has experience in the development of spectrophotometric methods for the determination of various APIs using sulfonephthalein dyes as reagents, so we tested sulfonephthalein dyes as potential reagents for future method development. During the analysis of the scientific literature related to the development of spectrophotometric methods for the determination of ramipril in dosage forms, no analytical method was found where sulfonephthalein dyes were used as reagents. Sulfonephthalein dyes exist in solution in two protonated forms – monoprotonated (the proton is split off from the sulfogroup) and in the dianionic form (the second proton is split off from one of the phenolic hydroxyls) [31]. We have tested various sulfophthalein dyes (bromophenol blue, bromocresol green, bromthymol blue, thymol blue, CR) in order to choose the optimal for the further method development. When processing reagents bromocresol green, bromthymol blue, thymol blue there were problems that required in-depth study however in the future these dyes may also be potential reagents. Given the results we obtained in our initial studies, we settled on BPB and CR (Fig. 2).

In the presence of ramipril, the acid-base balance of the BPB shifts towards the diionized form since ramipril forms a more stable ionic associates with this form of the dye (BPB) (Fig. 3). ramipril forms complexes with BPB with an absorbance maximum at a wavelength of 598 nm in acetonitrile medium. The optimal concentration of BPB is 2.35×10^{-4} M. It was determined that 1.0 mL of BPB was needed to achieve the highest absorbance. In the presence of ramipril, the acid-base balance of the CR shifts towards

the mono ionized form since ramipril forms more stable ionic associates with this form of the dye (CR) (Fig. 3). Ramipril forms complexes with CR with an absorbance maximum at a wavelength of 395 nm in acetonitrile medium. The optimal concentration of CR is 1.33×10^{-4} M. It was determined that 1.0 mL of CR was needed to achieve the highest absorbance. The spectra of absorbance of the reaction product of ramipril-BPB and ramipril-CR complex are shown in Fig. 3.



a



b

Fig. 2. The chemical structure of:
a – BPB [32]; *b* – CR (b) [33]

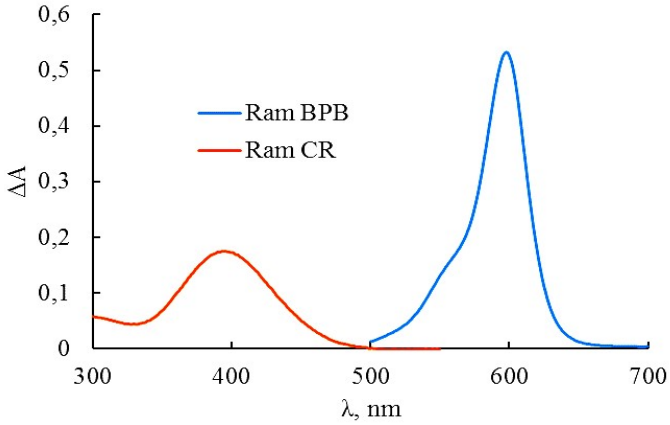


Fig. 3. Absorption spectra of ramipril (9.56×10^{-6} M) – BPB (2.35×10^{-5} M in acetonitrile) complex, ramipril (1.11×10^{-5} M) – CR (1.33×10^{-4} M in acetonitrile) complex

In the next stage of research, we have worked on the selection of the optimal solvent. The choice of solvents is presented in Fig. 4, 5. The optimal solvent was acetonitrile for both dyes. Based on the Hansen space green solvent selection tool, acetonitrile had a G score of 5.8 [34], as shown in Fig. 6 (waste=2.8, health=5.9, environment=8.9, safety=7.7).

The stability of the ion-pair complexes ramipril with BPB and CR was studied. Despite the fact that the ion pairs were formed immediately, steady absorbance values were measured after at least 5 min of remaining at a constant temperature (25±2 °C) and remaining stable for twenty-four hours.

At this stage, we have selected the reagent, its concentration and amount, optimal solvent and analytical wavelength, and we can already think about the further development of the spectrophotometric methods; however, the choice of stoichiometric coefficients of the reacting components is important. Stoichiometric coefficients of the reacting components were determined by the method of continuous changes (Job's method) and the saturation method (the method of molar ratios). As seen from Fig. 7, 8, the stoichiometric coefficients of the reacting components between ramipril and dyes equals 1: 1.

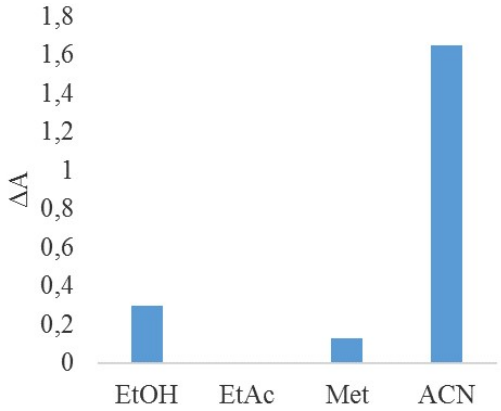


Fig. 4. Solvents impact on the generation of ramipril – BPB (2.35×10^{-4} M) complex

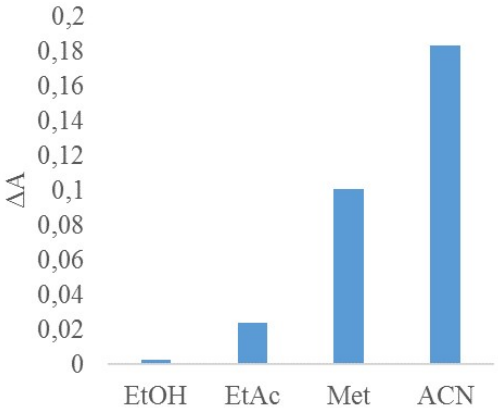


Fig. 5. Solvents impact on the generation of ramipril – CR (1.33×10^{-4} M) complex

The optimal parameters for ramipril spectrophotometric analysis via complex formation using BPB and CR are presented in Table 1.

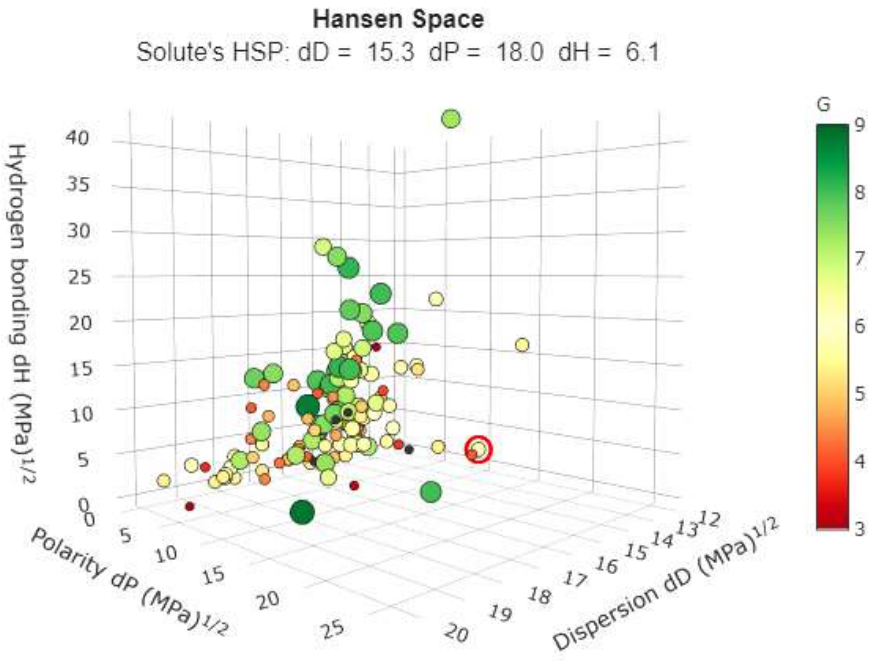


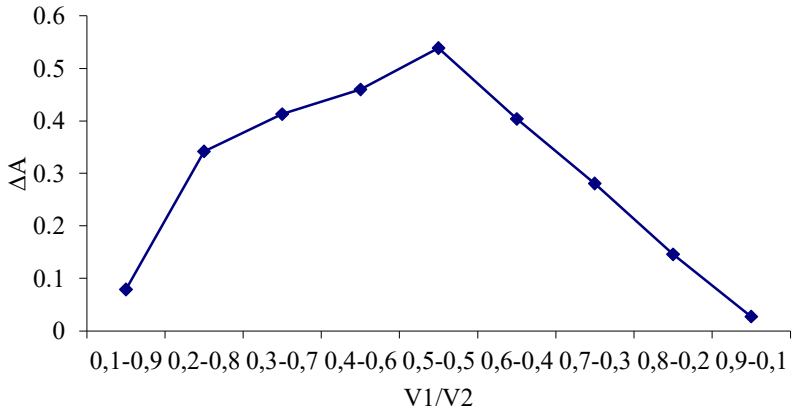
Fig. 6. Acetonitrile solvent sustainability level generated by the Hensen space green solvent selection tool

Table 1

The optimal parameters for ramipril spectrophotometric analysis via complex formation using BPB and CR

Conditions	CR	BPB
Reagent concentration, mol/L	1.33×10^{-4}	2.35×10^{-4}
Reagent volume, mL	1.0	1.0
Optimal solvent	acetonitrile	
Optimal wavelength, nm	395	598
Reaction time, min	5	
Stoichiometric coefficients	1:1	
Temperature of solution, °C	25±5	

Table 1 presents the optimal parameters for the spectrophotometric determination of ramipril via the ion-pair formation of complexes utilizing BPB and CR.



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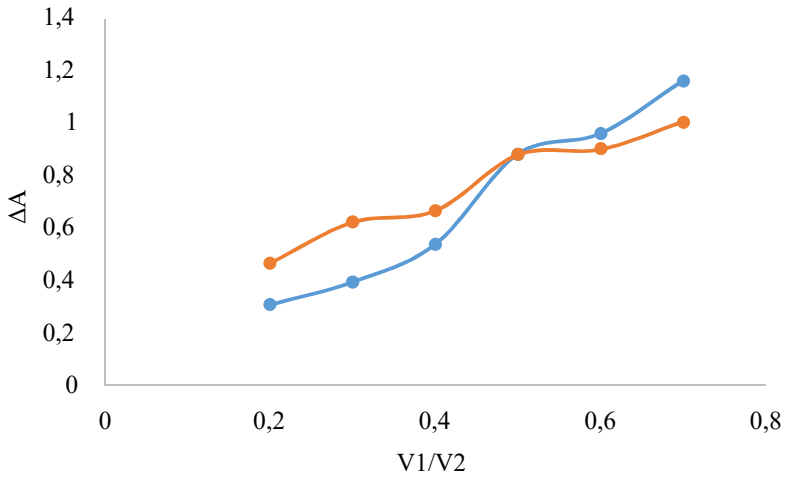


b

Fig. 7. Study of stoichiometric coefficients by the reaction with BPB:
a – Ramipril: BPB complex continuous variation method at λ=598 nm (C_M=2.35×10^{-4} M);
b – Molar ratio method of ramipril:BPB complex at λ=598 nm ($C_{M\ BPB}$=3.09×10^{-4} M)

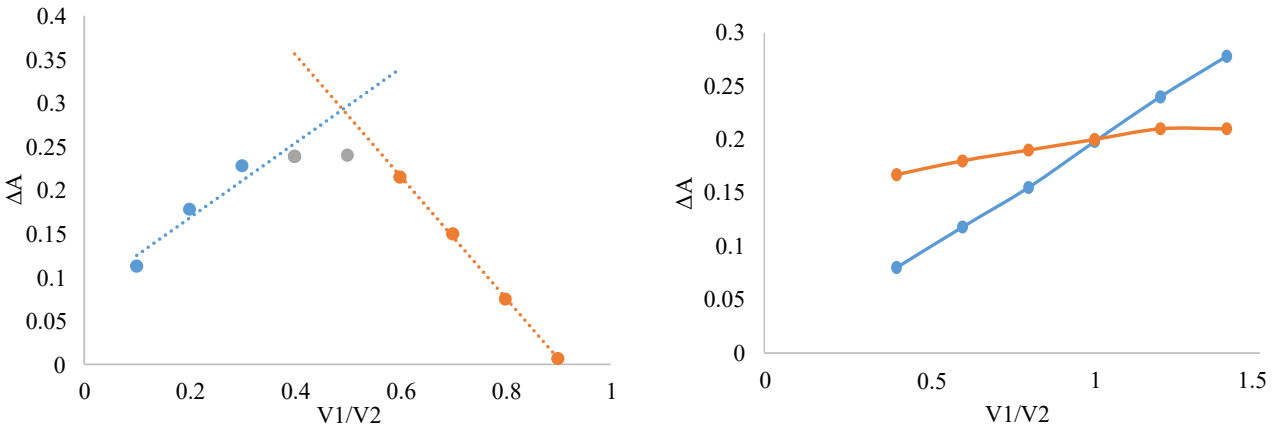


Fig. 8. Study of stoichiometric coefficients by the reaction with CR: *a* – Ramipril:CR complex continuous variation method at λ=395 nm (C_M=4.75×10^{-4} M); *b* – Molar ratio method of ramipril:CR complex at λ=395 nm ($C_{M\,CR}$=1.33×10^{-4} M)

4. 2. Determination of validation characteristics

Three spectrophotometric methods for the determination of ramipril in tablets has been validated in accordance with the requirements of SPhU [35] for the parameters: robustness, accuracy and precision, linearity, range of application.

4. 2. 1. Robustness study

The robustness was studied during the method development (stability of solutions, change in the volume of the reagent, time of reaction). In the previous experiments during method development, it was determined that changes during robustness study within ±10 % do not significantly affect the value of the absorbance (Table 2).

Table 2

Robustness for determination of ramipril by the developed approach

Method Parameters	BPB	CR
	(%) Recovery*±SD	
Stability of solutions, h 1	99.95±0.83	99.35±1.48
5	99.65±0.95	100.42±0.73
10	98.80±1.28	98.82±1.02
Volume of reagent, mL 0.9	99.23±0.59	99.28± 0.83
1.0	99.11±1.74	100.48±0.90
1.1	100.08±1.02	100.91±1.98
Time of reaction, min 5	100.28±0.89	98.49±1.39
10	99.12±1.36	99.03±0.92
15	98.03±1.24	98.29±1.20

Note: mean of three determinations

All calculated results comply with the acceptance criteria (within the range of 98.0–102.0 %).

4. 2. 2. Linearity and range of application

The linearity of the proposed spectrophotometric methods for the determination of ramipril by reactions with BPB and CR was studied in the concentration range of 1.99–5.96 mg/mL (BPB) and 0.42–5.44 mg/mL (CR) in accordance with the requirements of the SPhU (regression analysis). Spectral features and validation parameters for the studied spectrophotometric approach are given in Table 3.

The correlation coefficient exceeded 0.998, i.e. linearity of the analytical procedure is sufficient.

The limit of detection (LOD) and limit of quantification (LOQ) were calculated to be 0.20 μg/mL and 0.60 μg/mL for BPB and 0.10 μg/mL and 0.36 μg/mL for CR.

Table 3

Spectral features and validation parameters for the studied spectrophotometric approach

Parameters BPB CR		
λ_{ex} (nm)	598	395
Linear range (μg/mL)	1.99–5.96	0.42–5.44
Correlation coefficient (r)	0.9985	0.9994
Intercept±SD*	–0.1325±2.39×10^{-2}	–0.0043±1.0520×10^{-3}
Slope±SD	0.1721±5.73×10^{-3}	0.0385±3.5500×10^{-3}
**LOD (μg mL^{-1})	0.20	0.10
***LOQ (μg mL^{-1})	0.60	0.36

*Note : SD – Standard Deviation; ** – LOD: Limit of detection; *** – LOQ: Limit of quantitation*

4. 2. 3. Accuracy and precision

Three drug concentration levels (1.99, 3.98 and 5.96 μg mL^{-1}) and (0.42, 2.93, and 5.44 μg mL^{-1}) for BPB and CR, respectively, were examined to evaluate the suggested method's accuracy. The calculated data showed a good agreement between the measured and actual values, proving the accuracy of the developed methods, as shown in Table 4.

The average recovery values are within the range 99.0–101.0 %. The individual values of recovery for each of the concentration levels are within the range of 98.0–102.0 %. The RSD for individual values of recovery is less than 1.0 %.

The closeness of the experimental values to each other was assessed by intra- and inter-day precision. Intra-day precision has been performed by replicating analysis of three different concentrations of ramipril at three different times along the day, while inter-day precision – by checking the same concentrations through successive three days. All data are illustrated in Table 5. The results of the quantitative determination of ramipril in tablets are shown in Table 6.

Based on the obtained data, the minimum necessary number of independent preparations of the reference standard and sample was calculated in accordance with the recommendations [36]. When using BPB, at least 1 preparation of the reference standard and 2 preparations of the sample are required. When using CR, at least 2 preparations of the reference standard and 2 preparations of the sample are required.

The accuracy and repeatability of the analytical procedure are sufficient.

Table 4

Evaluation of the accuracy of the proposed spectrophotometric approach

Sample no.	BPB			CR		
	Taken conc. (μg mL^{-1})	Found conc. (μg mL^{-1})	% Recovery*	Taken conc. (μg mL^{-1})	Found conc. (μg mL^{-1})	% Recovery*
1	1.99	1.9823	99.61	0.42	0.4157	98.98
2	3.98	4.0217	101.05	2.93	2.9467	100.57
3	5.96	5.9485	99.81	5.44	5.4483	100.15
Mean*	–		100.16	–		99.90
SD			0.73			0.77
RSD			0.70			0.74

*Note: RSD – relative standard deviation; * – mean: of three replicate measurements*

Table 5

Intra- and inter-day precision evaluation

Concentration levels	BPB		CR	
	% Mean Recovery* ± SD			
	Intra-day	Inter-day	Intra-day	Inter-day
1	100.17±1.25	100.49±0.93	100.05±0.73	100.67±1.48
2	99.10±1.74	98.82±0.84	99.07±1.65	99.82±1.92
3	99.84±1.05	101.12±1.85	99.92±0.70	98.13±1.94

*Note: * – Mean of three determinations*

Table 6

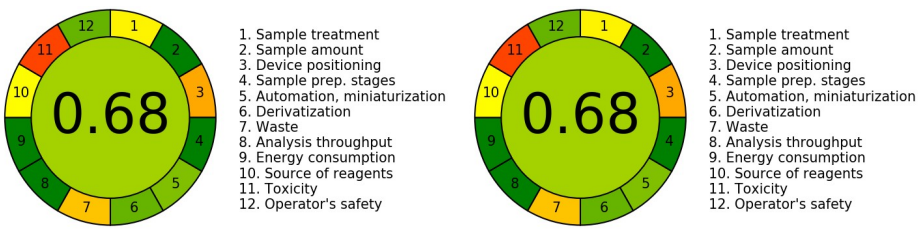
The results of quantitative determination of ramipril in tablets

	5		10	
	BPB	CR	BPB	CR
Dosage forms, mg	5.150	5.189	10.093	9.975
	5.035	5.279	10.258	10.258
	5.119	4.983	10.119	10.008
	5.149	5.239	9.986	9.989
	5.197	5.289	10.058	10.118
	5.047	4.988	10.349	10.267
Average	5.122	5.162	10.144	10.115
SD	0.069	0.141	0.135	0.152
RSD	1.337	2.724	1.328	1.506

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

Environmental friendliness of analytical methods is important and necessary in the 21st century. Before starting our research, we set a goal to develop ecological, and therefore «green», spectrophotometric methods. We took into consideration 12 principles of «green» chemistry in the method development. The use of acetonitrile allows you to avoid extraction of the ramipril-dye complex with toxic organic solvents and, therefore, to significantly increase the «greenness» of the proposed method. One of the advantages of our methods is the speed and simplicity of sample preparation (absence of heating). We evaluated the «greenness» using the Analytical GREEnness (AGREE) [37] and GAPI [38] tools, which were proposed by scientists from the Gdansk University of Technology (Poland). Pictograms of analytical methods using AGREE tool and GAPI are shown in Fig. 9, 10 respectively.

«Greenness» pictograms of the AGREE and GAPI of both methods look the same since they differ only in minor sample preparation. The score for the AGREE method is 0.68, which indicates an excellent «green» analysis.



BPB CR

Fig. 9. Pictograms of analytical methods using AGREE tool

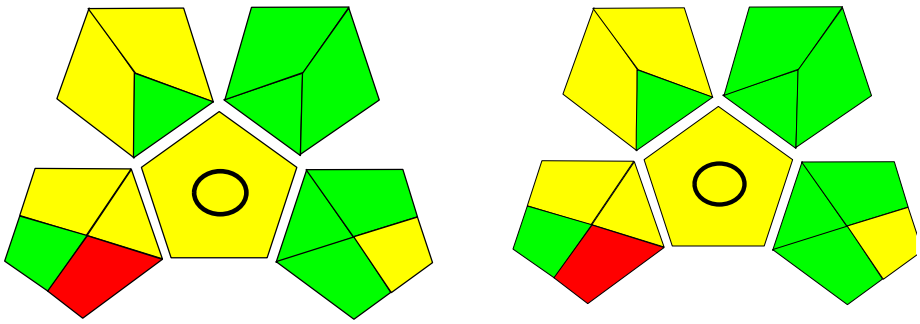


Fig. 10. Pictograms of analyticals method using GAPI

5. Discussion of research results

Our review of the scientific literature indicates the need to replenish the base of spectrophotometric methods for the determination of ramipril in tablets for the purposes of routine pharmaceutical analysis. Sulfonephthalein dyes are promising reagents in the spectrophotometric analysis of dosage forms, as evidenced by numerous researches. No spectrophotometric method for the determination of ramipril by reaction with sulfonephthalein dyes was described in the scientific literature. We have tested various sulfophthalein dyes (BPB, bromocresol green, bromthymol blue, thymol blue, CR) in order to choose the optimal for the method development. According to the results of the experimental studies, we chose BPB and CR as reagents (Fig. 3), and the solvent was acetonitrile for both methods (Fig. 5, 6). The optimal conditions for the quantitative determination of ramipril in tablets by using BPB were established (Table 1): dye concentration – 2.35×10^{-4} mol/L, volume of BPB solution – 1.0 ml, without heating, wavelength – 598 nm, reaction time – 5 min, temperature of the solution – 25 °C. The optimal conditions for the quantitative determination of ramipril in tablets by using CR were established (Table 1): dye concentration – 1.33×10^{-4} mol/L, volume of CR solution – 1.0 ml, without heating, wavelength – 395 nm, reaction time – 5 min, temperature of the solution – 25 °C. The stoichiometric coefficients corresponded 1 to 1 (Fig. 7, 8). The spectrophotometric method by using BPB was linear in the concentration range of 1.99–5.96 μg/mL (Table 3). The regression equation was $y=0.1721x-0.1325$, R^2 – 0.9985, LOD – 0.20 μg/mL, LOQ – 0.60 μg/mL. The spectrophotometric method by using CR was linear in the concentration range of 0.42–5.44 μg/mL (Table 3). Regression equation was $y=0.0385x-0.0043$, R^2 – 0.9994, LOD – 0.10 μg/mL, LOQ – 0.36 μg/mL. The robustness study was evaluated by investigating the stability of solutions (1–20 h), volume of reagents (0.9–1.1 mL), and time of reaction – 5–15 min (Table 2). These variations did not affect the results of the analysis. The results of the accuracy and precision study were within the acceptance criteria. The results of studying the «greenness» of both methods indicate an excellent «green» analysis, which is evidenced by pictograms of the AGREE and GAPI (Fig. 9, 10).

Practical Relevance. The proposed analytical methods can be used to determine ramipril in tablets.

Study limitations. The proposed spectrophotometric methods cannot be used to determine ramipril in the presence of other antihypertensive API in medicines.

Prospects for further research. The next stage of research is planned to investigate the problems in the method development of ramipril by using bromocresol green as a potential reagent.

6. Conclusions

We have developed two simple, rapid, economic, alternative spectrophotometric methods for the determination of ramipril in tablets based on the reaction with BPB and CR. We have selected simple sample preparation and quantification conditions that provide precise, rapid and «green» analysis of ramipril in tablets. The analytical methods were linear in the concentration range of 1.99–5.96 μg/mL (for BPB) and 0.42–5.44 μg/mL (for CR). In summary, two spectrophotometric methods have been developed that can be used as an alternative method for the routine analysis of ramipril tablets.

Conflict of interests

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 made available on reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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 09.01.2024
Accepted date 22.04.2024
Published date 30.04.2024

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