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Four ecofriendly spectrophotometric methods for the determination of perindopril through derivatization with sulphophtalein dyes: application to tablet analysis

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Abstract

Nowadays, there is a need to expand the bank of spectrophotometric methods for the determination of perindopril in dosage forms for the purposes of routine pharmaceutical analysis, which would be simple, express, «green» and inexpensive. In the present work, perindopril in tablets was quantified via a direct simple, «green», and non-extracting spectrophotometric approach based on the formation of ion-pair complexes with sulphophtalein dyes. The absorbances of the colored reaction products were registered at 405 nm (bromocresol green, BCG), 397 nm (bromocresol purple, BCP, and bromothymol blue, BTB) and 598 nm (bromophenol blue, BPB). To achieve the highest intensity of absorbance, optimum conditions were established by the screening of many experimental factors such as optimal concentration and volume of dyes, and the time consumed for the reaction. Beer's law was obeyed in the ranges of 0.44–3.96 µg/mL (BCG), 3.00–7.00 µg/mL (BCP), 4.00–12.00 µg/mL (BTB) and 0.44–3.52 µg/mL (BPB). All four methods were validated in accordance with ICH guidelines, confirming specificity and linearity, accuracy and precision, limits of detection and quantification, robustness. These validated methods provide a reliable and green approach for the quantitative analysis of perindopril in tablets, contributing to safer and more sustainable laboratory practices in pharmaceutical analysis.

Keywords Ionic associates, Perindopril, Spectrophotometry, Sulphophtalein dyes, Tablet

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Introduction

Perindopril tert-butylamine, chemically designated as 2-methylpropan-2-amine (2 S,3aS,7aS)-1-[(2 S)-2-[[(1 S)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1 H- indole-2-carboxylate, an inhibitor of the enzyme that converts angiotensin I to angiotensin II (ACE-converting enzyme) [1]. Perindopril is an effective drug for the treatment of hypertension and heart failure. Perindopril tert-butylamine acts through its active metabolite - perindoprilat. Perindopril tert-butylamine is officially reported in the European Pharmacopoeia (Ph. Eur.) [2].

Numerous analytical strategies for the analysis of perindopril dosage forms based on spectrophotometric [3–14] spectrofluorimetric [15–17], liquid chromatographic (LC) [14, 18–35] assays were reported. As well known, separative techniques such as HPLC (High performance liquid chromatography) consume large amounts of energy, need well-experienced chemists, and have complex and costly instrumentation (equipment, columns, filters, purified solvents). Spectrophotometry is currently an alternative to chromatographic methods for laboratories with limited funding in low-income countries. In pharmaceutical analysis, where the sample matrix is not complicated (for example, monocomponent drugs), and the concentration of the analyte is high, the development of simple, fast, cost-effective methods is promising for routine analysis. According to the last literature data, reported spectrophotometric procedures for the determination of perindopril in dosage forms for the purposes of pharmaceutical analysis associated with numerous disadvantages, such as extraction, using toxic solvents, adjustment of pH control, labor-intensive and non-ecologically safe, as indicated in Suppl. Table 1 [3–14]. Reported method [8] required using toxic «non-green» organic solvent (chloroform). The procedure described by the authors [13] was quite interesting however for the purposes of routine pharmaceutical analysis it will not be used due to the length of time and complexity. Nowadays, there is a need to expand the bank of spectrophotometric methods for the determination of perindopril in dosage forms for the purposes of routine pharmaceutical analysis, which would be simple, express, «green» and inexpensive. Related to the other analytical technique, article was laborious, time-consuming and unsuitable for routine pharmaceutical analysis [36]. Numerous bioanalytical techniques using LC-MS (Liquid chromatography mass spectrometry) were presented in the scientific literature [37–40]. However, such techniques are expensive and impractical for routine pharmaceutical analysis, but are ideal for the bioequivalence study.

The aim of this study was to develop direct, simple, eco-friendly and extraction-free spectrophotometric procedures for the determination of perindopril in tablets. These procedures can be used in routine drug quality control.

Experimental

Apparatus

Used analytical instrumentation: Shimadzu UV-1800 double beam UV-VIS spectrophotometer (Japan) with software UV-Probe ver. 2.70, analytical balance RAD WAG AS 200/C precise (Poland).

Reagents and standards

Perindopril tert-butylamine (CRS, purity ≥ 98%, HPLC) was purchased from Sigma-Aldrich Chemicals Co. (St. Louis, MO, USA). Perindopril 4 mg and 8 mg tablets were acquired from a nearby pharmacy. The purity of perindopril tert-butylamine was 99.4% [41]. All used solvents (acetonitrile, ethyl acetate, methanol, ethanol, chloroform) were produced by Honeywell and had a purity of 99.9%. Bromocresol green (BCG), bromocresol purple (BCP), bromothymol blue (BTB), bromophenol blue (BPB) were acquired from Sigma-Aldrich Chemicals Co. (USA, St. Louis). All chemicals were of analytical grade.

Preparation of dye's solution

Preparation of BCG solution

A 8.3×10^{-4} M of BCG were prepared in a 25.00 mL measuring flask by dissolving 14.50 mg of BCG in 15 mL of ethyl acetate and adjusting to the mark with the same solvent.

Preparation of BCP solution

A 2.3×10^{-4} M of BCP were prepared in a 25.00 mL measuring flask by dissolving 30.5 mg of BCP in 15 mL of ethyl acetate and adjusting to the mark with the same solvent. Aliquot 2.50 mL was transferred to a 25.00 mL measuring flask and dissolved with ethyl acetate.

Preparation of BTB solution

A 4.6×10^{-4} M of BTB were prepared in a 25.00 mL measuring flask by dissolving 36.0 mg of BTB in 15 mL of ethyl acetate and adjusting to the mark with the same solvent. Aliquot 5.00 mL was transferred to a 25.00 mL measuring flask and dissolved with ethyl acetate.

Preparation of BPB solution

A 4.3×10^{-4} M of BPB were prepared in a 50.00 mL measuring flask by dissolving 14.40 mg of BPB in 35 mL of acetonitrile and adjusting to the mark with the same solvent.

Preparation of standard solutions

Preparation of standard solutions for BCP and BTB methods

Primary standard stock solution of Perindopril was prepared by dissolving 50 mg in 35 ml of ethyl acetate, followed by dilution to a final volume in 50 ml vessels.

Preparation of standard solution of perindopril for BCP method 2.5 mL of obtained solution in Sect. "Preparation of standard solutions for BCP and BTB methods" was diluted to 25 mL using ethyl acetate to obtain a concentration of 100 µg/mL Perindopril.

Preparation of standard solution of perindopril for BTB method 5.0 mL of obtained solution in Sect. "Preparation of standard solutions for BCP and BTB methods" was diluted to 25 mL using ethyl acetate to obtain a concentration of 200 µg/mL Perindopril.

Preparation of standard solutions for BCG and BPB methods

Primary standard stock solution of Perindopril was prepared by dissolving 22 mg in 35 ml of ethyl acetate (for BCG method)/acetonitrile (for BPB method), followed by dilution to a final volume in 50 ml vessels.

Preparation of standard solution of perindopril for BCG method 2.5 mL of obtained solution in Sect. "Preparation of standard solutions for BCG and BPB methods" was diluted to 25 mL using ethyl acetate to obtain a concentration of 44 µg/mL Perindopril.

Preparation of standard solution of perindopril for BPB method 2.5 mL of obtained solution in Sect. "Preparation of standard solutions for BCG and BPB methods" was diluted to 25 mL using acetonitrile to obtain a concentration 44 µg/mL Perindopril.

Calibration curve construction

Standard stock solutions were transferred to a series of 10 mL volumetric flasks. The volume transferred varied to achieve the desired concentration ranges: (0.1–0.9 mL) for BCG, (0.3–0.7 mL) for BCP, (0.2–0.6 mL) for BTB and (0.1–0.8 mL) for BPB. These concentration ranges allowed for the concentration ranges of 0.44–3.96 µg/ml, 3.00–7.00 µg/ml, 4.00–12.00 µg/ml and 0.44–3.52 µg/ml for BCG, BCP, BTB and BPB, respectively. The solutions were analyzed by adding 1.0 mL of 8.3×10^{-4} M BCG/1.0 mL of 2.3×10^{-4} M BCP/1.0 mL of 4.6×10^{-4} M BTB/0.4 mL of 4.3×10^{-4} M BPB and making up to the mark by solvent (ethyl acetate for BCG, BCP, BTB/acetonitrile for BPB). The absorbance of the resulting mixture was recorded at 405 nm for BCG, 397 nm for BCP, BTB and 598 nm for BPB against a reference solutions prepared in the same way without adding the analyte.

Application to tablet analysis

Twenty tablets of perindopril were thoroughly crushed and weighed. Sample preparation was carried out as described in Sect. "Preparation of Standard solutions" with filtration using a Whatman No. 42 filtering paper.

Results and discussion

Methodology for choosing of reagents and reactions

Sulphophtalein dyes are widely used in pharmaceutical analysis for the spectrophotometric determination of nitrogen-containing compounds [42]. The advantages of such chemical reactions are their ease of execution, not time-consuming, ecofriendly, provided that modern approaches are used, taking into consideration the principles of «green» chemistry. Sakur and Balid [8] described the usage of BCG as a reagent for the spectrophotometric determination of perindopril at an analytical wavelength of 414 nm however this technique required the usage of chloroform and did not comply with the principles of modern «green» chemistry. We performed screening experiments to study sulphophtalein dyes as potential reagents for the further method development for the determination of perindopril in dosage forms and selected BCG, BCP, BTB, BPB. Proposed reaction scheme on example of BPB with perindopril tert-butylamine is presented in Fig. 1. Absorbance spectra of reaction product of perindopril (5.1×10^{-6} M) - BCG (8.3×10^{-5} M in ethyl acetate), perindopril (1.1×10^{-5} M) - BCP (2.3×10^{-5} M in in ethyl acetate), perindopril (1.8×10^{-5} M) - BTB (4.6×10^{-5} M in ethyl acetate), perindopril (4.0×10^{-6} M) - BPB (1.7×10^{-5} M in acetonitrile) are shown in Fig. 2. The reaction of BPB with perindopril in the medium of acetonitrile led to the strengthening of the blue color of the solution and the redistribution of band intensities of single- and double-charged forms of the dye. The intensity of the band of the monoanionic form of BPB at 400 nm decreased, and the intensity of the dianionic form at 598 nm increased when perindopril was added. A more stable ionic bond was formed precisely with the dianionic form of the dye. That is, the formation of ionic associates led to the displacement of one of the protons of the phenolic groups in BPB. When using other sulphophtalein dyes (BCG, BCP, BTB) in ethyl acetate, a band of the singly ionized form was observed in the range 397–405 nm with high intensity. Therefore, 598 nm was chose as an analytical wavelength with BPB in acetonitrile, 405 nm – with BCG in ethyl acetate and 397 nm - BCP and BTB in ethyl acetate.

Optimum reaction conditions

Selection of organic solvent

The nature of the organic solvent in this type of reaction of the formation of ionic associates is one of the most important factors. The choice of solvent was determined

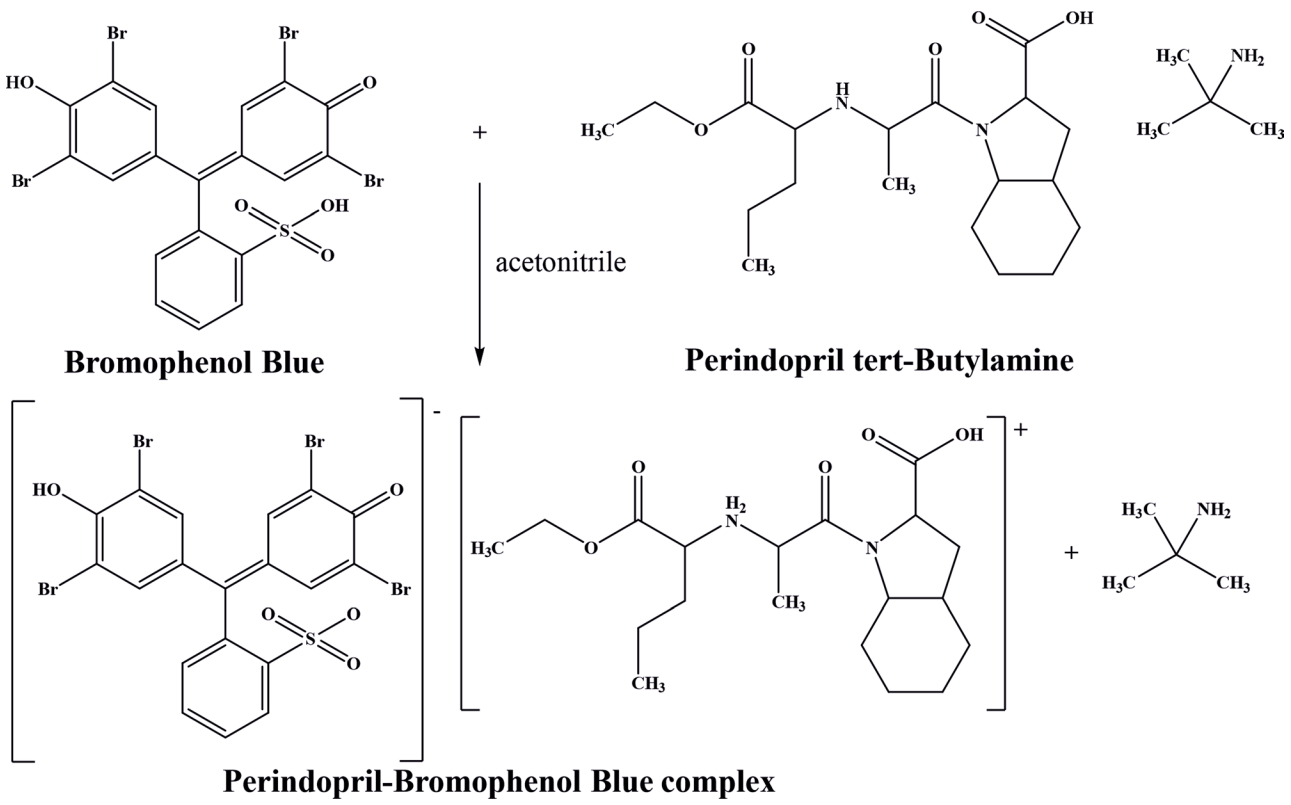

Fig. 1 Proposed reaction scheme of perindopril tert-butylamine with BPB

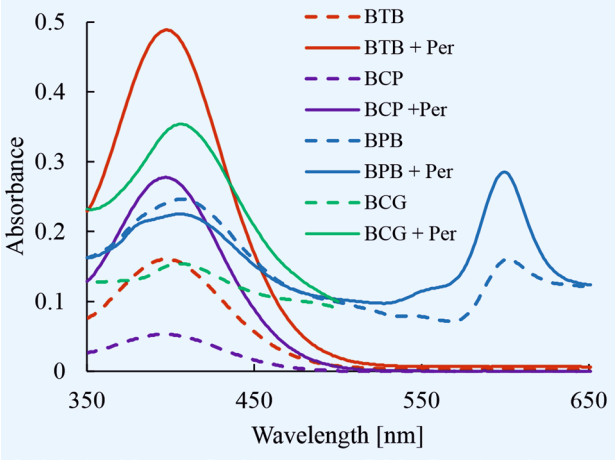

Fig. 2 Absorbance spectra of perindopril (5.1×10^{-6} M) - BCG (8.3×10^{-5} M in ethyl acetate), perindopril (1.1×10^{-5} M) - BCP (2.3×10^{-5} M in in ethyl acetate), perindopril (1.8×10^{-5} M) - BTB (4.6×10^{-5} M in ethyl acetate), perindopril (4.0×10^{-6} M) - BPB (1.7×10^{-5} M in acetonitrile) complexes against the appropriate reagent blanks

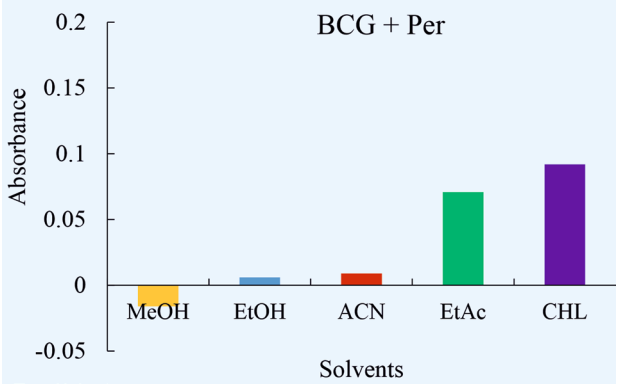

Fig. 3 Solvents impact on the generation of perindopril-BCG complex ($C_{M\ BCG}=1.49\times10^{-5}$ M)

by the solubility of analyte. We tested the most commonly used solvents. Their use is the most beneficial, as they allow to achieve the highest sensitivity. As already mentioned earlier, the authors Sakur and Balid [8] used chloroform, which was a toxic solvent. Toxic solvents were not taken into consideration during our research. Effects of solvents on the formation of perindopril-BCG (Fig. 3), perindopril-BCP (Fig. 4), perindopril-BTB (Fig. 5), perindopril-BPB (Fig. 6) complexes are presented on Figs. 3, 4, 5 and 6. The optimal solvent was ethyl acetate for three dyes (BCG, BCP, BTB), while in the case of the formation of perindopril-BPB complex (Fig. 6) was acetonitrile. In recent decades, new analytical methods based on the formation of ionic associates have been appeared without an extraction stage. In fact, our four methods also offer approaches without extraction, which significantly increases the ecofriendly of the proposed methods.

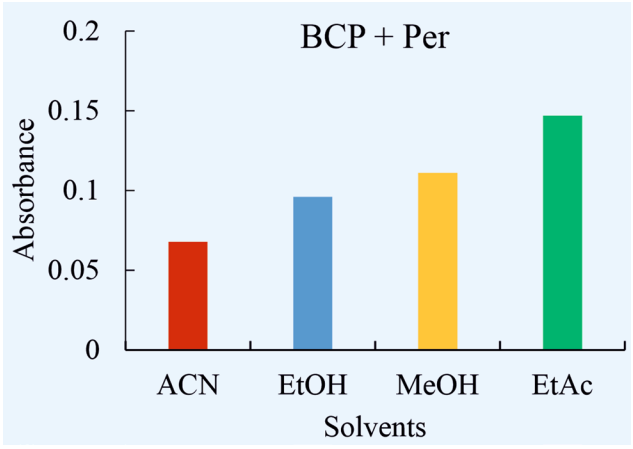

Fig. 4 Solvents impact on the generation of perindopril-BCP complex ($C_{M\ BCP}$=2.26×10^{-5} M)

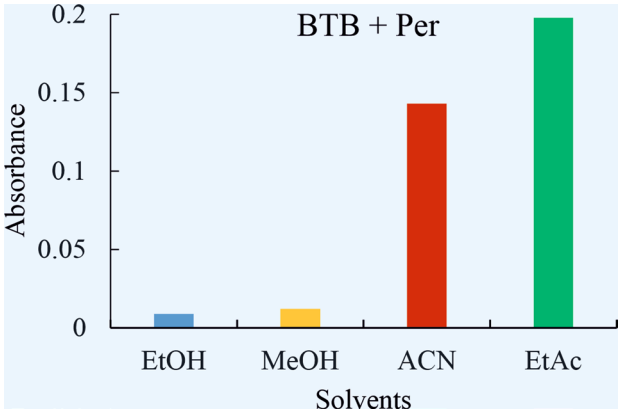

Fig. 5 Solvents impact on the generation of perindopril-BTB complex ($C_{M\ BTB}$=4.61×10^{-5} M)

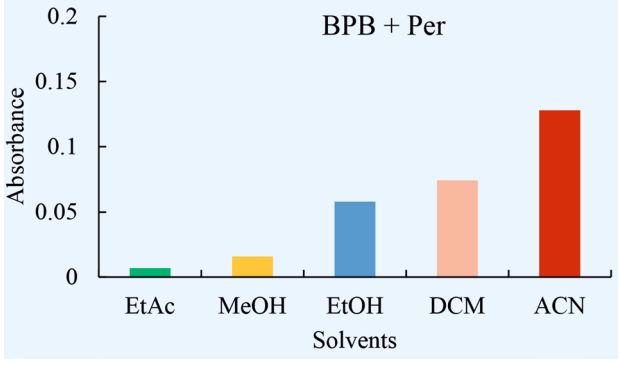

Fig. 6 Solvents impact on the generation of perindopril-BPB complex ($C_{M\ BPB}$=4.61×10^{-5} M)

Influence of dye concentration and volume

The difficulty in working with sulphophtalein dyes during the method development is frequent non-linearity in validation of analytical method. In order to solve this problem, sulphophtalein dyes should be given in excess. During the conducted research, the optimal concentrations of sulphophtalein dyes were experimentally established which corresponded to 1 mL of 8.3×10^{-4} M BCG, 1 mL of 2.3×10^{-4} M BCP, 1 mL of 4.6×10^{-4} M BTB and 0.4 mL of 4.3×10^{-4} M BPB.

Influence of reaction time

The reaction between perindopril and sulphophtalein dye takes place instantaneously at room temperature, which was typical for reactions of the formation of ionic associates. The analytical form, which was formed in the reaction between perindopril and the dye, was stable for a long time (not less than 6 h). This allows, together with other factors that affect reproducibility, to achieve a relative error of 1.0%.

Composition of perindopril: dye complexes by job's method

Job's method is a more accurate method for the determination of stoichiometry than the saturation method. However Job's method mainly limited to situations where the solution is dominated by an ionic associate of one specific composition. In Job's method we combined 1.00×10^{-4} M solutions of BCG and 1.00×10^{-4} M perindopril, 2.26×10^{-4} M solutions of BCP and 2.26×10^{-4} M perindopril, 5.00×10^{-4} M solutions of BTB and 5.00×10^{-4} M perindopril, 5.00×10^{-4} M solutions of BPB and 5.00×10^{-4} M perindopril. Total volume of each mixture was the same. The presented results of the reacting components' stoichiometric ratios using Job's method are shown in Fig. 7. The stoichiometric coefficients of the reaction mixture components between perindopril and dye (BCG, BCP, BTB, BPB) were equal to 1:1.

Molar absorptivity of method BCG was 8.82×10^{4} L mole^{-1} cm^{-1}, method BCP −4.41×10^{5} L mole^{-1} cm^{-1}, method BTB −5.55×10^{5} L mole^{-1} cm^{-1}, method BPB −11.86×10^{4} L mole^{-1} cm^{-1}. It should also be noted that the high sensitivity of the methods allows the use of minimal amounts of dosage forms and reagents, which is excellent for routine quality control procedures, to reduce the volumes of organic solvents, not to use toxic

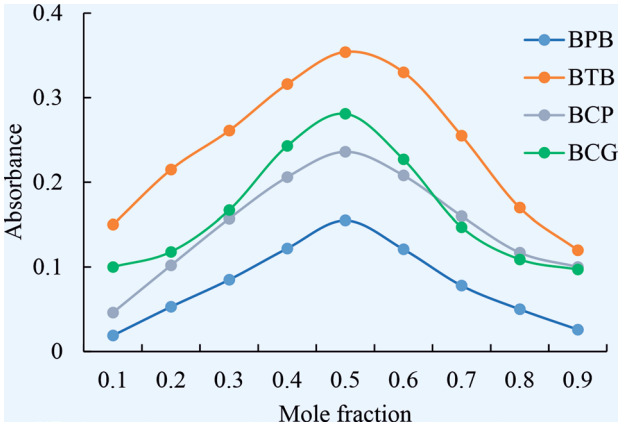

Fig. 7 Mole fraction [Per]/[Per]+[dye]

Table 1 Analytical parameters for the spectrophotometric determination of perindopril through derivatization with sulphophtalein dyes

Analytical parameters	BCG	BCP	BTB	BPB
λ_{max}, nm	405	397	397	598
Linearity range, µg/mL	0.44–3.96	3.00–7.00	4.00–12.00	0.44–3.52
Intercept (*a*)	0.0431	0.0043	0.0348	0.0205
Slope (*b*)	0.1034	0.0479	0.0413	0.2229
Correlation coefficient (*r*)	0.9997	0.9997	0.9990	0.9996
S.D. of slope (*Sb*)	0.0007	0.0005	0.0007	0.0018
S.D. of intercept (*Sa*)	0.0017	0.0025	0.0063	0.0040
LOD, µg/mL	0.0543	0.1722	0.5034	0.0592
LOQ, µg/mL	0.1644	0.5219	1.5254	0.1795
Molar absorptivity, l. mol^{-1}. cm^{-1}	8.82×10^4	4.41×10^5	5.55×10^5	11.86×10^4
Ringbom optimum concentration range, µg/mL	1.77–3.09	5.00–7.00	6.00–8.00	1.32–2.65

solvents, to carry out non-extractive determinations, not to adjust the pH value. Reactions were carried out in volumetric flasks of 10.00 mL, which also significantly reduces wastes and increases the ecofriendly of the methods when calculating the pictograms of «greenness».

Validation study

Proposed spectrophotometric methods have been validated to meet the requirements specified by the International Conference on Harmonization (ICH) [43].

Specificity and linearity

In order to study the specificity of spectrophotometric techniques, a solutions of excipients ("placebo") were prepared. The results of the study of the specificity of analytical methods indicated that the absorbance of excipients ("placebo") was insignificant and did not exceed the acceptance criterion (not more than 0.5%).

The study of linearity when carrying out spectrophotometric methods based on reactions with sulfophthalein dyes is not a simple task, since such methods are often not linear, which is due to different tautomeric forms in solutions. It is important to choose the correct concentrations, as well as to set a narrow range. The study of the linearity of analytical methods was carried out by regression analysis using the method of least squares.

The absorbance and concentration of perindopril were shown in the following ranges: 0.44–3.96 µg/mL (method BCG), 3.00–7.00 µg/mL (method BCP), 4.00–12.00 µg/mL (method BTB) and 0.44–3.52 µg/mL (method BPB). The regression parameters are displayed in Table 1. Out of the four suggested approaches, the BCG and BPB methods are the most, sensitive, as seen by the low LOD (limit of detection) (0.0534 µg/mL and 0.0592 µg/mL) and LOQ (limit of quantification) (0.1644 µg/mL and 0.1795 µg/mL) values. According to the published work [8], LOD was 0.125 µg/mL. It gives advantages to our methods. The linearity parameters satisfied the criteria established by ICH.

Accuracy and precision

The intra-day and inter-day precision and accuracy results from the four proposed methods are summarized in Table 2. The intra-day and inter-day RSD values were determined to be less than 1.5% and RE% was less than 3%. The obtained results of high recovery, along with low error values, showed high precision for four proposed methods for the determination of perindopril. The precision and accuracy parameters satisfied the criteria established by ICH.

Robustness

The robustness of the proposed analytical methods was examined. These variables included the volume of reagent (BCG, BCP, BTB, BPB) as well as reaction times, each adjusted by 10% from their optimal values. The used concentrations of the drug were 2.21 µg/mL (BCG), 5.00 µg/mL (BCP), 8.00 µg/mL BTB, 1.77 µg/mL BPB to study robustness. Robustness results for the determination of perindopril by the proposed methods are summarized in Table 3. It was observed that these adjustments had no significant effect on the methods' efficacy. The recovery values fell within the range of 98.39–101.78%, RSD values ranging from 0.67 to 1.93%. Although the solutions were stable over time, we recommend that the absorbance be determined instantaneously. These findings validate the suitability of the four proposed methods for the routine pharmaceutical analysis of perindopril.

Application to tablet analysis

The suitability of the proposed four analytical methods for the purpose of the routine quantification of

Table 2 Assessment of the methods' intra-day and inter-day accuracy and precision

Method	Concentration, µg/mL	Intra-day accuracy and precision ($n=7$)			Inter-day accuracy and precision ($n=7$)		
		Recovery, %	%RSD	%RE	Recovery, %	%RSD	%RE
BCG	0.44	100.08	1.25	2.87	98.94	1.07	2.76
	2.21	101.05	0.67	1.05	99.38	1.42	1.84
	3.97	99.83	1.36	1.94	101.94	0.87	1.90
BCP	3.00	99.19	0.78	1.78	100.06	0.92	1.37
	5.00	100.27	1.21	1.03	99.08	1.38	1.99
	7.00	99.84	0.92	1.53	101.84	1.31	1.53
BTB	4.00	99.92	0.94	1.93	99.93	0.75	2.53
	8.00	98.76	0.88	1.05	101.26	1.09	2.42
	12.00	100.67	1.38	1.85	99.60	1.44	1.63
BPB	0.44	101.84	0.55	2.36	100.56	1.42	1.50
	2.21	99.80	1.07	1.56	100.45	1.05	1.11
	3.53	100.53	1.46	1.84	99.40	1.24	1.38

RSD - Relative standard deviation; RE - Relative error

Table 3 Robustness for the determination of perindopril by the proposed methods

Method	Method parameters			
	Volume of reagent, mL	%Recovery*±SD	Time of reaction, min	%Recovery*±SD
BCG	0.9	101.78 ± 0.88	0	98.56 ± 1.38
	1.0	100.34 ± 1.43	5	100.09 ± 0.89
	1.1	100.67 ± 0.95	15	100.56 ± 1.42
BCP	0.9	101.91 ± 0.67	0	99.73 ± 1.28
	1.0	100.56 ± 1.56	5	101.35 ± 1.82
	1.1	100.81 ± 0.82	15	99.56 ± 0.91
BTB	0.9	99.21 ± 1.72	0	98.39 ± 1.70
	1.0	101.08 ± 1.42	5	100.56 ± 0.68
	1.1	99.07 ± 1.84	15	101.45 ± 1.89
BPB	0.3	99.28 ± 0.93	0	100.42 ± 1.93
	0.4	100.34 ± 1.27	5	100.63 ± 1.20
	0.5	98.73 ± 1.76	15	99.81 ± 0.97

* Average of 3 determinations

Table 4 Application of the proposed methods to tablet analysis

Method	Concentration level, µg/mL	Recovery %±SD[a] Dosage form (tablets) 1	Recovery %±SD[a] Dosage form (tablets) 2
BCG	0.44	98.94 ± 1.63	100.10 ± 1.42
	2.21	100.06 ± 1.28	101.27 ± 1.93
	3.97	99.11 ± 1.36	99.83 ± 1.62
		Mean 99.37 ± 1.42	100.40 ± 1.66
BCP	3.00	100.72 ± 0.59	99.05 ± 1.69
	5.00	101.62 ± 1.28	101.37 ± 0.67
	7.00	101.08 ± 1.82	100.02 ± 1.85
		Mean 101.14 ± 1.23	100.14 ± 1.40
BTB	4.00	98.20 ± 1.83	98.37 ± 1.11
	8.00	100.93 ± 1.30	100.56 ± 0.97
	12.00	101.39 ± 1.08	101.83 ± 1.78
		Mean 100.17 ± 1.40	100.25 ± 1.29
BPB	0.44	100.45 ± 0.78	98.58 ± 1.98
	2.21	101.62 ± 1.20	101.57 ± 1.09
	3.53	98.74 ± 1.52	100.34 ± 1.60
		Mean 100.27 ± 1.17	100.16 ± 1.56

[a] Average of 3 determinations

perindopril was evaluated on tablets from two different manufacturers at three concentration levels, as described in Table 4. The findings revealed label claim percentages with mean values of 99.37 ± 1.42% (Method BCG), 101.14 ± 1.23% (Method BCP), 100.17 ± 1.40% (Method BTB) and 100.27 ± 1.17% (Method BPB) for dosage form 1, and 99.67 ± 1.66% (Method BCG), 100.14 ± 1.40% (Method BCP), 100.25 ± 1.29% (Method BTB) and 100.16 ± 1.56% (Method BPB) for dosage form 2. The obtained results of the quantitative determination of perindopril from two different manufacturers demonstrate the excellent accuracy of the analysis performed by the proposed four methods and the suitability of these methods for the purposes of routine quantitative determination.

Greenness levels of the proposed spectrophotometric methods

In accordance with modern approaches in the development of analytical methods for the determination of APIs in dosage forms for the purposes of routine

Table 5 Analytical Eco-scale for the determination the «greenness» of the recommended spectrophotometric procedures for the assay of perindopril through derivatization with sulphophtalein dyes

Eco-scale score parameters	Penalty points (PPs)			
	Method BCG	Method BCP	Method BTB	Method BPB
Amount of solvent/reagent Solvent:	10–100 mL (mL (g) per sample) (2)	10–100 mL (mL (g) per sample) (2)	10–100 mL (mL (g) per sample) (2)	10–100 mL (mL (g) per sample) (2)
Reagent:	Reagent: <1 mL (mL (g) per sample) (1)	Reagent: <1 mL (mL (g) per sample) (1)	Reagent: <1 mL (mL (g) per sample) (1)	Reagent: <1 mL (mL (g) per sample) (1)
Hazard of solvent/reagent				
Solvent:	3	3	3	3
Reagent:	3	3	3	3
Instrument: energy used (0.1 kWh per sample)	0	0	0	0
Occupational hazards				
Analytical process is hermetic	0	0	0	0
Emission of vapors and gases to the air	0	0	0	0
Waste				
Production	(> 10 mL (g) per sample) (5)	(> 10 mL (g) per sample) (5)	(> 10 mL (g) per sample) (5)	(> 10 mL (g) per sample) (5)
Treatment (no treatment involved)	3	3	3	3
Total PPs	17	17	17	17
Eco-Scale score	83	83	83	83

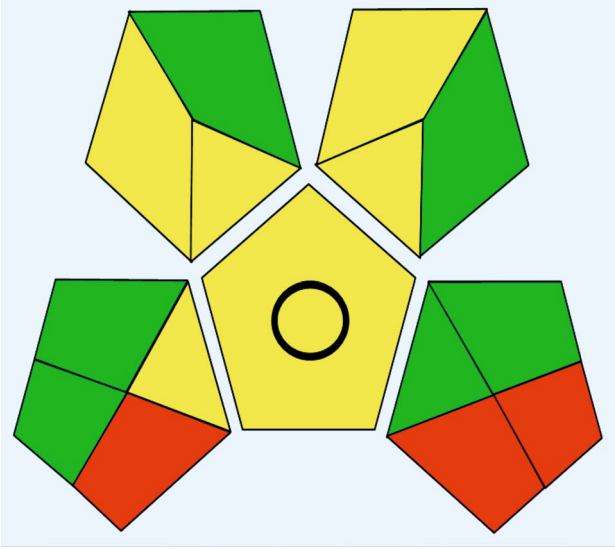

Fig. 8 GAPI pictogram for the determination of the «greenness» of the analyzed procedures

pharmaceutical analysis, «green» chemistry approaches should be taken into consideration and applied, which involves minimising the wastes of solvents and analytes, avoiding extraction (it is especially important in the development of methods for reactions with sulphophtalein dyes). To calculate the «greenness» of analytical techniques, three metric tools of the «greenness» were used (Analytical Eco-Scale (AES) [44], Green Analytical Procedure Index (GAPI) [45], Analytical Greenness Metric Approach (AGREE) [46]). The first calculation method was AES, which is presented in Table 5. The general penalty points (PP) for each method's was 17, and the analyses' corresponding environmental scale scores were 83 (100–17). This high score demonstrated the suggested approaches' excellent result of greenness in compliance with metric requirements. The high score of «greenness» by metric tool AES demonstrated excellent «green» analysis, which was a significant achievement for the spectrophotometric techniques based on the reactions with sulphophtalein dyes, which often required the extraction and usage of toxic solvents. The obtained pictogram using the GAPI tool is shown in Fig. 8. Three of the fifteen parameters (2, 14 and 15) were colored in red color on the pictogram. Other parameters that complied with guidelines and the «green» processes' requirements were colored green and yellow. The obtained pictogram using the AGREE tool is shown in Fig. 9. Pictograms are identical due to similar conditions of sample preparation and usage of ethyl acetate (BCG, BCP, BTB) and acetonitrile (BPB) as a solvents in all four techniques. The obtained AGREE score was quite high (0.75). None of the operations were red and were not critical. Comparison of the three «greenness» tools outputs attested to the suggested four spectrophotometric methods' greenness and adherence to the «green» chemistry principles.

Matching the analyzed methods' greenness levels with the reported methods

The «greenness» of the proposed spectrophotometric methods were compared with the greenness» of existing spectrophotometric method [8]. AGREE tool was utilized for conducting comparisons, and Fig. 10 shows the pictograms prepared for the described method using these approach. The AGREE tool gave a score of 0.57 for

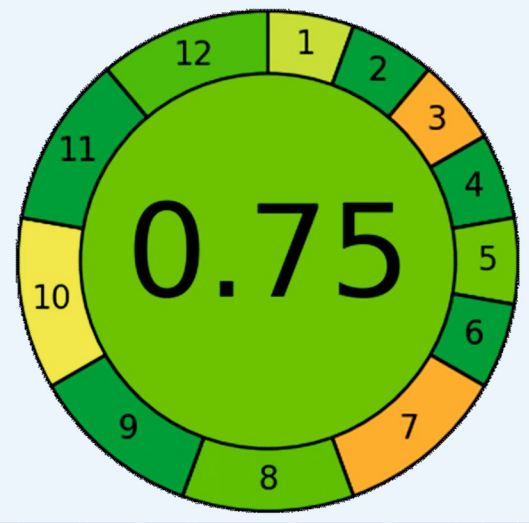

Fig. 9 AGREE pictogram for the determination of the «greenness» of the analyzed procedures

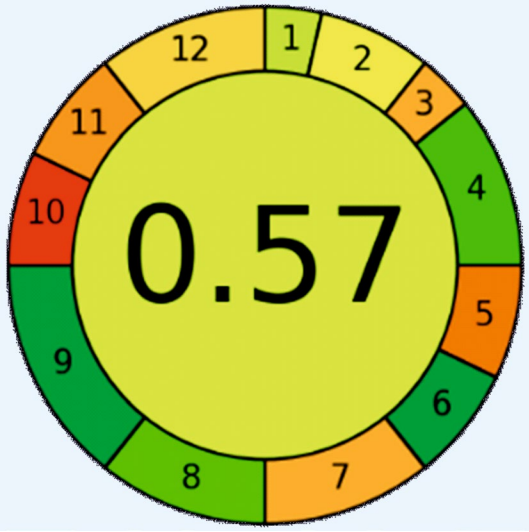

Fig. 10 Comparison of the reported methods' «greenness» according to the AGREE metric tool [8]

the method [8], which is unsatisfactory due to the use of chloroform. One of our proposed method required also usage a BCG however in ethyl acetate medium ([8] - in chloroform medium), range of application of our method BCG was 0.44–3.97 μg/mL ([8] – 2–20 μg/mL), molar absorptivity of our method BCG was 8.82×10^4 l. mol-^{1}. cm^{-1} ([8] – 4.41×10^4 l. mol-^{1}. cm^{-1}). Summing up, we can note a significant advantage of the proposed method BCG in comparison with method [8] in «greenness» and sensitivity. The developed methods using four sulphophtalein dyes significantly expand the bank of spectrophotometric techniques and can be an alternative to HPLC techniques.

Conclusion

Perindopril in tablets was quantified by employing a simple, express, «green», sensitive, and economical spectrophotometric approach by reactions with sulphophtalein dyes (BCG, BCP, BTB, BPB). The produced complexes were soluble in ethyl acetate for three dyes (BCG, BCP, BTB) and acetonitrile for BPB and it was making the methodology safer for the environment. Furthermore, the suggested approach was more efficient in terms of time reliability, sensitivity and «greenness» than other reported spectrophotometric methods. The described approach can be easily implemented for the routine assay of the perindopril instead of the previously published techniques in quality control laboratories. The carried out studies expand the bank of spectrophotometric methods.

Abbreviations

LC	Liquid chromatography
HPLC	High performance liquid chromatography
Ph. Eur.	European Pharmacopoeia
BCG	Bromocresol green
BCP	Bromocresol purple
BTB	Bromothymol blue
BPB	Bromophenol blue
AES	Analytical Eco-Scale
GAPI	Green Analytical Procedure Index
AGREE	Analytical Greenness Metric Approach

Supplementary Information

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Supplementary Material 1

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Author contributions

Liudmyla Halka (L.H): Methodology and writing the original draft, Validation and reviewing Tetyana Kucher (T.K.), Marjan Piponski (M.P.), Liubomyr Kryskiw (L.K.), Nadiya Zarivna (N.Z.), Mariana Horyn (M.H.), Nataliia Horlachuk (N.H.), Khrystyna Duve (K.D.), Liliya Logoyda (L.L.): Validation and reviewing, Liliya Logoyda (L.L.): reviewing and publishing editing and supervision.

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Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

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