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"NASAL PREPARATIONS"

Drug Formulations

Green Easily Implemented Spectrophotometric Methods for Concurrent Determination of Ephedrine Hydrochloride and Naphazoline Nitrate in Nasal Preparations Containing Methylparaben

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Abstract

Background: Spectrophotometric resolution of a mixture of several drugs is considered a cheaper, simpler, and more versatile alternative compared to costly chromatographic instruments.

Objective: The work aims to resolve the interfering spectra of ephedrine hydrochloride, naphazoline nitrate, and methylparaben in nasal preparations using smart spectrophotometric methods.

Method: In our work, derivative and dual-wavelength methods were combined to eliminate this interference, under the name of derivative dual-wavelength method. Other methods, namely successive derivative subtraction and chemometric analysis, were also able to eliminate this interference. The methods have proven their applicability as they follow the International Conference on Harmonization (ICH) requirements regarding repeatability, precision, accuracy, selectivity, and linearity. Eco-scale, GAPI, and AGREE tools were used to estimate the possible environmental effects of the methods.

Results: Acceptable results for repeatability, precision, accuracy, selectivity, and linearity were obtained. Limit of detection (LOD) values were 2.2 for ephedrine and 0.3 for naphazoline. The correlation coefficients were above 0.999. The methods were proven to be safe for application.

Conclusions: The introduced methods are cheap and easily implemented compared to chromatographic techniques. They can be used in purity-checking of raw material and estimation of concentrations in market formulations. The replacement of the published chromatographic techniques with our developed methods is useful when needing to save money, effort, and time.

Highlights: The three components of a decongestant nasal preparation were determined using cheap, green, and versatile spectrophotometric methods that keep the advantages of chromatographic techniques, including accuracy, reproducibility, and selectivity.

Selective determination of drugs in the presence of other interferents is very important. Spectrophotometric estimation of drug mixtures is characterized by simplicity and the saving of cost and effort while maintaining the accuracy and reproducibility of chromatographic methods. It can eliminate the interference caused by other co-formulated drugs and excipients using a cheap, reliable, and easy-to-use instrument (1,2).

Ephedrine hydrochloride (EPH; Figure 1) is a sympathomimetic amine. It is an alpha- and beta-adrenergic receptor agonist and is used as a nasal decongestant as it causes constriction of the dilated blood vessels and tissues (3).

Naphazoline hydrochloride (NAP; Figure 1) is one of the alpha receptor agonists of the vascular smooth muscle, and it causes vasoconstriction to ocular or nasal arterioles and reduces secretion and mucosal swelling (3).

EPH and NAP are co-formulated to reduce nasal congestion caused by sinus inflammation, common cold, or viral infections of nose and throat.

Methylparaben (MET; Figure 1) is a bactericidal and fungicidal preservative (3).

EPH and NAP were both individually determined by HPLC (4–8), TLC densitometry (9,10), GC (11,12), and spectrophotometry (13–16).

The two drugs were determined together by chromatographic methods either in the absence of MET (17) or in its presence (18,19). Our new methods outperform the published ones in terms of greenness, simplicity, and cost-cutting. Moreover, they can eliminate the interference of MET, which exists as a preservative in the pharmaceutical preparation. Therefore, they can be considered useful alternatives to the reported chromatographic methods when the costly GC and HPLC instruments are not

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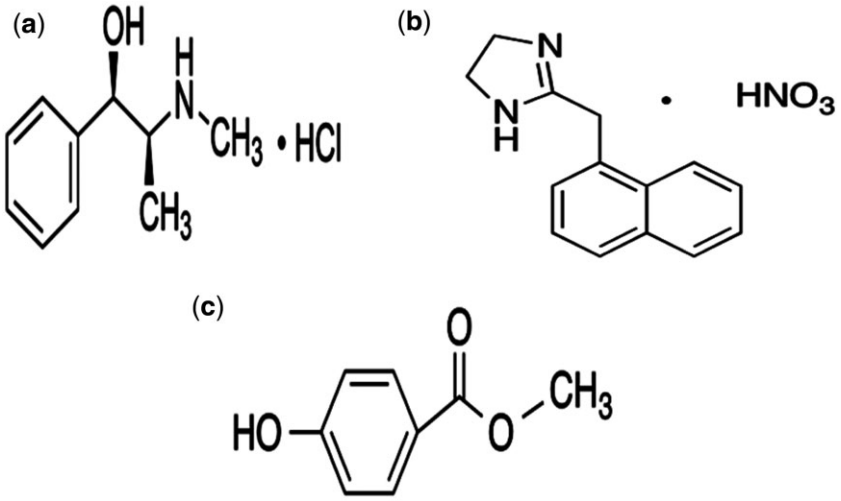

Figure 1. Chemical structures of EPH (1a), NAP (1 b), and MET (1c).

available. The first introduced method applies the dual-wavelength method (20) on ternary mixtures, not only binary ones, using very simple steps, while the other two used simple and convenient spectra manipulation. All the introduced methods have met International Conference on Harmonization (ICH) requirements (21).

Experimental

Instruments

A double-beam UV-visible spectrophotometer (model UV-1601 PC, Shimadzu, Japan) was used, with a 1 cm path length quartz cell, 2800 nm/min scanning speed, and 2 nm spectral bandwidth, connected to an IBM-compatible computer. Chemometric analysis was done using MATLAB®, version 6.5.

Materials

(a) *Pure standards.*—Chemical Industries Development (CID) Company and Global Napi pharmaceuticals company, Egypt, were the suppliers of EPH, NAP, and MET with purities of 99.9, 99.4 and 100.7%, respectively.

(b) *Pharmaceutical formulation.*—Deltarhino® nasal spray, batch no. 1321016, containing 5 mg of EPH, 1.25 mg of NAP, and 2 mg MET per 1 mL, is produced by Global Napi pharmaceuticals company.

(c) *Chemicals.*—HPLC grade ethanol was bought from Sigma-Aldrich Chemie Gmbh, Germany.

(d) *Standard solutions.*—EPH, NAP, and MET stock solutions (1000 μg/mL) were prepared in ethanol. EPH, NAP, and MET working solutions (100 μg/mL) were prepared from stock solution by dilution in ethanol.

(e) *Synthetic mixtures.*—EPH, NAP, and MET were prepared in various ratios (including the ratio of the marketed formulation) using their working solutions.

Procedures

Spectral Characteristics of EPH, NAP, and MET

The spectra of 8 μg/mL of EPH and 2 μg/mL each of NAP and MET, respectively, were scanned using ethanol as a blank in the UV range 200–400 nm, as shown in Figure 2.

Construction of Calibration Curves

Concentration ranges of 7–27, 1–10, and 1–3 μg/mL of EPH, NAP, and MET, respectively, were prepared in ethanol and scanned at 200–400 nm.

(a) *For the derivative dual-wavelength method.*—The second derivative (D^2) of NAP spectra was obtained using $\Delta\lambda = 4$ and scaling factor = 100. A curve relating the peak amplitudes at 284.4 nm to the concentrations was constructed (cal.1). Another curve relating the peak amplitudes of NAP at 284.4 nm (λ_a) to the absorption difference (D) of NAP zero-order spectra at 215.4 and 263.4 nm (λ_b-λ_c) (cal.2) was obtained. For the determination of EPH, a curve relating the difference in absorbance of zero-order spectra of EPH (E) at 215.4 and 263.4 nm (λ_b - λ_c) to its concentrations was constructed (cal.3).

(b) *For successive derivative subtraction.*—The first derivative of EPH and NAP spectra was obtained using $\Delta\lambda = 2$ and a scaling factor = 10. Two curves relating the peak amplitudes at 270.2 nm for EPH and 224.8 nm for NAP to their concentrations were constructed.

Models Construction for Chemometric Analysis

A five-level, three-factor calibration design was used. Twenty-five samples containing various ratios of EPH, NAP, and MET in the range of 4–12, 1–5, and 1–3 μg/mL, respectively (Table 1), were prepared in ethanol to build the calibration model. The spectra, each 1 nm, for these samples were collected from 215 to 250 nm, and then were transferred to MATLAB for data treatment. Eight different mixtures of EPH, NAP, and MET were prepared as the validation set as shown in Table 2, where the calibration model was allowed to estimate the concentrations of the three drugs in this validation set.

Application to Laboratory-Prepared Mixtures

(a) *Derivative dual-wavelength method.*—The spectra of synthetic mixtures were obtained in the UV range, and then the concentrations of EPH and NAP in each mixture were determined as follows: the second derivative spectra of the mixtures were obtained, from which the concentration of NAP could be determined at 284.4 nm (λ_a) using (cal.1). For the determination of EPH, the difference in absorbance at

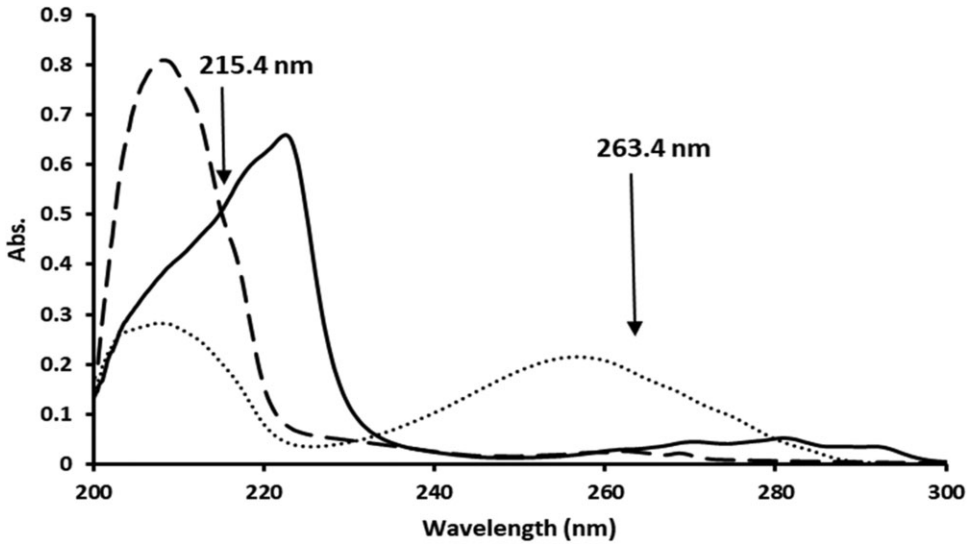

Figure 2. Zero-order absorption spectra of 8 μg/mL of EPH (- - -), 2 μg/mL of NAP (-), and 2 μg/mL of MET (….) using ethanol as a blank.

Table 1. The concentration of mixtures of EPH, NAP, and MET used in the training and validation sets

Mixture no.	EPH, μg/mL	NAP, μg/mL	MB, μg/mL
1	8	3	2
2	6	1	1.5
3	4	2	2
4[a]	6	3	1
5	8	1	1
6	4	1	3
7	4	5	1.5
8[a]	12	2	3
9	6	5	2
10[a]	12	3	1.5
11	8	4	1.5
12	6	4	2.5
13	6	4	3
14[a]	10	5	2.5
15	12	4	2
16	10	3	3
17[a]	8	5	3
18	12	5	1
19	12	1	2.5
20[a]	4	4	1
21[a]	10	1	2
22	4	3	2.5
23	8	4	2.5
24[a]	10	4	1.5
25	10	2	1

[a] Mixture ratios used in preparation of the validation set.

215.4 and 263.4 nm of the zero-order spectra of the mixture corresponding to the concentration of NAP (D) in the mixture was determined from (cal.2), and then E could be determined from the relation E =A (mix) - D, where A (mix) is the difference in absorbance at 215.4 and 263.4 nm of the zero-order spectra of the mixture. The concentration of EPH was obtained from (cal.3).

(b) *Successive derivative subtraction method*.—The first derivative spectra of the mixtures at $\Delta\lambda = 2$ and a scaling factor = 10 were obtained, divided by the first derivative spectrum of 6 μg/mL of NAP, and then the resulting spectra were subtracted from the value of the constant at 298–303 nm. For NAP estimation, the constant values at (298–303 nm) were multiplied by the first derivative spectrum of 6 μg/mL of NAP (the divisor), where NAP could be determined at 224.8 nm using the equation of the constructed curve. For determination of EPH, after subtraction of the constant value at 298–303 nm, the obtained spectra were multiplied by the first derivative spectrum of 6 μg/mL of NAP, and then were divided by 6 μg/mL of the first derivative spectrum of MET, followed by subtraction of the constant value at 281.4–288 nm and then multiplication by 6 μg/mL of MET. The resulting spectra were used to determine EPH at 270.2 nm using the equation of the constructed curve.

Application to the Pharmaceutical Formulation

A volume of 2 mL of the nasal spray was transferred into 100 mL volumetric flasks and was adjusted with ethanol to prepare a working solution of 100 μg/mL of EPH and 25 μg/mL of NAP. Suitable concentrations were prepared from this solution and were analyzed as under Sections 3.4, for derivative dual-wavelength and successive derivative subtraction methods, and Section 3.3, for chemometric methods.

Results and Discussion

This work introduces simpler, cheaper, and more versatile alternatives to the published chromatographic methods for the determination of a drug mixture consisting of EPH, NAP, and MET used for the relief of nasal congestion. The spectra of the three components overlap severely (Figure 2); therefore, smart methods for resolving this overlap should be applied. Many convenient methods were tried to resolve the spectra of this mixture, including derivative, derivative ratio, mean centering of spectra, and ratio difference, but they were useless. In this work, a simple and accurate method, namely the derivative dual-wavelength method, was developed for the analysis of NAP and EPH in their ternary mixture with MET, in addition to the convenient, successive derivative subtraction, principal components regression (PCR), and partial least squares (PLS) methods.

Method Development

(a) *For the derivative dual-wavelength method*.—NAP can be determined in a mixture with EPH and MET by obtaining its D^2 spectra using $\Delta\lambda = 4$ and scaling factor = 100 at

Table 2. Regression equations and correlation coefficient

Component	Method	Regression equation[a]	Correlation coefficient
EPH	Derivative dual-wavelength	Ya = 0.0570 X – 0.0018	0.9997
	Successive derivative subtraction	Yb = 0.0051 X – 0.0031	0.9999
NAP	Derivative dual-wavelength	Yc = 0.0051 X – 0.0031	0.9995
		Yc = 0.1732 dif – 0.0002	0.9997
	Successive derivative subtraction	Yd = 0.0324 X – 0.0051	0.9999

[a] Ya and dif are the difference in absorbance at the two selected wavelengths; Yb, Yc, Yd are the peak amplitudes at the specified wavelengths; and X is the concentration in μg/mL.

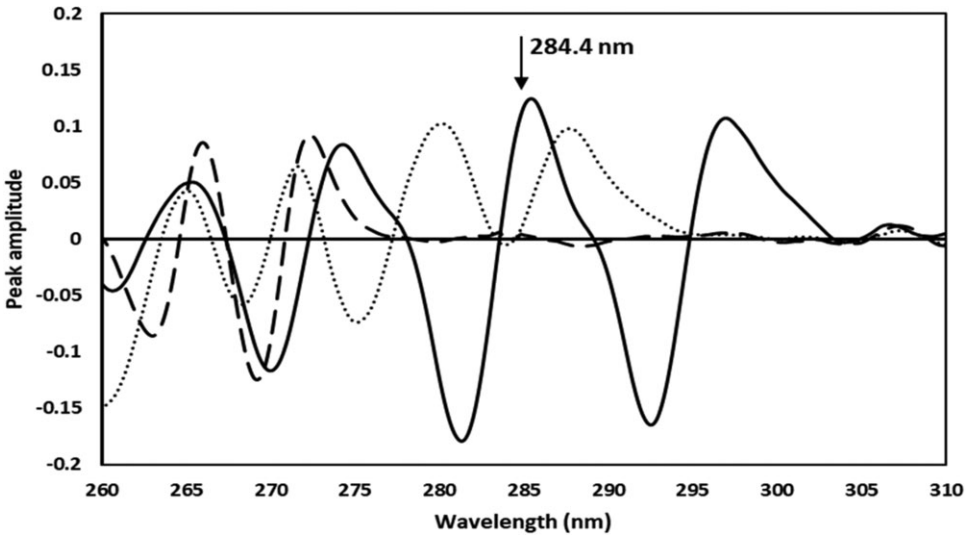

Figure 3. Second derivative of 8 μg/mL of EPH (———), 2 μg/mL of NAP (-), and 2 μg/mL of MET .....) using ethanol as a blank.

284.4 nm with no interference from the other two components (Figure 3) using the regression equation (cal.1). Two wavelengths were selected in the D° spectrum of the mixture (215.4 and 263.4 nm), at which MET has the same absorbance, whereas both EPH and NAP have considerable absorbance difference. The amplitude value of NAP at 284.4 nm was constructed against the difference in absorbance at the two wavelengths 215.4 and 263.4 nm (D) of D° spectra of NAP and the regression equation was calculated (cal.2). The difference in absorbance at the two selected wavelengths corresponding to EPH (E) in the D° spectrum of the mixture can be determined from the relation E =A (mix) – D (Figure 2), where A (mix) is the difference in absorbance at 215.4 and 263.4 nm in the D° spectrum of the mixture. The concentration of EPH is obtained from (cal.3) relating E to the pure concentrations of EPH. Many factors were optimized, including $\Delta\lambda$, the scaling factor, and the two selected wavelengths, where the most suitable ones are those mentioned above.

(b) *Successive derivative subtraction method*.—The method was developed by Lofty et al. (22) for resolving ternary and quaternary mixtures and was applied successfully for the determination of our described ternary mixture. In this method, the first derivative spectrum of the mixture using $\Delta\lambda = 2$ and a scaling factor = 10 was divided by the first derivative spectrum of 6 μg/mL of NAP, where a plateau region (298–303 nm) representing the constant NAP/NAP′ (constant 1) was obtained. To eliminate the interfering D^1 spectrum of NAP in the mixture, constant 1 was subtracted from the obtained ratio spectrum of the mixture, and then

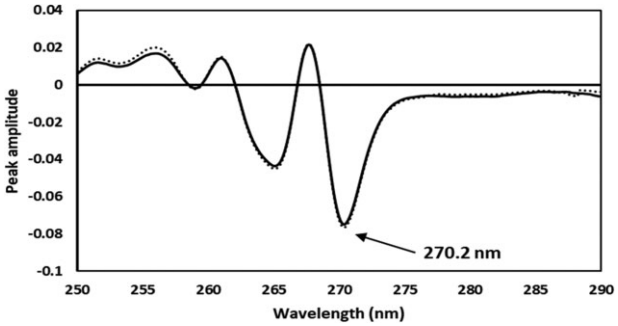

Figure 4. The first derivative spectra of EPH in the mixture (-) and the same concentration of the pure drug (. . .).

the resulting spectrum was multiplied by the divisor (6 μg/mL of NAP). The previous steps were repeated on the resulting spectrum to eliminate the interfering D^1 spectrum of MET using 6 μg/mL of MET as a divisor, subtracting the constant value at 281.4–288 nm (constant 2), and then multiplying by the divisor (6 μg/mL of MET) to obtain the first derivative spectrum of EPH found in the mixture from which EPH can be determined at 270.2 nm using the corresponding regression equation (Figure 4). For determination of NAP in the mixture, the value of constant 1 is multiplied by the divisor (6 μg/mL of NAP) to obtain the D^1 spectrum of NAP found in the mixture, where it could be determined at 224.8 nm using the specified regression equation (Figure 5).

(c) *Multivariate calibration techniques*.—In this method, PCR and PLS regressors were used for the determination of EPH and

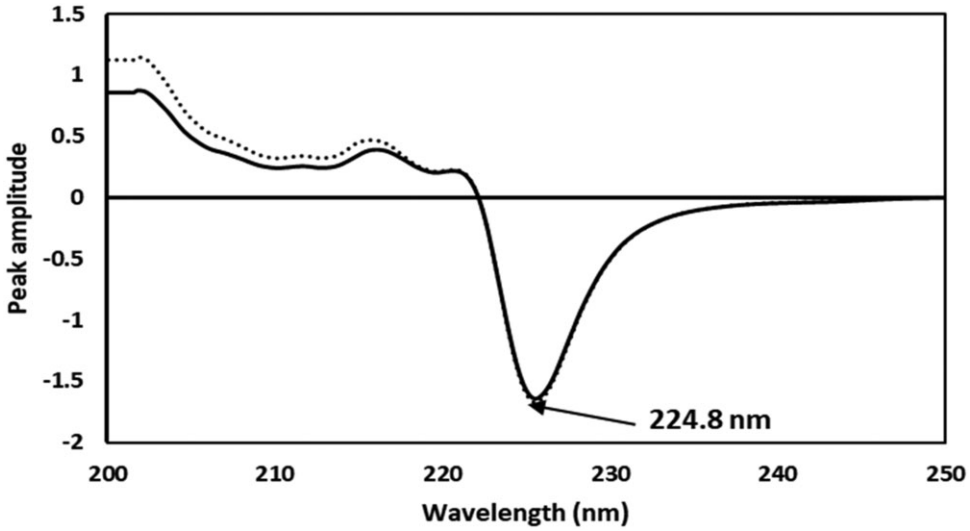

Figure 5. The first derivative spectra of NAP in the mixture (-) and the same concentration of the pure drug (. . .).

NAP in the presence of MET with high accuracy and predictive ability.

Twenty-five mixtures of EPH, NAP, and MB were used as the calibration set as given in Table 1. The UV range used was 215–250 nm. Both models used the leave-one-out cross-validation method, and the prediction error (RMSEP) was calculated for each analyte. Five factors were found to be suitable for both the PCR and PLS models. The prediction ability of the two developed models was validated by allowing them to estimate the drugs in the validation set, where good results were obtained (Table 3).

The predicted concentrations were plotted against the true concentration, where the slope approaches 1, the intercept was near zero, and the correlation coefficient was >0.999 (Table 3). The concentration residuals of the validation samples appeared to be randomly distributed around zero, indicating high accuracy in predicting new samples (Figure 6).

The RMSEP tool was used for checking the errors in the predicted concentrations. Results are shown in Table 3.

Method Validation

ICH recommendations (21) were followed to check the validity of the derivative dual-wavelength and successive derivative subtraction methods.

Linearity

Different concentrations of EPH and NAP were analyzed using the suggested methods and correlated to the corresponding responses by measuring either the absorbance or the amplitudes at the selected wavelengths, and then the calibration curve was constructed. The range of linearity, slope, intercept, and correlation coefficients of the regression equations are shown in Table 2.

Accuracy

The accuracy could be checked in two ways. The first is by analysis of various concentrations of pure EPH and NAP along the linearity range. The second is by estimation of pure drugs added to the dosage form. Results found in Tables 3 and 5 prove the accuracy of the methods.

Precision

The precision of the described methods was assured by calculating RSD, % using the following concentrations: 10, 13, and 20 μg/mL of EPH and 2, 3, and 5 μg/mL of NAP. The concentrations were determined within the same day and on three consecutive days. RSD, % values are presented in Table 3.

Specificity

The methods are specific if they can determine each analyte without any interference from the accompanying components as other drugs and excipients. This can be verified by the analysis of synthetic mixtures of EPH, NAP, and MET as well as the nasal spray. Table 4 confirms the high specificity of the described methods.

Limits of Detection and Quantitation (LOD and LOQ)

LOD and LOQ values were calculated for both EPH and NAP as presented in Table 3, indicating the ability of the methods to detect and quantify small concentrations of both drugs.

Application to the Pharmaceutical Formulation

The marketed pharmaceutical formulation Deltarhino nasal spray containing EPH, NAP, and MET was analyzed using the three described methods, where acceptable results were obtained with good accuracy (Table 5).

The suggested methods were compared to the reported HPLC method (24) using *F* and *t*-tests; the obtained results indicated no significant difference between them (Table 6).

Greenness Evaluation

Greenness evaluation gives an indication about possible environmental hazards of analytical methods. In the reported GC-MS method (19), greenness has been evaluated, using GAPI an AGREE tools, and compared to the reported HPLC method (18). In our work, a comparison between our introduced methods and all the previously reported chromatographic methods (17–19), used for the determination of the proposed mixture, has been done using three smart tools. The first is the Eco-scale analytical tool (23), in which each the chemicals and apparatus used in the analytical procedure will have a score according to its environmental

Table 3. Parameters of method validation

Parameter	EPH				NAP			
	Derivative dual-wavelength	Successive derivative subtraction	PCR	PLS	Derivative dual-wavelength	Successive derivative subtraction	PCR	PLS
Range	7–27 μg/mL		4–12 μg/mL		1–10 μg/mL		1–5 μg/mL	
Slope	0.0570	0.0051	1.0177	1.0166	0.0570	0.0051	1.0177	1.0166
Intercept	−0.0018	−0.0031	−0.0903	−0.1257	−0.0018	−0.0031	−0.0903	−0.1257
Mean	100.24	100.65	99.67	100.14	100.24	100.65	99.67	100.14
SD	0.856	0.981	0.799	0.811	0.856	0.981	0.799	0.811
r	0.9997	0.9999	0.9997	0.9998	0.9997	0.9999	0.9997	0.9998
RMSEP	–	–	0.1070	0.0735	–	–	0.1070	0.0735
Accuracy ± SD	100.22 ± 0.075	101.09 ± 0.346	–	–	100.22 ± 0.075	101.09 ± 0.346	–	–
Intra-day precision (RSD, %)	0.237	0.400	–	–	0.237	0.400	–	–
Inter-day precision (RSD, %)	0.368	0.317	–	–	0.368	0.317	–	–
LOD[a]	2.24	2.16	–	–	2.24	2.16	–	–
LOQ[a]	6.72	2.48	–	–	6.72	2.48	–	–

[a] LOD = (SD of the response/slope) × 3.3; LOQ = (SD of the response/slope) × 10.

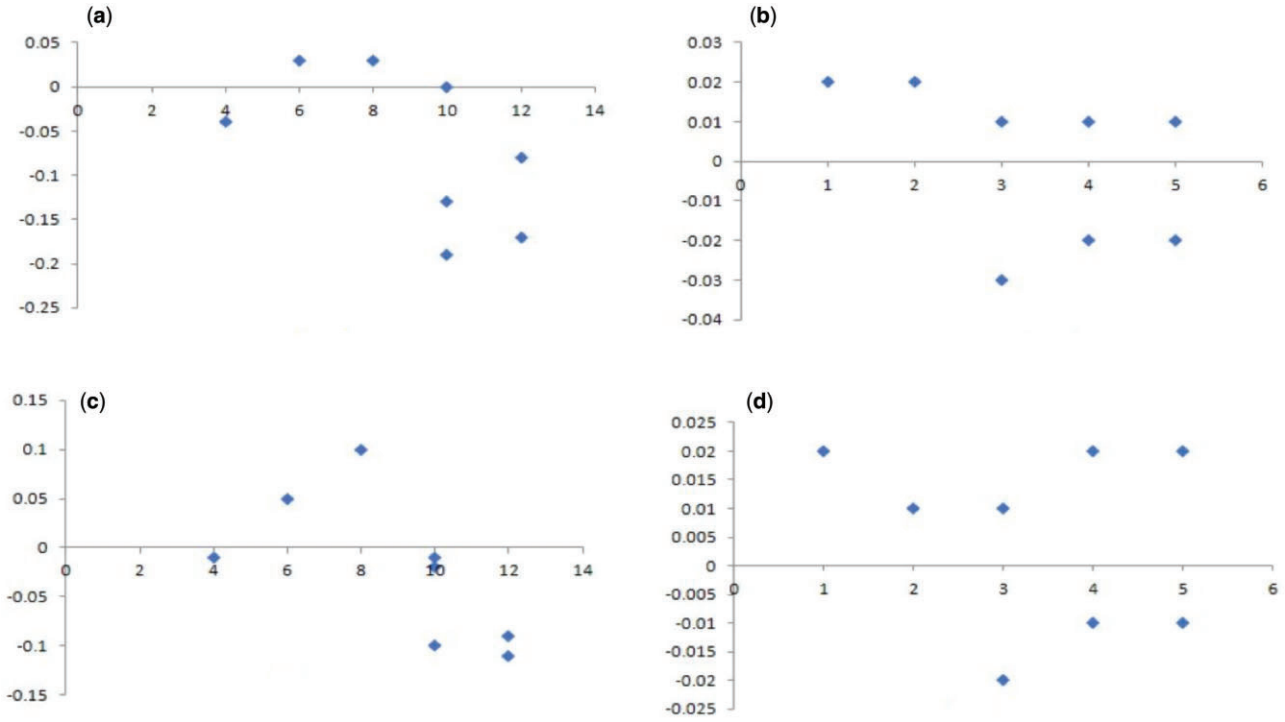

Figure 6. Concentration residuals against the actual concentrations for the validation samples, (a) and (c) for EPH, (b) and (d) for NAP using the proposed PCR and PLS models, respectively.

Table 4. Results of determination of EPH and NAP in laboratory-prepared mixtures

		EPH				NAP			
Mix no.	Mix ratio	Derivative dual-wave-length	Successive derivative subtraction	PCR	PLS	Derivative dual-wave-length	Successive derivative subtraction	PCR	PLS
1	1:4:1[a]	99.25	99.09	101.42	99.00	100.48	100.35	100.92	99.50
2	1:3:2	99.63	99.80	99.50	101.01	99.92	99.67	99.17	100.67
3	1:2:1	100.22	99.38	100.67	99.67	100.34	98.57	100.75	99.67
4	1:1:1	99.29	99.01	101.30	99.80	100.37	99.34	100.20	99.60
5	1:5:2	101.52	100.46	99.62	100.41	101.58	100.58	98.75	100.20
6	2:3:2	101.03	99.48	101.00	99.75	101.67	99.64	100.25	99.50
7	2:1:1	100.36	98.87	100.00	98.38	99.40	99.56	100.10	98.00
8	3:1:2	99.64	100.47	101.90	100.50	100.67	101.74	101.00	100.25
Mean ±SD		100.12 ± 0.826	99.57 ± 0.625	100.68 ± 0.887	99.82 ± 0.845	100.55 ± 0.768	99.93 ± 0.953	100.14 ± 0.812	99.67 ± 0.799

[a] The dosage form ratio.

Table 5. Determination of EPH and NAP in the pharmaceutical formulation

	EPH[a]	NAP[b]	Standard addition technique			
			EPH		NAP	
Method	Found, % ± SD[c]		Pure added, μg/mL	Pure found, % ± SD[d]	Pure added, μg/mL	Pure found, % ± SD[d]
Derivative dual-wavelength	99.30 ± 0.292	103.74 ± 0.582	9	101.05 ± 0.837	1.5	100.66 ± 1.225
			12	100.35 ± 1.035	3	99.22 ± 1.003
			15	99.76 ± 0.336	5	100.69 ± 0.456
Successive derivative subtraction	100.15 ± 0.118	102.86 ± 0.771	9	100.85 ± 0.937	1.5	99.37 ± 0.524
			12	99.45 ± 0.746	3	100.46 ± 0.929
			15	100.35 ± 1.221	5	100.57 ± 0.307
PLS	100.25 ± 0.351	103.67 ± 0.781	4	101.24 ± 0.262	1	100.54 ± 0.747
			5	101.35 ± 0.237	2	99.83 ± 0.782
			6	99.89 ± 0.785	3	101.84 ± 0.880
PCR	99.75 ± 0.252	103.21 ± 0.732	4	100.85 ± 0.337	1	101.05 ± 0.927
			5	98.96 ± 0.677	2	101.24 ± 0.625
			6	99.87 ± 0.896	3	100.67 ± 1.113

[a] Taken concentration = 12 μg/mL for derivative dual-wavelength and successive derivative subtraction methods and 5 μg/mL for PCR and PLS methods.
[b] Taken concentration = 3 μg/mL for derivative dual-wavelength and successive derivative subtraction methods and 2 μg/mL for PCR and PLS methods.
[c] Average of six determinations.
[d] Average of three determinations.

Table 6. Statistical comparison of the results obtained by the proposed and the reported (17) methods for determination of pure EPH and NAP

	Derivative dual-wavelength PCR		Successive derivative subtraction		PCR		PLS		Reported method (17)[a]	
Parameter	EPH	NAP	EPH	NAP	EPH	NAP	EPH	NAP	EPH	NAP
Mean	100.24	99.59	100.65	99.16	99.67	99.76	100.14	100.12	100.03	99.72
SD	0.856	1.082	0.981	1.130	0.799	0.939	0.811	0.886	0.857	0.939
N	10	10	10	10	10	10	10	10	10	10
Student's *t*-test (2.262)[a]	0.548	0.287	1.505	1.205	0.971	0.095	0.295	0.980	–	–
F-test (3.180)[a]	0.998	1.328	0.694	1.448	0.869	1.002	0.896	0.890	–	–

[a] Figures in parentheses are the corresponding tabulated values at $P = 0.05$.

impact. The sum of all scores is calculated and subtracted from 100, where the higher the score, the greener the method. If the method gets a score above 75, then it will be considered an excellent green analytical method. The second one is the GAPI pictogram (24), which evaluates the methods from sample collection to the last steps of analysis. Fifteen experimental conditions are evaluated, and then each one gets a color, either red, yellow, or green, depending on its environmental effects. The colors are represented in a pictogram. In the AGREE tool (25), 12 experimental conditions are evaluated, in which each one takes a color from red to green and the colors are represented in a plot. The comparison is illustrated in Table 7, which confirms that our methods are greener than the published chromatographic ones.

Conclusions

This work introduces the first green, versatile, validated, and easily implemented spectrophotometric methods for estimation of the concentration of two components of a nasal preparation containing MET as a preservative. Simple manipulation steps have been applied for the analysis. The methods succeeded in fulfilling all ICH validation requirements. Greenness estimation was done using three tools, including Eco-scale, GAPI, and AGREE. The introduced methods are greener than the previously published chromatographic ones. These advantages recommend the application of the introduced methods for the analysis of these drugs in nasal preparations with low cost and high accuracy.

CRediT Author Statement

Rehab M. Abdelfatah: Formal analysis, software, and writing the original draft; Mainmana A. Magdy: Project supervision, methodology, and writing—reviewing and editing.

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Conflict of Interest

All authors declare no conflict of interest.

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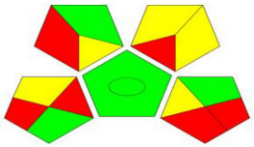
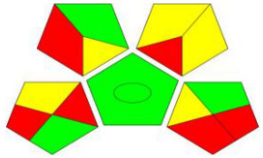
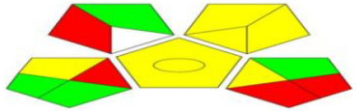
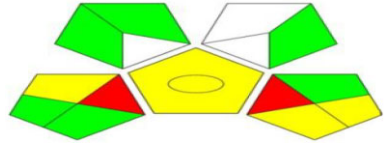
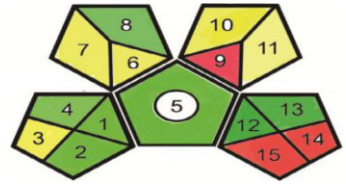
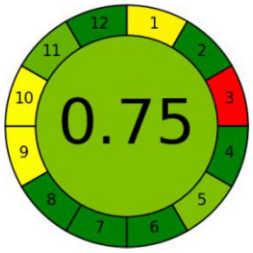
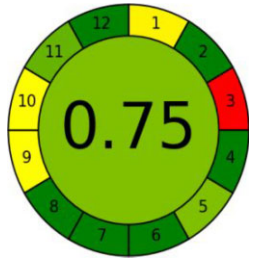
Table 7. Comparison between our introduced methods and the reported ones (17–19) regarding greenness using the Eco-scale, GAPI, and AGREE tools

		Reported method (18)			
Greenness tool	**Reported method (17)**	**HPTLC**	**HPLC**	**Reported method (19)**	**Our proposed methods**
Eco-scale score	80	71	78	78	83
GAPI					
AGREE					

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