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Original Article

APPLICATION OF TWO ADVANCED DERIVATIVE SPECTROPHOTOMETRIC METHODS FOR SIMULTANEOUS ESTIMATION OF SALBUTAMOL SULPHATE, AMBROXOL HYDROCHLORIDE AND THEOPHYLLINE IN PURE AND COMMERCIAL FORMULATIONS

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ABSTRACT

Objective: Two advanced spectrophotometric methods have been proposed for the simultaneous determination of Salbutamol sulphate, Ambroxol hydrochloride and Theophylline in pure and pharmaceutical formulations. The proposed methods exclude the hectic steps of time-consuming sample preparations or purification or separation steps. There is no any spectrophotometric method has been avail for simultaneous estimation of the ternary mixture containing Salbutamol sulphate, Ambroxol hydrochloride and Theophylline.

Methods: The methods are derivative ratio spectra zero-crossing method and double divisor ratio spectra derivative method respectively. Both the methods are found to be rapid, accurate, precise, reliable and economical as well. The developed methods show best results in terms of linearity, accuracy, precision, limit of detection and limit of quantification for standard laboratory mixtures of pure drugs and marketed formulations.

Results: The range for Salbutamol sulphate, Ambroxol hydrochloride and Theophyllineare found to be 1-35 µg ml^{-1}, 5-35 µg $ml^{-1}$and 6-60 µg ml^{-1} respectively. For the derivative ratio spectra zero-crossing method, the values of the limit of detection are found to be 0.3161 µg ml^{-1}, 0.2212 µg ml^{-1} and 0.2910 µg ml^{-1} and the values limit of quantification are found to be 0.9571 µg ml^{-1}, 0.7412 µg ml^{-1} and 0.9671 µg ml^{-1} for Salbutamol sulphate, Ambroxol hydrochloride and Theophylline respectively. For double divisor ratio spectra derivative method, limit of detection values is found to be 0.3251 µg ml^{-1}, 0.2591 µg ml^{-1} and 0.2640 µg ml^{-1} and the limit of quantification values are found to be 0.9870 µg ml^{-1}, 0.8650 µg ml^{-1} and 0.8812 µg ml^{-1} for Salbutamol sulphate, Ambroxol hydrochloride and Theophylline respectively.

Conclusion: The common excipients and additives did not interfere in the determinations of any of the drugs while being analysed for commercial formulations. These two spectrophotometric methods, which determine SS, AH, and THE simultaneously, are simple, specific, accurate, precise, rapidly, and economically, indicating that they can be used routinely in pharmaceutical analysis. As a result, derivative spectrophotometry may be used effectively for the simultaneous determination of SS, AH and THE in the combined dosage forms without any prior separation of individual drugs.

Keywords: Ambroxol hydrochloride, Derivative Spectrophotometric method, Derivative ratio spectra zero-crossing spectrophotometry, Double divisor ratio spectra derivative spectrophotometry, Salbutamol sulphate, Theophylline

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INTRODUCTION

Salbutamol sulphate (SS), chemically known as bis [(1RS)-2-[(1, 1-dimethyl ethyl) amino]-1-[4-hydroxy-3-(hydroxymethyl) phenyl] ethanol] sulphate, is beta-adenocepter agonist used as an anti-asthmatic drug, Ambroxol hydrochloride (AH), Trans-4-(2-amino-3, 5-dibromobenzylamino) cychlohexanol hydrochloride, is an expectorant and enhanced mucolytic agent used in the treatment of various respiratory disorders. Theophylline (THE), 3, 7-Dihydro-1, 3-dimethyl-1*H*-purine-2, 6-dione, is a xanthine bronchodilator used for the treatment of respiratory diseases and asthma in combination with SS. SS [1], AH [2] and THE [3] are official in BP. The official methods involve the determination of SS [1] and AH [2] using potentiometry and determination of THE [3] using conventional titrimetric method.

It has been described some procedures for the assessment of either SS or AH or THE in a single dosage form [4–7]. For the determination of SS and AH in combined dosage forms, a spectrophotometric method has been reported [8]. In their combined dosage forms, SS and THE were measured by spectrophotometry [9]. There are no official pharmacopeial guidelines for the mixture of SS, AH and THE. In literature, no analytical method could be found for the analysis of the combination of SS, AH, and THE in pharmaceutical dosage forms. For simultaneous estimation of these drugs in mixtures, simple, rapid, economical and reliable methods were required.

There are additional advantages of the spectrophotometric method in the form of ease of experiment and overall list sample preparation. Therefore Uv spectroscopic method is the most preferable method for individual component determination and simultaneous determination of multiple components. Derivative spectroscopy is most widely used technique for multiple component analysis with the use of advance software tools [10]. Many of the research articles are already published which showing the powerful use of uv visible spectroscopy for multi-component analysis especially analysis or determination of ternary mixture simultaneously [11, 12]. The fundamental aim of the current research work is based on the utility of the advance uv spectroscopic method for simultaneous determination of SS, AH and THE in their pure form and with the available commercial formulations. The zero-order spectra of SS, AH and THE were completely overlapped with one another therefore it is not possible to use zero-order direct spectroscopy with the said ingredients for simultaneous determination. For the same reason, we represented the use of derivative spectroscopy as an advance tool with added advantages of rapid determination and ease of determination without any hectic pretreatment or sample preparations. [13-20]. There are several derivative orders and different types of measurements analysed in the present study, i.e., ratio-spectra first derivative zero-crossing [21, 22] and double divisor ratio spectral derivative method [23, 24]. We successfully used ratio-spectra first derivative zero-crossing and double divisor ratio spectral derivative method for simultaneous determination of ternary mixture containing SS, AH and THE. A short assessment of some of the usefulness of various tactics have become tried.

Aim

There is no any spectrophotometric approach has been to be had for simultaneous estimation of the ternary combination containing salbutamol sulphate, ambroxol hydrochloride and theophylline in pure and in industrial formulations. For that reason, simple intention is to broaden simple, rapid, correct and price-effective strengthen spinoff spectrophotometric techniques for simultaneous determination of those tablets in pure and commercial formulations. The techniques are targeted to expand with the exclusion of any prior extraction or different pre-treatment in the course of the entire development and validation for all three tablets simultaneously.

MATERIALS AND METHODS

Instruments

Our spectrophotometer of choice was the Shimadzu 1700 double beam UV visible spectrophotometer paired with a HP7540 computer loaded with Shimadzu UV PC software of 2.0 and an EPSON-three hundred printer.

Reagents

All chemical substances used were of analytical grade and double distilled water turned into used throughout. Pure SS and AH were received from sehat pharmaceuticals pvt. Ltd., india and the turned into obtained from cadila healthcare pvt. Ltd., india. Diverse pharmaceutical formulations of ss, ah and the in their mixed dosage paperwork have been acquired commercially.

Solutions

The stock solutions of SS, AH, and THE were freshly prepared individually, each containing 0.1 mg ml-1 of SS, AH, and THE. For the study, commercial formulations containing tablets containing 2 mg of SS, 30 mg of AH, and 100 mg of THE per tablet were used: Ambrolite-ST (Tablets India Pvt. Ltd., India), and Ambro TS (Grandix Pharmaceutical Ltd., India).

Procedure

All reagents had been examined for stability in solution and in the course of real evaluation. After about 72 h from the start of the experiment, the behaviour of the analytes remained unchanged. All three drugs were found to be stable throughout each kind of experimental measurement, which was conducted at room temperature.

Derivative ratio spectra zero crossing spectrophotometry (method 1)

The absorbance spectra of API and their ternary combinations had been recorded between 200-300 nm. In addition to analysing the absorbance spectra of pure SS and ternary mixtures, each spectrum was divided by the standard spectrum of AH, the spectrum of AH and ternary mixtures were divided by the standard spectrum of THE, and the spectrum of THE and their ternary mixtures were divided by the standard spectrum of SS, with the first derivative of the ratio spectra being plotted using delta lambda 8 nm and scaling factor 1 There was a linear relationship between the concentration of SS, AH and THE in the ternary mixture and the first derivative ratio signals at 217.4 nm (zero crossing point for THE with 30µg ml-1 of AH as a divisor), 249.6 nm (zero crossing point for SS with 8µg ml-1 of THE as a divisor) and 276.2 nm (zero crossing point for AH with 15µg ml-1 of was used as divisor) respectively. To obtain calibration graphs, derivative ratios of SS, AH, and THE were multiplied by different divisors, and their amplitudes were measured. In standard laboratory mixtures and commercial formulations, the SS, AH, and THE contents were determined with the above procedure. For the commercial formulation analysis, twenty tablets were weighed and ground to a fine powder after following the above mentioned procedure. The resultant powder was accurately weighed into a calibrated volumetric flask filled with double distilled water. Filtered solution was measured by spectroscopic absorbance in relation to ratio derivative spectra at 217.4 nm, 249.6 nm and 276.2 nm for SS, AH, and THE, respectively. The procedure described above was followed for testing all brands of tablets.

Double divisor ratio spectra derivative method (method 2)

The absorbance spectra of API and their ternary combinations had been recorded between 200-300 nm. The absorption spectra of SS and their ternary combination were divided via a standard spectrum received by way of the addition of the saved spectrum of 20 µg ml-1 of AH and 20 µg ml-1 of THE and first derivative of the ratio spectra was plotted the usage of delta lambda 8 nm and scaling factor 1. in the ternary mixture, the concentration of SS was proportional to the first derivative ratio signals at 233.8 nm. Calibration graph become obtained with the aid of measuring the derivative ratio amplitudes towards the increasing concentration of pure SS through the usage of same divisor defined above. For the determination of SS, the calibration graph noted above was used. Similarly, AH is determined by adding a saved spectrum of 8 g ml-1 from SS and 8 g ml-1 from THE as the divisor, and THE is determined by using a general spectrum created by adding a saved spectrum of 15 g ml-1 from SS and 15 g ml-1 from AH as divisor. Based on a delta lambda of 8 nm and scaling of 1, the first derivative of ratio spectra had been plotted. As the first derivative ratio signals at 237.4 nm and 260.2 nm are proportional, the concentration of AH and THE have been proportional inside the ternary mixture. Calibration graphs had been obtained via measuring the first derivative ratio amplitudes towards the increasing concentration of pure AH and THE by using the same respective divisors described above while for the commercial formulation evaluation, the same method was applied as implemented in the previous technique and observed by noted procedure.

Validation parameters

Accuracy

Recovery experiments were conducted to determine the accuracy of the proposed method and possible interference from excipients. The standard addition method was used to conduct recovery experiments. As part of the study, known amounts of SS, AH, and THE were added to commercial tablets of a known concentration. The amounts of standard recovered were calculated in the terms of mean recovery with the upper and lower limits of percent relative standard deviation.

Precision

Precision is performed by repeating the complete procedure five times a day (Intraday) and for five different days (Interday). The relative standard deviation was calculated for each repetition and percentage was calculated.

Limit of detection (LOD) and limit of quantitation (LOQ)

Limit of Detection (LOD) and Limit of Quantitation (LOQ) were calculated according to the standard procedure of analytical method validation as per ICH.

Reproducibility

The reproducibility of the method was determined Wwith the use of two different instruments. The model number of Uv visible spectrophotometers were: Shimadzu UV 1700 and Shimadzu UV 1601. The results were determined in the form of percentage relative standard deviation.

RESULTS AND DISCUSSION

A detailed comparison of the absorption spectra of SS, AH, and THE is provided in fig. 1.

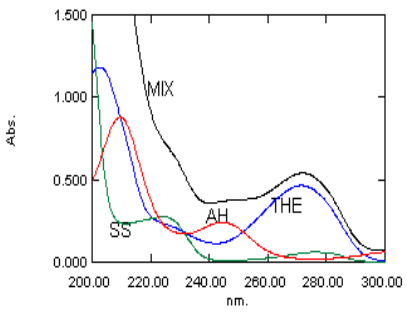

Fig. 1: Zero-order overlain spectra of SS (10 µg ml^{-1}), AH (10 µg ml^{-1}), THE (10 µg ml^{-1}) and their ternary mixture

Because of this, direct measurement of absorption in zero order spectra was not possible for the determination of the above compounds. Furthermore, derivative spectroscopy indicates better resolution and allows analysis of the drugs in combination with one another and with any additional excipients without any pre-treatment.

Derivative ratio spectra zero crossing spectrophotometry (method 1)

For this technique, selecting an accurate working wavelength or standard divisor is crucial. In particular, Increase or decrease of the divisor concentration results in derivative values, for this reason, slopes of regression lines are proportionately decreased or increased, hence, sensitivity and linearity ranges are also influenced. Standard divisors of 5 to 35 g ml-1 concentration were used in a preliminary investigation in order to conduct several tests. For the SS determination, 30 µg ml-1 of AH was used as the divisor for SS, 8 µg ml-1 of THE for-AH determination, and 15 µg ml-1 of SS for the THE determination. This produced the best results for signal-to-noise ratio, sensitivity, repeatability, and range of validity of Beer's law. The ratio spectra of respective drugs are listed below with fig. 2a to 2c.

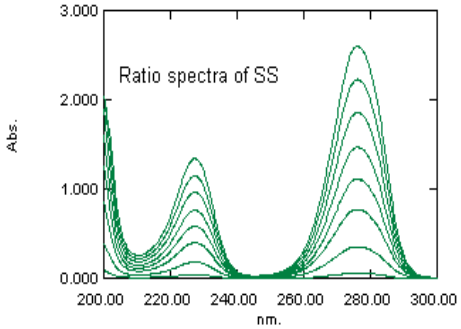

Fig. 2a: Ratio spectra of SS using AH (30 µg ml^{-1}) as divisor using method 1

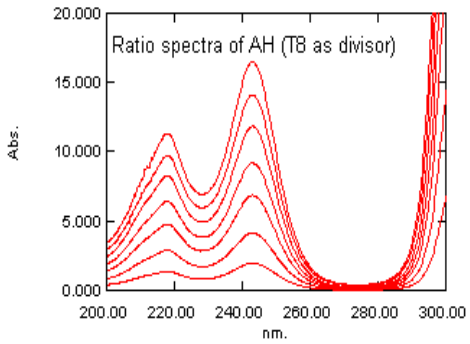

Fig. 2b: Ratio spectra of AH using THE (8 µg ml^{-1}) as divisor using method 1

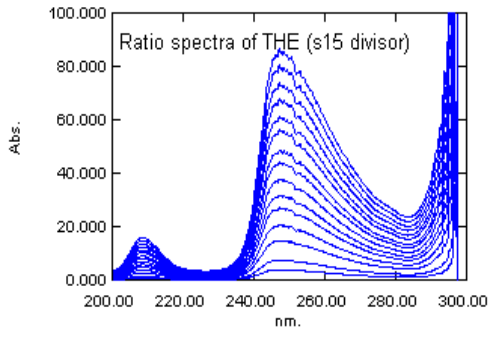

Fig. 2c: Ratio spectra of THE using SS (15 µg ml^{-1}) as divisor using method 1

For the first derivative wavelengths, 217.4 nm was considered for the SS determination, 249.6 nm for the AH determination, and 276.6 nm for the THE determination. We used 217.4 nm as the wavelength for SS measurement because the contribution of the THE at this wavelength (30 µg ml-1 AH as divisor) cannot be determined. 3a. In the same way, 249.6 nm was used for the AH measurement since SS (8 µg ml-1 THE as the divisor) crosses this wavelength at the point shown in fig. 3b. A wavelength of 276.6 nm was used for the determination of THE because AH shows zero absorbance (15 µg ml-1 SS as a divisor) at this wavelength. 3c.

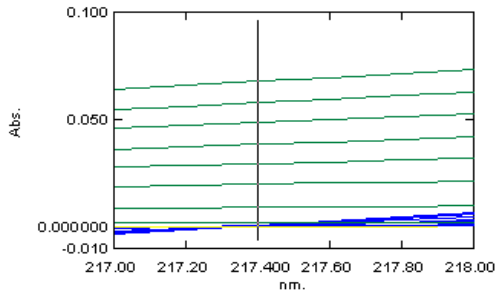

Fig. 3a: Determination of SS at 217.4 nm by method 1 in the presence of THE using AH (30 µg ml^{-1}) as the divisor

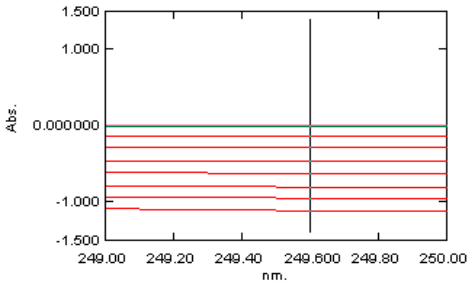

Fig. 3b: Determination of AH at 249.6 nm by method 1 in the presence of SS using THE (8 µg ml^{-1}) as divisor

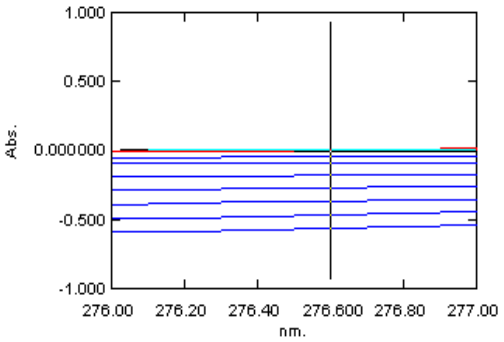

Fig. 3c: Determination of THE at 276.2 nm by method 1 in the presence of AH using SS (15 µg ml^{-1}) as divisor

The combined results of Validation parameters and accuracy were represented in the table after the complete explanation of Method 2. However, the results of recovery studies are represented with table 3a as below:

Double divisor ratio spectra derivative method (method 2)

It is necessary to study and optimize standard divisor concentrations, scaling factors, delta lambdas, etc. in order to obtain the best spectra recoveries for SS, AH, and THE. As a divisor for SS determination, a standard spectrum obtained by adding the spectrum of 20 µg ml-1 of

AH to 20 µg ml-1 of THE yields the best results in terms of signal-to-noise ratio, sensitivity, repeatability, and range of validity of Beer's law. In order to estimate AH, it is best to use a standard spectrum obtained by adding stored spectra of 8 µg ml-1 SS and 8 µg ml-1 THE as a divisor. Similar results were obtained for the THE determination when a standard spectrum obtained by adding 15 µg ml-1 of SS and 15 µg ml-1 of AH was used as the divisor. The respective fig. are represented below with the fig. number 4a to 4c.

Table 3a: Assay results of SS, AH and THE in combined commercial formulations by method 1

Formulation	% Labelled claim obtained for SS[a]	% Labelled claim obtained for AH[a]	% Labelled claim obtained for THE[a]
Brand I[b]	101.51±0.431	101.40±0.524	100.24±0.547
Brand II[c]	101.21±0.419	101.91±0.544	101.20±0.647

[a]Mean and standard deviation for 10 determinations. Here±sign indicates the upper and lower limits of % relative standard deviation of 10 determinations, [b]Brand I tablets, [c]Brand II tablets, ation of method 2.

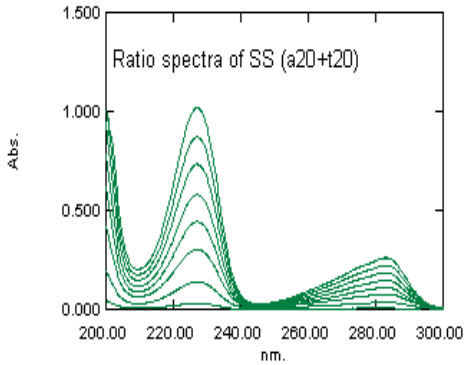

Fig. 4a: Ratio spectra of SS using method 2

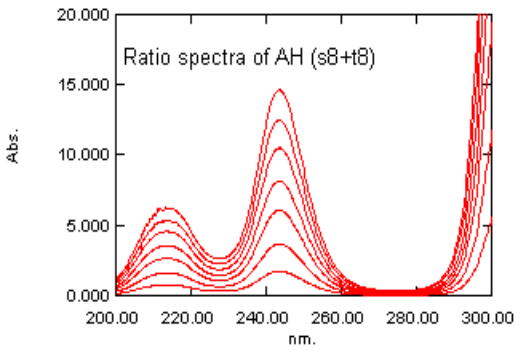

Fig. 4b: Ratio spectra of AH using method 2

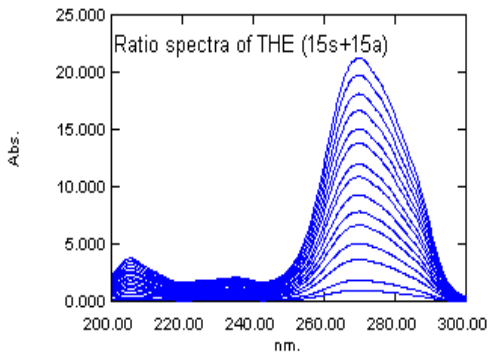

Fig. 4c: Ratio spectra of THE using method 2

First derivative spectra are obtained after dividing which are represented in fig. 5a to 5c.

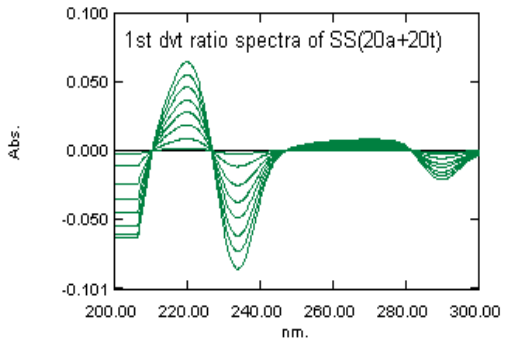

Fig. 5a: Determination of SS at 233.8 nm by method 2

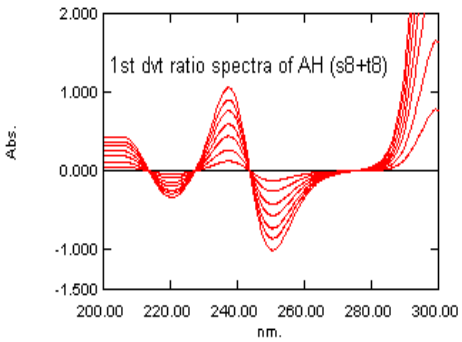

Fig. 5b: Determination of BH at 237.4 nm by method 2

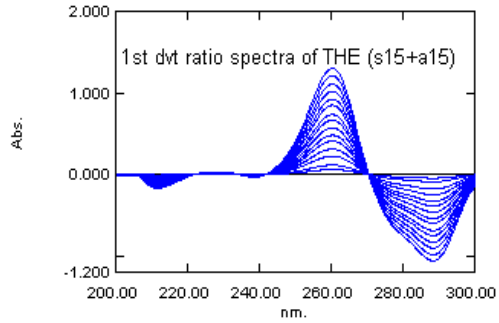

Fig. 5c: Determination of ET at 260.2 nm by method 2

Based on the developed method, results of accuracy were summarized in table 1, results of various validation parameters were summarized in table 2, results of tested formulations were summarized in table 3b, respectively.

Table 1: Results of recovery study of SS, AH and THE by the developed methods

Amt added (µg ml^{-1})			% Recovery[a] method 1[b]			% Recovery[a] method 2[c]		
SS	AH	THE	SS	AH	THE	SS	AH	THE
0.8	12	40	101.32	99.50	99.21	102.00	101.21	99.79
1.0	15	50	102.00	100.79	99.45	101.64	101.36	100.56
1.2	18	60	101.54	100.45	100.39	101.37	100.42	101.10
Mean Recovery			101.62	100.25	99.68	101.67	100.99	100.48
%RSD			0.34	0.67	0.62	0.311	0.49	0.65

[a]Mean and standard deviation for 10 determinations, [b]Method: 1 Derivative ratio spectra zero-crossing method, [c]Method: 2 Double divisor ratio spectra derivative method

Table 2: Results of validation parameters obtained by method 1 and method 2

Parameters	Method 1[a]			Method 2[b]		
	SS	AH	THE	SS	AH	THE
Range (µg ml^{-1})	1-35	5-35	6-60	1-35	5-35	6-60
Slope	0.0019	0.033	0.0188	0.0025	0.0314	0.0226
Intercept	-0.000006	-0.0346	-0.0511	0.0004	-0.0344	-0.0615
Correlation-coefficient(R^2)	0.9997	0.9993	0.9994	0.9998	0.9994	0.9993
Accuracy	101.62±0.34	100.25±0.67	99.68±0.620	101.67±0.31	100.99±0.49	100.48±0.65
Precision (% RSD)	0.521	0.592	0.511	0.562	0.612	0.437
LOD (µg ml^{-1})	0.3161	0.2212	0.2910	0.3251	0.2591	0.2640
LOQ (µg ml^{-1})	0.9571	0.7412	0.9671	0.9870	0.8650	0.8812
Reproducibility (% RSD)	0.33	0.47	0.46	0.14	0.32	0.47

[a]method: 1 Derivative ratio spectra zero-crossing method, [b]method: 2 Double divisor ratio spectra derivative method

Table 3b: Assay results of SS, AH and THE in combined commercial formulations by method 2

Formulation	% Labelled claim obtained for SS[a]	% Labelled claim obtained for AH[a]	% Labelled claim obtained for THE[a]
Brand I	102.00±0.398	101.73±0.614	101.00±0.542
Brand II	101.10±0.281	101.61±0.519	100.98±0.611

[a]Mean and standard deviation for 10 determinations. Here±sign indicates the upper and lower limits of % relative standard deviation of 10 determinations. [b]Brand A tablets, [c]Brand B tablets

Statistical comparison of the results of the developed two methods

SS, AH, and THE in combination pharmaceutical formulations were successfully analyzed without interference from excipients or pretreatments by the proposed methods. Statistical analyses were performed for Student t-tests and variance ratio F-tests to compare each method's results with those from the other. There were no significant differences between the calculated Student t-values and variance ratio F-values at 95 % confidence level, which indicates there were no significant differences among the results of the four methods presented in table 4.

Table 4: Statistical comparison of the results obtained by the developed methods

Drugs	Method 1	Method 2
SS	101.62±0.34	101.67±0.31
mean±%RSD	$t_{calculated}$= 0.641	$t_{calculated}$= 0.544
	$t_{theoretical}$= 2.26	$t_{theoretical}$= 2.26
	$F_{calculated}$= 0.437	$F_{calculated}$= 0.412
	$F_{theoretical}$= 3.18	$F_{theoretical}$= 3.18
AH	100.25±0.67	100.99±0.49
mean±%RSD	$t_{calculated}$= 0.767	$t_{calculated}$= 0.647
	$t_{theoretical}$= 2.26	$t_{theoretical}$= 2.26
	$F_{calculated}$= 0.562	$F_{calculated}$= 0.511
	$F_{theoretical}$= 3.18	$F_{theoretical}$= 3.18
THE	99.68±0.62	100.48±0.65
mean±%RSD	$t_{calculated}$= 1.021	$t_{calculated}$= 1.241
	$t_{theoretical}$= 2.26	$t_{theoretical}$= 2.26
	$F_{calculated}$= 0.818	$F_{calculated}$= 0.892
	$F_{theoretical}$= 3.18	$F_{theoretical}$= 3.18

CONCLUSION

These two spectrophotometric methods, which determine SS, AH, and THE simultaneously, are simple, specific, accurate, precise, rapidly, and economically, indicating that they can be used routinely in pharmaceutical analysis. As a result, derivative spectrophotometry may be used effectively for the simultaneous determination of SS, AH and THE in the combined dosage forms without any prior separation of individual drugs. In the absence of an official monograph, their determination may still be possible even without an official monograph.

ABBREVIATIONS

SS–Salbutamol sulphate, AH–Amroxol hydrochloride, THE–Theophylline, LOD–Limit of Detection, LOQ–Limit of Quantitation, RSD–Relative Standard Deviation, SD–Standard Deviation

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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