Original Article

Development and Validation of Chemometric Assisted UV Methods for the Simultaneous Determination of Ambroxol Hydrochloride, Terbutaline Sulphate and Guaiphenesin in Pharmaceutical Dosage Form

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ABSTRACT

Aim: The present study aimed to develop and validate chemometric assisted UV-spectrophotometric methods for the simultaneous determination of ambroxol hydrochloride (ABH), terbutaline sulphate (TES) and guaiphenesin (GPN) in their combined dosage form. **Materials and Methods:** The two chemometric models applied for the UV spectroscopic data were principal component regression (PCR) and partial least squares regression (PLS). Standard mixture solutions containing different ratios of ABH, TES and GPN in the calibration ranges of 5-30 μg/mL, 25-125 μg/mL and 15-75 μg/mL respectively were prepared and their UV absorption spectra was recorded. Calibration data set and validation data set comprising of thirteen and nine standard mixture solutions respectively were constructed and computations were made using UNSCRAMBLER X version 10.0 software for both the models in the wavelength region of 240-310 nm. **Results:** The results obtained by the optimized chemometric calibration models depicted the accuracy of the models and the assay results of PCR and PLS for the quantification of ABH, TES and GPN in the syrup dosage form were found to be within the acceptance criteria. **Conclusion:** The developed PCR and PLS models were found to simple, economical, accurate and do not require any separation process.

Keywords: Chemometric models, Principal component regression, Partial least squares regression, Ambroxol hydrochloride, Terbutaline sulphate, Guaiphenesin.

INTRODUCTION

The approved fixed dose combination of ambroxol hydrochloride (ABH), terbutaline sulphate (TES) and guaiphenesin (GPN) is prescribed for the treatment of chronic bronchitis and in the relief of bronchospasm symptoms in bronchial asthma.[1] The combination of these drugs is available in the market in expectorant dosage form under various brand names. A review of the literature revealed that no chemometric assisted UV-spectrophotometric method for the simultaneous determination of ABH, TES and GPN in pharmaceutical dosage form had been reported. In the literature, very few analytical methods on this combination were reported. For the simultaneous determination of ABH, TES and GPN in liquid dosage form, three RP-HPLC methods and only one spectrophotometric method was reported.[2-4] UV-vis spectroscopic methods have the advantage of being simple, easy to use, and relatively less expensive when compared to other popular quantitative methods, and have been widely used in quantitative analysis. However, it is difficult to analyze multi-component formulations that exhibit significant overlapping

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in their absorption spectra when using direct and conventional UV-spectrophotometric methods without any prior separation.[5-7] Furthermore, conventional spectrophotometric methods require more time, and the results obtained were deplorable and contrived due to low resolution.[8-9] Chemometrics, an advanced trend in analytical chemistry, extracts large amounts of data through the use of statistical and mathematical methods.[10-12] It is used to help UV spectroscopic methods overcome drawbacks and difficulties. The use of chemometric models in UV spectral data analysis has grown in popularity, efficiency, and power in determining components in multi-component formulations.[13-16] Hence, the present study was aimed to develop and validate chemometric assisted UV-spectrophotometric and for the simultaneous determination of ABH, TES and GPN in liquid dosage form.

MATERIALS AND METHODS

Instruments and Software

The spectral data was collected using a Shimadzu (UV 1800) double beam UV-Visible spectrophotometer equipped with 1 cm quartz cells and linked to a computer loaded with UV probe software. Weighing the samples was done with a Shimadzu electronic balance (AY 220). UNSCRAMBLER X version 10.5 was used to run all chemometric tools (Camo analytics). Microsoft Excel 2010 was used for statistical and regression analysis.

Materials and solvents

Raffles Pharmaceuticals, Tirupati, and TCI Chemicals (India) Pvt. Ltd., Chennai provided pure samples of ABH (98.9%), TES (98.9%) and GPN (98.7%). Distilled water was used as the solvent for the current study. Marketed formulation NORVENT expectorant containing 15 mg ABH, 1.25 mg TES and 50 mg GPN manufactured by Indchemie Health Specialties Pvt. Ltd., purchased from local pharmacy (Tirupati, Andhra Pradesh, India) was the sample selected for the study.

UV-spectrophotometric method development

The present study employed two chemometric assisted UV-spectrophotometric methods namely Principal component regression (PCR) and Partial least squares regression (PLS) for the quantification of ABH, TES and GPN in dosage form. Working standard stock solutions of ABH, TES and GPN were individually prepared in distilled water to achieve a concentration of 1000g/mL. From these stock solutions, the calibration curves ranging from 5-30 µg/mL for ABH, 25-125 µg/mL for TES and 15-75 µg/mL for GPN were established. The sample solution was prepared from the chosen formulation to get a concentration of 15 µg/mL of ABH, 50 µg/mL of TES and 50 µg/mL of GPN.

Application of Chemometric models

For the application of chemometric models, standard mixture solutions containing different ratios of ABH, TES and GPN in their calibration curve range were prepared and their spectra was recorded in the spectral wavelength range of 200-400 nm. The spectral data from the standard mixture solutions was entered into MS-EXCEL. The absorbance and concentrations of the mixture solutions were organized into rows in the excel spreadsheet, and the names of the drugs and wavelengths were organized into columns, resulting in a massive matrix. The wavelength range selected for the spectral analysis is 220-300 nm with 5 nm data interval**.** The spectral data of the standard mixture solutions was imported into the software and the standard mixture solutions were divided into two groups. The first set is the training set, which was used to build calibrated models, and the second set is the prediction set which was used to predict the unknown concentrations of standard mixture solutions. Computations were made in the software by applying PCR and PLS models to predict the concentrations in the marketed formulation.

RESULTS AND DISCUSSION

Selectivity is a common issue in UV-vis spectroscopy with complex samples due to interferences of a few components with absorption spectra of target analytes. Furthermore, the use of standard UV spectral methods for multi-component analysis is less common in the literature. Another reason for this is that traditional methods, which are based on univariate calibration, may be incapable of resolving complex spectra. Chemometric tools have been found to be extremely useful in determining the drug content of multicomponent formulations in this type of analytical situations. Figure 1 depicted a grievous overlapping of the absorption spectra of ABH, TES and GPN and this was resolved by the applied chemometric PCR and PLS models.

Chemometric PCR and PLS models

The wavelength range chosen for the spectral analysis is 220-300 nm, with a data interval of 5 nm. Data below 220 nm was discarded due to noise, and data above 300 nm was not chosen due to infinitesimal absorbance. Data sets (training and prediction) were generated, and the calibration set was optimized using optimal factors.

On the calibration data set, a cross validation method with the K-fold procedure was applied to select the

optimal number of principal components (PCs) and latent variables (LVs) in the PCR and PLS models, respectively. The predicted concentrations in each test sample were compared to the actual concentrations, and errors were identified using RMSECV values. The RMSECV should be as low as possible because it indicates the accuracy and precision.

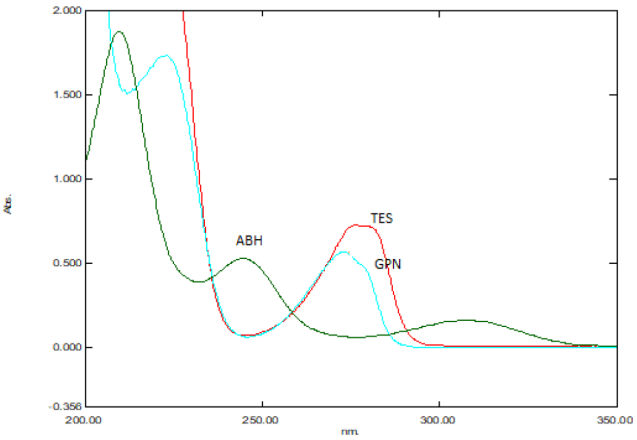

Figure 1: Overlay absorption spectra of ABH, TES and GPN.

The number of PCs in PCR and LVs in PLS was determined by the cross validation RMSECV values. The optimal number of PCs for ABH, TES and GPN for the PCR method were found to be 6, 3, and 5, respectively. The optimal number of LVs for ABH, TES and GPN for the PLS method were found to be 6, 3, and 7, respectively as shown in Figure 2. For the simultaneous determination of ABH, TES and GPN, the calibration set with the lowest RMSECV values was optimized. Tables 1 and 2 showed the results of the optimized PCR and PLS calibration models respectively. The actual and predicted values showed good correlation at the selected PCs and LVs, indicating the accuracy of the developed models. The statistical

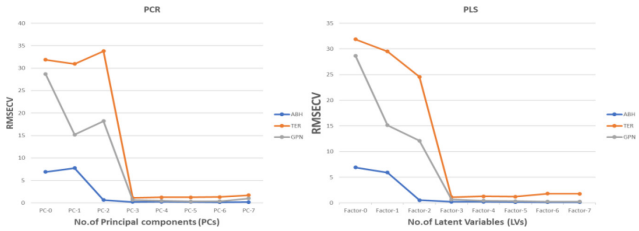

Figure 2: RMSECV values of ABH, TES and GPN.

Table 1: Results obtained for training set of ABH, TES and GPN by PCR.

Calibration mixture	Principal Component Regression [PCR]					
	Predicted values (µg/mL)			% Recovery		
	ABH	TES	GPN	ABH	TES	GPN
1.	5.016	99.955	50.186	100.312	99.955	100.372
2.	4.873	100.544	69.977	97.451	100.544	99.968
3.	5.080	98.936	29.921	101.604	98.936	99.737
4.	15.069	51.076	69.616	100.458	102.151	99.451
5.	20.036	49.550	70.121	100.182	99.101	100.173
6.	9.953	99.805	10.057	99.527	99.805	100.566
7.	15.091	98.861	49.825	100.610	98.861	99.649
8.	24.991	125.399	49.998	99.965	100.319	99.997
9.	9.958	50.599	49.580	99.581	101.197	99.160
10.	14.975	49.502	90.430	99.836	99.003	100.478
11.	9.962	76.797	10.129	99.621	102.396	101.290
12.	19.932	24.543	10.035	99.658	98.174	100.354
13.	5.064	49.433	10.125	101.278	98.866	101.253
MEAN				100.006	99.947	100.188
SD				0.965	1.273	0.609
%RSD				0.965	1.273	0.608
Coefficient of correlation (R^2)				0.9999	0.9992	0.9999
RMSEC				0.063	0.815	0.220
RMSECV				0.156	1.127	0.330

Table 2: Results obtained for training set of ABH, TES and GPN by PLS.

Calibration mixture	Partial least squares regression [PLS]					
	Predicted values (µg/mL)			% Recovery		
	ABH	TES	GPN	ABH	TES	GPN
1.	5.012	99.955	49.981	100.237	99.955	99.962
2.	4.946	100.544	69.995	98.922	100.544	99.993
3.	5.039	98.936	30.072	100.776	98.936	100.241
4.	15.030	51.075	69.985	100.201	102.150	99.978
5.	20.008	49.551	69.988	100.042	99.101	99.983
6.	9.951	99.805	9.947	99.510	99.805	99.465
7.	15.042	98.861	50.042	100.282	98.861	100.084
8.	25.006	125.399	49.977	100.025	100.319	99.953
9.	9.951	50.599	49.955	99.512	101.197	99.911
10.	14.996	49.502	90.028	99.973	99.003	100.031
11.	9.982	76.797	10.029	99.824	102.396	100.292
12.	19.975	24.543	10.029	99.875	98.173	100.285
13.	5.061	49.433	9.972	101.212	98.866	99.722
MEAN				100.030	99.947	99.992
SD				0.549	1.273	0.216
%RSD				0.549	1.273	0.216
Coefficient of correlation (R^2)				0.9999	0.9992	0.9999
RMSEC				0.035	0.815	0.035
RMSECV				0.129	1.127	0.244

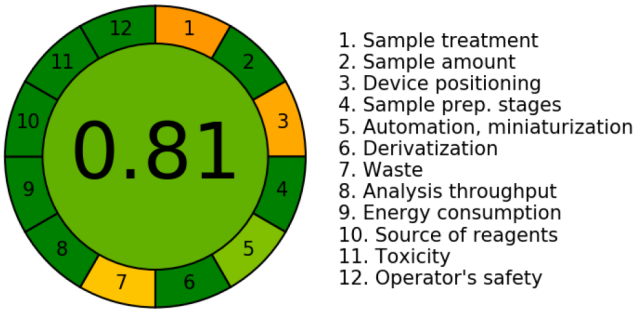

Figure 3: Results of AGREE analysis for proposed Chemometric assisted UV method.

parameters obtained for the calibration set, such as mean, standard deviation (SD), percent RSD, Root mean square errors of calibration (RMSEC), and Root mean square error of cross validation (RMSECV), were found to be within the acceptance criteria for both the PCR and PLS models. Hence, this calibration set was optimized and used to analyze the sample solution.

Validation of the optimized chemometric PCR and PLS models

To determine the predictive ability of the PCR and PLS models, external validation was performed on the test set, which comprised of nine standard mixture solutions that were not used in the calibration set. To predict the concentrations of ABH, TES and GPN, the optimized calibration set in PCR and PLS models was applied to the test set. The results of the test set revealed the accuracy of the developed models and the Root mean square error of prediction (RMSEP) values obtained from both models were found to be very low, indicating minor prediction errors. The percent recovery, RMSEP, and correlation coefficient values obtained from the validation set demonstrated the PCR and PLS models ability to accurately predict the concentrations in the marketed formulation.

Analysis of marketed formulation

The optimized and validated PCR and PLS models were applied to determine the concentrations of ABH, TES and GPN in the sample solution and assay results were shown in Tables 3 and 4 respectively. The assay results obtained for ABH, TES and GPN in the marketed formulation by PCR and PLS models were found to be within the acceptance criteria which depicted that both the PCR and PLS models could be applied for the simultaneous determination of drugs without any prior separation. The statistical parameters obtained for the training set, test set and sample solution by PCR and PLS models were summarized and presented in Tables 5 and 6 respectively.

Table 3: Assay results obtained for ABH, TES and GPN by PCR.

Marketed formulation [NORVENT]	Principal Component Regression [PCR]					
	Predicted values (µg/mL)			% Assay		
	ABH	TES	GPN	ABH	TES	GPN
1.	14.828	48.917	50.730	98.858	97.834	101.460
2.	15.074	49.785	50.674	100.498	99.570	101.349
3.	15.126	50.527	50.947	100.844	101.055	101.895
MEAN				100.067	99.486	101.568
SD				1.061	1.612	0.288
%RSD				1.060	1.620	0.284

Table 4: Assay results obtained for ABH, TES and GPN by PLS.

Marketed formulation [NORVENT]	Partial least squares regression [PLS]					
	Predicted values (µg/mL)			% Assay		
	ABH	TES	GPN	ABH	TES	GPN
1.	14.837	48.917	50.970	98.915	97.834	101.941
2.	15.092	49.784	51.082	100.620	99.568	102.165
3.	15.148	50.527	51.187	100.990	101.055	102.375
MEAN				100.175	99.486	102.161
SD				1.107	1.612	0.217
%RSD				1.105	1.620	0.212

Table 5: Statistical parameters obtained for ABH, TES and GPN by PCR.

Statistical parameters	Principal Component Regression [PCR]		
	ABH	TES	GPN
Concentration range (µg/mL)	5-30	25-125	15-75
No. of PCs	6	3	5
R^2	0.9999	0.9992	0.9999
RMSEC	0.063	0.815	0.220
RMSECV	0.156	1.127	0.330
RMSEP	0.060	0.291	0.232
Calibration set Mean ±SD	100.006±0.965	99.947±1.273	100.188±0.609
Validation set Mean ± SD	100.550±1.507	100.339±1.344	99.831±1.961
Assay Mean ± SD	100.067±1.061	99.486±1.612	101.568±0.288

Table 6: Statistical parameters obtained for ABH, TES and GPN by PLS.

Statistical parameters	Partial least squares regression [PLS]		
	ABH	TES	GPN
Concentration range (µg/mL)	5-30	25-125	15-75
No. of PCs	6	3	7
R^2	0.9999	0.9992	0.9999
RMSEC	0.035	0.815	0.035
RMSECV	0.129	1.127	0.244
RMSEP	0.061	0.291	0.222
Calibration set Mean ±SD	100.030±0.549	99.947±1.273	99.992±0.216
Validation set Mean ± SD	100.454±1.500	100.339±1.343	99.791±2.132
Assay Mean ± SD	100.175±1.107	99.486±1.612	102.161±0.217

Table 7: AGREE report sheet of the developed method.

Principle	Criteria	Response	Score	Weight
1	Direct analytical techniques should be applied to avoid sample treatment.	External pre- and treatment and batch analysis (reduced number of steps).	0.3	2
2	Minimal sample size and minimal number of samples are goals.	0.0025 g	1	2
3	If possible, measurements should be performed *in situ*. What is the position of the analytical device.	at-line	0.33	2
4	Integration of analytical processes and operations saves energy and reduces the use of reagents. How many major, distinct steps are there in the sample preparation procedure? These include sonication, mineralization, centrifugation, derivatization, extraction etc.	3 or fewer	1	2
5	Automated and miniaturized methods should be selected. Degree of automation and Sample preparation	Semi-automatic and none or miniaturized.	0.75	2
6	Derivatization should be avoided.	Not used	1	2
7	Generation of a large volume of analytical waste should be avoided, and proper management of analytical waste should be provided.	10ml	0.39	2
8	Multi-analyte or multi-parameter methods are preferred versus methods using one analyte at a time. No.of analytes determined in a single run and sample throughput (samples analysed per hour).	3 and 50	1	2
9	The use of energy should be minimized.	UV-vis spectrophotometry	1	2
10	Reagents obtained from renewable sources should be preferred.	No reagents	1	2
11	Toxic reagents should be eliminated or replaced.	Not used	1	2
12	Operator's safety should be increased.	Yes	1	2
	Score		0.81	-

Table 8: Comparison of analytical method parameters for the reported and proposed methods.

Parameter	RP-HPLC method for oral liquid	RP-HPLC-UV method for pure and dosage forms	Chemometric-assisted RP-HPLC method for combined dosage form	Proposed Method
Linearity	63.40-95.11 µg/mL (ABH) 68.00-302.52 µg/mL (GPN) 4.88-7.20 µg/mL (TES)	1.5—7.5 mg/mL (ABH), 4.0—14.0 mg/mL (GPN) 1.0—7.0 mg/mL (TES)	10-30 µg/mL (ABH) 10-30 µg/mL (GPN) 10-30 µg/mL (TES)	5-30 µg/mL (ABH), 15-75 µg/mL (GPN) 25-125 µg/mL (TES)
Correlation coefficient	0.9997(ABH) 0.9989(GPN) 0.9984(TES)	0.999(ABH) 0.999(GPN) 0.999(TES)	0.9998(ABH) 0.9995(GPN) 0.9998(TES)	0.9999(ABH) 0.9999(GPN) 0.9992(TES)
Accuracy	101.67% (ABH) 101.68% (GPN) 99.45% (TES)	100.66(ABH) 100.53(GPN) 100.43(TES)	99.52±0.31(ABH) 99.43±0.31(GPN) 101.62±0.83(TES)	PCR Method: 100.550±1.507(ABH) 99.831±1.961(GPN) 100.339±1.344(TES) PLS Method: 100.454±1.500(ABH) 99.791±2.132(GPN) 100.339±1.343(TES)
Assay	100.76(ABH), 101.34(GPN) 99.68(TES)	99.3(ABH), 99(GPN) 99.2(TES)	99.33±0.77(ABH), 98.70±0.46(GPN) 101.23±0.89(TES)	PCR Method: 100.067±1.061(ABH) 101.568±0.288(GPN) 99.486±1.612(TES) PLS Method: 100.175±1.107(ABH) 102.161±0.217(GPN) 99.486±1.612(TES)

Table 8: con't				
Applicability	Oral liquid formulation	Pure and dosage forms	Syrup	Syrup
Advantages of proposed method over reported methods	The proposed method is simple, economical, ability to resolve the spectra without prior separation of components can be used in regular and routine analysis in quality control laboratories.			

Greenness assessment of the method

The greenness assessment of the developed method was conducted using AGREE[17] to demonstrate its applicability and convenience. By default, equal weights have been set for all 12 principles evaluated, thus 355 assuming that all assessment criteria are equally important. The assessment criteria, method responses and the scores were shown in Table 7 and Figure 3. The greenness score of the developed method was assessed to be 0.81.

CONCLUSION

The current study illustrated the application of chemometric models PCR and PLS for the simultaneous determination of ABH, TES and GPN in the chosen multi-component formulation. Despite the fact that the three drugs in the study had severe overlapping in their absorption spectra, the developed models were able to determine drug content simultaneously without any prior separation. Data modelling using PCR and PLS methods was performed and the results obtained from both the models demonstrated the efficacy of chemometric tools in multicomponent analysis. The results of the proposed methods were compared with the reported methods as shown in Table 8. The models developed in this study can be used in regular and routine analysis in quality control laboratories.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ABH: Ambroxol hydrochloride; **GPN:** Guaiphenesin; **LVs:** Latent variables; **PCR:** Principal component regression; **PCs:** Principal components; **PLS:** Partial least squares regression; **RMSEC:** Root mean square errors of calibration; **RMSECV:** Root mean square error of cross validation; **RMSEP:** Root mean square error of prediction; **RP-HPLC:** Reverse Phase High Performance Liquid Chromatography; **RSD:** Relative standard deviation; **SD:** Standard deviation; **TES:** Terbutaline sulphate; **UV:** Ultra-violet.

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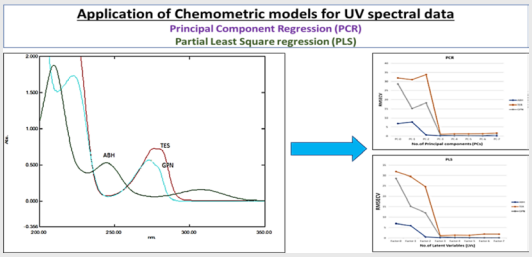
PICTORIAL ABSTRACT



SUMMARY

Quantification of multicomponent dosage forms with conventional UV spectroscopic methods poses a difficult problem to the analyst. Implementation of chemometric models like PCR and PLS to the UV spectral data makes the analysis of multicomponent dosage forms an easier task. In the current study, the formulation chosen was Norvent expectorant containing Ambroxol hydrochloride (ABH), Terbutaline sulfate (TES) and Guaiphenesin (GPN) which is prescribed for the treatment of chronic bronchitis. Training data set with thirteen standard mixture solutions of ABH, TES and GPN was prepared to apply the PCR and PLS models. The models were executed in the wavelength range of 240-310 nm with 1 nm data interval. Average % purity obtained for ABH, TES and GPN by PCR method was 100.06%, 99.48% and 101.56% respectively and by PLS method was 100.17%, 99.48% and 102.16% respectively.

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