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Salbutamol sulfate and beclomethasone dipropionate in capsules are simultaneously estimated using a chemometrically assisted UV-spectrophotometric technique.

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Abstract
This work describes a practical novel technique for the simultaneous measurement of salbutamol sulphate and beclomethasone dipropionate with little sample pretreatment. The process has been assessed using the partial least squares method (based on the SIMPLS algorithm) and multivariate analysis of spectral data in the 220–260 nm band. The root mean square error of calibration (RMSEC) and coefficient of determination (R2) are used to evaluate the calibration model. While the RMSEC values (0.8637) obtained were relatively low, indicating acceptable precision of the analytical method, the coefficient of determination (R2) for the relationship between actual values and predicted values of both drugs was higher than 0.9930, indicating good accuracy of the developed method. 55 samples were used to produce the experimental calibration matrix, and 24 samples were used to construct the validation matrix. For both medications, the concentration range taken into consideration was 10.0-60.0 µg/ml. According to recovery investigations, the technique was effectively used for drug quantification in pharmaceutical formulations without interfering with excipients. The suggested approach is quick, easy, and suitable for use as a substitute for other analysis techniques in drug quality control.

Key Words: Chemometric partial least squares, Salbutamol sulfate and beclomethasone dipropionate

Introduction
Salbutamol sulfate (SAL) is chemically known as (RS)-1-(4-hydroxy-3-hydroxy-methylphenyl)-2-(tert-butylamino) ethanol sulphate, whereas beclomethasone dipropionate (BEC) is chemically known as 9 α-chloro-11β-hydroxy-16 β-methyl-3, 20-dioxopregna-1, 4-diene-17, and 21-diyl dipropionate (Fig. 1 A). Salbutamol Sulphate is a β2 agonist, and beclomethasone dipropionate is a steroidal medication used to treat asthma. For the treatment of bronchial asthma, a variety of medications are available on the market in both solo and combination forms; however, beclomethasone dipropionate and salbutamol sulfate are frequently given together1.
Simple UV2, RP-HPLC3,4, stability indicating HPLC5, and UPLC6 approaches for estimating beclomethasone dipropionate and salbutamol sulphate in combination are shown by the literature review. Chemometric techniques (multivariate calibration) are becoming increasingly important in the multicomponent investigation of mixtures using UV-VIS spectrophotometry7 under computer-controlled apparatus. In quantitative analysis, the method is helpful for resolving band overlap. The chemometric For complexed mixtures, approaches have been determined to be the preferred approach. The benefit of multivariate calibration in multicomponent analysis is that it allows for the quick identification of mixture components without the need for an initial separation step. It has been demonstrated that the chemometric method of control analysis on medicinal preparations is a reliable substitute for HPLC.
The work was done since, to the best of our knowledge, no chemometric-assisted UV spectrophotometric approach has been published for the simultaneous quantification of salbutamol sulfate and beclomethasone dipropionate.

Materials and Methods

Instrumentation: All solutions' spectra were recorded using a double beam UV-Vis spectrophotometer (Jasco V-550, Japan) equipped with a matched pair of 1 cm quartz cells. Spectra were obtained from 41 distinct wavelengths, or between 220 and 260 nm (data pitch 1 nm). At a scanning speed of 400 nm/min, the spectra were captured. Chemometric calculations and mathematical computations were applied using the PLS toolbox (version 4) in conjunction with MATLAB 7.0 and Microsoft Excel 2007.

Chemicals and reagents: As gift samples, genuine samples of salbutamol sulfate and beclomethasone dipropionate were acquired from Cipla Pharmaceuticals Ltd. (Mumbai, MH, India). The Aerocort Rotacaps® formulation (Cipla Pharmaceuticals Ltd., Mumbai, MH, India) was purchased from the local market and was labeled to contain 100 mg of beclomethasone dipropionate (IP) and 100 mg of levosalbutamol sulfate (IP), which is comparable to salbutamol. AR for MethanolS.D. Fine Chem. Ltd. (Mumbai, MH, India) provided the grade.

Getting working solutions and standard stock ready: 10 mg of each drug, BEC and SAL, were individually dissolved in 10 ml of methanol (1000 µg/ml) to create standard solutions. A further 1 ml of this solution was pipetted and diluted to 10 ml (100 µg/ml). To achieve a final concentration of 10.0–60.0 µg/ml for both medicines, working solutions were made from a standard stock solution of 100 µg/ml by appropriately diluting it.

Building the validation and calibration set: The BEC and SAL solutions were combined in various ways to create the calibration and validation mixture sets.

BEC and SAL were quantitatively analyzed using the multivariate approach (PLS) calibration. In multivariate approaches, creating the calibration matrix is the initial step. The 2D scores plot for the first two latent variables (LVs) of the entire calibration matrix was acquired to verify the mixtures' well-positioned position in space, orthogonality, symmetry, and rotatability, as shown in Fig. 3, in order to validate the developed model's high predictability. To achieve the best results, the data was mean-centered. Our study used leave one out (LOO) cross validation, which is computed using the formula below, to optimize the number of PLS components. (2)2 ratios that vary from 10.0 to 60.0 µg/ml, which is their individual linearity range. Seventy-nine mixes were made.

Where,

RMSECV is equal to √¹ *Ic* Of them, twenty-four were used as validation sets and fifty-five were used as calibration sets (Table 1 and Table 2). From the linearity range, the validation set was chosen at random. Every blend was scanned in the 220–260 nm range. MATLAB software was used to create the PLS model using absorption data.

Assay sample solution preparation: Twenty Aerocort Rotacaps® capsules were weighed after being emptied. After being transferred to a 10 ml volumetric flask, the powder containing 10 mg of BEC and 12.04 mg of SAL (or 10 mg of salbutamol) was diluted with methanol, sonicated for 10 minutes, and the volume was adjusted to 10 ml. After filtering the solution and making additional methanol dilutions, the final concentrations were 10.04 µg/ml of SAL and 10.04 µg/ml of BEC. The process was carried out six times. The constructed PLS model was used to calculate the percentage recovery (Table 3).

Accuracy: Recovery experiments were conducted by spiking the standard medication to the Aerocort Rotacaps® sample solution (assay solution) at three distinct levels of 50, 100, and 150% in order to verify the method's accuracy. For BEC and SAL, the sample solution's basic concentration was 10 µg/ml and 12.04 µg/ml, respectively. Table 4 shows the results as a percentage of recovery.

Findings and Conversation

Figure 2 shows the overlay of the absorption UV spectra of pure BEC and SAL in methanol in the wavelength range of 220-260 nm. The

medications showed considerable overlap, making it difficult to analyze them using UV spectrophotometry without treatment; for this reason, PLS was used.

Root mean square error of cross validation (RMSECV) Cact is the calibration set's actual concentration.

Cpre is the validation set's anticipated concentration. Ic is the total number of calibration set samples.

The RMSECV value of 0.9088 was displayed by the created model. One crucial preconstruction phase was choosing the ideal number of LVs; if too many elements were kept, more noise would be introduced into the data; if too few, essential information that would be needed for the calibration might be lost. Following the construction of the PLS model, it was discovered that, as Fig. 4 illustrates, the ideal number of LVs described by the developed models was two factors.

Following parameter adjustment and the calibration phase, the model was successfully used to analyze BEC and SAL in a validation set of 24 samples (Table 2). Fig. 5 plots the actual data against the projected concentration. The low root mean square error (RMSE) and relative error of prediction (REP) values for the validation set indicated that the current approach is accurate with regard to the validation samples. The generated model was utilized to forecast the BEC and SAL concentrations in pharmaceutical formulation in order to evaluate the practicability of the suggested approach. For BEC and SAL, the mean assay values were 100.04% and 99.99%, respectively (Table 3). With a percentage RSD of less than two, the accuracy findings likewise demonstrated nearly 100% recovery for both medications (Table 4).

Table 1: Concentration data of the different mixtures of BEC and SAL used in the calibration set

Mix. No.	BEC (µg/ml)	SAL (µg/ml)	Mix. No.	BEC (µg/ml)	SAL (µg/ml)
1	10	10	29	30	10
2	10	15	30	30	15
3	10	20	31	30	20
4	10	25	32	30	25
5	10	30	33	30	30
6	10	35	34	30	35
7	10	40	35	30	40
8	15	10	36	35	10
9	15	15	37	35	15
10	15	20	38	35	20
11	15	25	39	35	25
12	15	30	40	35	30
13	15	35	41	35	35
14	15	40	42	35	40
15	20	10	43	40	10
16	20	15	44	40	15
17	20	20	45	40	20
18	20	25	46	40	25
19	20	30	47	40	30
20	20	35	48	40	35
21	20	40	49	40	40
22	25	10	50	50	10
23	25	15	51	50	20
24	25	20	52	10	50
25	25	25	53	15	60
26	25	30	54	10	60
27	25	35	55	60	15
28	25	40	-	-	-

Table 2: Concentration data of the different mixtures of BEC and SAL used in the validation set along with its prediction data and % recovery

Mix. No.	BEC Actual (µg/ml)	SAL Actual (µg/ml)	BEC Predicted (µg/ml)	BEC % recovery	SAL Predicted (µg/ml)	SAL % recovery
1	10	15	10.024	100.241	14.882	99.213
2	10	25	10.018	100.184	25.101	100.406
3	10	35	10.051	100.510	35.073	100.208
4	15	10	14.931	99.541	9.991	99.907
5	15	20	14.880	99.197	19.888	99.439
6	15	30	14.885	99.232	29.963	99.877
7	15	40	14.898	99.318	40.090	100.225
8	20	15	19.901	99.503	14.879	99.191
9	20	25	20.371	101.854	25.013	100.052
10	20	35	20.206	101.031	34.874	99.640
11	25	10	25.313	101.253	10.119	101.186
12	25	20	24.894	99.576	19.997	99.984
13	25	30	25.258	101.032	30.044	100.146
14	25	40	25.190	100.761	40.422	101.055
15	30	15	30.292	100.972	15.203	101.353
16	30	25	30.261	100.870	25.278	101.111
17	30	35	30.015	100.052	35.112	100.319
18	35	10	34.887	99.678	10.106	101.058
19	35	20	34.859	99.598	19.808	99.040
20	35	30	35.055	100.157	30.186	100.619
21	35	40	34.960	99.885	39.875	99.688
22	40	15	40.112	100.281	14.982	99.877
23	40	25	40.134	100.335	25.188	100.751
24	40	35	39.890	99.726	34.802	99.435
Mean % recovery			-	100.199	-	100.157

Table 3: Result for BEC and SAL obtained from commercial formulations (assay)

Mix. No	BEC			SAL		
	Actual Conc. (µg/ml)	Predicted Conc. (µg/ml)	% Purity	Actual Conc. (µg/ml)	Predicted Conc. (µg/ml)	% Purity
1	10	9.8983	98.983	12.04	12.0116	99.6896
2	10	9.9708	99.708	12.04	12.2321	101.52
3	10	10.1038	101.038	12.04	12.1136	100.536
4	10	10.0212	100.212	12.04	12.1001	100.424
5	10	9.9191	99.191	12.04	11.9212	98.9393
6	10	10.1104	101.104	12.04	11.9111	98.8555
Mean	-	10.0039	100.039	-	12.0483	99.9941
SD		0.09062	0.9062		0.12414	1.0303
%RSD		0.90584	0.90584		1.03036	8.55143

Table 4: Accuracy results for BEC and SAL by proposed PLS method

Level	Sample (µg/ml)		Standard (µg/ml)		Predicted concentration (µg/ml)		% Recovery	
	BEC	SAL	BEC	SAL	BEC	SAL	BEC	SAL
50%	10	12.04	5	5	15.036	16.949	100.24	99.413
					15.113	17.135	100.753	100.504
					15.104	16.972	100.693	99.548
						Mean	99.399	100.156
						SD	0.280	0.594
						% RSD	0.278	0.595
100%	10	12.04	10	10	19.892	22.023	99.46	99.882
					20.112	21.974	100.56	99.659
					20.072	22.136	100.36	100.394
						Mean	100.182	100.057
						SD	0.585	0.376
						% RSD	0.585	0.376
150%	10	12.04	15	15	25.036	27.028	100.144	100.103
					24.985	26.887	99.94	99.581
					25.024	27.249	100.096	100.922
						Mean	101.980	101.524
						SD	0.106	0.675
						% RSD	0.106	0.674

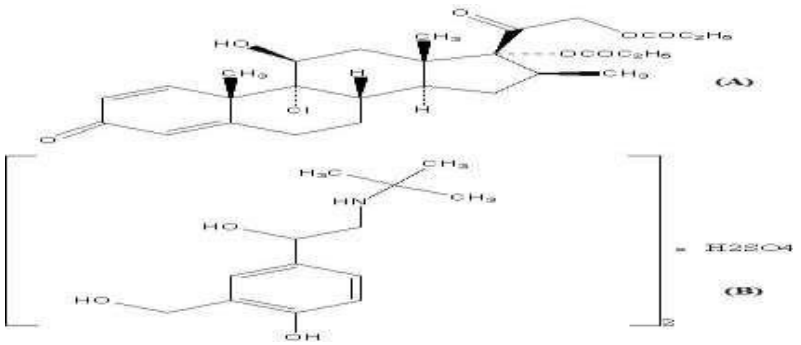

Fig. 1: Chemical structures of (A) Beclomethasone dipropionate and (B) Salbutamol sulphate

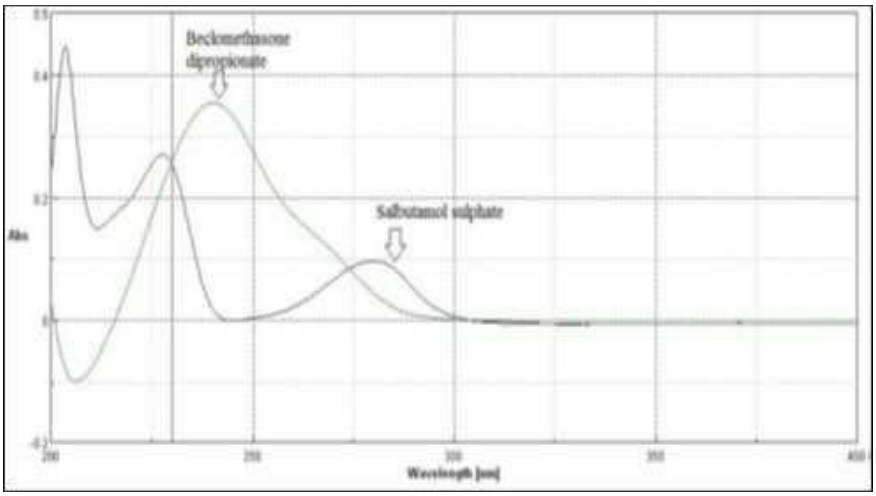

Fig. 2: Overlaid spectra of Beclomethasone dipropionate and Salbutamol sulphate (10 µg/ml each)

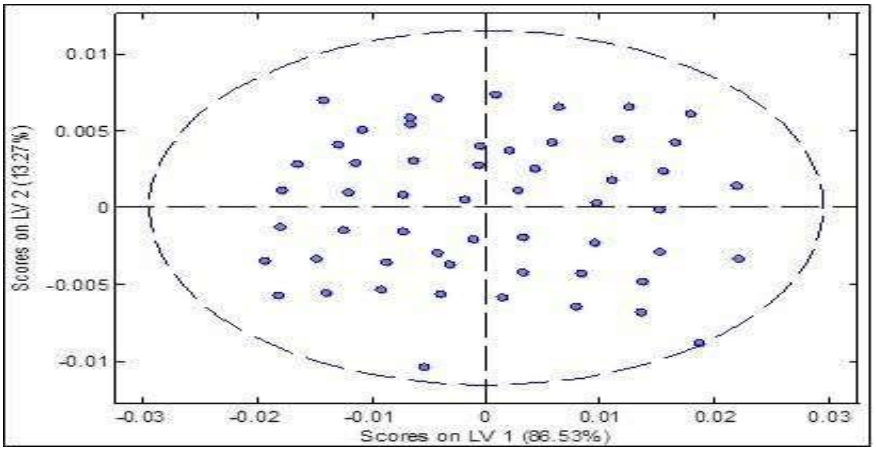

Fig. 3: 2D scores plot for the first two latent variables (LV 1 Versus LV 2) generated by using MATLAB software

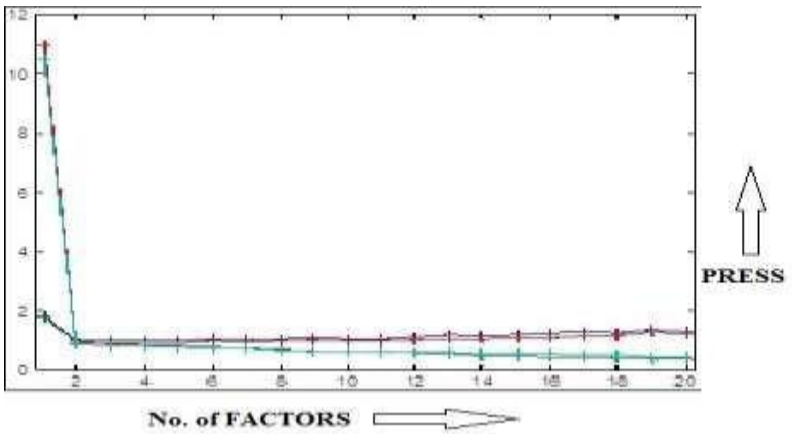

Fig. 4: Plot of PRESS versus number of factors by PLS method

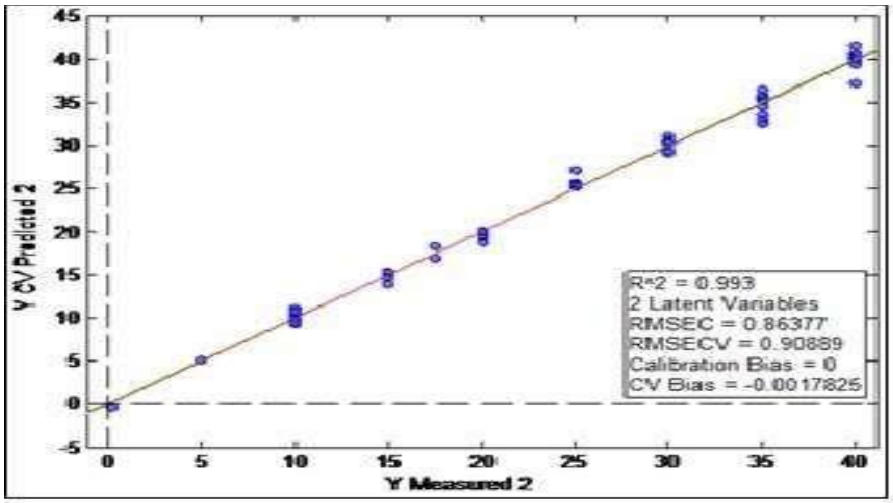

Fig. 5: Plots of predicted concentration versus actual concentration for BEC and SAL by PLS method

Conclusion

Salbutamol sulfate and beclomethasone dipropionate were successfully determined using a partial least-square regression model. The identification of these medications in test set samples demonstrated the effectiveness of the developed model. Drugs do not need to be separated before analysis using the suggested methods. The content of these medications in Aerocort Rotacaps® capsules was also effectively assessed using the model. Furthermore, the suggested techniques can be used for both in-process and medication analysis in quality control labs.

Recognitions

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