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Original Article

Spectrophotometric-Chemometric Method for the Quantitative Determination of Two-Component Cholesterol Drugs

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ABSTRACT

A novel spectrophotometric-chemometric approach has been developed for the concurrent quantitative determination of cholesterol-lowering drugs ezetimibe and simvastatin in pharmaceutical formulations. The proposed method integrates spectrophotometry with chemometric techniques, thereby enhancing analytical precision and accuracy. The spectral data were obtained in the ultraviolet-visible (UV-Vis) range and processed using multivariate calibration methods, including principal component regression (PCR) and partial least squares (PLS) regression.. This approach offers a cost-effective and efficient alternative for routine quality control and analysis of combination cholesterol therapies. In the case of simvastatin and ezetimibe, the solutions prepared for the analysis of their spectroscopic properties were prepared in a concentration range of 1-40 µg/mL. The evaluation of the mean values and RMSD values has served as the foundation for determining the suitability of the analytical approach (0.0063; 0.008; 0.0018; 0.015). The calculated PRESS value is nearly negligible, thereby enhancing the degree of precision. The obtained PRESS values are sufficiently diminished (0.0082; 0.020; 0.0044; 0.010). The chemometric models effectively resolved the overlapping absorption spectra of ezetimibe and simvastatin, enabling their concurrent quantification without prior separation. The method was validated in accordance with ICH guidelines, demonstrating satisfactory linearity, sensitivity, and robustness. Application to commercial pharmaceutical samples yielded results consistent with labeled claims, confirming the method's reliability and practical applicability.

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Introduction

The combination of ezetimibe and simvastatin has been the subject of extensive study in a variety of settings. The addition of ezetimibe to statin therapy, such as simvastatin, has been demonstrated to result in incremental reductions in low-density lipoprotein cholesterol (LDL-C) levels and improved

cardiovascular outcomes [1]. Moreover, ezetimibe has been demonstrated to augment the anti-inflammatory effects of simvastatin and enhance its impact on plasma adipokine levels [2]. Furthermore, this combination has been linked to a reduction in the necessity for coronary artery bypass grafting in patients with aortic stenosis [3].

Furthermore, the molecular mechanisms underlying the reduction of LDL apoB-100 by ezetimibe plus simvastatin include a reduction in VLDL production and an increase in LDL receptor-mediated LDL clearance [4]. The combination of ezetimibe and simvastatin has been demonstrated to result in greater reductions in plaque inflammation and proinflammatory markers than either drug alone [5]. Furthermore, the combination of simvastatin and ezetimibe has been shown to have a synergistic effect on lipid and pro-inflammatory profiles in subjects with prediabetes [6].

The combination of simvastatin and ezetimibe has demonstrated efficacy in reducing LDL-C levels and improving other lipid parameters in a range of patient populations [7]. Furthermore, studies have demonstrated that this combination therapy results in a notable additional reduction in C-reactive protein levels and improves insulin resistance in patients with hypercholesterolemia. However, it is crucial to acknowledge that there have been reports of adverse effects, including liver failure necessitating liver transplantation, associated with simvastatin-ezetimibe therapy [8].

A number of analytical methodologies have been devised and validated for the simultaneous determination of simvastatin and ezetimibe using chemometry [9] developed a derivative spectrophotometric method for the simultaneous determination of simvastatin and ezetimibe using the zero-crossing technique. Furthermore, [10] developed a high-performance liquid chromatographic method for the simultaneous determination of ezetimibe and simvastatin in pharmaceutical formulations.

Ezetimibe has been demonstrated to impede cholesterol absorption across the intestinal wall, resulting in diminished plasma cholesterol levels in preclinical animal models [11]. Conversely, simvastatin, an HMG-CoA reductase inhibitor, is understood to reduce circulating cholesterol levels and prevent myocardial infarction [12]. Furthermore, simvastatin has been examined in conjunction with other substances, including grapefruit juice, to evaluate its pharmacokinetics [13].

In conclusion, the development of analytical methods such as spectrophotometry and chromatography, in conjunction with the pharmacological actions of simvastatin and ezetimibe, provides a comprehensive approach to the determination of these compounds. The application of chemometric techniques serves to augment the precision and dependability of the analytical process, thereby facilitating the quality control of pharmaceutical formulations comprising simvastatin and ezetimibe.

Principal Component Regression (PCR) and Partial Least Squares (PLS) are two widely utilized methods across a multitude of research domains, including food analysis, drug analysis, and environmental studies. Principal Component Regression (PCR) is a regression analysis technique based on Principal Component Analysis (PCA). It employs the principal components identified through PCA in regression models. In contrast, PLS is a method that integrates the characteristics of principal component analysis and multiple linear regression to develop predictive models. Both PCR and PLS are effective in handling multicollinearity and reducing the dimensionality of data, thus making them valuable tools in chemometrics and data analysis [14-19].

PCR and PLS have been successfully applied in a number of domains, including pharmaceutical formulations, drug analysis, and environmental forecasting. These methods have demonstrated effectiveness in extracting pertinent information from intricate datasets, facilitating precise predictions and analysis. In the context of drug analysis, for instance, PCR and PLS have been instrumental in determining the components of pharmaceutical formulations and in analyzing the presence of specific compounds in biological samples [17,18]. Moreover, in the field of environmental studies, PCR has been employed to forecast rainfall patterns, while PLS has been utilized in air quality analysis, thereby demonstrating the versatility and robustness of these techniques [19, 20].

Moreover, the comparison between PCR and PLS has been a subject of considerable research interest, particularly in fields such as flight load calculation and spectroscopic data analysis. The results of studies have demonstrated that both methods exhibit high learning efficiency and strong generalization capabilities, rendering them suitable for a variety of applications [21].

Moreover, recent developments in PCR, including sparse PCR and Bayesian PCR, have further augmented the predictive capacity and interpretability of the models, thereby offering more insights into the relationships within the data [15,22].

In conclusion, PCR and PLS are valuable tools in data analysis, offering researchers effective methods for handling complex datasets, reducing dimensionality, and making accurate predictions. These methods have

been widely employed across diverse disciplines and have undergone continuous evolution to meet the demands of modern research, thereby underscoring their significance in the field of chemometrics and beyond. The use of chemometric techniques further enhances the accuracy and reliability of the analysis, contributing to the quality control of pharmaceutical formulations containing simvastatin and ezetimibe.

Material and Method

This study employed ultraviolet spectrophotometry to quantify the concentration of simvastatin and ezetimibe—two pharmaceutical agents used in the management of elevated cholesterol—within a test sample. Subsequently, the acquired absorption data underwent statistical assessment via Minitab 17 software [23]. In this study, a chemometric approach was employed for the simultaneous determination of the active pharmaceutical ingredients. In the initial stages of the experimental phase, each substance was subjected to analysis with the objective of ascertaining the spectroscopic characteristics of simvastatin and ezetimibe. Subsequently, the spectral data of synthetic mixtures prepared in identical ratios to the drug tablets obtained from the pharmacy were subjected to analysis. Subsequently, the suitability of the method and the resulting analytical data were evaluated. Subsequently, an analysis of the drug tablet sample was performed.

Equipment Used

UV-Visible Region Spectrophotometer

The spectra were recorded using a UV 1700 PHARMASPEC SHIMADZU spectrophotometer equipped with a 1 cm long cell controlled by a computer. The data of the recorded spectra were chemometrically evaluated.

Chemical Materials Used

The solvent of choice, methanol, was used for the preparation of simvastatin and ezetimibe, as well as all other chemicals utilized in the study. All solvents and chemicals were of analytical purity. In this study, stock solutions of simvastatin and ezetimibe were prepared at a concentration of 100 µg/mL using methanol as the solvent.

Method

In this study, spectrophotometric measurements were performed on the spectra of the active ingredients simvastatin and ezetimibe, first in single form and then in synthetic mixtures (1-40 µg/mL) systematically prepared in identical proportions to the drug mixture. Finally, measurements were performed on a sample of drug tablets obtained from a pharmacy. The spectrophotometric data were calculated and evaluated by different multivariate calibration methods. In the first step, the UV spectrophotometer was calibrated (zeroed). The calibration was first performed against air, leaving both cells empty. Then the same procedure was performed, this time with a blind sample prepared with the solvent we used in both light paths. The blind was always prepared in this way for all readings. When choosing the blind, the solvent was preferred as a blind to eliminate interfering effects. In the last step, the commercial tablet (Inegy) was analyzed. To prepare the drug sample, all the tablets in the package were crushed in an agate mortar, diluted and mixed. One tablet is weighed, dissolved in the solvent, homogenized by stirring in a magnetic stirrer and the absorbance is measured.

Result

100 µg/mL solutions of simvastatin and ezetimibe, used in the treatment of cholesterol diseases, were prepared using methanol as a solvent at 25 mg/250 mL. For simvastatin and ezetimibe, the solutions prepared to analyze the spectroscopic properties of each substance were prepared in the concentration range of 1-40 µg/mL. The wavelength at which simvastatin and ezetimibe gave maximum spectra was determined to be 236 nm and 242.5 nm, respectively.

Principal Component Analysis (PCA) of Active Pharmaceutical Ingredients Used in Cholesterol Treatment

Synthetic mixtures containing simvastatin and ezetimibe were prepared in the range of 1-40 µg/mL (Table 1.).

Table 1: Simvastatin and ezetimibe synthetic mixture calibration assay

S. No.	Simvasatin µg/mL	Ezetimibe µg/mL		Simvasatin µg/mL	Ezetimibe µg/mL
1	8	1	9	16	5
2	8	2	10	24	3
3	8	3	11	24	4
4	8	4	12	24	5
5	8	5	13	32	4
6	16	2	14	32	5
7	16	3	15	40	5
8	16	4			

All synthetic mixture data in Table 4.1. were statistically evaluated chemometrically. The absorption and concentration values of each mixture were the subject of analysis. Chemometric methods, which are multivariate calibration methods, are methods used to quantify each component of samples containing two or more components more quickly and reliably.

Simvastatin for the Treatment of Cholesterol Using Principal Component Regression (PCR) and Partial Least Squares (PLS)

One of the chemometric procedures used in this study is the partial least squares (PLS) procedure [24, 25]. The chemometric model is created with the help of the matrix that is formed from the relationship between the absorbance and the concentration and the chemometric calculations are made [26].

Table 2: Simvastatin mixture results calculated by principal component regression and partial least squares.

S. No	Simvastatin- PCR			Simvastatin- PLS		
	Added (µg/mL)	Calculated (µg/mL)	%Recovery	Added (µg/mL)	Calculated (µg/mL)	%Recovery
1	8	7.99	99.88	8	8.01	100.13
2	8	7.85	98.13	8	7.95	99.38
3	8	8.01	100.13	8	7.96	99.5
4	8	7.86	98.25	8	7.88	98.5
5	8	7.89	98.63	8	7.84	98
6	16	15.96	99.75	16	15.86	99.13
7	16	15.94	99.63	16	15.88	99.25
8	16	15.9	99.38	16	15.92	99.5
9	16	15.97	99.81	16	15.56	97.25
10	24	23.85	99.38	24	23.94	99.75
11	24	23.96	99.83	24	23.95	99.8

12	24	23.91	99.63	24	23.9	99.58
13	32	31.86	99.56	32	31.98	99.94
14	32	31.97	99.91	32	31.94	99.81
15	40	40.01	100.03	40	39.94	99.85
			Mean: 99.46 RMSD:0.0063 VK:0.63 R^2: 0.9999			Mean:99.29 RMSD:0.008 VK:0.80 R^2: 0.9998

RMSD: Relative Standard Deviation, VK: Coefficient of Variation

The calculated recovery and relative standard deviation (RMSD) data for each of the active pharmaceutical ingredients are shown in Table 2. The analysis of the mean values and RMSD values has been the basis for the determination of the analytical suitability.

Anova Test for PCR and PLS Methods for Simvastatin Active Pharmaceutical Ingredient

The calculated results were analyzed by ANOVA test [27] to ensure the appropriateness of the principal component regression method and partial least squares method among the multivariate calibration methods. When the values added and found in the principal component regression method of simvastatin were analyzed through ANOVA, the calculated F value was 0.0004 and the Fcritical (criterion) value was 4.20; for the partial least squares method, these values were F calculated value was 0.000070 and the Fcritical (criterion) value was 4.20. The fact that the Fcritical (criterion) value is greater than the Fcalculated value is one of the parameters considered to check the adequacy of the method. The calculated p-value is 0.98. The Pearson's correlation coefficient with the p value should also be greater than 0.05. The calculated ANOVA data were evaluated according to these steps.

Parametric Evaluation of PCR and PLS for the Drug Simvastatin

The minimum data of Predicted Residual Error Some of Squares→ PRESS were obtained in the cross-validation process in the arrangement of PLS and PCR calibrations for quantifying substances in mixtures prepared in certain ratios of simvastatin and ezetimibe drugs used in cholesterol treatment. The calculated PRESS value is close to zero, which increases the degree of accuracy [28]. The obtained PRESS values are small enough. The other parameters in the validation process are the standard error of the calibration: SEC and the root mean square error of the estimate: RMSEC [29].

Table 3: Validation Parameters for Principal Component Regression and Partial Least Squares Method.

Parameter	Simvastatin-PLS	Simvastatin-PCR
SEC	0.025	0.034
PRESS	0.0082	0.020
RMSEC	0.0023	0.037
LOD	0.107	0.194
LOQ	0.324	0.585

Application of Principal Component Regression and Partial Least Squares to Simvastatin Active Ingredient in Pharmacy-Delivered Tablets

Table 4: Drug Sample Results

S. No.	Simvastatin gram PCR	Simvastatin gram PLS
1	79.89	80.01
2	79.96	79.86
3	78.96	79.84
4	79.65	79.78
5	79.91	78.99
Mean	79.67	79.70
Relative Standard Deviation	0.0052	0.0038

It has been studied with the drug Inegy (Organon). It contains 80 mg of simvastatin and 10 mg of ezetimibe.

Ezetimibe for the Treatment of Cholesterol Using Principal Component Regression (PCR) and Partial Least Squares (PLS)

Table 5: Ezetimibe mixture results calculated by principal component regression and partial least squares.

S. No.	Ezetimibe- PCR			Ezetimibe - PLS		
	Added (µg/mL)	Calculated (µg/mL)	%Recovery	Added (µg/mL)	Calculated (µg/mL)	%Recovery
1	8	0.95	95.00	8	0.97	97,00
2	8	1.89	94.50	8	1.94	97,00
3	8	2.94	98.00	8	2.98	99,33
4	8	3.97	99.25	8	3.89	97,25
5	8	4.89	97.80	8	4.78	95,60
6	16	1.92	96.00	16	1.9	95,00
7	16	2.97	99.00	16	2.96	98,67
8	16	3.99	99.75	16	3.95	98,75
9	16	4.98	99.60	16	4.89	97,80
10	24	2.88	96.00	24	2.86	95,33
11	24	3.94	98.50	24	3.96	99,00
12	24	4.93	98.60	24	4.92	98,40
13	32	3.98	99.50	32	3.92	98,00

14	32	4.95	99.00	32	4.97	99,40
15	40	4.96	99.20	40	4.85	97,00
			Mean: 97.98 RSD:0.0018 VK:1.76 R^2: 0.9996			Mean:97.57 RSD:0.015 VK:1.46 R^2: 0.9992

In multivariate calibration methods, cross-validation was employed to calculate the concentrations found against the added concentration, thereby aiming to circumvent potential errors that may arise in the drug sample [30,31].

Anova Test for PCR and PLS Methods for Ezetimibe Active Pharmaceutical Ingredient

A statistical analysis was conducted to evaluate the efficacy of principal component regression (PCR) and partial least squares (PLS) methods for ezetimib, a pharmacologically active pharmaceutical ingredient. The F calculated value for PCR was 0.014, while the corresponding F critical value was 4.20. Similarly, the F calculated value for PLS was 0.032, with the F critical value equaling 4.20. One of the parameters that must be verified to ensure the suitability of the method is that the F critical (criterion) value must exceed the F calculated value. Furthermore, the Pearson correlation coefficient, which is the p-value, must also be greater than 0.05. The calculated p-values are 0.98 and 0.85, respectively. The calculated ANOVA data were subjected to an evaluation in accordance with the aforementioned steps.

Parametric Evaluation of PCR and PLS for the Drug Ezetimib

The validation parameters were calculated with the objective of quantifying the ezetimibe active substance present in mixtures.

Table 6: Validation Parameters for Principal Component Regression and Partial Least Squares Method.

Parameter	Ezetimibe-PLS	Ezetimibe-PCR
SEC	0.019	0.028
PRESS	0.0044	0.010
RMSEC	0.017	0.026
LOD	0.092	0.142
LOQ	2.788	0.431

Application of Principal Component Regression and Partial Least Squares to Ezetimibe Active Ingredient in Pharmacy-Delivered Tablets

Table 7: Drug Sample Results

S. No.	Ezetimibe gram	Ezetimibe gram
	PCR	PLS
1	9.95	9.89
2	8.99	9.05
3	9.84	9.82
4	9.91	9.95

5	9.98	9.86
Mean	9.73	9.71
Relative Standard Deviation	0.043	0.038

Discussion and Conclusion

A quantitative determination of the drug Inegy (Organon), which contains the active ingredients simvastatin and ezetimibe, was performed using chemometric and spectrophotometric methods. This determination was conducted for the purpose of assessing its efficacy in the treatment of elevated cholesterol. The spectrophotometric data were subjected to evaluation through the implementation of a chemometric program and associated methodologies.

In the initial experimental phase, the spectroscopic characteristics of the active pharmaceutical ingredients simvastatin and ezetimibe, utilized in the treatment of elevated cholesterol, were determined. This included the identification of the wavelength at which the maximum spectrum was observed, as well as the analysis of their respective absorbance spectra. Subsequently, the values of the synthetic mixture, prepared in a form suitable for a drug tablet combination procured from a pharmacy, were examined. The values obtained at this juncture were subjected to multivariate chemometric analysis and subsequently evaluated statistically. The values were initially quantified through principal component analysis (PCA). Subsequently, the partial least squares (PLS) and principal component regression (PCR) chemometric methods were employed.

In order to ascertain the accuracy of the PLS and PCR methods employed, an ANOVA test was applied to both methods. The quantities of substances introduced to the synthetic model were then compared with the results of the experimental procedures conducted using the chemometric program. An F-test was conducted with the assistance of degrees of freedom within and between groups. The F-test results informed the decision regarding the applicability of the model to the drug sample mixture. The model was applied when the value of FH was less than that of FT. In the final stage of the process, a synthetic mixture that was identical to the drug sample obtained from the pharmacy was prepared, and spectra were taken. In the case of simvastatin and ezetimibe, the method was subjected to statistical calculation through the application of chemometrics.

The multivariate chemometric methods of PCR and PLS were employed to ascertain the average values for the synthetic blend, which were subsequently found to represent the recovery of simvastatin and ezetimibe. The recoveries were found to be within an acceptable range, and the standard deviations were calculated in accordance with the study's specifications. The accuracy of the values obtained was evaluated using the F-test, which was applied to the PLS and PCR methods. It is evident that the calculated F-values are less than the theoretical values. In the cross-validation process for the establishment of PLS and PCR calibrations for the quantification of these substances in mixtures containing binary drug substances, the sum of squares of predicted errors (Predicted Residual Error Some of Squares→PRESS) and standard error of calibration (SEC) values close to zero enhance the accuracy and reliability of the results. As demonstrated in Tables 4.3 and 4.6, the PRESS and SEC values are sufficiently small, approaching zero. Furthermore, the LOQ values are notably smaller than the LOD values.

The chemometric-spectrophotometric method, as applied in this study, demonstrated reproducibility, high sensitivity, accuracy, and rapidity. It is therefore recommended for the analysis of different drug samples containing simvastatin and ezetimibe.

Author Contributions

Conceptualization: G.P..; Investigation: K.K., G.P..; Material and Methodology: A.H.A..; Supervision: G.P..; Visualization: K.K., G.P..; Writing-Original Draft: G.P.; A.H.A..; Writing-review & Editing: G.P.; A.H.A.; Other: All authors have read and agreed to the published version of manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethical Approval

Not applicable.

Data Availability

The raw data supporting the conclusions of this manuscript will be made available on genuine request.

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