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Chemometric Determination of Coloring Agents Used in Drugs

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Abstract

The chemometric determination of titanium dioxide and indigotin in drug by the principal component regression (PCR) was performed with spectrophotometric method. Chemometric methods are used in spectral data analysis of mixtures containing two or more compounds. With chemometric techniques, even complex systems are allowed to be analyzed spectrophotometrically as is without any pre-separation process. In this study, an alternative, lower cost and more reliable method has been developed in chemometric analysis of the colorants used in drugs. The investigation of the accuracy and repeatability of the two methods resulted in high recovery rates and lower standard deviation values. Achieving high recovery rates and lower standard deviation values, this study encouraged us to proceed further in drug analysis. The proposed methods are highly sensitive and precise as they have been successfully applied to quantify active substances in pharmaceutical samples.

Keywords: Titanium Dioxide; Indigotin; Chemometry

Introduction

Titanium dioxide, TiO2, is a naturally occurring, processed and refined mineral on the earth, and is also used as a pigment [1]. Indigotin is a natural origin pigment obtained from the leaves of the "Indigofera Tinctoria" plant [2]. In the literature, studies involving both color substances are as follows: Titanium dioxide is quantified by voltammetric analysis [3]; Indigotin is quantified by FTIR [4], chromatography [5,6]. When studies are examined, a study that makes room for chemometry has not been carried out yet.

The chemometric techniques are supported by mathematical models [7]. Principal component regression (PCR) is the most frequently used chemometric methods [8]. The analyses of multicomponent pharmaceutical products using these methods are well-accepted [9]. In this study, Minitab 17 program was used as chemometric program. The Minitab 17 program (Inova, Ankara, Turkey) [10] is a statistical analysis software used not only for performing statistical analyses but for training in statistics as well. It allows statistical analysis by using the relationship between Minitab and absorbance-concentration. In this study; the quantification of titanium dioxide and indigotin in drug performed by PCR. In first step, using the available medications of these two molecules, we prepared a drug sample containing a combination of titanium dioxide and indigotin. The validation of the chemometric-spectrophotometric method used in this study is included as an appendix to this article presenting the precision, accuracy, and selectivity of the methods. PCR method successfully identified and quantified colors in the drug simultaneously without any prior separation. The data were statistically crosschecked with their respective counterparts.

Experimental

Stock solutions were prepared at 25 mg/250 ml concentration using titanium dioxide and indigotin with hot H_2SO_4 in analytical purity. A training set and a validation set were prepared to contain these two drugs in various proportions. Consequently, 25 distinct synthetic mixtures were prepared to be used for validation and calibration and the absorption measurement of the substance was done with s Shimadzu UV-1700 PharmaSpec Spectrophotometer. Absorption values of titanium dioxide and indigotin were recorded λ_{TiO_2}:220 nm and $\lambda_{Indigotin}$: 630 nm. The calibration matrix and the training and validation sets containing two component mixtures in different proportions were used for calculating the concentrations and the concentration sets. The analysis of the drug mixtures was performed using PLS and PCR. Samples of 5.0 and 10.0 ppm of colors were placed in volumetric flasks (25 ml) and dissolved in hot H_2SO_4. A training set, a validation set, and 25 synthetic mixtures (for validation and calibration) containing the drugs in various proportions were prepared. They are presented in Table 1. In the last step, the coated part on the commercial tablet was prepared by stripping (in the hot) and color substances were determined and absorbance reading was done.

No.	Concentration, ppm	
	Titanium dioxide	Indigotin
1	2	1
2	2	2
3	2	3
4	2	4
5	2	5
6	4	2
7	4	3
8	4	4
9	4	5
10	6	3
11	6	4
12	6	5
13	8	4
14	8	5
5	10	5

Table 1: Concentration set for titanium dioxide and indigotin.

Results and Discussion

When the absorbance-concentration for titanium dioxide and indigotin were examined, it was observed that the absorbance value increases as the concentration increases. The linear relationship [11] between the absorbance and concentration values was confirmed by the fact that the regression coefficient [12] was close to the individual values (Table 4). The concentration values in the range of 1.0-10.00 ppm used in the study are the area where the linearity for each component was to be determined. According to Lambert-Beer [11], when the relationship between absorbance and concentration is examined, it is observed that the linear correlation coefficient [13] between the two variables is close to each other (Table 3).

Principal Component Regression (PCR)

Recovery and relative standard deviation (BSS) values calculated for each chemometric method from the contour sets in Table 1 are shown in Table 2, and Table 3.

No	Titanium dioxide			Indigotin		
	Added (ppm)	Found (ppm)	Mix No	Added (ppm)	Found (ppm)	Mix No
1	2	2.05	102.5	1	0.98	98
2	2	2	100	2	1.84	92
3	2	1.89	94.5	3	2.94	98
4	2	1.88	94	4	3.87	96.75
5	2	1.89	94.5	5	4.92	98.4
6	4	4.01	100.25	2	2.05	102.5
7	4	3.96	99	3	3.04	101.33
8	4	3.87	96.75	4	4.06	101.5
9	4	3.97	99.25	5	4.87	97.4
10	6	6.04	100.67	3	2.82	94
11	6	5.99	99.83	4	4	100
12	6	5.86	97.67	5	4.98	99.6
13	8	7.65	95.63	4	3.97	99.25
14	8	7.96	99.5	5	5.01	100.2
15	10	10.01	100.1	5	4.97	99.4
			Mean=98.27 % RSD=2.61			Mean =98.56 %RSD =2.78

Table 2: Composition of prediction set and recovery results obtained in synthetic mixtures for PCR method.

The statistical parameters were found to produce a satisfactory validity for PCR methods. The results are presented in Table 2. The results demonstrated that the standard deviation values were sufficiently small, and the recovery values were sufficiently close to 100. This shows us that the elicited results were appropriate.

Validation of the Method

The chemometric method was validated in accordance with ICH guidelines [14-16] with respect to linearity, accuracy, intraday and interday precision, limit of detection, and limit of quantitation. For calibration, the prediction of the residual error sum-of-squares (PRESS) was calculated from the added concentration of the drug and predicted concentration. According to the actual and predicted concentrations of the samples, *PRESS* values of colors were calculated and listed in Table 3. It is important to emphasize that this is not a correct way to normalize the *PRESS* values when not all of the data sets contain the same number of samples. But the standard error of prediction (*SEP*) values contains the number of samples. Some statistical parameters determined the effectiveness of the calibration where *n* – the total number of synthetic mixtures. *PRESS* and *SEP* values were close to zero with the PCR method. The degree of accuracy showed an increasing pattern.

The observable limit (LOD) and the detection limit (LOQ) parameters are interrelated but have different definitions (equation 1-2) [17].

LOD=3Sa/3 LOD=3Sa/m (1)
LOQ=10Sa/m LOQ=10Sa/m (2)
m: Slope
LOQ> LOD and LOQ = LOD were taken into consideration while evaluating the calculated LOD values [18].

Parameters	Method	Titanium dioxide	Indigotin
Correlation Coefficient (R^2)		0.998	0.996
SEC	PCR	0.026	0.022
PRESS	PCR	0.014	0.007
LOQ(µg/mL)	PCR	0.189	0.189
LOQ(µg/mL)	PCR	0.716	0.63

Table 3: Statistical parameter values for calibration step-simultaneous determination of paracetamol and amoxicillin using PLS and PCR methods.

Analysis of Drug

The experimental results of the two methods for the pharmaceutical formulation are given in Table 4 one can see that the obtained results are very close to each other.

	Titanium dioxide (mg)	Indigotin (mg)
NO	PCR	PCR
1	0.000017	1.45E-05
2	0.000016	1.37E-05
3	0.00002	1.25E-05
4	0.000015	1.36E-05
5	1.58E-05	1.42E-05
Mean	1.68E-05	1.37E-05
SD*	1.9E-06	7.65E-07

Table 4: Determination of colors in pharmaceutical formulation using PCR method.
*SD: Standard Deviation
All statistical parameters and numeric values were appropriate for simultaneous identification in drug.

Conclusion

The proposed principal component regression is rapid, precise and accurate for the simultaneous resolution of drug containing titanium dioxide and indigotin. In this study, PCR method is applied to the simultaneous quantitative prediction of titanium dioxide and indigotin in drug without requiring any separation step. For all values, low prediction errors and high correlation coefficients emphasized the high linear relationship between the predicted and actual concentrations.

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