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CHEMOMETRIC ANALYSIS OF PARACETAMOL AND METACLOPROMIDE IN BINARY DRUG COMBINATIONS

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ABSTRACT: In this study, the stomach environment of paracetamol and metaclopramide active substances was prepared with the aid of chemometric method and UV spectrophotometer and their concentrations were measured at certain ratios. Spectra of these two active substances were observed separately in UV spectroscopy at different concentrations. Spectra of paracetamol and metaclopromide were observed by UV spectroscopy at certain ratios and concentrations. These observed spectra gave us an idea by using the chemometric method to generate numerical data indicating whether these two drugs should be used together. Absorbance and concentration values were used in Minitab and other chemometric programs to calculate estimated concentrations with PCR and PLS. In the first step, the synthetic mixtures including paracetamol and metaclopromide were prepared and absorbance values are obtained from spectrophotometry. The second step, in drug tablets (Parol and Metpamid) was calculated amounts for paracetamol and metaclopromide. Because of recovery and standard deviation were accomplished, this study encouraged us to applied for drug analysis.

INTRODUCTION: Paracetamol is used as an analgesic in medicines, and metaclopromide is also used as medicinal medicines. These two drugs have obtained mixture spectra with certain persons or with certain drugs, spectrophotometry [1, 2]. It is a chemometric method calculated by small squares method according to the obtained data. Drug substances in this study [3]. Chemometric calibration methods are observed that it is the best techniques to determinate the amount of each component in the complex mixture. The most accepted chemometric methods in drug analysis are principal component regression (PCR) and partial least squares regression (PLS) [4].

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A relationship to be established between matrices of chemical data is determinated at chemometric methods [5].

In this study, principal component regression (PCR) and partial least squares regression (PLS) were successfully performed to simultaneous determination of paracetamol and metaclopromide in a commercial tablet formulation, tablets without any separation method. Mean recoveries (%) and standard deviation of principal component regression (PCR) and partial least squares regression (PLS) methods were calculated for the validation of the methods. The acquired results were statistically compared each other.

MATERIALS AND METHODS:

Chemicals and Reagents: All materials used were analytical grade. 0.025 g / 250 ml metoclopromide 0.025 g / 250 ml paracetamol stock solutions were made up with 0.1 M HCl. Mixtures were prepared at various ratios.

26 synthetic mixtures and 6 metaclopromide at certain concentrations were mixed with 6 paracetamol. Low conductivity water (0.05 S/cm) was obtained using Millipore's Milli-Q Integral lab water purification system.

Instruments and Software: A Shimadzu UV-1700 PharmaSpec Spectrophotometer connected to an IBM PS with UV Probe Software was used for all measurements and data processing. A pair of 1.0 cm quart cuvettes were used for absorbance measurements.

Absorbance Measurements: Interval corresponding to the difference 0.5 between 200 - 350 nm were recorded for the active ingredients of the absorbance spectra. Calibration matrix and training verification sets contain two component mixtures that are optimized at different ratios. Spectra analysis of pure agents and PLS and PCR were used to calculate the concentrations.

Samples of 1, 25 - 9 (µg / ml) (either alone or in combination) between the active substances were taken up into 25 ml volumetric flask volumes and completed with 0.1 M HCl. The mixtures were agitated for thorough mixing.

Concentrations of metoclopromide and paracetamol for PLS and PCR calibrations are shown in **Fig. 1**.

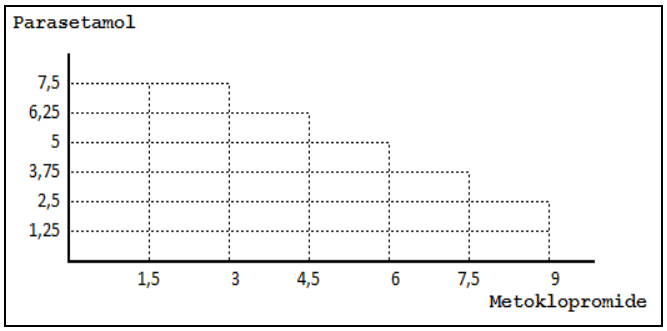

FIG. 1: CONCENTRATION SET DESIGN FOR THE PREPARATION OF THE PCR AND PCR CALIBRATIONS

Procedure for Real Sample: For this purpose, the active substance samples were transferred to 25 ml flasks and mechanically mixed in 0.1 M HCl in a medium similar to the stomach environment.

Chemometric Method: Partial least squares regression (PLS-regression) is the most commonly used chemometric multivariate calibration method[6].

PLS is done using both experimental (or x) and concentration (or c) data simultaneously. Usually PLS is presented in the form of equations. There are a few ways to express them, the most suitable for our purpose being:

$$X = T.P. + E \quad .....1$$
$$c = T.q + f \quad .....2$$

Where X refers to the experimental measurements (*e.g*. spectra) and c is the concentration. There is a correlation with an installation for vector vector q. Matrix T is common to both equations. E is an error matrix and error to prevent the x vector c to block scores f orthogonal, but non-orthogonal (P) loads, generally are non-normalized [7].

The Minitab 17 program (İnova, Ankara, Turkey) was used for the analysis of all the concentration and absorbance data and to do the statistical calculations. Minitab is a statistical analysis software. In addition to statistical research, statistics can be used to learn [8].

RESULTS AND DISCUSSION: Paracetamol and metaclopramide spectra are not in the visible region. **Fig. 2** shows the absorbance-wave length (nm) curves. The spectrum of paracetamol and metaclopramide is in the range of 200 - 350 nm.

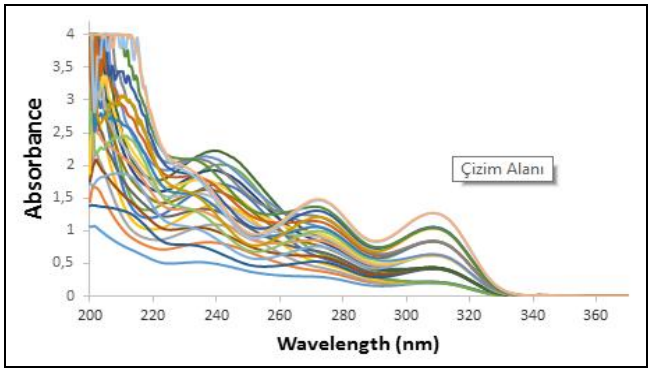

FIG. 2: THE SPECTRUM OF PARACETAMOL AND METOKLOPRAMIDE

Fig. 2 shows absorption spectra for Paracetamol, Metaclopramide and their binary mixture in 0.1 M HCl. Our objective in this study is to develop a lower-cost but more quick and reliable analytical method using chemometry. With this method, active ingredients can be analyzed without pre-separation, and loss of time and work due to the trial and error method will be prevented.

With the spectrophotometric-chemometric method used, the pharmaceutical industry will be faster and less costly. As a result, drug prices can be lowered so people can buy drugs more cheaply. The PLS method and absorption spectra can be used individually or overlapping for multiple simultaneous detection of very linear components. Concentrations of MET-PAR mixtures are listed in **Table 1**.

TABLE 1: CONCENTRATION SET CONTAINING MET AND PAR COMPOUNDS FOR THE PREPARATION OF THE PCR AND PLS CALIBRATION (µG ML-^{1})

	Concentration (µg mL^{-1})	
S. No	**MET**	**PAR**
1	6.0	5.0
2	6.0	10.0
3	6.0	15.0
4	6.0	20.0
5	6.0	25.0
6	6.0	30.0
7	12.0	5.0
8	12.0	10.0
9	12.0	15.0
10	12.0	20.0
11	12.0	25.0
12	12.0	30.0
13	18.0	5.0
14	18.0	10.0
15	18.0	15.0
16	18.0	20.0
17	18.0	25.0
18	24.0	5.0
19	24.0	10.0
20	24.0	15.0
21	24.0	20.0
22	30.0	5.0
23	30.0	10.0
24	30.0	15.0
25	36.0	5.0
26	36.0	10.0

The training set of 26 standard mixture solutions contain different concentrations of MET and PAR.

Prediction of the calibration methods was done by resolution of ten synthetic mixtures in a working concentration range for food colorants. Predicted concentration data of MET-PAR mixtures is shown in **Table 2**. The percentage recovered and relative standard deviations are also listed in **Table 2**.

TABLE 3: COMPOSITION OF PREDICTION SET AND RECOVERY RESULTS OBTAINED IN SYNTHETIC MIXTURES FOR PLS AND PCR METHODS

	Paracetamol-PLS			Metoclopramıde-PLS		
S. no.	**Actual (ppm)**	**Prediction (ppm)**	**% Recovery**	**Actual (ppm)**	**Prediction (ppm)**	**% Recovery**
1	5	4.98	99.6	6	5.98	99.66
2	10	9.97	99.7	6	5.86	97.66
3	15	14.96	99.73	6	5.97	99.5
4	20	19.97	99.85	6	5.94	99
5	25	24.97	99.88	6	5.92	98.66
6	30	29.96	99.86	6	5.86	97.66
7	5	4.98	99.6	12	11.96	99.66
8	10	9.96	99.6	12	11.98	99.83
9	15	14.97	99.8	12	11.84	98.66
10	20	19.98	99.9	12	11.97	99.75
11	25	24.96	99.84	12	11.93	99.41

12	30	29.89	99.633	12	11.97	99.75
13	5	4.96	99.2	18	17.98	99.88
14	10	9.98	99.8	18	17.99	99.94
15	15	14.97	99.8	18	17.94	99.66
16	20	19.96	99.8	18	17.92	99.55
17	25	24.98	99.92	18	17.93	99.61
18	5	4.96	99.2	24	23.98	99.91
19	10	9.98	99.8	24	23.97	99.87
20	15	15.01	100.06	24	23.85	99.37
21	20	19.56	97.8	24	23.96	99.83
22	5	4.96	99.2	30	29.98	99.93
23	10	9.96	99.6	30	29.95	99.83
24	15	14.98	99.86	30	29.96	99.86
25	5	4.93	98.6	36	35.94	99.83
26	10	9.93	99.3	36	35.87	99.63
			Mean=99.46			Mean= 99.57
			SS= 0.633			SS= 0.480

Paracetamol-PCR				**Metoklopramide-PCR**		
Karışım No	**Actual (ppm)**	**Prediction (ppm)**	**% Recovery**	**Actual (ppm)**	**Prediction (ppm)**	**% Recovery**
1	5	5.01	100.2	6	5.92	98.66
2	10	9.93	99.3	6	5.94	99
3	15	14.96	99.73	6	5.96	99.33
4	20	19.89	99.45	6	5.88	98
5	25	24.96	99.84	6	6.01	100.16
6	30	29.95	99.833	6	5.87	97.833
7	5	5.01	100.2	12	11.97	99.75
8	10	9.95	99.5	12	11.96	99.66
9	15	15.01	100.06	12	11.85	98.75
10	20	19.93	99.65	12	11.84	98.66
11	25	24.93	99.72	12	11.86	98.83
12	30	29.96	99.86	12	11.96	99.66
13	5	4.95	99	18	17.99	99.94
14	10	9.97	99.7	18	17.95	99.72
15	15	14.97	99.8	18	17.96	99.77
16	20	19.95	99.75	18	17.98	99.88
17	25	25.01	100.04	18	17.96	99.77
18	5	4.95	99	24	23.98	99.91
19	10	9.86	98.6	24	23.96	99.83
20	15	14.98	99.86	24	23.97	99.87
21	20	19.97	99.85	24	23.96	99.83
22	5	4.87	97.4	30	30.01	100.03
23	10	10.01	100.01	30	29.86	99.53
24	15	14.98	99.86	30	29.95	99.83
25	5	4.96	99.2	36	35.96	99.88
26	10	9.98	99.8	36	35.94	99.83
			Mean=99.59			Mean=99.46
			SS=0.591			SS=0.631

This study, the statistical parameters were found to produce a satisfactory validity for the PLS and PCR methods. The PLS and PCR methods have reliable accuracy and higher precision. For calibration the prediction residual error sum-of-squares (PRESS) was calculated as:

$$PRESS = \sum_{i=1}^{n} (C_i^{added} - C_i^{found})^2 \qquad ..... 3$$

C_i^{added}: True Concentration, additional concentration of drug substance

C_i^{found}: Estimated Concentration, calculate concentration of drug substance

Some statistical parameters determined the effectiveness of the calibration. The standard error of prediction (SEP) was calculated using the following expression:

$$SEP = \sqrt{\frac{\sum_{i=1}^{n}(C_i^{added} - C_i^{found})^2}{n-1}} \quad \ldots 4$$

C_i^{added}: Actual Concentration, the added concentration of drug

C_i^{found}: Predicted Concentration, the calculated concentration of drug

n: the total number of synthetic mixtures

According to the actual and predicted concentrations of the samples, SEP and PRESS values of Paracetamol and Metoklopromid were calculated and listed in **Table 3**.

TABLE 3: STATISTICAL PARAMETER VALUES FOR CALIBRATION STEP- SIMULTANEOUS DETERMINATION OF PARASETAMOL AND METOKLOPROMIDE USING PARTIAL LEAST SQUARE AND PRINCIPAL COMPONENT REGRESSION METHODS

Parameter	Method	Paracetamol	Metoclopromide
SEP	PLS	0.097	0.077
	PCR	0.058	0.078
PRESS	PLS	1.33	1.6
	PCR	1.11	1.55

Analysis of real samples: Table 4 lists the experimental results of the two numerical methods for commercial products and as you can see the obtained results are very close to each other. (Metpamid and parol)

TABLE 4: DETERMINATION OF PARACETAMOL AND METAKLOPROMID IN COMMERCIAL PRODUCTS USING PLS AND PCR METHODS

S. No.	Paracetamol (gram)		Metoklopromid (gram)	
	PLS	PCR	PLS	PCR
1	0.492	0.458	0.0098	0.0094
2	0.451	0.427	0.095	0.0096
3	0.424	0.409	0.086	0.0097
4	0.498	0.456	0.088	0.0093
5	0.429	0.489	0.089	0.0087
Mean	0.459	0.448	0.074	0.009
Standard Deviation	0.035	0.031	0.036	0.0004

In this study, chemometric methods can be applied to simultaneously measure spectra data processing based paracetamol and metaclopromide samples containing mixtures of homogeneously mixed binary drug samples. In order to compare the performances of the investigated chemometric techniques according to UV spectrophotometric method for real samples we applied Snedecor's *F*-test.

The method used to compare the differences between the one-way ANOVA tests was applied to real samples of the drug sample. In this study, F values of Snedecor were calculated and compared with F values (p = 0.05). The ANOVA test results for paracetamol were 0.0005 (PLS) and 0.0005 (PCR), Metaclopromide 0.0004 (PLS) and 0.0005 (PCR) for Paracetamol. Experimental (calculated) F values did not exceed F-value (4.03) in analysis of variance. This is the result of a meaningful difference between all these methods. All statistical parameters and numerical values are suitable for real-time simultaneous identification.

CONCLUSION: The partial least squares method and the main component regression, which were successfully applied, were able to identify the active ingredients in the synthetic solutions separately. For all values, low prediction errors and high correlation coefficients emphasize the high linear relationship between predicted and actual concentrations. The results obtained with this binary mixture and some ratios of component concentrations indicate excellent prediction ability with these methods.

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CONFLICT OF INTEREST: Nil

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