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Spectrophotometric Determination of Paracetamol, Propyphenazone and Caffeine in Tablets by Multivariate Calibration Approach

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Abstract

In this study, the simultaneous determination of Paracetamol (PAR), Propyphenazone (PRO) and Caffeine (CAF) in drug samples by chemometric approaches using UV spectrophotometry has been reported as a simple alternative to use separate models for each component. Spectra of Paracetamol PAR, PRO and CAF were recorded at several concentrations within their ranges and were used to compute the calibration mixture between wavelengths 220 and 280 nm at an interval of 5 nm was used for data acquisition. Principal component regression and Partial least squares regression were used for chemometric analysis of data and the parameters of the chemometric procedures were optimized. The analytical performances of these chemometric methods were characterized by predicted residual error sum of squares (PRESS), Standard Error of Prediction (SEP) and recoveries (%) and were compared with each other. A series of synthetic solution containing different concentrations of PAR, PRO and CAF were used to check the prediction ability of the principal component regression and partial least squares. These two methods were successfully applied to real samples, with no interference from excipients as indicated by recovery study results. The outcomes acquired in this examination firmly urge us to apply these strategies for a standard investigation and quality control of the three medications.

***Keywords:** Paracetamol; Propyphenazone; Caffeine; Spectrophotometry; Multivariate calibration*

Introduction

Analytical chemists are pushing the limits of each applicable mathematical method, from abstraction to simple, to applying them to solve analytical problems. The simplest method makes life easier and provides faster analysis of compounds.

Paracetamol (4-Hydroxyacetadenil), Propyphenazone (4-isopropyl-2, 3-dimethyl-1-phenyl-3-Pyrazolin-5-on) and caffeine (3,7-dihydroxy-1,3,7-trimethyl-1H-purine-2.6-Diony) are among the most commonly used pain relievers. This combination results in a decrease in the amount of prostaglandin, where CAF increases the analgesic effect of PAR and PRO, as well as

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relieves symptoms such as headache, muscle aches, neuralgia, back pain, joint pain, rheumatic pain, migraine, pain, toothache and menstrual pain [1]. Worked in the chemical structures of these three substances are shown in **FIG. 1**.

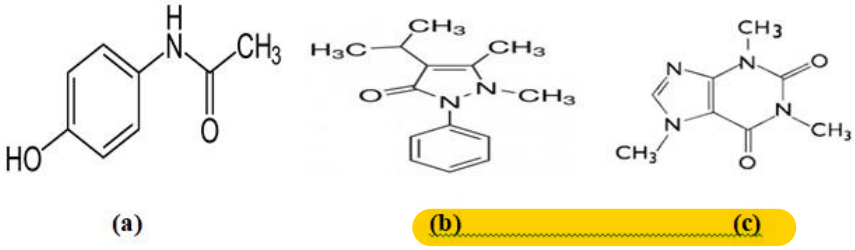

FIG. 1. **Structure of the drugs a). Paracetamol b). Propyphenazone c). Caffeine.**

The most used techniques for the determination of ternary and binary mixtures of these analytes (or for their individual determination) are the chromatographic ones, such as gas chromatography [2], HPLC [3-5], supercritical fluid chromatography [6] and micellar electro kinetic chromatography [7]. Other techniques used are FTIR spectrometry [8,9] and derivative spectrophotometry [10,11].

Amid the most recent decade the incredible chemometric strategies chief segment investigation (PCR) and halfway slightest squares (PLS) were utilized in phantom information examination for the blends containing at least two mixes with covering spectra [12]. These techniques have wide range applications, example give spectrometric [13,14], chromatographic [15] and electrochemical [16] quantitative investigation.

PLS and other chemometric methods can be applied to complex pharmaceutical mixtures with great success. These chemometric methods have to use abstract mathematical content, and in particular, it is not easy to apply and understand the theory of these chemometric techniques, such as PCR and PLS calibration theory. Although they have abstract theories and other deficiencies, they have been applied to analytical chemistry in addition to applied science. For these reasons, we believe that new methods should be introduced for quality control, quantitative analysis and routine analysis of the drugs in the samples.

The multivariate alignment strategies utilize full range, full computerization, multivariate information examination and the decrease of clamor and the benefits of the choice adjustment demonstrate. What's more these multivariate alignments needn't bother with any partition strategy, they are exceptionally shoddy, simple to apply what's more, extremely touchy. Consequently these multivariate strategies are well known today.

In this investigation two chemometric techniques were connected to break down the manufactured blends and tablets comprising of PAR, PRO and CAF within the sight of obstructions of the ingestion spectra. The utilization of chemometrics

permits the elucidation of multivariate information and is crucial to the accomplishment of the synchronous assurance of the clinical medications.

Experimental Section

Apparatus

A Shimadzu (Model UV-1700) UV-Visible spectrometer (Shimadzu, Kyoto, Japan), outfitted with 1cm coordinated quartz cells was utilized for spectrometric estimations.

Standard solutions

100 mg/100 ml CAF, PAR and PRO stock solution were used at 0.1 M HCl to install calibration set samples. A concentration set of 16 mixture solutions consisting of CAF, PAR and PRO in the concentration range of 4.0-12.0 µg/mL; 3.0-15.0 µg/mL and 10.0-30.0 µg/mL for CAF, PAR and PRO in the same solvent were symmetrically prepared from the prepared stock solutions respectively (**FIG. 2**). Symmetrical calibration set is preferred. This may occur during analysis to minimize calibration errors. To check the recommended methods, we used an independent verification set of synthetic blend solutions of CAF, PAR and PRO in the above study concentration ranges. The arrangements were steady for the slightest two weeks on the off chance that they had been put away in a cool (<25°C) and dull place.

Pharmaceutical preparations

A business sedate arrangements; Minoset Plus® tablet created by Bayer Pharm. Ind., Istanbul, Turkey, containing 30 mg caffeine, 250 mg paracetamol and 150 mg propyphenazone, per tablet were broke down by the proposed chemometric procedures.

Procedure for dosage forms

A precisely weighed pummeled tablet comparable to 100 mg of the considered medications was separated with 10 mL of 0.1 M HCl, weakened with water, and sonicated for around 15 min. The concentrates were separated into 100 mL volumetric carafes at that point washed and weakened to volume with refined water. Aliquots these arrangements were moved into a progression of 10 mL volumetric jars and the examination were finished as spectrometric method. Every one of the systems was connected to the last arrangement.

Chemometrics methods

PLS and PCR are factor investigation technique, in view of a two phase method; an adjustment venture, in which a scientific model is worked by utilizing part focuses and ghostly information from an arrangement of references, trailed by a forecast venture in which the model is utilized to ascertain the fixations obscure example from its range. These techniques are likewise called factor strategies since they change the first factors into fewer symmetrical factors called elements or essential segments (PCs), which are straight blends of the first factors. At the point when multivariate adjustment approaches are

connected in spectrophotometric multi segment examination, a connection among unearthly and fixation information from reference tests, speaking to the factors of the framework, is built up. Another grid established by the new factors PCs and scores is constructed. The computation of this new lattice is arranged by calculation explicit to the relapse technique embraced.

The real distinction in the prescient capacities of these two strategies is that PLS appears to foresee superior to PCR when there are arbitrary direct baselines or freely differing major ghostly segments which cover with the phantom highlights of the examination. The ideal of adjustment technique rely upon the specific test conditions. Be that as it may, PLS appears to a sensible decision over an extensive variety of conditions.

Results and Discussion

FIG. 2 shows the absorption spectra for PAR, PRO and CAF and their mixture in 0.1 M HCl.

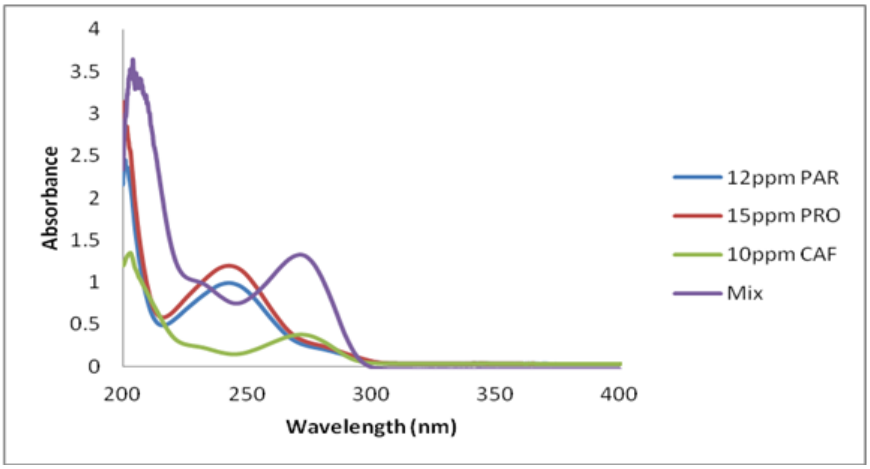

FIG. 2. **Original absorption spectra of 12 µg/mL PAR, 15 µg/mL PRO, 10 µg/mL CAF and their mixture in 0.1 M HCl.**

With the end goal to fabricate the two chemometric alignment, a preparation set was haphazardly arranged by utilizing the standard blend arrangement containing 4.0-12.0 µg/mL CAF, 3.0-15.0 µg/mL PAR and 10.0-30.0 µg/mL PRO in the variable extents as appeared in **FIG. 3**.

The absorbance information network were gotten by estimating at the 13 wavelengths with the interims ΔƛA=5 nm in the 220-280 nm otherworldly area. The readied alignments of three strategies utilizing the absorbance informational indexes were utilized to anticipate convergence of the obscure estimations of CAF, PAR and PRO in their blend.

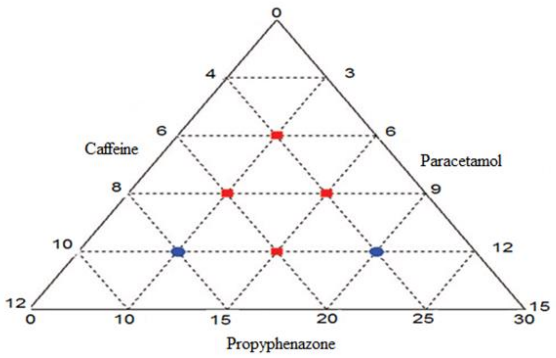

FIG. 3. **Concentration set design for the preparation of PCR and PLS calibrations.**

An adjustment for every strategy was processed in the MINITAB 16.0 and PLS Toolbox 4.0 programming by utilizing set comprising of three medications and their absorbance information. The multivariate alignments of two systems were utilized to anticipate the obscure convergences of CAF, PAR and PRO in the examples.

Some factual parameters were given for the approval of the developed adjustments for the preparation set and engineered ternary blends of medications.

The application skill of an alignment model can be clarified in a few different ways. We can likewise inspect these outcomes numerically. Extraordinary compared to other approaches to do this by looking at the anticipated leftover mistake whole of-squares or PRESS. To ascertain PRESS we figure the blunders between the normal and anticipated qualities for every one of the examples, square them, and whole them together.

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

Strikingly, this is certifiably not a right method to standardize the PRESS esteems when not the majority of the informational collections contain a similar number of tests. On the off chance that we need effectively look at PRESS esteems for informational collections that contain varying quantities of tests, we should change over to standard mistake of forecast (SEP), which is given by following recipe.

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

Where C_i^{added} the added concentration of drug is, C_i^{found} is the found concentration of drug and n is the total number of the synthetic mixtures. The SEP can give a decent proportion of how well, by and large, the adjustment demonstrates performs. Regularly, in any case, the execution of the alignment demonstrates changes relying upon the analyte level.

In the use of two chemometric procedures to the engineered blends containing three medications in factor creations, the mean recuperations and relative standard deviations for PCR and PLS were observed to be 100.04%, 1.57 and 100.06%, 2.12 individually for CAF, 100.36%, 5.31, 101.75% , 10.10 separately for PRO and 100.32%, 6.54 and 100.87%, 4.52 PAR (**TABLES 1 and 2**).

TABLE 1. **Results obtained for CAF, PRO and PAR indifferent synthetic mixtures by using PCR technique.**

Mixture (µg/mL)			**Found (µg/mL)**			**Recovery (%)**		
CAF	**PRO**	**PAR**	**CAF**	**PRO**	**PAR**	**CAF**	**PRO**	**PAR**
10	10	3	9.98	9.77	3.15	99.86	97.73	105.04
10	10	12	10.04	9.67	12.13	100.44	96.75	101.14
10	15	3	10.21	14.53	3	102.16	96.92	100.16
10	15	12	9.99	14.82	12.11	99.94	98.82	100.92
8	10	3	7.97	10.75	2.58	99.65	107.59	86.14
8	10	12	7.91	11.31	11.32	98.92	113.12	94.4
8	15	3	7.94	14.43	3.4	99.3	96.2	113.55
8	15	12	7.91	14.91	12.14	98.98	99.44	101.24
10	20	9	9.72	21.54	8.43	97.22	107.7	93.68
10	20	12	9.97	19.14	12.54	99.72	95.7	104.52
10	25	9	9.93	25.45	8.8	99.39	101.82	97.82
10	25	12	10.18	24.53	12.04	101.87	98.14	100.34
6	20	9	6	19.16	9.48	100.13	95.83	105.37
6	20	12	6.23	20.26	11.54	130.96	101.31	96.23
6	25	9	6.02	23.57	9.8	100.49	94.3	108.97
6	25	12	5.91	26.07	11.46	98.54	104.31	95.57
					$\overline{X}$	100.04	100.36	100.32
					RSD*	1.57	5.31	6.54
RSD*: Relative Standard Deviation								

TABLE 2. **Results obtained for LAN and DOM indifferent synthetic mixtures by using PLS technique.**

Mixture (µg/mL)			**Found (µg/mL)**			**Recovery (%)**		
CAF	PRO	PAR	CAF	PRO	PAR	CAF	PRO	PAR
10	10	3	9.88	10.18	3.13	98.89	101.83	104.61
10	10	12	10.03	10.2	11.45	100.34	102.08	95.49
10	15	3	10.34	14.77	3.37	103.45	98.53	112.56
10	15	12	9.95	15.21	11.96	99.55	98.82	99.73
8	10	3	7.89	10.92	2.89	98.65	101.46	96.59
8	10	12	7.85	11.92	11.65	98.19	109.2	97.13
8	15	3	8.12	14.98	3.16	101.6	119.27	105.53
8	15	12	7.9	14.29	12.31	98.75	99.91	102.64
10	20	9	9.77	19.94	8.93	97.71	95.32	99.25
10	20	12	9.97	20.66	12.06	99.75	99.71	100.53
10	25	9	9.66	19.24	8.92	96.66	103.3	99.17
10	25	12	10.33	24.03	11.87	103.39	76.96	98.94
6	20	9	6.09	24.6	9.56	101.5	96.15	106.33
6	20	12	6.1	19.85	11.5	101.71	123.03	95.86
6	25	9	5.87	24.96	9.07	97.99	99.29	100.84
6	25	12	6.17	25.51	11.85	102.88	102.06	98.78
					$\overline{X}$	100.06	101.75	100.87
					RSD*	2.12	10.1	4.52

RSD*: Relative Standard Deviation

As indicated by the additional fixation and the focus found in tests, the SEP and PRESS estimations of PCR and PLS procedures were determined 0.4254, 0.1830 and 0.2486, 0.5360 respectively for CAF, 0.8110, 0.4936 and 10.5238, 3.8988 respectively for PRO, 0.1246, 0.2893 and 2.8961, 1.3392 and PAR (**TABLE 3**).

TABLE 3. **Statistical parameters in the calibration-prediction.**

Parameter	**Method**	**CAF**	**PRO**	**PAR**
PRESS	PCR	0.2486	10.5238	2.8961
	PLS	0.536	3.8988	1.3392

SEP	PCR	0.4254	0.811	0.1246
	PLS	0.183	0.4936	0.2893
r	PCR	0.9943	0.979	0.9866
	PLS	0.9878	0.9929	0.9946
Intercept	PCR	0.0482	0.3681	0.1208
	PLS	0.1035	0.5413	0.2938
Slope	PCR	0.9943	0.9789	0.9866
	PLS	0.9878	0.9668	0.9658

The straight relapse examination of the additional focus and the fixation found in the engineered blends were acknowledged for each medication and for every alignment procedure. In this relapse examination, the connection coefficient (r), block, incline and relative standard deviation esteems were discovered palatable for the proposed chemometric systems in Table3. As can be seen, all the measurement esteems showed that all systems are helpful for the assurance of three medications in engineered blends.

An outline of the test results for the pharmaceutical detailing is given **TABLE 4**. The consequences of all strategies were extremely to one another and in addition to the name estimation of business medicate plan.

TABLE 4. **Assay results for the pharmaceutical formulation (mg/tablet).**

Drug	**PCR**	**PLS**
CAF (Mean ± SD*)	50.02 ± 0.12	50.12 ± 1.18
PRO (Mean ± SD*)	150.98 ± 0.84	150.05 ± 2.60
PAR (Mean ± SD*)	249.56 ± 0.52	250 ± 1.12
*SD : Standard deviation		

Results obtained are average of six experiments for each technique.

In this study, chemometric methods can be applied for simultaneous measurement of spectrum data-processing based caffeine, propyphenazone, and paracetamol samples containing mixtures of homogeneously mixed triple drug samples. We performed Snedecor's F-test to compare the performance of the investigated chemometric techniques according to the UV spectrophotometric method of actual samples.

The method used to compare the differences between one-way ANOVA tests was applied to the actual samples of the drug sample. In this study, the F values of Snedecor's were calculated and compared with the F values (p=0.05). The results of the

ANOVA test were 0.0024 (PLS) and 0.0005 (PCR) for caffeine, and 0.0018 (PLS) and 0.0006 (PCR) for propyphenazone, and 0.0001 (PLS) and 0.0018 (PCR) for paracetamol. Experimental (calculated) f values did not exceed F-value (4.17) in variance analysis. This is the result of a significant difference between all these methods. All statistical parameters and numerical values are suitable for real-time concurrent identification.

Conclusion

Two chemometric method in spectrophotometric investigation, PCR and PLS, were proposed for the synchronous assurance of CAF, PRO and PAR in their ternary blends. These strategies were connected with extraordinary accomplishment to business pharmaceutical tablets. The goals of exceptionally covering medication blends was accomplished by the utilization of PCR and PLS methods. A determination of working wavelength having high relationship esteems with fixation because of impedance originating from framework test or extra analytes outside the working extent. As indicated by the got outcomes, it was seen that the PCR strategy gave more exact outcomes than the PLS strategy in this mix of three drugs. The proposed chemometric methods can be connected for the normal examination of three medications in the tablet definition with no from the earlier concoction partition and without tedious.

Acknowledgement

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