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Simultaneous Determination of Acetylsalicylic Acid, Paracetamol and Ascorbic Acid in Effervescent Tablet by Different Chemometric Methods

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ABSTRACT

The spectrophotometric identification of acetylsalicylic acid, paracetamol, and ascorbic acid in the effervescent tablet.was investigated in this work. For acetylsalicylic acid, paracetamol, and ascorbic acid, chemometric analysis of the effervescent tablet.has proved successful. The spectrophotometric analysis of the effervescent tablet was done using the multivariate calibration methods: The multiple linear regression (UV-MLR) and The classical least squares approach (UV-CLS). Two spectrophotometric-chemometric methods were presented for the simultaneous prediction of the effervescent tablet in prepared mixes and pharmaceutical tablets without prior separation. The artificial mixtures were initially made with acetylsalicylic acid, paracetamol, and ascorbic acid, and the absorbance values were calculated using spectrophotometry. In the second stage, the amounts of common cold infection medications in the pharmaceutical tablets were calculated. Each medication's calibration curves are linear in the synthetic mix's concentration range. High recoveries and small standard deviations were determined, and the two techniques were evaluated for accuracy and repeatability. In the UV-MLR method, the SEC, PRESS, LOD and LOQ values were respectively; 0.032, 0.0040, 0.085, 0.283 for acetylsalicylic acid, 0.012, 0.0052, 0.091, 0.303 for paracetamol, 0,035, 0,0065, 0,084, 0,280 for ascorbic acid. In the UV-CLS method, the SEC, PRESS, LOD and LOQ values were respectively; 0.042, 0.0038, 0.057, 0.190 for acetylsalicylic acid, 0.025, 0.0057, 0.092, 0.307 for paracetamol, 0.054, 0.0058, 0.056, 0.187 for ascorbic acid.
The applied chemometric approaches give quick, simple, and reliable findings. The proposed methods have been successfully used to identify the active compounds (acetylsalicylic acid, paracetamol, and ascorbic acid) in the effervescent tablet because they are very sensitive and accurate.

Introduction

In this work, the multiple linear regression (UV-MLR) and the classical least squares approach (UV-CLS) were used to analyze the active components of the effervescent tablet, including paracetamol (PAR), acetylsalicylic acid (ASA), and ascorbic acid (AA). In the treatment of febrile illnesses and for pain relief, triple formulations of the active substances PAR, ASA, and AA are frequently utilized [1]. Acetylsalicylic acid

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is a medication with analgesic and antipyretic properties. It is frequently used to treat illnesses like the flu, headaches, menstrual cramps, joint pain, and muscular aches. Additionally, it can lower the risk of heart attack and stroke and stop blood from clotting. Additionally, acetylsalicylic acid has anti-inflammatory properties that might lessen bodily inflammation. Inflammatory disorders like rheumatoid arthritis may benefit from this [2, 3]. Acetaminophen, also referred to as paracetamol, is a popular antipyretic and painkiller available over-the-counter. It is a member of the analgesic (painkiller) and antipyretic (antipyretic) drug class. For mild to severe pain, such as headaches, toothaches, muscle pains, and menstrual cramps, paracetamol is frequently used. Additionally, it effectively lowers the temperature brought on by colds and the flu. The way that paracetamol works is by preventing the brain's generation of particular molecules that cause pain and fever. Although it is typically regarded as safe when used as advised, it is crucial to adhere to the suggested dosage and prevent overdosing because doing so can harm the liver [4,5]. The substance ascorbic acid is also referred to as vitamin C. It is a crucial nutrient for the body of a human. Due to its antioxidant capabilities, ascorbic acid acts as a barrier between the body and the damaging effects of free radicals. Additionally, it maintains the health of bones and teeth and enhances the immune system. Lack of vitamin C can cause exhaustion, immunological issues, and other health issues. Citrus fruits, green leafy vegetables, and some fruits naturally contain it. Ascorbic acid can also be found in dietary supplements and pharmaceuticals [6, 7].

The employment of concurrent chemometric approaches, statistics, and analytical methodologies has grown in relevance recently. The simultaneous determination of many compounds in the same sample is known as simultaneous chemometric determination. Despite the complex sample matrices, this method enables simultaneous determination of chemicals. Different methods of determination are employed for the simultaneous chemometric measurement of various analytes.

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One visual spectroscopic technique is the use of a spectrophotometer. By detecting the absorbance of the chemicals in samples, this instrument can determine the molecular concentration of those compounds. Additionally, a variety of techniques are available for concurrent chemometric determination. UV-MLR [8,9,10] and UV-CLS [11,12] are two techniques that employ spectral data to estimate the concentrations of various analytes.

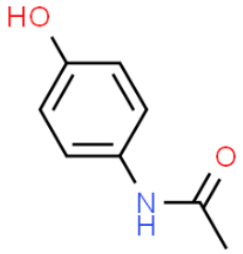
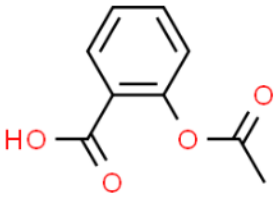
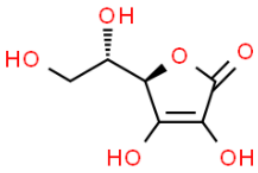
Paracetamol	
Acetylsalicylic acid	
Ascorbic acid	

Figure 1: Chemical structures of the active ingredients used in the study.

In several application domains, simultaneous chemometric analysis is used. It is employed, for instance, in the food and drug industries. Different chemicals in a sample can be determined simultaneously, cutting down on analysis time and expenses. As a result, simultaneous chemometric determination is a technique that enables simultaneous determination of many analytes in a single sample without the need for prior separation. These techniques are applied in numerous fields, speeding up analyses and cutting costs. Studies of PAR, ASA, and AA active chemicals in single or triple-binary form using various chemometric and analytical techniques are published in the literature [13–24]. The objective of this study is to perform adequate analytical quality the multiple linear regression (UV-MLR) and the classical least squares method (UV-CLS) analyses of the active ingredients

paracetamol (PAR), acetylsalicylic acid (ASA), and ascorbic acid (AA) in the effervescent tablet.

The employment of concurrent chemometric approaches, statistics, and analytical methodologies has grown in relevance recently. The simultaneous determination of many compounds in the same sample is known as simultaneous chemometric determination. Despite the complex sample matrices, this method enables simultaneous determination of chemicals. Different methods of determination are employed for the simultaneous chemometric measurement of various analytes. One visual spectroscopic technique is the use of a spectrophotometer. By detecting the absorbance of the chemicals in samples, this instrument can determine the molecular concentration of those compounds. Additionally, a variety of techniques are available for concurrent chemometric determination. UV-MLR [8,9,10] and UV-CLS [11,12] are two techniques that employ spectral data to estimate the concentrations of various analytes.

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Materials and Methods

Materials and Equipment's

Analytical grade stock solutions of 100 g/mL acetylsalicylic acid (≥99.0%) (Aldrich), paracetamol (>=97%) (Aldrich), and ascorbic acid (99.0%) (Aldrich) were dissolved in 0.1 M HCl (37%) . A Shimadzu UV-1700 PharmaSpec Spectrophotometer (Kyoto, Japan) was connected to an IBM PC running UV Probe software for all measurements and data processing.

Spectrophotometric Method

Absorption spectra for PAR, ASA, and AA were kept between 200 and 400 nm. The training and validation sets both contained three-component mixes with different concentrations. Calculating concentration levels and analyzing an effervescent tablet (Afebryl®) were done using UV-MLR and UV-CLS. Drug samples with concentrations of 5.0 µg/mL and 35.0 µg/mL were put in volumetric flasks (25 mL), and 0.1 M HCl was used to dissolve them. In a training set and a validation set, the drugs were given at various rates, and 19 synthetic combinations (for calibration and validation) were produced (Table 1). HCl is commonly used as a solvent to assist in the separation of the components of a mixture. The solvent of choice should have the ability to dissolve the components of the mixture. It is often an additive to drugs in order to improve their stability and solubility in water. A partial factorial design was employed in the calibration set's construction. Chemometric methods are founded on a carefully planned experiment. After the data was analyzed in accordance with the experimental design, 19 samples were produced.

Table 1: Concentration set for PAR, ASA, AA [25].

No.	Concentration, µg/mL		
	Acetylsalicylic acid	Paracetamol	Ascorbic acid
1	6	7	5
2	12	7	10
3	18	7	15
4	24	7	20
5	30	7	25
6	6	14	5
7	12	14	10
8	18	14	15
9	24	14	20

10	30	14	25
11	6	21	5
12	12	21	10
13	18	21	15
14	24	21	20
15	6	28	5
16	12	28	10
17	18	28	15
18	6	35	5
19	12	35	10

As a pharmaceutical tablet, Galepharma's Afebryl® effervescent tablets were analyzed using multiple linear regression (UV-MLR) and the classical least squares method (UV-CLS) chemometric techniques. Each tablet contained 0.300 g of acetylsalicylic acid, 0.300 g of ascorbic acid, and 0.200 g of paracetamol. 1 g of the materials were mechanically combined with 0.1 M HCl for this purpose, then put into a 25 ml vial.

Results

Between particular wavelengths, the absorption spectra of the PAR, ASA, AA, and combination solution were measured. Figure 2 displays the absorbance-wavelength plots.

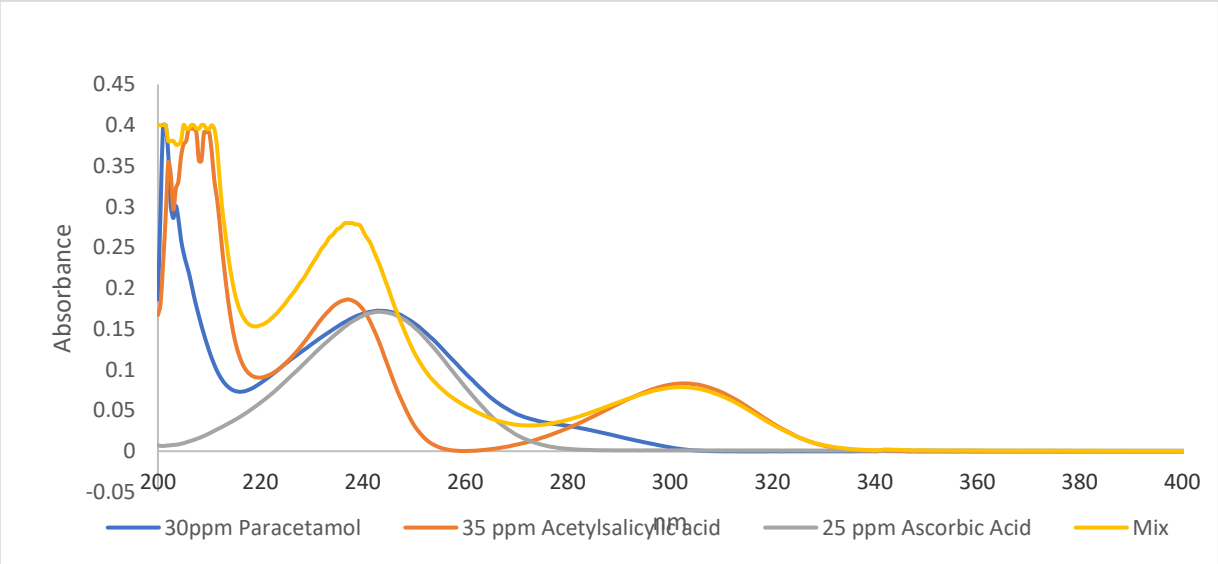

Figure 2: Original absorption spectra of paracetamol (30 ppm), acetylsalicylic acid (35 ppm), and ascorbic acid (25 ppm) in 0.1M HCl [25].

The absorbance values increase as the concentration increases, as seen by the plotted absorbance-concentration curves for three distinct medicines. The fact that the regression coefficient [27] is relatively close to the individual values (Table 2) confirms the linear relationship [26] between absorbance and concentration.

Table 2: Spectroscopic properties of drugs.

	λ_{max}	Correlation coefficient
Paracetamol	243 nm	0.9998
Acetylsalicylic acid	302,5 nm	0.9997
Ascorbic Acid	243 nm	0.9995

The Multiple Linear Regression (UV-MLR) and The Classical Least Squares (UV-CLS)

Using the statistical criteria used to evaluate the acetylsalicylic acid, paracetamol, and caffeine calibrations, the UV-MLR and UV-CLS procedures were determined to be reliable. The UV-MLR and UV-CLS techniques are incredibly accurate. According to the results (Tables 3), the standard deviation values are low enough and the recovery values are close enough to 100 to indicate that the results were reasonable.

Table 3: The composition of the prediction set and the recovery results obtained in synthetic mixes for the UV-MLR and UV-CLS approach

% Recovery UV-MLR			% Recovery UV-CLS		
Acetylsalicylic acid	**Paracetamol**	**Ascorbic Acid**	**Acetylsalicylic acid**	**Paracetamol**	**Ascorbic Acid**
98.90	96.58	97.56	99.66	99.84	98.97
99.85	99.85	97.96	98.96	98.56	98.94
99.73	99.29	98.56	98.96	98.64	99.95
99.68	98.68	99.86	99.32	99.87	99.61
99.72	99.22	99.93	99.65	98.69	98.96
99.50	98.75	98.89	99.52	99.65	99.87
99.80	98.85	98.95	98.97	99.84	99.89
99.53	98.89	99.67	98.74	99.75	98.94
99.90	99.96	99	99.62	98.94	99.01
99.62	99.94	99.02	98.96	98.92	99.55
99.70	99.86	98.95	98.74	98.99	98.86
99.25	99.92	98.94	98.92	98.74	98.84
99.87	98.74	98.98	99.26	99.69	98.72
99.95	98.56	98.63	99.56	99.87	98.7
99.72	97.99	96.56	98.63	99.84	95.63
98.50	98.96	97.96	97.54	99.68	97.54
88.90	98.93	98.92	99.64	99.96	97.53
97.65	99.36	96.63	99.88	98.9	96.61
99.63	99.45	99.56	98.74	98.63	99.23
Mean :99.44 % RSD:0.59	Mean :99.04 % RSD:0.82	Mean :98.66 % RSD:0.97	Mean :99.12 % RSD:0.55	Mean :99.32 % RSD:0.54	Mean :98.70 % RSD:1.14

Validation of the Method

According to ICH criteria, the chemometric technique was validated in terms of linearity, accuracy, precision between one and two days, limit of detection, and limit of quantification [28,29,30]. Equation 1's calibration uses the PRESS, or prediction residual error, sum. The formula for [31] was as follows:

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

where C_i^{added} is actual concentration, the added concentration of drug; and C_i^{found} is predicted concentration, the calculated concentration of drug. For acetylsalicylic acid, paracetamol, and caffeine, PRESS values were determined (Table 4) based on the samples' actual and expected to concentrations.

It is crucial to highlight that unless all data sets contain the same number of samples, this approach of normalizing PRESS values is flawed. However, the standard error of prediction (SEC) (Equation 2) takes the number of samples into account. Several statistical factors determined the calibration's effectiveness. The following formula was used to determine the SEC:

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

(2)

where n represents the overall number of artificial mixtures. RMSEC (equation 3.) [32], which is depicted in equation 3, is an additional validation parameter.

RMSEC=$\sqrt{PRESS/n}$ (3)

Although related, the definitions of the observation limit (LOD) and detection limit (LOQ) parameters differ (Equations 4 and 5) [33].

LOD=3Sa/b (4)

LOQ=10Sa/b (5)

b: Slope, Sa: The corrected standard deviation value

LOQ > LOD and LOQ = LOD were considered in the evaluation of the calculated LOD values [34].

The values of PRESS and SEC are nearly zero, indicating an increasing level of precision. For the UV-MLR and UV-CLS techniques, the computed PRESS and SEC values are nearly negative (Table 4).

Table 4: Values for the statistical parameters used to calibrate the UV-MLR and UV-CLS methods for determining step-simultaneous PAR, ASA, and AA measurements.

Parameters	Method	Acetylsalicylic acid	Paracetamol	Ascorbic Acid
SEC	**UV-MLR**	0.032	0.012	0.035
	UV-CLS	0.042	0.025	0.054
PRESS	**UV-MLR**	0.0040	0.0052	0.0065
	UV-CLS	0.0038	0.0057	0.0058
RMSEC	**UV-MLR**	0.0405	0.0521	0.0485
	UV-CLS	0.0127	0.0457	0.0158
LOD (µg/mL)	**UV-MLR**	0.085	0.091	0.084
	UV-CLS	0.057	0.092	0.056
LOQ(µg/mL)	**UV-MLR**	0.283	0.303	0.280
	UV-CLS	0.190	0.307	0.187
Accuracy (%Recovery±SD)	**UV-MLR**	99.44±0.59	99.04±0.82	98.66±0.97
	UV-CLS	99.12±0.55	99.32±0.54	98.70±1.14
Precision (Reproducibility)				
Intraday (% Recovery ±SD) (n:6)	**UV-MLR**	99.85±0.89	98.52±0.50	98.89±0.88
	UV-CLS	98.21±0.36	99.85±0.65	99.45±0.96
Interday (% Recovery ±SD) (n:6)	**UV-MLR**	97.42±0.35	98.89±0.96	99.87±0.85
	UV-CLS	98.22±0.96	99.05±0.69	97.96±0.57

Snedecor's F-test was used to assess the effectiveness of the examined chemometric techniques using the UV spectrophotometric method for material analysis [35]. On the genuine samples for each medicine, the ANOVA approach was utilized to examine the variations between the disposable tests. The Snedecor F-values were computed and compared to the experimental F-values in this inquiry. For each medicine, the exact same mathematical procedure was used. The F-values in the analysis of variance were not exceeded by the experimental (calculated) F-values. The within-group degrees of freedom for the two chemometric methods were 1 and 37, respectively, and the F-table value with a 96 percent confidence range for both was 4.01 for both. The F-test value for acetylsalicylic acid was estimated using the UV-MLR methodology to be

0.00054, with a p-value of 0.97; the F-test value for paracetamol was calculated using the same method to be 0.00059; and the F-test value for ascorbic acid was calculated using the same method to be 0.00069, with a p-value of 0.97. Acetylsalicylic acid had an F-test value of 0.00035 with a p-value of 0.97, paracetamol had an F-test value of 0.00045 with a p-value of 0.97, and caffeine had an F-test value of 0.00052 with a p-value of 0.97 in the UV-CLS technique. As a result, it was established that each of these methods differed greatly from one another.

Analysis of Pharmaceutical Tablet

Table 5. shows the experimental values of the UV-MLR and UV-CLS techniques for Pharmaceutical Tablet (Afebryl®Galepharma: 0.300 g acetylsalicylic acid; 0.300 g ascorbic acid; 0.200 g paracetamol) . The resulting results can be shown to be extremely near.

Table 5: Determination of PAR, ASA, and AA in human urine using UV-MLR and UV-CLS methods.

	Acetlysalicilic Acid (UV-MLR)			**Paracetamol (UV-MLR)**		**Ascorbic Acid (UV-MLR)**	
Mix No	**Found**	**Recovery**		**Found**	**Recovery**	**Found**	**Recovery**
		(% mean)			**(% mean)**		**(% mean)**
1	0.2988	99.6		0.1956	97.8	0.2964	98.8
2	0.2909	96.97		0.1964	98.2	0.2861	95.37
3	0.2945	98.17		0.1889	94.45	0.2881	96.03
4	0.2857	95.23		0.1874	93.7	0.2854	95.13
5	0.2878	95.93		0.1992	99.6	0.2997	99.9
Mean±SD		97.18±1.75			96.75±2.47		97.05±2.16
	Acetlysalicilic Acid (UV-CLS)			**Paracetamol (UV-CLS)**		**Ascorbic Acid(UV-CLS)**	
Mix No	**Found**		**Recovery (% mean)**	**Found**	**Recovery (% mean)**	**Found**	**Recovery (% mean)**
1	0.2876		95.87	0.1886	94.3	0.2847	94.9
2	0.2837		94.57	0.1974	98.7	0.2896	96.53
3	0.2942		98.07	0.1962	98.1	0.2789	92.97
4	0.2908		96.93	0.1852	92.6	0.2846	94.87
5	0.2888		96.27	0.1968	98.4	0.2987	99.57
Mean±SD		96.34±1.30			96.45±2.79		95.77±2.47

Discussion

Pharmaceuticals in synthetic solutions with pharmaceutical formulations could be found successfully using UV-MLR and UV-CLS at the same time. The tight linear relationship between anticipated and actual values for all values is shown by low error rates for estimation and high correlation coefficients. These methods have excellent predictive power, as shown by the outcomes with this ternary mixture and component concentration ratios. The sample had three separate active components, thus the UV spectroscopy data were examined chemometrically to analyze the drug molecules in the sample. By enhancing the UV spectrum, the strategy was statistically supported for PAR, ASA, and AA. The method's standard curves were subjected to regression analysis, and the findings were statistically calculated. The examination of the data collected using the chemometric program took the F-test into account. Analytical studies were carried out, and the UV spectra of the active components PAR, ASA, and AA were recorded to ascertain the purity at

which the study could be undertaken. By enhancing the UV the spectrum, the strategy was statistically supported for PAR, ASA, and AA. The method's standard curves were subjected to regression analysis, and the findings were statistically calculated. The examination of the data collected using the chemometric program took the F-test into account. Prior to employing the effervescent tablet sample, the outcomes were also compared to the synthetic model produced during the experimental design. The experimental outcomes produced from the chemometric program were compared with the synthetic models. Both the between-group and within-group degrees of freedom were used while conducting the F-test. Following the F-test result, we made the decision to apply the model we utilized to the drug sample mixture, however we were unable to do so. When FH, the model is utilized.

Conclusion

The excellent recovery rates also demonstrated that the medicines were not attached to the proteins in the urine. The validation process predicted the combinations having PAR, ASA, and AA faults. Additionally calculated are the calibration's standard error (SEC) and sum of squares (PRESS) values. SEC and PRESS values should be zero. The accuracy improves with proximity. The chemometric techniques are performed drug samples. For drug analysis, the sensitivity is great, therefore the outcomes are repeatable. According to the results, this method may be appropriate for determining PAR, ASA, and AA simultaneously in pharmaceutical formulations.

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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