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Original Article

A MODEST UV SPECTROPHOTOMETRIC ASSISTED BY CHEMOMETRIC APPROACH FOR VERIFICATION OF ACETAMINOPHEN LEVEL IN VARIOUS MANUFACTURED TABLETS AND SYRUPS IN INDONESIAN PHARMACIES

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ABSTRACT

Objective: This study aimed to verify the paracetamol level in some fabricated tablets and syrups in Indonesian pharmacies.

Methods: The fabricated tablets and syrups were analyzed using a spectrophotometer UV that was assisted by the chemometric approach. Partial least squares (PLS) and principal component regression (PCR) were the chemometric methods employed to verify the paracetamol level in pharmaceutical products. There were 25 different samples (tablets and syrups) applied in this study. The validation study was employed in this study to verify the approach according to the ICH guidelines. The double-distilled water was applied as a solvent before the samples were analyzed using a spectrophotometer.

Results: This technique was efficient and require double-distilled water only as a solvent. The results of this study reveal that there was a deviation in absorbance of the samples with RSD ranging from (0.15-0.45). The technique was linear, ranging from 1.0–6.0 µg·ml$^{-1,}$ with an R^2 (0.9991) obtained at 242 nm. The percentage recovery was applied to study the accuracy of the technique and was acquired at 99.18%. The results have shown that the approach was the potential to be applied in estimating the level of paracetamol in tablets and syrups.

Conclusion: The detection of paracetamol levels in tablets and syrups using UV spectrophotometric showed satisfactory outcomes. The application of the chemometric approach by using PLC and PCR as the statistical assessment indicated that there was no significant distinction among the validated methods. Furthermore, the method can be used by industries particularly small industries to secure medicines that comply with Indonesian rules.

Keywords: Acetaminophen, Pharmacies, Spectrophotometer, Syrups, Tablets

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INTRODUCTION

Indonesia is one of the developed countries and the pharmaceutical sector is a potential sector that contributes to the economy of Indonesia. Thus, the quality of the drugs spreading all over the country becomes great attention for many stakeholders such as the government, the manufacturers, and consumers [1]. Developing pharmaceutical products must be related to product quality. Furthermore, finding a suitable method for verifying the quality of pharmaceutical products becomes an imperative task [2].

Paracetamol (PAR) or known as acetaminophen, is generally applied as an antipyretic, anti-inflammatory, and analgesic. These effects occur owing to the production of cyclooxygenase (COX) 1 and 2 by prostaglandin is impeded by PAR [3]. The chemical structure of PAR that is illustrated in (fig. 1) shows that PAR activity is different compared to the other non-steroidal anti-inflammatory drugs (NSAIDs) owing to in peripheral tissues, the PAR has a mild impact on COX. Hereafter, the PAR influences blood platelet function and increases blood clotting time [4]. However, the application of PAR can be used for several issues such as fever, muscle ache, toothache, and arthritis [5].

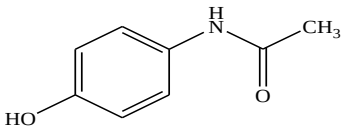


Fig. 1: The chemical structure of N-(4-Hydroxyphenyl) acetamide

Nowadays, the Covid-19 becomes a specter that haunted us and it can lead to several symptoms, whether heavy or mild such as fever, cold, and flu. However, some people who have good immunity want to continue their activity without worrying about those symptoms. Thus, fast healing is demanded to do the treatment, particularly for people with busy rosters, and demand to be vigilant and focused as soon as possible. Furthermore, it has been achieved successfully by pharmaceutical industries by merging two and more substances in their drug productions to medicate those symptoms in order to enhance PAR activity. Various components have been applied for PAR production, as illustrated in (fig. 2) [5]. However, verification of a specific substance in multicomponent formulations is a huge challenge for many researchers in order to improve the health care system. This is also imperative to access the drugs before spreading the medicines to the pharmacies [6]. Thus, the development of analytical techniques is imperative. Consideration of a suitable method is required, such as fast, modest, inexpensive, and at the same time, the method does not influence the reliability, precision, and accuracy of the results. The studies have unveiled numerous techniques for the detection of drugs, whether in single or multi-components [7-9]. Furthermore, only HPLC and UV approaches can be applied for the determination of paracetamol [10-14].

According to their studies, chromatographic methods are time-consuming and require too many solvents, which is not suitable for quality control laboratories. Furthermore, analytical experts are required to operate the instruments. Meanwhile, spectrophotometric techniques are considered inexpensive and fast. This instrument is not only can be purchased and easily found in most labs but also can be operated by anyone who is not an expert in

analytical instruments. The spectrophotometers offer substitute resolutions for complex mixtures of analytes with the requirement of prior separation or extraction [15-17].

Finding a selective and sensitive method to analyze paracetamol in tablets and syrups using a modest technique has encouraged us to develop a spectrophotometric approach that can be applied to the determination of the various combination. This technique applied a handy procedure with slight modification and does not apply sophisticated tools. Furthermore, the solvent used should be an eco-friendly product, such as the use of double-distilled water. The purpose of this study is to apply a spectrophotometric method supported by a chemometrics technique to increase the selectivity of this study. Partial Least Squares (PLS) and Principal Component Regression (PCR) are the chemometrics technique applied to verify the quantity of PAR in the products chosen. Chemometrics can be described as the interaction between the statistical and mathematical approaches in chemical analysis to stipulate the information by arranging the data. In this study, this method was applied to collect data from the spectrum and supply fast analysis with acceptable precision and accuracy without the requirement of sample preparation, which takes time [18-21].

The application of chemometric techniques offers several advantages when applied for the verification of pharmaceutical products, such as being free from disturbances and the determination being more accurate. Furthermore, the PLS application can improve the selectivity owing to the capability of PLS such as the errors can be minimized and the processing of data is faster with several absorbances and concentrations of analytes [22,23], whereas the least significant principal substances can be deleted by the PCR technique. The PLS and PCR models are specified by several parameters such as (1) root mean square error of calibration (RMSEC), (2) predicted residual sum of squares (PRESS), (3) root mean standard error of prediction (RMSEP), (4) root mean square error of cross-validation (RMSECV) and (5) merit fig. that can be described into several parameters such as selectivity, sensitivity, detection limit, and quantification limit [24, 25].

MATERIALS AND METHODS

Instrumentation

UV visible spectrophotometer model Thermo Scientific Evolution 201 double beam was applied. The scan was performed at intervals of 0.1 nm ranging from 230 to 400 nm, integration time at 0.05 sec, and scan speed at 1200 nm·min^{-1}. UV Insight Software was employed. Balance Fujitsu (Japan), stirring hot plate (Australia), sonic bath (India), and shaking water bath (China) were used in this research. The Unscrambler software was applied to interpret the data obtained from the spectrophotometer analysis.

Reagents (Chemicals and materials)

PAR (99.72% purity) was supplied from Sigma Aldrich, Indonesia as a reference standard. Marketed tablets and syrups containing PAR with various compositions are purchased from Indonesian pharmacies and listed in table 1. Double distilled water (Merck) was used throughout the experiment.

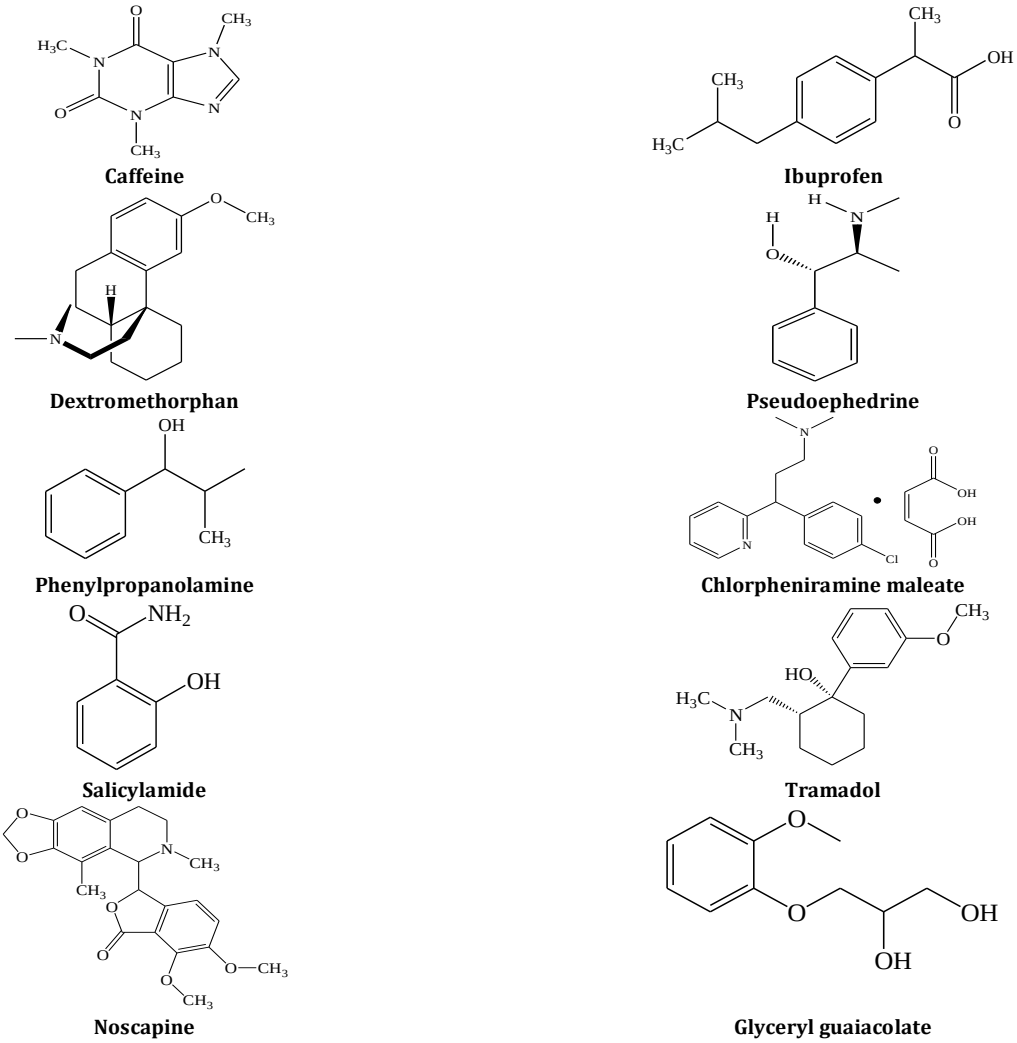


Fig. 2: Chemical structures of several compounds that are generally applied in several drugs fabricated in Indonesian pharmacies to support the activity of paracetamol

Table 1: List of samples (tablets and syrups) used in this research

Sample name	Paracetamol composition (mg)	Other ingredients (mg)
Biogesic	500	-
Panadol	500	-
Sanmol	500	-
Demacolin	500	Pseudoephedrine HCl (7.5 mg) and chlorpheniramine maleate (2 mg)
Ultracet	325	Tramadol HCl (37.5 mg)
Zetamol	500	-
Pyrexin	500	-
Paratusin	500	Noscapine (10 mg), chlorpheniramine maleate (2 mg), glyceryl guaiacolate (50 mg) and phenylpropanolamine HCl (15 mg)
Paracetamol capsule	500	-
Paracetamol Actavis	500	-
Neozep Forte	250	Chlorpheniramine maleate (2 mg), salicylamide (150 mg) and phenylpropanolamine HCl (15 mg)
Novagesic	500	-
Promed	500	-
Dapyrin	500	-
Fasidol	500	-
Bodrex	600	Caffeine (50 mg)
Procold	500	Dextromethorphan HBr (10 mg) and pseudoephedrine HCl (30 mg)
Farsifen plus	350	Ibuprofen (200 mg) and caffeine (50 mg)
Tempra syrup	160 mg/5 ml	-
Termorex syrup	160 mg/5 ml	-
Sanmol syrup	120 mg/5 ml	-
Praxion syrup	120 mg/5 ml	-
Panadol syrup	35 mg/1 ml	-
Pamol syrup	10 mg/0.6 mg	-
Alphamol syrup	120 mg/5 ml	-

"-": There are no additives in this product except paracetamol

Preparation of stock solution of paracetamol (50 µg·ml^{-1})

A standard stock solution of PAR was prepared by dissolving 2.5 mg that was transferred to a 50 ml volumetric flask and completed to the tag with double-distilled water. Several diluted solutions were also prepared to range from 1-6 µg·mL^{-1} by simple dilution of stock solution.

The verification of paracetamol level in tablets and syrups

For tablet formulation, ten tablets were accurately weighed and ground to a powder and homogenized. A tablet powder was weighed at 50 mg equivalent to PAR and moved to a 50 ml volumetric flask. The mixture was homogenized using a centrifuge for 3 min and filtered using Whatman filter paper (150 mm diameter). The filtrate was diluted to obtain a 10 µg·ml^{-1} of PAR. Whereas for syrup formulation, 0.1 ml of syrup was transferred to a 25 ml volumetric flask. The solution was homogenized using a centrifuge for 3 min and filtered using Whatman filter paper (150 mm diameter). The filtrate was diluted to obtain a 10 µg·mL^{-1} of PAR. The absorbance was gauged using the chosen wavelengths and the calibration curve was applied to determine the level of PAR in the pharmaceutical products.

Validation study

The validation study complied with the ICH guidelines [26]. The PAR concentration vs. absorbance was used to establish a calibration curve. Furthermore, by plotting the calibration curves at 1-6 µg·ml^{-1} of PAR, linearity was obtained. The accuracy was carried out using the PAR standard at different concentrations such as 80%, 100%, and 120%, meanwhile the precision was determined using the intraday and inter-day assessment. The detection and quantification limits are determined by calculating using the formula 3.3 (SD/n) and 10 (SD/n), concurrently.

PLS and PCR techniques

The scheming of the experiment

The calibration and prediction sets are established by arranging several codes to represent the eleven concentrations. The codes were-5,-4,-3,-2,-1, 0,+1,+2,+3,+4,+5; thus the central level of PAR was coded as (0) [27]. The central level for the design was 3.5 µg·ml^{-1} and the measured drug concentration was chosen in their mixture and its spectral sensitivity. The codes and PAR levels are presented in table 2.

The calibration and prediction sets arrangement

Several PAR concentrations (C_{cal}) were organized from a stock solution to obtain various concentrations as illustrated in table 2. The absorbance (A_{cal}) was recorded while the scan for the calibration set ranged from 230-400 nm. Whereas, for the prediction set, the PLS and PCR approaches were applied to predict the concentration of the mixtures by organizing the various PAR levels (C_{cal}) as presented in table 2. The absorbance (A_{cal}) was recorded while the scan for the calibration set ranged from 230-400 nm.

The development of PCR and PLS models

The spectral data of the calibration set was applied to establish the PCR and PLS models. By using the interval of 1 nm, the absorbance data were recorded ranging from 230-400 nm. A regression equation is acquired by plotting the C_{cal} and A_{cal}. The absorbance and concentration data were put into the computer and calculated to acquire the PLS and PCR models. Using the established model, the PRESS, RMSECV, RMSEC, RMSEP, and the correlation coefficient were determined [28, 29]. Furthermore, the merit fig. such as selectivity, sensitivity, detection limit, and quantification limit, were also analyzed. The sensitivity was determined by obtaining the slope of the analytical signal, while the selectivity was referred to as the difference between two concentrations determined by the PLS and PCR models. Furthermore, the detection and quantification limits were obtained by using the formula mentioned in *Validation Study*.

RESULTS AND DISCUSSION

Paracetamol standard analysis

The analysis of PAR at a wavelength of 242 nm. Thus, the spectrum of PAR (4 µg·ml^{-1}) is shown in (fig. 3) and indicated that the analysis was acceptable for PAR analysis.

Table 2: The establishment of 11 levels 3 factors to develop a calibration set illustrated as concentrations and coding levels of the substance

Paracetamol					
Standard	**Coding level**	**Conc. (µg·ml^{-1})**	**Standard**	**Coding level**	**Conc. (µg·ml^{-1})**
Calibration set			26	-4	1.5
1	1	4.0	27	1	4.0
2	0	3.5	28	0	3.5
3	0	3.5	29	0	3.5
4	-1	3.0	30	-1	3.0
5	-5	1.0	31	-5	1.0
6	4	5.5	32	4	5.5
7	3	5.0	33	3	5.0
8	-3	2.0	34	-3	2.0
9	0	3.5	35	0	3.5
10	5	6.0	36	5	6.0
11	2	4.5	37	2	4.5
12	-2	2.5	38	-2	2.5
13	-4	1.5	39	-4	1.5
14	1	4.0	40	5	6.0
15	0	3.5	Prediction set		
16	0	3.5	41	0	3.5
17	-1	3.0	42	4	5.5
18	-5	1.0	43	-5	1.0
19	4	5.5	44	3	5.0
20	3	5.0	45	2	4.5
21	-3	2.0	46	-3	2.0
22	0	3.5	47	1	4.0
23	5	6.0	48	-1	3.0
24	2	4.5	49	-2	2.5
25	-2	2.5	50	-4	1.5

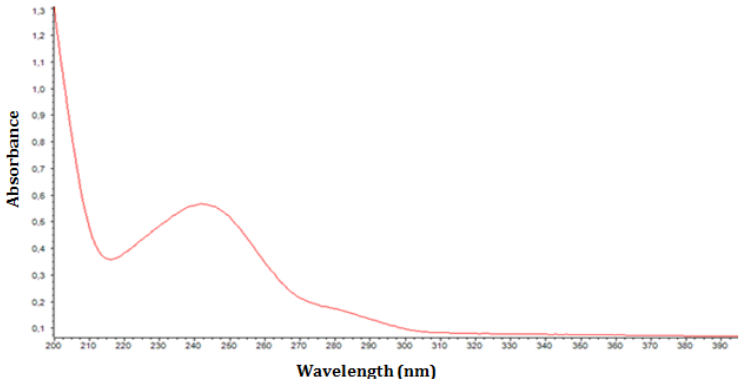


Fig. 3: The absorption spectrum of 4 µg·ml^{-1} of paracetamol (242 nm)

Fig. 4 illustrates that the calibration curves of PAR were linear. The solution stability was below±1% compared to the new solution to discover the assay results as shown in table 3.

Various data convey in table 3, such as the detection limit, quantification limit, correlation coefficient, and regression equation. Furthermore, the precision was obtained by calculating the inter and intraday and showing the value below 2%, exhibiting satisfactory precision, whereas the accuracy was determined by recovery percentage.

The wavelength preference

The application of PLS and PCR models can be employed to select a wavelength owing to the selection can use predicting the concentration of the analyte. The range for the analysis was 230 to 300 nm. Due to the presence of noise, the data below 240 nm and above 300 nm were removed owing to the appearance of tiny absorbance and the appearance of tiny absorbance, respectively.

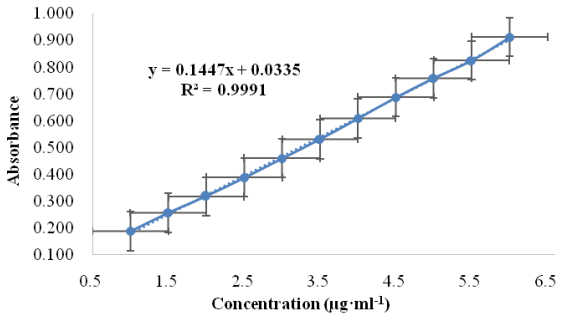


Fig. 4: Calibration curve of paracetamol (1-6 µg·ml^{-1})

Table 3: The outcome of the validation study after PAR was determined using the spectrophotometric method

Description	Data obtained[a]
Detection wavelength (nm)	242
Slope	0.1447±0.0014
Detection limit (µg·ml^{-1})	0.1693
Quantification limit (µg·ml^{-1})	0.5131
Linearity (µg·ml^{-1})	1-6
Intercept	0.0335±0.0054
Confidence limit for Interday Precision	0.357±0.47
Confidence limit for Intraday Precision	0.6732±0.22
Confidence limit for System Precision	0.0178±0.15
Accuracy, % *w/w*	99.18±0.789
Regression coefficient (R^2)	0.9991

[a]mean±SD (n=6)

Spectrophotometric technique supported by PLS and PCR models

The absorption spectra of the PAR drugs that are combined with several drugs show broad overlapping; furthermore, a conventional method can be applied to determine simultaneous components.

Thus, to tackle this issue, the PLS and PCR were employed. These methods are the common chemometric technique applied for the determination of various substances in pharmaceutical formulation concurrently and particularly for the products that have broad overlapping in their spectrum.

Furthermore, the application of these models in this study unveiled several facts, such as the very potential to analyze the concentration of multi-component drugs and lastly, they can interfere with the absorbance measurement with various wavelengths. Furthermore, if this method is applied in spectrophotometric analysis, various advantages can be acquired, such as it can magnify the accuracy of analysis, selecting suitable data, and deleting unimportant data. Consequently, the PLS and PCR models used to assist the spectrophotometric methods were discovered to be more suitable, acceptable, and have various benefits, such as being fast, modest, inexpensive, and sensitive compared to conventional methods without support from chemometric techniques.

Selection of principal components and variables

The Unscramble 11 software was used to study the selected range absorbance. The optimum factors were applied to elevate the calibration models of PLS and PCR. The assessment of the PLS and PCR predictive potentials was acquired using the prediction sets by plotting expected levels against known levels for each analyte. Table 4 shows the calibration and prediction set, meanwhile (fig. 5) illustrates the values of RMSEC, PRESS, RMSEP, and RMSECV for the predicted vs. reference after plotting by the PLS and PCR models, whereas, (fig. 6 and 7) present the regression coefficient plotted by the PLS and PCR models.

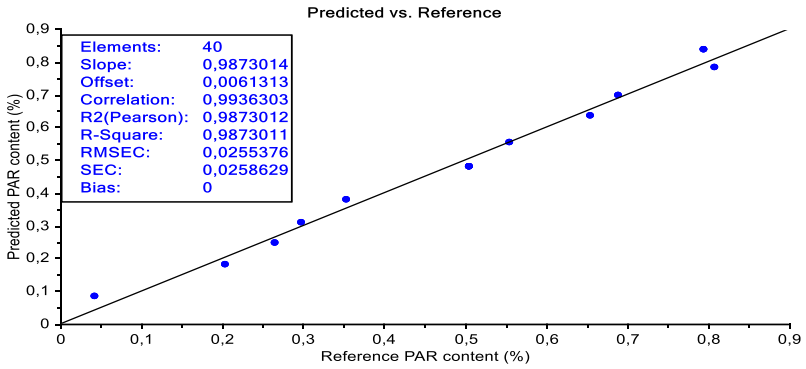
Table 4: The forecast of calibration and prediction models by using the PLS and PCR

Standard	PAR			
	PLS		PCR	
	Total obtained (µg·ml^{-1})	Recovery (%)	Total obtained (µg·ml^{-1})	Recovery (%)
Calibration				
1	4.02	100.5	4.16	104
2	3.57	102	3.71	106
3	3.56	101.71	3.70	105.71
4	2.95	98.33	3.09	103
5	0.99	99	1.13	113
6	5.71	103.82	5.85	106.36
7	5.06	101.2	5.20	104
8	1.98	99	2.12	106
9	3.6	102.86	3.74	106.86
10	6.17	102.83	6.31	105.17
11	4.59	102	4.73	105.11
12	2.52	100.8	2.66	106.4
13	1.6	106.67	1.74	116
14	3.99	99.75	4.13	103.25
15	3.51	100.29	3.65	104.29
16	3.51	100.29	3.65	104.29
17	3.03	101	3.17	105.67
18	1.01	101	1.15	115
19	5.29	96.18	5.43	98.73
20	4.98	99.6	5.12	102.4
21	2.00	100	2.14	107
22	3.51	100.29	3.65	104.29
23	6.09	101.5	6.23	103.83
24	4.32	96	4.46	99.11
25	2.59	103.6	2.73	109.2
26	1.49	99.4	1.63	108.67
27	4.11	102.75	4.25	106.25

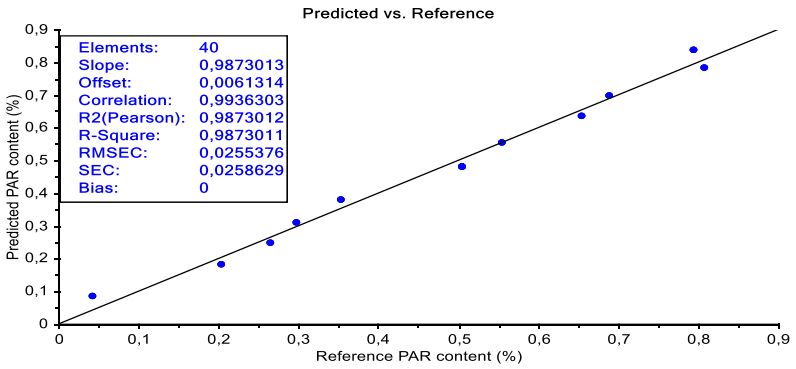
Standard	PAR			
	PLS		PCR	
	Total obtained (µg·ml⁻¹)	Recovery (%)	Total obtained (µg·ml⁻¹)	Recovery (%)
28	3.57	102	3.71	106
29	3.61	103.14	3.75	107.14
30	2.98	99.33	3.12	104
31	1.01	101	1.15	115
32	5.5	100	5.64	102.55
33	5.17	103.4	5.31	106.2
34	2.3	115	2.44	122
35	3.48	99.43	3.62	103.43
36	5.99	99.83	6.13	102.17
37	4.37	97.11	4.51	100.22
38	2.5	100	2.64	105.6
39	1.56	104	1.70	113.33
40	5.98	99.67	6.12	102
Prediction				
41	3.64	104	3.78	108
42	5.5	100	5.64	102.55
43	0.899	89.9	1.04	104
44	5.23	104.6	5.37	107.4
45	4.49	99.78	4.63	102.89
46	2.05	102.5	2.19	109.5
47	3.99	99.75	4.13	103.25
48	2.99	99.67	3.13	104.33
49	2.48	99.2	2.62	104.8
50	1.49	99.27	1.63	108.67

PLS: Partial Least Squares; PCR: Principal Component Regression

Fig. 5 shows satisfactory statistical parameters of the developed PLS and PCR models. This fig. also presents several important values such as RMSEC, SLOPE, R^2, and SEC that were acquired by building satisfactory precision and accuracy and then optimizing the calibration matrix of absorbance spectra. The obtained outcomes indicate that PAR in the pharmaceutical products produced by various pharmacy companies with the PLS and PCR models is acceptable.



(a)



(b)

Fig. 5: The predicted vs. reference for (a) PLS and (b) PCR models

The prediction of components can be done by using the latent variables (LV) and principal components (PC) provided by the PLS and PCR models. The LV and PC can also be applied to enhance the accuracy of models. The loadings and coefficients were calculated to acquire the number of LV and PC. Furthermore, in order to evade the under and over-fitting data, the best number of LV and PC are selected.

The ideal numbers of LV and PC were determined using the cross-validation technique and the minimum value of RMSECV was chosen as the factor number [30]. In the assessment of the quality of the established designs (PLS and PCR), the explained variance was plotted as illustrated in fig. 6 and 7. The plots of variances are divided into two lines; the blue line was the calibration variance, whereas the red line was the validation variance. Testing the model on data was employed to build the validation variance, on the other hand, corresponding to the calibration data to build the calibration variance.

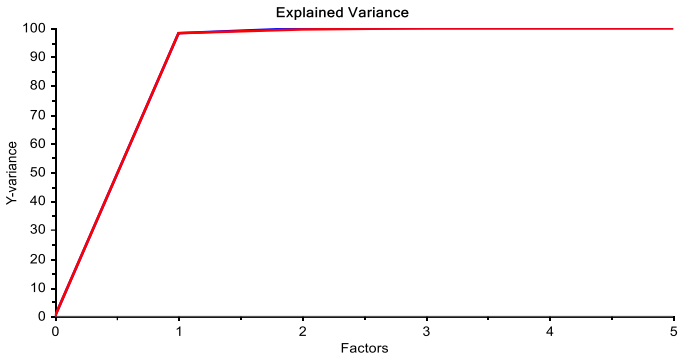


Fig. 6: The PLS model plotting an explained variance

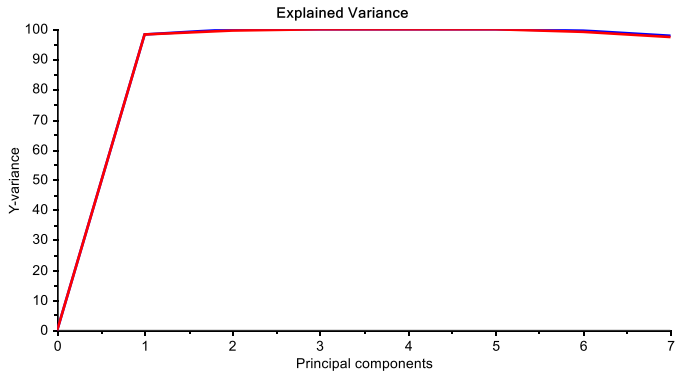
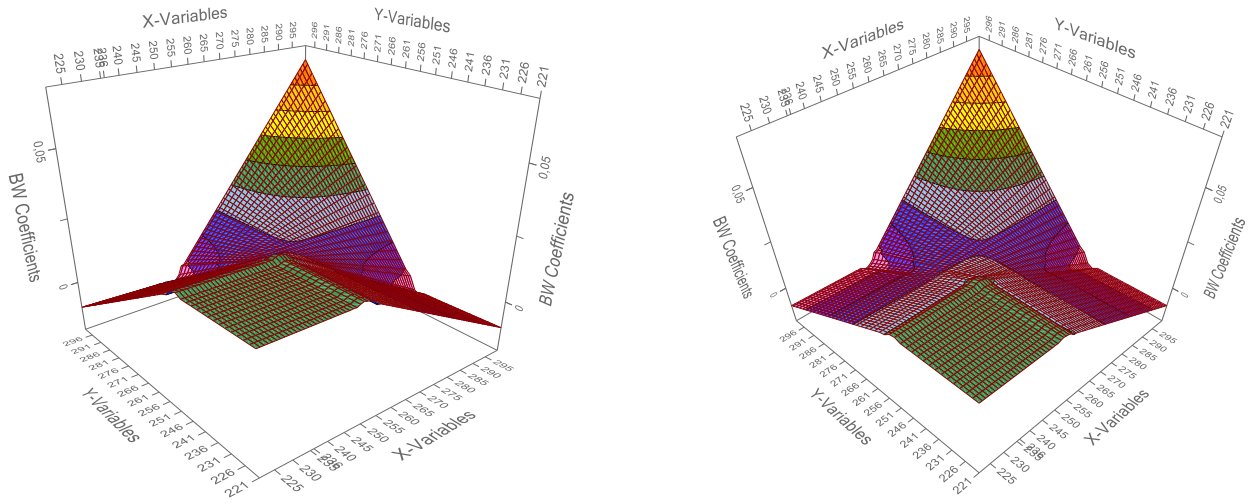


Fig. 7: The PCR model plotting an explained variance



(a) **(b)**

Fig. 8: The regression coefficient plotted by (a) PLS and (b) PCR models

The dimensionality can be determined after the variance spans the plateau. According to the obtained data, if the Y-variance is large and the plateau is small, it indicates a satisfactory model. Furthermore, the model is demonstrative based on fig. 6 and 7 due to the curves of validation and calibration being identical. The latent variables (PLS and PCR) and the component numbers of explained variance are also presented in fig. 6 and 7, whereas fig. 8 presents the regression coefficient plotted by PLS and PCR models.

Application of the validated and developed approaches in PAR products

The determination of PAR in various pharmaceutical products (tablets and syrups) was analyzed in six replicates using the validated methods, and the outcomes are illustrated in table 6. The determination of the products was analyzed using Spectrophotometric UV; according to table 5, all pharmaceutical products were dissolved with ethanol before being analyzed using Spectrophotometer.

Table 5: The tablet weights of paracetamol products

Sample name	The mean tablet weights (mg)[a]
Biogesic	552.3±0.40
Panadol	603.0±0.66
Sanmol	546.6±1.16
Demacolin	550.7±0.89
Ultracet	401.6±0.85
Zetamol	547.5±1.20
Pyrexin	547.6±1.09
Paratusin	601.5±0.84
Paracetamol capsule	602.6±0.51
Paracetamol Actavis	548.8±1.12
Neozep Forte	451.7±0.44
Novagesic	548.6±0.90
Promed	549.2±0.97
Dapyrin	550.3±0.83
Fasidol	549.8±0.84
Bodrex	701.4±0.33
Procold	552.2±0.70
Farsifen plus	652.6±0.43

[a]mean±SD (n=10)

Furthermore, the equation of PAR standard was employed to estimate the concentration of PAR in their tablets and syrups formulations, furthermore, chemometric techniques such as PLS and PCR were established to estimate the concentration of each analyte present in their formulation. The results were attained in table 6 and all of them were acceptable.

Table 6: The outcomes obtained with the pharmaceutical formulation

Paracetamol production	Illustration	Simultaneous formula technique	Chemometrics technique	
			PCR	PLS
Biogesic	Label Claim (mg)	500	500	500
	Amount found (mg)	499.65	499.71	499.73
	% Label Claim	99.93	99.94	99.95
Panadol	Label Claim (mg)	500	500	500
	Amount found (mg)	499.82	499.11	499.01
	% Label Claim	99.96	99.82	99.80
Sanmol	Label Claim (mg)	500	500	500
	Amount found (mg)	498.92	499.12	499.15
	% Label Claim	99.78	99.82	99.83
Demacolin	Label Claim (mg)	500	500	500
	Amount found (mg)	499.58	499.92	498.99
	% Label Claim	99.92	99.98	99.80
Ultracet	Label Claim (mg)	325	325	325
	Amount found (mg)	324.09	323.98	324.71
	% Label Claim	99.72	99.69	99.91
Zetamol	Label Claim (mg)	500	500	500
	Amount found (mg)	496.98	498.79	499.01
	% Label Claim	99.40	99.76	99.80
Pyrexin	Label Claim (mg)	500	500	500
	Amount found (mg)	499,45	499.71	499.83
	% Label Claim	99,89	99.94	99,97
Paratusin	Label Claim (mg)	500	500	500
	Amount found (mg)	498.95	498.79	499.02
	% Label Claim	99.79	99.76	99.80
Paracetamol capsule	Label Claim (mg)	500	500	500
	Amount found (mg)	499.09	499.79	499.19
	% Label Claim	99.82	99.96	99.84
Paracetamol Actavis	Label Claim (mg)	500	500	500
	Amount found (mg)	498.38	499.22	499.78
	% Label Claim	99.68	99.84	99.96
Neozep Forte	Label Claim (mg)	250	250	250
	Amount found (mg)	248.78	249.19	249.69
	% Label Claim	99.51	99,68	99.88
Novagesic	Label Claim (mg)	500	500	500
	Amount found (mg)	498.12	499.19	499.18
	% Label Claim	99.62	99.84	99.84

Paracetamol production	Illustration	Simultaneous formula technique	Chemometrics technique	
			PCR	PLS
Promed	Label Claim (mg)	500	500	500
	Amount found (mg)	499.28	499.38	498.78
	% Label Claim	99.86	99.88	99.76
Dapyrin	Label Claim (mg)	500	500	500
	Amount found (mg)	498.77	499.79	499.67
	% Label Claim	99.75	99.96	99.93
Fasidol	Label Claim (mg)	500	500	500
	Amount found (mg)	499.13	499.09	499.17
	% Label Claim	99.83	99.82	99.83
Bodrex	Label Claim (mg)	600	600	600
	Amount found (mg)	599.13	599.71	599.71
	% Label Claim	99.86	99.95	99.95
Procold	Label Claim (mg)	500	500	500
	Amount found (mg)	499.71	499.79	499.73
	% Label Claim	99.94	99.96	99.95
Farsifen plus	Label Claim (mg)	350	350	350
	Amount found (mg)	349.71	349.15	349.27
	% Label Claim	99.92	99.76	99.79
Tempra syrup	Label Claim (mg)	32	32	32
	Amount found (mg)	31.89	31.71	31.69
	% Label Claim	99.66	99.09	99.03
Termorex syrup	Label Claim (mg)	32	32	32
	Amount found (mg)	31.78	31.91	31.09
	% Label Claim	99.31	99.72	97.16
Sanmol syrup	Label Claim (mg)	24	24	24
	Amount found (mg)	23.82	23.99	23.49
	% Label Claim	99.25	99.96	97.88
Praxion syrup	Label Claim (mg)	24	24	24
	Amount found (mg)	23.94	23.18	23.68
	% Label Claim	99.75	96.58	98.67
Panadol syrup	Label Claim (mg)	35	35	35
	Amount found (mg)	34.22	34.79	34.38
	% Label Claim	97.77	99.40	98.23
Pamol syrup	Label Claim (mg)	24	24	24
	Amount found (mg)	23.29	23.22	23.79
	% Label Claim	97.04	96.75	99.13
Alphamol syrup	Label Claim (mg)	24	24	24
	Amount found (mg)	23.27	23.17	23.77
	% Label Claim	96.96	96.54	99.04

PLS: Partial Least Squares; PCR: Principal Component Regression

Numerous studies have analyzed PAR as a single component or in combination with other components in several dosage forms. Table 7 presents several studies of paracetamol analysis using the spectrophotometric approach. UV spectrophotometric determination is commonly applied in quality control testing and ordinary laboratories owing to its stability, simplicity, and broader availability. This study exhibited accurate, precise, and cheap assays for these medicines in mixtures. Based on the previous studies, Vidal *et al.* (2002) reported a single triparameter flow with UV analysis for the simultaneous analysis of caffeine, aspirin, and paracetamol. The calibration curve ranged from 4–50, 40–500, and 10–100 μg⍰ml^{-1}, respectively, whereas the detection limits were from 0.3–0.8 μg⍰ml^{-1} [31]. Meanwhile, Cemal *et al.* (2008) presented a technique for paracetamol and aspirin detection using spectrophotometric UV and verified by HPLC. The linear range was applied at 0.5–4 and 0.75–6 μg.ml^{-1} for acetaminophen and aspirin, respectively [32].

Table 7: Several studies of paracetamol detection using a spectrophotometric approach

Sample	Technique	LoD	Linear range	References
Aspirin and Paracetamol	Spectrophotometer UV	0.73 and 0.59 μgml^{-1}	2–64 μgml^{-1}	[33]
Tramadol and Paracetamol	Spectrophotometer UV that validated using UHPLC and assisted by genetic algorithm coupled with PLS (GA-PLS)	Not reported	1.7–4.0 and 16–37 μgml^{-1}	[34]
Paracetamol	Spectrophotometer UV that verified using FTIR	0.19 μgml^{-1}	0.3–20 μgml^{-1}	[35]
Paracetamol, caffeine and acetylsalicylic acid	Spectrophotometer UV and assisted PLS	Not reported	10–15 and 2–6 μgml^{-1}	[36]
Aspirin, paracetamol, caffeine and chlorphenamine	Spectrophotometer UV assisted by PCR and PLS	Not reported	4.11–19.53, 3.33–16.65, 2–14 and 2.37–13.27 μgml^{-1}	[37]
Mefenamic acid and paracetamol	Spectrophotometer UV assisted by PCR	1.15 and 2.50 μgml^{-1}	2–10 and 4–20 μgml^{-1}	[38]
Paracetamol, ibuprofen and caffeine	Spectrophotometer UV assisted by genetic algorithm coupled with PLS (GA-PLS) and principal component-artificial neural network (PC-ANN)	0.21, 0.52 and 0.67 μgml^{-1}	0.6–11, 1–24 and 1–18 μgml^{-1}	[39]
Paracetamol	Spectrophotometer UV assisted by PCR and PLS	0.17 μgml^{-1}	1–6 μgml^{-1}	This study

UV: Ultraviolet; UHPLC: Ultra High-Performance Liquid Chromatography; FTIR: Fourier Transform Infra Red; PLS: Partial Least Squares; PCR: Principal Component Regression

CONCLUSION

The current study achieved paracetamol analysis in various pharmaceutical products (tablets and syrups). The developed and validated methods using UV spectrophotometric assisted by chemometric technique revealed satisfactory precision, accuracy, and fast to verify the selected analyte. The application of this method that assisted by statistical assessment (PLS and PCR) indicated that there was no significant distinction among the validated methods. The developed and validated methods give several benefits in terms of the analysis cost and using eco-friendly solvents owing to not all pharmacy industries in Indonesia having a sophisticated instrument to do the analysis, such as FTIR and NMR. Thus, this validated approach can be applied by small industries to ensure the drugs produced follow the regulation of the Indonesian government. Furthermore, these methods can be employed in routine quantity and quality controls to determine the paracetamol level in pharmaceutical products.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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