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The Chemometric Approach for Verification of Paracetamol Level in Pharmacies Products Using Spectrophotometer UV-Vis

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The objective of this study is to inspect paracetamol levels in Indonesian pharmacies and whether the level of paracetamol is matched the label given. The verification of paracetamol level using a chemometric approach such as partial least squares (PLS) and principal component regression (PCR) after measured with spectrophotometer UV. The outcome of this study showed the absorbance at 242 with an R^2 (0.9991) and the linear range at 1.0 – 6.0 $\mu g \cdot mL^{-1}$. The accuracy was satisfactory and obtained at 99.18%. The satisfactory outcomes revealed the identification method has a good potential to be used in inspecting the paracetamol level in pharmaceutical products. Furthermore, the chemometric method used as a statistical measurement showed that there was no specific distinction to the validated approach. Thus, this approach can be applied in pharmacy industries specifically for small industries to ensure the medicine's safety before being distributed to the pharmacies.

Keywords: Chemometric; Paracetamol; Spectrophotometric

I. INTRODUCTION

In this era, the pharmaceutical sector becomes a potential sector that contributes to the worldwide economy. It happens because the demand for fast medicines is increasing. Every year, there are new medicines with their advantages are distributed to the pharmacies. Nevertheless, several industries only think about the profit but sometimes they forget to study the quality of the products. Nowadays, it is normal to read a report about drug poisoning owing to the drug not being properly produced. Because of this issue, many stakeholders such as consumers, researchers, and even the government are interested to study the quality of the pharmacy products before distributing them to the pharmacies (Thanacoody & Anderson, 2020). Furthermore, a pharmaceutical product that has been manufactured should hand in hand with product quality. Thus, a perfect and fast technique must be found so the patient feels safe when applying for the medicines (Yaguchi-Saito *et al.*, 2021). One of the most popular drugs used without a prescription is paracetamol is known as acetaminophen and is even familiar with the term Over-The-Counter (OTC) (Bloukh *et al.*, 2021).

Paracetamol as presented in Figure 1 has many effects such as analgesic, antipyretic, and anti-inflammatory. Paracetamol can impede cyclooxygenase (COX) 1 & 2 productions (Garcia-Lopeze *et al.*, 2021). Paracetamol causes a light impact on COX 1 & 2 in peripheral tissues and because of this, the drug is dissimilar to other non-steroidal anti-inflammatory drugs (NSAIDs). Furthermore, several studies reported that paracetamol can increase blood clotting time (Pathan *et al.*, 2018). Thus, it can be applied to several ailments such as arthritis, fever, toothache, and muscle pain (Saroj *et al.*, 2022).

Started 2019 until now, the coronavirus-19 has become a huge issue in the world. The disease is very deadly with several symptoms, light or heavy, such as cold, fever, and

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breathing problems. Nevertheless, people with good immunity can handle the issue caused by COVID-19, and in order to tackle the symptoms they need an efficient drug and paracetamol is their choice. Moreover, several users combine the application of paracetamol with other pharmaceutical products as illustrated in Figure 2 (Saroj *et al.*, 2022).

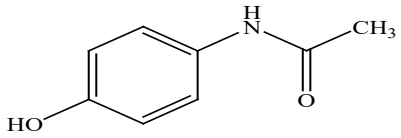
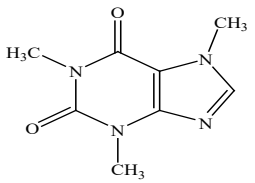


Figure 1. The chemical structure of paracetamol

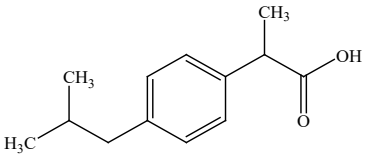
Somehow, the inspection of a pharmaceutical product with several active compounds is a challenge for every researcher to rectify the medication system in pharmacy industries. It is also important for stakeholders to access the pharmaceutical products prior to distributing the pharmaceutical products to the pharmacies (Alshargabi, 2021). Furthermore, finding a modest, inexpensive, and swift technique is very important and at the same time, ensuring the technique does not disturb the accuracy, reliability, and precision of the outcomes. Several studies have reported the pharmaceutical products analysis (Aly & Nahed, 2017; Inayatullah *et al.*, 2021; Mohamed *et al.*, 2018). However, the application of HPLC and UV approaches are promising to do the verification of paracetamol level in pharmaceutical products (Dang *et al.*, 2020; Dave & Mashru, 2022; Alkhafaji & Mahood, 2019; Munir *et al.*, 2021; Palur *et al.*, 2020).

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 (Tantawy *et al.*, 2021; Mohamed *et al.*, 2021; Munir *et al.*, 2022).

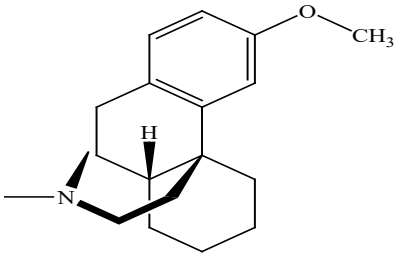
Finding a selective and sensitive method to analyse paracetamol in tablets and syrups using a modest technique has encouraged us to develop a spectrophotometric approach that can be applied for the determination of the various combination. This technique applied a handy procedure with slight modification 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 destination of this study is to stipulate a spectrophotometric method supported by a chemometrics technique to increase the selectivity of this study (Mishra *et al.*, 2021; Liu *et al.*, 2021; Kalogiouri & Samanidou, 2021; da Costa *et al.*, 2021). 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 minimised and the processing of data is faster with several absorbances and concentrations of analytes (Agrawal *et al.*, 2021; Chen *et al.*, 2021), 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 figures that can be described into several parameters such as selectivity, sensitivity, detection limit, and quantification limit (Purwanto & Sudargini, 2021; Cheah *et al.*, 2021).



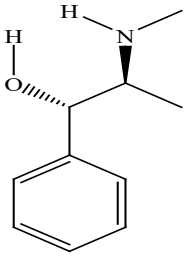
Caffeine



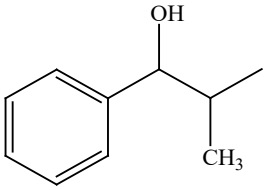
Ibuprofen



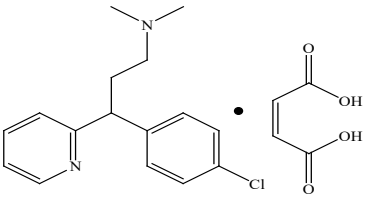
Dextromethorphan



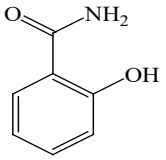
Pseudoephedrine



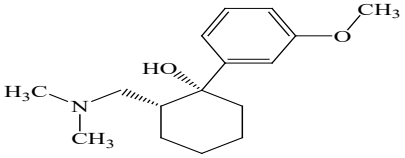
Phenylpropanolamine



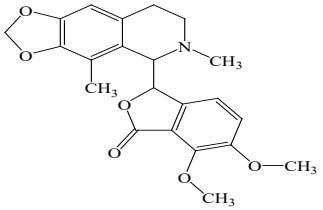
Chlorpheniramine maleate



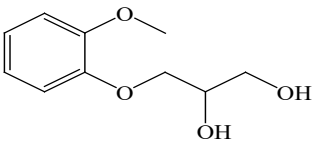
Salicylamide



Tramadol



Noscapine



Glyceryl guaiacolate

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

II. MATERIALS AND METHOD

A. 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.

B. Chemical Items

Paracetamol (99.72%) was supplied from Sigma Aldrich, Indonesia. Pharmaceutical products such as tablets and syrups containing paracetamol with various compositions and listed in Table 1. Deionised water (Sigma Aldrich) was used throughout the experiment.

Table 1. List of pharmaceutical products (Tablets & Syrups) applied

Sample Name	Paracetamol composition (mg)	Other ingredients (mg)	The mean tablet weights (mg)[a]
Biogesic	500	-	552.3±0.40
Panadol	500	-	603.0±0.66
Sanmol	500	-	546.6±1.16
Demacolin	500	Pseudoephedrine HCl (7.5 mg) & chlorpheniramine maleate (2 mg)	550.7±0.89
Ultracet	325	Tramadol HCl (37.5 mg)	401.6±0.85
Zetamol	500	-	547.5±1.20
Pyrexin	500	-	547.6±1.09
Paratusin	500	Noscapine (10 mg), chlorpheniramine maleate (2 mg), glyceryl guaiacolate (50 mg) & phenylpropanolamine HCl (15 mg)	601.5±0.84
Paracetamol capsule	500	-	602.6±0.51
Paracetamol Actavis	500	-	548.8±1.12
Neozep Forte	250	Chlorpheniramine maleate (2 mg), salicylamide (150 mg) & phenylpropanolamine HCl (15 mg)	451.7±0.44
Novagesic	500	-	548.6±0.90
Promed	500	-	549.2±0.97
Dapyrin	500	-	550.3±0.83
Fasidol	500	-	549.8±0.84
Bodrex	600	Caffeine (50 mg)	701.4±0.33
Procold	500	Dextromethorphan HBr (10 mg) & pseudoephedrine HCl (30 mg)	552.2±0.70
Farsifen plus	350	Ibuprofen (200 mg) & caffeine (50 mg)	652.6±0.43
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	0 mg/0.6 mg	-	
Alphamol syrup	120 mg/5 ml	-	

[a]standard deviation: each sample was weighed 10 replicates

C. Preparation of Stock Solution of Paracetamol (50 µg·mL^{-1})

A standard stock solution of paracetamol was prepared by dissolving 2.5 mg which was moved to a 50 mL volumetric flask and finished to the tag with deionised water. Several diluted solutions were also prepared to range from 1-6 µg·mL^{-1} by simple dilution of stock solution.

D. The Verification of Paracetamol Level in Tablets and Syrups

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

E. Validation Study

The validation study complied with the ICH guidelines (Beg *et al.*, 2021). The paracetamol concentration vs. absorbance was used to establish a calibration curve. Furthermore, by plotting the calibration curves at 1-6 µg·mL^{-1} of paracetamol, linearity was obtained. The accuracy was carried out using the paracetamol 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.

F. PLS and PCR Techniques

1. The scheming of 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, and +5 thus the central level of paracetamol was coded as (0) (Shi *et al.*, 2019). 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 paracetamol levels are presented in Table 2.

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

2. The calibration and prediction sets arrangement

Several paracetamol concentrations (C_{cal}) were organised 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 organising the various paracetamol 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.

3. 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 (Agnoletti *et al.*, 2022; El-Zeiny *et al.*, 2021; *Ibrahim et al.,* 2019). Furthermore, the merit figures such as selectivity, sensitivity, detection limit, and quantification limit were also analysed. 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*.

III. RESULTS AND DISCUSSION

A. Paracetamol Standard Analysis

The analysis of paracetamol at a wavelength of 242 nm. Thus, the spectrum of paracetamol (4 $\mu g \cdot mL^{-1}$) is shown in (Figure 3) and indicated that the analysis was acceptable for paracetamol analysis. Similar absorbance reported by Glavanovic *et al.* (2016) that reported the absorbance of paracetamol acquired at 242 nm.

Figure 4 illustrates that the calibration curves of paracetamol were linear. The solution stability was below ±1% when the deionised water applied in this study 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.

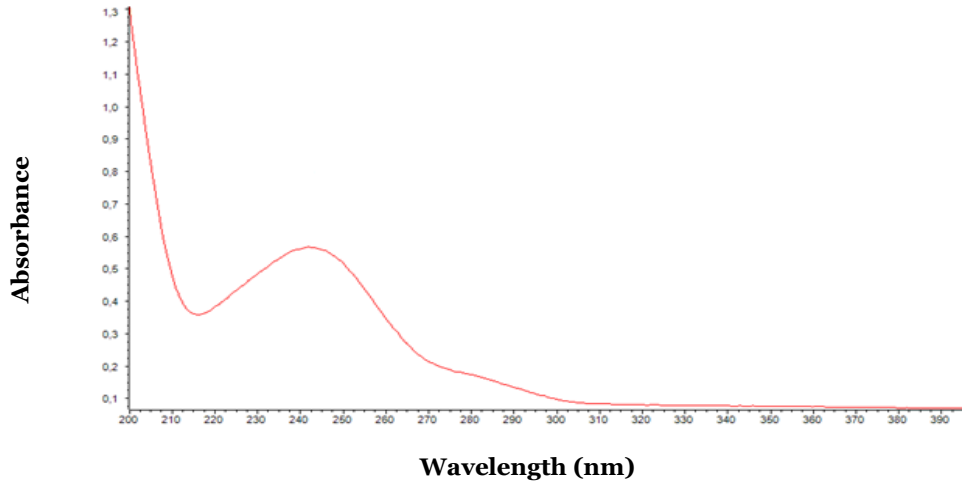


Figure 3. The absorption spectrum of 4 μg·mL^{-1} of paracetamol (242 nm)

B. 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 absorbances, respectively.

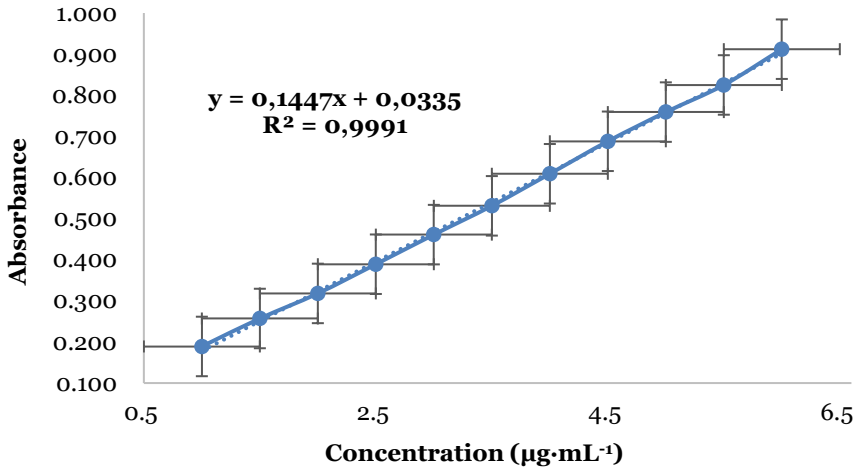


Figure 4. Calibration curve of paracetamol (1-6 μg·mL^{-1})

C. Spectrophotometric Technique Supported by PLS and PCR Models

The absorption spectra of the paracetamol 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 popular chemometric approach used for the detection of multi-substances in pharmaceutical products 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 analyse 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.

Table 3. The outcome of the validation study after paracetamol 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]standard deviation; each sample was measured in three replicates

D. The Preference of Principal Components and Variables

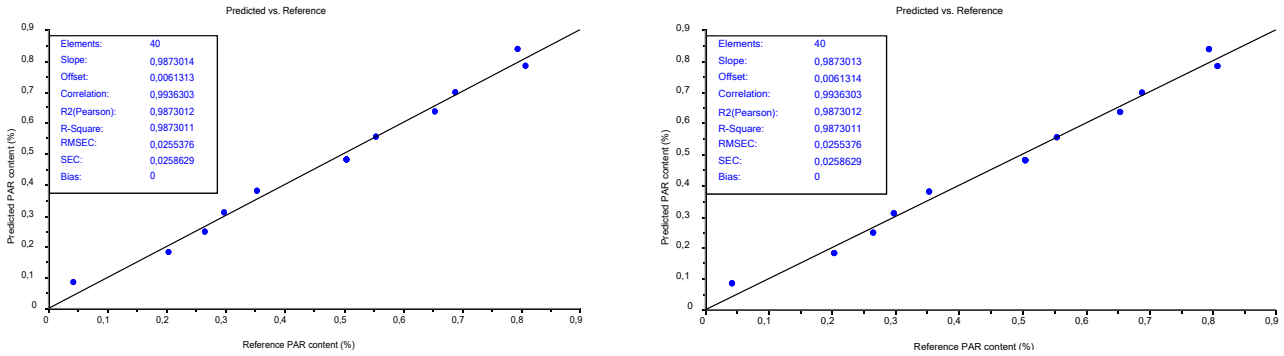
The Unscramble 11 software was used to study the selected range absorbance. The optimum factors were applied to elevate the calibration models of PLS and PCR. The assessment of the PLS and PCR predictive potentials was acquired using the prediction sets by plotting expected levels against known levels for each analyte. Table 4 shows the calibration and prediction set, meanwhile (Figure 5) illustrates the values of RMSEC, PRESS, RMSEP, and RMSECV for the predicted vs. reference after plotting the PLS and PCR models, whereas, (Figure 6) presents 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})	**Accuracy (%)**	**Total Obtained (μg·mL^{-1})**	**Accuracy (%)**
		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	1,491	99,4	1,63	108,67
27	4,11	102,75	4,25	106,25
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	1,489	99,27	1,63	108,67

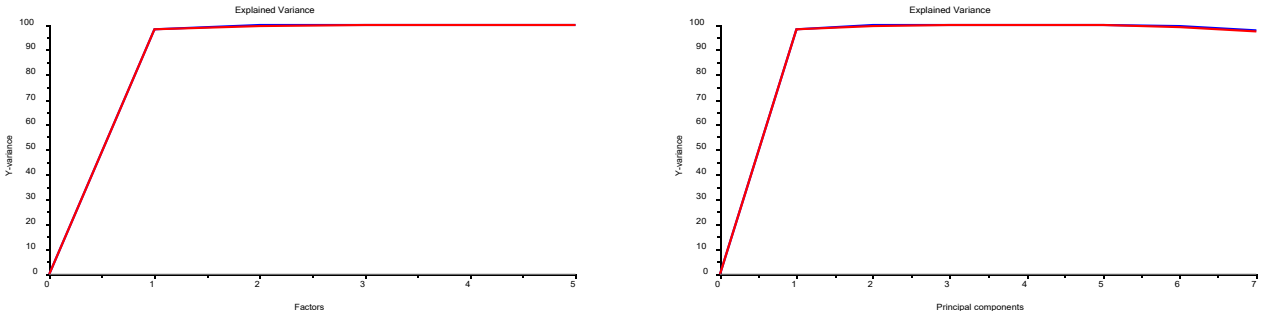
Figure 5 shows satisfactory statistical parameters of the developed PLS and PCR models. This figure also presents several important values such as RMSEC, SLOPE, R^2, and SEC that were acquired by building satisfactory precision and accuracy and then optimising the calibration matrix of absorbance spectra.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



(a) (b)

Figure 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.

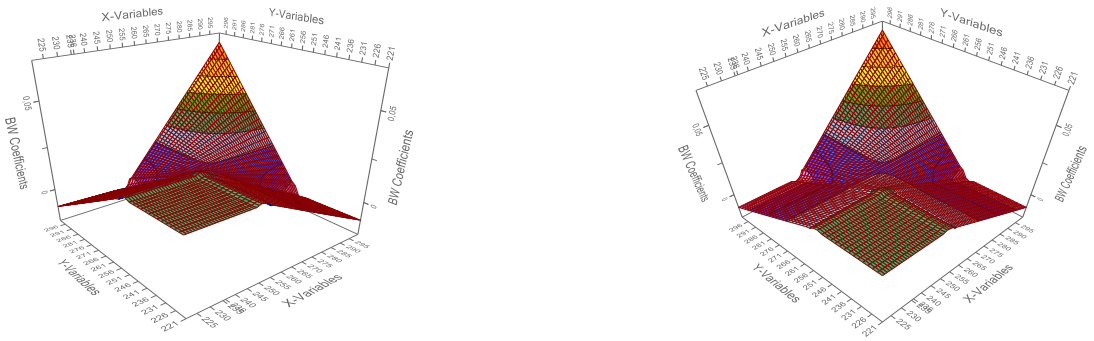


(a) (b)

Figure 6. (a) The PLS model plotting an explained variance and (b) The PCR model plotting an explained variance

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 (MacArthur *et al.*, 2020). In the assessment of the quality of the established designs (PLS and PCR), the explained variance was plotted as illustrated in Figure 6. 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.

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 Figure 6 due to the curves of validation and calibration being identical. The latent variables (PLS & PCR) and the component numbers of explained variance are also presented in Figure 6, whereas Figure 7 presents the regression coefficient plotted by PLS and PCR models.



(a) (b)

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

E. Application of the Validated and Developed Approaches in Paracetamol Products

The determination of paracetamol in various pharmaceutical products (tablets & syrups) was analysed in six replicates using the validated methods, and the outcomes are illustrated in Table 5. The determination of the products was analysed using Spectrophotometric UV, according to Table 1, all pharmaceutical products were dissolved in deionised water before being analysed using Spectrophotometer.

Furthermore, the equation of paracetamol standard was employed to estimate the concentration of paracetamol in their tablets and syrups formulations, moreover, 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 5 and all of them were acceptable.

Table 5. The outcomes obtained with the pharmaceutical formulation

Paracetamol Production	Illustration	Simultaneous Formula Technique	Chemometrics Technique	
			PCR	PLS
Biogesic	Label Tag(mg)	500	500	500
	Level found (mg)	499,65	499,71	499,73
	% Label Tag	99,93	99,94	99,95
Panadol	Label Tag(mg)	500	500	500
	Level found (mg)	499,82	499,11	499,01
	% Label Tag	99,96	99,82	99,80
Sanmol	Label Tag(mg)	500	500	500
	Level found (mg)	498,92	499,12	499,15
	% Label Tag	99,78	99,82	99,83
Demacolin	Label Tag(mg)	500	500	500
	Level found (mg)	499,58	499,92	498,99
	% Label Tag	99,92	99,98	99,80
Ultracet	Label Tag(mg)	325	325	325
	Level found (mg)	324,09	323,98	324,71
	% Label Tag	99,72	99,69	99,91
Zetamol	Label Tag(mg)	500	500	500
	Level found (mg)	496,98	498,79	499,01
	% Label Tag	99,40	99,76	99,80
Pyrexin	Label Tag(mg)	500	500	500
	Level found (mg)	499,45	499,71	499,83
	% Label Tag	99,89	99,94	99,97
Paratusin	Label Tag(mg)	500	500	500
	Level found (mg)	498,95	498,79	499,02
	% Label Tag	99,79	99,76	99,80
Paracetamol capsule	Label Tag(mg)	500	500	500
	Level found (mg)	499,09	499,79	499,19
	% Label Tag	99,82	99,96	99,84
Paracetamol Actavis	Label Tag(mg)	500	500	500
	Level found (mg)	498,38	499,22	499,78
	% Label Tag	99,68	99,84	99,96
Neozep Forte	Label Tag(mg)	250	250	250
	Level found (mg)	248,78	249,19	249,69
	% Label Tag	99,51	99,68	99,88
Novagesic	Label Tag(mg)	500	500	500
	Level found (mg)	498,12	499,19	499,18
	% Label Tag	99,62	99,84	99,84
Promed	Label Tag(mg)	500	500	500
	Level found (mg)	499,28	499,38	498,78
	% Label Tag	99,86	99,88	99,76
Dapyrin	Label Tag(mg)	500	500	500
	Level found (mg)	498,77	499,79	499,67
	% Label Tag	99,75	99,96	99,93
Fasidol	Label Tag(mg)	500	500	500
	Level found (mg)	499,13	499,09	499,17
	% Label Tag	99,83	99,82	99,83
Bodrex	Label Tag(mg)	600	600	600
	Level found (mg)	599,13	599,71	599,71

	% Label Tag	99,86	99,95	99,95
Procold	Label Tag(mg)	500	500	500
	Level found (mg)	499,71	499,79	499,73
	% Label Tag	99,94	99,96	99,95
Farsifen plus	Label Tag(mg)	350	350	350
	Level found (mg)	349,71	349,15	349,27
	% Label Tag	99,92	99,76	99,79
Tempra syrup	Label Tag(mg)	32	32	32
	Level found (mg)	31,89	31,71	31,69
	% Label Tag	99,66	99,09	99,03
Termorex syrup	Label Tag(mg)	32	32	32
	Level found (mg)	31,78	31,91	31,09
	% Label Tag	99,31	99,72	97,16
Sanmol syrup	Label Tag(mg)	24	24	24
	Level found (mg)	23,82	23,99	23,49
	% Label Tag	99,25	99,96	97,88
Praxion syrup	Label Tag(mg)	24	24	24
	Level found (mg)	23,94	23,18	23,68
	% Label Tag	99,75	96,58	98,67
Panadol syrup	Label Tag(mg)	35	35	35
	Level found (mg)	34,22	34,79	34,38
	% Label Tag	97,77	99,40	98,23
Pamol syrup	Label Tag(mg)	24	24	24
	Level found (mg)	23,29	23,22	23,79
	% Label Tag	97,04	96,75	99,13
Alphamol syrup	Label Tag(mg)	24	24	24
	Level found (mg)	23,27	23,17	23,77
	% Label Tag	96,96	96,54	99,04

Numerous studies have analysed paracetamol as a single component or in combination with other components in several dosage forms. Table 6 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.

Table 6. Several studies of paracetamol detection using spectrophotometric approach

Sample	Technique	LoD	Linear range	References
Aspirin & Paracetamol	Spectrophotometer UV	0.73 & 0.59 $\mu g \cdot mL^{-1}$	2 – 64 $\mu g \cdot mL^{-1}$	(Murtaza *et al.*, 2011)
Tramadol & Paracetamol	Spectrophotometer UV that validated using UHPLC and assisted by genetic algorithm coupled with PLS (GA-PLS)	Not reported	1.7 – 4.0 & 16 – 37 $\mu g \cdot mL^{-1}$	(Glavanovic *et al.*, 2016)
Paracetamol	Spectrophotometer UV that verified using FTIR	0.19 $\mu g \cdot mL^{-1}$	0.3 – 20 $\mu g \cdot mL^{-1}$	(Sirajuddin *et al.*, 2007)
Paracetamol, caffeine & acetylsalicylic acid	Spectrophotometer UV and assisted PLS	Not reported	10 – 15 & 2 – 6 $\mu g \cdot mL^{-1}$	(Sena & Poppi, 2004)
Aspirin, paracetamol, caffeine & chlorphenamine	Spectrophotometer UV assisted by PCR and PLS	Not reported	4.11 – 19.53, 3.33 – 16.65, 2 – 14 & 2.37 – 13.27 $\mu g \cdot mL^{-1}$	(Mot *et al.*, 2010)
Mefenamic acid & paracetamol	Spectrophotometer UV assisted by PCR	1.15 & 2.50 $\mu g \cdot mL^{-1}$	2 – 10 & 4 – 20 $\mu g \cdot mL^{-1}$	(Dinc *et al.*, 2002)
Paracetamol, ibuprofen	Spectrophotometer UV assisted by	0.21, 0.52 &	0.6 – 11, 1 – 24 &	(Khoshayand

& caffeine	genetic algorithm coupled with PLS (GA-PLS) and principal component-artificial neural network (PC-ANN)	0.67 μg·mL^{-1}	1 – 18 μg·mL^{-1}	*et al.*, 2008)
Paracetamol	Spectrophotometer UV assisted by PCR and PLS	0.17 μg·mL^{-1}	1 – 6 μg·mL^{-1}	This study

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 tri-parameter 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} (Vidal *et al.*, 2002). 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 (Cemal *et al.*, 2008).

IV. CONCLUSION

The current study achieved the paracetamol analysis in various pharmaceutical products (tablets & 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 assisted by statistical assessment (PLS and PCR) denoted there was no notable different refer to the validated approaches. 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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VI. CONFLICTS OF INTEREST

None.

VII. REFERENCES

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