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Research Article

APPLICATION AND VALIDATION OF DERIVATIVE SPECTROPHOTOMETRIC FOR DETERMINATION LEVELS OF TERNARY MIXTURES OF PARACETAMOL, PROPYPHENAZONE, AND CAFFEINE IN TABLET DOSAGE FORM

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ABSTRACT

Objective: This study was to develop a spectrophotometric method with derivative zero-crossing for determines the levels of paracetamol (PCT), propyphenazone (PRO), and caffeine (CAF) in tablet dosage form without prior separation.

Method: The study begins with optimizing the type of solvent, phosphate buffer (pH 7.2) and a mixture of phosphate buffer (pH 7.2) with methanol at ratio 90:10; 70:30; 50:50; 30:70; and 10:90. Spectrophotometric method with zero-crossing, tested validity based on linearity, accuracy, precision, limit of detection, and limit of quantification. Then, the method applied to determine the levels of PCT, PRO, and CAF in tablet.

Result: The mixture of phosphate buffer (pH 7.2) with methanol at ratio 70:30 can be used for analysis. Applications zero-crossing technique on assay of PCT and CAF performed on the first derivative and Δλ 2 with λ 239.4 nm for PCT and Δλ 8 with λ 245.6 nm for CAF while PRO in the third derivative and Δλ 8 with λ 249.6 nm, resulting 100.91%, 104.75%, and 103.33% for levels of PCT, PRO, and CAF, respectively.

Conclusion: Spectrophotometric derivative method with zero-crossing qualified in validation parameters.

Keywords: Paracetamol, Propyphenazone, Caffeine, Derivative spectrophotometry, Zero-crossing, Phosphate buffer (pH 7.2), Methanol.

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INTRODUCTION

Most circulating drugs are a combination of several active ingredients, each of which aims to enhance the effects of drug therapy and ease of use [1]. One of the most commonly used mixtures of active substances is paracetamol (PCT), propyphenazone (PRO), and caffeine (CAF) used to treat headache, rheumatism, toothache, migraine, and menstrual pain [2].

In its marketing, the quality inspection of a medical preparation is absolutely necessary to ensure that the preparation of the drug contains the ingredients of predetermined quality and amount and follows standard analytical procedures, thereby promoting the expected therapeutic effect [1].

Literature survey reveals that few high-performance liquid chromatography (HPLC) methods [3,4] have been reported for the estimation of PCT, PRO, and CAF. The results showed that six degradation products contained in the mixture can be detected and determined simultaneously and HPLC method has satisfied good validation requirements, especially with a fast retention time of 3.8; 4.7; and 5.7 min for PCT, PRO, and CAF, respectively. This makes HPLC method has high analytical sensitivity but requires relatively high cost compared to spectrophotometry [1].

The derivative spectrophotometric method is one of the spectrophotometric methods that can be used to analyze the mixture of several substances directly without having to do separation first though with adjacent wavelengths [5]. Derivative spectrophotometric methods are relatively simple, and operating costs are cheaper compared to HPLC [6].

The zero-crossing method is the most common method used in derivative spectrophotometry, although this method is rarely used for the determination of ternary mixtures with application to higher derivatives, the determination of the levels of ternary mixtures can be performed. This method is faster and simpler. Literature survey reveals that derivative spectrophotometry methods [2] have been reported for the estimation of PCT, PRO, and CAF simultaneously in tablet preparations.

The aim of this study is to develop a simple, precise, and accurate spectrophotometric method for the estimation of PCT, PRO, and CAF in pharmaceutical dosage forms.

METHODS

Chemical and reagents

All material and reagents were analytical reagent grade. PCT, PRO, and CAF were purchased from National Agency of Drugs and Foods Control Indonesia and Kimia Farma Company.

APPARATUS

The spectrophotometric measurements were carried out on a Shimadzu UV-1800 spectrophotometer. The absorption spectra were measured using 1 cm quartz cells. For the derivative method, the absorption spectra were recorded on the same spectrophotometer, with 1 cm quartz cells and supported with UV-Probe 2.34 software.

Optimization of solvents

An optimization was performed by measuring the absorbance of PCT, PRO, and CAF in HCl 0.1 N, phosphate buffer pH 7.2, and phosphate buffer mixture pH 7.2 with methanol at a ratio of 90:10; 70; 30; 50:50; 30:70; and 10:90 [7].

Preparation standard solution

Stock solutions containing 25 µg/mL PCT, 25 µg/mL PRO, and 25 µg/mL CAF were prepared in phosphate buffer mixture pH 7.2 with methanol at a ratio 70:30 (PM 7:3). Further dilutions were done using PM 7:3 as described under construction of calibration graphs.

Construction of calibration graphs

Different aliquots of the standard solution of PCT, PRO, and CAF were transferred into 25 ml volumetric flask. The solutions were then

completed to the volume with PM 7:3, so the final concentration for PCT was 4.5; 5.5; 6.5; 8.5; 9.5; and 10.5 µg/mL, PRO was 8.0; 9.5; 11.5; 12.5; 14.0; and 15.5 µg/mL, and CAF was 4.6; 6.6; 8.6; 10.6; 12.6; and 14.6 µg/mL. The absorption spectrum of each solution was recorded within the wavelength range 200–400 nm and stored.

Assay of tablet formulation by derivative spectrophotometry

Twenty commercial tablets were weighed accurately. A powder quantity equivalent to 50 mg PCT was accurately weighed and transferred to volumetric flask of 50 ml capacity. 25 ml PM 7:3 was transferred to this volumetric flask and sonicated 15 min. The flask was shaken, and the volume was made up to the mark with PM 7:3. The above solution was filtered through Whatman filter paper no. 42. Pipette 0.16 mL of filtrate into a 25 mL volumetric flask, added with 0.48 ml and 1 ml of standard solution of PRO and CAF, respectively, then added with a solvent to the mark line. The absorbance is then measured at 200–400 nm to obtain absorbance. The quantitation was carried out by keeping these values to the straight line equation of calibration curve.

Method validation

The proposed method has been extensively validated in terms of linearity, accuracy, and precision. The accuracy of the method was determined by calculating recovery of PCT, PRO, and CAF by the standard addition method.

RESULTS

Optimization of solvent type

Phosphate buffer pH 7.2, HCl 0.1 N, and phosphate buffer mixture pH 7.2 with methanol at a ratio of 90:10; 70; 30; 50:50; 30:70; and 10:90 is the type of solvent that will be optimized. Table 1 shows the value of photometric errors.

The normal absorption spectrum

Fig. 1 shows the absorption spectra of 6.5 µg/mL PCT, 11.0 µg/mL PRO, and 6.6 µg/mL CAF, and the ternary mixture.

The derivative spectra

Figs. 2-4 show the derivative spectra of 6.5 µg/mL PCT, 11.0 µg/mL PRO, and 6.6 µg/mL CAF

Method validation

Table 2 shows the validation parameters for derivative spectrophotometry.

Application of the method in commercial tablet

The proposed method was applied for the determination of PCT, PRO, and CAF in their combined commercial tablet and the result is shown in Table 3.

DISCUSSION

Based on the result of solvent optimization shows that the solvent PM 7:3 has the smallest of photometric errors number so the solvent used in this research is PM 7:3.

These results indicate that there is a difference between the results of research conducted by Saraan (2015), which in this study the optimal solvent for the determination of PCT, ibuprofen, and CAF levels is phosphate buffer pH 7.2, while in this study obtained an optimal solvent for determination PCT, PRO, and CAF is PM 7:3. This is because propyphenazone is more soluble in water than ibuprofen so in the presence of methanol will increase the solubility of PRO [7-10].

The absorption spectra of three components are strongly overlapped (Fig. 1) that was sufficiently enough to demonstrate the resolving power of the proposed method. In this respect, different solutions of PCT, PRO, and CAF were prepared in the concentration ranges stated in the construction of calibration graph. The absorption spectra of these concentrations were recorded and stored.

For the determination of PCT, the first derivative the stored spectra of standard solutions of PCT, PRO, and CAF and a solution of their mixture were calculated with Δλ 2 nm (Fig. 2). From this figure, PCT can be determined in this mixture by measuring the amplitude at 239.4 nm where there is no contribution from PRO and CAF (zero-crossing point of PRO and CAF).

For the determination of PRO, the third derivative the stored spectra of standard solutions of PCT, PRO, and CAF and a solution of their mixture were calculated with Δλ 8 nm (Fig. 3). From this figure, PRO can be determined in this mixture by measuring the amplitude at 249.6 nm where there is no contribution from PCT and CAF (zero-crossing point of PCT and CAF).

For the determination of CAF, the first derivative the stored spectra of standard solutions of PCT, PRO, and CAF and a solution of their mixture were calculated with Δλ 8 nm (Fig. 4). From this figure, CAF can be determined in this mixture by measuring the amplitude at 245.6 nm where there is no contribution from PCT and PRO (zero-crossing point of PCT and PRO). The wavelengths 239.4 nm, 249.6 nm, and 245.6 nm in each condition were selected for analysis of PCT, PRO, and CAF, respectively [11-13].

The linearity of the proposed method was evaluated for each drug by analyzing the different concentration of each PCT, PRO, and CAF, within the concentration range in construction calibration graph. The assay was performed according to the previously stated conditions. A straight line was obtained in each case. Analysis of these graphs showed excellent linearity of the calibration graph and agreement to Beer's law.

As shown in Table 2, the resulting mixtures were assayed according to the above-stated procedure, and the results were calculated as the percentage of analyte recovered. Limit of detection and limit of quantification values were indicated that the method shows high sensitivity. The good recovery values assure the high accuracy of the proposed method.

CONCLUSION

The proposed method provides a simple and accurate quantitative analysis for the determination of PCT, PRO, and CAF as a ternary

Table 1. Photometric errors

Type of solvent	Photometric errors (%)			Reduction with 2.7185 (%)			Amount (%)
	PCT	PRO	CAF	PCT	PRO	CAF	
P	2.7297	2.7195	2.7280	0.0112	0.0010	0.0095	0.0217
PM 1:9	2.7947	2.7195	2.7435	0.0762	0.0010	0.0250	0.1022
PM 3:7	2.7715	2.7332	2.7366	0.0530	0.0147	0.0181	0.0858
PM 5:5	2.7383	2.7178	2.7332	0.0198	-0.0007	0.0147	0.0352
PM 7:3	2.7229	2.7195	2.7178	0.0044	0.0010	-0.0007	0.0061
PM 9:1	2.7212	2.7195	2.7229	0.0027	0.0010	0.0044	0.0081
HCl 0.1 N	2.7178	2.7195	2.7610	0.0007	0.0010	0.0425	0.0428

P: Phosphate buffer pH 7.2. PM 5:5: phosphate buffer pH 7.2:methanol (50:50). PM 1:9: Phosphate buffer pH 7.2:methanol (10:90). PM 7:3: Phosphate buffer pH 7.2:methanol (70:30). PM 3:7: Phosphate buffer pH 7.2:methanol (30:70). PM 9:1: Phosphate buffer pH 7.2:methanol (90:10). PCT: Paracetamol, PRO: Propyphenazone, CAF: Caffeine

Table 2: Validation parameters for derivative spectrophotometry

Parameters	PCT	PRO	CAF
Linearity	0.9960	0.9950	0.9999
Accuracy (%)	99.67	101.11	101.3
Precision (RSD) (%)	1.82	1.42	0.80
LOD	1.1531	2.0871	0.3928
LOQ	3.4942	6.3246	1.1902

LOD: Limit of detection, LOQ: Limit of quantification, PCT: Paracetamol, PRO: Propyphenazone, CAF: Caffeine, RSD: Relative standard deviation

Table 3: Result of quantification of PCT, PRO, and CAF in marketed formulation by derivative spectrophotometry method

Drug	Label claim (mg/tablet)	Amount found (mg/tablet
PCT	350	100.91%
PRO	150	104.75%
CAF	50	103.33%

PCT: Paracetamol, PRO: Propyphenazone, CAF: Caffeine,

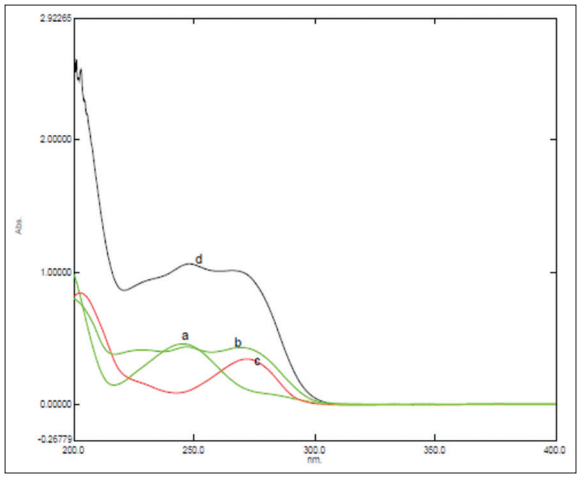

Fig. 1. Absorption spectra of (a) 6.5 µg/mL paracetamol, (b) 11.0 µg/mL propyphenazone, (c) 6.6 µg/mL caffeine, (d) the ternary mixture

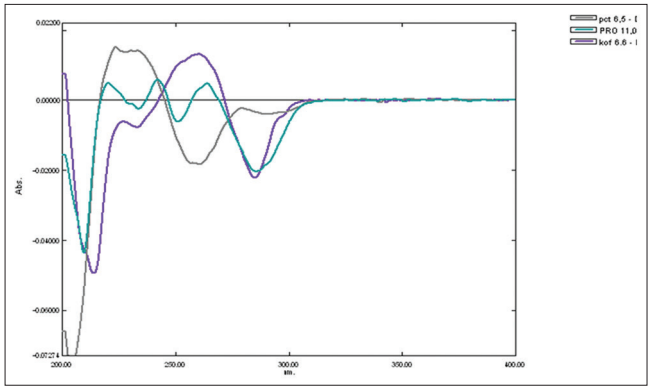

Fig. 2: First derivative spectra were calculated with Δλ 2 nm

mixture. The proposed method is simple as there is no need for solvent extraction and direct as it estimates each component independent of the other, and also the method is rapid, low cost, and harmless to the environment. Hence, it could be applied in quality control laboratories.

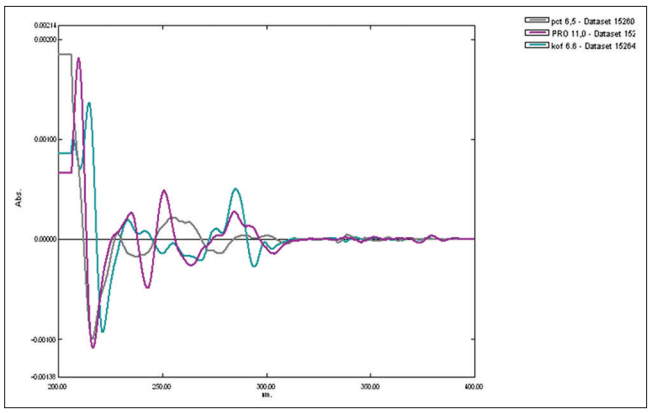

Fig. 3: Third derivative spectra were calculated with Δλ 8 nm

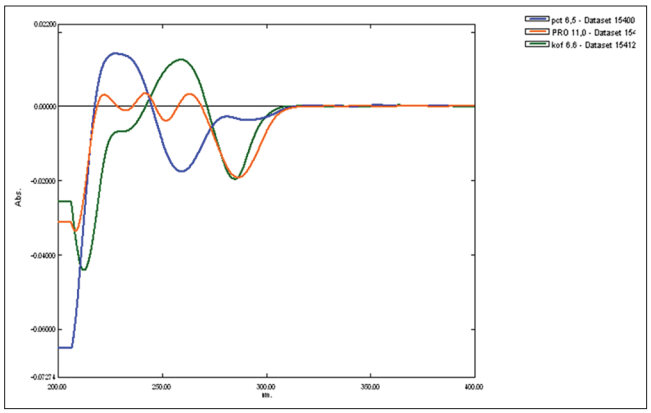

Fig. 4: First derivative spectra were calculated with Δλ 8 nm

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