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Original Article

APPLICATION MEAN CENTERING RATIO SPECTRA METHOD FOR TERNARY MIXTURE OF DEXTROMETHORPHAN HBr, DOXYLAMINE SUCCINATE, AND PSEUDOEPHEDRINE HCl IN TABLET PREPARATIONS

RIDA EVALINA TARIGAN*, HENDRI FAISAL, IMAN KRISTIAN lASE, SAFURA PUTRI HAFIFAH

Departement of Pharmaceutical Chemistry, Faculty of Pharmacy and Health, Institut Kesehatan Helvetia, Medan, Sumatera Utara-20124, Indonesia

***Corresponding author: Rida Evalina Tarigan; *Email: ridaevalinatarigan@helvetia.ac.id**

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ABSTRACT

Objective: The aim of this research is to apply the mean Centering Ratio Spectra (MCRS) method for a ternary mixture of Dextromethorphan Hydrobromide (DE), Doxylamine Succinate (DO), and Pseudoephedrine Hydrochloride (PS) in tablet preparations.

Methods: The absorption spectra of DE (40-430 µg/ml), DO (20-430 µg/ml), and PS (230-630 µg/ml) were scanned in the 200-400 nm range. DE determination involved dividing DE spectra by PS (430 µg/ml) and mean-centered the ratio spectra. DO spectra were divided by DE (40 µg/ml) to obtain mean-centered ratio spectra. The mean-centered ratio spectra for PS were obtained by dividing the scanned spectra of its prepared solutions by the standard spectrum of DE, which had a concentration of 70 µg/ml.

Results: Method validation parameters, including linearity, accuracy, precision, limit of Detection (LOD), and limit of Quantification (LOQ), were assessed. The results indicated linearity values of 0.9988, 0.9992, and 0.9998, respectively, for DE, DO, and PS. Accuracy: 99.84%, 100.15%, and 100.33%, respectively, for DE, DO, and PS. Precision: 0.53%, 0.54%, and 0.74%, respectively, for DE, DO, and PS. lOD: 1.85 µg/ml, 2.09 µg/ml, and 1.56 µg/ml, respectively, for DE, DO, and PS. lOQ: 6.19 µg/ml, 6.97 µg/ml, and 5.22 µg/ml, respectively, for DE, DO, and PS. All validation method parameters meet International Conference of Harmonization (ICH) validation requirements.

Conclusion: The MCRS method can be applied for the simultaneous ternary mixtures of DE, DO, and PS in tablet preparations. Its successful application, combined with rigorous validation results, suggests its potential for adoption in routine pharmaceutical analysis, contributing to the advancement of quality control practices in the industry.

Keywords: Mean centering ratio spectra, Ternary mixtures, Dextromethorphan HBr, Doxylamine succinate, Pseudoephedrine HCl

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INTRODUCTION

The accurate and simultaneous determination of multiple components in pharmaceutical formulations is a crucial aspect of quality control and assurance [1, 2]. In recent years, the focus has shifted towards the development of efficient and reliable analytical methods for the analysis of ternary mixtures, which commonly consist of complex combinations of Active Pharmaceutical Ingredients (APIs) [3, 4]. Dextromethorphan hydrobromide (DE), Doxylamine Succinate (DO), and Pseudoephedrine Hydrochloride (PS) represent a notable ternary mixture frequently encountered in over-the-counter cold and cough medications, pose analytical challenges due to overlapping spectra [5].

Traditional analytical methods often face challenges when dealing with ternary mixtures due to issues such as overlapping spectra and potential interference [6, 7]. To overcome these challenges, the mean Centering Ratio Spectra (MCRS) method has emerged as a promising technique for the simultaneous determination of multiple components in complex mixtures [8-11].

DE is an antitussive drug commonly used as a cough suppressant that acts centrally to suppress the cough center in the medulla, in combination with DO, usually used in expectorant cough medicines acting by blocking histamine and acetylcholine, and PS, namely as a decongestant or as an anti-allergy. The combination of these three drugs is very effective in the treatment of cough [6-8]. The MCRS method involves the application of mathematical transformations to the absorbance spectra of the individual components and their mixtures. This method is particularly advantageous as it helps in resolving issues related to spectral overlap and provides enhanced selectivity, making it suitable for the analysis of ternary mixtures [12-15].

Spectrophotometry [16, 17], double divisor ratio spectra derivative spectrophotometry [3], area under curve spectrophotometry [5], High-Performance liquid Chromatography (HPLC) [18-20], High-Performance Thin layer Chromatography (HPTLC) [21], Thin layer Chromatography-Densitometric (TLC-densitometric) [22], and voltammetry [23] have all been used to determine ternary mixtures of DE, DO, and PS, either alone or in combination with other compounds. Based on these references, there is no MCRS method for determining ternary mixtures of DE, DO, and PS in tablet preparations. The aim of this research is to apply the MCRS method for ternary mixture of DE, DO, and PS in tablet preparations.

MATERIALS AND METHODS

Materials

Raw materials for DE, DO, and PS were purchased from PT. Konimex, Indonesia. The standards for DE, DO, and PS were obtained from the National Agency for Drug and Food Control of the Republic of Indonesia. Ethanol (E. Merck) was used as the solvent.

Instrumentation

A Shimadzu UV-Vis Spectrophotometer 1800 and a collection of Personal Computers (PCs) are included. Matlab® version R2016a was utilized.

Preparation of a standard solution

A quantity of DE, DO, and PS standard, each weighing 50 mg was separately put into a volumetric flask containing 50 ml and dissolved in ethanol to produce solutions containing 1000 µg/ml of DE, DO, and PS.

Zero-order absorption spectra of DE, DO and PS

In the region of 200-400 nm, the zero-order absorption spectra of 70 µg/ml DE, 40 µg/ml DO, and 430 µg/ml PS were recorded.

MCRS method

The absorption spectra of solutions produced at different concentrations of DE (40-430 µg/ml), DO (20-430 µg/ml), and PS

(230-630 µg/ml) were scanned in the 200-400 nm range. DE determination involved dividing DE spectra by PS (430 µg/ml) and mean-centered the ratio spectra. DO spectra were divided by DE (40 µg/ml) to obtain mean-centered ratio spectra. The mean-centered ratio spectra for PS were obtained by dividing the scanned spectra of its prepared solutions by the standard spectrum of DE, which had a concentration of 70 µg/ml.

Validation of the method

Linearity

Linearity for the MCRS method was constructed using various concentrations for DE (40–430 µg/ml), DO (20–430 µg/ml), and PS (230–630 µg/ml). MCRS regression revealed the linearity.

Accuracy

A recovery analysis was conducted using standard addition in order to validate the effectiveness and reliability of the proposed methods. The percentage recovery in three distinct areas (80%, 100%, and 120%) was utilized to conduct the recovery test [24].

Precision

Precision, also known as Relative Standard Deviation (RSD), is calculated from the regression equation in the calibration curve using the following formula:

$$\text{RSD} = \frac{\text{SD}}{\text{X}} \times 100\%$$

The variables are described as follows: RSD is the Relative Standard Deviation, SD is the Standard Deviation, and X is the average data [24, 25].

Limit of detection (LOD) and limit of quantification (LOQ)

LOD and the lOQ of DE, DO, and PS were computed utilising the equation provided below in order to ascertain the sensitivity of the proposed approaches in accordance with International Conference of Harmonization (ICH) recommendations.

$$\text{LOD} = 3.3\frac{\sigma}{\text{S}}$$

$$\text{LOQ} = 10\frac{\sigma}{\text{S}}$$

σ denotes the standard deviation of the response and S represents the slope of the linear graph [5, 24].

RESULTS AND DISCUSSION

Zero-order absorption spectra of DE, DO, and PS

The Zero Order Absorption Spectrum of DE, DO, and PS can be seen in fig. 1.

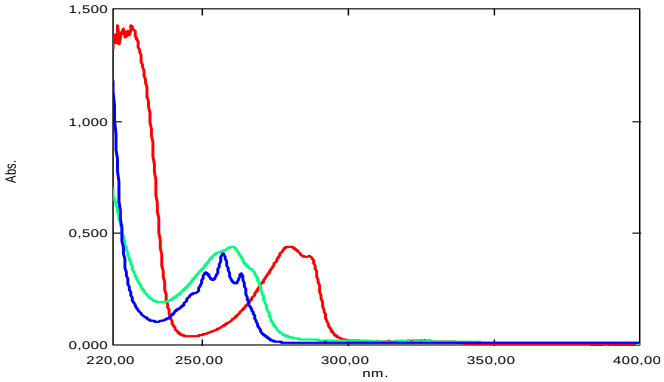

Fig. 1: Zero-order absorption spectra of DE ( ), DO ( ), and PS ( )

Fig. 1 shows the zero-order absorption spectra of DE, DO, and PS, which overlap seriously enough that direct determination of DE, DO, and PS is not possible. The problem of overlapped spectra of DE, DO, and PS is solved using MCRS to determine DE, DO, and PS [26-28].

MCRS method

The MCRS approach relies on the utilization of mean centering of ratio spectra, hence eliminating the need for derivative procedures. The technique has been used to resolve binary and ternary mixes in complicated samples with unknown matrices by improving signal-to-noise ratios. In order to calculate the ratio spectra, the absorption spectra of each component drug were first divided by the spectrum of a chosen divisor (the other component drug). Following this, the method of MCRS was utilized [28, 29].

Ratio spectra of DE, DO, and PS can be observed in fig. 2, 3, and 4 after undergoing division by the divisor and were then mean centered, as illustrated in fig. 5, 6, and 7.

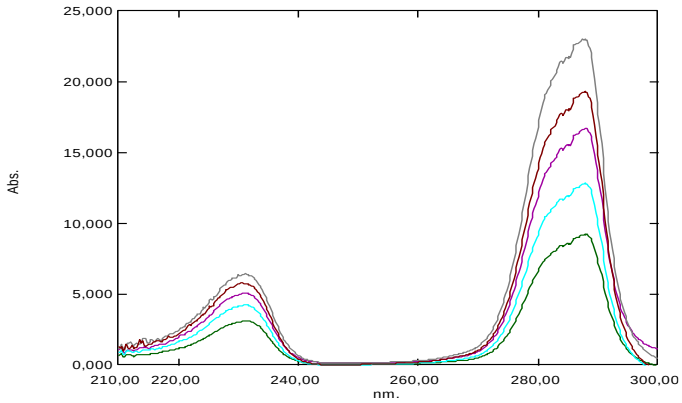

Fig. 2: Ratio spectra of DE (40–430 µg/ml) using PS (430 µg/ml) as a divisor

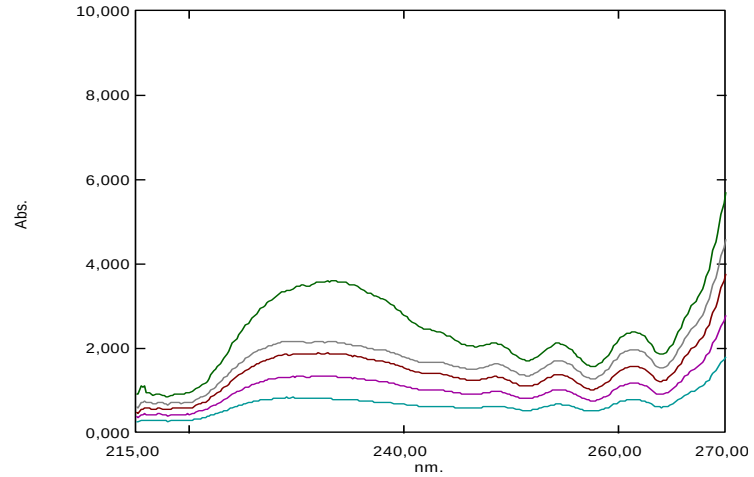

Fig. 3: Ratio spectra of DO (20–430 µg/ml) using DE (40 µg/ml) as a divisor

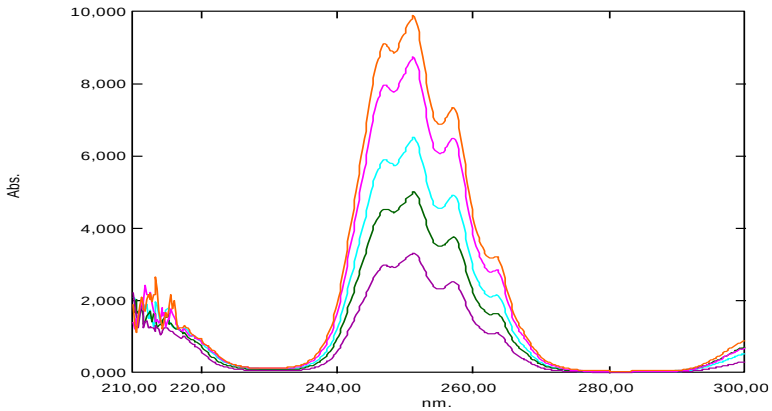

Fig. 4: Ratio spectra of PS (230–630 µg/ml) using DE70 µg/ml as a divisor

Based on fig. 2, 3, and 4, the ratio spectrum boosts the signals that are associated with the analyte of interest while simultaneously reducing the signals that are caused by chemicals that interfere or by the matrix. This is because the process of division causes common aspects to cancel out, leaving just the distinctive spectral characteristics of the analyte behind [30-32].

Based on fig. 5, 6, and 7, the spectrum of DE, DO, and PS has been separated without interference from each substance. DE (wavelength 273 nm), DO (wavelength 245 nm), and PS (wavelength 248 nm) have undergone separation into single substances, enabling the determination of the quantity of each active ingredient without the need for further separation [8, 29-32].

Application MCRS method for ternary mixture of DE, DO and PS in tablet preparations

Application MCRS method for a ternary mixture of DE, DO and PS in tablet formulations can be seen in table 1.

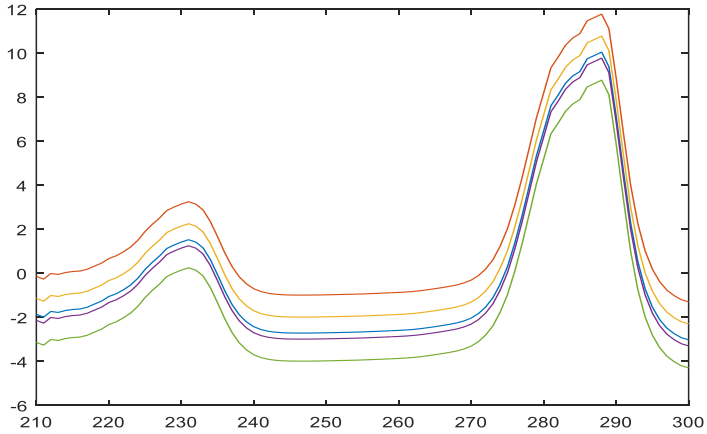

Fig. 5: MCRS of DE

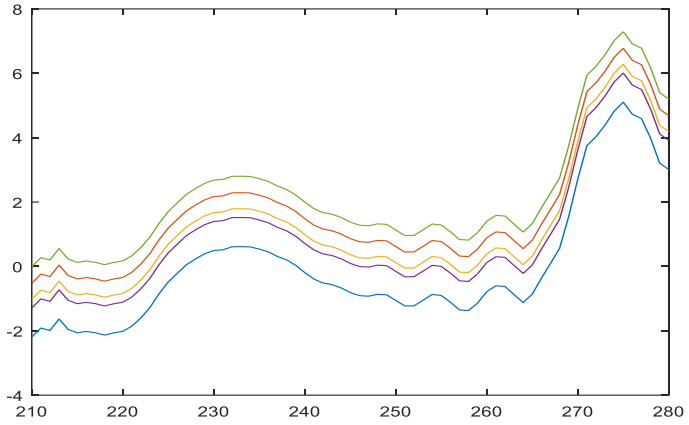

Fig. 6: MCRS of DO

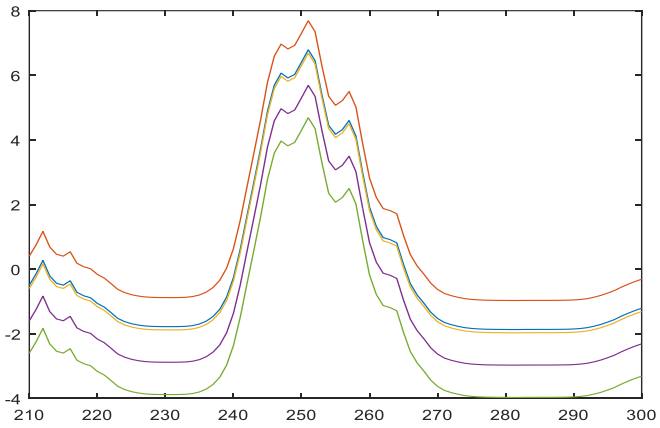

Fig. 7: MCRS of PS

Table 1: Application MCRS method for ternary mixture of DE, DO and PS

No	Component of drug	Level	Requirements based on Indonesian pharmacopoeia edition VI)
1	DE	(100.12±0.52)%	(90-110)%
2	DO	(100.05±0.26)%	(92-108)%
3	PS	(99.72±0.17)%	(90-110) %

Data are presented as mean ± Standard Error of mean (SEM), n = 3.

Table 1 shows the application MCRS method for ternary mixture of DE, DO and PS in tablet formulations meet the levels in accordance with the requirements of the Indonesian Pharmacopoeia Edition VI. It signifies that the ternary mixture of DE, DO, and PS in pharmaceutical tablet formulations can be determined simultaneously using the method [33].

Table 2: Result method validation

Parameters	DE	DO	PS
linearity	0.9988	0.9992	0.9998
Accuracy (%)	99.84	100.15	100.37
Precision (%)	0.53	0.54	0.74
LOD (µg/ml)	1.85	2.09	1.56
LOQ (µg/ml)	6.19	6.97	5.22

Method validation

The method was validated based on linearity, accuracy, precision, lOD and lOQ. The validation results are shown in table 2.

According to table 2, this study has a good result-validation method for simultaneous DE, DO, and PS in pharmaceutical tablet formulations since all parameters of the validation method meet the ICH validation requirements. This method offers a significant amount of potential for use in the pharmaceutical industry's routine quality control procedures [11].

CONCLUSION

The MCRS method can be applied for the simultaneous ternary mixtures of DE, DO, and PS in tablet preparations. Its successful

application, combined with rigorous validation results, suggests its potential for adoption in routine pharmaceutical analysis, contributing to the advancement of quality control practices in the industry.

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AUTHORS CONTRIBUTIONS

Concept and design-Rida Evalina Tarigan, Hendri Faisal.

Data analysis/interpretation-Rida Evalina Tarigan, Hendri Faisal, Iman Kristian lase.

Statistical analysis-Rida Evalina Tarigan, Iman Kristian lase, Safura Putri Hafifah.

Final approval-Rida Evalina Tarigan, Hendri Faisal, Iman Kristian lase, Safura Putri Hafifah.

CONFLICT OF INTERESTS

There is no conflict of interest

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