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PLS CALCULATION OF FTIR AND SPECTROPHOTOMETRIC METHODS FOR DETERMINATION SIMULTANEOUS OF DEXTROMETHORPHAN HBR AND GLYCERYL GUAIACOLATE IN TABLET MIXTURE

Muchlisyam Bachri✉, Yade M. Permata and H. Syahputra
Pharmaceutical Chemistry Department, Pharmacy Faculty, Universitas Sumatera Utara, Kampus USU, Padang Bulan, Medan, 20155. Indonesia.
✉E-mail: muchlisyam@usu.ac.id

ABSTRACT

Practical, easy, correct, and perfection of Partial least squares regression (PLS) calculations with Fourier transform infrared (FTIR) and Spectrophotometric methods to the simultaneous determination of Dextromethorphan HBr and Glyceryl Guaiacolate mixtures without separation in tablet formulations. The research was using PLS regression for FTIR at a wavelength of 806.24-844.82 nm and for dextromethorphan HBr and on 705.94-744.52 nm for Glyceryl Guaiacolate, while by spectrophotometric method at 230-300 nm with 2 nm intervals. The results showed that The PLS calculation for Dextromethorphan HBr has 110.07% and Glyceryl Guaiacolate was 110.01% with FTIR methods and Spectrophotometric methods were 104.73 % for Dextromethorphan HBr and 101.78 for Glyceryl Guaiacolate. The results showed that the simultaneous determination of the mixture of dextromethorphan HBr and Glyceryl Guaiacolate utilizing FTIR, and spectrophotometric methods with PLS calculation can be used and meets the validation requirements.

Keywords: Dextromethorphan HBr, Glyceryl Guaiacolate, FTIR, Spectrophotometry, Multi-component, PLS.
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INTRODUCTION

The combination of dextromethorphan HBr and glyceryl guaiacolate is a cough medicine combination for children whose composition consists of 3.5 mg dextromethorphan HBr and 50 mg glyceryl guaiacolate, while for adults, the composition per tablet is 15 mg and 100 mg. This combination is available in tablets and syrup form.[1,2]

The primary use of dextromethorphan HBr (DEX) is to relieve coughs. To provide temporary relief from coughs caused by bronchial irritation. As well as coughs caused by irritating particles that are inhaled.[1.2] Glyceryl guaiacolate (GG) is an expectorant type drug that can relieve coughs and increase the expectoration of phlegm in the airways.[3] This drug works by increasing the volume of phlegm and making it thinner so that it is easier to remove from the respiratory tract through the airway by coughing.[4.5]

In various journals, the determination of drug mixtures without separation has been published, among others, the application of the spectrophotometric method and HPLC.[5-7] Besides it, the literature shows that assay for both drugs can be done individually or in combination. Dextromethorphan HBr was determined by spectrophotometric, RP-HPLC, and HPLC methods. While glyceryl guaiacolate was carried out by spectrophotometry, RP-HPLC,[7.8] and HPLC methods.[9-11]

Combined mathematical methods and computation have been developed using statistical formulas in order to pattern analytical chemistry, used by specific and experimental optimal analytical procedures. PLS calculation in determining the levels of the components in the drug mixtures, which have bordering wavelengths when the spectra overlap. This technique has successfully applied analytical methods in spectrophotometry and FTIR.[12-15]

Several researchers have conducted single component research using PLS calculation with FTIR spectroscopy equipment and spectrophotometric methods, including the determination of the levels of Diclofenac sodium, Clinidipine, Teneligliptine hydrobromide and in the form of a mixture of Acetaminophen and Ibuprofen, Cefepime-Metronidazole, and Cefoperazone-Sulbactam.[15-18]

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The aims of this research are to the judgment of level DEX and GG by PLS calculation with spectrophotometric and FTIR methods.

EXPERIMENTAL

Material

FTIR Spectroscopy (IRPrestige-21 Shimadzu) equipped with computer and IR solution software Microsoft Excel, Minitab software version 18.2.4.4., Analytical balance (Sartorius), DEX(BPFI), GG (BPFI), potassium bromide, Methanol pro analysis (E.Merck) Rudang Jaya, Meda, Indonesia. Tablets local production.

Construction of the Absorption Spectrum with Spectrophotometric Methods

Construction absorption spectrum performed at a wavelength of 200-400 nm. Determination of the maximum absorption spectrum of 80 mcg / ml DEX, and 35 mcg / ml GG.[2]

Validation Methods for Spectrophotometric Methods and FTIR

Determination of the validation on the spectrophotometric and FTIR methods was carried out by measuring the linearity, precision, LOD, and LOQ and measuring the accuracy of the sample with conditions of 80,100 and 120% with a sample ratio of 70% and 30%.[20,21] If it met the requirements, followed by the PLS validation test.[14,15]

Absorption Spectrum for PLS with Spectrophotometry Methods

The absorption spectrum of 120 ppm DEX was measured at a wavelength of 230-300 nm and 35 ppm GG, and to obtain the spectrum by calculating the absorbance value is using UV Probe 2.82 software. The wavelength range that gives the best linearity is selected if the relationship between the PLS value and the concentration is indicated by the r value ≤ 1.[14,15] The processing data is carried out by Minitab version 18.2.4.4.

Preparation of DEX and GG Absorption Spectra by FTIR Methods

The 50 mg of raw stock, respectively, is carefully weighed and added to the amount of KBr pellets up to 1000 mg and ground again and it is called the working standard. The working standard is pressed by a hydraulic pressure system in the die press in FTIR apparatus to obtain sample discs. Then the FTIR spectrum was measured in diffuse transmission mode. The spectrum was recorded in the range 4000-500 cm^{-1}.

Construction of Calibration Curves and Validation Test for PLS

Calibration was evaluated using the root mean-squared-error on calibration (RMSEC) model and the coefficient of determination (R2). The eliminated sample is then calculated using the newly developed PLS model. This procedure is performed repeatedly, eliminating one by one the calibration samples to the desired R2 value.[14,15]

Construction Solution of DEX and GG Mixture in Tablet Preparation

Weighed 20 tablets, and powders are weighed tablets equivalent to 5 mg GG, and count the DEX, put 25 mL volumetric flask, and diluted with methanol (homogenized for 15 minutes), to mark the line, shaken until homogeneous. The solution is used for determination by the spectrophotometric method.[2]

Determination of DEX an GG in Sample Solution by Spectrophotometric Method

Pipetted 1.75 ml solution for DEX and 0.5 mL solution for GG, and respectively transferred in 50 mL flask, and dissolved up to line mark with methanol. The absorption is measured at a wavelength of 200-400 nm. The absorption is divisor with GG for determination DEX, and made at a wavelength of 230-300 nm.[15] The absorption of GG was made with DEX as a divisor and made at a wavelength of 210-300 nm with intervals of 2 nm.[2]

Determination of DEX an GG in the Sample by FTIR Method

The powder is equivalent to 50 mg DEX and calculated the GG equivalence in it. Enough with KBr up to 500 mg and homogenized. The absorption was measured at a wavelength of 500-4000 cm^{-1} and a partial least squares DEX spectrum was made at a wavelength of 844-805 cm^{-1} and a spectrum of partial least squares GG at a wavelength of 745-705 cm^{-1}.[14,15]

Statistical Components

a. The variables in the sample calculation are divided into 2 parts, namely: 1. Response variable 2. Predictor variable. The multivariate calibration for the determination of the concentration of components in the analyte mixture is based on the absorbance values at various wavenumbers from 1200 to 1000 cm^{-1}. So the concentration of the analyte is a predictor variable while the absorbance is the response variable.

b. R2 value of the variance of each variable predictor associated with the response variable.

c. Root Mean Square Error (RMSE) The amount of the error rate from the prediction, where the smaller (close to 0) the RMSE value, the more accurate it is. RMSE is used to evaluate the suitability of a predictive model.[14.15]

RESULTS AND DISCUSSION

The research results in Fig.-1 were obtained that the spectrum maximum of (80 µg/ml) DEX at 280 nm (Fig.-1a) and 35 µg/ml GG at 274.20 nm (Fig.-1b) . The overlapping maximum absorption spectrum of two-component Fig.-1c).

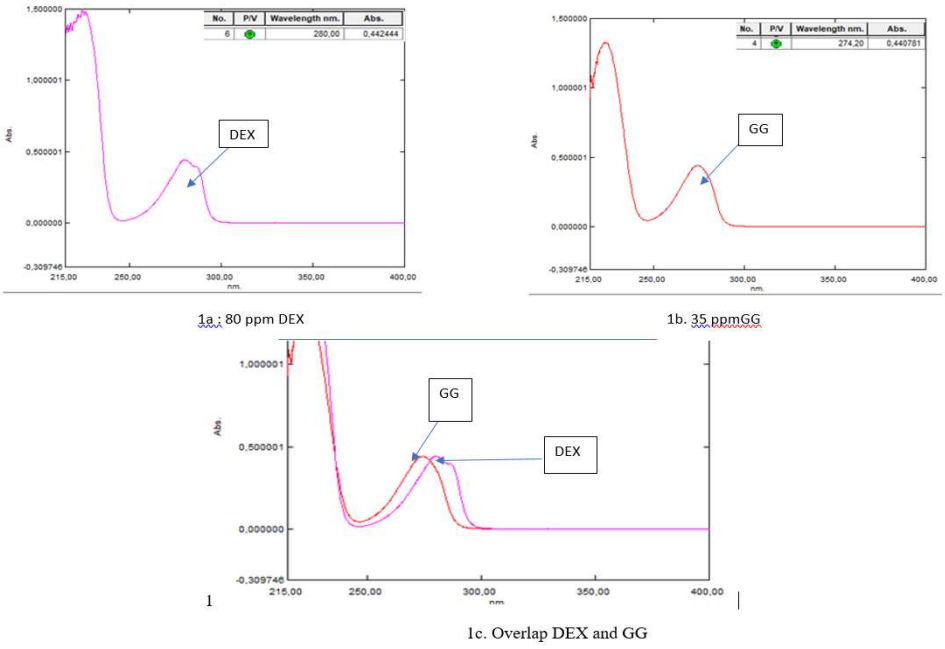


Fig.-1: The Absorption Spectrum (a.) DEX at 280 nm, (b.) GG at 274.2 nm, (c.) Overlapped DEX and GG

Figure-1 shows that the measurement of the sample spectrum meets the requirements of the Lambert-Beer rule, and is in line with a lot of literature that states that the wavelength of DEX in methanol is at 280 nm, meanwhile for GG in methanol at 274.20 nm. The literature above states that the difference in the respective wavelengths of DEX and GG is permitted if it is still below 2 nm.[3] In this research was shown that, means that this absorption spectrum can be used because a spectrum of the two components meets the requirements.[3]

The molecular absorption method in Ultra-violet spectrophotometry has been widely used in developing simpler, more reliable analytical methods.[2] This technique is used for level determination because it has the necessity that the operative drug mixture has a spectrum close to the Ultra-violet area and overlapping spectrums, making it difficult to determine the mixture simultaneously.[2,3]

The Vibration Spectrum in FTIR with KBr Pellet

Based on fig.-2, it's shown that the determination of the vibration spectrum is carried out at a wavelength of 500 - 4000 cm^{-1}. The specific vibrational regions for DEX can be seen at 1041.1072,1242,1280, and 1303 cm^{-1} wavelengths, while GG at 1022,1230,1256, and 1512 cm^{-1} wavelengths.[3]

Determination of DEX and GG Absorption Spectrums with FTIR

The absorption spectrum overlaps the standard absorption spectrum for DEX and GG, After the vibration form is converted into an absorption spectrum, it can be seen in Fig.-2.

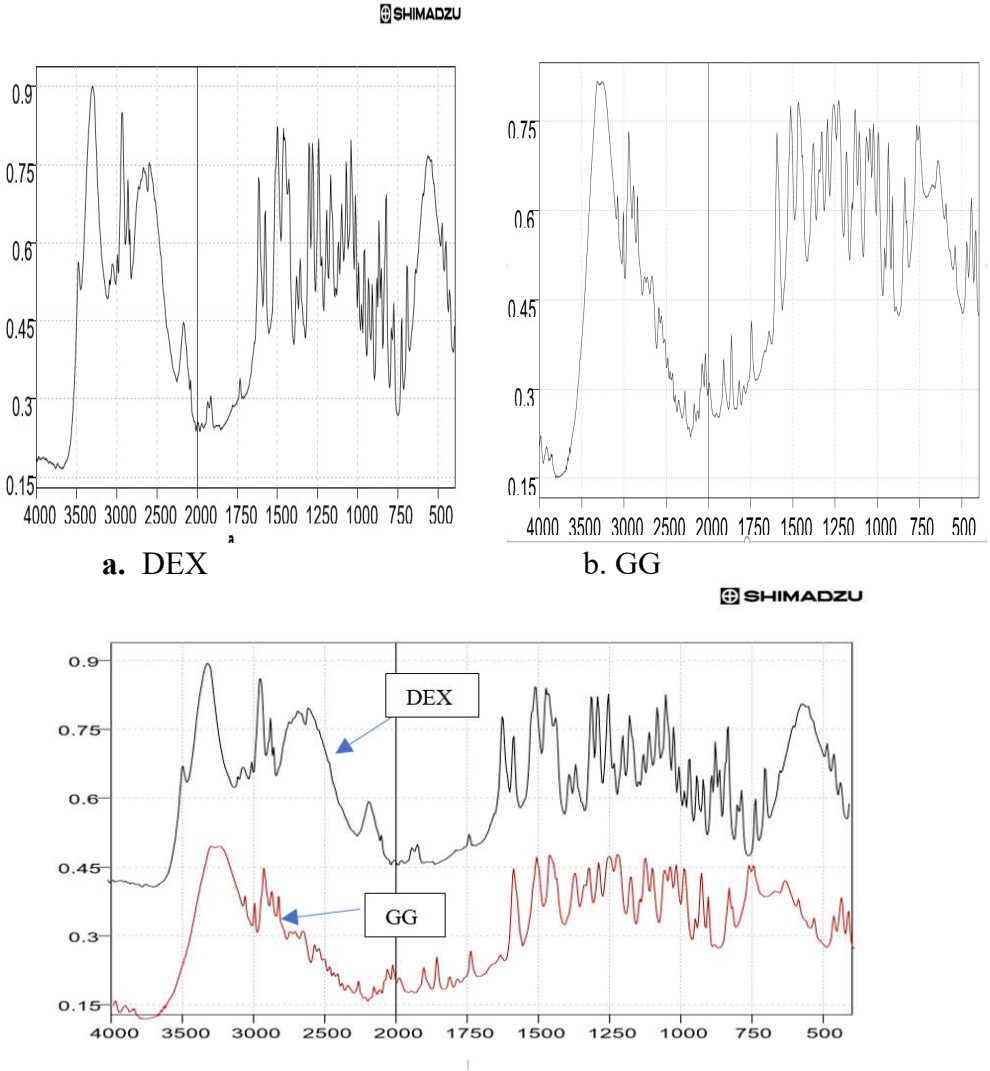


Fig.-2: Spectrum Absorption of (a) DEX, (b) GG and (c) it's overlapped at 4000-500 cm^{-1}

Result of DEX and GG with Spectrophotometric Methods

The measurement of the DEX standard at a concentration of (40-120) mcg / ml and the standard GG at a concentration of (21-49) mcg / ml was carried out at a wavelength of (230-300) nm with an interval of 2 nm then the results obtained were calculated with PLS which results can be seen in Fig.-3.[15-17]

The calibration curve of DEX and GG on Fig.-3 was shown by calculation by PLS multivariate model with r value of DEX is 0.99964 and GG is 0.9997. Modeling is conducted with 2 nm intervals at wavelength areas 230- 300 nm and 210-300 nm. This selection aims to obtain optimal model performance with the PLS computerized method, which can cover the entire spectrum obtained. The regression equation of DEX are $y = 0.00678x-0.00634$ and GG are $y = 0.01290x-0.00111$.[14.15]

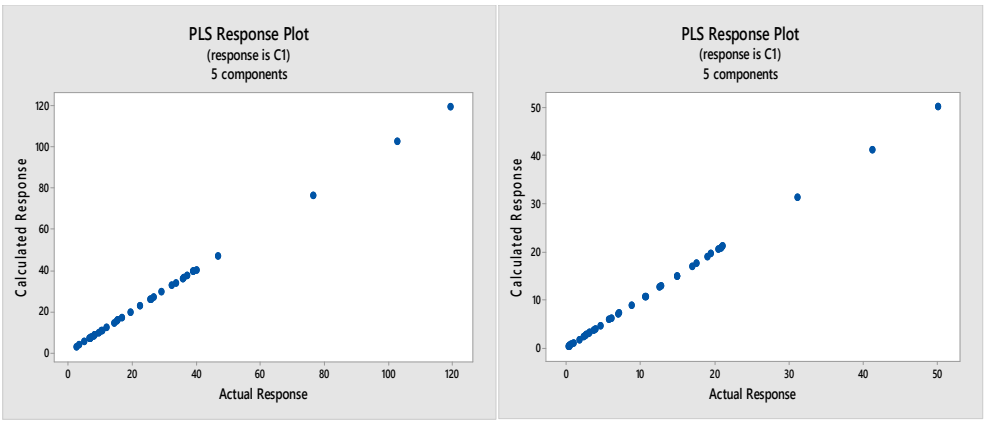
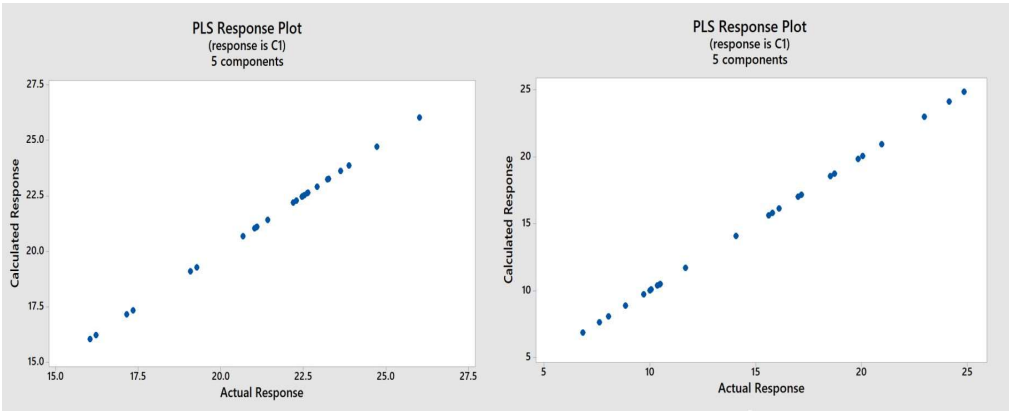


Fig.-3: Relation Curve of Level (a) DEX and (b) GG between Actual Response and Calculated Response with Spectrophotometric Methods without Cross-validation

Calculation of DEX level for local production of Tablet Mixture

The absorbance calculation is carried out at each wavelength range and entered into the PLS equation to obtain the concentration for each wavelength range.



a. DEX **b.GG**

Fig.-4: Calibration Curve of (a)DEX and (b) GG in FTIR With PLS Calculation

Based on Fig.-4 above shown, the actual response and calculated response regression in Partial Least Squares regression are linear, so it can be used for the calculation of DEX concentrations and levels.

Calibration Curve with FTIR Data

The data processing is done with PLS regression methods to produce a calibration model with good results on large data obtained from a single measurement. Absorbance data for DEX and GG were measured in the region on 745-705 cm^{-1} for GG and 850-805 cm^{-1} for DEX. The specific area ranges selected to provide the best linearity relationship between calculated response and actual response, which is indicated by the value of the correlation coefficient value ≤ 1.

The Validation Method of Spectrophotometric and FTIR Method

The validation parameters tested were certainty, particularity, termination of detection (LOD) and the ultimate of quantitation (LOQ). Certainty is expressed as a percentage of the recovery by the standard addition method. Test certainty by drafting three unique unity of the sample with a range of 80%, 100% and 120%, respectively specific ranges of analytes containing 70% the analyte solution, and 30% in addition to the standard solution. The result can be seen in Table-1 and Table-2.

Based on Table-1 and Table-2 above was shown, the two methods have met the requirement the parameter of the validation methods. The cross-validation, respectively, of DEX and GG were ten components. The predictive ability of the PLS calibration model will be obtained from the treatment of the cross-validation

stage. The predictive value that can be accepted on external validation is shown by the R2 value, PRESS, and RMSECV of DEX and GG.

Table-1: Validation parameters of Spectrophotometric for DEX and GG

No	Parameter	Dex	GG	Requerement
1.	Linierity	0.9996	0.9997	= 1
2.	Accuracy (%)	99.88	100.05	98-101%
3.	Precision (%)	0.4812	0.3373	< 2%
=4.	LOD	3.5697	1.2063	
5.	LOQ	11.8991	4.0209	
6.	R2	0.9996	0.9997	>0.9
7-	PRESS Value	0.0769	0.0769	
8.	RMSEC	0.1437	0.0090	

Table-2: Validation parameters of FTIR for DEX and GG

No	Parameter	Dex	GG	Requerement
1.	Linierity	0.9930	0.9910	= 1
2.	Accuracy (%)	99.39	99.05	98-101%
3.	Precision (%)	0.3763	0.2454	< 2%
=4.	LOD	1.0083	0.69097	
5.	LOQ	3.3612	2.3032	
6.	R2	0.9930	0.9910	>0.9
7-	PRESS Value	0.0002321	0.0006855	
8.	RMSEC	0.00002987	0.0005236	

The cross-validation test results with the technique of a leave-one-out and external validation that this model can still be used well for the determination of the content of samples with grades. of R2> 0.9, and RMSECV PRESS small value. So the model is predicted well because of the coefficient of determination with the resulting value of R> 0.9 and the RMSECV value close to zero. Cross-validation was performed to determine the optimal number of components that characterize the data.[14.15]

The Assays Result of DEX and GG levels in Tablet Preparations

The assays of DEX and GG levels were determined by FTIR and spectrophotometric methods using PLS regressions counting for measuring components and the results of the two methods can be seen in Table-3.

Table-3: DEX and GG levels in Tablet Formulation by PLS Calculation

Component	FTIR	Spectrophotometric (%)	Requirement USP XXII (%)
DEX	110.07	104.21	90-110
GG	110.01	101.72	90-110

Table-3 shows that's the DEX and GG levels in the sample tablets are local products, respectively 110.07% and 110.01% by PLS calculation with the FTIR method while using the spectrophotometric method 104.21% and 101.72%. The result is shown in Table-3. Both methods have met the requirements for the levels listed in USP XXII, namely 90-110% for DEX and GG, respectively.[1]

CONCLUSION

Based on the research conducted, the PLS calculation with Spectrophotometric and FTIR methods was validated and can be determined the tablet preparation containing DEX, and GG and the levels of the components met the requirements of USP XXX.

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