Available online on 15.8.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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Fourier Transform Infrared Spectrophotometry-Partial Least Square for Simultaneous Quantification of Paracetamol, Guaifenesin, Phenylpropanolamine, and Chlorpeniramine Maleate in Tablet

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A B S T R A C T

The aim of this research is to develop a method usingFourier Transform Infrared Spectrophotometry-Partial Least Square (FTIR-PLS) for the simultaneous analysis of Paracetamol (PA), Guaifenesin (GU), Phenylpropanolamine (PH), and Chlorpheniramine Maleate (CH) in tablet. The method in this research was to create calibration and validation model using FTIR-PLS, where the wavenumbers for quantitative analysis of PA, GU, PH, and CH are respectively 1625-1575 cm^{-1}, 1280-1230 cm^{-1}, 1615-1565 cm^{-1}, and 1709-1575 cm^{-1}. The results of this research are the R^2 values for calibration and validation for PA, GU, PH, CH are 0.967, 0.965, 0.970, and 0.964 respectively. Root Mean Square Error Of Cross Validation (RMSECV) PA, GU, PH and CH were 0.0362, 0.0415, 0.1372 and 0.0141 respectively. Prediction Sum Of Residual Squared Errors (PRESS) PA, GU, PH and CH are 0.0328, 0.0431, 0.0470, and 0.005 respectively. FTIR-PLS has proven to be an effective method for the simultaneous quantification of PA, GU, PH, and CH in tablet.

Keywords: FTIR-PLS, Paracetamol, Guaifenesin, Phenylpropanomine, Chlorpheniramine Maleate

A R T I C L E I N F O: Received 02 Jan. 2025; Review Complete 18 March. 2025; Accepted 12 April 2025. ; Available online15 August. 2025

Cite this article as:
Tarigan R E, Melya S, Lisda R N, Fourier Transform Infrared Spectrophotometry-Partial Least Square for Simultaneous Quantification of Paracetamol, Guaifenesin, Phenylpropanolamine, and Chlorpeniramine Maleate in Tablet, Asian Journal of Pharmaceutical Research and Development. 2025; 13(4):01-05, DOI: http://dx.doi.org/10.22270/ajprd.v13i4.1583

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INTRODUCTION

Pharmaceutical formulations often contain a combination of Paracetamol (PA), Guaifenesin (GU), Phenylpropanolamine Hydrochloride (PH), and Chlorpheniramine Maleate (CH) in tablet, capsule and syrup. This combination was chosen because it is often commonly used to treat many symptoms, including pain, cough, and nasal congestion[1-3].

PA, widely used as an analgesic and antipyretic to relieve pain and fever[4-6].GU, commonly used as an expectorant to thin and loosen mucus in the airways[7-9]. PH acts as a decongestant, alleviating nasal congestion[1], while CH, an effective antihistamine for relieving allergy symptoms such as sneezing, itching, and watery eyes[10,11].

Pharmaceutical analysis plays a pivotal role in ensuring the quality, safety, and efficacy of pharmaceutical products. The ability to develop efficient analytical methods that can simultaneously determine multiple Active Pharmaceutical Ingredients (APIs) in complex formulations is crucial for robust pharmaceutical quality control[12-14].

Simultaneous determination offers significant advantages in pharmaceutical analysis. It allows for comprehensive assessment of the entire formulation, ensuring that each API is present within specified limits and maintaining the desired therapeutic effect[12]. This method enhances accuracy by reducing variability and potential errors that may arise from separate analyses of individual components. Moreover, it optimizes resources and time, making the quality control process more efficient and cost-effective[12, 13].

In practice, simultaneous determination addresses the complexities of modern drug formulations, where interactions

between APIs and excipients can affect overall product stability and efficacy. By detecting and quantifying multiple compounds in a single analysis, this approach mitigates risks associated with formulation inconsistencies, batch-to-batch variations, and regulatory non-compliance[12-14].

Several analytical methods have been utilized for the determination of PA, GU, PH, and CH in pharmaceutical products, both individually and in combination. High Performance Liquid Chromatography (HPLC) is renowned for its sensitivity and specificity in separating complex mixtures but requires extensive sample preparation and is relatively time-consuming[1,15]. High Performance Thin Layer Chromatography (HPTLC) offers cost-effective analysis with minimal sample preparation but lacks the sensitivity of HPLC[16].

Ultra Performance Liquid Chromatography (UPLC) provides higher resolution and faster analysis than HPLC but at similar operational costs[17]. Liquid Chromatography Tandem-mass Spectrometry (LC-MS) combines chromatographic separation with mass spectrometric sensitivity but demands significant initial investment and expertise[18]. Thin Layer Chromatography (TLC) is quick and suitable for qualitative analysis but lacks quantitative accuracy compared to chromatographic methods[19].

UV-Visible spectrophotometry offers simplicity and cost-effectiveness but limited specificity[20]. Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR) provides rapid, non-destructive analysis with minimal sample preparation but lower sensitivity compared to chromatography[21].

In contrast, Fourier Transform Infrared Spectrophotometry-Partial Least Squares (FTIR-PLS) stands out by enabling simultaneous determination of PA, GU, PH, and CH in pharmaceutical formulations. This method offers advantages such as non-destructive analysis, minimal sample preparation, and rapid results, which streamline quality control processes[20]. FTIR-PLS is particularly cost-effective compared to LC-MS, HPLC, and UPLC, making it suitable for routine analysis. Its capability to handle complex matrices through PLS regression ensures reliable quantification, meeting stringent regulatory standards for pharmaceutical products. Choosing FTIR-PLS over traditional methods thus enhances efficiency, reduces costs, and maintains high analytical precision, supporting robust pharmaceutical quality assurance practices[20,22].

FTIR-PLS has gained prominence in drug analysis due to its robust capabilities in quantitative assessment. Recent research has underscored its efficiency, rapidity, sensitivity, cost-effectiveness, and non-destructive nature. These attributes make FTIR-PLS highly suitable for pharmaceutical applications where quick and accurate analysis is paramount[22-25].

Recent advancements in FTIR-PLS technology have further enhanced its utility. Improved algorithms for data processing and enhanced instrument sensitivity have bolstered its accuracy in analyzing complex sample matrices. Moreover, advancements in chemometric modeling have strengthened FTIR-PLS's ability to handle spectral overlap and improve predictive capabilities[20, 25].

Despite these advantages, FTIR-PLS does have limitations to consider. Spectral interference from sample matrices can affect accuracy, requiring careful calibration and validation against reference methods[22-23].

The aim of this research is to develop a method using FTIR-PLS for the simultaneous analysis of PA, GU, PH, and CH in tablet.

MATERIAL AND METHODS

Instrumentation

FTIR (IRPrestige-21, Shimadzu) equipped with a computer and minitab software version 20, MS Excel, analytical balance (Sartorius), mortar and pestle (Medstuff), glassware (Iwaki).

Chemicals and Reagents

Standard PA, GU, PH, and CH (from National Agency of Drug and Food Control), potassium bromide (KBr), Tera-F® tablets (each tablet contains PA 650 mg, GU 50 mg, PH 15 mg, CH 2 mg) PT. Rama Emerald Multi Sukses, Surabaya, Indonesia.

Preparation of Calibration and Validation

Standard mixtures containing PA, GU, PH and CH, were prepared for calibration and validation purposes. These mixtures covered a concentration range of 30 mg-70 mg and were carefully combined with KBr to create powders totaling 500 mg each. Each underwent FTIR spectrophotometry analysis, scanning from 4500cm^{-1} to 500 cm^{-1}.

Sample Preparation

Weighed 20 tablets, then crushed them in a mortar until homogeneous. Carefully weigh the powder equivalent to 50 mg of PA and calculate the equivalent of GU, PH, and CH, add KBr to 500 mg and homogenize. The absorption was measured at a wavelength of 4500 cm^{-1}-500 cm^{-1}.

Statistical Analysis

The spectral absorbance data were transferred to MS Excel to enable data processing with Minitab software version 20. Various parameter criteria, including the coefficient of determination (R^2), Root Mean Square Error Of Cross-Validation (RMSECV), and Predicted Residual Sum Of Squares (PRESS), were assessed using Minitab version 20.

RESULTS AND DISCUSSION

Calibration and Validation

Figure 1 displays the calibration graph, illustrating how absorbance values measured by FTIR spectrophotometry correlate with known concentrations of PA, GU, PH, and CH. This graph is crucial as it visually demonstrates the method's accuracy in quantifying these compounds across different concentration levels. By plotting absorbance against known standards, it shows how changes in concentration directly affect absorbance readings, highlighting the method's sensitivity and precision.

Calibration verification involved using statistical analyses like correlation coefficients (R^2) and Root Mean Square Error of Calibration (RMSEC) to ensure the reliability of the calibration.

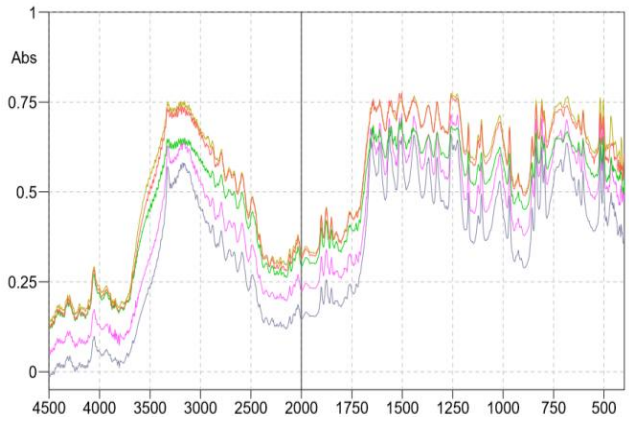

Figure 1: Infrared Spectra Calibration of PA, GU, PH, and CH

Figure 1 presents the FTIR spectra of a mixture containing PA, GU, PH, and CH in the calibration. The initial step in analyzing PA, GU, PH, and CH involves optimizing the wavenumber range to achieve the highest coefficient of determination (R^2) and the lowest error values. While multivariate calibration using PLS can utilize all wavenumbers in FTIR spectra for quantitative analysis, including non-informative spectral wavelengths can degrade the performance of the calibration model. Therefore, careful selection of appropriate wavenumbers is recommended[25,26].

Based on these criteria, the wavenumber region of 1625-1575 cm^{-1} was selected for the quantitative analysis of PA, the region of 1280-1230 cm^{-1} for the analysis of GU, the region of 1615-1565 cm^{-1} for PH, and the region of 1709-1575 cm^{-1} for CH. Selection of these wavenumber regions, because all components exhibited R^2 values close to 1 which can be seen in Table-1, indicating a strong correlation between the actual values of PA, GU, PH, and CH and the FTIR-PLS predicted values which can be seen in Figure 2-5. These results suggest that the calibration model developed using these wavenumber regions is highly satisfactory[23, 25].

Cross-validation using the leave-one-out technique to evaluate the performance of the Partial Least Squares (PLS) model in FTIR spectrum data analysis. This process begins by preparing an FTIR dataset containing absorbance spectra as features and substance concentrations as labels. This dataset consists of a matrix of FTIR spectra, where each row represents a spectrum and each column represents a wavelength, as well as an array of substance concentrations corresponding to each spectrum[23]. The difference between the actual and predicted values for each sample is computed, and the sum of the squares of these differences is termed the Predicted Residual Error Sum of Squares (PRESS) which can be seen in Table 1.

Furthermore, Figures 2-5 depict the Root Mean Square Errors Of Cross-Validation (RMSECV) and coefficients of determination (R^2) calculated during cross-validation to assess the correlation between actual values and FTIR-predicted values for PA, GU, PH, and CM [25-26]. RMSECV measures the average deviation between actual and predicted values, indicating the model's accuracy, with lower values indicating better performance. R^2 quantifies how well the model fits the data, with values closer to 1 indicating a stronger correlation. These figures serve to visually represent the model's predictive capabilities and its reliability in pharmaceutical analysis.

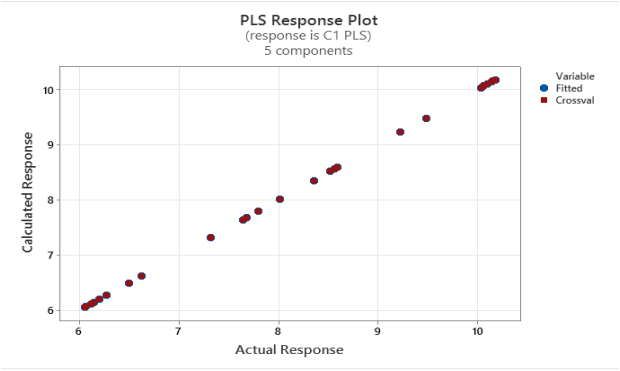

Figure 2: Correlation between actual values and FTIR predicted values for PA

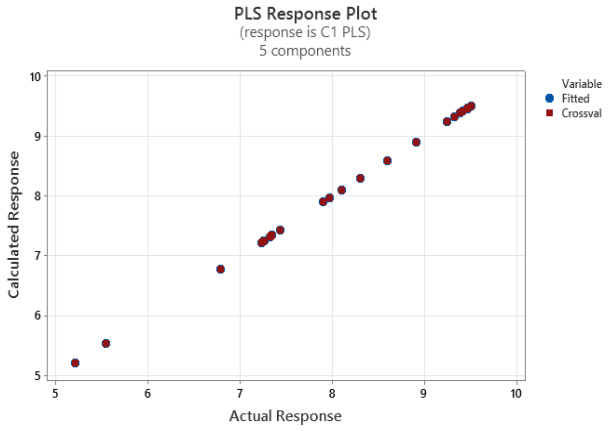

Figure 3: Correlation between actual values and FTIR predicted values for GU

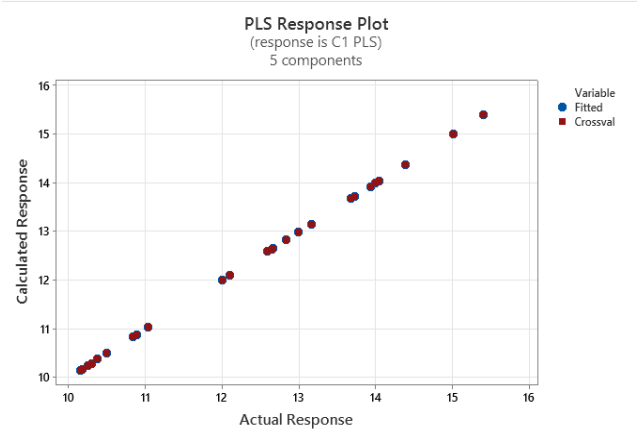

Figure 4: Correlation between actual values and FTIR predicted values for PH

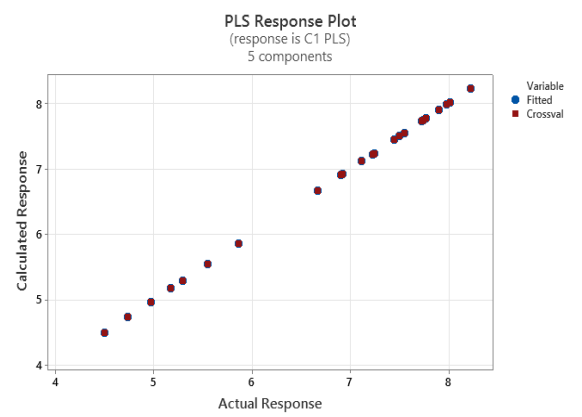

Figure 5: Correlation between actual values and FTIR predicted values for CM

Table 1 presents the R^2 value, PRESS, and RMSECV for PA, GU, PH, and CM, indicating their predictive capability in validation.

Table 1: Validation parameters of FTIR-PLS for PA, GU, PH, and CM

No	Parameter	PA	GU	PH	CM
1	Linearity (r)	0.967	0.965	0.970	0.964
2	Accuracy (%)	99.9	100.04	100.13	100.29
3	Precision (RSD) %	0.6070	1.1189	1.1485	0.8174
4	LOD (µg/mL)	2.0940	3.0657	1.7616	2.1331
5	LOQ (µg/mL)	3.8231	5.5972	2.1331	3.8964
6	R^2	0.967	0.965	0.970	0.964
7	PRESS	0.0328	0.0431	0.0470	0.005
8	RMSECV	0.0362	0.0415	0.1372	0.0141

Determination PA, GU, PH, and CH in Tablets Using FTIR-PLS Method

The results of the simultaneous quantification of PA, GU, PH, and CH levels in tablets are presented in Table 2 below. These findings are crucial as they demonstrate the method's effectiveness in accurately measuring these compounds within pharmaceutical formulations. The implications of these results are significant for quality control in the pharmaceutical industry, ensuring that tablet formulations meet specified standards for active ingredient content. Practical implications include enhancing product consistency and efficacy, as well as ensuring compliance with regulatory requirements. Furthermore, these quantification results pave the way for potential applications in pharmaceutical research and development, aiming to improve drug formulation and dosage accuracy.

Table2: PA, GU, PH and CH levels in tablet

No	Component	Drugs Levels		Claim on the Label	Requirements According to the Indonesian Pharmacopeia	
		(%)	(mg)	(mg)	(%)	(mg)
1	PA	98.08±0.60	637.52	650	90.0-110.0	585-715
2	GU	97.95±1.11	48.97	50	90.0-110.0	45-55
3	PH	99.83±1.15	14.97	15	98.0-101.0	14.7-15.15
4	CM	96.78±0.81	1.93	2	90.0-110.0	1.8-2.2

Based on Table 2, the levels of PA, GU, PH, and CH in the tablet meet the standards outlined in the Indonesian Pharmacopoeia (Edition VI 2024). The Indonesian Pharmacopoeia sets stringent guidelines to ensure the quality and safety of pharmaceutical products. These standards specify the exact concentrations of active ingredients like PA, GU, PH, and CH that tablets must meet for effectiveness and patient safety[27].

CONCLUSION

FTIR-PLS has proven to be an effective method for the simultaneous quantification of PA, GU, PH, and CH in tablet.

ACKNOWLEDGMENTS

The author wishes to extend sincere thanks to the research laboratory at the Faculty of Pharmacy, University of North Sumatera, for generously providing the research facilities for FTIR equipment.

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