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DETERMINATION OF THE LEVEL OF PARACETAMOL AND TRAMADOL HCL MIXTURE IN TABLETS BY CHEMOMETRIC METHOD BY FOURIER TRANSFORM INFRARED SPECTROPHOTOMETRY

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ABSTRACT

Fixed-dose combinations of paracetamol and tramadol HCl are effective in the treatment of moderate to severe pain. Therefore, the determination of the levels of the mixture of paracetamol and tramadol HCl is very important for the pharmaceutical industry. The purpose of this study was to determine the levels of paracetamol and tramadol HCl mixture using Fourier Transform Infrared combined with partial least square (PLS) chemometric method. This study was conducted by making a calibration model and chemometric validation of each of the five concentrations measured absorbance at specific wave numbers of paracetamol and tramadol HCl. The results of the study on PLS multivariate calibration of paracetamol and tramadol HCl with RMSECV values of 0.06279 and 0.03785, PRESS values of 0.02366 and 0.00860, and R2 values of 0.9995 0.9998, respectively. All validation parameters are within the acceptable range. This indicates that the method can be used to accurately determine drug levels without separation.

KEYWORDS paracetamol, tramadol hcl, ftir, chemometrics

INTRODUCTION

Paracetamol has analgesic and antipyretic effects on the body by reducing the intensity of pain signals to the brain and regulating body temperature the brain (Bührer et al., 2021; Mirrasekhian, 2020). quickly absorbed by the digestive tract when taken orally (Ashford, 2017; Borgström et al., 1957). Used for the treatment of various types of pain such as headache, migraine, toothache, flu, neuralgia, and others. This is achieved by reducing the production of prostaglandins in the central nervous system, thereby reducing the pain response in the peripheral nervous system. Tramadol HCl is an opioid agent used for the treatment of acute and chronic pain. The monoaminergic effects of tramadol are similar to those of antidepressant

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drugs. Tramadol HCl has been widely used alone in pharmaceutical formulations or with other active compounds (Selimoğlu & Pinarcik, 2023).

The combination of tramadol HCl and fixed-dose paracetamol is indicated to treat moderate to severe pain symptoms. This combination is effective in providing pain relief in adult patients with postoperative pain after minor surgery, musculoskeletal pain, diabetic peripheral neuropathy pain, or migraine pain. As both drugs have complementary modes of action and target multiple sites, and their combination provides better analgesic action against multiple types and sources of pain (Boccella et al., 2023).

Infrared spectroscopy is a very popular analytical technique. This spectroscopic method is often referred to as spectrophotometry because it involves light (photons). A spectrophotometer is a device used to measure spectra. Specific infrared spectra provide information about the functional groups of a compound (Rohman, 2022).

Chemometric methods are used to construct drug calibration curves, especially for mixture and multicomponent analysis with overlapping spectra. Chemometrics can perform better calculations because it can measure nonselective signals and then combine them in a multivariate model (Muchlisyam, 2017). Partial least squares (PLS) is a chemometric method that has long been used for quantitative analysis of spectroscopic data to reduce the dimensionality of variables and extract only relevant information (Biancolillo & Marini, 2018; Zhang, Tang, & Li, 2018). The advantage of PLS lies in the formation of regression components that can show the correlation between variables (Issa, 2024).

Several studies have been conducted in determining the levels of paracetamol and tramadol HCl mixtures, namely by High Performance Liquid Chromatography (HPLC) (Selimoğlu & Pinarcik, 2023), multiple lamda ultraviolet spectrophotometry (Thalij et al., 2019), Derivative UV-Vis absorption spectrophotometry (El-Zinati & Abdel-Latif, 2015), UV absorption spectrophotometry and chemometric methods (León et al., 2024; Marcheafave et al., 2024).

Based on this description, researchers are interested in determining the levels of the mixture of paracetamol and tramadol HCl in tablets by Fourier Transform Infrared (FTIR) spectrophotometry using KBr powder with the chemometric method.

RESEARCH METHOD

Materials

Pure drug samples Paracetamol BPFI and Tramadol HCl BPFI were provided by the Food and Drug Administration (BPOM), Potassium Bromide (Uvasol® - Merck), Tablet A (PT. Lapi), Tablet S (PT.Kalbe).

Equipment And Conditions

In this study, infrared spectrophotometry (IRPrestige-21 Shimadzu) was used. IRsolution software and Minitab software version 21 were used to analyze the data.

Sample Preparation Procedure

Weighed 10 mg of each standard Paracetamol and tramadol HCl then added with KBr to 100 mg and crushed until homogeneous. The final concentration of paracetamol was 100 µg/mg. Furthermore, the absorbance was measured in the region of 4000-500cm (-1)

FTIR Calibration Study

Paracetamol concentrations of 7 - 11 µg/mg and tramadol HCl of 4 - 12 µg/mg were made in 100 mg KBr. Then the absorption was measured in the specific region of paracetamol 1265.30-1199.72 cm-1 and Tramadol HCl 1321.24-1255.66 cm-1.

Statistical Parameters Of Calibration

Variable

The variables for each sample can be divided into two groups: response variables and predictor variables. This kind of situation arises in multivariate calibration, for example, determining the concentration of components in a mixture of analytes based on absorbance values at many wave numbers 1350-1250 cm-1. Here the analyte concentration is the predictor variable and the absorbance at different wave numbers is the response variable.

R2

The R2 value shows how much variance of each Y variable (concentration) can be explained by the independent variable (X).

RMSE

Root Mean Square Error (RMSE) is the average error value obtained during calibration modeling. RMSE is used to evaluate the suitability of the prediction model.

RESULT AND DISCUSSION

Determination of Standard and Calibration Absorption Spectra

Paracetamol peaks appeared at wave numbers 1510, 1651, 1562, 1253, 1232, 1610 cm-1 and tramadol HCl at wave numbers 1288, 1604, 1047, 1244, 1577, 702 cm-1 spectra of paracetamol and tramadol HCl substances can be seen in Figure 2, then the wave number 1232 for paracetamol and 1288 for tramadol HCl was selected as the PLS region to quantify the two substances

The basis for selecting wave numbers refers to the correlation coefficient value which is close to one. The correlation coefficient is a number used to determine the strong, moderate, or weak relationship between the variables being studied. The selection of wave numbers whose correlation coefficient value is

close to one indicates that a linear relationship has been obtained between the concentration and absorbance spectrum of the active substance.

The results of this study provide considerable benefits in terms of speed, convenience and expediency with the use of FTIR spectroscopy to calculate the amount of active species of interest during quality control analysis of pharmaceuticals. Figure 1 and Figure 2 show the FTIR spectra of paracetamol and tramadol HCl standards in various concentrations used for calibration.

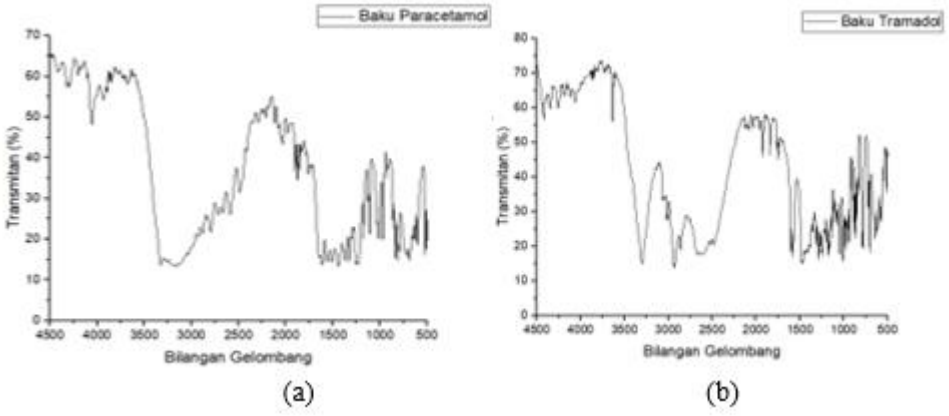

Figure 1. Peak View of Paracetamol (a) and Tramadol HCl (b)

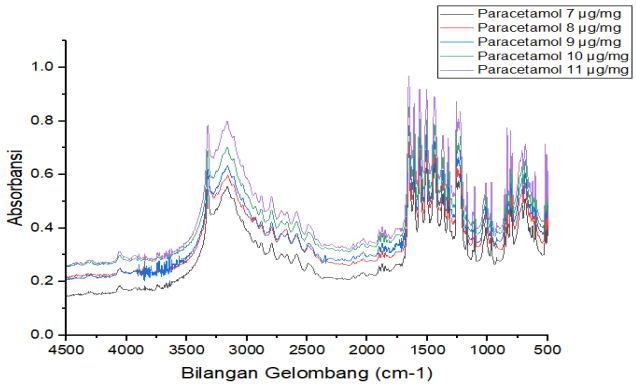

Figure 2. ***Absorption Spectrum of Paracetamol at Concentrations of 7-11 µg/mg***

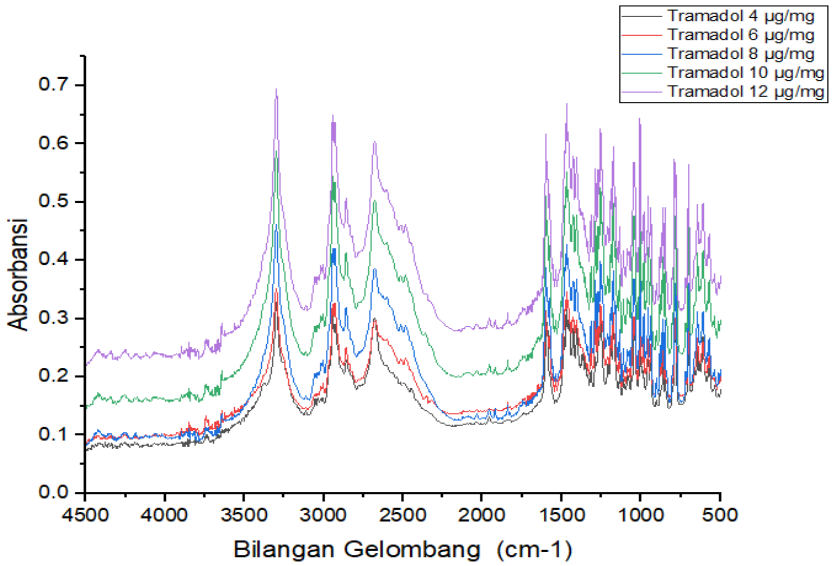

Figure 3. Tramadol HCl absorption spectrum at Concentrations of 4-12 µg/mg

PLS Regression

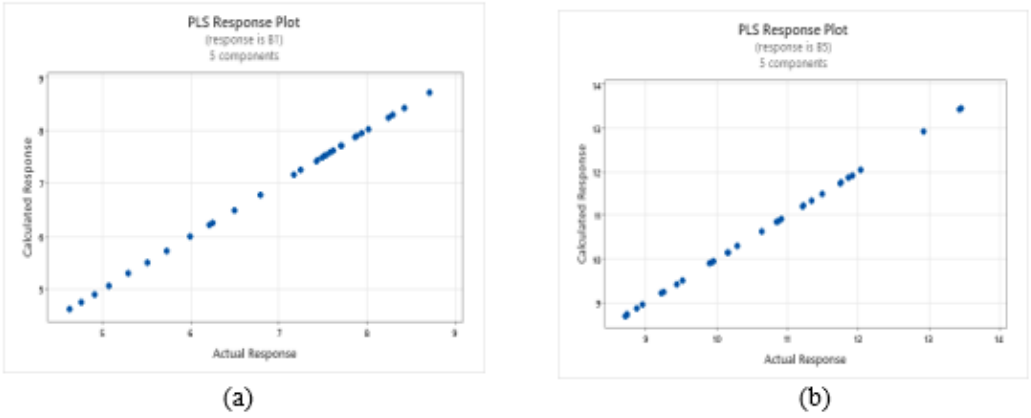

Figure 4. ***Relationship Curve between Actual and Calculated Values of Paracetamol (a) and Tramadol HCl (b)***

In Figure 4a and Figure 4b it can be seen that the regression between the true and calculated levels of paracetamol and tramadol HCl using the Partial Least Squares (PLS) method is linear. This indicates that the PLS method can be effectively used to calculate the concentrations and levels of paracetamol and tramadol HCl based on the measured absorbance data.

1. Results of Paracetamol and Tramadol HCL Level Determination

In determining the levels of paracetamol and tramadol HCl, a divisor factor is used in the sample spectrum. The sample spectrum is divided by each single

spectrum of standard paracetamol and tramadol HCl in order to obtain the absorbance value of each drug, for example the sample spectrum of tablet S in the specific region of paracetamol is divided by the standard spectrum of tramadol HCl to obtain the absorbance of paracetamol and vice versa and is also done on tablet A. The results of the range of paracetamol and tramadol HCl levels in the sample are listed in Table 1.

Table 1. Levels and Standard Deviation of Paracetamol and Tramadol HCl in Samples with PLS Chemometric Method

Medicine	Sample	Content (%)
Paracetamol	Tablet S	99,0116 ±7,1083
	Tablet A	101.4483± 2.8726
Tramadol HCl	Tablet S	101,6633 ± 4,1539
	Tablet A	101.5533± 3.5767

The range of paracetamol levels in tablets S and A were 99.0116 ± 7.1083 and 101.4483 ± 2.8726, while the range of tramadol HCl levels in tablets S and A were 101.6633 ± 4.1539 and 101.5533 ± 3.5767. The levels obtained are in accordance with the content requirements stated in FI Edition VI in 2020, namely 90.0-110.0% (Directorate General of Pharmaceuticals and Medical Devices, 2020).

Method Validation

Correlation Coefficient (R2)

The R2 value indicates how close the relationship is between the actual and predicted values of the analyte on FTIR. The more the R2 value approaches 1, the better the relationship is

PRESS (Predicted Residual Error Sum of Squares)

Predicted Residual Error Sum of Squares (PRESS) is a precision parameter which is the square result of the difference between the predicted level and the actual level in each sample. PRESS is an indicator that is commonly used to describe the goodness of the model in making predictions. The smaller the PRESS value, the better the model's ability to predict.

$$\text{PRESS} = \sum_{i=1}^{n} (actual - calculated)$$

RMSECV (Root Mean Square Error Cross Validation)

Root Mean Square Error Cross Validation (RMSECV) is a prediction parameter that is useful for predicting the uncertainty value of the validation model. The RMSECV value is obtained through PRESS, the closer to 0 the RMSECV value of the result is said to be valid.

$$\text{RMSECV} = \sqrt{\frac{PRESS}{n}}$$

Based on the results of the calculation of the chemometric method in Partial Least Square (PLS) for paracetamol and tramadol HCl, it has met the requirements of method validation which can be seen from the values of R2, PRESS, and RMSECV in Table 2.

Table 2. Values of R^2, PRESS, RMSECV of Paracetamol and Tramadol HCl

No.	Parameters	Paracetamol	Tramadol HCl
1.	PRESS	0,02366	0,00860
2.	R^2	0,99954	0,99988
3.	RMSECV	0,06279	0,03785

CONCLUSION

The Fourier Transform Infra Red (FTIR) Spectrophotometric method with PLS chemometrics can determine the levels of a mixture of Paracetamol and Tramadol HCl in tablets at once without separation. This analysis method is cheap and faster because it does not require lengthy sample preparation and is environmentally friendly because it does not use harmful organic chemicals. Thus, it can be applied in routine analysis of the pharmaceutical industry because the method is fast and economical.

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