

## Application of Fourier Transform Infrared Spectrophotometry Method for Analysis of Metformin Hydrochloride in Marketed Tablet Dosage Form

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### Abstract

The first line drug given for monotherapy for diabetes mellitus type 2 is metformin hydrochloride, which is a biguanide antihyperglycemic drug. The aim of this research was to develop, validate, and apply the Fourier Transform Infrared spectrophotometry method to identify and determine metformin hydrochloride in marketed tablet dosage form. This research included preparation of standard, analysis of samples, and validation of method. The specific wavenumber obtained for qualitative analysis was  $1645.68\text{ cm}^{-1}$  and  $1574.8\text{ cm}^{-1}$ . The specific area obtained for quantitative analysis with a single baseline ranged from  $1701.53\text{ cm}^{-1}$  to  $1535.66\text{ cm}^{-1}$ . All metformin hydrochloride marketed tablet dosage forms were analyzed and met all of the qualitative and quantitative requirements. The methods met the requirements of method validation for accuracy with a percentage of recovery of 100.22 %, precision with relative standard deviation of 0.48 %, linearity with a correlation coefficient of 0.9992, limit of detection of 11.17 mg per mL, limit of quantitation of 33.84 mg per mL, and good specificity results. In this study, the Fourier Transform Infrared spectrophotometry method was successfully developed and validated for application in identification and determination of metformin hydrochloride in marketed tablet dosage form.

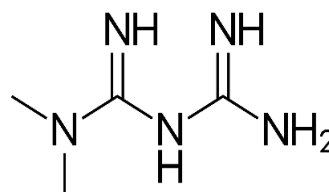
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### 1. INTRODUCTION

Metformin hydrochloride belongs to the biguanide group and act as an antihyperglycemic group to treat type 2 diabetes, or non-insulin dependent diabetes mellitus. Metformin hydrochloride can be used as monotherapy to decrease hepatic glucose production and increase the sensitivity of muscle tissue and as an adipose to insulin. This effect occurs due to the activation of kinase in cells (Rena *et al.*, 2017). The most common side effects observed in patients taking metformin hydrochloride are nausea, vomiting, and diarrhea. Metformin

hydrochloride is the first drug of choice for overweight patients when a strict diet fails to control diabetes mellitus (Marín-Peñalver *et al.*, 2016). Figure 1 shows the molecular structure of metformin hydrochloride.



**Figure 1.** The molecular structure of metformin hydrochloride

The quality, safety, and efficacy of drugs has always been a concern of the World Health Organization, since without the guarantee that these pharmaceutical products meet the required standards of quality, safety, and effectiveness, any health service will be negatively affected (Aggarwala *et al.*, 2019). In the manufacture of drugs, the examination of the levels of active substances is a requirement that must be met to ensure the quality, safety, and efficacy of drug preparations. Quality drug preparations will support the achievement of the desired therapeutic effect. Because of this, attention to the quality control of drugs is important (Fogel, 2018).

Several methods have been developed for the analysis of metformin hydrochloride in tablet preparation, such as: high performance liquid chromatography (Gedawy *et al.*, 2019), ultraviolet spectrophotometry (Dange *et al.*, 2017), and visible spectrophotometry (Ahmad, 2012). The high-performance liquid chromatography method requires expensive tools and high operational costs, as well as a relatively long analysis time (Dong, 2013). The ultraviolet spectrophotometric method is less specific for qualitative and quantitative analysis. The visible spectrophotometry method has a weakness that requires a specific reaction and limited operating time for the analysis (Adegoke, 2012).

The benefits of an alternative analytical method include but are not limited to; an easier method for preparation, a more specific means for of analysis, lower costs, faster analysis, methods that are more environmentally friendly, and can provide results with better accuracy and precision. Simultaneously qualitative and quantitative analysis by Fourier Transform Infrared has already been successfully implemented in several areas of industrial pharmacy (Marson *et al.*, 2016). The Fourier Transform Infrared is simple, specific, cheap, fast, and a green method. The Fourier Transform Infrared can analyze any sample with little to no preparation, covers a wide range of spectrums to analyze most pharmaceutical products, and has a high resolution (Bansal *et al.*, 2021).

As mentioned before, this method is environmentally friendly since no harmful reagents are required for the complete analysis. Determination of levels using Fourier Transform Infrared has also previously been

carried out on various types of pharmaceutical ingredients, such as determining levels of mineral drugs (Ouhaddouch *et al.*, 2019), hypertension drugs (Padmavathi *et al.*, 2020), and cholesterol drugs (Mounika *et al.*, 2018). The researchers were interested in applying metformin hydrochloride analysis on marketed tablet dosages form with a developed and validated Fourier Transform Infrared spectrophotometry method with methanol as a solvent.

## 2. MATERIALS AND METHODS

### Research

This research is a kind of descriptive research using the Fourier Transform Infrared spectrophotometry method to identify and determine the level of metformin hydrochloride contained in marketed tablet dosages. The method used in this research included preparation of standard, analysis of sample, and validation of method with a slight modification from previous research (Robaina *et al.*, 2013).

### Tools

The tools used in this study was a set of Fourier Transform Infrared for light source, interferometer, detector (Agilent - Cary 630 Series), Computer (Lenovo - V530 Series), Printer (Epson - L550 Series), analytical balance (Radwag - X2 Series), multipette (Eppendorf - E3X Series), sonicator (Krisbow - PS40A Series), mortar and pestle (Medstuff), filter paper (Whatman), tissue (Paseo), and glassware (Iwaki).

### Materials

The materials used in this study were methanol (Merck), and metformin hydrochloride standard (Merck).

### Sample

The samples used in this study were Diabit<sup>®</sup> tablets (PT. Hexpharm Jaya), Eraphage<sup>®</sup> tablets (PT. Guardian Pharmatama), Glikos<sup>®</sup> tablets (PT. Ifars), Glucophage<sup>®</sup> tablets (PT. Merck), Gludepatic<sup>®</sup> tablets (PT. Pratapa Nirmala), Metformin Hydrochloride tablets (PT. Bernofarm), Metformin Hydrochloride tablets (PT. Dexa Medica), and Metformin Hydrochloride tablets (PT. Hexpharm Jaya).

### Preparation of Standard

A standard stock of metformin hydrochloride solution was prepared with a weight of 5 g, which was then dissolved in 50 mL of methanol to obtain a standard stock solution with a concentration of 100 mg per mL. Standard solution was prepared by diluting 5 mL standard stock solution with 10 mL methanol to obtain a stock solution with a concentration of 50 mg per mL. The vibration spectrum of standard solution and methanol (as blank) were separately measured at wavenumbers ranging from 4000  $\text{cm}^{-1}$  to 650  $\text{cm}^{-1}$ . The specific wavenumber of metformin hydrochloride was obtained from overlay between vibration spectrums of standard solution and the methanol used for qualitative analysis. Each measurement was replicated six times. Standard series solutions were prepared by separately diluting 3 mL, 4 mL, 5 mL, 6 mL, and 7 mL of standard stock solution with 10 mL of methanol to obtain stock solutions with concentrations of 30 mg per mL, 40 mg per mL, 50 mg per mL, 60 mg per mL, and 70 mg per mL. The series vibration spectra of standard series solutions and methanol (as blank) were separately measured at wavenumbers ranging from 4000  $\text{cm}^{-1}$  to 650  $\text{cm}^{-1}$ . The area for a specific wavenumber was obtained and calculated with the determination coefficient ( $R^2$ ), slope (a), intercept (b), and regression equation ( $Y = a \times X + b$ ) used for quantitative analysis. Each measurement was replicated six times.

### Analysis of Sample

A sample solution was prepared using 20 powdered tablets and weighed. The powder was weighed out to 500 mg of metformin hydrochloride, and then dissolved in 10 mL of methanol to obtain a sample solution with a theoretical concentration of 50 mg per mL. The vibration spectrum of the sample solution and methanol (as blank) were separately measured at wavenumbers ranging from 4000  $\text{cm}^{-1}$  to 650  $\text{cm}^{-1}$ . The specific wavenumber of metformin hydrochloride was obtained from overlay between the vibration spectrum of standard solution and the methanol used for qualitative analysis. The areas for specific wavenumbers were obtained and used for quantitative analysis (calculating the concentration by regression equation obtained from standard series solutions). Each measurement was replicated six times.

### Validation of Method

Accuracy was tested by measuring the percentage of recovery with the standard addition method in three specific ranges, namely: 80%, 100% and 120%. Each specific range contained 70% of the analyzed samples (samples with levels of metformin hydrochloride closest to 100 %) and 30% standard added. Precision was calculated using the relative standard deviation, based on the percentage of recovery obtained from the accuracy test. Linearity was analyzed by calculating the coefficient of correlation (R) based on data obtained from the standard series solutions measurement. The limit of detection and limit of quantitation were calculated based on data obtained from the standard series solutions measurement. The specificity was analyzed from the samples analysis results.

## 3. RESULTS AND DISCUSSION

### Maximum Vibration Spectrum Determination Results

This research begins with the measurement of the vibrational spectrum of methanol as a blank. The vibration spectrum of methanol can be seen in Figure 2.

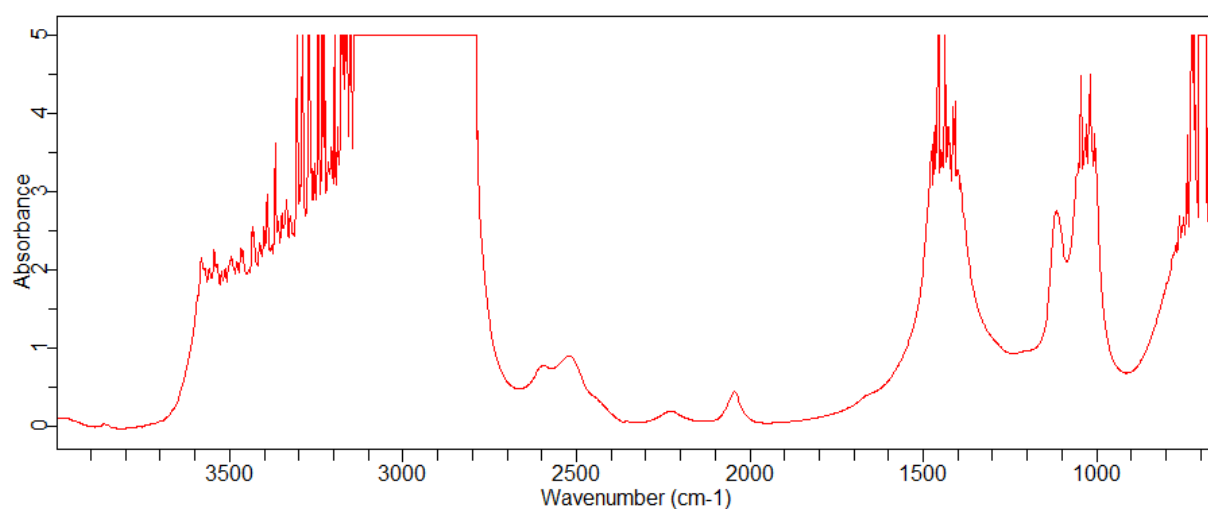
The research continued with the measurement of the vibrational spectrum of metformin hydrochloride standard solution in methanol with a concentration of 50 mg per mL. The vibration spectrum of metformin hydrochloride standard solution in methanol (concentration of 50 mg per mL) can be seen in Figure 3.

After obtaining the vibration spectrum of methanol and the vibration spectrum of metformin hydrochloride standard solution in methanol with concentrations of 50 mg per mL; an overlay was carried out to determine the specific wavenumber of metformin hydrochloride for qualitative analysis and quantitative analysis. The overlay between the vibration spectrum of methanol and the vibration spectrum of metformin hydrochloride standard solution in methanol (concentration of 50 mg per mL) can be seen in Figure 4.

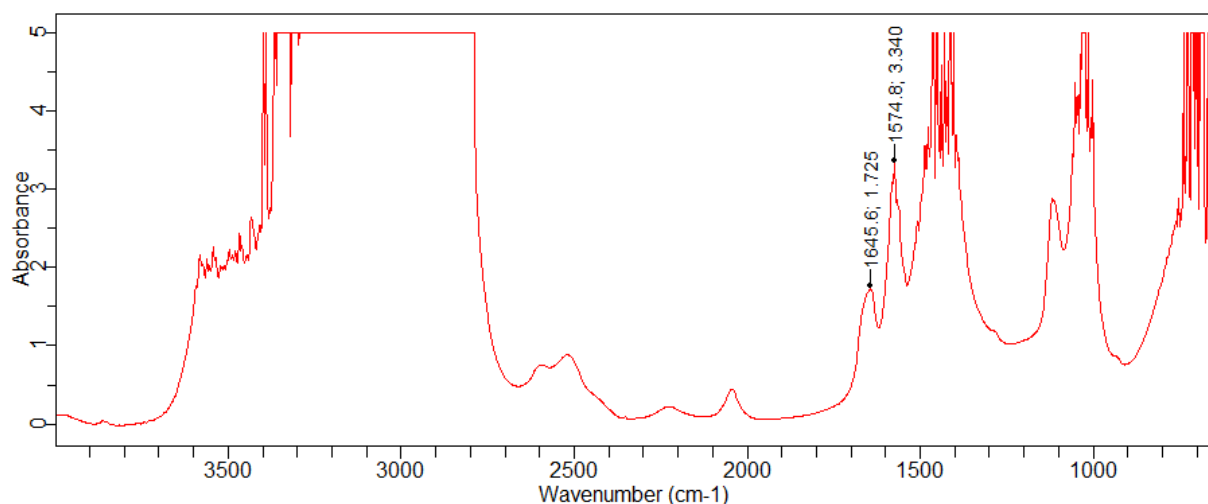
Overlay results show that there was a significant difference between the vibration spectrum of methanol and the vibration spectrum of metformin hydrochloride standard solution in methanol (concentration of 50 mg per mL). Significant spectrum differences can be seen between wavenumbers 1500  $\text{cm}^{-1}$  to

$1700\text{ cm}^{-1}$ , which is  $1645.68\text{ cm}^{-1}$  and  $1574.84\text{ cm}^{-1}$ . Strong absorbance on the metformin hydrochloride spectrum was observed between wavenumbers  $1500\text{ cm}^{-1}$  to  $1700\text{ cm}^{-1}$  (Ramalingam *et al.*, 2014). These wavenumbers are specific wavenumbers that are owned by metformin hydrochloride and not owned by methanol, so a qualitative analysis can be performed on these wavenumbers. A good region for qualitative analysis and quantitative analysis was the fingerprint region between wavenumbers  $1500\text{ cm}^{-1}$  to  $1800\text{ cm}^{-1}$  (Mata-Miranda *et al.*, 2019).

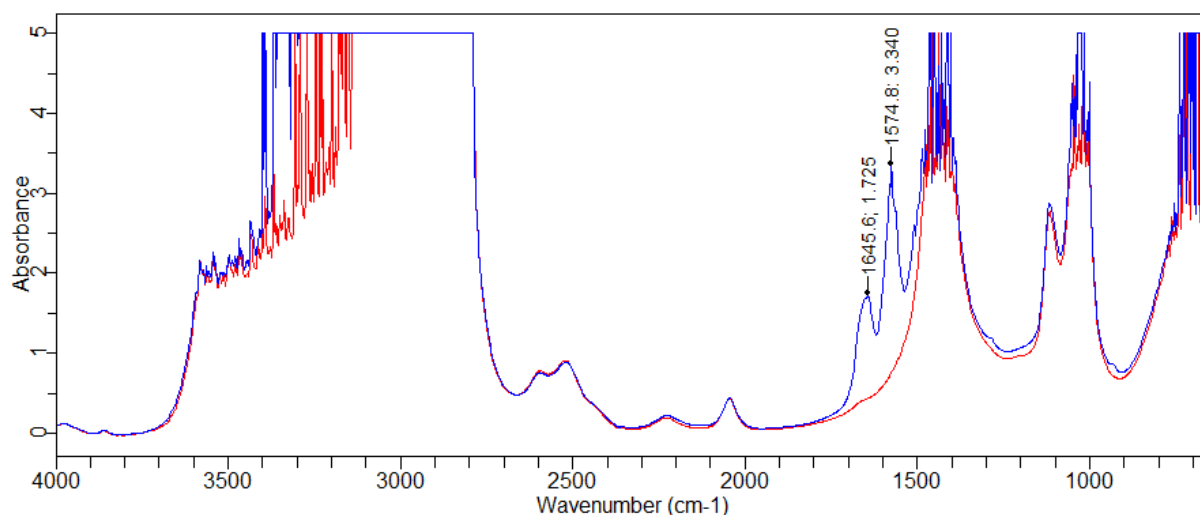
Quantitative analysis was carried out using the peak area at specific wavenumbers of metformin hydrochloride, namely  $1645.68\text{ cm}^{-1}$  and  $1574.8\text{ cm}^{-1}$ . The results of the observation of the peak area at a specific wavenumber determined that the peak analysis was carried out with a single baseline start wavenumber of  $1701.53\text{ cm}^{-1}$  and a baseline end wavenumber of  $1535.66\text{ cm}^{-1}$ . The peak area obtained can be used for quantitative analysis of metformin hydrochloride. The peak area determination of the vibration spectrum of metformin hydrochloride standard solution in methanol (concentration of  $50\text{ mg per mL}$ ) can be seen in Figure 5.



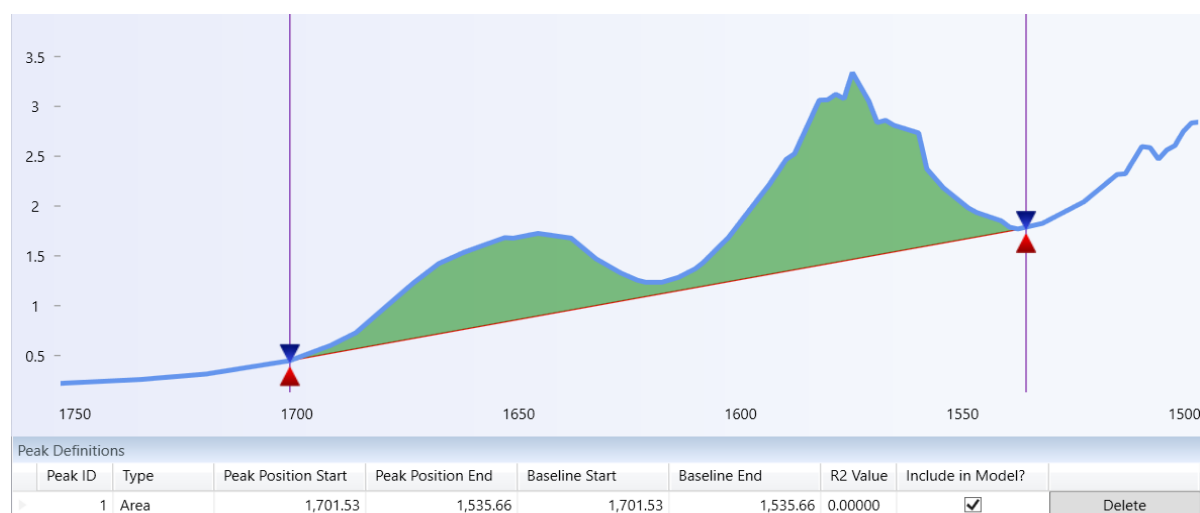
**Figure 2.** The vibration spectrum of methanol



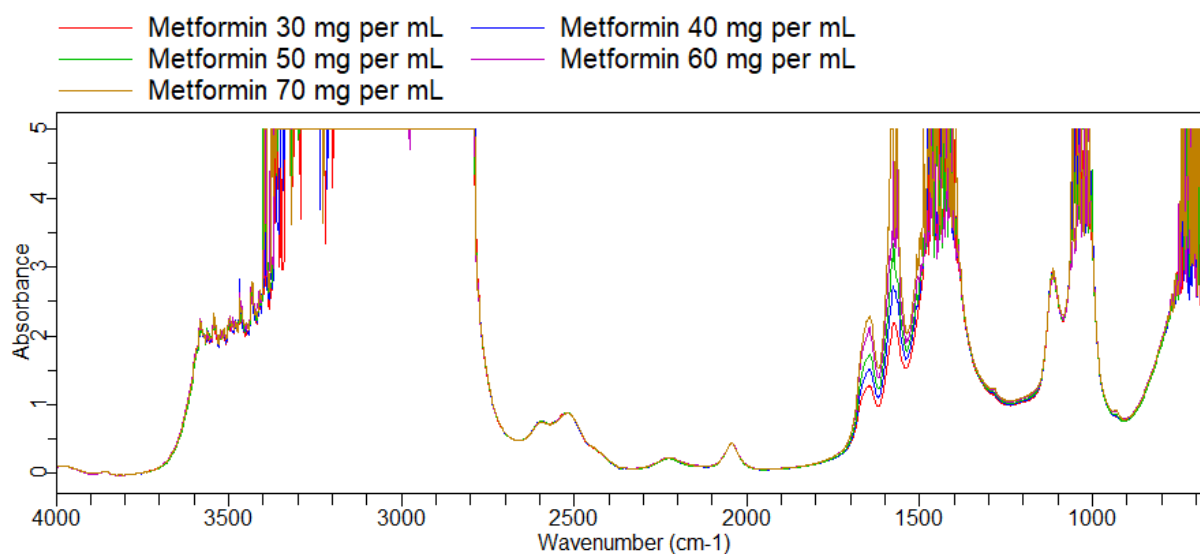
**Figure 3.** The vibration spectrum of metformin hydrochloride standard solution in methanol (concentration of  $50\text{ mg per mL}$ )



**Figure 4.** The overlay between vibration spectrum of methanol (red line) and vibration spectrum of metformin hydrochloride standard solution in methanol (concentration of 50 mg per mL) (blue line)



**Figure 5.** The peak area determination of the vibration spectrum of metformin hydrochloride standard solution in methanol (concentration of 50 mg per mL)



**Figure 6.** The overlay of series vibration spectra of metformin hydrochloride standard series solutions in methanol (30 mg per mL to 70 mg per mL)

**Table 1.** The peak area data of metformin hydrochloride standard series solutions in methanol (30 mg per mL to 70 mg per mL)

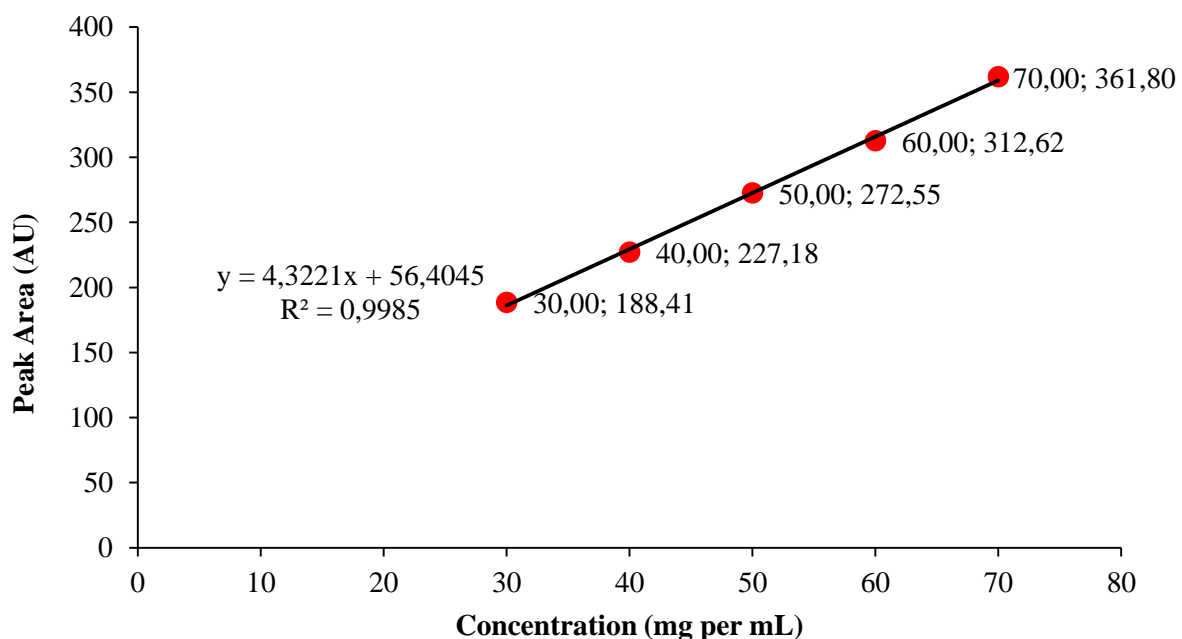
Number	X - Concentration (mg per mL)	Y – Peak Area (AU)
1.	30	188.41
2.	40	227.18
3.	50	272.55
4.	60	312.62
5.	70	361.80

Prior to quantitative analysis, a regression equation was determined which was used for quantitative calculation of the concentration and levels of metformin hydrochloride in the marketed tablet dosage form. The regression equation was obtained by measuring metformin hydrochloride standard series solutions in methanol with concentrations ranging from 30 mg per mL to 70 mg per mL. The overlay of series vibration spectra of metformin hydrochloride standard series solutions in methanol (30 mg per mL to 70 mg per mL) can be seen in Figure 6. The peak area data of metformin hydrochloride standard series solutions in methanol (30 mg per mL to 70 mg per mL) can be seen in Table 1. The calibration curve of metformin hydrochloride standard series solutions in

methanol (30 mg per mL to 70 mg per mL) can be seen in Figure 7.

The metformin hydrochloride series vibrational spectra at various concentrations of metformin hydrochloride in methanol shows that the concentrations do not change the spectrum shape of each concentration on  $1645.68\text{ cm}^{-1}$  and  $1574.84\text{ cm}^{-1}$ , which means the use of methanol as a solvent is stable against metformin hydrochloride (Benmessaoud *et al.*, 2016). From these results it can be seen that the higher the measured concentration is, the greater the peak area will be. The coefficient of determination obtained was 0.9985 with a regression equation of  $Y = 4.3221 \times X + 56.4045$ . The determination coefficient obtained was appropriate with values more than 0.99, which indicated that the peak area (Y or ordinate) can be used for determination of concentration (X or abscis) (Kueté *et al.*, 2020).

Determination of the levels of metformin hydrochloride was carried out by Fourier Transform Infrared spectrophotometry with peak area analysis. The peak area obtained was used to calculate the concentration based on the regression equation and finalized with the level of metformin hydrochloride calculation. The data related to metformin levels in marketed tablet dosage form can be seen in Table 2.



**Figure 7.** The calibration curve of metformin hydrochloride standard series solutions in methanol (30 mg per mL to 70 mg per mL)

**Table 2.** The metformin levels data in marketed tablet dosage form

Number	Sample	Level of Metformin Hydrochloride
1	Diabit <sup>®</sup> (PT. Hexpharm Jaya)	98.59 % ± 0.17 %
2	Eraphage <sup>®</sup> (PT. Guardian Pharmatama)	102.79 % ± 0.22 %
3	Glikos <sup>®</sup> (PT. Ifars)	98.73 % ± 0.22 %
4	Glucophage <sup>®</sup> (PT. Merck)	101.74 % ± 0.27 %
5	Gludepatic <sup>®</sup> (PT. Pratapa Nirmala)	99.40 % ± 0.19 %
6	Metformin Hydrochloride (PT. Bernofarm)	97.51 % ± 0.20 %
7	Metformin Hydrochloride (PT. Dexa Medica)	99.67 % ± 0.21 %
8	Metformin Hydrochloride (PT. Hexpharm Jaya)	101.53 % ± 0.24 %

**Table 3.** The validation data of the Fourier Transform Infrared spectrophotometry method

Number	Category	Results
1	Percentage of Recovery for 80 % Specific Range (40 mg per mL)	100.19 %
2		100.33 %
3		100.26 %
4	Percentage of Recovery for 100 % Specific Range (50 mg per mL)	100.83 %
5		100.75 %
6		100.67 %
7	Percentage of Recovery for 120 % Specific Range (60 mg per mL)	99.75 %
8		99.54 %
9		99.65 %
-	Accuracy (Percentage of Recovery)	100.22 %
-	Precision (Relative Standards Deviation)	0.48 %
-	Linearity (Coefficient of Correlation)	0.9992
-	Limit of Detection	11.17 mg per mL
-	Limit of Quantitation	33.84 mg per mL

The results indicate that metformin hydrochloride levels in marketed tablet dosage form range from 97.51 % to 102.79 % which meet the requirements of the monograph. The metformin hydrochloride tablet dosage form is in accordance with the requirements listed in the Indonesian Pharmacopoeia, 6<sup>th</sup> edition, year 2020; which detailed metformin hydrochloride tablets that contained levels of metformin hydrochloride that were not under 95.0 % and not more than 105.0 % of the amount stated on the label (Ministry of Health Republic of Indonesia, 2020). It is important that drug preparations contain appropriate levels of active substances as one of the main parameters to ensure that a drug meets the requirements for quality, safety, and efficacy (Seo *et al.*, 2020). The Fourier Transform Infrared spectrophotometry method is a useful tool that can be used to prove the validity of results for qualitative and quantitative analysis (Mendes and Duerte, 2021). The validation data of the Fourier Transform Infrared

spectrophotometry method can be seen in Table 3.

The accuracy of the method met the accuracy requirements for method validation with a range recovery percentage of 98 % to 102 % (Pinto *et al.*, 2017). The precision of the method was met with the precision requirements for method validation with a relative standard deviation of less than 2% (Assali *et al.*, 2020). The linearity of the method met the linearity requirements for method validation with a correlation coefficient of no less than 0.99 (Shaikh and Jadhav, 2020). The limit of detection and limit of quantitation obtained were 11.17 mg per mL and 33.84 mg per mL respectively. The detection limit and quantitation limit obtained were lower than the expected concentrations for identification and determination of the levels of metformin hydrochloride in marketed tablet dosage form. The results indicated that the method has adequate sensitivity (Sengul, 2016). The range of the developed Fourier

Transform Infrared spectrophotometry method was 40 mg per mL to 60 mg per mL, which was 80 % from the targeted concentration to 120 % of the targeted concentration. The range must cover all the accuracy, precision, linearity, limit of detection, and limit of quantitation (Marson *et al.*, 2020). The developed method also successfully identified and determined all the metformin hydrochloride in marketed tablet dosage form, which means this method could also be applied to other tablet matrixes. This proves that the method possesses a high level of specificity (Ramakrishna *et al.*, 2020).

#### 4. CONCLUSION

The Fourier Transform Infrared spectrophotometry method has been successfully developed and validated for identification and determination of metformin hydrochloride in marketed tablet dosage form. All the metformin hydrochloride in marketed tablet dosage form met the requirements for qualitative analysis and quantitative analysis. The method also met the requirements of method validation for accuracy, precision, linearity, limit of detection, limit of quantitation, range, and specificity.

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