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UTILIZATION OF NEAR-INFRARED SPECTROSCOPY COMBINED WITH PLS-2 REGRESSION LEARNER TO PREDICT METFORMIN HCL TABLET DISSOLUTION PROFILE

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ABSTRACT

One of the assurances of pharmaceutical tablet's quality, effectivity, and safety is the dissolution test, which is commonly known by pharmaceutical manufacturers. Conventionally, this test is performed by simulating the release rate of a drug using a Dissolution Tester, which mimics the human gastrointestinal condition. As stated by the current compendial for tablet dosage form, the dissolution rate is mandatory, with no exception for Metformin HCl tablets. This laboratory method is often time-consuming, unsafe for organic reagent exposure, and produces waste. This problem requires rapid, simple, and nondestructive technologies, hence having powerful analytical performance. One of the technologies that is widely used is Near Infrared (NIR) spectroscopy. This study utilized the NIR spectrum as a predictor to generate a mathematical model using Partial Least Square Regression (PLS-2) to build a dissolution rate model for the Metformin HCl tablet, which uses the Farmakope Indonesia IV <1231> (FI-IV) dissolution method as the compendial reference method. The PLS-2 model was built, which shows the low difference between SEC and SECV in each sampling point and a good correlation in the coefficient of determination (R2) of each point's time of dissolution within 0.900 to 0.953. The challenge test was performed to prove the predictability of the PLS-2 model with NIR against the actual reference FI-IV method using differential and similarity Factors (f2 & f1), enabling real-time release testing (RTRT).

KEYWORDS *Dissolution Rate, Metformin, NIR, SVR*

INTRODUCTION

About 19.5 million Indonesian people suffer the Diabetes Mellitus Type 2 (DM2), and projected to be 28.6 million people in 2045. Based on the clinical pathway of the disease, the first line of DM2 is often a biguanide antidiabetic drug: Metformin HCl tablet, which is used orally (PERKENI, 2021). This fact might affect the demand for Metformin HCl in the market for diabetic patients would increase significantly over the years. The data in 2024 shows there are five times

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market share increases of Metformin HCl from 2021 and potentially increases by ten times in 2030.

Despite its excellent solubility, Metformin is absorbed slowly and incompletely orally. The dose form of the oral solution is bioequivalent to an immediate-release tablet that dissolves entirely in an hour, making it fall into BCS class III. Drugs in Class III of the BCS, including Metformin, have a rapid dissolution permission requirement of about 45 minutes. In the development stage, to determine the equivalence of the dissolution profile, Zeng et al. (2022) explained that there are two valuable methods use the Differential Factor (f_1) and Similarity Factor (f_2), where these two statistical methods are already recognized and established by food and drug regulators (*i.e.*, Indonesian Badan POM).

Traditionally, according to Farmakope Indonesia Ed. VI <1231>, the dissolution test for Metformin HCl tablet is tested using a second apparatus (paddle) for 100 rpm in medium dissolution of phosphate buffer 6.8 (1000 mL) for 45 minutes ($Q \geq 70\%$). This conventional method is prone to several disadvantages; the main is that it is time-consuming, requires more laboratory utilities, is unsafe (mainly using inorganic reagents), and has ecological risks by producing dangerous waste.

A new technique known as "predictive dissolution modeling" has emerged to solve the disadvantages of traditional dissolution tests. This method refers to the capacity to compute a temporal profile of an API's dissolved amount using data on material characteristics, dissolution method parameters, formulation composition, and process factors (Zaborenko et al., 2019). These characteristics are probably easier to obtain simply, yet they need complex interpretation using NIR spectroscopy.

In recent days, NIR has often been used as a tool to evaluate the physicochemical characteristics of samples. It is widely used in multidisciplinary research such as in food and beverages (Márquez et al., 2016; Porep et al., 2015), geologies (Wening & Kuswurjanto, 2023; Zhang et al., 2021), agricultural (Devianti et al., 2019; Sutari et al., 2018), and pharmaceutical (Ojala et al., 2020; Shi et al., 2022). Numbers of chemometric and multivariate statistics is embedded to the NIR technology such as Moving Block (Fonteyne et al., 2016), Principal Component Analysis (Gosselin et al., 2017), Principal Component Regression (Martelo-Vidal & Vázquez, 2014), Multiple Linear Regression (Jiménez-Romero et al., 2020), and Partial Least Square Regression (Tsanaktsidou et al., 2020).

This study aims to compare the NIR spectroscopy predictive dissolution model of Metformin HCl tablet dissolution using multilevel Partial Least Square Regression (PLS-2) against the Farmakope Indonesia Ed. VI (FI-VI) as a compendial method. The comparative dissolution between the two methods will be

compared using the differential factor (f_1) and similarity factor parameter (f_2) as comparative dissolution test.

RESEARCH METHOD

Materials

In this study, the analyte of interest was Metformin HCl, while PVP 25 served as the binder for tablet formation, Croscarmellose Sodium acted as the disintegrant, and Aerosil was utilized for weight adjustment approximately up to 600 mg per tablet. All of these components were of pharmaceutical grade, prepared at the R&D laboratory PT. Kalbe Farma using 20 batches (referred to as “Calibration Batch”) designated as calibration batches (kindly gift from PT. Kalbe Farma, Indonesia). Subsequently, three additional batches of commercial Metformin HCl tablets from PT. Kalbe Farma were selected for comparative dissolution testing. These batches were referred to as the "Test Batch" with batch numbers of HTMFNB36220 (TB1), HTMFNB2404 (TB2), and HTMFNB35211 (TB3) were produced from November 2023 to December 2023.

Equipment

Each Calibration Batch was prepared on a scale of 1,000 tablets, weighed using an XPR305D5Q Analytical Balance (Mettler Toledo, Switzerland), and then transferred for mixing using a 10L Drum Mixer (IMF, Italy). Tablet compression was carried out using a JCMCO R&D Single Press (JCMCO, Taiwan). NIR acquisition for prediction was performed using a MicroNIR PAT-W Linear Variable Filter (Viavi, USA). The conventional compendial method FI-VI used a Hanson Dissolution Tester (Teledyne, USA), and the PLS-2 model was built using the Unscrambler v.10.4.1 (CAMO, Germany) software.

Methods

1. NIR Acquisition of Metformin HCl

   12 tablets from each Calibration Batch were scanned in triplicate using NIR spectroscopy across the full NIR region of 950 – 1650 nm (~10,500 – 6100 cm^{-1}), with a pixel resolution of 6.2 nm in a diffuse reflectance configuration. Each scan consisted of 100 scans, resulting in 125 absorbance readings per sample acquisition.
2. Analysis Method of Dissolution Rate (FI-VI)

   The acquisition tablet was then analyzed for its dissolution rate using the FI-VI method, using 1000 mL of phosphate buffer dissolution medium at pH 6.8 with a Type 1 (basket) apparatus. The acceptance criterion was that not less than 70% of Metformin HCl must dissolve in the dissolution medium within 45 minutes. Sample points were taken using an autosampler, carried out at time

intervals of 5, 10, 15, 20, 30 and 45 minutes, and then analyzed using a UV-Vis spectrophotometer at a maximum absorption wavelength of approximately 233 nm.

3. Prediction Model Development Method (PLS-2)

The PLS-2 prediction model was created by pairing NIR absorption data as a predictor (variable X) and dissolution rate data according to the sampling point (at n minutes) as the response (Y_n variable). A cross-validation (CV) approach was used, in which the random principle with a sample size of 20 and samples per segment of 70 samples (Cobbinah et al., 2022) was applied. The error rate was indicated by the values of Root Mean Square Error of Calibration (RMSEC), Root Mean Square Error of Cross-Validation (RMSECV), and Coefficient of Determination (R^2), which are denoted in the following equation (Mateo-Ortiz et al., 2014):

$$RMSEC = \sqrt{\frac{\sum_{i=I}^{p}(y-\hat{y}_i)^2}{Nc_{-f-1}}} \quad (1)$$

$$RMSECV = \sqrt{\frac{\sum_{i=I}^{p}(y-\hat{y}_i)^2}{N_P}} \quad (2)$$

Where N is the number of samples in the calibration set, yi is the actual dissolution value, and $\hat{y}i$ is the predicted dissolution value.

4. Comparative Dissolution Testing Method

Three Test Batches were taken to compare the results of the two testing methods. The similarity level of the two mathematical methods can be compared using the comparative dissolution test (Mrad et al., 2022). This comparative dissolution test was calculated based on the value of the differential factor (f_1) and similarity factor (f_2). The closer to zero the f_1 value means the average dissolution profiles are comparable, and conversely, the higher the value, it indicates that the profile difference is quite significant. Meanwhile, the f_2 value which is getting closer to 100 indicates that the profile values for the two are identical. This method act as a comparative dissolution test method to prove the dissolution release profiles of two drugs or two test methods are comparable.

$$f_1 = 100\ x\ \left\{\frac{\sum_{i=1}^{n}|Ri-Pi|}{\sum_{i=1}^{n}Ri}\right\} \quad (3)$$

$$f_2 = 50x\ \log\left\{\frac{100}{\sqrt{1+\frac{1}{n}\sum_{i=1}^{n}(Ri-Pi)^2}}\right\} \quad (4)$$

where the R_i and T_i are functions of the dissolution concentration value of the reference sample and test sample, while the n is the sampling time point at which the dissolution test was carried out.

In this study, dissolution concentration data of Metformin HCl tablets (in several time units predicted by NIR using the PLS-2 method) has been compared with actual results using the FI-VI method which is calculated to be equivalent to the f_1 and f_2 methods to prove that the predictive method with NIR as good as the compendial method.

RESULT AND DISCUSSION

Metformin HCl Tablet NIR Spectrum

The results of the Calibration Batch scan (20 batches @ 12 tablets) using the NIR technology method (with a wavelength of 950 – 1650 nm) can be seen in **Figure 1.** The presence of a peak at a wavelength of approximately 1453 – 1580 nm in this sample is by research (Pyzowski et al., 2017), which shows the existence of overtone absorption of secondary amines contained in the Metformin HCl functional group. Besides chemical factors that have absorption at NIR wavelengths, measurements can also be influenced by the physical properties of materials, such as particle size, temperature, porosity, and others.

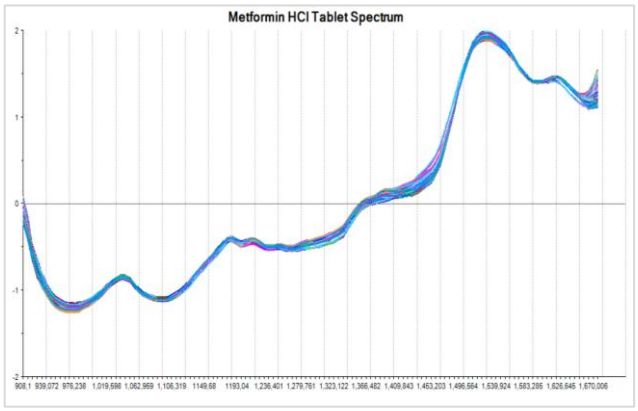

Figure 1. NIR Absorption of Metformin HCl Tablet

Dissolution Rate (FI-VI) of Calibration Batch

Using the same tablet scanned with NIR, a dissolution test was carried out to characterize the dissolution profile of Metformin HCl Tablets. Of the 12 tablets tested, the average value at each sampling point was calculated in **Figure 2**. The dissolution data per point per sample was then embedded with NIR absorption data, and a predictive method with PLS-2 was defined.

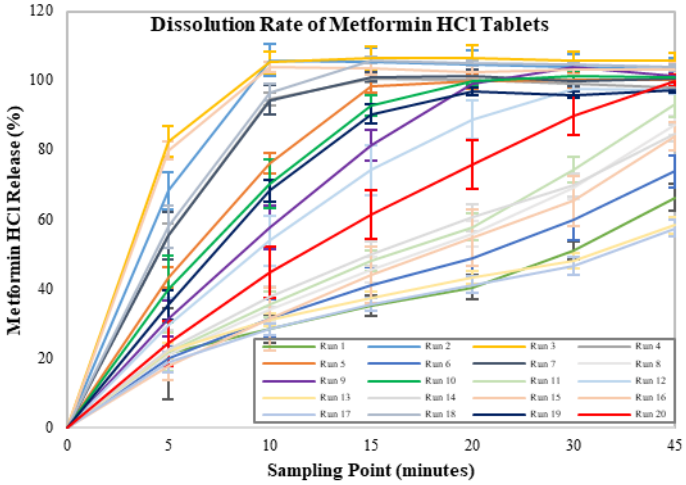

Figure 2. Dissolution profiles of Metformin HCl for Calibration Batch with FI-VI Method

PLS-2 Development: Error Evaluation

The PLS-2 model development process involved creating a calibration model, which was then tested for reliability using cross-validation across the spectrum (950 – 1650 nm). A factor of 10 was utilized for data processing rationalization to prevent the model from overfitting, ensuring accurate model outcomes.

Table 1. The Model From Overfitting

Sampling Point		5 minutes	10 minutes	15 minutes	20 minutes	30 minutes	45 minutes
Standard Error (%)	SEC	4.370	6.393	7.321	6.476	5.132	4.084
	SECV	4.437	6.508	7.470	6.616	5.255	4.181
Root Mean Square Error (%)	RMSEC	4.307	6.389	7.316	6.472	5.128	4.081
	RMSECV	4.344	6.503	7.465	6.611	5.252	4.178
Correlation	R^2C	0.954	0.935	0.902	0.909	0.922	0.910
	R^2CV	0.953	0.934	0.900	0.907	0.920	0.906

Table 1 indicates the error value by the RMSE-(C and CV) value at each Metformin HCl dissolution rate time. RMSEC values at 5, 10, 15, 20, 30, and 45 minutes were 4.307%, 6.389%, 7.316%, 6.472%, 5.128%, and 4.081%, respectively, while the RMSECV values were 4.344%, 6.503%, 7.465%, 6.611%, 5.252%, and 4.178%, respectively. These results showed good statistical values, where the closer or not significantly different the RMSEC and RMSECV values are, the better the model predictability will be (Ferreira & Tobyn, 2015).

Other parameters, namely the SEC and SECV values, respectively, the dissolution rate of Metformin HCl were 4.370% and 4.437% at 5 minutes; 6.393% and 6.508% at 10 minutes; 7.316% and 7.465% at 15 minutes; 6.472% and 6.611% at 20 minutes; 5.128% and 5.252% at 30 minutes; and 4,081% and 4,178 at 45 minutes. The values between SEC and SECV produced values that were close to each other, indicating that the model optimization was carried out optimally (Murphy et al., 2022). It's important to note that a good SE value is close to zero. However, in these results, the values were relatively high. This might be due to the diverse dissolution rates of the designed tablets, leading to a wide range of reference dissolution rate values across FI-VI, which consequently implies high error values in the PLS-2 model calibration.

PLS-2 Development: Correlation Evaluation

The coefficent of determination (R^2) was calculated based on the PLS-2 linear regression line at each dissolution rate prediction time to express the correlated relationship between the NIR spectrum of Metformin HCl tablets and the actual data using the FI-VI reference method. **Figure 3** shows a good correlation with a value of ≥ 0.90 (Molano et al., 2016) which shows a positive relationship between the NIR spectrum and the dissolution rate data of Metformin HCl tablets. Adequate R^2CV values were obtained in each dissolution rate model, namely at 5 minutes (0.953), 10 minutes (0.934), 15 minutes (0.900), 20 minutes (0.908), 30 minutes (0.920), and 45 minutes (0.906).

This good relationship between the NIR spectrum as a predictor and the dissolution rate data as a reference is quite promising for predicting other Metformin HCl tablet samples with the PLS-2 model. The resulting R^2 correlation value will be better (closer to 1) if the SE value can be reduced (Fonseca et al., 2019).

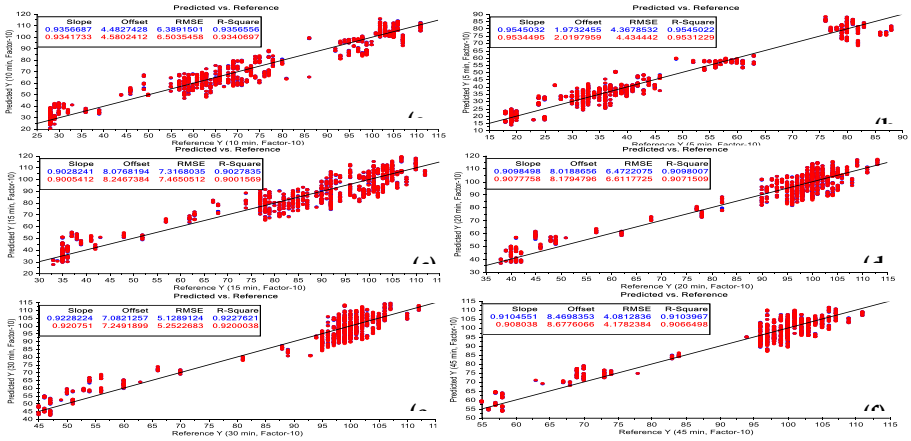

Figure 3. Predictor vs Reference: Linear Regression PLS-2 for **(a)** 5, **(b)** 10, **(c)** 15, **(d)** 20, **(e)** 30, and **(f)** 45 minutes.

Comparative Dissolution Test of PLS-2 vs FI-IV

The dissolution rate values of Metformin HCl in the three Test Batches can be seen in **Table 2**. A total of 12 tablets at each sampling point were tested using the FI-IV and PLS-2 methods, where the average dissolved value of Metformin HCl was calculated, and the difference between the average values. The dissolved average in FI-IV and PLS-2 at each sampling point was also calculated as the residual average. The results showed that the minimum average residual value was found in the PLS-2 prediction at 5 minutes (0.4 – 0.7%), which was in line with the coefficient of determination R^2 at 5 minutes (indicating good values). On the other hand, the relatively higher R^2 value at 20 minutes also produced a reasonably wide residual average (-10.9 – 15.7%).

Table 2. FI-IV vs PLS-2 Test Batch sample

Sample	Method	5 min	10 min	15 min	20 min	30 min	45 min
TB1	%Dissolved (FI-IV)	35	65	86	96	96	95
	%Dissolved (PLS-2)	35	69	93	107	109	106
	%Residual Average*	**0.7**	**-4.1**	**-7.3**	**-10.9**	**-13.3**	**-10.3**
TB2	%Dissolved (FI-IV)	36	70	93	99	98	97
	%Dissolved (PLS-2)	36	61	77	85	91	97
	%Residual Average*	**0.4**	**9.2**	**15.7**	**13.2**	**6.8**	**0.4**
TB3	%Dissolved (FI-IV)	30	56	78	92	98	97
	%Dissolved (PLS-2)	29	61	84	99	102	101
	%Residual Average*	**0.9**	**-4.4**	**-6.9**	**-6.6**	**-4.6**	**-3.6**

* calculated from the actual value (%Dissolved PLS-2 - %Dissolve FI-IV)

By dividing the average residual for each sample at each sampling point by the total number of predictions, the % bias value per sample for TB1 was -7.5%, TB2 was 7.6%, and TB3 was -4.2%. By calculating the average % bias for all

samples, the total % bias value was -1.4%. This indicates a good correlation between NIR predictions with PLS-2 and the reference FI-IV test.

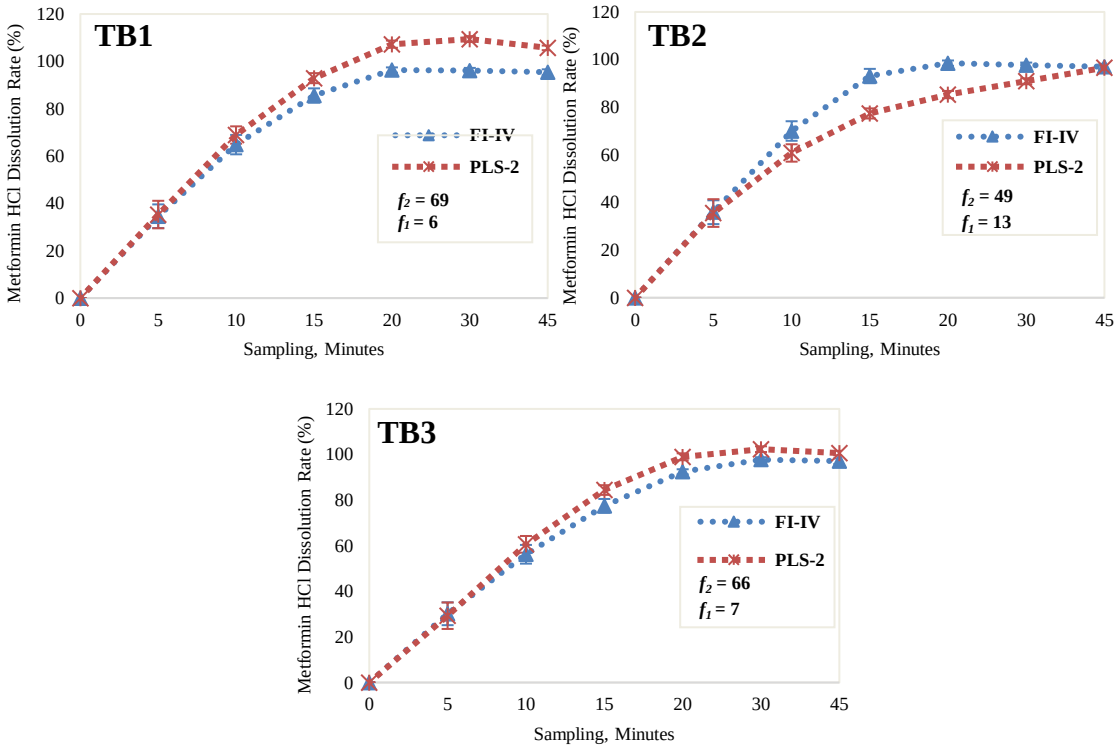

Figure 4. PLS-2 vs FI-IV: Metformin HCl Comparative Dissolution Profile

Figure 4 shows the comparative test results of the dissolution rate profile of Metformin HCl between the FI-IV reference method and the PLS-2 prediction method in NIR. The f_1 values resulting from TB1, TB2, and TB3 were 6, 13, and 7, respectively, indicating no significant difference between the two compared methods ($f_1 \leq 15$). When comparing the f_2 values on TB1 and TB3, similar results were obtained between the two test methods (f_2 = 69 and 66; requirement $f_2 \geq 50$). However, on TB-2, the f_2, the value of 49, is obtained, which indicates that the similarity in the study batch is not equivalent. This can be seen at the 15 and 20-minutes sampling points, where there is a significant difference between the FI-IV and PLS-2 methods caused by the high SE value and the Coefficient of Determination (R^2) value close to the borderline. However, this can still be considered satisfactory because the three test Batches have f_1 values that meet the requirements and f_2 values that are satisfactory in 2 batches and almost satisfactory in 1 other batch.

CONCLUSION

This work has illustrated the advantages of using NIR spectroscopy, which has the powerful performance to predict the dissolution rate of Metformin HCl tablet, with the PLS-2 method as the predictive model. The PLS-2 acts as a predictor, and the dissolution rate of compendial FI-IV acts as a reference, which shows excellent correlation based on the Standard Error and Coefficient of Correlation. The external validation has been tested, resulting in a good predictor of NIR with PLS-2 against the reference by FI-IV. These results give the probability of fast, simple, nondestructive, and cost reduction in the production of commercial Metformin HCl tablets. For daily applications, however, complete analytical method validation should be performed.

In the regular manufacturing process, more complex formulation, drug release modification, process variability, or environmental conditions might be highly affecting the spectrum of NIR, thus affecting the reliability of the PLS-2 model. It is essential to consider all the factors that affect the NIR spectrum and tablet dissolution to build a robust predictive model.

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