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# Artificial Intelligence-based Prediction of *In Vitro* Dissolution Profile of Immediate Release Tablets with Near-infrared and Raman Spectroscopy

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**Abstract**

The objective of the present work was to develop an artificial neural network (ANN) model to accurately predict the dissolution profile of immediate release tablets based on non-destructive spectral data. Six different tablet formulations with varying API (caffeine) and disintegrant (potato starch) concentrations were prepared. The near-infrared (NIR) and Raman spectra of each tablet were collected in both reflection and transmission modes, then principal component analysis (PCA) was conducted. The training of the ANN was performed at each hidden neuron number from 1 to 10 in order to determine the optimal number of neurons in the hidden layer. The best results were obtained when a small number of neurons (1–3) was used. In the case of all four spectroscopic methods, the average similarity values ($f_2$) of the optimized ANN models were above 59 for the validation tablets, indicating that the predicted dissolution profiles were similar to the measured dissolution curves. The optimized model based on reflection Raman spectra exhibited the best predictive ability. The results demonstrated the potential of ANN models in the implementation of the real-time release testing of tablet dissolution.

**Keywords**

PAT, Raman spectroscopy, NIR spectroscopy, dissolution prediction, real-time release testing

## 1 Introduction

Process Analytical Technology (PAT) is an important tool for controlling pharmaceutical processes using inline, online or at line analyzers during manufacturing [1]. PAT represents the means to achieve the automatic control of the end product quality as desired by the Quality by Design (QbD) approach [2]. Both PAT and QbD concepts were described in detail by the Food and Drug Administration (FDA) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in their Q8, Q9 and Q10 guidelines released since 2004 [3–5]. The ICH Q8 guideline describes PAT as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality" [6]. QbD focuses on identifying critical quality attributes (CQAs) through target product profile and risk assessment to ensure product quality, safety and efficacy. Critical material attributes (CMAs) and critical process parameters (CPPs) have a direct and significant influence on CQAs and should be monitored and controlled [7]. PAT enables the identification and monitoring of these variables through a fast, non-destructive and consecutive analysis, therefore real-time monitoring of large-scale production can be accomplished. The data provided by PAT can be used for the feedback control of the system to ensure that the quality of the output introduced into the following manufacturing stage is within the prescribed range [8]. Over the past decade the QbD and PAT initiatives enabled the transition from the more time-consuming and labor-intensive batch manufacturing to continuous processes which could decrease production costs and reduce manufacturing time while improving end product quality [9–11].

Dissolution profile is considered a CQA of solid oral dosage forms as it affects drug bioavailability and it is

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influenced by process conditions and the properties of the components (including active pharmaceutical ingredients (API) and excipients) [12]. *In vitro* release tests are one of the most frequently used quality control measure of solid oral dosage forms, required at various stages of development and production [13]. Dissolution tests are conducted in accordance with the standardized methods described in pharmacopoeias, in which the apparatus design, dissolution medium and the conditions of operation are specified [14]. However, traditional dissolution tests are time-consuming and destructive measurements, and therefore not suitable for continuous manufacturing. Alternatively, PAT sensors together with multivariate modeling can be used to predict the dissolution behavior of a dosage form, which enables the real-time monitoring required by continuous processes [15].

In-process measurements can be performed using PAT sensors based on near infrared (NIR), Raman, ultraviolet-visible (UV-VIS), Terahertz pulse, light-induced fluorescence, X-ray and laser light scattering signals [16–18]. NIR and Raman spectroscopy have become the frequently used real-time monitoring tools in the pharmaceutical industry. The two spectroscopic techniques are complementary; NIR spectroscopy is active for anti-symmetric vibrations that generate a change in the dipole moment, while Raman measurements are more sensitive to symmetric vibrations that alter the molecular polarizability [19, 20]. The industrial case study conducted by Brouckaert et al. [21] presented the 100% in-line quality control of tablets using NIR spatially resolved spectroscopy (NIR-SRS) for API content and 3D microwave resonance technology (MRT) for mass prediction. The dosage of each individual tablet was predicted with satisfying accuracy and precision based on a combination of NIR-SRS and MRT techniques, which in conjunction with feedback loops connected to upstream processes could minimize deviations and drifts.

Both Raman and NIR spectra provide qualitative and quantitative information on the chemical composition and the physical properties of pharmaceutical dosage forms. The original spectral data are multivariate due to the large number of data points (one at each wavelength, for each sample), therefore multivariate data analysis techniques such as principal component analysis (PCA) and partial least squares (PLS) can be used to extract valuable information and reduce the dimension of data [22].

The data obtained with spectroscopic methods can be used to predict the dissolution profile of the dosage form by using it as the input of various machine learning methods [23]. Artificial neural networks (ANNs) were repeatedly proven to be extremely versatile for regression tasks, even in cases where nonlinearities are involved [24, 25]. ANNs have been applied for a long time to predict the dissolution profile of formulations during development based on the theoretical composition and off-line measured material properties. However, recently their utility in processing data from PAT sensors has also been demonstrated [26]. In our previous works, ANNs have been applied for the prediction of the dissolution profile of sustained release formulations on multiple occasions [26–28]. However, this dissolution prediction technique should also be tested in the case of immediate release formulations, which give a significant portion of all tablets. In such a formulation, drug release rate is mainly determined by the concentration of the disintegrant in the tablet and the properties of the disintegrant such as particle size [29]. Earlier works have used NIR diffuse reflectance technique combined with PLS regression to predict the dissolution of formulations in which the dissolution rate was influenced by the amount of disintegrant [29–31]. However, Raman spectroscopy might have a better capability of measuring the concentration of the disintegrant in tablets, as compounds yield more distinct peaks when measured with this technique. Thus, the performance of NIR and Raman spectroscopy should be compared.

Traditionally, during the characterization of the prepared tablets, only the concentration of the API is measured in the samples. However, spectroscopic techniques make it possible to predict the concentration of multiple components based on one non-destructive measurement. This can be especially useful in the case of continuous manufacturing, where it is possible that the composition of the product deviates from the target value for short intervals. When spectroscopic techniques are utilized as a real-time sensor, such tablets can be identified and removed.

A common problem associated with the application of ANNs is that a large training dataset is required to achieve accurate predictions, this might deter pharmaceutical companies from utilizing this technique. However, we found that when the modelled system does not have great complexity, even a smaller training dataset could be sufficient for the ANN to learn the effect of the parameters [28].

Therefore, the goal of the current work is to demonstrate that an ANN can accurately predict the dissolution profile of immediate release tablets by extracting information about disintegrant and API content from NIR and Raman spectra. We intend to compare the performance of the reflection and transmission method of NIR and Raman

spectroscopy based on their ability to distinguish between the formulations with different compositions. The results of the research can contribute to the realization of real-time release testing of immediate release products.

## 2 Materials and methods

### 2.1 Materials

In this study, anhydrous caffeine (BASF, Ludwigshafen, Germany) was used as model API. The formulated tablets contained four excipients: potato starch (Roquette Pharma, Lestrem, France) as disintegrant, microcrystalline cellulose (MCC) (Vivapur grade 200, JRS Pharma GmbH, Rosenberg, Germany) and dibasic calcium phosphate (DCP) (Anhydrous Emcompress, JRS Pharma GmbH, Rosenberg, Germany) as filler and magnesium stearate (MgSt) (Faci S.P.A., Carasco, Italy) as lubricant.

### 2.2 Preparation of the tablets

A total of six formulations were prepared by changing the amount of API (6.25%, 12%) and potato starch (0%, 5%, 10%) used. The DCP content varied depending on the API and starch concentrations (Table 1). The amounts of all other excipients were kept constant, the concentration of MCC and MgSt were 40% and 2%, respectively. With the exception of MgSt, all the components were manually mixed by shaking them for five minutes in 100 mL plastic pharmaceutical bottles. Then, 2% of MgSt was added and the mixture was shaken for one additional minute. The batch size for each formulation was 50 g.

The powder blends were directly compressed at 19 kN compression force level using a Dott Bonapace Cpr6 (Dott Bonapace, Italy) eccentric tablet press, equipped with a single concave punch with a diameter of 9 mm. A total of 60 tablets were prepared (with 10 tablets per formulation). The target weight of tablets was 200 ± 4 mg.

### 2.3 Raman spectroscopy

Raman spectra were collected using a Kaiser Raman RXN2 Hybrid Analyzer (Ann Arbor, MI, USA) equipped with a 400 mW, 785 nm Invictus diode laser and a Pharmaceutical Area Testing (PhAT) probe. Reflection and transmission spectra were obtained with a 10 and 45 s exposure times, respectively, each measurement consisted of 2 scans. In the case of backscattering mode, the tablets were illuminated from above using the PhAT probe, while during transmission measurements, the samples were irradiated from underneath with the transmission accessory. Raman shifts from 200 to 1890 $cm^{-1}$ were collected with a resolution of 1 $cm^{-1}$.

**Table 1** Composition of tablet formulations

| Batch | API content (w/w %) | Starch content (w/w %) | DCP content (w/w %) | MCC content (w/w %) | MgSt content (w/w %) |
|---|---|---|---|---|---|
| A | 12.5 | 0 | 45.5 | 40 | 2 |
| B | 12.5 | 5 | 40.5 | 40 | 2 |
| C | 12.5 | 10 | 35.5 | 40 | 2 |
| D | 6.25 | 0 | 51.75 | 40 | 2 |
| E | 6.25 | 5 | 46.75 | 40 | 2 |
| F | 6.25 | 10 | 41.75 | 40 | 2 |

### 2.4 Fourier transformation near-infrared spectroscopy

Fourier-transformed Near Infrared (FT-NIR) spectra were acquired using a Bruker Optics MPA (Multi Purpose Analyzer) FT-NIR spectrometer (Billerica, MA, USA) in diffuse reflection and transmission measurement mode. The spectra were collected with the Opus 7.5 software (Bruker OPTIK GmbH, Germany). The spectral range chosen for transmission NIR spectra was 4000–15,000 $cm^{-1}$ with a resolution of 8 $cm^{-1}$. The diffuse reflection spectra were recorded between 3,800–10,000 $cm^{-1}$ with a resolution of 8 $cm^{-1}$. All spectra were obtained by averaging 64 scans.

### 2.5 *In vitro* dissolution testing

The dissolution of the caffeine tablets was performed using the USP 23 Apparatus 2 (Hanson SR8-Plus, dissolution tester, Chatsworth, CA, USA). The dissolution media was 900 mL of distilled water, set to a temperature of 37 ± 0.5 °C during the test, and the paddle rotation speed was 50 rpm. The samples were withdrawn at 12 predetermined time points for a total duration of 60 min using a Hanson Autoplus Maximizer 8 (Chatsworth, CA, USA) automatic syringe pump through 10 µm filters. 5 mL samples were drawn every 2.5 min until 20 min, then at 20, 25, 30, 45 and 60 min.

The amount of caffeine dissolved was determined spectrophotometrically with an on-line coupled Agilent 8453 UV–Vis spectrophotometer (Hewlett-Packard, USA) at 272 nm 10 mm cuvettes based on a preliminary calibration.

### 2.6 Data analysis

Data analysis was performed in MATLAB 8.2. (MathWorks, USA) equipped with the PLS_Toolbox 7.8.2. (Eigenvector Research, USA) and Neural Network Toolbox 8.3. Firstly, the spectra were preprocessed to remove variability which was not caused by the differences in the composition of the tablets. NIR reflection and transmission spectra were first smoothed (Savitzky-Golay method, second order polynomial, filter width of 31), then their first derivative

was calculated (Savitzky-Golay method, second order polynomial, filter width of 15). The spectral regions with poor signal-to-noise ratio were cut from the spectra, the following regions were retained: 3800–7600 $cm^{-1}$ for reflection and 7000–11000 $cm^{-1}$ for transmission spectra. The Raman spectra were also subjected to smoothing (Savitzky-Golay method, second order polynomial, filter width of 15 in the case of reflection and 31 for transmission spectra), then baseline removal was performed using the automatic Whittaker filter method ($\lambda$ = 10000, $p$ = 0.001) and lastly the spectra were normalized to an area of 1 under the whole spectrum. The Raman shift range of 400–1890 $cm^{-1}$ was retained for both reflection and transmission spectra, as under 400 $cm^{-1}$ the signal had a poor quality. As the last step of preprocessing, all spectra were also mean centered.

The preprocessed spectra were then subjected to PCA. Afterwards, the first two principal components (PCs) were obtained for each spectrum. These values were used as inputs of a feedforward backpropagation ANN. The ANNs predicted the dissolution profile of the tablets consisting of 12 time points based on the two PC values. The constructed ANNs consisted of an input layer with two neurons, one hidden layer with 1–10 neurons and an output layer with 12 neurons (one for each time point of the dissolution curve). The Bayesian regularization learning algorithm was applied, the neurons in the hidden layer used a tangent sigmoid transfer function, and a linear transfer function in the output layer. Each network was created with randomly generated weight and bias values, training epochs were repeated until the mean squared error performance function's value become less than $10^{-7}$ or until 1000 epochs were reached. From the 6 formulations, four were used as training and two as validation. The training samples were split into 3 categories. 70% of the data was used to train the ANN, 15% was utilized for cross-validation and the last 15% for testing. The number of neurons in the hidden layer was optimized by performing the training at each neuron number from 1 to 10.

As the ANNs were generated with random weight and bias values, the results of the training had a large variation, as the different initial states resulted in different outcomes, some of which have a poor performance. Therefore, the training was repeated 100 times and the best model was chosen from them. The performance of the ANNs was evaluated using the $f_2$ similarity parameter (Eq. (1)):

$$f_2 = 50\log_{10}\left\{\left[1+\frac{1}{n}\sum_{i=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{0.5}\times 100\right\}, \qquad (1)$$

where $T_t$ is the predicted dissolution value and $R_t$ is the measured dissolution value at time point $t$, $n$ is the number of points in the dissolution curve and $w_t$ is an optional weighing factor which was not applied here. The calculation was performed by considering only those points of the dissolution curve where the dissolution is less than 85%, and a single point after that. This way, the end of the curve which is easy to predict as it is simply a flat line will not improve the result undeservingly.

## 3 Results and discussion

### 3.1 Analysis of the spectra

The raw spectra of the 60 tablets is shown in Fig. A1 in the Appendix A. It can be observed that both kinds of NIR spectra contain regions which are noisy or do not contain any peaks and thus information about the composition of the samples. In the case of Raman measurements, the region below 400 $cm^{-1}$ is notably devoid of peaks and is dominated by a strong baseline shift.

After the removal of the noisy regions and the application of the prepocessing techniques, the information content of the spectra appears to be much higher (Fig. 1). NIR transmission (NIR TR) spectra have a broad peak centered around 8750 $cm^{-1}$ which correlates with the composition of the tablets. Similarly, both Raman reflection (RA RE) and Raman transmission (RA TR) spectra have a peak at 980 $cm^{-1}$ where the spectra are clearly separated based on tablet composition. NIR reflection (NIR RE) spectra do not have such easily observable patterns.

PCA was performed on the preprocessed spectra to reduce the number of variables, models utilizing 2 PCs were built in the case of all four spectrum types. This choice was made after evaluating the percentage of variability explained by the PCs, the first 2 PCs cover more than 83% of all cases (Fig. 2).

In all cases, the first PC accounts for the majority of the variability (74.71–89.28%), by observing the grouping of the spectra, this PC can be identified as the caffeine content. The tablets with the same caffeine content but different amount of starch are separated along the second PC, which accounts for 8.23–10.88% of the variability. This implies that changing the starch content has a less prominent effect in the spectra compared to caffeine. Generally, the groups are better separated in the Raman spectra (especially in the case of RA RE), while NIR spectra are less reliable in the differentiation based on composition.

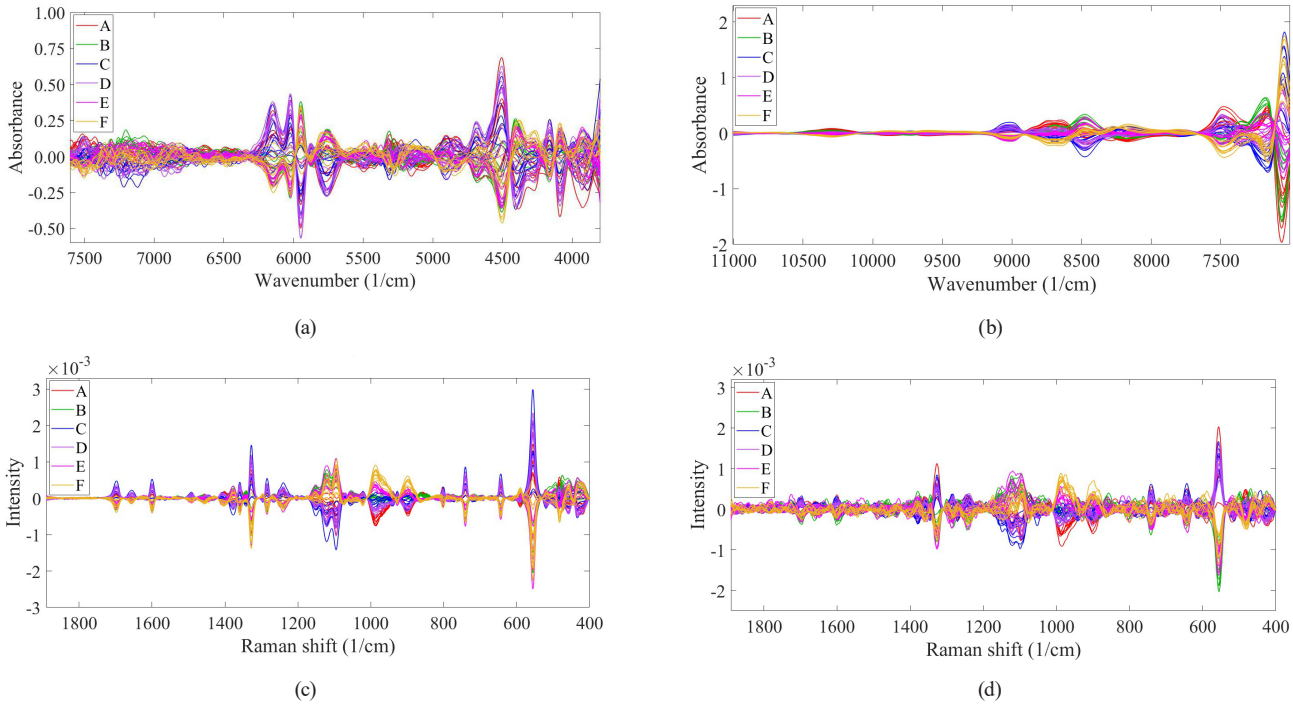



**Fig. 1** Preprocessed spectra of the tablets. (a) NIR reflection; (b) NIR transmission; (c) Raman reflection; (d) Raman transmission

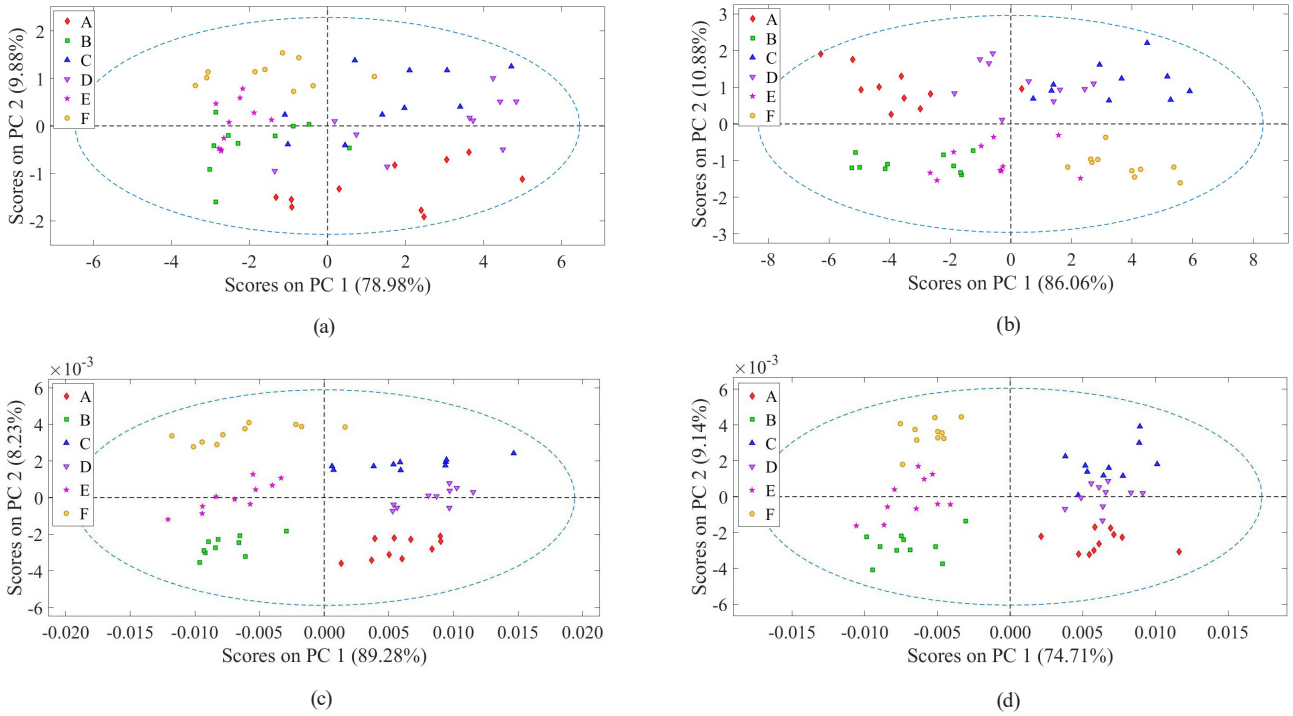



**Fig. 2** PCA of the spectra. (a) NIR reflection; (b) NIR transmission; (c) Raman reflection; (d) Raman transmission

### 3.2 Prediction of the dissolution profiles using ANN

The tablet dissolution profiles were influenced by the API and disintegrant content. Fig. 3. illustrates the effect of these factors on the average dissolution curves. The API was released faster from the tablets with a higher starch concentration. Samples without disintegrant were characterized by slow dissolution.

After 100 ANN training cycles were completed with each spectroscopic input data and at each neuron number, the average $f_2$ value for the validation tablets and the standard deviation of the $f_2$ values were calculated for each hidden layer neuron number (Fig. 4).

It can be observed that the best results are obtained with a small number of neurons, the average $f_2$ has its maximum

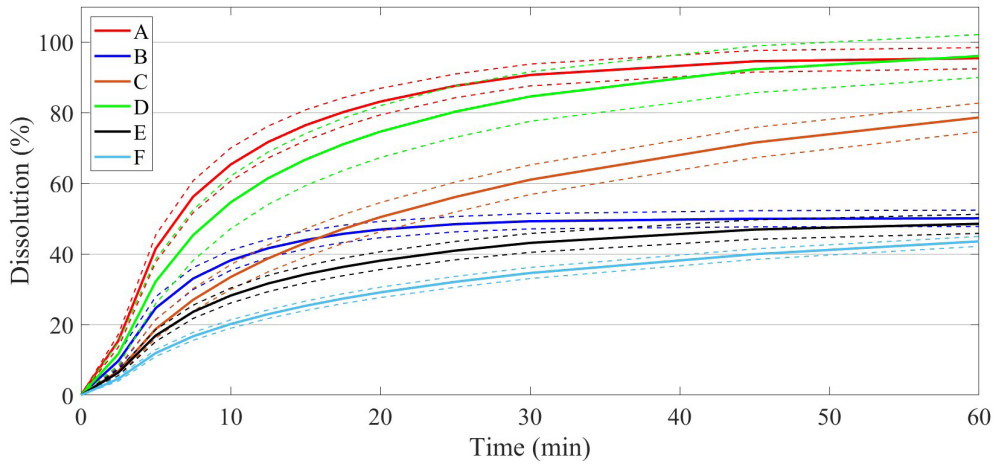



**Fig. 3** Average dissolution curve of the six formulations, dashed lines represent the standard deviation

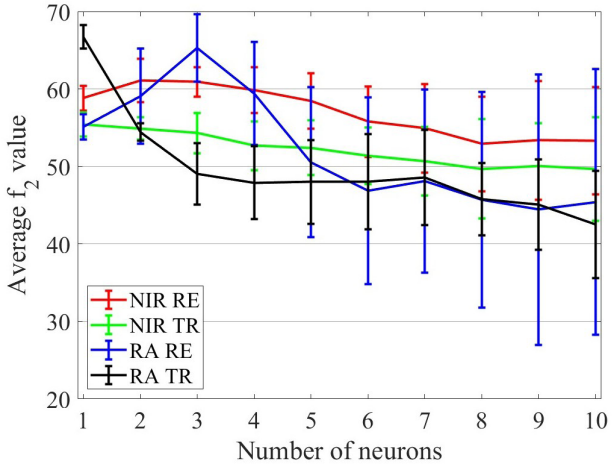



**Fig. 4** Average and standard deviation of $f_2$ values with the 4 types of spectroscopic measurement as a function of neuron number in the hidden layer

at 1 neuron for NIR TR and RA TR, at 2 for NIR RE and at 3 for RA RE. This implies that the impact of caffeine and starch content on the dissolution rate can be described with a simple function, which requires only a handful of neurons in the ANN. Furthermore, the standard deviation of the $f_2$ values gets higher as the number of neurons increases. This shows that the training becomes less reliable and creating a good model depends on the lucky generation of the initial weight and bias values. When the initial values are chosen with unfortunate values, the training is not able to reach a good optimum, instead it finds a local minimum which results in a poor model. The limited amount of training data might be another reason why larger neuron numbers are not preferred.

With each type of input data, the best model was chosen at the neuron number where the average $f_2$ was the highest, the $f_2$ value of these models is shown in Table 2.

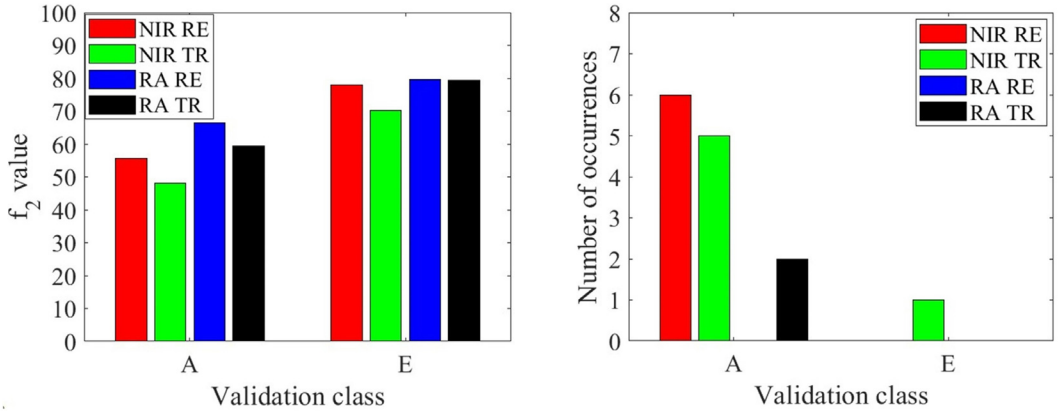
**Table 2** Average $f_2$ value of the predictions for validation tablets of the best ANN models at each input data type

| Spectroscopic method | Hidden layer neuron number | $f_2$ value |
|---|---|---|
| NIR RE | 2 | 66.79 |
| NIR TR | 1 | 59.15 |
| RA RE | 3 | 73.09 |
| RA TR | 1 | 69.35 |

The accuracy of the predictions also varied between the two validation classes (Fig. 5 (a)), class A was predicted with lower $f_2$ values than class E. The number of predictions with an $f_2$ below 50 is also much higher in the case of class A (Fig. 5 (b)).

It is also conspicuous that Raman-based predictions have only a total of 2 cases where the $f_2$ is lower than 50, both of these belong to the RA TR method, while the $f_2$ of RA RE predictions was never below 50. The most likely explanation of the lower predictive ability in the case of class A is that these tablets contain no starch, and the ANNs were not able to accurately learn the shape of the dissolution curve in this scenario. Upon analyzing the individual predictions and the measured curve in the case of all 4 spectroscopic methods (Figs. A2–A5 in the Appendix A), it appears that the models usually underestimate the drug release speed from these tablets. The predicted curves usually go below the measured one, while in the case of class E tablets, the two curves are more aligned.

Generally, the performance of the different spectroscopic methods correlates well with the qualitative analysis of the PCA results. When Raman spectroscopy is used, the classes can be more effectively separated based on the first two PCs, while the samples of different compositions are intermixing in the case of NIR-based methods. This is




(a) (b)

**Fig. 5** (a) Average $f_2$ value of predictions belonging to the two validation classes; (b) Number of predictions with an $f_2$ value lower than 50

not surprising based on the shape of the raw and preprocessed spectra, as in all cases, Raman spectra have more and sharper peaks, which is beneficial when our goal is to distinguish the components. Although the lower sensitivity of NIR spectroscopy might result in less accurate models, currently its instrumentation is better suited for in-line analysis compared to Raman spectroscopy [32].

## 4 Conclusions

In this study, ANN models were applied to successfully estimate the *in vitro* dissolution profile of immediate-release tablets using data from NIR and Raman spectroscopy. Compared with the traditional analytical method for dissolution testing, the developed technique is fast, simple, and non-destructive. Although a relatively small training dataset was used, the obtained surrogate model presented good predictive ability. The study also revealed that a large number of hidden neurons for an ANN model does not always result in better prediction. Among the four tested spectral methods (NIR RE, NIR TR, RA RE, RA TR), the models based on Raman spectra provided the most accurate predictions. However, NIR presents some advantages over Raman spectroscopy: less expensive instrumentation, rapid and easy analysis. Future studies could investigate the predictive relationship between dissolution and additional process and material variables, such as compression force, particle size distribution of API and key excipients, or the type of starch.

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## Appendix A

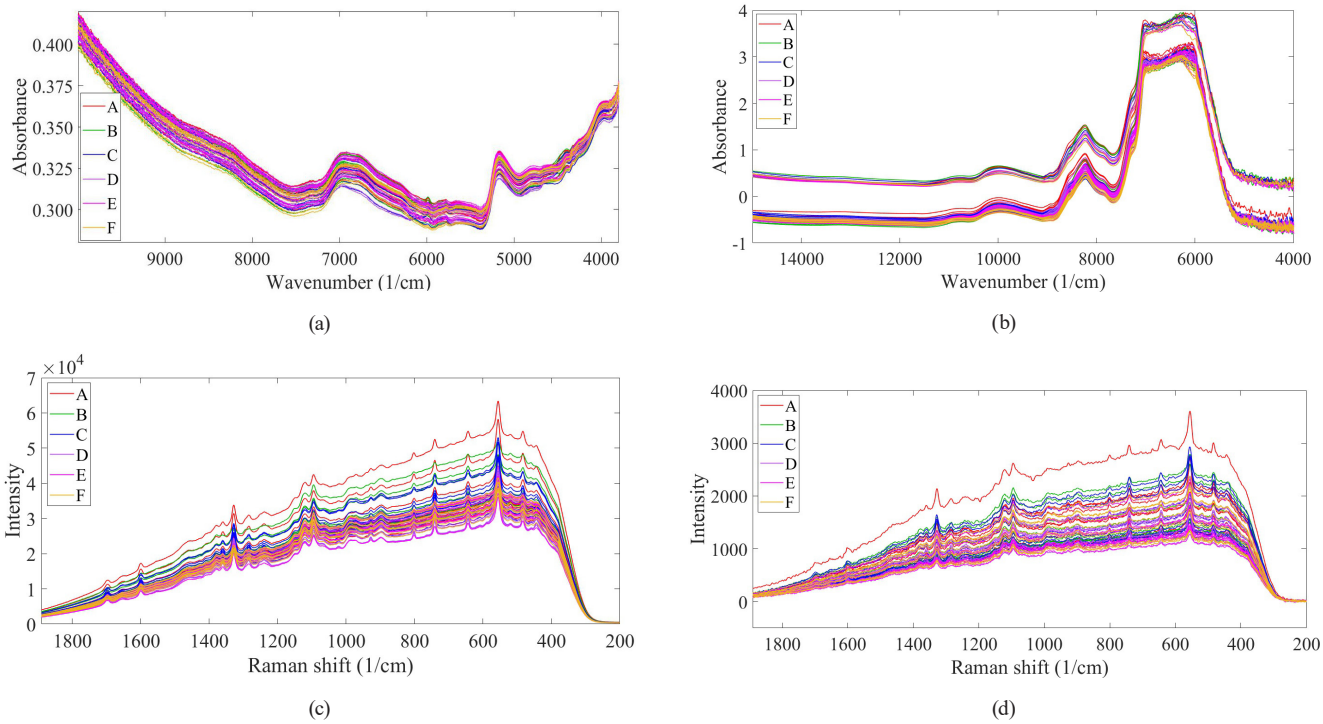


**Fig. A1** Raw spectra of the tablets: (a) NIR reflection; (b) NIR transmission; (c) Raman reflection; (d) Raman transmission

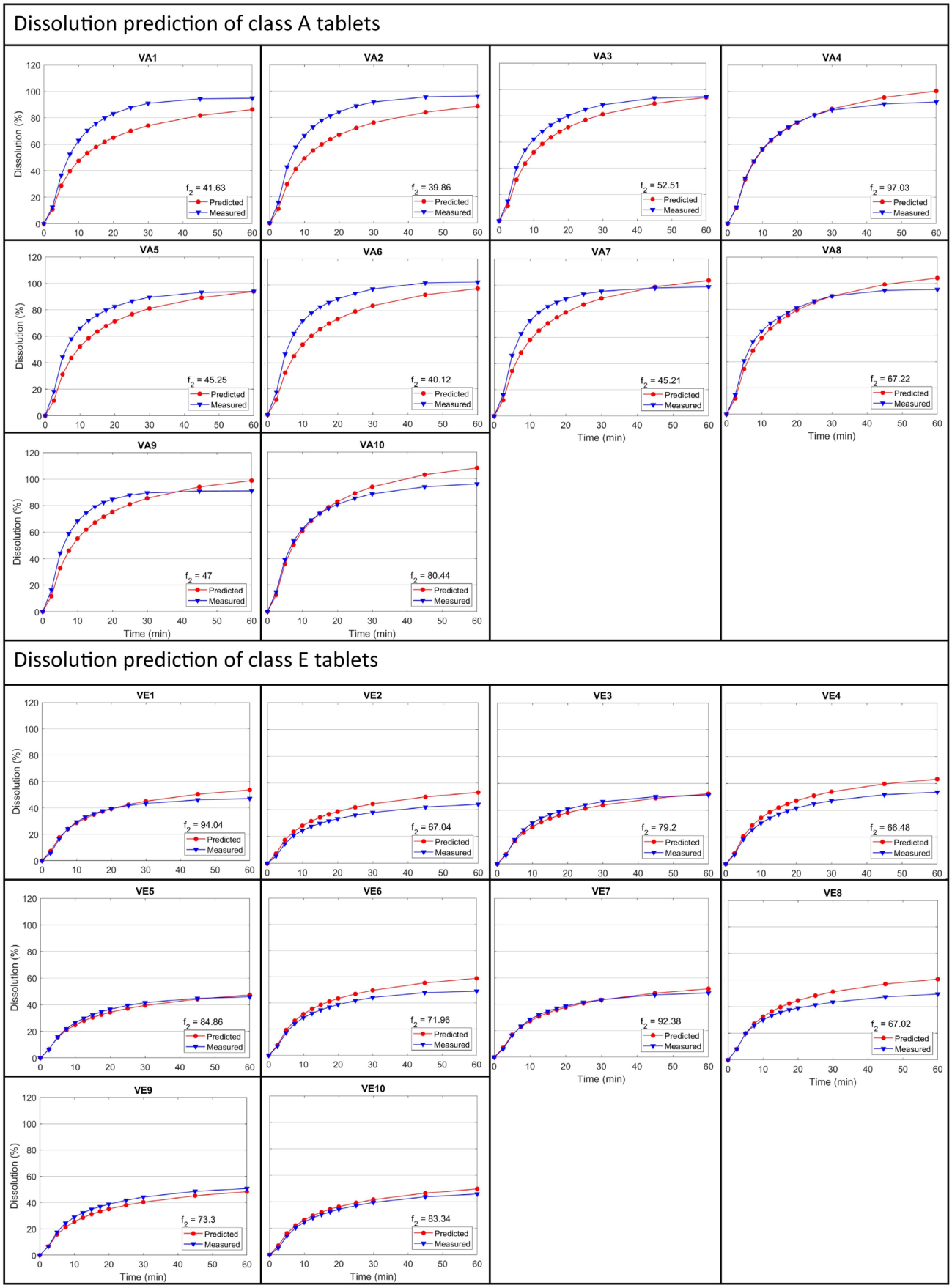


**Fig. A2** Predicted and measured dissolution profile of all test tablets using reflection NIR spectra

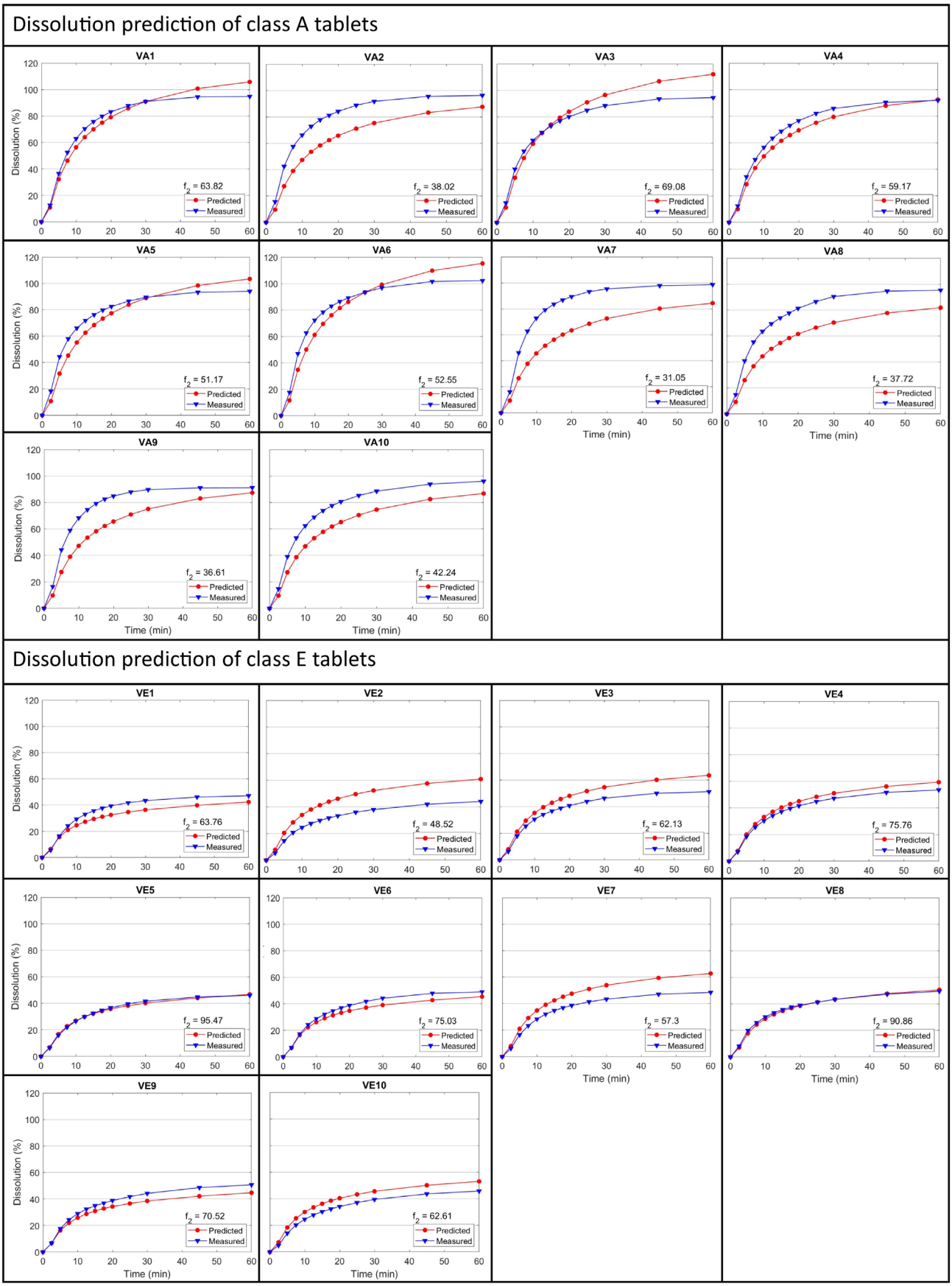


**Fig. A3** Predicted and measured dissolution profile of all test tablets using transmission NIR spectra

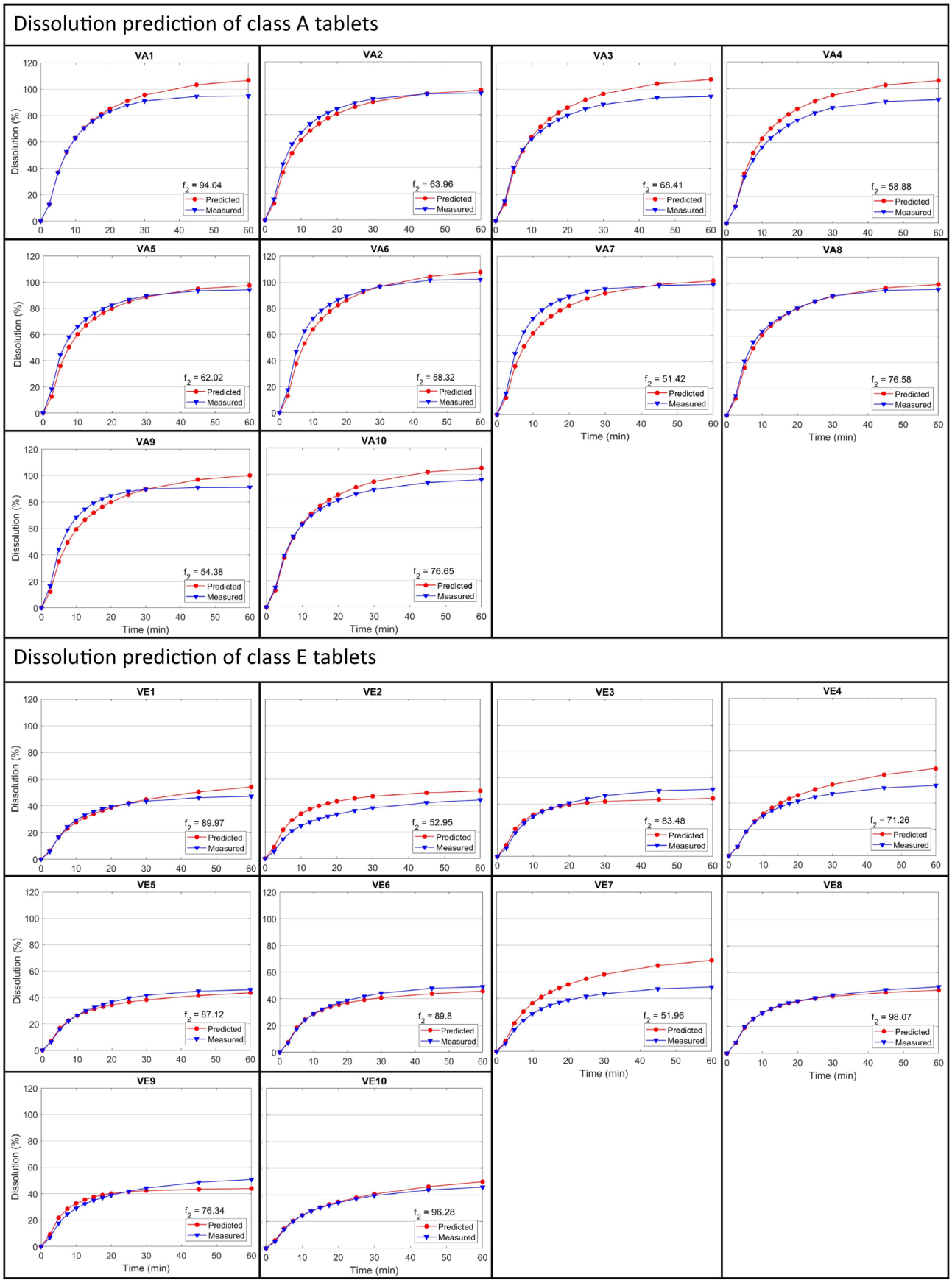


**Fig. A4** Predicted and measured dissolution profile of all test tablets using reflection Raman spectra

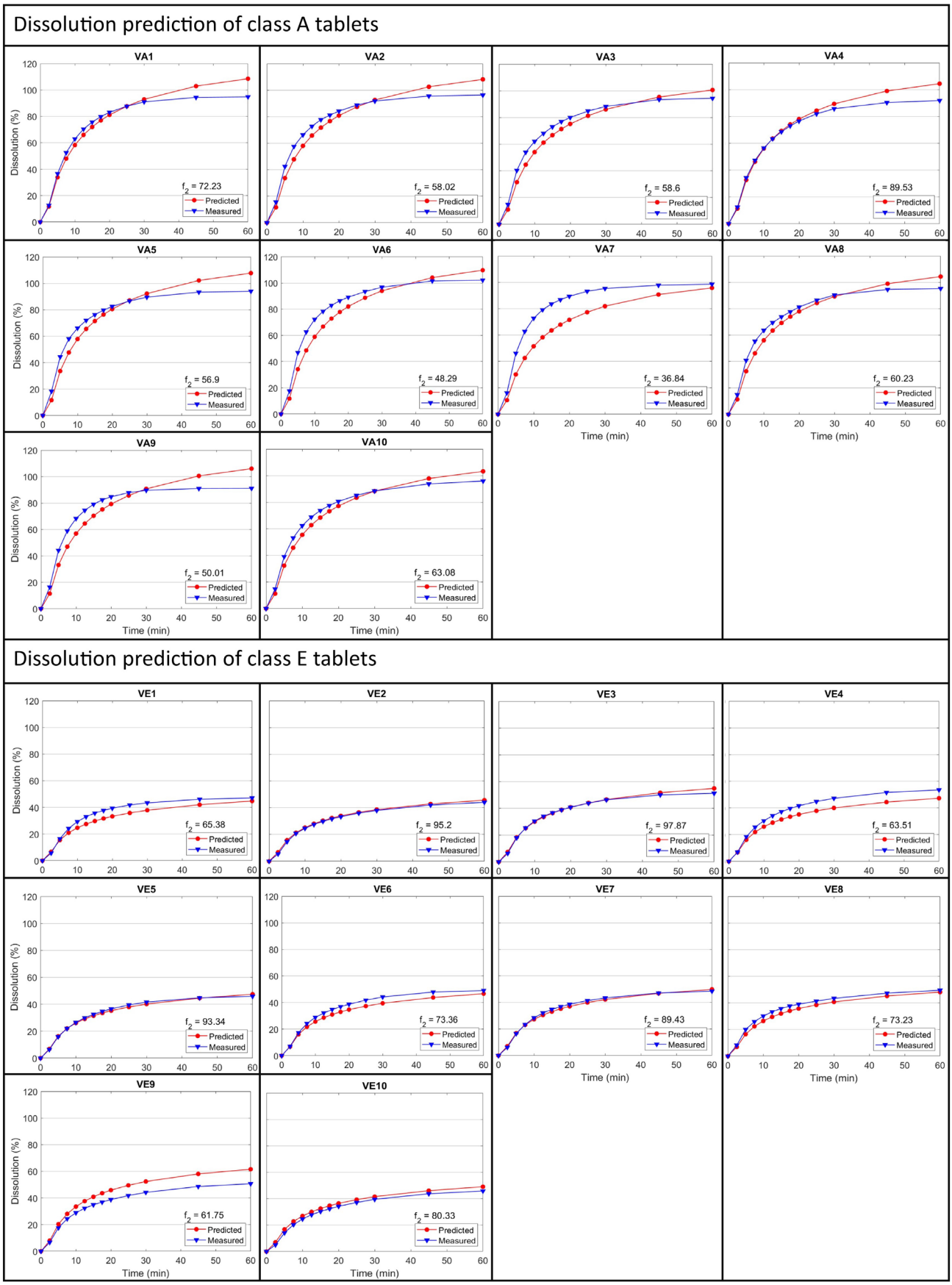


**Fig. A5** Predicted and measured dissolution profile of all test tablets using transmission Raman spectra