

PREDICTING THE DISSOLUTION OF TABLETS BASED ON RAMAN MAPS USING A LINEAR REGRESSION MODEL

Gábor Knyihár, Kristóf Csorba and Hassan Charaf

Department of Automation and Applied Informatics
Faculty of Electrical Engineering and Informatics
Budapest University of Technology and Economics
Budapest, Hungary

ABSTRACT

Investigation of the dissolution of tablets is an important area of pharmaceutical research. Such research aims to predict the dissolution process as accurately as possible without destroying the tablets. Several methods have been published that can estimate dissolution with approximate accuracy, but they are mostly complex and time-consuming. This article seeks to answer whether these complex models are necessary or whether a similar result can be achieved with the help of more straightforward methods. Therefore, during this work, a simpler linear regression model was created and analysed its effectiveness in estimating the dissolution curves. The investigation concluded that the results are not as accurate as in the case of more complex methods, but they are not far behind. Thus, even similar results may be achieved by fine-tuning and possibly developing these methods.

KEYWORDS

Raman spectroscopy, Dissolution curve, Linear regression, Principal Component Analysis

1. INTRODUCTION

One of the much-studied areas of pharmacy is the dissolution test of sustained-release tablets. The purpose of such a tablet is not to dissolve immediately after entering the body but to continuously distribute the amount of active ingredient (API) determined by pharmacists into the body for a specific period. The dissolution of tablets is usually characterised by dissolution curves, which show the percentage of the dissolved API in the proportion of the time. Today, the most reliable and frequently used method for determining the dissolution curve is a physical measurement, during which the tablet is placed in a liquid similar to stomach acid, and the amount of dissolved API is measured [1]. The method gives accurate results, but its major drawback is that it is incredibly time-consuming (it can take up to 12 or 24 hours to dissolve one tablet). Furthermore, it destroys the only tablet whose dissolution process is known.

For this reason, many types of research aim to estimate the progress of dissolution as simply, quickly and most importantly, non-destructively as possible. Many try to estimate the dissolution curve using modern artificial intelligence methods [2] [3] [4] [5]. The crushing strength of tablets, compression force applied during production, and Raman and near-infrared (NIR) spectra are commonly used as inputs [6]. Other papers try to solve the problem analytically [7], but the dissolution process can depend on many parameters, making these models complex.

This article examines the accuracy of a simpler linear regression (LR) model compared to more complex neural network methods. The authors of the article [5] present two methods for estimating the dissolution curve, which they refer to as discretisation (DI) and wavelet analysis (WA) methods. In this article, the same dataset is used as the authors of the reference article, so the obtained results can be directly compared.

Raman maps of the tablets were used as input. In pharmaceutical research, light-based spectral analysis methods are often used, among which near-infrared and Raman spectroscopy are widespread [8]. With the latter, we can take pictures of a small surface, based on which the ratio and arrangement of the elements that make up the surface can be determined without destroying it. While preparing the Raman map, a certain device, the Raman spectrometer, illuminates the tablet's surface at each grid point with laser light and records the variations in the wavelength of the reflected light [9] [10]. From the obtained spectra, compared with the reference spectra of the pure components, the percentage occurrence of the components in each point can be determined using the classical least squares (CLS) method [11] [12].

With Raman maps, the goal is to investigate the tablet's composition since these tablets contain a hydrophilic matrix that directly affects the time course of dissolution. These hydrophilic matrix contains cellulose derivatives that swell in contact with water, slow the API's outflow, and hold the tablet together. Hence, the wetting of the internal parts occurs much later [7]. For this reason, we look for the amount and location of this material in Raman maps, as this provides the most information about the dissolution process [5].

2. THE USED DATA AND METHODS

2.1. The Tested Tablets

The measurement results presented in the article [5] were used for the calculations. The dataset contains information on 28 tablets, of which 18 were used for training and 10 for validation. Each tablet consists of 4 components: the API (drotaverin, DR), the hydrophilic matrix polymer (hydroxypropyl methylcellulose, HPMC), the filler (lactose) and the lubricant (magnesium stearate, MgSt). Their proportions are presented in Table 1. The factor that most influence the tablets' dissolution is the matrix polymer's ratio and particle size. So the dataset distinguishes between small (<45 μm) and large (>125 μm) HPMC tablets and varies the proportion of HPMC. The training dataset contains 6 different compositions (3 tablets each), while the validation data set contains 10 different compositions (1 tablet each).

Table 1. The parameters of investigated tablets

Name	DR (%)	HPMC (%)	Lactose (%)	MgSt (%)	HPMC Particle size (μm)
Training dataset (3 tablets at each)					
T10S(1-3)	8	10	81	1	< 45
T20S(1-3)	8	20	71	1	< 45
T30S(1-3)	8	30	61	1	< 45
T10L(1-3)	8	10	81	1	> 125
T20L(1-3)	8	20	71	1	> 125
T30L(1-3)	8	30	61	1	> 125

Name	DR (%)	HPMC (%)	Lactose (%)	MgSt (%)	HPMC Particle size (μm)
Validation dataset (1 tablet at each)					
V10S	8	10	81	1	< 45
V15S	8	15	76	1	< 45
V20S	8	20	71	1	< 45
V25S	8	25	66	1	< 45
V30S	8	30	61	1	< 45
V10L	8	10	81	1	> 125
V15L	8	15	76	1	> 125
V20L	8	20	71	1	> 125
V25L	8	25	66	1	> 125
V30L	8	30	61	1	> 125

2.2. Raman Maps

There are 4 Raman maps available for each tablet, 1 for each component. These were made on a small $1.2 \times 1.2 \text{ mm}^2$ part of the tablet surface with a step interval of $40 \mu\text{m}$, in a total of $31 \times 31 = 961$ points. Each point on the map shows the proportion of the given component in the tablet. Figure 1 shows an example of the Raman maps available for tablets.

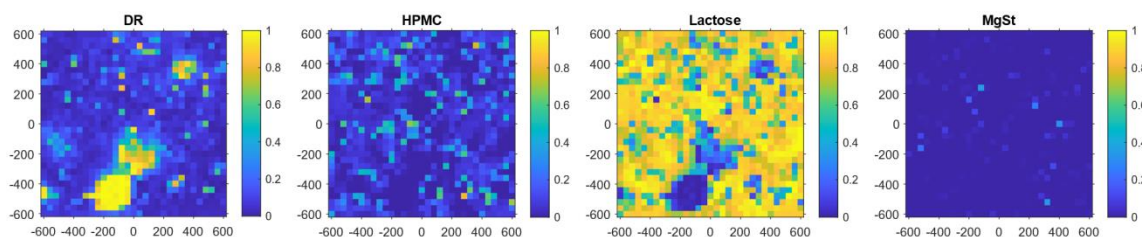


Figure 1. Raman maps for the tablet T10S1. The first map shows the ratio of DR, the second of HPMC, the third of Lactose, and the fourth of MgSt on the tablet's surface. The x and y axes of the maps show the distance relative to the centre in μm .

2.3. Dissolution Curves

In addition to the Raman maps, the dissolution curve of each tablet is available. The curves give the concentration of the dissolved API at a total of 38 points in time. These points are 0, 2, 5, 10, 15, 30, 45 and 60 minutes from the beginning of the measurement and every 30 minutes after that up to 960 minutes. An example of this is shown in Figure 2.

2.4. Software

To perform the calculations, Matlab 2021b (v9.11) software developed by Mathworks supplemented with the Image Processing Toolbox (v11.4) and the Statistics and Machine Learning Toolbox (v12.2) was used.

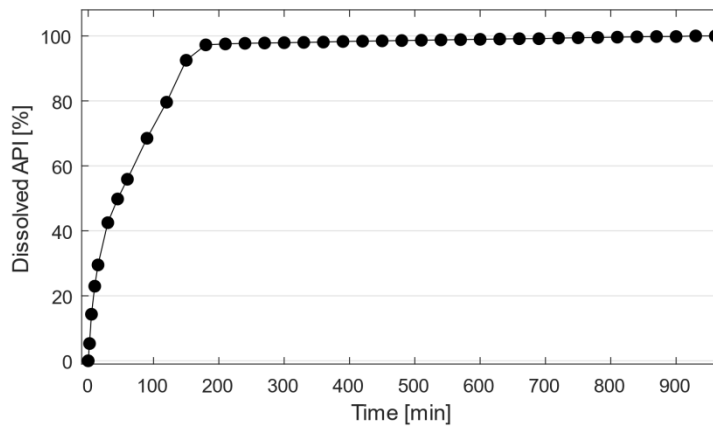


Figure 2. Dissolution curve for the T10S1 tablet. The bottom axis shows the time from the beginning of the measurement in minutes, and the left axis shows the percentage of the dissolved API.

2.5. Processing of Raman Maps

Only the HPMC ratio of the tablets was considered during the work since the dissolution process depends mainly on this component. The HPMC map was discretised as a first step by assigning a group denoted by numbers between 1-10 to each pixel. The assignment is given by the Equation 1.

$$f: x \mapsto [10x], \text{ where } x \in [0,1] \quad (1)$$

So, for example, the pixels whose value is greater than 0 and less than or equal to 0.1 belong to Group 1. The individual groups are meant to symbolise connected HPMC parts, and the higher the value of each group, the higher the proportion of HPMC found there.

Figure 3 shows an example of two discretised maps with different HPMC content. The figure clearly shows that in the case of the T30L1 sample, which contains a higher percentage of HPMC, significantly more regions can be found that belong to the groups denoted with larger numbers.

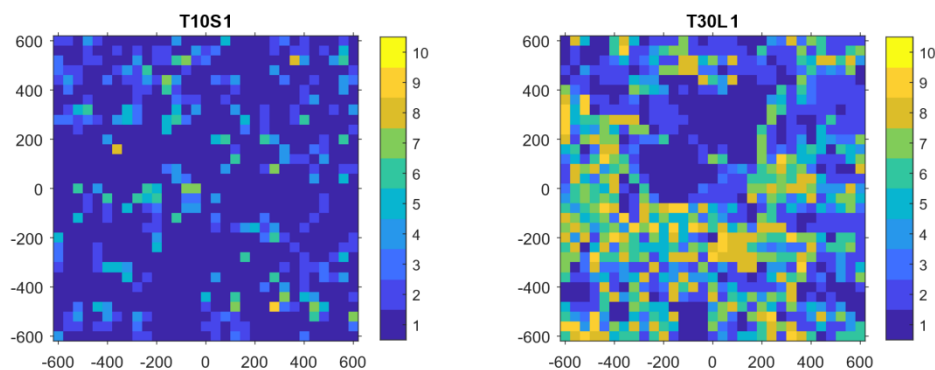


Figure 3. Discretised HPMC maps for T10S1 and T30L1 tablets. The x and y axes of the maps show the distance relative to the centre in μm , and the colours symbolise the individual groups between 1 and 10.

In order to characterise the regions with different HPMC content, the groups were summarised. The number of pixels in each row and column belonging to each group was counted. This method resulted in $2 \times 31 = 62$ values for each group, i.e. a total of 620 values. After calculating the parameters for the maps, we get a matrix of size 18×620 , where the parameters belonging to one tablet are located in each row of the matrix. To make this matrix a manageable size and eliminate unnecessary parameters, the dataset was reduced to 17 principal components (PC) using principal component analysis (PCA). After that, the input became 18×17 in size. Several PC numbers were tried, but the best results were obtained when the number of PC was chosen to be 17 or more.

2.6. Creation of a Linear Regression Model for the Prediction of Dissolution Curves

In order to create the LR model, the set of parameters described in the previous chapter was used as input. For the output, the values of the reference dissolution curves were arranged in an 18×38 matrix. In the matrix, each row belongs to a tablet, and each column belongs to a particular time moment. Then, using the method of least squares, the \mathbf{M} matrix was searched that balances the Equation 2 with the smallest possible ϵ error. \mathbf{P} is the parameter matrix used as input, and \mathbf{C} is the dissolution curve matrix used as output.

$$\mathbf{C} = \mathbf{M} \cdot \mathbf{P}^T + \epsilon \quad (2)$$

After that, the model was validated. The input parameter matrix was calculated for the validation maps, as in the training set.

The only difference was that the transformation obtained during training was used instead of PCA, and the input parameters were transformed into the same PC as the training set. The dissolution curves were determined using a matrix multiplication between the received inputs and the model defined during training. The results were then bounded using the assumption that the dissolution values could only be interpreted between 0-100, so the values that did not fit into this range were corrected.

2.7. Evaluation of the Accuracy of the Estimated Curves

For the comparison of the calculated and measured dissolution curves, the f_2 value described in the article [13] was used according to the Equation 3, where R_t and T_t are the calculated and measured dissolution values at the time of t , and n is the number of time moments.

$$f_2 = 50 \cdot \log_{10} \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\} \quad (3)$$

The f_2 value is 100 if the two analysed curves are equivalent and less than 100 if they differ. So the goal is to make the f_2 value as large as possible.

3. RESULTS

Based on the obtained LR model, the dissolution curves for the 10 validation maps were calculated and compared with the measured curves by determining the already described f_2 value for each sample (Figure 4). The best-performing model gave an average of 47.08 for the f_2 value, which is a relatively good result.

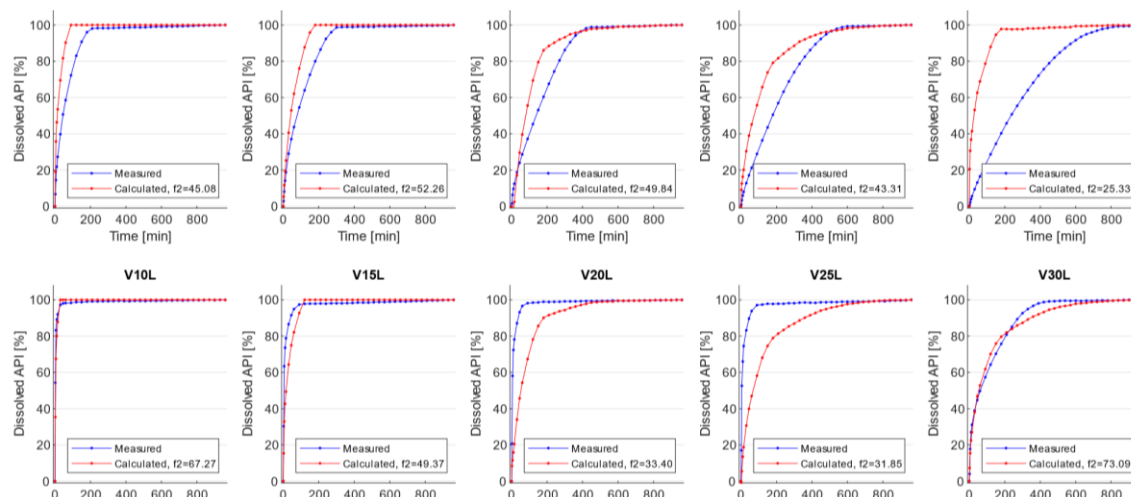


Figure 4. The calculated dissolution curves of the validation dataset compared to the measured values. The bottom axes of the figures show the time from the beginning of the measurement in minutes, and the left axes show the percentage of the dissolved API.

The obtained results were compared with the results coming from the article [5] (Table 2). It is visible that the LR model is, on average inadequate to the DI and WA methods reported in the article. However, the LR method is significantly more straightforward, as all the methods explained in the article use a neural network, the training and calibration of which is a lengthy and complex procedure.

Table 2. Comparison of the f_2 value of the DI and WA methods [5] with the results of the LR method.

Name	f_2 value of method DI	f_2 value of method WA	f_2 value of method LR	Best method
V10S	75.58	39.43	45.08	DI
V15S	39.32	32.58	52.26	LR
V20S	87.89	86.27	49.84	DI
V25S	50.79	32.36	43.31	DI
V30S	96.11	81.50	25.33	DI
V10L	51.68	48.33	67.27	LR
V15L	77.31	56.04	49.37	DI
V20L	47.53	75.15	33.40	WA
V25L	46.71	68.00	31.85	WA
V30L	50.60	74.69	73.09	WA
Average	62.35	59.44	47.08	DI

Furthermore, if validation samples are analysed individually, in some cases, the LR model gives better results than the ones reported in the reference article. Consequently, it may be possible to achieve better results by combining these methods.

4. CONCLUSIONS

This article analysed a linear regression model's accuracy in predicting tablets' dissolution curves based on their Raman map. The results showed that although the model cannot achieve better results than the methods that do the same with the help of a neural network, the accuracy of the results is not much lower compared to them. This result indicates a strong correlation between the

metrics determined based on the Raman maps and the dissolution. Compared to methods using neural networks, the advantage of the linear regression model is that the training time is significantly less, and the characterisation of the relationships between individual parameters is much more transparent. Among the regression models, the linear one is the simplest, so there are still many opportunities for further development to achieve better results in dissolution prediction by examining different models.

ACKNOWLEDGEMENTS

The work presented in this paper has been carried out in the frame of project no. 2019-1.1.1-PIACI-KFI-2019-00263, which has been implemented with the support provided from the National Research, Development and Innovation Fund of Hungary, financed under the 2019-1.1. funding scheme.

REFERENCES

- [1] J. B. Dressman and J. Krämer, *Pharmaceutical dissolution testing*, Taylor & Francis Boca Raton, FL., 2005.
- [2] B. Nagy, D. Petra, D. L. Galata, B. Démuth, E. Borbás, G. Marosi, Z. K. Nagy and A. Farkas, "Application of artificial neural networks for Process Analytical Technology-based dissolution testing," *International journal of pharmaceutics*, vol. 567, p. 118464, 2019.
- [3] D. L. Galata, A. Farkas, Z. Könyves, L. A. Mészáros, E. Szabó, I. Csontos, A. Pálos, G. Marosi, Z. K. Nagy and B. Nagy, "Fast, Spectroscopy-Based Prediction of In Vitro Dissolution Profile of Extended Release Tablets Using Artificial Neural Networks," *Pharmaceutics*, vol. 11, p. 400, 2019.
- [4] D. L. Galata, Z. Könyves, B. Nagy, M. Novák, L. A. Mészáros, E. Szabó, A. Farkas, G. Marosi and Z. K. Nagy, "Real-time release testing of dissolution based on surrogate models developed by machine learning algorithms using NIR spectra, compression force and particle size distribution as input data," *International Journal of Pharmaceutics*, vol. 597, p. 120338, 2021.
- [5] D. L. Galata, B. Zsiros, L. A. Mészáros, B. Nagy, E. Szabó, A. Farkas and Z. K. Nagy, "Raman mapping-based non-destructive dissolution prediction of sustained-release tablets," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 212, p. 114661, 2022.
- [6] K. Yekpe, N. Abatzoglou, B. Bataille, R. Gosselin, T. Sharkawi, J.-S. Simard and A. Cournoyer, "Predicting the dissolution behavior of pharmaceutical tablets with NIR chemical imaging," *International journal of pharmaceutics*, vol. 486, p. 242–251, 2015.
- [7] C. Maderuelo, A. Zarzuelo and J. M. Lanao, "Critical factors in the release of drugs from sustained release hydrophilic matrices," *Journal of controlled release*, vol. 154, p. 2–19, 2011.
- [8] K. C. Gordon and C. M. McGoverin, "Raman mapping of pharmaceuticals," *International journal of pharmaceutics*, vol. 417, p. 151–162, 2011.
- [9] J. R. Ferraro, *Introductory raman spectroscopy*, Elsevier, 2003.
- [10] F. A. Miller and G. B. Kauffman, "CV Raman and the discovery of the Raman effect," *Journal of Chemical Education*, vol. 66, p. 795, 1989.
- [11] J. F. Kauffman, M. Dellibovi and C. R. Cunningham, "Raman spectroscopy of coated pharmaceutical tablets and physical models for multivariate calibration to tablet coating thickness," *Journal of pharmaceutical and biomedical analysis*, vol. 43, p. 39–48, 2007.
- [12] L. A. Mészáros, D. L. Galata, L. Madarász, Á. Kóte, K. Csorba, Á. Z. Dávid, A. Domokos, E. Szabó, B. Nagy, G. Marosi and others, "Digital UV/VIS imaging: A rapid PAT tool for crushing strength, drug content and particle size distribution determination in tablets," *International Journal of Pharmaceutics*, p. 119174, 2020.
- [13] J. Z. Duan, K. Riviere and P. Marroum, "In vivo bioequivalence and in vitro similarity factor (f₂) for dissolution profile comparisons of extended release formulations: how and when do they match?," *Pharmaceutical research*, vol. 28, p. 1144–1156, 2011.