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Interpretable artificial neural networks for retrospective QbD of pharmaceutical tablet manufacturing based on a pilot-scale developmental dataset

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ABSTRACT

As the pharmaceutical industry increasingly adopts the Pharma 4.0. concept, there is a growing need to effectively predict the product quality based on manufacturing or in-process data. Although artificial neural networks (ANNs) have emerged as powerful tools in data-rich environments, their implementation in pharmaceutical manufacturing is hindered by their black-box nature. In this work, ANNs were developed and interpreted to demonstrate their applicability to increase process understanding by retrospective analysis of developmental or manufacturing data. The *in vitro* dissolution and hardness of extended-release, directly compressed tablets were predicted from manufacturing and spectroscopic data of pilot-scale development. The ANNs using material attributes and operational parameters provided better results than using NIR or Raman spectra as predictors. ANNs were interpreted by sensitivity analysis, helping to identify the root cause of the batch-to-batch variability, *e.g.*, the variability in particle size, grade, or substitution of the hydroxypropyl methylcellulose excipient. An ANN-based control strategy was also successfully utilized to mitigate the batch-to-batch variability by flexibly operating the tableting process. The presented methodology can be adapted to arbitrary data-rich manufacturing steps from active substance synthesis to formulation to predict the quality from manufacturing or development data and gain process understanding and consistent product quality.

1. Introduction

In recent years, the pharmaceutical industry has been stirred by modernization efforts aiming for more agile and efficient processes, to reduce the cost and time of R&D and manufacturing, and to ensure more consistent product quality. Regulatory initiatives, such as the Quality by Design (QbD) (ICH, 2009), Process Analytical Technology (PAT) (FDA, 2004), and the Real-time release testing (RTRT) (EMA, 2012) concepts, as well as the digitalization (Hole et al., 2021) and Pharma 4.0 (Arden et al., 2021) principles drive these endeavors. QbD promotes knowledge- and risk-based operation by mapping the critical material attributes (CMAs) and process parameters (CPPs) that impact the products' critical quality attributes (CQAs) and defining a design space (*i.e.*, a combination of the CMAs and CPPs) within which acceptable CQAs can be reached. The PAT initiative aims for the in-process analysis and control of the CQAs, CPPs, or CMAs by utilizing in-process analyzers and multivariate data analysis. QbD and PAT can also lead to an RTRT strategy, as the established design space and the real-time analysis can assure the product quality without end-product testing.

The practical implementation of these principles has been extensively researched in the past years. QbD – mainly statistical design of experiments (DoEs) – has been widely used in many steps, from active pharmaceutical ingredient (API) (Weissman and Anderson, 2015) to solid oral dosage form (Bai et al., 2019; Tho and Bauer-Brandl, 2011) development, and has also become an important part of new drug submissions (Bai et al., 2019). Real-time analysis techniques, *e.g.*, near-infrared (NIR) (De Beer et al., 2011), Raman (De Beer et al., 2011; Nagy et al., 2018), and terahertz spectroscopy (Markl et al., 2020) have

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also been implemented for non-destructive, in situ analysis and even RTRT (Markl et al., 2020) throughout the manufacturing process (Laske et al., 2017; Simon et al., 2015). Using surrogate mathematical models coupled with the PAT measurements, even CQAs not directly measurable by PAT tools could be predicted, *e.g.*, the tablets' hardness (Casian et al., 2017; Otsuka and Yamane, 2006; Peeters et al., 2016) (Virtanen et al., 2008) or dissolution profile (Galata et al., 2019; Galata et al., 2021; Galata et al., 2022; Hernandez et al., 2016; Nagy et al., 2019; Pawar et al., 2016; Yekpe et al., 2015).

However, research gaps could also be pointed out (Grangeia et al., 2020; Tho and Bauer-Brandl, 2011). Firstly, QbD has been widely utilized to analyze the effect of, *e.g.*, the granulation steps, but direct tablet compression is still predominantly based on empirical observations, resulting in sub-optimal operation and the inability to respond to process deviations (Grangeia et al., 2020; Grymonpré et al., 2018; Tho and Bauer-Brandl, 2011). Secondly, the need to account for the variability of the raw materials in the design spaces has also been identified (Dave et al., 2015; Grangeia et al., 2020). A few studies have already been focused on the effect of the excipient and API variability, *e.g.*, particle size, crystallinity, viscosity, and moisture content, on the outcome of the granulation and tableting (Casian et al., 2022; Ilyes et al., 2021; Kushner et al., 2011; Portier et al., 2021; Stauffer et al., 2019). Different approaches have been examined to handle these unintended effects, such as involving it in a DoE to select the most robust formulation (Casian et al., 2022), defining a multivariate specification (García-Muñoz, 2009), or using an adaptive design space to compensate for the long-term variability (Igne et al., 2012). Risk-based multivariate control strategies (Ilyes et al., 2021; Portier et al., 2021) or feedforward control (García-Muñoz et al., 2010) were also proposed to compensate for the raw material variability. Thirdly, the emerging trend of retrospective QbD is also highlighted in (Grangeia et al., 2020), *i.e.,* the utilization of the QbD principles on historical data. This could assist root cause analysis, achieve greater process understanding and consequently improve product quality in a later development stage without extensive additional experimenting (Puñal Peces et al., 2016; Silva et al., 2017; Yacoub et al., 2011). As historical data is increasingly getting available due to digitalization, this concept is expected to gain enormous attention.

Currently, QbD and PAT models are mainly built relying on factorial DoEs, using, *e.g.*, response surface fitting or multivariate data analysis, such as principal component analysis (PCA) or partial least squares (PLS) regression. However, the structure of historical data is most often not ideal for such conventional methods. Machine learning (ML) tools, such as artificial neural networks (ANNs), emerge as potential tools to tackle these tasks due to their flexibility, suitability for big data processing, and ability to handle non-linearity, missing, and unstructured data. Consequently, their application is expected to spread in the following years as the Pharma 4.0. concept and digitalization are increasingly adopted in the pharmaceutical industry (Arden et al., 2021; Đuriš et al., 2021; Nagy et al., 2022). ANNs have already been identified as powerful methods in several pharmaceutical tasks (Agatonovic-Kustrin and Beresford, 2000; Nagy et al., 2022), *e.g.*, to characterize, predict and optimize the production of both active pharmaceutical ingredients (API) (Nagy et al., 2022) and pharmaceutical formulations (Wang et al., 2022). Furthermore, PAT data could be fused and evaluated to predict product quality (Nagy et al., 2022), *e.g.*, *in vitro* dissolution profiles (Galata et al., 2019; Galata et al., 2021; Nagy et al., 2019).

Nevertheless, a general preconception of ANNs, *i.e.*, their black-box nature, might inhibit the introduction of ANN-based solutions, as it goes against the aims of the regulatory initiatives to improve process understanding and reach knowledge and risk-based production. The need for gaining physical insight from the ML models has been identified, and studies dealing with interpretable ML, or explainable artificial intelligence (XAI) are exponentially growing (Molnar et al., 2020). The interpretation could be achieved by several methods (Esterhuizen et al., 2022; Molnar et al., 2020), *e.g.*, using interpretable surrogate models, analyzing the model components (*e.g.*, the weights of the neurons), or using sensitivity analysis (Ruben et al., 2018; Srivastava et al., 2021) to study the response of the model outcome to the perturbations of the inputs. Despite the promising trends, few pharmaceutical-related studies have been published so far capitalizing on this approach. Korteby *et al.* used the Garson equation to quantify the importance of the input variables on the outcome of a fluid bed melt granulation, predicted by an ANN model (Korteby et al., 2018). In another study, the parameters affecting the production of monoclonal antibodies were identified by evaluating the weights in the ANN by response surface methodology (Gentiluomo et al., 2019).

This work aims to demonstrate the applicability of interpretable ANNs to evaluate existing developmental pharmaceutical data to predict the product quality, gain process understanding and consequently improve the manufacturing process. The *in vitro* dissolution and hardness of direct compressed extended-release tablets were predicted from a dataset obtained during pilot-scale development and optimization. Our goal was to identify the root cause of batch-to-batch variability and aid the optimization and control of the process to achieve robust and consistent product quality. Different ANN models were developed, using either Raman, NIR spectra, process variables, and material attributes. The application of sensitivity analysis was proposed for the interpretation of the ANNs, which also contributed to an ANN-based control strategy. The presented methodology is aimed to serve as a general approach for developing interpretable ANNs in any data-rich production step, from the drug synthesis to the quality assurance of the final dosage form to support the identification, optimization, and control of the CMAs and CPPs.

2. Materials and methods

2.1. Materials and analyzed samples

A controlled-release tablet formulation was studied, containing the API in two different doses, silicified microcrystalline cellulose (PROSOLV® SMCC HD 90, JRS PHARMA GmbH & Co. KG) and lactose monohydrate (FlowLac® 100, Meggle, MEGGLE GmbH & Co. KG) as fillers, and magnesium stearate (Faci Asia Pacific Pte ltd.) as a lubricant. Furthermore, 25 % w/w hydroxypropyl methylcellulose (HPMC) (METHOCEL™ K4M, DuPont) was used in controlled release ('CR') and direct compression grade ('DC') to form a hydrophilic gel layer, hence ensuring an extended release. The used K4M grade is a medium-molecular weight HPMC with approx. 4000 cPs viscosity (2 % solution in water). Its DC and CR grades are chemically identical, with the same target viscosities and degrees of methyl and hydroxypropyl substitution (although batch-to-batch variabilities might occur due to the manufacturing). However, the DC grade has less fines and more spherical morphology to obtain a better powder flow rate, better processability and reproducibility in tablet weight and content uniformity. The exact composition of the drug formulation and the name and characteristics of the active pharmaceutical ingredient (API) are confidential.

During the pilot development and optimization stage, tablets were manufactured with 20 kg batch sizes using direct compression. After appropriately blending at a container blender the API and excipients, flat-faced cylindrical tablets were compressed using a Fette 1200i rotary tablet press (Fette Compacting GmbH, Germany).

Data and samples from the production of nine different tablet batches were available, where the tablets were prepared at two API dose levels and using different API and HPMC batches of varying material attributes. Furthermore, the ratio of the CR and DC grade HPMC in the formulation was also varied while the total HPMC content was kept constant. With these nine batches, tablet compression optimization studies were conducted, changing the pre-, and main compression forces, the force feeder rotational speed, and the productivity of the tableting. As a result, tablets produced with a total of 224 different (random) combinations of 13 potential critical material attributes

(MAs)/ process parameters (PPs) were available for further analysis. These parameters and their ranges are summarized in Table 1.

The hardness and friability of all the 224 experimental settings were measured. *In vitro* dissolution, Raman, and NIR spectroscopic measurements were performed on only 34 selected experiments.

2.2. Analytical methods

2.2.1. Near-infrared spectroscopy

The NIR spectra of 5 tablets per experiment were recorded using a Bruker MPA Multi-Purpose FT-NIR Analyzer (Bruker Optik GmbH, Germany) in diffuse reflectance mode and the OPUS 7.5 software (Bruker Optik GmbH, Germany). A high-intensity Tungsten NIR source was used with a PbS detector. The spectra were collected in the 10 000 – 3800 cm^{-1} with a resolution of 8 cm^{-1}, using 64 scans per spectrum, double-sided, forward–backward acquisition, and 10 kHz scanner velocity.

2.2.2. Raman spectroscopy

Raman spectra of 5 tablets per experiment were recorded by a Kaiser Raman Rxn2^{TM} Hybrid (Kaiser Optical Systems, Ann Arbor, USA) in situ Raman spectroscope and iC Raman 4.1 (Mettler-Toledo AutoChem Inc., USA) software. The measurements were performed in reflection mode, using a 400 mW, 785 nm Invictus diode laser and the PhAT (Pharmaceutical Area Testing) probe, which illuminates the samples in a 6 mm diameter with a nominal focus length of 250 mm. The spectra were collected in the 200 – 1800 cm^{-1} spectral range and 4 cm^{-1} resolution with 30 s illumination time.

2.2.3. In vitro dissolution

In vitro dissolution tests of 5 tablets per experiment were performed in a Hanson SR8-Plus (Hanson Research, USA) dissolution tester, following the Ph.Eur./ USP paddle method and using spiral sinkers. 500 mL of pH 4.5 acetate buffer was used as dissolution medium, stirred at 75 rpm, and kept at a constant temperature of 37.0 ± 0.5 °C. Sampling and automated concentration measurements were performed by using a Hanson Autoplus Maximizer 8 (Hanson Research, USA) automatic pump and an online coupled Agilent 8453 UV–VIS spectrophotometer (Hewlett-Packard, USA). 20 h long dissolution tests were performed, sampling at 5, 10, 30, and 60 min, and every 60 min afterward. A univariate calibration with $R^2 = 0.99992$ was used to determine the API concentration based on a distinctive UV absorbance peak.

Table 1
Changing material attributes and process parameters and their ranges across the different batches.

Material attribute (MA)/ process parameter (PP)	Parameter name	Unit	Parameter range
API dose	Dose	[mg]	Undisclosed
API particle size distribution	API d_{10}	[μm]	2 – 6
	API d_{50}	[μm]	10 – 18
	API d_{90}	[μm]	27 – 42
HPMC particle size distribution	HPMC PSD	[% w/w < 63 μm]	32 – 60.3
HPMC methoxy substitution	M%	[% w/w]	22.6 – 23.1
HPMC hydroxypropyl substitution	HP%	[% w/w]	8.3 – 9.2
HPMC viscosity	Visc	[mPas]	3746 – 4749
HPMC CR content	CR%	[% of HPMC content]	0 – 100
Tableting pre-compression force	Pre-CF	[kN]	1 – 3
Tableting main compression force	Main-CF	[kN]	5 – 18
Tableting force feeder speed	Feed	[rpm]	15 – 45
Tableting productivity	Prod	[1000 tablets/h]	30 – 65

2.2.4. Hardness and friability

A Pharma Test WHT-3ME fully automated 4 in 1 tablet testing instrument (Pharma Test, Germany) was applied to determine the hardness (and weight, thickness and diameter) of 20 tablets, and the average hardness was used for further calculations. Friability studies were conducted according to Ph.Eur. 2.9.7. with 6.5 g tablets per run using a Pharma Test PTF-10E friabilator (Pharma Test, Germany) with 100 rotations.

2.3. Multivariate data analysis

All data analysis was performed in MATLAB 9.8. (MathWorks, USA) using Statistics and Machine Learning Toolbox 11.7, Deep Learning Toolbox 14.0. and the PLS Toolbox 8.8.1. (Eigenvector Research, USA). Sampling for sensitivity analysis was performed using the SAFE Toolbox (Pianosi et al., 2015).

2.3.1. Principal component analysis

PCA was performed on the NIR and Raman spectra to reduce the spectral dimension and qualitatively analyze the main effects contributing to the variability of the spectra. PCA transforms the original $n \times \lambda$ size spectral dataset (n and λ referring to the number of the spectra and the spectral variables (wavenumbers), respectively) to a new coordinate, where the first few new variables (principal components, PCs) describe the variance of the dataset and keeping the PCs orthogonal to each other. Before PCA, standard normal variate (SNV) and mean centering were applied to the NIR spectra as preprocessing. Raman spectra were preprocessed by Automatic Whittaker Filter baseline correction (asymmetry parameter $p = 0.001$ and smoothing parameter $\lambda = 10\ 000$), normalization to a unit area, and mean centering.

2.3.2. Artificial neural network

Inspired by the information processing of the human brain, ANNs map the connection between input and output variables by interconnected information processing units, called artificial neurons or nodes. To achieve this, the neurons receive the inputs, an activation function weight and summarize them, and then a transfer function calculates the output. A neural network contains several neurons, organized into layers based on their role, and the information is passed through these neurons during calculation.

In this work, feedforward, fully-connected neural networks have been developed to predict the *in vitro* dissolution curve and hardness of the tablets from the process parameters or non-destructive spectroscopic data. Each ANN consisted of one input, one hidden, and one output layer. The number of neurons in the input layer corresponds to the number of input variables. ANNs with different input variable combinations were tested to obtain the best model performance, using either the MAs/PPs summarized in Table 1, the Raman spectra reduced to 3 PCs, or the NIR spectra reduced to 5 PCs. In the case of *in vitro* dissolution prediction, 23 output neurons were used, corresponding to the 23 time points of the dissolution curve, while the ANNs predicting the hardness contained one output node. The number of the neurons in the hidden layers was optimized for each ANN model, for which ANNs were systematically built, varying the number of hidden neurons between 1 and 10, with 50 repetitions. As relatively few input parameters were used, it was expected that the optimal hidden neuron number will be in the 1 – 10 range. Indeed, when the errors of the networks with different hidden neuron numbers were studied, signs of overfitting around 10 neurons were observed, proving that the optimization in this range is sufficient. The neuron number providing the lowest validation error was used in the final model. In the hidden and output neurons, tangent sigmoid and linear functions were used as transfer functions.

ANNs were trained using a dataset of known input–output (target) pairs by error backpropagation, which means adjusting the weights and biases of the neurons in an iterative calculation so that the difference between the calculated output and known target is minimized. Before

training, the weights and biases were initialized using the Nguyen-Widrow layer initialization function (Nguyen and Widrow, 1990), which contains a degree of randomness, *i.e.,* training the ANN multiple times produces different results. The training was performed using Bayesian regularization as a training algorithm for better generalization (MacKay, 1992) and the mean squared error (MSE) between the output and target as a cost function. In the case of the *in vitro* dissolution prediction models, the goodness of the models was also characterized after the model training by calculating the f_1 difference and f_2 similarity factors between the target and output dissolution curves (Costa and Sousa Lobo, 2001), which are common indicators of the agreement of two dissolution curves. Their values range between 0 and 100; the lower the f_1 and the higher the f_2 value, the better the agreement. The goodness of the ANNs predicting the hardness was evaluated by calculating the coefficient of determination and root mean square error of training (R^2_C, RMSEC) and prediction (R^2_P, RMSEP).

During ANN modeling, the randomness of the ANN model building and the fact that ANNs can result in a different model if the training dataset is slightly changing has to be tackled. Therefore, the bootstrap resampling technique with 1000 resampling was implemented, and 1000 ANN retraining was performed in the case of each ANN model. In this way, the distribution of the ANN model results and the confidence intervals could be estimated. Therefore, further in this work, the results of an 'ANN model' always refer to the average outcome of the 1000 bootstrapped submodels. The 95 % confidence interval of the results is estimated as the 2.5 and 97.5 percentiles of the 1000 repetitions.

2.3.3. Sensitivity analysis

Sensitivity analysis (SA) was performed on ANN models using the material attributes/process parameters to interpret the ANN, *i.e.*, to analyze the effect of the ANN input variables on the output variability and consequently determine and rank the importance of the variables.

The effect of the API dose was omitted from SA, as it could only take two distinct levels. Instead, SA was repeated at both dose levels separately. With the remaining 12 parameters included in Table 1, 10 000 parameter combinations were created by Latin hypercube sampling, assuming a uniform distribution of the parameters within their ranges given in Table 1. Then, the 10 000 parameter combinations were simulated using the ANN models.

Partial Rank Correlation Coefficients (PRCC) were calculated between each input variable – output pair, which describes the correlation between the input–output pairs while removing the effect of the additional input variables. The magnitude of the PRCC value characterizes the strength of the connection. Furthermore, the direction of the association is also characterized, as the sign of the PRCC indicates if the two values move in the same or the opposite direction. This is why PRCC is a widely used, robust sensitivity index applied for nonlinear relationships, but limited to monotonic relationships, as the direction could not be defined for non-monotonic relationships and could lead to misleading conclusions (Marino et al., 2008). Consequently, before SA, monotonicity tests were carried out by changing one input at a time while keeping the other parameters at their central value. The responses were analyzed in scatter plots to evaluate if the monotonicity criterium is fulfilled. In our study, no non-monotonic relationship was found. Otherwise, different SA techniques could be used, such as variance-based sensitivity analysis, *e.g.,* Sobol, eFAST, which are applicable for nonlinear, non-monotonic relationships but have a much higher computational demand (Marino et al., 2008).

3. Results and Discussion

3.1. Qualitative analysis of experimental data

A total of 224 combinations of 13 varying material attributes/process parameters (see Table 1) were available to analyze the *in vitro* dissolution, hardness, and friability of the manufactured tablets. The *in vitro* dissolution curves of 34 selected settings were measured with 5 repetitions (*i.e.*, 170 tablets were dissolved). Fig. 1 shows significant variation between these experiments, while a low standard deviation within the repeated measurements was observed. However, as multiple factors changed simultaneously, the main reasons for the variations could not be identified by visual inspection. Fig. 2 depicts the dissolution curves of five batches of the same API dose and changing main compression forces. Batch 1 and Batch 2 were prepared with 100 % DC grade HPMC, Batch 3 contained 100 % CR grade, while Batch 4 and Batch 5 contained both DC and CR grades in a 50 %-50 % ratio. Furthermore, the batches were prepared using different API and HPMC batches, causing differences in the particle size and HPMC viscosity, and substitution levels due to the raw materials' batch-to-batch variation. Fig. 2 shows that the compression force influenced the dissolution to a changing extent, as well as the used HPMC grades were suspected to be influential. Batch 1 had the fastest dissolution, which, however, could be associated with either the different API or HPMC batch. The f_1 and f_2 values are commonly used indicators of the agreement of the dissolution curves in the pharmaceutical industry; f_1 below 15 and f_2 above 50 are the acceptance limits for agreement. The calculated f_1 and f_2 values between the samples ranged between 0.8 and 32.7 and 34.8 – 96.5, respectively, *i.e.*, significant differences between the profiles were detected. The largest difference was observed between Batch 1 (7 kN) and Batch 5 (15 kN) with $f_1 = 32.7$ and $f_2 = 34.8$. Even when batches were produced with the same main compression force, unacceptable f_1 and f_2 values were obtained, *e.g.,* the f_2 values between Batch 1 (15 kN) – Batch 4 (15 kN), Batch 1 (15 kN) – Batch 5 (15 kN) and Batch 3 (15 kN) – Batch 5 (15 kN) were 46.9, 45.8, 48.2, respectively. These values indicate a high risk of producing out-of-specification tablets. Therefore, it was aimed to identify the main factors causing the variation in the dissolution profiles by mathematical modeling and develop a method to predict the quality of the tablets for real-time release testing and optimization purposes.

Besides the *in vitro* dissolution, the hardness and friability of the tablets are also important quality attributes, so their variation along the 224 settings was also studied (see Fig. 1). The hardness showed a significant variation between approx. 40–110 N with an average of 75 N, and the friability changed between 0 and 0.2 %. Generally, the friability should not exceed 1 % for directly compressed tablets, therefore, it could be concluded that the friability stays well below the acceptance criteria and was not further studied.

Previous studies have shown that NIR and Raman spectra can be effectively used for predicting the *in vitro* dissolution of tablets if the critical material attributes/process parameters impacting the dissolution can be detected by spectroscopy (Galata et al., 2019; Galata et al., 2021; Nagy et al., 2019). Therefore, the NIR and Raman spectra of the 170 dissolved tablets were recorded before the *in vitro* dissolution tests, and the spectral variability was studied by PCA modeling. The NIR and Raman PCA models using all the measured spectra indicated that the major spectral variance is caused by having two API doses. Therefore, PCA models using a single dose were also built. As for the PCA model of the Raman spectra, the first three PCs were associated with 85.97, 1.24, and 1.10 % variance, respectively, while further PCs were deemed negligible with variances below 1 %. Observing the samples in the three-dimensional principal component space (Fig. 3.a), samples from Batch 1 and Batch 2 (green squares in Fig. 3.a) showed significant variability in the direction of PC 1, which might be caused by the difference in the PSD of API batches. The samples were clustered based on the HPMC grade in the PC 2 – PC 3 plane. Consequently, Raman spectroscopy is expected to be suitable for RTRT of the *in vitro* dissolution if the API PSD and the HPMC grade are CMAs of the dissolution. As for the PCA model of the NIR spectra, PC 1 accounted for 98.89 % variance. However, it could not be associated with any known process parameters or material attributes, but it reflected the difference in measurement days; therefore, it is not depicted in Fig. 3. PC 2 accounted for 1.01 % variance, where the clustering of the samples based on the changing pre- and main

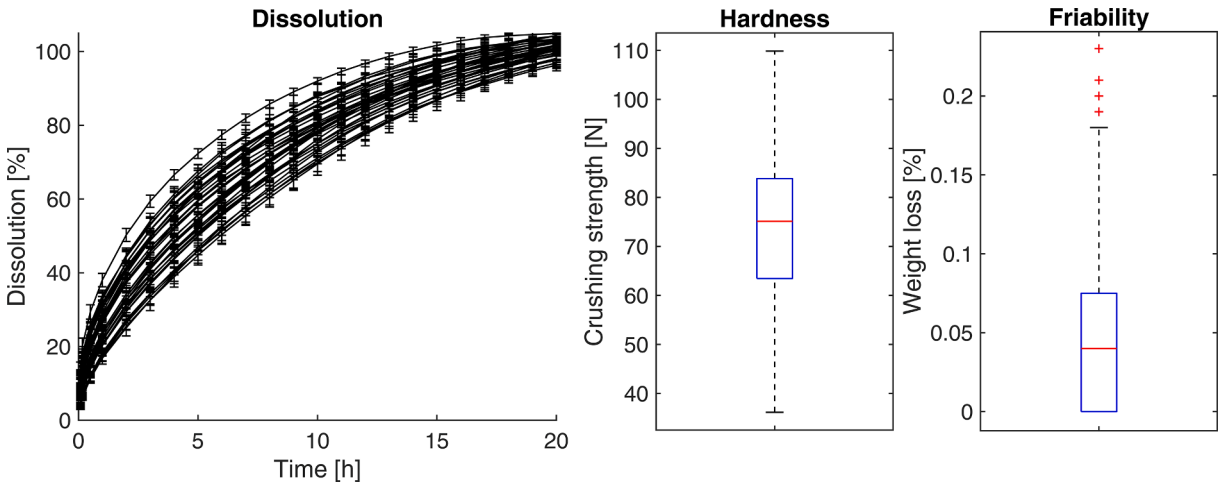

Fig. 1. Variability of quality attributes of the studied tablets.

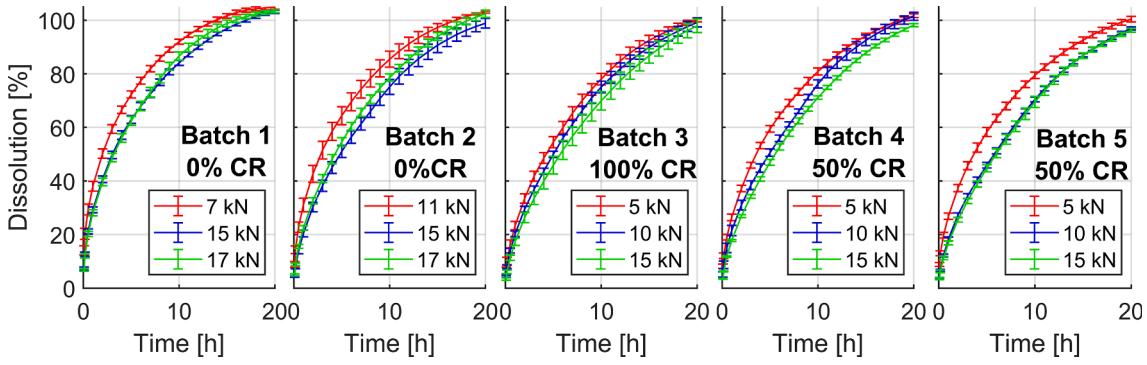

Fig. 2. *In vitro* dissolution of 5 tablet batches, with different main compression forces.

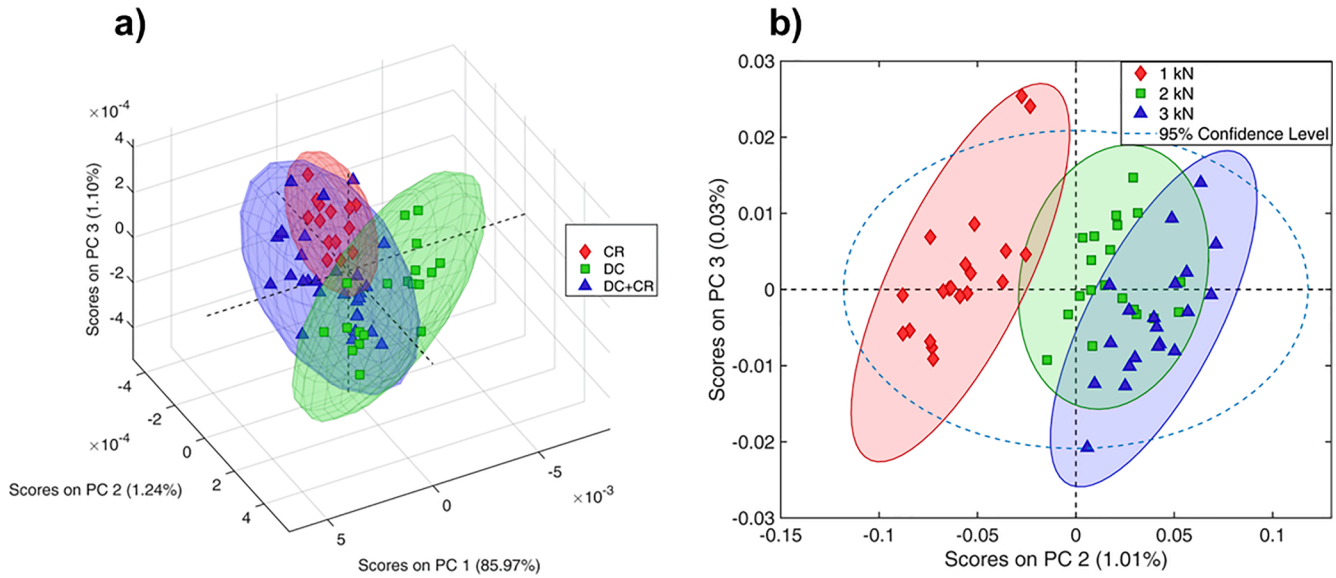

Fig. 3. PCA score plots of a. Raman spectra, samples colored based on the HPMC grades, b. NIR spectra, colored based on the pre-compression forces, with 95% confidence ellipses.

compression forces was observed (in Fig. 3, only the change per the pre-compression force is visualized, and the main compression force changed proportionally). Consequently, NIR spectroscopy might be used to reflect differences in the *in vitro* dissolution when the main CPP is the tablet compression force.

3.2. *Development of the ANN models*

Several ANNs were built with different input variables to find the best approach for predicting the *in vitro* dissolution profile. From the 34 tableting settings (170 tablets), 8 settings (40 tablets) were separated for

validation purposes, and the models were built and optimized using the remaining 24 settings (130 tablets) as a training set. The 8 selected validation samples belonged to 6 different batches (Batch 1, 2, 4, 5, plotted in Fig. 2), as well as Batch 6, 7, which were manufactured as validation batches during the pilot development). The CMAs and CPPs of the validation samples varied, *e.g.*, CR% was either 0 or 50 % CR%; Main-CF changed between 7 and 15 kN), and the batches were manufactured with different API and HPMC raw material batches. The measured dissolution profiles are depicted in Fig. 4.

Table 2 summarizes the characteristics of the models. *ANN 1 – ANN 3* models were built using different combinations of the material attributes/process parameters summarized in Table 1. The subset of parameters used for *ANN 3* was selected based on sensitivity analysis (see Section 3.3 for details). When both CR and DC grades of HPMC were used in the tablet, the related MAs (viscosity, M%, HP%, PSD) were calculated as the mass fraction-weighted average of the two excipients. In *ANN 1,* only these MAs were used to characterize the effect of HPMC, while in *ANN 2*, the mass fraction of the CR grade was also used as input. Additionally, models using the NIR (*ANN 4*) and Raman (*ANN 5*) PC scores were also built, and using the hardness as a fast in-process control measurement as a surrogate of dissolution was also tested (*ANN 6*). The individual dissolution curve of each tablet was used as a target value. When ANNs with Raman, NIR spectra, and hardness (*ANN 4 – ANN 6*) were built, the inputs were also individual, as the spectra could be clearly assigned to the given tablets. When PPs, MAs were used as inputs (*ANN 1 – ANN 3*), only the average values for the batches were available; therefore, the inputs were these average values. However, as it can be seen, *e.g.,* in Fig. 2, the standard deviation of the tablets within a batch is low; therefore, it did not significantly increase the fitting error.

It is apparent from Table 2 that *ANN 6* resulted in the lowest f_2 value both for the training and validation, followed by the model based on the Raman spectra. The NIR spectroscopic technique outperformed the Raman method but still resulted in significantly lower f_2 than the models using the MAs/PPs. *ANN 2* resulted in the best training accuracy (f_2 = 96.58), while the best validation performance was obtained when only the most significant factors were selected (see Section 3.3 for details) as inputs.

In Fig. 4, the measured and predicted *in vitro* dissolution curves of the validation samples can be compared. It can be observed that there is a significant variation in the measured dissolution curves of the validation samples, which was best captured by the *ANN 1 – ANN 3* models (*ANN 2* and *3* provided visually the same results; therefore, only *ANN 2* is plotted). *ANN 5* and *ANN 6* basically predicted the average dissolution curve of the studied dataset, *i.e.*, they were not capable of predicting the changing dissolution curves appropriately, *e.g.*, identifying out-of-specification tablets. *ANN 4* performed better to an extent, implying that the NIR spectra capture the critical MA/PP affecting the dissolution better than the Raman spectra. Comparing the order of the measured and predicted dissolution curves, it is also visible that the *ANN 2* and *3* predictions agreed with the target, *e.g.*, it indicated well that the Valid 2 and Valid 8 samples had the fastest release, while Valid 5 had the most extended dissolution. The good agreement between the measurements and predictions is also apparent when plotting the measured and predicted dissolution curves of each validation sample individually (Fig. 5).

Based on these results, it can be stated that by registering the MAs of the raw materials and the tableting parameters, the *in vitro* dissolution of the tablets could be predicted non-destructively, without the need for any analytical measurement of the tablets. This could significantly contribute to more consistent product quality and reduce waste.

ANN 7 and *ANN 8* models were built to predict the hardness of the tablets from the MAs/PPs. The obtained regression curve of *ANN 8* is illustrated in Fig. 6, where the input parameters of *ANN 8* were selected based on sensitivity analysis (see Section 3.3 for details). The model resulted in 2.71 and 3.50 N RMSEC and RMSEP values, respectively, which are deemed sufficient to predict potential problems in the tablet quality.

3.3. Interpretation of the ANN models by sensitivity analysis

ANN 2 and *ANN 7* were further studied by SA to investigate how the input MAs/PPs affect the dissolution profile and hardness. SA enables the interpretation of the ANN, which can be crucial both from the modeling perspective to increase credibility and support the process and product understanding.

Before SA, it was checked if the monotonicity criterium for utilizing the PRCC measures was fulfilled. The inputs showed monotonicity in the studied ranges while keeping the other parameters at their central value. Consequently, the 10 000 combinations of the input parameters created by the Latin Hypercube sampling were simulated using the trained *ANN 2* and *ANN 7* models, and the PRCC measures were calculated. It is worth mentioning that the 10 000 parameter combinations could be simulated in approx. 1 – 2 min (using GPU acceleration with an NVIDIA GeForce 930MX GPU), *i.e.*, the ANN model could be a powerful tool to generate virtual DoEs and to make real-time predictions and optimizations.

The SA was repeated for the two API doses separately, but no difference was observed between the outcome of the SA; therefore, it was concluded that the API dose does not significantly influence the importance of the other parameters. The mean value of the PRCC and the width of the confidence interval – calculated based on the 1000 replicated ANN models – are important indicators of the sensitivity of

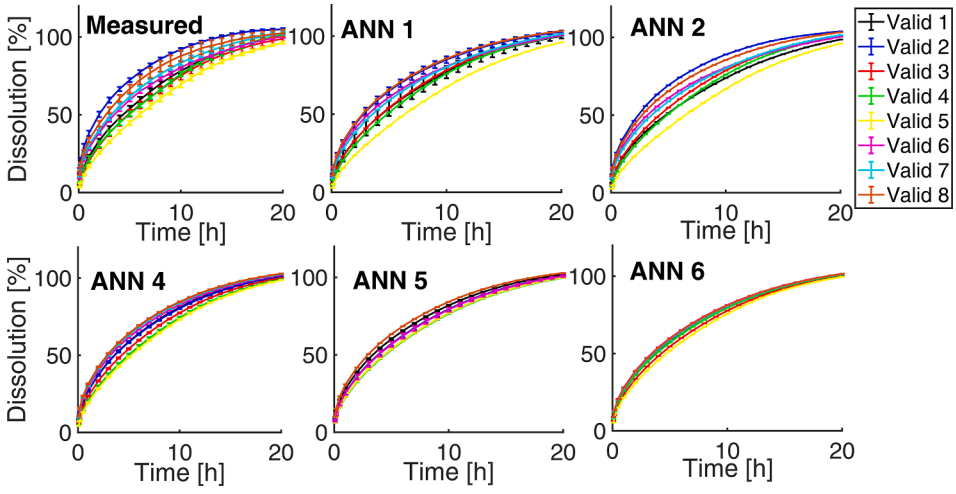

Fig. 4. Measured and predicted validation samples with the different models.

Table 2
Properties of the developed ANN models.

Output: In vitro dissolution curve (Dissolution % at 23 time points)						
Model name	**Input data**	**No. of hidden neurons**	**Training f_2**		**Validation f_2**	
ANN 1	12 MA/PP	4	96.49		83.79	
ANN 2	(Table 1 without CR%) 13 MA/PP parameters	5	96.58		82.49	
ANN 3	(Table 1) Main-CF, HPMC PSD, CR%, HP%, M%	6	93.61		85.54	
ANN 4	NIR (5 PCs)	2	84.17		77.43	
ANN 5	Raman (3 PCs)	1	77.72		74.40	
ANN 6	Hardness	1	76.13		70.48	
Output: Hardness (N)						
Model name	**Input data**	**No. of hidden neurons**	**R_C^2**	**RMSEC [N]**	**R_P^2**	**RMSEP [N]**
ANN 7	13 MA/PP parameters	2	0.9654	2.83	0.9447	3.79
ANN 8	(Table 1) Main-CF, Feed, Visc, HPMC PSD, CR%	4	0.9686	2.71	0.9538	3.50

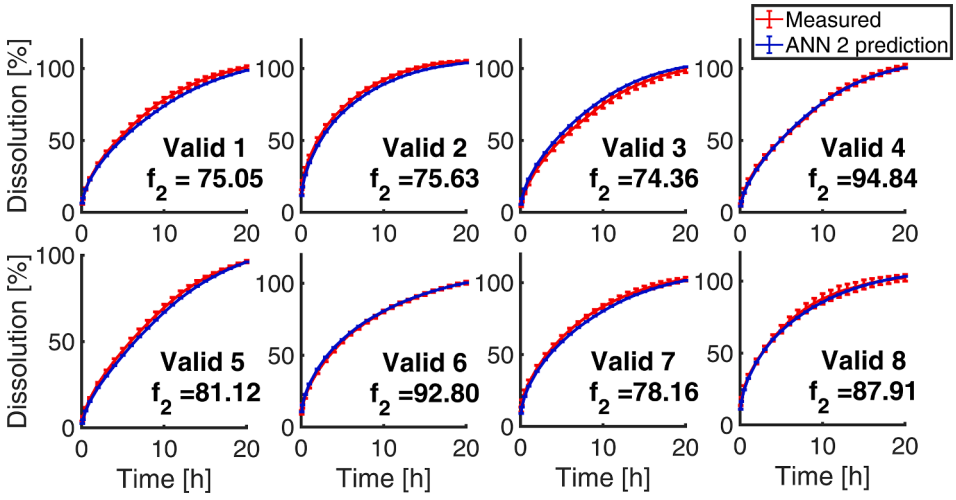

Fig. 5. Measured and predicted by ANN 2 model *in vitro* dissolution curves of the validation samples.

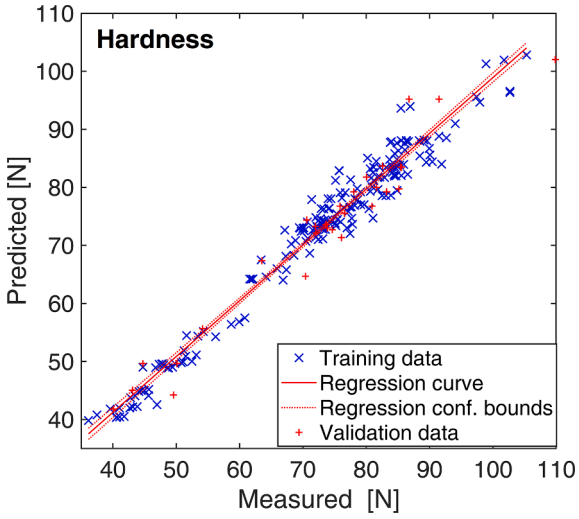

Fig. 6. Regression curve of ANN 8.

the input parameters. Due to the empirical nature of the training, networks with different weights can result in the same output. Therefore, wide confidence intervals can be obtained for a given input if the weights connected to the input can take random values. That is, a wide confidence interval also indicates that the input variable – in the range of the study – is not an important parameter for model fitting, and its influence on the modeled output (*i.e.*, dissolution, hardness) is uncertain. However, the confidence interval can also incorporate the uncertainty caused by the limited training data. Therefore, expanding the training dataset could decrease the confidence intervals of the PRCC values, but mainly for those parameters that have great importance in the model.

As for the dissolution model, the PRCC values and their confidence intervals could be calculated for each of the 23 dissolution time points, among which the 1, 5, 10, and 20 h points are illustrated in Fig. 7. Conducting the SA for the individual time points of the dissolution profile enables us to draw conclusions from the dynamic changes of parameter importance throughout the dissolution process, which could even reflect the mechanism of the process. The obtained coefficients for *ANN 2* revealed that the main compression force (Main-CF), the particle size of the HPMC, and the percentage of the CR grade are the most influential factors throughout the dissolution curve. The sign of the PRCCs corresponds to the expectations, *i.e.*, increasing the Main-CF decreases the dissolution rate. Moreover, increasing the HPMC particle size (*i.e.*, decreasing the HPMC fraction with particle size below 63 μm) and the CR% increase the dissolution rate. As for the dynamic of the parameter importance, the hydroxypropyl substitution (HP%) appears

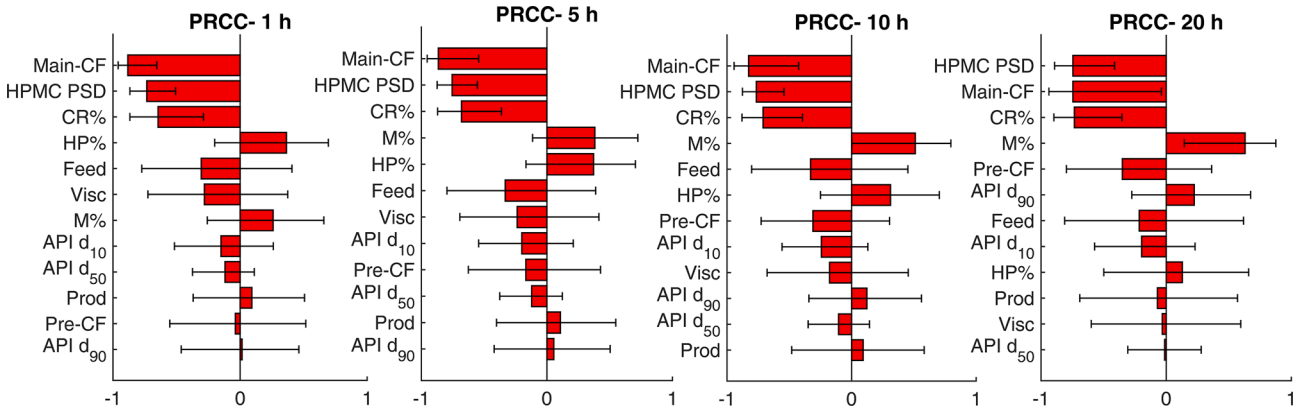

Fig. 7. Effect of the input parameters on the 1, 5, 10, and 20 h dissolution values.

as the fourth most important factor at the beginning of the dissolution, but in the end, it merges into the insignificant factors. The effect of the Main-CF is also decreased by the end of the dissolution process. These observations could be associated with the formation of the retarding gel in the initial phase of the dissolution, hence aiding the understanding of the product. Furthermore, the results can assist the definition of the specification limits of the critical MAs. For example, the API particle size distribution appears to be insignificant, which indicates that – from the perspective of the dissolution – wider specification limits could be set for the API PSD, which is an essential technological benefit for the API production, *e.g.*, crystallization steps. In contrast, the results showed that controlling better the PSD of the HPMC is a crucial factor in decreasing the undesirable batch-to-batch variability of the dissolution. Furthermore, the SA highlights the importance of controlling the HP% and M%, which are often overlooked MAs, although they can vary batch-to-batch even when using the same supplier. The acceptable ranges of these parameters could be calculated using the ANN model, where the CQA (here, the dissolution profile and hardness) comply with the regulatory or technological requirements.

The SA of the *ANN 7* model was also performed to rank the sensitivity of the hardness to the input variables. As expected, the study showed (see Fig. 8) that increasing the main compression force has the most pronounced effect on increasing the hardness. Following the Main-CF, it was found that a slower rotation of the force feeder significantly increases the hardness, which also corresponds to the observation of previous studies (Narang et al., 2010; Wünsch et al., 2020) and has been mainly attributed to shear effects. The CR% and the HPMC viscosity also

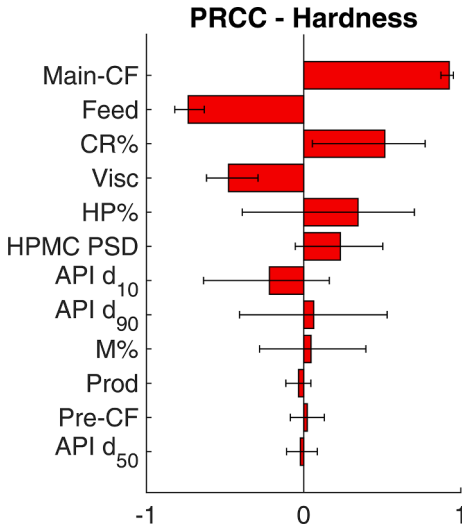

Fig. 8. Effect of the input parameters on the hardness.

impacted the hardness, which has also been reported (Nokhodchi et al., 1996). Nokhodchi *et al.* associated the higher viscosity of HPMC with less plasticity, resulting in worse deformation and consequently weaker tablets.

Based on the SA results, it can be concluded that the application of SA on the ANN models provides multiple benefits. First of all, it greatly increases the interpretability of the model. As the results show, the ANNs captured genuine physical relationships between the MAs/PPs, which, from the technological point of view, increases the process and product understanding and aids the selection of the CMAs and CPPs from the list of the potential parameters. Furthermore, it can be an essential part of the risk analysis and setting the specification limits.

From the modeling perspective, the interpretability increases the method's reliability, which could also serve as additional insurance of validity for the regulatory. SA could also be used as a variable selection method as *ANN 3* and *ANN 8* were built using only the most important inputs (see Table 2). The selection was made by visually analyzing the PRCC plots, choosing the first few relevant parameters with large PRCC values and relatively small confidence intervals. In this way, the cut-off point is somewhat subjective, but when the choice is not straightforward, models could be built with different numbers of parameters to find the most optimal subset. *ANN 3* and *ANN 8* resulted in the best prediction performance, which indicates that no relevant factors were omitted, and the generalization capability of the models was improved. In addition, using fewer input variables also decreases the computational time, which could be beneficial in a real-time application.

In light of the SA, the performance of the *ANN 4 – 6* models could also be better understood. As the PCA results (Section 3.1) showed, the Raman spectra mainly capture the effect of the API PSD, which is, however, not a CMA, *i.e.*, *ANN 5* did not yield satisfactory results. *ANN 4* gave a marginally better result as the NIR spectra were affected by the compression force, the main CPPs. It is worth noting that the spectroscopy-based surrogate modeling could be used either for immediate or controlled-released formulations, as they do not directly measure the dissolution profile itself, but the CMAs/CPPs affecting the dissolution. It is demonstrated by the results, that for a successful surrogate dissolution model, the important criterium is that the variation of the CMA/CPP could be detected by the spectroscopic technique. The hardness could also not be utilized as a good surrogate of dissolution, as different CMAs and CPPs impact them. Consequently, a proposed RTRT model could use the compression force (*e.g.*, registered in-line) and the CMAs of the HPMC (HP%, M%, PSD). If segregation might occur during manufacturing, an in-line PSD measurement and a method for measuring CR% in real-time might be necessary.

The pilot scale developmental data used in this work has provided us with an unstructured dataset compared to a factorial DoE generally used for QbD studies. This entails that the factors (inputs) are not orthogonal to each other, *i.e.,* the dataset is not balanced to ensure that all levels and

factors are considered equally. This can cause additional uncertainty, especially for limited-sized data, and interactions of some inputs might not be sufficiently explored. Furthermore, some inputs might not be independent variables from each other. However, it is also worth noting that conducting and analyzing factorial DoEs also get more limited and complicated when a large number of inputs need to be accounted for, due to the increasing number of required experiments and the confounding factors. In contrast, ANNs – as the presented results demonstrate – can easily tackle data with many potential input values. Moreover, they can effectively capitalize on continuously growing datasets (*e.g.*, manufacturing data) to become increasingly accurate in the range of the operation. As digitalization is getting more prevalent in the pharma industry, such unstructured datasets are getting more widespread, which could become a valuable source of information by using interpretable ANNs, without any additional experimental burden. Furthermore, if deemed necessary, the results of the interpretable ANN could be further used to construct a factorial DoE with the selected most important inputs.

3.4. Using ANN models for manufacturing optimization

As the SA showed, the changing MAs of the HPMC batches significantly influence the *in vitro* dissolution and hardness, causing undesirable batch-to-batch variability, *i.e.*, inconsistent product quality. One possible solution to avoid this would be setting stringent specification limits for these CMAs, which, however, could increase the cost of the raw material or even result in supply problems. Instead, by embracing the possibilities provided by the QbD approach, the critical process parameters could be flexibly set to compensate for the changing CMAs.

The developed ANN models could be utilized coupled with an optimization algorithm to predict the optimal process parameters. This approach was demonstrated by studying the dissolution and hardness of two batches by *ANN 3* and *8*. Both batches contained different DC and CR grade HPMC batches, which properties are summarized in Table 3. *ANN 3* predicted significantly different dissolution profiles when the tableting parameters were kept constant (at 15 kN Main-CF, 50 % CR%, and 25 rpm Feed), as illustrated in Fig. 9.a, and *ANN 8* predicted 95.2 and 89.2 N hardness for Batch 1 and 2, respectively.

Based on the SA, the dissolution was influenced by the HPMC PSD, HP%, and M%, which are dictated based on the available raw material, while the Main-CF and CR% could be flexibly varied. As for the hardness, the HPMC PSD and Visc are fixed input factors, while the CR% and the Feed could be varied to achieve the required hardness. Consequently, the Main-CF, CR%, and Force had to be optimized to achieve the required target dissolution profile and acceptable hardness. For this, the *fmincon* function of MATLAB was used, where the objective was to maximize the f_2 value (*i.e.*, minimize the 100- f_2 objective function) between the simulated and target dissolution profile. In this work, the target dissolution profile was defined as the average dissolution profile of the training dataset used for the model building, but arbitrary targets could be defined based on, *e.g.*, technological, *in vivo* performance, or bioequivalence considerations. The hardness was used as a constraint to keep its value between 50 and 70 N. The optimal values of Main-CF, CR %, and Force were searched between the 5–20 kN, 0–100 %, and 15–45 rpm bounds, respectively.

Table 3
Properties of HPMC batches used in the optimization study.

	Batch 1		Batch 2	
	DC grade HPMC	CR grade HPMC	DC grade HPMC	CR grade HPMC
PSD	32	60.3	43	56.3
Visc.	3826	3746	4232	4749
HP%	8.8	8.8	8.3	9.2
M%	23.1	22.6	23.1	23.1

Table 4 summarizes the optimization results, and Fig. 9.b illustrates the dissolution profiles predicted using the optimized process parameters. Fig. 9 clearly shows that it is possible to reach the required dissolution profile by modifying the tableting parameters, and the differences caused by the different HPMC batches could be efficiently eliminated. Using fixed parameters, Batch 1 and 2 provided f_2 values of 61.19 and 52.12 with the target dissolution, which could be significantly increased by the process optimization to 95.21 and 98.80, respectively. Moreover, the hardnesses of the two batches are also predicted to be 60.0 N. The optimization resulted in a significantly different CR – DC ratio to compensate for the different CMAs, while the Main-CF was only marginally different. The force-feeding rate could be set with a 10 rpm difference to achieve consistent hardness. Consequently, it can be concluded that using flexible manufacturing parameters permitted by the QbD principles and ANN-based optimization can significantly contribute to achieving consistent product quality.

4. Conclusions

In this work, ANN models were successfully developed to characterize the *in vitro* dissolution profiles and hardness of direct compressed extended-release tablets using an existing dataset accumulated during pilot-scale development. Using the raw material attributes and process parameters, these CQAs could be effectively predicted, and the batch-to-batch variability captured. The results showed that ANNs could effectively tackle unstructured, *e.g.*, historical data without needing a dedicated DoE, which shows its potential for Pharma 4.0. applications as the available manufacturing and developmental data are drastically growing due to the digitalization efforts.

Although ANNs are often deemed as inscrutable black boxes, the results of this study show that coupled with the sensitivity analysis, ANNs could be interpreted, *i.e.*, could be associated with genuine physical relationships between the CMAs/CPPs and CQAs. The presented methodology is not specific to direct compression and the prediction of dissolution or hardness but can be applied as a general framework to characterize arbitrary CQAs in data-rich processes from the drug synthesis steps to the final product manufacturing. It was demonstrated that this methodology not only enhances the models' credibility but also increases the process knowledge, contributes to risk analysis, to establish specification limits and control strategies, ensuring consistent product quality. In this way, interpretable ANNs can embrace the QbD and PAT concepts, using the ever-increasing databases of pharmaceutical development and manufacturing, which could become a goldmine of process knowledge with adequate data processing.

CRediT authorship contribution statement

Brigitta Nagy: Conceptualization, Methodology, Software, Writing – original draft, Visualization, Funding acquisition. **Ágnes Szabados-Nacsa:** Investigation, Resources, Data curation, Writing – original draft. **Gergő Fülöp:** Project administration, Writing – original draft. **Anikó Turák Nagyné:** Investigation, Resources. **Dorián László Galata:** Formal analysis, Writing – review & editing. **Attila Farkas:** Formal analysis, Writing – review & editing. **Lilla Alexandra Mészáros:** Formal analysis, Software, Writing – review & editing. **Zsombor Kristóf Nagy:** Writing – review & editing, Supervision, Funding acquisition. **György Marosi:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

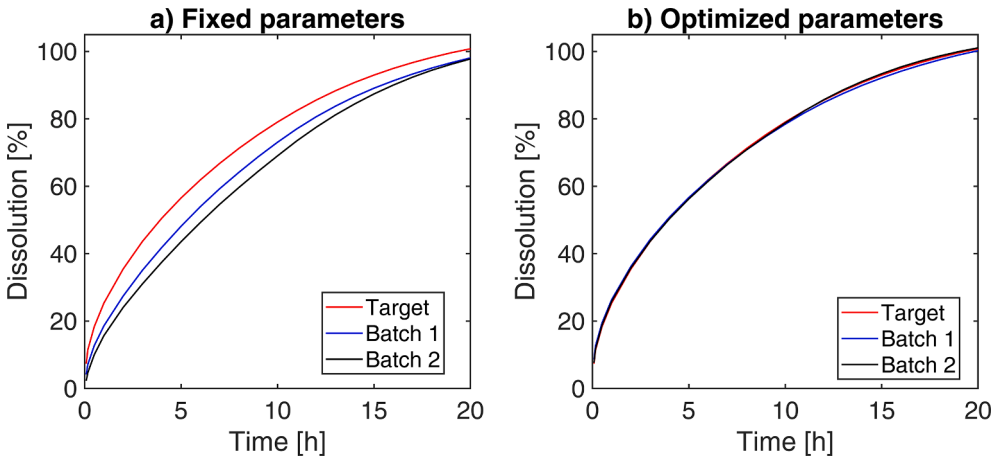

Fig. 9. Dissolution profiles with (a) fixed process parameters and (b) parameters optimized by ANN.

Table 4
Tableting parameters and process outcome with fixed and the optimized flexible operational parameters.

	Batch 1		Batch 2	
	Fixed process	Optimized process	Fixed process	Optimized process
Main-CF [kN]	15	6.9	15	7.2
CR% [w/w %]	50	48.3	50	15.0
Feed [rpm]	25	30.6	25	21.9
f_2 with target dissolution	61.19	95.21	52.12	98.80
Hardness [N]	95.2	60.0	89.2	60.0

Data availability

The data that has been used is confidential.

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