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Mathematical modeling for the quality assurance of continuous pharmaceutical manufacturing processes

Summary of Ph.D. Thesis

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1. INTRODUCTION

The new century has brought a paradigm shift in the pharmaceutical industry, aiming for more efficient and agile drug development and manufacturing. To achieve this, continuous pharmaceutical manufacturing has received increasing attention as one of the key elements in the modernization of the pharmaceutical industry, thanks to its advantages over batch processing, such as eliminating scale-up problems and hold-up times between steps or decreasing safety hazards and the time to market[1]. As a result, most of the widely used unit operations have now continuous alternatives, but there are still limited examples of the operation of fully integrated, end-to-end continuous manufacturing lines. To ensure the system-wide performance of a continuous manufacturing process while providing the required product quality, the entire process must be monitored and controlled in real-time to compensate for the process variations. Consequently, the conversion from batch to continuous manufacturing also entails the necessity of changing the current quality assurance approaches. Addressing these challenges, the Process Analytical Technology (PAT)[2] and Quality by Design (QbD)[3] initiatives emerged over the last few years to support the design, analysis and control of critical quality attributes (CQAs) of the pharmaceutical processes through timely measurements. Based on the thorough understanding of the processes, a real-time release (RTR)[4] strategy also becomes viable, which is based on the combination of the process knowledge and in-process analysis to demonstrate that the product conforms with the specifications, without the need for the end-product quality tests.

These new concepts require the implementation of several modern techniques, such as big data analytics, artificial intelligence, and digital twins, which also leads to the ever-increasing importance of mathematical modeling. Consequently, mechanistic (first principles) or empirical (data-based) mathematical models play a central role in the operation of continuous manufacturing lines and the realization of the QbD and PAT initiatives[5]. Mechanistic models provide a more detailed description of the process and are applied primarily for obtaining process knowledge and developing design space. However, a trend toward empirical models is noticeable as the implementation of QbD progresses toward its last building blocks (control of the process), where, from the regulatory perspective, the models bear a higher impact. However, it has been also recognized, that the risk analysis methods and the different types of design of experiments (DoEs) are the most widely used method and the common practice is to consider each unit operation separated, therefore the understanding of a full continuous line as a whole is still very limited[6].

The literature review of upstream pharmaceutical manufacturing also confirmed that the application of relatively simple factorial designs is the most prevalent in the field of continuous synthesis, but the development of kinetic models is also getting more attention as it enables the integrated modeling of the downstream (*e.g.* crystallization) process steps. In the case of

[1] Lee, S. L et al. *Journal of Pharmaceutical Innovation* **2015**, *10*, 191.
[2] FDA. Guidance for Industry: Pat – a Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. **2004**.
[3] ICH. Quality Guideline Q8 Pharmaceutical Development, **2009**.
[4] EMA. Guideline on Real Time Release Testing (Formerly Guideline on Parametric Release), **2012**.
[5] Djuris, J.; Djuric, Z. *International Journal of Pharmaceutics* **2017**, *533*, 346.
[6] Grangeia, H. B. et al. *European Journal of Pharmaceutics and Biopharmaceutics* **2020**, *147*, 19.

crystallization studies, population balance models (PBM) coupled with mass and energy balances are appearing far more common than statistical DoE models, and the publications indicate a trend toward the more detailed models[7].

Overall, the literature on API crystallization reflects the maturity of the mathematical methods of the continuous crystallization step, while the subsequent filtration and drying processes are less studied areas, both from the experimental and modeling perspective. This is mainly associated with its less established technologies and the lack of industrial-scale, off-the-shelf equipment[8]. The continuous filtration studies mostly present experimental approaches with limited mathematical insight, and even for the batch operations mainly data-based modeling can be found. Most commonly Darcy's equation combined with the Carman-Kozeny permeation theory is applied to estimate the filtration rate, the cake and media resistance based on experimental data.

Considerable gaps can be found in the integrated modeling of upstream processing, too. For example, in most of the crystallization studies, a predefined model mother liquor is prepared by adding API into a given solvent, which is rarely a reality in an integrated continuous synthesis-crystallization process[7]. Studies aimed for the development of a continuous flowsheet model of synthesis, extraction, crystallization and filtration[9] with the aim of process control, dynamic optimization, or techno-econometric analysis. In these cases, the complexity of the developed models was found to lagging behind that of the standalone unit steps, and as for the filtration, the effect of varying crystal size distribution (CSD) has been rarely accounted, yet.

Continuous downstream manufacturing is also extensively studied, and the critical quality attributes of the final dosage forms (*e.g.* tablets) are of major interest in these studies. To ensure the quality of the product, NIR and Raman spectroscopy coupled with chemometric data evaluation techniques has emerged as potential analytical techniques to provide RTRT alternative, and Principal Component Analysis (PCA) and Partial Least Squares (PLS) regression are becoming routine techniques for the spectral analysis. It was also demonstrated that machine learning techniques, such as artificial neural networks (ANN) can provide similar accuracy and robustness but have the advantage of being more adaptable to new data and requiring minimal pre-processing[10].

While the real-time analysis of dosage strength and content uniformity by NIR and Raman spectroscopy is straightforward and already widely applied, the quality assurance could greatly benefit from an RTRT alternative of the physical properties of tablets (*e.g.* crushing strength) and the dissolution profiles, for which Raman spectroscopy has not been applied before. Both properties are affected by several critical material attributes and process parameters, such as the composition of the tablet, blending efficiency, or tableting force. Previous studies have shown the importance of the lubrication properties in continuous tablet manufacturing[11], but no PAT study has been performed so far to analyze the impact of lubrication in a continuous

[7] Wood, B. et al. *Organic Process Research & Development* **2019**, *23*, 122.
[8] Simon, L. L. et al. *Current Opinion in Chemical Engineering* **2019**, *25*, 114.
[9] Diab, S.; Gerogiorgis, D. I. *Pharmaceutics* **2020**, *12*, 235.
[10] O'Mahony, N. et al. Small-scale Intelligent Manufacturing Systems (SIMS), 2018 2nd International Symposium, 2018; p 1.
[11] Taipale-Kovalainen, K. et al. *European Journal of Pharmaceutical Sciences* **2018**, *115*, 1.

manufacturing line. As for the *in vitro* dissolution, its potential surrogate modeling is a widely used example for RTRT, yet its modeling methodology is not yet established[12].

Based on the identified gaps regarding the plant-wide integrated continuous processes and real-time release testing strategies, the **main objectives of this work** were set:

- **to develop a mechanistic filtration model** that enables predicting the filterability of slurries coming from a crystallizer, especially by focusing on the varying crystal size distribution.
- to apply the filtration model for the **characterization of the operation of an integrated continuous crystallizer and continuous filtration device** the first time.
- to develop a **flowsheet model for an integrated upstream manufacturing process** based on experimental data of continuous unit operations. We aimed to gain a better understanding of the integration and the operation of the integrated processes and to enable the **digital design of the final product quality (*in vitro* dissolution) by mechanistic modeling.**
- to analyze the effect of the **lubrication during continuous blending and tableting** and to investigate the **real-time release testing possibilities in a continuous blending-tableting** process with emphasis on the lubrication properties using Raman and NIR spectroscopy.
- to systematically examine and compare the possibilities of the empirical modeling of the *in vitro* dissolution using spectroscopic data. We also aimed to test the **applicability of ANNs** for this purpose the first time.

2. EXPERIMENTAL AND MODELING METHODS

2.1. Flowsheet modeling of integrated upstream processing

The fully integrated continuous upstream manufacturing of acetylsalicylic acid (ASA) was studied and modeled based on previously developed continuous technologies. The two-step flow synthesis[13] consisted of the acetylation of salicylic acid (SA) with acetic acid (AA) and the subsequent quenching of the reaction mixture with ethanol, performed in tube reactors. The reaction mixture was crystallized in a 235 ml mixed-suspension, mixed-product removal (MSMPR) crystallizer[14] using a combined cooling- antisolvent crystallization, and the filtration experiments were performed in a CCF20 (Alconbury Weston Ltd., UK) continuous filter device[15]. The dissolution of ASA powders and capsules with different CSDs was performed using a USP II dissolution test in 0.1 N HCl dissolution medium with a 2 h long measurement time.

The synthesis steps were modeled using rate law equations of the reactions and the continuous reactors were described using the tank-in-series approximation with 4 continuously stirred tank reactors. The crystallization was described using a PBM, accounting for the secondary nucleation, crystal growth and agglomeration, while in the case of the in vitro dissolution modeling, a PBM with a dissolution term was used. The filtration model was

[12] Zaborenko, N. et al. *The AAPS Journal* **2019**, *21*, 32.
[13] Balogh, A. et al. *Chemical Engineering Journal* **2018**, *350*, 290.
[14] Tacsi, K. et al. *Crystal Growth & Design* **2020**, *20*, 4433.
[15] Domokos, A. et al. *International Journal of Pharmaceutics* **2020**, *581*, 119297.

developed using Darcy's equation, coupled with the calculation of the specific cake resistance using the Endo-Alonso equation[16], and the calculation of the cake porosity based on a random packing theory[17]. The models for the unit operations were developed and the parameter estimations were performed in MATLAB R2020a (MathWorks®, USA), the integrated flowsheet simulation was implemented in Simulink 10.1 (MathWorks®, USA).

The integrated crystallization and filtration process was studied separately from the synthesis and dissolution units, using a virtual 46-point design of experiment (DoE) to analyze the effect of the slurry solid concentration, CSD, flow rate and the filter rotation time and pressure difference. Validation simulations were also performed to compare the model with the experiments. The integrated flowsheet model is depicted in **Figure 1**, which was utilized for optimization and sensitivity analysis, where the temperature of the reactors and crystallizer, the amount of reagents and the antisolvent and the residence time were studied. Morris sensitivity analysis was performed to analyze the effect of the operational parameters and 11 kinetic parameters on critical quality attributes such as productivity, mean particle size and dissolution time.

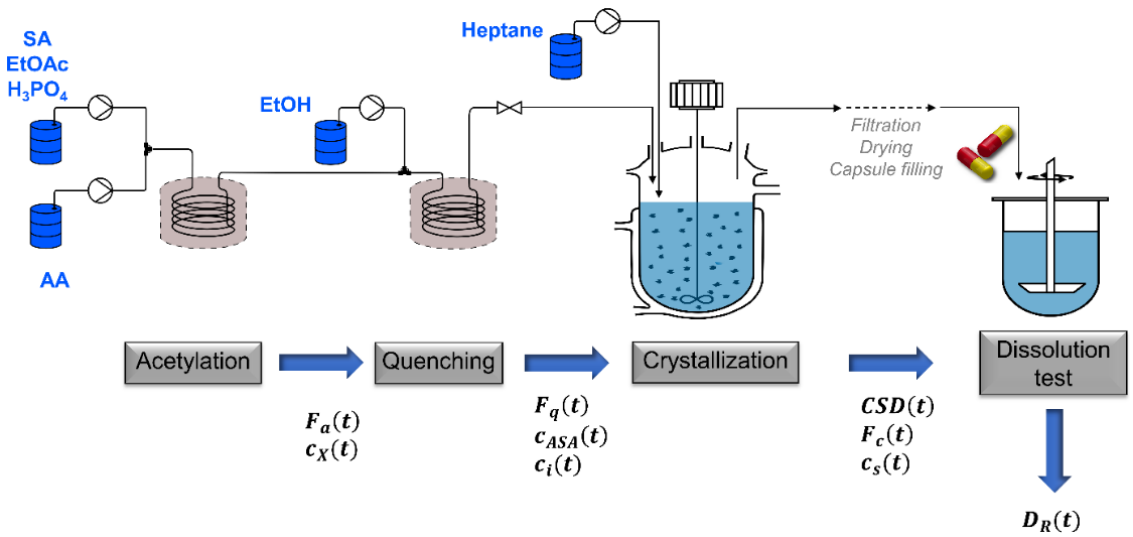

Figure 1 *Dynamic flowsheet model of continuous ASA production.*

2.2. PAT in an integrated continuous powder blending and tableting process

A two-step continuous powder blending and tableting manufacturing line was used to manufacture 250 mg direct compressed tablets containing 5 % w/w anhydrous caffeine as API, 2 % w/w magnesium stearate (MgSt) as lubricant and glucose monohydrate as filler with a 15 kN target compression force. A continuous twin-screw blender was used to blend the caffeine and glucose, and the addition of the MgSt was tested either as a pre-blend with glucose (*Cont 1* experiment) or just before the tableting of the blend (*Cont 2* experiment). The effect of lubrication was studied in a batch study in a 16-point face-centered composite DoE, where the amount of the MgSt, the lubricant mixing time and the compression force of the tablets were

[16] Endo, Y.; Alonso, M. *Filtration & Separation* **2001**, *38*, 42.
[17] Ouchiyama, N.; Tanaka, T. *Industrial & Engineering Chemistry Fundamentals* **1986**, *25*, 125.

used as factors. The reflection and transmission Raman and NIR spectra, the dissolution curve, the crushing strength and friability of the tablets were measured for both the batch and continuous tablets. The NIR spectra were measured using a Bruker MPA Multi-Purpose FT-NIR Analyzer, the Raman spectra were recorded with the Kaiser RamanRxn2® Hybrid *in situ* analyzer. PLS calibration models were built to determine the API and MgSt content as well as the compression force of the tablets based on the NIR and Raman spectra. The effect of the different lubricant addition in the continuous experiments was then analyzed using the developed models. The models were built in MATLAB 2015a (MathWorks®, USA) using the PLS Toolbox 7.8.2. (Eigenvector Research, USA), the DoE was created in Statistica 13 (TIBCO Software Inc., USA).

2.3. Surrogate modeling of the *in vitro* dissolution of tablets

Dissolution prediction modeling was performed in an extended-release tablet formulation, containing 15 % w/w anhydrous caffeine as API, 15 % w/w polyethylene oxide (PEO), which ensures the extended release by forming a hydrophilic matrix, 2 % w/w magnesium stearate as a lubricant and microcrystalline cellulose (MCC) as filler. The tablets were prepared by direct compression, using a 13.24 kN target compression force. The effect of three experimental factors, (API and PEO content, compression force) on the dissolution curve of the tablets was investigated following a 16-point face-centered composite DoE and 5 additional validation runs. The API and PEO content were varied in the 13.5-16.5 % w/w and 10- 20 % w/w concentration range, respectively, and the compression force was set between 3.92 and 22.56 kN. Each tablet was measured by Raman and NIR spectroscopy and then a 10 h long USP II dissolution test was performed.

The relationship between the spectra and the dissolution curve was analyzed using four different techniques: for the *Weibull-RS-PLS* and *Weibull-PLS* methods, the Weibull dissolution model with three parameters (α_W, β, F_{max}) was first fitted to the dissolution curves. In the case of the *Weibull-RS-PLS* method, the experimental factors were estimated from the spectra using PLS models and the relationship between the factors and the Weibull parameters was estimated using response surfaces. In the *Weibull-PLS* approach, the Weibull parameters were estimated directly from the spectra using PLS models. In the case of the *Direct PLS* and *Direct ANN* models, the dissolution rate at each sampling point was directly estimated from the spectra using a PLS model or an ANN, respectively. The modeling was performed in MATLAB 2015a (MathWorks®, USA) using the PLS Toolbox 7.8.2. (Eigenvector Research, USA) and Neural Network Toolbox 8.3. (MathWorks, USA).

3. RESULTS

3.1. Flowsheet modeling of integrated upstream processing

Before the construction of the dynamic, integrated flowsheet model, the model parameters for each unit operation were estimated based on experimental data. In the case of the acetylation and quenching steps, the pre-exponential factors and the activation energies were estimated for each reaction. Using the steady-state concentrations for the parameter estimation, the trends between the different continuous experimental settings were followed well and even the dynamics of the concentration changes could be described. For the crystallization model, the

inclusion of the activation energy of the crystal growth was found critical for the model accuracy, while the agglomeration did not significantly improve it. Hence, in the integrated model, the agglomeration term was neglected. The parameter estimation result of the dissolution of the ASA powders and capsules showed that a size-independent dissolution expression can describe the dissolution process. Furthermore, as the experiments were performed under sink conditions, the change in the supersaturation did not need to be accounted for.

For the modeling of the integrated crystallization- filtration, the virtual DoE showed that the CSD is one of the most important parameters influencing the filterability, and approx. 20 µm was detected as the critical filterability region, which results in high specific cake resistance and hence longer filtration times. Nevertheless, the DoE results also revealed, that the modification of the applied flow rates, pressure difference and filter chamber rotation time could facilitate the filtration of slurries with bad filterability. Consequently, a design space could be generated, as illustrated in **Figure 2**, to determine the necessary filtration time, the expected residual moisture content, and to predict when the filtration becomes unattainable with the given slurry properties (black region in **Figure 2**). It was also possible to control the continuous filter operation to fit the preceding crystallization process, and *e.g.* keep the filtration time and the residual moisture content constant.

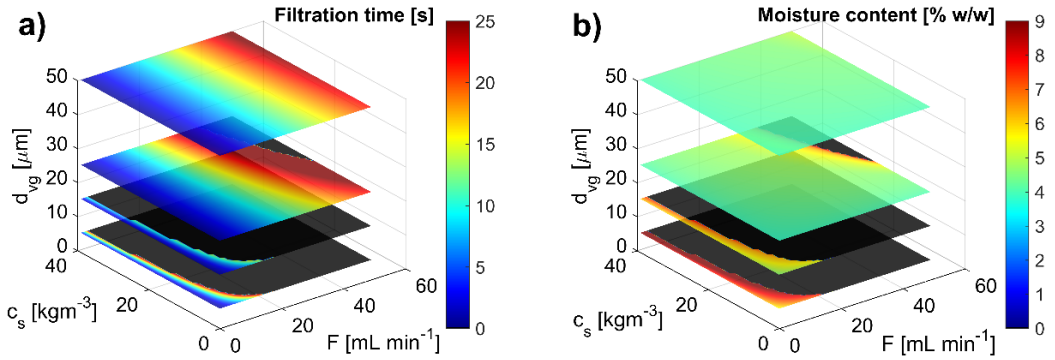

Figure 2 *Effect of flow rate, solid concentration and the geometric mean of the CSD on a) the filtration time b) on the residual moisture content.*

For the integrated flowsheet model, it was assumed that appropriate filtration and drying occur and the moisture content of the ASA powder can be neglected, *i.e.* the *in vitro* dissolution prediction model was directly connected to the crystallization simulation as illustrated in **Figure 1**. To investigate how the integrated flowsheet simulation can contribute to the better understanding and operation of the continuous manufacturing line, several optimization problems were defined and solved. First, the standalone synthesis was considered, followed by the plant-wide optimization of the integrated process using the developed flowsheet model. The synthesis was optimized first to maximize the conversion: the integrated approach of the synthesis resulted in a 10 % higher conversion compared to a step-by-step synthesis procedure, along with the significant increase in the purity of the reaction mixture. Then, the integrated continuous synthesis- crystallization process was optimized to provide the highest productivity. The integrated plant-wide optimization resulted in a 3.2-fold overall productivity improvement compared to the optimization of individual units, which demonstrates the benefit of the

development of flowsheet simulations. Furthermore, these results were reached with lower excess of AA and EtOH, that is not only the productivity can be increased, but the material costs and environmental footprints can be also reduced.

Sensitivity analyses were conducted with the optimized process settings. The objective was to identify the effects and risks associated with the involuntary changes in the process parameters and the uncertainty of the kinetic parameters. This way, the flowsheet modeling can help the development and operation of the integrated continuous manufacturing lines and it also contributes to the determination of PAT and control strategies. The Morris indices (μ_M and σ_M^2) were calculated for each simulation time point. μ_M indicates the influence of the given input factor, while σ_M^2 reflects non-linear effect or interaction with the other factors. The dynamic change of μ_M and σ_M^2 was used to analyze the error propagation through the system as illustrated in **Figure 3**. The results showed that the crystallization temperature (T_c) is the most influential parameter on the productivity, mean crystal size (D[1,0]) and dissolution time (T85) and its disturbance cause an immediate change in the output, while *e.g.* a change in the AA amount or the residence time result in a longer transitional time.

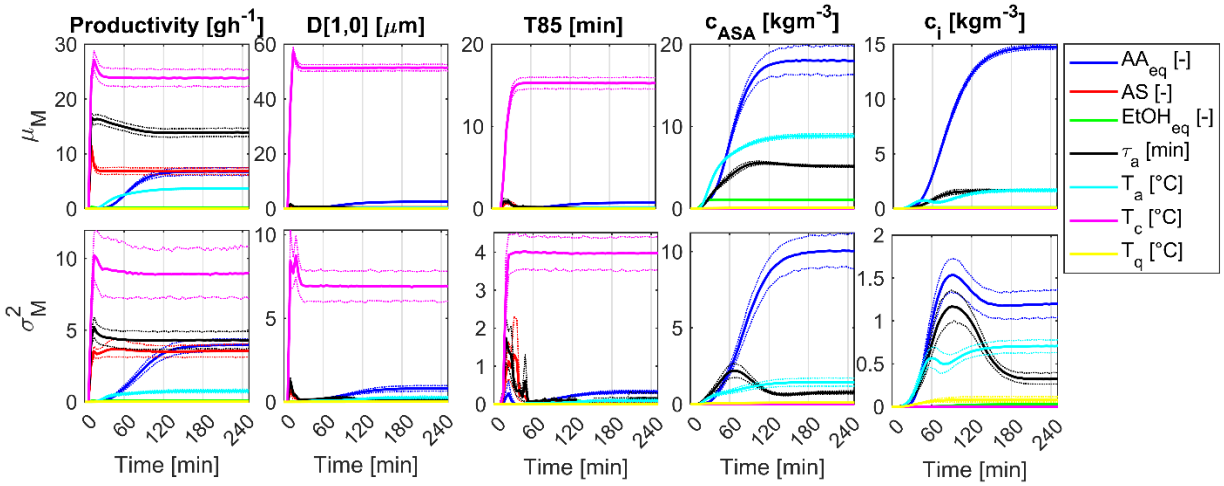

Figure 3 *Time-varying Morris sensitivity indices. The dotted lines represent the 95 % confidence interval of the indices. (D[1,0]: mean particle size, T85: time necessary for the dissolution of 85 % of the API, c_{ASA}: ASA concentration in the reaction mixture, c_i: impurity concentration in the reaction mixture. AA_{eq}, $EtOH_{eq}$,: AA and EtOH equivalent, AS: antisolvent-solvent ratio, τ_a : residence time in the acetylation reactor, T_a, T_q, T_c :temperatures of the acetylation, quenching and crystallization).*

3.2. PAT in an integrated continuous powder blending and tableting process

The objective of the study was to develop spectroscopic methods to nondestructively characterize the quality of tablets manufactured in an integrated powder blending and tableting process. First, the batch DoE was analyzed, which revealed that the lubricant content and the mixing time has the highest impact on the crushing strength and dissolution of the manufactured tablets. These results highlighted the importance of the accurate quantification and control of these factors to avoid overlubrication-related quality problems, while the compression force had less impact when overlubrication occurred.

The PCA of the NIR and Raman spectra showed that both the reflection and transmission NIR spectra were mainly affected by the compression force and the MgSt content, while in the

case of the Raman spectra, the varying lubricant and API content could be associated with the main spectral variations. That is, the two techniques provided complementary information about the studied formulation and their simultaneous application could result in better process understanding and control when multiple quality attributes need to be considered. Consequently, a PLS model for the quantification of the API was developed using Raman spectra which provided a 0.845 root mean square error of prediction (RMSEP). For the estimation of the compression force, the PLS model with the NIR spectra performed remarkably better, providing RMSE values below 2 kN, and for the MgSt quantitative method, the NIR and Raman models provided similar RMSEP values, but the predictions with the NIR models were significantly interfered by the compression force.

The analysis of the continuous experiments showed that overlubrication happened when the MgSt was continuously mixed (*Cont 1*), resulting in a prolonged dissolution. Considerable difference was observed in the prediction of MgSt content using the different spectroscopic techniques, too. In the case of the *Cont 1* experiment, all models predicted the 2 % w/w content well, while for the *Cont 2* experiment (lubricant added just before the tableting), only the Raman transmission model detect the small amount of the lubricant heterogeneously distributed within the tablets (**Figure 4**). This could be explained by the different analyzed sample volumes: in transmission mode, Raman photons coming from the deeper layers of the tablets are detected, which results in lower detection limits, whereas the reflection mode carries information mainly on the surface layers. In this way, the reflection and transmission methods used together could indicate overlubrication in real-time, as the transmission mode is applicable regardless of the distribution, while the reflection mode is sensitive to the distribution and is only applicable for the quantification of the low lubricant content when the lubricant is on the surface of the tablets.

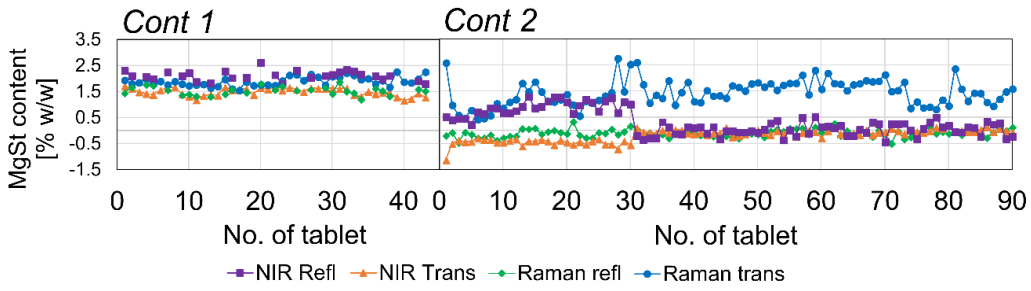

Figure 4 *Predicted MgSt content for Cont 1 and Cont 2 experiments.*

3.3. Surrogate modeling of the *in vitro* dissolution of tablets

We aimed to systematically compare empirical modeling approaches applicable for the surrogate modeling of the *in vitro* dissolution using an extended-release tablet formulation. The effect of three critical factors (API and PEO concentration, tablet compression force (CF)) was studied on the dissolution properties using NIR and Raman spectra of the tablets. The response surface fitted for the *Weibull-RS-PLS* method showed that all factors critically influence the dissolution curve. The F_{max} parameter of the Weibull equation (denotes the maximum achievable API concentration) was linearly influenced by the API content, and $log\ \alpha_W$ (time scale parameter) and β (shape parameter) was primarily affected nonlinearly by the CF and PEO content, and their interaction also needed to be accounted. The PLS modeling of the factors

showed that the compression force can be quantified the best by NIR spectroscopy, and the NIR and Raman method performed comparably for the PEO content determination, which suggested that the NIR technique could be the most suitable to characterize the changes in the dissolution curve. However, the API calibration method still needs improvement to ensure a good content determination. The direct prediction of the Weibull parameters (*Weibull-PLS*) from the spectra also showed similar results, as $log\,\alpha_W$ and β could be predicted with sufficient accuracy but the model for F_{max} provided high error. This method was assumed to be advantageous due to the ease of the development and application, as the response surface fitting step is skipped, but a certain degree of process understanding is lost, just like in the case of *Direct PLS* and *Direct ANN*, as the relationship between the dissolution model parameter and process conditions is not explained.

To compare the four modeling techniques, the mean RMSEP (mRMSEP) of the validation dissolution curves were calculated, which revealed that the best fitting can be achieved by the *Direct ANN* method (mRMSEP =6.77), followed by the *Direct PLS* (mRMSEP =9.59), while the Weibull equation-based methods provided the highest errors (mRMSEP~12-14). Analyzing the RMSEP through the dissolution time points showed that at the end of the dissolution, the RMSEP values of the *Direct PLS* are basically identical to that of the *Direct ANN*, but a non-linear decreasing trend could be observed until approx. 200-300 min. This was explained by the fact, that *Direct PLS* is a purely linear model as opposed to the other three techniques, while it was concluded that the *Direct ANN* is the most efficient method for handling the non-linearity in the dataset.

The distribution of the f_1 difference factors (the smaller the f_1, the better the agreement with the reference curve) calculated for all the samples and all the models are represented in the box-plot in **Figure 5**. The range of the f_1 values of the *Direct ANN* with the NIR reflection and data fused dataset remained in the acceptance limit, indicating that the accuracy of the prediction could reach the regulatory-set requirements.

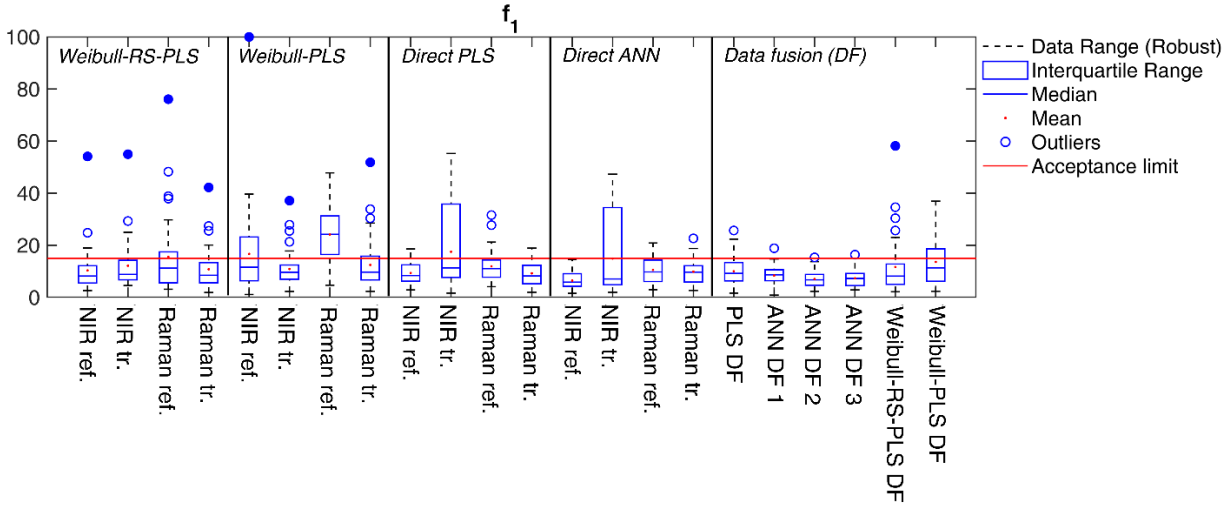

Figure 5 *Statistical representation of the distribution of the f_1 values of the predicted validation samples.*

The comparison revealed the superiority of the direct approaches, but the application of the

Weibull-RS-PLS had the advantage of obtaining an additional understanding of the relationship between the process parameters and dissolution. However, the most common *Direct PLS* technique showed a significant nonlinear trend in the error, mostly at the critical initial phase of the dissolution profile. Overall, a 10 h long dissolution test could be replaced by 5-15 s long non-destructive, real-time applicable spectroscopic measurements, which could significantly increase the analyzed sample size and enable RTRT.

4. THESIS FINDINGS

1. A new mathematical modeling approach has been proposed for the mechanistic estimation of the filterability of suspensions by accounting for the crystal size distribution (CSD) and solid concentration of the suspension. The model combines Darcy's equation with the calculation of the specific cake resistance from the CSD, which is performed by using a generalized form of the Carman-Kozeny permeability equation. The cake porosity is also estimated from the CSD using the random packing theory of spherical particles. The model provided good agreement with experimental filtration results. [I, II, III]

2. An automated Nutsche filtration-type continuous filter and its integration with continuous crystallization has been modeled the first time. It has been established that suspensions with high solid concentration and small particle size have better filterability in the continuous filtration device. Furthermore, by controlling the rotational cycle time of the filter chambers, it is possible to keep the filtration time and the residual cake moisture content constant even in the case of dynamically changing suspension properties. [I, II, III]

3. Population balance modeling has been applied the first time for the mechanistic modeling of the *in vitro* dissolution of pharmaceutical capsules and integrated into the dynamic flowsheet modeling of continuous active pharmaceutical ingredient manufacturing. The application of the dynamic flowsheet model confirmed that the integration of the units of the continuous upstream manufacturing – compared the standalone operation of the synthesis and crystallization steps – can contribute to the more efficient operation, for example the productivity can be increased and the amount of the reagents can be reduced. [III, IV]

4. The lubrication properties of a continuous, integrated powder blending-tableting system have been analyzed using NIR and Raman spectroscopy. The occurrence of overlubrication could be detected non-destructively by simultaneously applying reflection and transmission NIR and Raman spectroscopy. This could be explained by the changing spatial distribution of the lubricant within the tablets, and by the fact that the different spectroscopic techniques collect information from different depths of the samples. [V, VI, IX, X]

5. Artificial neural networks (ANNs) are applicable for the prediction of the full *in vitro* dissolution profiles of pharmaceutical formulations from Raman and NIR spectra. For this, the spectra need to carry information about the critical material attributes and process parameters affecting the dissolution properties. The method has proved to be effective for the fusion of data obtained by the analytical tools and to enable real-time testing of the *in vitro* dissolution. [VII, VIII, X, XI]

6. Different modeling methods have been compared for the prediction of *in vitro* dissolution curves, which predict either directly the profile or based on the fitting of a profile-defining equation. Using profile-defining equations has proved to be advantageous for the understanding of the underlying relationship between the dissolution and the critical material attributes and process parameters, while the direct prediction of the dissolution rate at given time points provided better agreement with the reference dissolution curves. The realization of non-linear modeling techniques has also proved to be important. [VII, VIII, IX, X]

5. APPLICATION OF THE RESULTS

This work covers a wide range of pharmaceutical manufacturing processing, and although the studies were conducted using model pharmaceutical formulations, the developed modeling methodologies can be directly transferred to further, commercial formulations and their manufacturing processes. As the pharmaceutical industry is increasingly turning to continuous manufacturing solutions and application of PAT and QbD, the presented modeling approaches are expected to receive growing interest. Consequently, the results could find applications in the pharmaceutical industry both at the development and manufacturing phases.

The proposed filtration model is applicable for the digital design and optimization of batch and continuous Nutsche filtration processes and it could be utilized in several fields of chemical engineering, therefore it bears general significance. The dynamic flowsheet modeling results could be used for the experimental integration of the existing unit operations, as well as it could contribute to the better understanding of the development and operation of further, even industrial-scale integrated manufacturing lines, that is it can promote the implementation of end-to-end manufacturing.

The studies regarding the applicability of Raman and NIR spectroscopy in downstream processing showed the potential of these PAT tools combined with chemometric methods for the real-time quality monitoring of continuous processes, even when multiple effects need to be accounted for at the same time. The surrogate dissolution modeling results show especially exceptional possibilities by providing a real-time alternative for the lengthy and destructive dissolution testing. ANNs could be applied to improve the accuracy and handle the non-linearity in the dissolution modeling, and the comparison of the dissolution prediction modeling strategies can serve as a guidance for method selection. Consequently, these results can contribute to achieving real-time release testing.

6. PUBLICATIONS

Scientific articles closely related to the theses:

I. **B. Nagy**, B. Szilágyi, A. Domokos, K. Tacsi, H. Pataki, G. Marosi, Z.K. Nagy, Z.K. Nagy, Modeling of pharmaceutical filtration and continuous integrated crystallization-filtration processes, *Chemical Engineering Journal*, **2020** 127566. http://doi.org/10.1016/j.cej.2020.127566 (IF: 10.65; IC: 1)

II. Domokos, **B. Nagy**, M. Gyürkés, A. Farkas, K. Tacsi, H. Pataki, Y.C. Liu, A. Balogh, P. Firth, B. Szilágyi, G. Marosi, Z.K. Nagy, Z.K. Nagy, End-to-end continuous manufacturing of conventional compressed tablets: From flow synthesis to tableting through integrated crystallization and filtration, *International Journal of Pharmaceutics*, 581, **2020** 119297 http://doi.org/10.1016/j.ijpharm.2020.119297 (IF: 4.845; IC: 3)

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IV. **B. Nagy,** B. Szilágyi, A. Domokos, B. Vészi, K. Tacsi, Zs. Rapi, H. Pataki, G. Marosi, Z. K. Nagy, Z. K. Nagy, Dynamic flowsheet model development and digital design of continuous pharmaceutical manufacturing with dissolution modeling of the final product *Chemical Engineering Journal*, **2021** 129947, https://doi.org/10.1016/j.cej.2021.129947 (IF: 10.65; IC: 0)

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