

Model-Based Control and Measurement of Granule Porosity using Novel Technology

Research proposal to the International Fine Particle Research Institute (IFPRI)

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Institute of Process and Particle Engineering, Graz University of Technology
& Research Center for Pharmaceutical Engineering (RCPE) GmbH

Lead Scientists:

Andreas Kottlan, Ph.D. (Principal Investigator)

Prof. Johannes G. Khinast, Ph.D. (Co-Principal Investigator)

Project Administration:

Anna Weissenbacher, BA

Michaela Cibulka, MA

Abstract

In this proposal we present the outline of a research project to establish model-based control of granule porosity in batch fluid bed granulation processes. The control strategy will be based on a data-driven process model and real-time process monitoring. The real-time process monitoring will be achieved by a combination of Process Analytical Technology (PAT) hardware sensors and soft sensors. The established data-driven model will be used to predict ideal trajectories of process parameters in silico, depending on the desired porosity and other optimization criteria. These trajectories of various process parameters can then be used as references for real-time process control. The research program aims to establish model-based control of granule porosity within 3 years, while laying the foundations for the long-term goal of controlling pore structure (size distribution) and presenting an approach for scaling the concept to industrial use cases.

1. Introduction

Due to the wide application in the bulk solids industry, wet granulation processes have received strong scientific interest over the last decades. Aiming to facilitate Quality-by-Design (QbD) and Quality-by-Control (QbC) based process development rather than the traditional empirical trial and error approach, academia and industry have strived to gain mechanistic understanding of these processes. The primary goal of granulation is the increase of particle size, this property has also received the most interest. Since particle size and its distribution has a major impact on the flowability of a given granular material (and therefore on subsequent processes), its importance is undeniable, making particle size control the prime objective (Celikovic et al., 2023, 2024b).

However, in addition to size and size distribution, the porosity of granules is another important quality attribute. In fact, the porosity of the granules can play a vital role when it comes to downstream processing steps and has a major impact on hardness, compactability, wettability, ability to absorb impregnation fluids (e.g., for catalyst preparation or pharmaceutical applications) and many other properties. Interestingly, control of porosity has been studied to a much lesser extent; the achieved porosity and distribution of pore sizes has been viewed simply as a result of a specific process route, not as controllable quality parameters. For example, in the manufacturing of pharmaceutical tablets, the porosity has a crucial impact on the compaction properties of granules, governing the mechanical strength and final porosity (and thus disintegration/dissolution) of a tablet. This final porosity determines the transport of liquid, i.e., gastric fluid in the tablet, responsible for disintegration of the tablet and hence for dissolution of the contained active pharmaceutical ingredient. In the food industry, porosity has a major impact on dissolution (for example instant coffee) or mouth feel.

Given this high relevance, the proposed project aims to develop a concept for model-based control of granule porosity. The basis for building a control concept is the identification of correlations between process parameters that can be manipulated and specific product quality attributes: the porosity and the pore size distribution. These correlations can be derived from a mechanistic analysis of the granulation process identifying potential critical process parameters followed by a structured experimental analysis to quantify the effects of said parameters on the quality attributes of interest.

Fluid bed granulation (FBG) will be used as model platform technology, because of its common application in industry and inherent flexibility. The possibility to tune various process parameters impacting particle agglomeration holds potential to simultaneously control both particle size and porosity. Besides, FBG rather yields granules with high porosity offering a range of options for controlling porosity. The proposed project will address FBG batch operation with the goal of implementing a control strategy based on systematically determined optimal process trajectories.

In the present proposal, we will outline how a combination of process analytical technology, process models, and a control algorithm can facilitate the implementation of model-based control of the pore structure of granules, demonstrating its advantages compared to conventional operating modes.

2. Proposed program

2.1. Process modeling

One crucial step in developing a model-based control strategy is to establish a model linking manipulable process parameters (PPs, input variables) to the product attributes (PAs, output variables). Several studies have been published discussing the influence of parameters in FBG, which can provide initial insights, as depicted in Figure 1 (Burggraeve et al., 2013; Thapa et al., 2019). Figure 1 shows a schematic of an FBG setup including common PPs (in blue) and PAs (in red). Since the focus of this project will be on process control rather than on establishing novel process models, the goal is to design a simple process model that accurately reflects process behavior within the investigated range and can be executed in real-time. In the model development phase, a series of experiments (DoE or preferably automated DoE depending on the availability of the PAT equipment) will be conducted to obtain training data to create a data-driven or hybrid process model. This dynamic model will be able to predict transient PAs based on the current value of PPs and their trajectory during the process time.

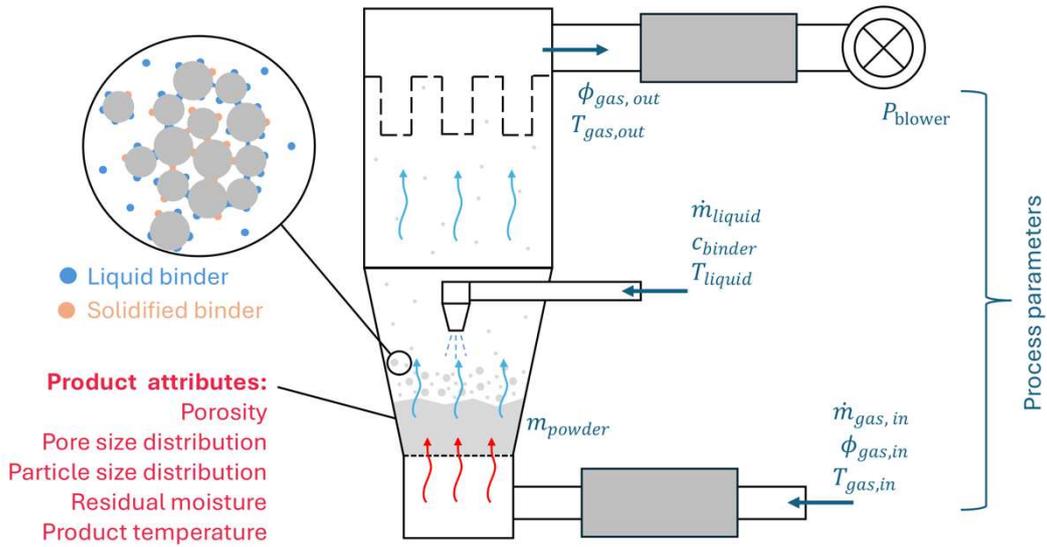


Figure 1: Schematic illustration of a top spray fluid bed granulation setup showing process parameters in blue and product attributes in red. Nomenclature: T ...temperature; m ...mass; c ...concentration, \dot{m} ...mass flow; P ...power; ϕ ... relative humidity.

To maximize the information gained from experimental data, an iterative process of gathering data via experiments and training the model will be implemented. This will allow us to achieve a high model quality while keeping the number of experiments as low as possible, which is important to provide scalability for industrial processes (i.e., to transfer existing algorithms to alternative products or scales). For that reason, hybrid process models will be favored over the purely data-driven ones. If it proves advantageous, population balance (PB) models will be used in the modelling procedure, especially to achieve goals, such as predicting pore size distribution. We consider PB models hybrid because they reflect phenomena like aggregation and breakage as source and sink terms but require parameterization using experimental data or data obtained using other simulation tools.

Aiming to reduce overall experimental effort, it is vital to maximize the amount of information gained from the experiments. To achieve this, product attributes (PAs), such as particle size distribution (PSD), product temperature and (optionally) residual moisture, will be measured in-line. Porosity and pore size distribution will be measured at-line or off-line using reference analytical methods like envelope density measurements (for porosity), gas-pycnometry, and gas physisorption (for pore size distribution), mercury porosimetry or image analysis of tomograms obtained for example via micro-CT. The samples for the respective measurements will be taken in short intervals to provide an accurate representation of the process dynamics.

Validation of the process model will be done using experimental data with process parameter (PP) combinations which were not used in the training data set. The validation data sets will span a relevant region of the design space used in model training. The state estimator approach introduced in 2.2.2 will provide an opportunity for continuous and repeated model quality checks and optional improvements and fine-tuning.

2.2. Development of process monitoring strategy

In general, in-line measurement of a material's porosity is a research field receiving wide interest in recent years associated with many challenges. First of all, distinguishing between intergranular and intragranular porosity complicates this application. Second, the lack of knowledge of a granule's geometry presents a challenge to currently applied methods, used for example for tablets (Anuschek et al., 2024; Bawuah et al., 2020) or in well-defined powder beds (Louge et al., 2024). Due to the lack of a "gold standard" for in-line porosity-measurement method, we propose a dual strategy for real-time measurement of pore structure. The focus in terms of monitoring will be the development of a reliable

hardware-based sensor technology to measure the granule porosity in real-time. In parallel, to gain deeper insights (e.g., on pore size distribution and pore structure) and as a back-up strategy, a soft sensor concept will be pursued.

Based on the performance of either approach, a final process monitoring strategy will be defined additionally utilizing commercial PAT-tools to measure PSD, residual moisture, and composition as for example in previous work (Celikovic et al., 2023, 2024a).

2.2.1. Hardware-based sensors

Since there are promising options for direct real-time measurement of granule porosity, evaluation and development of PAT-methods will be included in the project if interested industrial project partners can be identified. Specifically, Terahertz time-domain spectroscopy (THz-TDS), optical coherence tomography (OCT), and capacitance measurement and/or radar will be evaluated. Apart from measuring porosity in transmission, THz-TDS offers the possibility to derive porosity from the reflected signal at the surface of a sample, making it less dependent on sample geometry. The downside of reflective measurement is the lack of information on the pore structure inside the sample. An option to include the internal porosity of the sample is transfective THz-TDS using the signal reflected from the back of the sample. While this approach still requires information about the granule size, in contrast to transmission measurement, it should enable to exclude intergranular porosity (Anuschek et al., 2024).

OCT also showed promising results for determination of tablet porosity by analyzing a layer close to the surface (penetration depth 80-240 μm), which – as we have shown -is in many cases representative of the entire granules. This method utilizes a machine learning based clustering algorithm resulting in the penetration depth of the signal. Said penetration depth can be correlated with sample porosity, without the need to determine the granule size (Fink et al., 2024).

Currently, preliminary work at RCPE focuses on the feasibility of in-line and real-time measurement of the porosity of roller compactor ribbons, showing promising results regarding the correlation of OCT porosity metrics, the porosity and the compaction pressure. Thus, we believe that OCT can be a powerful tool for in-line porosity monitoring in the proposed project. As introduced by Fink et al. (2024) a ML-based clustering algorithm will be used as a first step of data treatment followed by a data-driven correlation model linking the measured parameters (e.g., penetration depth) to the physical porosity. If successful, the ability to measure granule density in real time will be a revolution in the monitoring of granulation processes.

2.2.2. Soft sensors

Soft sensors facilitate access to information that is otherwise inaccessible to direct measurement, either because of mechanical constraints (too small) or due to a lack of an appropriate characterization method/technique (no specificity). A soft sensor uses information available from process equipment

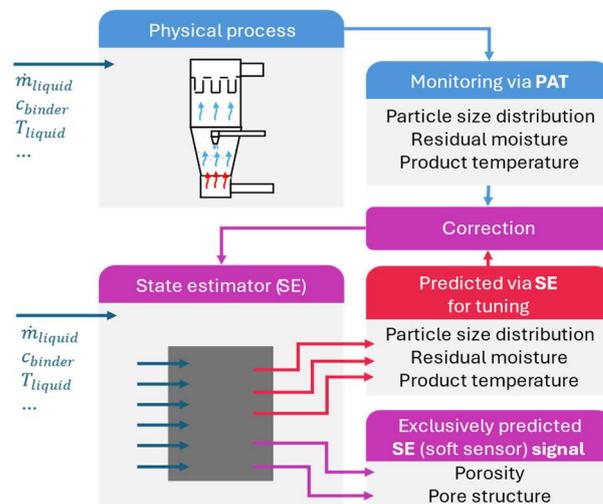


Figure 2: Illustration of the state estimator concept.

control units and complementary PAT-tools (e.g., for PSD and residual moisture) and a model to calculate the output of interest. Despite being a powerful tool, they are sometimes viewed as inappropriate for process control, as they are assumed to be sensitive to variations in model quality (e.g., inaccurate model prediction due to unconsidered factors such as variations in raw materials or aging). However, there is a powerful remedy: non-trivial state estimators can be utilized. In this concept, a process model as described in section 2.1 is used to predict the output variables based on the input variables. Some of the output variables (e.g., particle size) are in parallel measured in real-time. The state estimator will use this information to correct model prediction, if deviations between prediction and measurement are present, as depicted in Figure 2. This approach is commonly established in a control engineering field (Boker & Khalil, 2013; Ellis, 2012) and was also previously investigated by our group, to predict blender hold-up (Kirchengast et al., 2019).

2.3. Control concept

2.3.1. Optimization strategy

Using the available process model described in section 2.1 an in-silico process optimization will be conducted: The process model will be integrated into an optimization algorithm and used to determine the optimal trajectories for PPs needed to achieve the desired product attributes. This optimization will be executed within the design space which was covered by modeling data (optimization constraint) and can include additional objectives, such as minimizing energy consumption, process time or other economic factors. The result of this optimization will be the optimal trajectories of the process settings (that can be applied as a starting point and optimal process recipe) and product attributes which will then be used as reference trajectories (targets) for real-time process control.

2.3.2. Real-time process control

The proposed process control strategy rests on three pillars: (i) the process model described in 2.1 (ii) real-time measurement of PAs described in 2.2, and (iii) the ideal trajectories of PAs obtained as outlined in 2.3.1. These three pillars represent a necessary and sufficient foundation for the design of a model-predictive control (MPC) algorithm. In each process iteration, the MPC will compare target trajectories to the measured ones, and then based-on the model knowledge (and process/equipment limitations) predict and optimize process settings over the selected finite time horizon as illustrated in Figure 3.

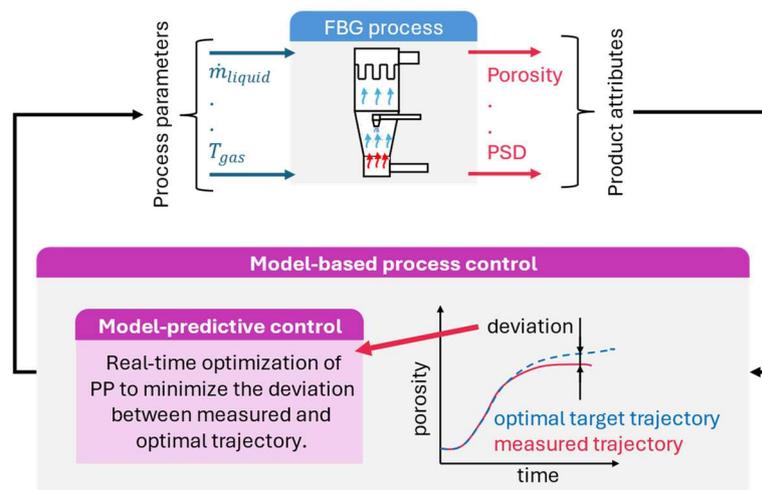


Figure 3: illustration of model-based process control loop.

Validation of the control concept will be done by introducing intentional disturbances to the process, to assess the capability of the controller to converge to the ideal trajectory.

2.4. Available infrastructure

RCPE is equipped with a wide range of process systems, including various continuous process lines (Consigma by GEA, direct compaction, HME, nano-manufacturing, HME-printing, a wide range of flow chemistry platforms), mills, coaters, fluid beds, tableting machines, compaction simulators, crystallizers, bioreactors, lyophilizers as well as analytic capabilities ranging from powders (e.g., SWAXS, X-Ray tomography, XRD, PSD via many complementary methods, electrostatic charging, porosity, gas adsorption, and much more) to nano-systems (DLS, SR-DSL, toxicity, and much more) to biologics. For this specific project, two different pilot scale fluid bed granulators which will be used in this project, namely a Solidlab 1 (Syntegon) and a GPCG 1 (Glatt Process Technologies). In-line monitoring of particle size will be realized using a spatially filter velocimetry probe (Parsum) available at RCPE's pilot plant. Thanks to the close collaboration with the RCPE-developed OCT supplier Phyllon at-line and in-line OCT devices are available in our working group. All complementary infrastructure for process control, off-line analysis and modeling activities is an inherent part of our center with many publications in this field.

2.5. Transferability of developed control concept

Although the proposed project is concerned with the development of a control concept for a fluidized bed low-shear granulation process, the fundamental outcomes of the project can be transferred to other granulation processes. Specifically, reliable sensor technology for in-line measurement of granule porosity can be highly useful for other granulation operations (high-shear wet granulation, low-shear granulation, TSWG, dry granulation, etc.). Beyond that the project will establish a generic workflow for developing a control concept for granulation processes which can then be applied on different scales and equipment types facilitating the maximum impact of the project outcomes.

2.6. Timeline

Based on the proposed program plan the following tasks are defined and are reflected in the timeline (Table 1):

- T1: Development of process models for particle size distribution and intragranular porosity distribution.
- T2: Development of process model additionally including pore size distribution.
- T3: Soft sensor design considering more detailed pore structure.
- T4: Development of OCT-based porosity measurement of hardware-based sensor options.
- T5: In-silico optimization considering desired quality attributes (including porosity, neglecting pore sized distribution) and efficiency.
- T6: Implementation and validation of model- based control considering desired quality attributes (including porosity, neglecting pore size distribution) and efficiency.
- T7: In-silico optimization additionally considering pore size distribution.
- T8: Implementation of extended model-based control considering pore size distribution.
- T9: Assessing scalability to industrial processes with industrial partners.

Table 1: Project timeline.

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
T1												
T2												
T3												
T4												
T5												
T6												
T7												
T8												
T9												

3. Collaboration with IFPRI members

RCPE has active collaboration with several IFPRI members focusing on various applications, including modeling, digital tools, sensor development, scale-up and process engineering of powder processing operations (such as mixing, granulation, coating, tableting, milling, sieving, melting, quality measurements, DEM, CFD-DEM and much more). Nevertheless, in this project we will strive to meet the highest quality expectations with respect to the project's objectives and will openly and proactively interact with IFPRI members to find a model system of interest for a majority of involved organizations.

3.1. Definition of model formulations

Input regarding relevant model systems and the desired product characteristics is expected and should enhance the impact of the research performed in the proposed project. To obtain a comprehensive conclusion regarding the applicability of the developed control concept, at least two different model formulations will be investigated in agreement with IFPRI members. Moreover, we will aim to have regular TCs to monitor the progress and direction of the project.

4. Potential risks and mitigation strategies

4.1. Strong interdependence of product attributes

Ideally, the different product attributes (PSD, porosity, hardness, etc.) can be controlled independently, allowing maximum flexibility in achieving the desired product properties. However, depending on the formulation design, a strong correlation of porosity, pore size distribution, granule size and hardness may be encountered. Hence, challenges may arise if two variables deviate from their desired values and decreasing the deviation of one variable increases the deviation for the other. As in every optimization problem, the mitigation strategy would be to define a cost function representing the importance of the different product attributes.

4.2. Challenging development of hardware-based porosity sensor

As pointed out above, the in-line measurement of porosity is not straightforward. Even though we are optimistic about the applicability of OCT for measuring the porosity of granules, we consider the development of a new, robust and deployable sensor application as a significant challenge. However, we are optimistic that a proof-of-concept and application deployment can be achieved, possibly leading to follow-up developments of a robust sensor technology with our partner Phyllon GmbH (www.phyllon.at).

4.3. Weak correlation of different product attributes, preventing implementation of accurate state estimator

Establishing a state estimator requires a reliable correlation between the observed variables and the predicted variables (measurement signal of the soft sensor). If no correlation can be established between the PAs, which can be measured via hard sensors and the variables planned to be measured via soft sensors, the concept of state estimators may not be applicable. As a fallback option a simple model-based soft sensor may be implemented, including a model lifecycle management strategy including periodic parallel testing to ensure model health.

5. Leveraging project outcomes in our research group

As described in the introduction, porosity is a critical quality attribute of pharmaceutical intermediates and the end products. Consequently, establishing model-based control for the porosity of pharmaceutical granules will allow tailoring certain critical quality attributes of the final product, such as hardness, compactability, disintegration and dissolution, as well as improving manufacturability of the granulated product. The project stream addressing the assessment of porosity measurement methods will also provide highly valuable learnings for applications in PAT, leveraging our current

interest in real time release applications which often include porosity as a predictor for dissolution performance.

Ideally, the results of the project can be utilized in follow-up projects with IFPRI partners.

Lastly, the project will be the basis for further projects of RCPE modeling the granulation process by mechanistic models including CFD and particle-interaction (DEM, liquid-bridge modeling, etc.).

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