

Process simulation and mathematical modelling for process scale-up and technology transfer: Development and manufacturing of active pharmaceutical ingredients



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KEYWORDS - Process simulation, mathematical modelling, process development, scale-up, optimisation, QbD, design space, virtual DoE, Peer Reviewed.

ABSTRACT - Mechanistic modelling and process simulation, based on first principle analysis, is a well-practiced tool in the chemical industry. A mechanistic model is a knowledge-based description of a system designed to help an observer understand how the system works and predict its behaviour. Mechanistic models can be used for process design, process scale-up, technology transfer, knowledge management, and risk analysis for forward decision-making. Model-based scale-up and optimisation is a powerful technique for achieving the desired product quality and for reducing the cost of experimentation and the time to market.

This paper aims to provide a short summary of the fundamentals, applications, benefits, and limitations of the use of mechanistic modelling for process scale-up and technology transfer for the development and manufacturing of active pharmaceutical ingredients. Two case studies of reactor and crystallisation process scale-up are provided here. Detailed mathematical equations and technical discussions of numerical methods are avoided for the sake of the general audience.

INTRODUCTION

Efficient process development for achieving high-quality active pharmaceutical ingredients (APIs) at high yield and low manufacturing cost is the prime goal for development studies and scale-up to manufacturing scale. Process development criteria and process development and scale-up practices are based on classic chemical engineering knowledge and can be carried out by expensive and lengthy trial-and-error or by fast and efficient mechanistic modelling. A mechanistic model (based on first-principle knowledge) is a predictive tool that through proper development, validation, and implementation enables applicants to reduce cost, time, and resources for scale-up and technology transfer. It helps by significantly reducing the DoE effort on a manufacturing scale and by finding optimal conditions for equipment sizing and process parameters.

The aim of this paper is to provide an overview of mechanistic modelling and simulation in the pharmaceutical manufacturing industry for equipment characterisation and scale-up. Deep technical discussions and mathematical expressions are beyond the scope of this work. Interested readers are referred to the literature and textbooks in this area (1-3) or contact the author for further information.

FUNDAMENTALS AND WORKFLOW

In broad terms, quantitative models can be divided into three categories: mechanistic, empirical, and hybrid models. In contrast with data-driven models, mechanistic models provide a true representation of the underlying phenomenon; therefore, predictions from these models can be extrapolated beyond the range covered by the input data, depending on the validity of the underlying assumptions. The two main challenges of mechanistic modelling are developing/deploying the true equations for the system and having the correct parameters. In case of a lack of fundamental knowledge for the models (such as surface tension models), hybrid approaches will be used by help of few empirical equations and fitted parameters for the mechanistic models. One of the most famous and widely used hybrid models is the model of crystal growth rate population balance for crystalliser design and scale-up (4).

Mechanistic models for scale-dependent processes are used for equipment characterisation and assessment. Characterisation is about building a high-confidence model of equipment or material constraints; assessment is about using that model to answer questions about how equipment/process will perform under scenarios of interest other than the test conditions.

Mechanistic models can be divided into two types based on their objectives:

- When the inputs to the process are known and the output variables are to be determined, the problem is called a rating simulation. For instance, for a given equipment size and process condition, such as temperature (existing equipment), the goal of the simulation could be determining the distillation performance for solvent recovery. This approach is common in retrofitting existing equipment for a new process, technology transfer between sites, and improving asset utilisation.
- On the other hand, if the outputs of the system are the desired values, and the model must determine the input variables to fulfil the desired output, the problem is called a design problem. The solution methodology consists of treating the problem as an optimisation problem. This case is the most common case for API CQAs where the target quality or yield is set and the CPPs or process set-up was optimised to fulfil the requirements.

The model development framework follows the SMART criteria:

PROCESS DEVELOPMENT

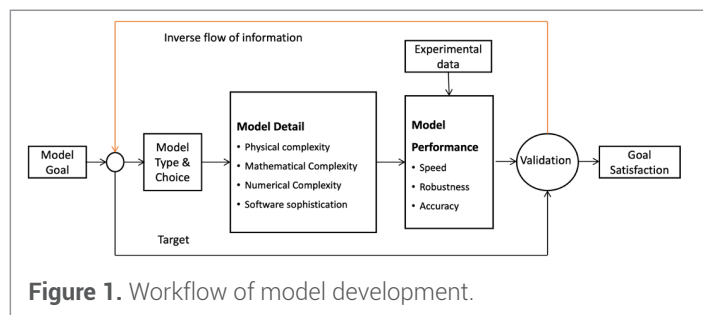
Specific: The model goal should be specific for the intended application and target a specific area of study.

- **Measurable:** The quantitative model outcome should be measurable. For example, the outcome could be the effect of a 20 °C increase in reactor temperature on the reaction rate.
- **Achievable:** The intended goals should be achievable by model and numerical tools based on the existing knowledge of the process and parameters.
- **Realistic/Reasonable:** The models should be able to run for a bounded time and with finite resources. Also, the model output should make sense in the physical world and be implementable.
- **Trackable/Testable:** The assumptions, source of parameter values, numerical method selections and set-up, methods, and outcomes of the model and simulations should be well documented. The model should pass code verification and model validation by experimental values.

Having the SMART criteria in mind, the workflow of the model development consists of the following sequential steps (Figure 1):

- Defining the model's objective and purpose.
- Deciding on the type of the model (e.g. a steady-state or a dynamic model) and the experimental methodology to support model development.
- Collecting equipment and experimental data and performing parameter estimation. The quality of the experimental data is highly important for the model set-up. Any mechanistic model is only as good as the parameters that have been considered during its development. Therefore, modellers and experimental scientists should work closely together with clear and regular communications to gather high-quality data for the model set-up.
- Developing the models and performing simulations based on input data, process/product knowledge, and representative equations.
- Verification and validation of the model by numerical techniques and comparing model results with experimental data.
- Documenting model development steps, parameters, assumptions, sources of information, and software and hardware tools.

In mathematical modelling, the experimental data are needed to determine the model parameters, whereas the quantitative description is a result of the model or process simulation. The solution of the scale effect requires answers to several questions about the similarity and the scale-up, the physical essence of the scale effect, and the possibilities of the scale-up theory and hydrodynamic modelling to predict the scale effect. The impact of the scale dependency is to increase the processing times on scale and to reduce productivity. However, more importantly, the impact could be the potential occurrence of additional phenomena that were not observed to the same extent in the laboratory, such as impurity-forming reactions, product degradation, catalyst poisoning or deactivation, crystal form change, agglomeration, or breakage.



The CQAs of the final APIs are somehow mandated by external factors (such as genotoxicity, bioavailability, and regulatory aspects) and are a key goal of the process development. The final CQAs depend on CPPs and equipment design and the attributes of the starting material (e.g. CMAs, impurity at the inlet, lot-to-lot variation). The tracking of impurity formation and the backpropagation of the final CQA quality measure are performed by an impurity fate map. For example, the high temperature at a reactor could generate more impurity at the synthesis step, which may impact the rejection capacity of the crystallisation and cause residual impurity in the crystalline APIs. Scale-dependent phenomena (such as heat transfer and mixing) are highly sensitive to such scaling-up approaches and could have a direct effect on the entire process performance and product quality.

Process yield is the economic metric of the scaled-up process. It can be evaluated based on costs (Capex and Opex), utility, waste per API product, labour, overall conversion or recovery, and manufacturing time. Also, overall GMP manufacturing cost could be a significant factor when the operational footprint and process performance are costly for the enterprise. Process intensification and switching from batch to continuous mode are two common endeavours in reducing such costs. Finding the optimal equipment size and operation parameters by mechanistic models, and utilising such models in advanced process control (such as model predictive control, feedforward control, or soft sensors), could reduce the manufacturing operation cost and reduce waste. The combination of mechanistic models and techno-economic analysis can be used for the economic optimisation of the process (case study 1).

The QbD approach requires the development of a design space in which the process may operate, with the flexibility to move operating conditions around in this space without needing to obtain additional regulatory approval. This implies a greater investment in understanding the development process during the development phase, balanced by flexibility, a reduced regulatory burden, and opportunities for continuous improvement once the process is in full-scale manufacturing. The development of this design space can be performed by expensive and lengthy experimental trial-and-error or by efficient and fast mechanistic modelling. The scale dependency of the reactions, crystallisation, distillation, and the like can be framed in terms of the chemical engineering rate constants or time constants required by the process (5). Factors such as the chemical reaction rate per unit volume and the solubility of the reagents are independent of scale. Reaction kinetics, crystallisation kinetics, heat and mass transfer in reactions, distillation, extraction, crystallisation, and drying are scale dependent.

The equipment and process characterisation and defining the design and control spaces are carried out by two types of mechanistic modelling approaches:

- **Steady-state models:** These models are used for process development, equipment sizing, scale-up for proper equipment sizing and design, and process parameter selection and definition. For example, the rate of heat transfer depends strongly on the ratio of surface area to volume, which reduces by scaling up. This means that heat transfer in the scaled-up process will be slower than in the laboratory, which in turn could significantly affect the exothermic/endothermic reactions and could impact side reactions (impurities).

Steady-state simulations, computational fluid dynamics (CFD), and other tools will be used for such steps.

- Dynamic simulation: The design of process control systems requires knowledge of the dynamic response of the process to disturbances. These aspects cannot be studied by steady-state simulations. A simulation study that considers time as a parameter is called a dynamic simulation. Dynamic simulation studies can be used to obtain optimal operating conditions for a process. Also, all possible process disturbances and the consequent downstream impacts on time lags, dispersions, and other time-dependent variables can be modelled in dynamic models for process control strategy development, risk analysis, mitigation plans, and process stability evaluation. A safe, feasible, and economical procedure for process start-up and shutdown can be developed by dynamic simulation as well.

Batch processes are dynamic, with variables such as concentrations, reaction rates, and adsorption rates constantly changing over time during a batch. The continuous processes are in a steady-state mode, so the variables and parameters remain constant and do not change with time. The differential equations thus obtained do not have any temporal derivative. The model equations are simple since time is not present in these equations. However, the steady-state simulations are not capable of predicting the dynamic behaviour of the process. Start-up and shutdown of a unit operating continuously also constitute dynamic processes (6).

Mechanistic models enable a powerful tool called virtual multidimensional DoE to be used, by which hundreds of DoE cases (for equipment design and process conditions) can be virtually run by global sensitivity analysis. The experimental DoE designs are limited to a few affordable or possible cases because of time and resource constraints. Therefore, the results might not be holistic or not capable of defining globally optimal conditions. Virtual multidimensional DoE is a strong and low-cost tool for optimal equipment sizing and finding the best process parameters to reach CQA at high profitability. Also, by performing what-if analysis, it can be used for risk analysis and process control strategy development.

CASE STUDY 1, CHEMICAL REACTION AND REACTOR SCALE-UP STUDY

Figure 2 shows a parametric study for the evaluation of a batch reactor (coupling reaction) scale-up for an intermediate compound. The lab-scale equipment was a 0.1 L EasyMax with a 400 rpm stirrer, a heating rate of 1.8 °C/min, and a heat transfer coefficient of 1.2 W/K. The reaction kinetic parameters were estimated from this scale. Physical properties were modelled by a thermodynamic model (NRTL-NRF) and by the help of the NIST database. The large vessel, in comparison, has a lower heat transfer coefficient of around 0.1 W/K (an effect of the surface-to-volume ratio) and a heating rate of 0.3 °C/min with a different type of impeller at 115–150 rpm. This means that the heat removal/addition in the scaled-up version will be slower than in the lab-scale version, unless specific measures are taken to provide additional surface area or a higher temperature, for example by an internal coil. Therefore, the time required to heat or cool a batch of material tends to increase in the scaled-up version. Also, the mixing effect on the reaction rate and the heat and mass transfer was significant, which was modelled by CFD. Various studies were performed to investigate heat and mass transfer and the mixing effect, side reactions, conversion, and the utility and material cost (the detailed results are not shown here).

The client is provided with a set of toolboxes for selecting the optimal size of the manufacturing-scale reactor that gives adequate yield and for assessing Capex and Opex expenses. An optimisation study was then carried out to find the best size and process parameters for increasing the yield and reducing the cost.

After selecting the scale, the overall yield and the product and impurity mass profile were modelled for the selected scale. As noted above, there would be an optimal temperature or pressure to set during the reaction and/or an optimal time at which to stop the reaction. Figure 3 shows the scale optimisation for processing time. The impurity threshold was defined from chemistry knowledge to reduce the impact on downstream processes and the final quality of the API product. The 15% w/w impurity concentration (equal to an overall 2 kg of impurity in the vessel) was defined as the cut-off point, which also happens to be in the high yield of the reaction. This cannot be generalised in all cases in which the conversion/yield (process economy) may need to be sacrificed for quality reasons. However, reducing the generation of impurities would improve the cost and performance of the purification stage, which could justify the upstream loss of yield. This study defined the optimal processing time on the manufacturing scale. The modelling practice was fast and cheap in comparison to the scaled-up manufacturing of a large batch and then finding too much impurity in the product.

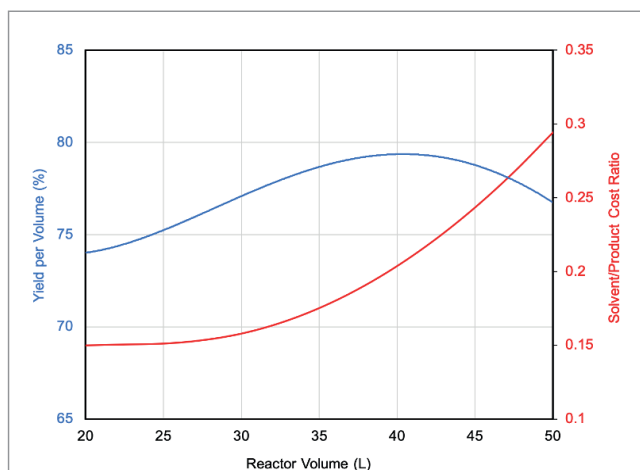


Figure 2. Results of the batch reactor scale-up model for scale selection based on yield and cost.

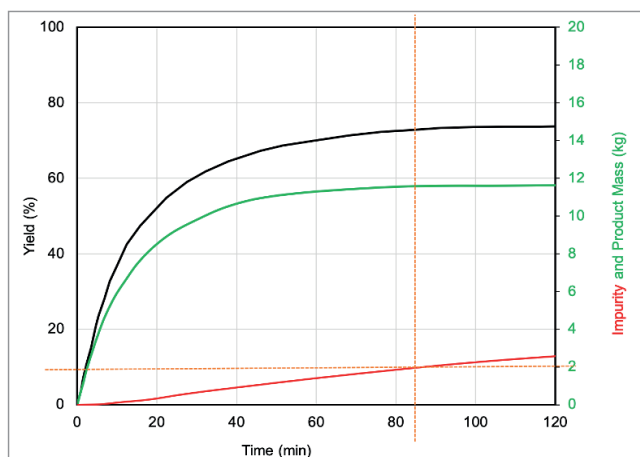
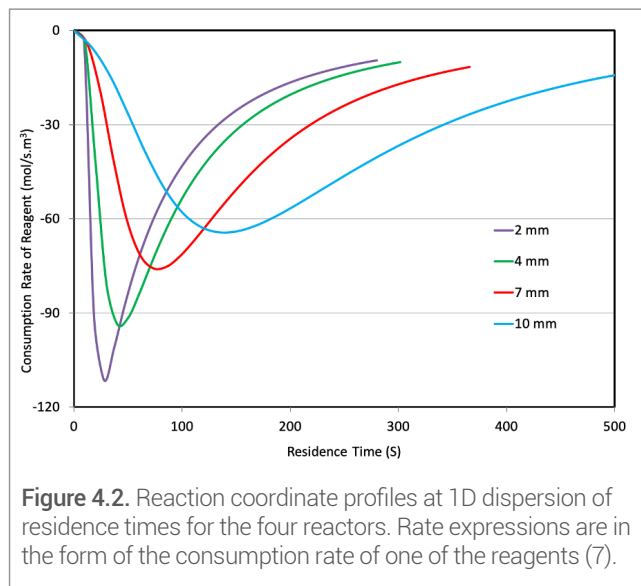
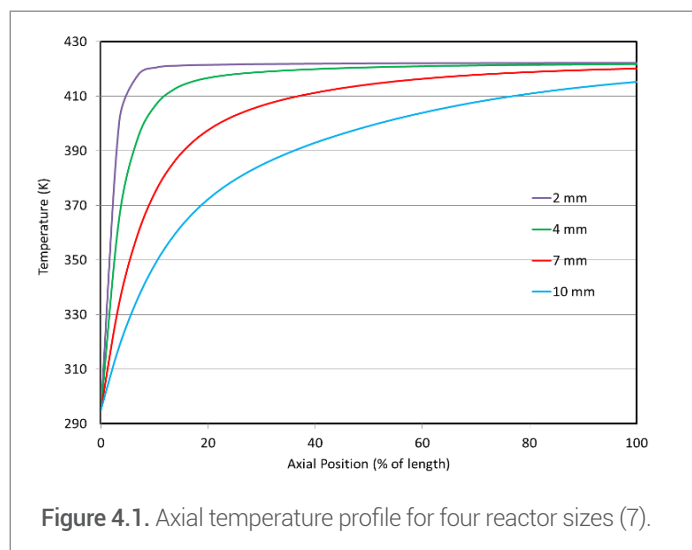


Figure 3. Large-scale reactor model for the concentration profile of product and impurity generation.

Another case study is the evaluation of a scaled-up plug flow reactor for flow chemistry. The technical details of the study are reported elsewhere (7). The diameter of the lab-scale reactor was 2 mm, and the scale-up to 7 and 10 mm and the effect of increased flow rate on reactor length, residence time, and conversion and yield were studied. In flow systems with low flow rates (low Reynolds number), increasing the reactor diameter would have a significant effect on axial and radial dispersion, macromixing, heat transfer, and concentration profile. Normally, static mixers are being used for PFRs with larger than 10 mm pipes to improve mixing and overcome these challenges.

The reaction is an endothermic Friedel-Crafts acylation reaction at 150 °C, with materials entering at room temperature and a jacket temperature of 150 °C. The heat transfer is from the wall surface to the core of the pipe; therefore, the boundary layer closer to the wall has a higher temperature. The result is that the reaction progresses faster at locations closer to the wall in comparison to the core of the pipe. This, in addition to the laminar flow velocity profile, causes radial dispersion and a radial concentration profile in the pipe. The average concentration over the length of the reactor levels off eventually. However, the effect of scale could be significant on side reactions and on localities with transport phenomena and reactions. For such reactive systems with a significant temperature change, the fluid properties (e.g. a mixture of solvents, reagents, products), such as viscosity, density, surface tension, and heat capacity, vary with changing concentration and temperature. Therefore, these variations impose considerable nonlinearities on the system, which means that the scale-up study requires multiphysics modelling (CFD, reaction, transport phenomena) (8).

Figure 4.1 shows the average axial temperature profile for four reactor sizes (diameters), which demonstrates that the smallest reactor reaches the equilibrium temperature quicker than the other reactors, whereas the largest reactor (without an internal static mixer) may never reach the equilibrium temperature. On the other hand, the reaction progress is temperature dependent (by activation energy). Figure 4.2 demonstrates the reaction coordinate profiles at 1D dispersion of residence times for the four reactors. The rate expressions are reported in the form of the consumption rate of one of the reagents.



CASE STUDY 2, CRYSTALLISATION SCALE-UP STUDY

Scaling up crystallisation processes is one of the most complex tasks as several target quantities must be kept within narrow boundaries, such as yield, selectivity, form, purity, and particle size distribution (9). The nucleation rate (an effect of the metastable zone width (MSZW)), crystal growth rate (mass transfer rate limitation), breakage or agglomeration, secondary nucleation, and the like are all somewhat kinetics and scale dependent. Most crystallisation models assume that there is a definable fixed value for MSZW, but attempts could be made to characterise its variability against process variables, such as agitation rates or the rate of change of supersaturation. CFD techniques that simultaneously solve population balance equations (PBEs) describing the nucleation and growth of crystals with momentum and mass transport equations for macro- and micromixing will be needed for scale-up studies (10). The use of PBEs is a hybrid approach that requires parameter estimation data on lab and manufacturing scales. Several operational parameters, such as temperature or impeller speed, need to be understood and controlled to achieve constant desupersaturation, a consistent narrow particle size distribution around the desired mean, minimal attritions (particle-particle, particle-wall, particle-impeller), and homogeneous growth conditions (11).

Three important aspects of large-scale crystallisation could directly impact the CQAs of the product:

- The particle size distribution could impact the downstream process for powder processing (such as a tablet press), drug release (dissolution rate), or direct application to dry powder inhalation. Proper modelling of shear rate, eddy diffusivity, mixing, mass transfer rate, and crystallisation kinetics on a large scale could provide repeatable results in comparison to the lab process development study (Figure 5).
- The impurity inclusion inside the crystal lattice (not surface impurity) depends on the effective distribution coefficient, which is a function of growth rate, agglomeration and solvent inclusion, and the equilibrium distribution coefficient (equation 8 in ref. (12)). A high growth rate could entrap more impurity molecules in the product. As mentioned above, the batch crystallisation process is a dynamic system, in

which the concentration ratio of impurity (kg impurity/kg of solute in the solution) in the mother liquid increases with crystallisation time. Therefore, the impurity inclusion rate increases during the process (based on the equilibrium distribution coefficient). Also, impurities could act as a shape modifier, which would also alter the final particle size distribution.

- Form change, polymorph, solvate formation, and solvent inclusion inside the crystalline particles that were not evident on a small scale could also take place in (not properly designed) large-scale equipment. This is more critical for enantiomeric and chiral systems and in conjunction with filtration and drying. Mixing issues and the generation of local heterogeneity could cause enantiomer and polymorph change around the local enantiomeric point. Scale-up evaluation and models are being developed to control the system far from this critical point, providing efficient mixing (but not so vigorous as to break down the crystal particles) for heat and mass transfer and a homogeneous system.

Figure 6.1 shows a scale-up study on the effect of impeller design and speed on mixing and shear rate. In this case, a multidimensional virtual DoE (with 300 cases) was developed for different design criteria (impeller, vessel, baffle) and supersaturation rates (concentration, cooling rate, and seeding cases). The white boxes in the top right corner of the screenshots show some design criteria and DoE case numbers. The model development for the system took less than two months, and the initial running of these 300 DoE cases took around 30 hours (multiphysics multiscale simulation by high-performance computation on a cloud cluster). The results helped in the optimal design of the large-scale system with respect to equipment design and process conditions and in reaching the required quality. In comparison, an experimental DoE study would not just be expensive or time-consuming, but it would be impossible to try all the different equipment sizes and designs. The developed tools provided the client with optimal equipment selection, CPPs, and design space optimisation, in a short time and at low cost. Figure 6.2 shows the 2D population balance modelling of the crystal size profile during the processing time. The time counter above the graph shows the corresponding processing time, indicating that the simulation took just a few seconds (use the QR code for a live demonstration of the model). The r2 parameter is the width and r1 is the length of the elongated crystals (the aspect ratio is around 2). The y-axis shows the number of crystals forming during the batch run.

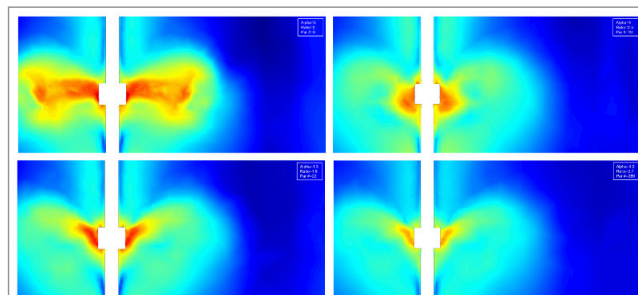


Figure 6.1. Scale-up study for the effect of mixing, shear rate, impeller design and speed, and supersaturation ratio.

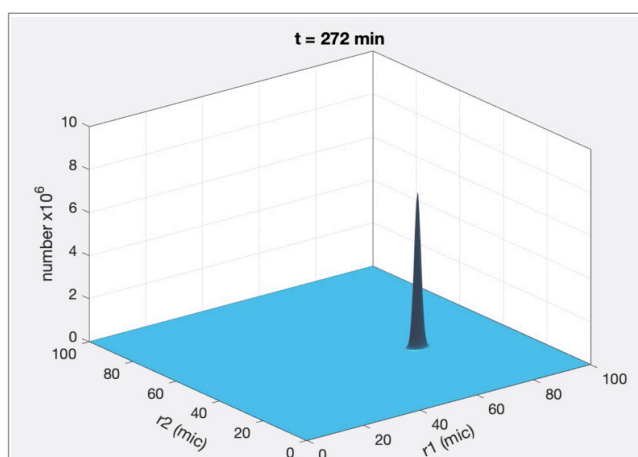


Figure 6.2. Results of 2D population balance modelling of crystal size profiles during the process.

FURTHER DISCUSSION AND FOLLOW-UP READING

This paper aimed to provide an overview of the modelling and simulations for process characterisation, equipment design, and scale-up. The paper was written for a diverse audience with a broad knowledge of process engineering, without deep technical discussions or 'boring' mathematical equations. Many important topics were not discussed because of page limitations, such as design space, risk management, sensitivity analysis, model verification and validation, and model life cycle management. A future paper will discuss applications of the modelling and simulations in QbD.



CONCLUSION

This paper aimed to provide an overview of the fundamentals, applications, benefits, and limitations of applications of mechanistic modelling for process and product development of APIs. The case studies demonstrated how mechanistic models can be used for process design, process scale-up, technology transfer, knowledge management, and risk analysis. In comparison to experimental DoE exploratory activities for defining process condition and equipment sizing, the model-based scale-up and optimisation is a powerful technique for achieving the desired product quality in a fast and low-cost fashion.

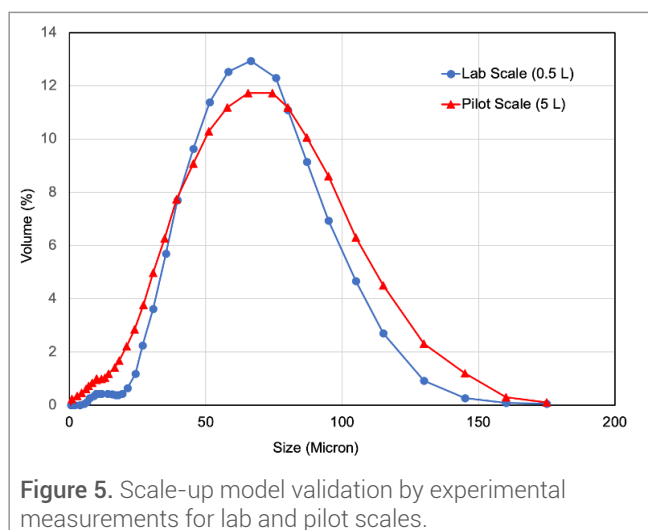


Figure 5. Scale-up model validation by experimental measurements for lab and pilot scales.

PROCESS DEVELOPMENT

Digital twin tools enable investigation of a large multidimensional virtual DoE for equipment characterization, developing an efficient design space, and intelligently mapping the CQAs to CPP to CMA correlation.

Conflict of Interest Statement: The author has no conflicts of interest to declare. All previously published works have been cited with provided references. Sensitive information in the case studies has been masked and renamed for confidentiality.

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