CESPE Conference 2023

Challenges & Solutions for transitioning to sustainable (bio)pharmaceutical manufacturing

Innovation Café

Pitch presentation & poster abstracts

GHENT UNIVERSITY

CESPE
CENTRE OF EXCELLENCE
SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

PITCH PRESENTATIONS

GHENT UNIVERSITY

CESPE
CENTRE OF EXCELLENCE
SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

Dichotomy of Single Use Plastics vs UN SDG's... can Big Pharma decarbonise its single use plastic ?

16h30

Malcolm Goggin

KPC International
Technological University Dublin

Confidential

GHENT UNIVERSITY

CESPE
CENTRE OF EXCELLENCE
SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

A holistic framework for integrated sustainability assessment for pharmaceuticals

16h37

Dr. Lisa Van Wilder

Department of Green Chemistry and Technology/Department of Public Health and Primary Care
Faculty of Bioscience Engineering/Faculty of Medicine and Health Sciences

GHENT UNIVERSITY

CESPE
CENTRE OF EXCELLENCE
SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

A holistic framework for integrated sustainability assessment for pharmaceuticals

Lisa Van Wilder[1,2]; Lieselot Boone[1]; Delphine De Smedt[2]; Jo Dewulf[1]

[1] Department of Green Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University
[2] Department of Public Health and Primary Care, Faculty of Medicine and Health Sciences, Ghent University

INTODUCTION

Over the past years, the pharmaceutical industry have been criticized for its large environmental impact [1]. Environmental pollution from pharmaceuticals occur during development and production, use and disposal of products and can damage ecosystems, increase antimicrobial resistance and generate substantial greenhouse gas emissions [2]. As a result, 'environmental sustainability' is increasingly present in today's society. Several sustainability assessment tools have been developed for pharmaceuticals, however, most assessments typically consider only parts of the pharmaceutical life cycle (e.g. drug production) and focus on the environmental burdens of resource use and emissions, defined as the 'footprint'. Indeed, these sustainability assessments usually do not simultaneously consider the beneficial impact of pharmaceutical care (e.g. human health benefit), the so-called handprint [3]. In addition, existing sustainability assessments are often limited to traditional impact categories, neglecting other dimensions of sustainability. Nevertheless, a comprehensive sustainability assessment should holistically capture the three pillars of sustainability, i.e. environment, social, and economic. Hence, environmental impacts should be considered together with other societal impacts such as welfare, equity, job creation or well-being. The European Union's Horizon Europe project "TransPharm" (grant agreement number: 101057816) aims to conceptualize and propose a holistic framework for integrated sustainability assessment for pharmaceuticals, based on the three pillars of sustainability and taking into account both footprint and handprint.

METHODS

In a first stage, a literature review was conducted to identify all building blocks from a theoretical point of view. In a second stage, the framework was checked with stakeholders and experts in the field of sustainability and/or healthcare involved in the TransPharm project.

RESULTS

The holistic framework has been developed and is illustrated in Figure 1.

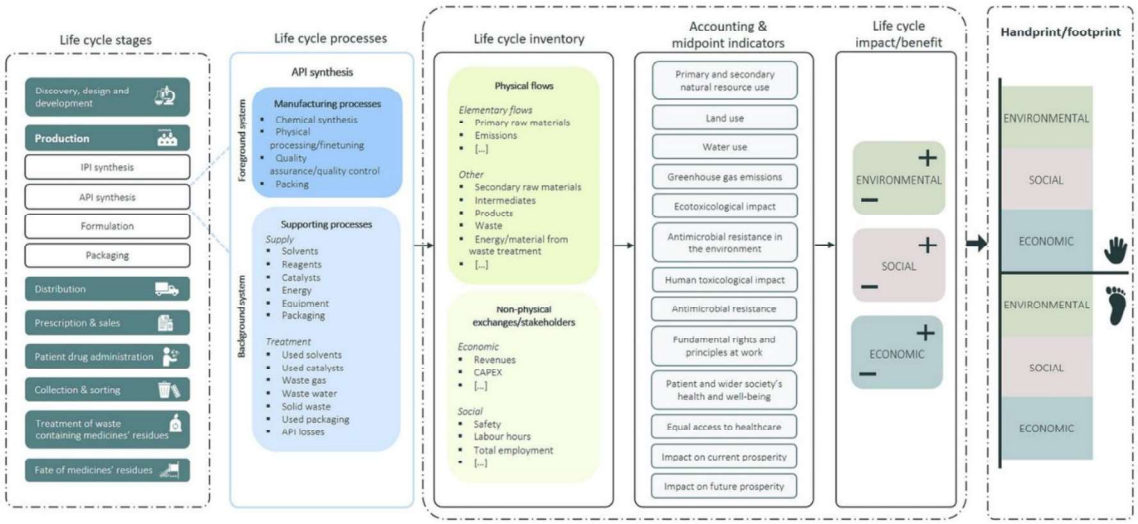


Figure 1. The holistic framework for integrated sustainability assessment for pharmaceuticals.

CONCLUSION

The framework is specifically tailored to the needs of end-users such as regulators, industry and the healthcare sector. It is generic in its applicability, hence allowing for crossover between industries, pharmaceutical type and/or stakeholders. Gaps, barriers and opportunities to achieve sustainability are identified and, accordingly, the holistic framework proposes the best available evidence for decision making. This work on the framework is on-going and future research will focus on how environment, society, and economy have to be weighted against each other and how this differs between stakeholders.

REFERENCES

(1) Van Snick, B.; Kumar, A.; Verstraeten, M.; Pandelaere, K.; Dhondt, J.; Di Pretoro, G.; De Beer, T.; Vervaet, C.; Vanhoorne, V. Impact of Material Properties and Process Variables on the Residence Time Distribution in Twin Screw Feeding Equipment. *Int. J. Pharm.* **2019**, *556*, 200–216. https://doi.org/10.1016/j.ijpharm.2018.11.076.

(1) Belkhir, L.; Elmeligi, A., Carbon footprint of the global pharmaceutical industry and relative impact of its major players. Journal of Cleaner Production **2019**, 214, 185-194.

(2) aus der Beek, T.; Weber, F. A.; Bergmann, A.; Hickmann, S.; Ebert, I.; Hein, A.; Küster, A., Pharmaceuticals in the environment—Global occurrences and perspectives. Environmental toxicology and chemistry **2016**, 35 (4), 823-835.

(3) Debaveye, S.; De Smedt, D.; Heirman, B.; Kavanagh, S.; Dewulf, J., Quantifying the handprint—Footprint balance into a single score: The example of pharmaceuticals. Plos one **2020**, 15 (2), e0229235.

Development of high drug-loaded pellets by means of PVA as a pelletisation aid to address swallowing difficulties in patients with dysphagia or for patients in need of personalized dosing

16h44

Goedele Craye

Laboratory of Pharmaceutical Technology
Faculty of Pharmaceutical Sciences

GHENT UNIVERSITY

CESPE
CENTRE OF EXCELLENCE
SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

Development of high drug-loaded pellets by means of PVA as a pelletisation aid to address swallowing difficulties in patients with dysphagia or for patients in need of personalized dosing

G. Craye[1]; A. Debunne[1]; C. Vervaet[1]; V. Vanhoorne[1]

[1] Laboratory of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, UGent, Ottergemsesteenweg 460, 9000 Gent, goedele.craye@ugent.be

INTRODUCTION

Aim of the DYSPEL project is the patient-centric development of a suitable drug dosage form for administration to patients with dysphagia and to patients in need of personalized dosing.

The shape and the size of conventional singe-unit solid drug dosage forms often limit the acceptability in these populations and negatively affect therapeutic adherence. This also leads to modification of the drug formulations by the patient or their caregivers, such as crushing the formulation and administering it with food, potentially resulting in an unvoluntary loss of bioavailability or, in case of modified release dosage forms, dose dumping and intoxication.

To increase acceptability of oral solid dosage forms in patients with dysphagia a multiparticulate drug delivery system (i.e. pellets), for high drug loading has been developed by means of an extrusion-spheronisation process. Advantages of pellets are dosing flexibility and ease of administration especially in combination with a swallowing gel. In a later stage coating can be applied to the pellets to further improve swallowability.

A patented UGent technology demonstrated that substituting microcrystalline cellulose (MCC) by a small amount of partially hydrolyzed polyvinyl alcohol (PVA) as pelletization aid, allowed to increase the drug load in pellets manufactured via extrusion-spheronisation up to 70 to 90% for acetaminophen (BCS class I-III) and metformin hydrochloride (BCS class III), respectively [1].

The current study aims to apply this technology to other drugs by evaluating partially hydrolyzed PVA as an alternative pelletization aid for MCC in the production of pellets with a high naproxen sodium load (NPX, BCS class II).

In parallel with the current study a clinical study was performed to evaluate the safety and acceptability of combinations of placebo pellets with swallowing gels in healthy volunteers. Aim of this clinical study is to determine the optimal combinations of (a) the amount of pellets and hence dose, (b) the average pellet size and (c) the commercial swallowing gel. The results from this clinical study will further guide the development of the pellet formulations.

MATERIALS AND METHODS

Various pellet formulations containing different concentrations of naproxen sodium (NPX 0, 20, 40, 60, 70, 80 and 90% w/w) and different ratios of PVA/MCC (0/100, 5/95, 10/90, 20/80) were manufactured via extrusion-spheronisation, using a single screw extruder (100 rpm) equipped with a dome-shaped extrusion screen (1 mm-perforations). Extrudates were spheronized (1000 rpm, 6 minutes) using a spheronizer having a cross-hatched geometry friction plate. The pellets were oven dried for 24 h at 40°C.

To evaluate the impact of the drug load and the amount of PVA on the pellet quality, pellets were characterized in terms of yield (fraction 710-1250 µm; >65%), particle shape (aspect ratio and sphericity; A50 and S50 > 0.80), particle surface (light microscopy and SEM) and friability (<1%).

A formulation meeting all the requirements was selected, and reproducibility (n=3) was verified.

In addition, batches of this formulation with a fixed drug load and varying PVA/MCC ratios were produced with an extrusion screen perforation diameter of 0.8mm and were characterised (fraction 500-1000 µm; friability <1%).

RESULTS

The addition of PVA as a pelletisation aid resulted in a decrease of the friability when compared to the use of MCC only and allowed for increased drug load while maintaining friability below 1%.

The formulation containing 60% NPX, 2% PVA and 38% MCC met all the predetermined pellet quality requirements and reproducibility (n=3 batches) was confirmed (yield: 74.7 ± 5.5; friability: 0.25 ± 0.10; A50: 0.79 ±0.01; S50: 0.81 ± 0.01).

Table 1 shows that the addition of PVA improved pellet friability compared to pellets with only MCC. The same findings were obtained for a smaller pellet size that was generated by means of an extrusion screen with 0.8 mm perforation diameter.

60% NPX	**Sieve fraction 710-1250 µm (Diameter Screen perforations 1mm)**	**Sieve fraction 500-1000 µm (Diameter Screen perforations 0,8mm)**
PVA/MCC ratio (% PVA in formulation)	Friability Mean ± sd (n=3)	Friability Mean ± sd (n=3)
0/100 (0%)	1,18 ± 0.20	2,13 ± 0.05
5/95 (2%)	0,14 ± 0.04	0,29 ± 0.04
10/90 (4%)	0,07 ± 0.03	0,12 ± 0.07
20/80 (8%)	0,06 ±0.01	0,03 ± 0.02

Table 1: Friability (%) of pellet formulations with 60% NPX load and different PVA/MCC ratios and 2 different pellet sizes

CONCLUSION

This study confirmed the applicability of the patented technology, which uses PVA as a pelletisation aid for the production of high drug-loaded pellets via extrusion-spheronization, with naproxen sodium and this was established for 2 different pellet sizes.

ACKNOWLEDGEMENTS

This research is financially supported by Bijzonder Onderzoeksfonds (BOF) UGent (IOF-Advanced/056).

REFERENCES

(1) Verstraete G.; De Jaeghere W.; Vercruysse J.; Grymonpré W.; Vanhoorne V.; Stauffer F.; De Beer T.; Bezuijen A.; Remon J.P.; Vervaet C.The use of partially hydrolysed polyvinylalcohol for the production of high drug-loaded sustained release pellets via extrusion-spheronization and coating: *in vitro* and *in vivo* evaluation, Int. J. Pharm.2017, 517, 88-95. https://doi.org/10.1016/j.ijpharm.2016.11.067

Accelerating drug product development by a model-based framework

16h51

Dr. Tuur Vandeputte

BIOMATH/Laboratory of Pharmaceutical Process Analytical Technology
Faculty of Pharmaceutical Sciences

GHENT UNIVERSITY

CESPE
CENTRE OF EXCELLENCE
SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

Accelerating drug product development by a model-based framework

Tuur Vandeputte[1,2]; Michael Ghijs[1,2]; Ingmar Nopens[1]; and Thomas De Beer[2]

[1] BIOMATH, Ghent University, Ghent, Belgium
[2] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Ghent, Belgium

INTRODUCTION

The pharmaceutical industry aims to boost drug product development (DPD) and production efficiency with concepts like continuous manufacturing, QbD, PAT, and Pharma 4.0. Within these frameworks, predictive models play a central role, resulting in extensive research and development (R&D) to mathematical models capable of describing the behavior of the various unit operations in the pharmaceutical manufacturing system.[1]

Within the scope of DPD, prediction models offer a significant advantage to reduce the experimental burden. However, model-based DPD approaches are not widely adopted in pharmaceutical R&D. Traditional Design of Experiments (DoE) methodologies remain widely used despite the challenges associated with this approach due to the scarcity of expensive active pharmaceutical ingredients (APIs), characteristic of this early stage of the DPD process. The limited use of model-based approaches is attributed to the lack of studies quantifying their benefits and pitfalls, especially when applied to entire production pathways.

This study presents a newly model-based DPD framework to optimize the manufacturing process (in this study continuous twin-screw wet granulation (TSWG)) of an unprecedented pharmaceutical formulation composition. The study identifies the most appropriate process conditions to meet the targeted quality attributes (QAs), and this starts from the material properties only. Finally, the study also quantifies the potential reduction in experimental efforts by comparing the conventional DoE approach with the proposed model-based framework.

MATERIAL AND METHODS

Industrial DPD assignments usually focus on new API components. This implies that there are often no prediction models available which were trained specifically on the materials for which the process is being optimized. Therefore, this optimization study was conducted by using a pharmaceutical formulation, which was not included in one of the different datasets used to develop the submodel structures.

Second, the ConsiGma 25™, a continuous TSWG powder-to-tablet manufacturing device, is utilized in this study for producing high-quality drug products. TSWG is employed in the pharmaceutical industry to enhance the powder flow properties for tableting.[2] The device is composed of several unit operations, of which the core processes are wet granulation and fluidized bed drying.

Further, three model structures are employed in the proposed model-based DPD framework. Two of the models focus on describing the system behavior of the core unit operations. While the third model struccture is dedicated to describing the energy consumption concerning the process settings.

To evaluate the DPD framework, a combined model structure connecting the manufacturing operation prediction models is used. This input-output model connection enables to take the impact of the granulation process settings on the product quality attributes in the subsequent drying stage into account during the process optimization. The combined model structure is constructed starting from the data-driven granulation model structure first suggested by Van Hauwermeiren[3] and the segregation-sensitive drying model described in the work of Vandeputte[4].

The primary objectives of the process optimization assignment were to achieve a high-quality drug product and maximize energy efficiency. Figure 1 gives a schematic overview of the model-based DPD framework followed in this study to determine the optimal process settings of the formulation studied. Overall, the proposed methodology in this study consists of three main tasks: (1) determining a workable Design Space (DS) through model evaluations, (2) characterizing the optimal process settings within the defined DS, and (3) experimentally validating the proposed combination of process settings.

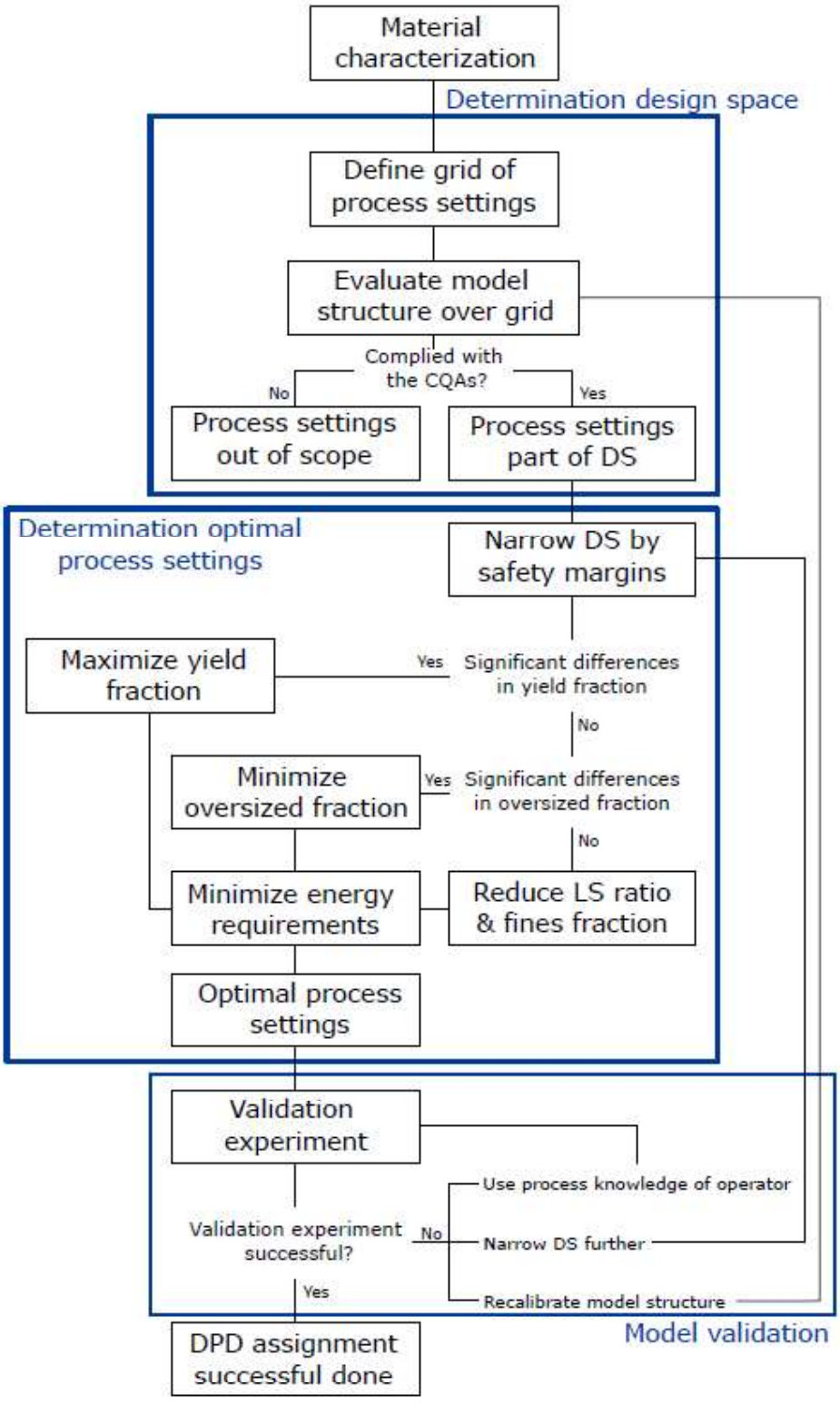


Figure 1: Overview of the model-based DPD framework [4]

RESULTS AND DISCUSSION

In the presented case study, the newly developed DPD framework is applied to an unprecedented formulation composition for the model structures. A process variable space, in which the end product was predicted to reach the quality targets was first defined. Subsequently, a certain safety margin on the quality targets and the energy efficiency was considered before the most appropriate set of process settings was determined. Finally, a validation experiment with the proposed process settings was performed, in which the granule and drying air features were monitored in function of drying time. Lastly, the QA of the final dried product was measured offline to validate the model predictions.

The results of the suggested experiments confirmed that the suggested operating points met the targeted QAs after granulation and drying of the new formulation. Dry and well-flowing granules were obtained at the proposed set of process settings. Moreover, an additional experiment, in which 13 consecutive cells were operated in sequence, demonstrated that the proposed continuous manufacturing procedure can operate stably. The 13 samples taken from different drying cells were subjected to the optimized drying conditions and a total drying time of 472 seconds. Subsequently, the QAs of the different samples were measured offline. From these analyses followed that all predetermined quality requirements were achieved in all samples. This result gives the scientific ground to claim that the proposed production process is stable.

Based on the preceding results, the applicability of the proposed model-based DPD framework is proven. Furthermore, a comparison with the conventional DoE approach has shown that the model-based DPD approach reduces the experimental work requirements significantly. It leads to a maximum reduction of 81.3% in time demand and 85.3% in material requirements to find the optimal process conditions for (new) pharmaceutical products. This reduction in material usage is particularly advantageous for the pharmaceutical industry, where API components are expensive and limited during the design phase of (new) drug products. However, it is essential to acknowledge that the case study was conducted in an academic setting, and further investigation is needed to transfer the findings accurately to an industrial environment.

CONCLUSION

This study presents an innovative mathematical approach to reduce the experimental effort during DPD. Different prediction models, each describing one of the core unit operations in the manufacturing process, were connected to obtain an overview of the entire production system. Furthermore, the study showed that the combined model structure combined with the proposed model-based DPD framework allowed the identification of an optimal set of process settings with less experimental work and consequently less API consumption.

Nevertheless, the proposed DPD framework was not able to eliminate all experimental work. Still, one validation experiment was required to verify if all QAs were achieved when the drug product was produced at the proposed set of process settings. It was concluded that the used mathematical models accurately predicted the process behavior of the continuous TSWG line, which resulted in high-quality pharmaceutical products at the proposed set of process settings.

Finally, the quantitative comparison between the conventional DoE approach and the proposed model-based DPD framework reveals that the latter achieved significant reductions in terms of the material and time requirements. Even though this study was conducted in a university setting, these results demonstrate the effectiveness of model-based approaches in efficiently optimizing pharmaceutical manufacturing processes.

REFERENCES

(1) European Medicines Agency (EMA). ICH guideline Q8 (R2) on pharmaceutical development. **2017**.

(2) Leane, M.; Pitt, K.; Reynolds, G. K.; Dawson, N.; Ziegler, I.; Szepes, A. Manufacturing classification system in the real world: factors influencing manufacturing process choices for filed commercial oral solid dosage formulations, case studies from industry and considerations for continuous processing. *Pharmaceutical development and technology* **2018**, 23, 964-977.

(3) Vandeputte, T.; Ghijs, M.; Nopens, I.; & De Beer, T. (2023). *Granule segregation as the vital component for a formulation-generic pharmaceutical fluidized bed drying model.* Ghent: Ghent University.

(4) Van Hauwermeiren, D.; Nopens, I.; & De Beer, T. (2020). *On the simulation of particle size distributions in continuous pharmaceutical wet granulation.* Ghent: Ghent University.

The application of Near-Infrared Spatially Resolved Spectroscopy in scope of achieving continuous real-time quality monitoring and control of tablets with challenging dimensions

16h58

Alexander De Man

Laboratory of Pharmaceutical Process Analytical Technology
Faculty of Pharmaceutical Sciences

GHENT UNIVERSITY

CESPE
CENTRE OF EXCELLENCE
SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

The application of Near-Infrared Spatially Resolved Spectroscopy in scope of achieving continuous real-time quality monitoring and control of tablets with challenging dimensions

A. De Man[1]; J.-S. Uyttersprot[2]; P.-F. Chavez[2]; F. Vandenbroucke[3]; F. Bovart[3]; T. De Beer[1,*]
[1] Ghent University, Laboratory of Pharmaceutical Process Analytical Technology, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[2] UCB Pharma, Pharma sciences, Chem. Du Foriest 1, 1420 Braine-l'Alleud, Belgium
[3] Pharma Technology, Rue Graham Bell 8, 1402 Thines (Nivelles), Belgium

INTRODUCTION

In scope of achieving real-time release of tablets, quality attributes need to be monitored and controlled through Process Analytical Technology tools such as Near-Infrared spectroscopy (NIRS). NIR spatially resolved spectroscopy (NIR-SRS) provides a balance between the fast but spatial information-lacking conventional NIRS and highly informative but time-consuming NIR chemical imaging (NIR-CI). NIR-SRS can be viewed as a simplified hyperspectral imaging system, where spatial and physicochemical information are obtained through fast multipoint NIR measurements. In this study, the suitability of NIR-SRS for continuous real-time quality monitoring and control of content uniformity, hardness and homogeneity of tablets with challenging dimensions was evaluated. A CUB-20 inspection unit (Pharma Technology, Nivelles, Belgium) with an integrated NIR-SRS probe (having nine built-in collection channels) was used as standalone equipment for the analysis of small oblong tablets (10.16 mm × 4.67 mm × 3.82 ± 0.18 mm) with deep cut break lines on both sides.

MATERIALS AND METHODS

A total of 66 tablets varying in tablet hardness (40 – 65 – 90 N) and Active Pharmaceutical Ingredient (API) content (70 to 130 % of the label claim) were inspected with the CUB-20. Each tablet was measured five times by reinserting the tablet in the CUB-20 inspection unit and measurements were repeated on three different days. Each tablet measurement resulted in a total of 45 individual spectra, obtained through five multipoint acquisitions (5 acquisitions x 9 collection channels) across the observed area of the tablet. Two different spectra selection methods were developed and applied to create different datasets for model development. The selection methods differed in the considered number of collection channels of the NIR-SRS probe and therefore the resulting number of spectra selected for model development. For a single tablet measurement, selected spectra were either averaged into a single spectrum or used as individual spectra in the development of Partial Least Squares (PLS) models for tablet content uniformity and hardness assessment. Spectra of the tablets were regressed against either their respective tableting blend API content (% of the label claim) or hardness (N) values. Model performance was evaluated through the Root Mean Square Error (RMSE) and coefficient of determination (R^2) of the calibration, cross-validation and test sets. Tablet homogeneity was visualized by regressing all 45 spectra obtained through a single tablet measurement using a content uniformity model.

RESULTS AND DISCUSSION

Various PLS models were developed and validated, of which the content uniformity models show higher accuracy. Tablet hardness models were developed as well, although the models obtained through the different spectra selection methods show similar model performance. Even though the hardness models are less accurate compared to those for content uniformity (relative RMSEp of 14 % vs 7.3 %), their predictions can be seen as sufficient to detect tablet deficiencies for downstream unit operations such as e.g. tablet coating. Tablet homogeneity was visualized by plotting a concentration heatmap on a tablet background image (mimicking the scanning pattern when the tablet moved past the NIR-SRS probe) in order to provide insight on API distribution.

CONCLUSION

The CUB-20 inspection unit offered a balance between fast and non-destructive measurements while still providing multipoint NIR data, allowing the monitoring of tablet API content, homogeneity and hardness. The PLS models showed favourable model performances, although future work should focus on using the true API content values of the inspected tablets to improve overall model performance and subsequent homogeneity analysis. The CUB-20 inspection unit is well-suited for fast analysis of tablet batches and could also be used for in-line inspection of tablets coming from a tablet press, although it would be limited to low-throughput experiments. However, the CU-120 production-scale counterpart allows high-throughput analysis up to 120 000 units/h. Future work should therefore investigate the scalability between these inspection units with regard to the analysis of tablets with challenging dimensions.

A mechanistic dynamic model of a continuous process of monoclonal antibody production in a perfusion bioreactor

17h05

Dr. Saba Daneshgar

BIOMATH

GHENT UNIVERSITY

CESPE
CENTRE OF EXCELLENCE
SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

A mechanistic dynamic model of a continuous process of monoclonal antibody production in a perfusion bioreactor

S. Daneshgar[1]; K. Solon[1]; T. Geuens[2]; E. Wouters[2]; K.Dierckx[2]; I. Nopens[1]; E. Torfs[1]

[1] BIOAMTH, Ghent University, Coupure Links 653, 9000 Gent, Belgium

[2] simAbs, BioVille, Agoralaan Abis, 3590 Diepenbeek, Belgium

INTRODUCTION

The production of monoclonal antibody (mAb) from mammalian cell cultures is an extremely complex process with a very large number inter-linked biochemical reactions. A dynamic model with sufficient prediction power can be potentially used to optimize the operational parameters of the process, perform scenario analysis, define different feeding strategies and provide online measurements for hard-to-measure variables (e.g., soft sensor for cell viability). To avoid building an unnecessary large and complex model, often a selection of macro reactions and species are used to construct the model. This usually involves selection of an a priori set of elementary reactions followed by a systematic model reduction to obtain a sufficiently simple model that can describe the process well enough for the purpose of project. The modelling studies on the mAb production process have been mostly focused on the batch or fed-batch processes [1-3] but the attention to continuous biomanufacturing has been increasing fast [4] . In this study, an innovative integrated continuous platform for mAb production using a bioreactor in perfusion mode is modelled. In perfusion mode, the bioreactor is fed with fresh cell culture medium (CCM) to replace the continually harvested CCM with the product. Through a bleed flow, the waste is also removed from the system and is replaced with fresh feed. This way, the bioreactor can run for much longer time periods than fed-batch mode.

MATERIALS & METHODS

The dynamic model was developed based on the mass balance equations for macro-components of the system including glucose, glutamine, lactate, ammonia, viable cells, dead cells and mAb composing a set of differential equations with 17 parameters in total. The growth rate equation was defined based on the monod kinetics for glucose, glutamine and ammonia while for the lactate a haldane kinetic was used to account for the inhibition effect on cell growth. The death rate of the cells was calculated with an inhibition form of the monod kinetic based on the growth rate. The model was then calibrated on a set of data from a 47-day perfusion experiment. The experiment starts with a few days of batch operation in which the cell growth starts after introducing an inoculum to the bioreactor. Since the models' parameters to fit the data showed different values in batch versus the perfusion operations, it was decided to first calibrate the model on the first few days of batch experiment. The last values of the model simulation at the end of the batch period were then considered as the initial points for the perfusion simulation. The calibration of the model parameters on the perfusion dataset was started from the previously calibrated values of the batch experiments. A variance-based sensitivity analysis, the Sobol method [5], was performed on the model parameters to identify the key parameters for the calibration of the model. The ranges for the parameters were selected based on expert knowledge and the available data in the literature. The calibrated model is then used to perform a scenario analysis to investigate different bleeding strategies. This included the current operation (1X bleeding per day), 5 times bleeding per day continuous bleeding all with the same total amount of bleed per day. The main objective is to be able to have a model-based estimation of the cell viability based on which a control system will be implemented for the continuous bleed flow rate. For this, a scenario was tested with a simple proportional controller and the viability set-point of 95%.

RESULTS

Figure 1a shows the results of the model calibration for glucose, viable cells and viability. In this experiment, the bleeding is done once a day, taking a fraction of the volume of the bioreactor and replacing it with the fresh media. The experimental data has a daily frequency and is measured before the bleeding thus making it difficult to see smaller dynamics due to the bleeding. Nevertheless, the model performs well in predicting the main dynamics of the system. It is important to note that the model seems to predict reductions in viability sooner than it is visible in the data. This can be explained with the fact that the dead cells are measured later than they are formed due to their attachment to the walls of the bioreactor at the initial phase of their formation. This results in counting no dead cells while they have been already produced in the system.

Figure 1b presents the results of the model simulation for the various bleeding scenarios. As there is yet no real experimentation for a bioreactor operating with continuous bleeding, it is difficult to validate the model simulations for the continuous bleeding scenarios based on the real data. However, the model output suggests that a much more stable operation could be achieved with the continuous bleeding. This can be seen in both manual and controlled continuous bleeding scenarios. In addition, the scenario with the controlled bleed flow rate shows a smaller peak in the death cells accumulation which leads to being able to avoid the viability to drop below 93% during the whole operation. By avoiding the complete depletion of the glucose, a higher viable cell concentration can be kept during the experiment.

CONCLUSION

With the ever increasing applications of continuous biopharmaceutical manufacturing, the attention has raised to using dynamic process models for on-line monitoring and optimisation. A novel perfusion bioreactor was designed for the continuous production of monoclonal antibody from animal cell culture. In this study a dynamic model has been developed for this process and was calibrated based on experimental data. The scenario analysis performed for the continuous bleeding strategy demonstrates the capability of the dynamic model to be used as a soft sensor for estimating cell viability (which is hard to measure in a continuous fashion) in a control system to keep the cell viability as high as possible for the long duration of the experiment. With the concept of digital twins (virtual replica of the physical system that simulates the operations in real-time) being introduced into the continuous biopharmaceutical manufacturing, a dynamic model with sufficient prediction power can be a great asset for moving towards a proactive control and management of such processes.

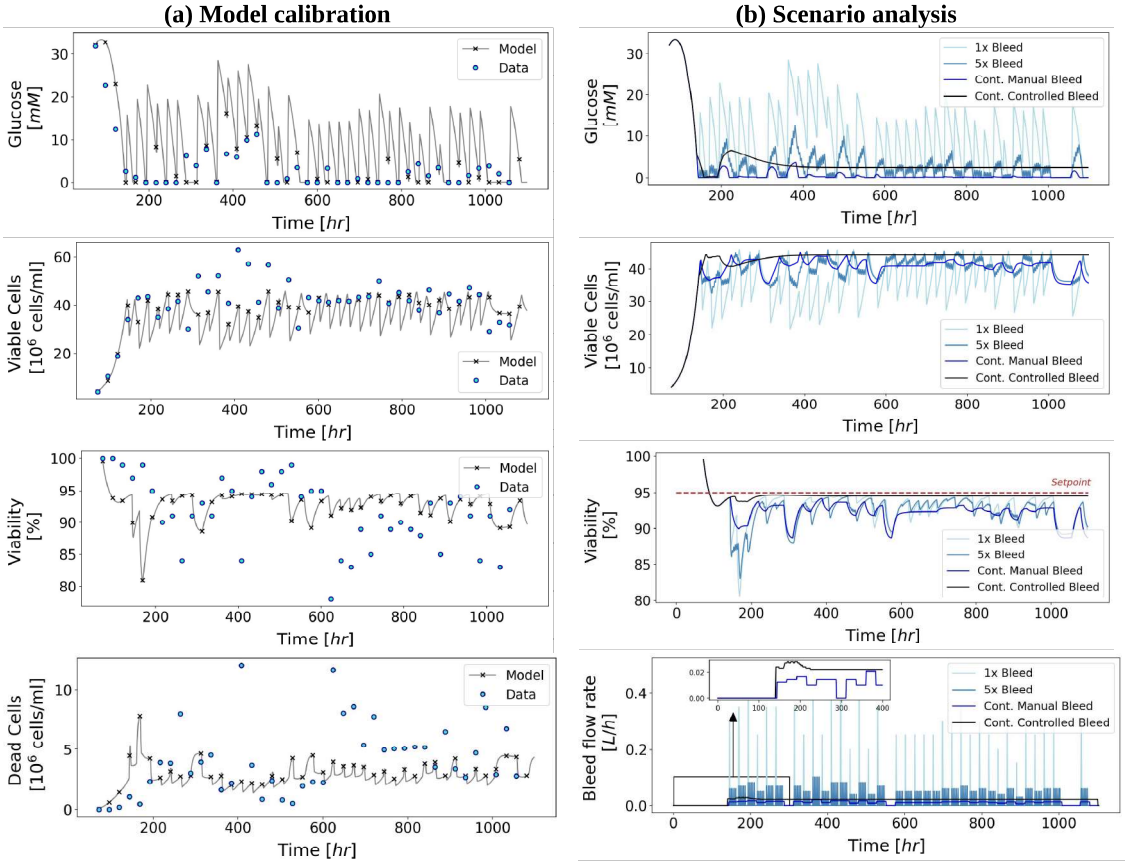


Figure 1. Results of the model calibration (left) and the scenario analysis (right) for glucose concentration, number of viable cells, percentage of cell viability and bleed flow rate.

REFERENCES

(1) Baughman, A.C.; Huang, X.; Sharfstein, S.T. and Martin, L.L. On the dynamic modeling of mammalian cell metabolism and mAb production. *Computers and Chemical Engineering*, **2010**, 34, 210-222.

(2) Gao, J., Gorenflo, V.M., Scharer, J.M. and Budman, H.M. Dynamic metabolic modeling for a MAB bioprocess. *Biotechnology Progress*, **2007**, 23, 168-181.

(3) Kontoravdi, C., Mantalaris, A., Pistikopoulos, E.N., Asprey, S.P., Katsika, A. and Gavrielides, Y. Towards the optimization of the production of monoclonal antibodies. *Computer Applications in Biotechnology*, **2004**, 213-218.

(4) Chopda, V., Gyorgypal, A., Yang, O., Singh, R., Ramachandran, R., Zhang, H., Tsilomelekis, G., Chundawat, S.P.S. and Ierapetritou, M.G., Recent advances in integrated process analytical techniques, modeling, and control strategies to enable continuous biomanufacturing of monoclonal antibodies. *J Chem Technol Biotechnol*, **2022**, 97: 2317-2335

(5) Saltelli, A., Ratto, M., Andres, T., Campolongo, F., Cariboni, J., Gatelli, D., Saisana, M., Tarantola, S. Global Sensitivity Analysis. The Primer, John Wiley & Sons, Ltd, Chichester, UK, **2007**, ISBN 9780470725184.

Towards the spin freeze-drying of cells: optimization of the freezing phase

17h12

Gust Nuytten

Laboratory of Pharmaceutical Process Analytical Technology
Faculty of Pharmaceutical Sciences

GHENT UNIVERSITY

CESPE
CENTRE OF EXCELLENCE
SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

Towards the spin freeze-drying of cells: optimization of the freezing phase

Gust Nuytten[1]; Thomas De Beer[1]

[1] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Ottergemsesteenweg 460, 9000 Gent, Belgium, gust.nuytten@ugent.be

INTRODUCTION

Cryopreservation is a common approach when cells need to be transported or stored for prolonged periods of time (e.g., in the context of cell therapies). For the proper freezing of cells, toxic cryoprotectants such as DMSO are often required, which results in side effects after administration to patients. Additionally, frozen cells need to be preserved at very cold temperatures (i.e., < -130 °C) in order to halt metabolism and prevent loss of function. This is a major drawback of cryopreservation, as the cost of sustaining complex cold chains is high, and not feasible everywhere across the globe. An alternative approach is to freeze-dry cells, which could enable less costly storage at higher temperatures.[1] The aim of this work was to take the first steps towards applying continuous spin freeze-drying to the freeze-drying of T-cells, as this approach may have important advantages with regards to the freeze-drying of cells, especially relating to the well-controlled freezing step.

MATERIALS & METHODS

Considering the importance of freezing in the context of cryopreservation, it is of interest to optimize the spin freezing step before proceeding to the optimization of the subsequent drying steps. To this end, the individual phases of the freezing process (see Figure 1) were controlled and investigated with regards to their effect on the cell viability of Jurkat T-cells. Additionally, both a DMSO-free and a DMSO-containing formulation were investigated. For the cooling phases, the cooling rate was varied between 1°C and 50°C. For the nucleation phase, the effect of inducing nucleation was investigated. Finally, the crystallization phase was varied by using freezing rates (i.e., the rate of energy transfer between rotating vial and cooling gas) between 1.8 and 60 W. Cell viability was measured using flow cytometry after fluorescent staining of the cells.

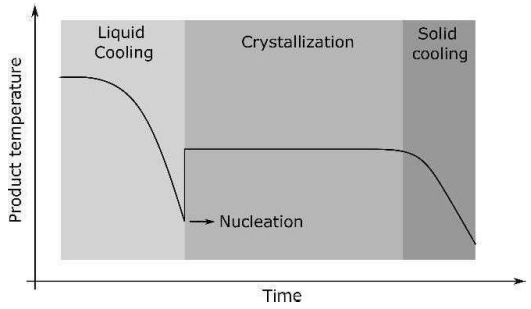


Figure 1 Product temperature over time during spin freezing.

RESULTS & DISCUSSION

The effects of freezing rate during the crystallization phase depend on the used formulation. The DMSO-containing formulation resulted in high viability at low to intermediate-high freezing rates, while the DMSO-free formulation reached comparable maximum cell viability, but performance at low freezing rates was poor. The effects of cooling rate during both cooling phases again depended on the used formulation. For the DMSO-containing formulation, an intermediate cooling rate proved to be optimal. The DMSO-free formulation resulted in high cell viability when a high cooling rate was used. Induced nucleation did not have a significant impact on cell viability in this work.

CONCLUSION

The obtained results indicate the relevance and opportunity of controlling the spin freezing step and its separate phases. The cooling and freezing phases in particular were important, while the nucleation phase was less relevant. By controlling the spin freezing step, viability after freezing may be maximized, and the use of toxic cryoprotectants such as DMSO may be avoided. This work provides a basis for the further investigation of the spin freeze-drying of T-cells.

REFERENCES

(1) Rockinger, U. Current Approaches of Preservation of Cells During (freeze-) Drying, J. Pharm. Sci 110 (8) 2873-2893 (2021).

POSTERS

Poster#	Title & Author
1	Automated visual inspection of continuously freeze-dried products using deep learning *Quentin Hervé, Laboratory of Pharmaceutical Process Analytical Technology*
2	Mechanistic modeling of the batch freeze-drying process with a revised outlook on product permeability *Gaia Sofia Comoli, Laboratory of Pharmaceutical Process Analytical Technology/Pharmaceutical Engineering Research Group*
3	Optimization of continuous spin freezing in single vial unit by implementing computational fluid dynamics *Isar Charmchi, Pharmaceutical Engineering Research Group*
4	Demonstration of Controlled Flexible Processing for an Optimised Continuous Freeze-Drying Cycle *Zarah Schaal, RheaVita/Laboratory of Pharmaceutical Process Analytical Technology*
5	Spin-freeze-drying of a live attenuated viral vaccine. *Frederik Laleman, Laboratory of Pharmaceutical Process Analytical Technology*
6	Validation of a new secondary drying model for spin-frozen formulations using in-line NIR spectroscopy *Laurens Leys, Laboratory of Pharmaceutical Process Analytical Technology*
7	Improving blend potency monitoring inside the feed frame of a rotary tablet press through the combined use of NIR and Raman spectroscopy *Alexander De Man, Laboratory of Pharmaceutical Process Analytical Technology*
8	Non Destructive THz TDS Quantification of Uncontrolled Agglomeration in Pharmaceutical Tablets *Dr. Alexander Ryckaert, Laboratory of Pharmaceutical Process Analytical Technology*
9	Impact of process settings on the quality attributes of low-dosed oral solid dosage forms produced via twin screw wet granulation *Louis Bouckaert, Laboratory of Pharmaceutical Technology*
10	The effect of filler particle size on the API homogeneity of controlled release formulations via continuous twin-screw granulation *Phaedra Denduyver, Laboratory of Pharmaceutical Technology*
11	Investigation of die filling performance during transfer from pilot to commercial scale production *Lisa De Souter, Laboratory of Pharmaceutical Process Analytical Technology*
12	An in silico framework for the robust tuning of a MPC for a continuous blender in a production line for pharmaceutical oral solid dosages *Ruben Waeytens, Laboratory of Pharmaceutical Process Analytical Technology/BIOMATH*
13	Model-based comparison of dissolution behavior between batch and continuous direct compression manufacturing platforms *Dr. Kensaku Matsunami, Laboratory of Pharmaceutical Process Analytical Technology/Pharmaceutical Engineering Research Group*
14	Impact of glidant addition on the continuous blending of cohesive active pharmaceutical ingredients *Tom Verbeek, Laboratory of Pharmaceutical Technology*
15	Analyzing the impact of screw-agitator rotational speed ratio on pharmaceutical powder feedability using DEM *Luz Naranjo, Pharmaceutical Engineering Research Group/Laboratory of Pharmaceutical Process Analytical Technology*
16	Implementation of a precursor transfer model within the CFD-DEM framework for a cold plasma fluidized bed coating reactor *Pedro Martin Salvador, Pharmaceutical Engineering Research Group/Laboratory of Pharmaceutical Process Analytical Technology*

GHENT UNIVERSITY

CESPE
CENTRE OF EXCELLENCE
SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

Automated visual inspection of continuously freeze-dried products using deep learning

Q. Herve[1], N. Ipek[2], J.Verwaeren[2], T. De Beer[1]

[1] 1 Laboratory of Pharmaceutical Process Analytical Technology, Department of Pharmaceutical Analysis, Ghent University, Ghent, Belgium

[2] 2 Research Unit Knowledge-based systems (BIOVISM lab), Department of Bioscience Engineering, Ghent University, Ghent, Belgium

INTRODUCTION

Continuous freeze drying has several manufacturing and process analytical control advantages compared to batch freeze-drying, including better visual inspection potential. Visual inspection of every freeze dried product is a key quality assessment after lyophilization of biopharmaceuticals to ensure that freeze-dried products are free from foreign particles and defects.

This quality assessment is labor-intensive for operators which needs to assess thousands of samples. The application of artificial intelligence, specifically deep learning and computer vision, on fast collected images from every freeze-dried product can quantitatively and qualitatively outperform the human visual inspection.

MATERIAL AND METHOD

For this study, continuously freeze dried samples were prepared based on a real world pharmaceutical product . Some samples were prepared correctly without any defects, while other samples were deliberately prepared in a way leading to defects and/or with particles. In this way, substantial diversity is ensured for model development. Images of all generated samples were captured using a dedicated image acquisition setup equipped with a high definition line scan camera.

RESULTS AND DISCUSSION

A two-step image analysis methodology was developed to address the inspection of freeze-dried vials. Initially, the goal was to determine the presence of foreign substances within the vials. To achieve this, advanced object detection algorithms, including Region-based Convolutional Neural Network (RCNN) and Faster R-CNN[1], were employed to detect fibers or other particulate matter in the freeze-dried product. The emphasis was on detection rather than precise localization To showcase the potential of this approach, specific metrics such as Intersection over Union[2] (IoU) were carefully considered and optimized, highlighting its effectiveness in detecting small objects.

In the second step, various Convolutional Neural Network architectures were investigated to classify the freeze-dried products based on quality attributes such as drug collapse, shrinkage, and cracks. Due to limited availability of data, Transfer Learning was utilized to enhance the training quality and compensate for the scarcity of training samples.

CONCLUSION

The performance of the particle detector and the defect classifier was evaluated on an unseen test set in comparison to a human visual inspection quality assessment. The validation results confirmed the robustness of the developed automated high-speed visual inspection method and the efficiency improvement in the visual inspection quality assessment.

REFERENCES

(1) Ren, S.; He, K.; Girshick, R.; Sun, J. Faster R-CNN: Towards Real-Time Object Detection with Region Proposal Networks. **2015**.

(2) Padilla, R.; Passos, W. L.; Dias, T. L. B.; Netto, S. L.; Da Silva, E. A. B. A Comparative Analysis of Object Detection Metrics with a Companion Open-Source Toolkit. *Electronics (Switzerland)* **2021**, *10* (3), 1–28. https://doi.org/10.3390/electronics10030279.

Mechanistic modeling of the batch freeze-drying process with an alternative expression for product permeability

Comoli G.S.[1,2]; Leys L.[1]; De Beer T.[1]; Kumar A.[2]

[1] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Ottergemsesteenweg 460, B-9000 Ghent, Belgium, GaiaSofia.Comoli@UGent.be

[2] Pharmaceutical Engineering Research Group, Ghent University, Ottergemsesteenweg 460, B-9000 Ghent, Belgium

INTRODUCTION

In the pharmaceutical domain, the use of mechanistic models has seen a steep rise in the last two decades, due to the introduction of Quality by Design framework. This study presents a model for the primary drying phase of batch freeze-drying, as classically described in literature[1], with an additional insight on the permeability parameter used to describe mass flow through the dried layer. The aim of the model is the description of the product temperature profile over time, given the shelf temperature and the chamber pressure. Permeability has been previously described as either a constant[1] or a linear relationship[2], being a function of the sublimation front position in the latter case. However, this research investigates the validity of a non-linear expression for the permeability.

MATERIALS AND METHODS

Theoretical equations

The model required the solution of Partial Differential Equations describing the heat transport in the frozen layer and vapor diffusion in the dried layer. The system is schematized in figure 1 and was solved with the software COMSOL Multiphysics® v.6.1. The proposed non-linear relationship for the permeability, inserted in Darcy's law equation, was as follows:

$$K = a + \frac{b * x}{1 + c * x}$$

with x [m] the sublimation front position coordinate and a,b,c fitting parameters. The choice of the best fitting values for all three permeability forms were obtained by parametric sweep, initialization values were found by trial-and-error.

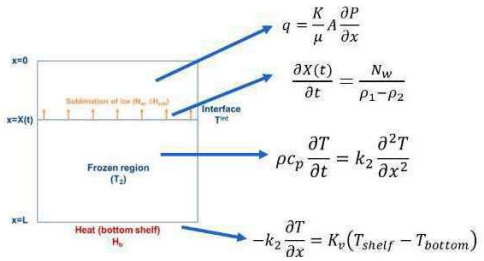


Figure 1. Schematic representation of the overall model framework to simulate primary drying step during freeze drying in a vial.

Experimental protocol

For the experimental validation a 3% m/V sucrose (Fagron) formulation was employed. 10R vials containing 3 ml of the formulation were disposed on a precooled shelf (3°C) of the freeze-dryer (Amsco FINNAQUA GT4, GEA). Freezing was performed at -40°C with a 1h equilibration time. Next, the pressure was set at 10 Pa and shelf temperature was increased to -20°C. Six center vials were monitored via type-K thermocouples.

RESULTS

The accuracy of the model prediction was compared for the three different cases. The discriminating results are the predicted primary drying time and the temperature profile difference of the model compared to the data. The former is indicated as a relative error, the latter as an absolute error. Both errors need to be minimized to have the best fit. The error on cycle duration and the product temperature were respectively 0.038 and 2.2°C for the constant case; 0.101 and 2.3°C for the linear case; 0.072 and 0.4°C for the non-linear case.

CONCLUSION

This study presented an improved expression of the permeability of the dried layer compared to the available literature. As shown in the results, neither of the two conventional options resulted in a good representation of the experimental data. The proposed non-linear relationship revealed an evident improvement. Further research supported by multiple validation cases is needed.

REFERENCES

(1) Liapis, A.I.; and R. Bruttini; A theory for the primary and secondary drying stages of the freeze-drying of pharmaceutical crystalline and amorphous solutes: comparison between experimental data and theory. *Separations Technology.* **1994**, *4(3)*, 144-155. https://doi.org/10.1016/0956-9618(94)80017-0

(2) Vilas, C.; A. Alonso, A.; Balsa-Canto, E.; López-Quiroga, E.; Trelea, I. C. Model-Based Real Time Operation of the Freeze-Drying Process. *Processes* **2020**, *8* (3), 325. https://doi.org/10.3390/pr8030325.

Optimization of continuous spin freezing in single vial unit by implementing computational fluid dynamics

Isar Charmchi[1,2]; Ashish Kumar[1]; Thomas De Beer[2]
[1] Pharmaceutical Engineering Research Group, Ghent University, Belgium
[2] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Belgium

INTRODUCTION

Freeze-drying is a widely used method for enhancing the stability and shelf life of heat sensitive and water-labile (bio)pharmaceuticals. As the pharmaceutical sector moves towards continuous manufacturing, a fundamental understanding of process dynamics is necessary to maintain control in continuous freeze-drying. The recently issued FDA guideline regarding continuous manufacturing of drug substances and drug products (Q13) emphasizes the importance of this understanding. The freeze-drying process consists of three consecutive phases: freezing, primary drying, and secondary drying. The freezing phase, which is the first step in the dehydration process, is crucial as it determines the ice shape, pore size, and drying conditions of the final dried product. In this work, a detailed computational fluid dynamics (CFD) model has been developed for the single vial unit (SVU) freeze dryer to understand the dynamics during the spin freezing step as part of a recently developed continuous freeze-drying process. The CFD simulation provides a local gas flow pattern inside the cooling chamber of the investigated system. Further, three different nozzle configuration is investigated in the SVU chamber by CFD simulation. Nozzle configuration is considered as the most important parameter in the freezing process. Further to conclude which nozzle configuration is suitable for spin freezing process, a separate simulation including the solidification of the drug product were performed.

MATERIAL AND METHODS

All internal aerodynamic simulations and solidification simulation were performed using ANSYS CFX 2022 R1 and ANSYS Fluent 2023 R1 respectively. The Menter Baseline (BSL) turbulence model [1] is used in both type of simulations. The details regarding in each simulation are discussed below.

Internal aerodynamics

The simplified geometry of SVU equipped with three different nozzle shapes is shown in Figure 1. All the simulation performed in steady state using Multi Reference Frame (MRF) approach to model spinning vial. A coupled approach is used for all simulations. Further, all simulations were performed using high resolution advection scheme and high resolution turbulence numerics available in Ansys CFX [1]. Inlet boundary conditions is set to mass flow of 0.00345 kg/s with the outlet boundary condition of relative pressure equal to 0 Pa for all the cases. Angular velocity in all the simulations are 5000 rpm.

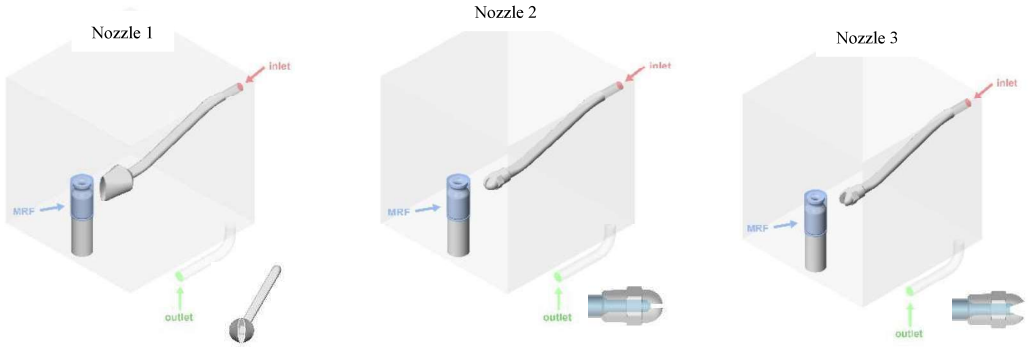


Figure 1: Geometry of SVU chamber equipped with three different nozzle shapes. Nozzle one designed at Ghent University. Nozzle 2 is flat spray nozzle and nozzle 3 is flat fan spray nozzle.

Solidification simulation

The Volume of Fluid (VOF) approach with implicit formulation of volume fraction is used to capture the interface between aqueous formulation and air inside the vial. Surface tension is captured by continuum surface force with 0.072 [N/m] as surface tension coefficient and wall adhesion is modeled with the 20^0 contact angle. Further, enthalpy-porosity [2] formulation was used to predict ice-solution interface. 10% sucrose solution is

used as aqueous formulation. Different material properties are set using compiled UDF for solid, liquid, and mushy region [3]. $T_{solidus}$ and $T_{liquidus}$ is 259.25 K and 272.52 K, respectively [3].

RESULTS AND DISCUSSION

Internal aerodynamics

Flow phenomena during spin freezing in the single vial freeze-dryer heavily depends on the nozzle configuration. Therefore, simulations of the single vial freeze-dryer with a variety of nozzle configurations have been performed. Streamlines of the cooling gas leaving different nozzle configurations indicates that the main cooling gas path from nozzle one is covering the vial wall much uniform than second and third nozzle (Figure 2). Further, the difference in the outlet velocity is due to the difference in the outlet area of the nozzles. These will effect the heat transfer coefficient of between cooling gas and the vial wall. Nozzle 2 focuses the cooling gas on one specific point, which could cause some parts of the product to freeze significantly faster than other parts.

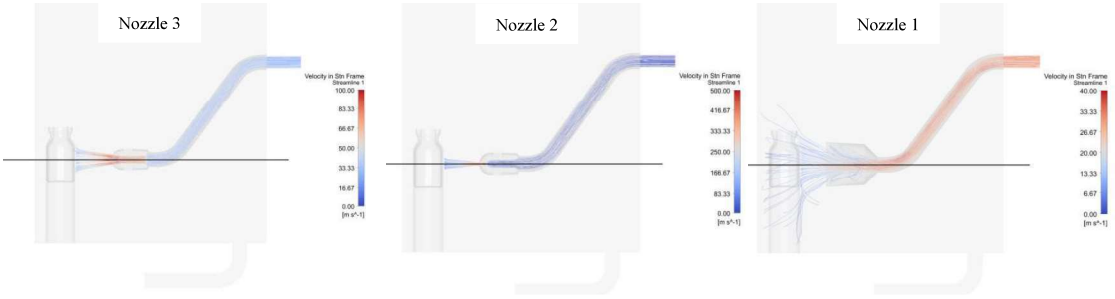


Figure 2: Streamlines of the cooling gas leaving different nozzle configurations. The full, black line indicates the center line of the nozzle outlet.

Figure 3 shows the turbulent kinetic energy (TKE) in different cases. In turbulent flows, higher TKE levels correspond to stronger turbulence and, consequently, a higher heat transfer coefficient, facilitating more efficient heat transfer between the fluid and the solid surface. Both nozzle 1 and nozzle 3 show a good vertical uniformity of TKE. However, for nozzle 3, TKE at the very bottom of the vial is lower than the middle of the vial.

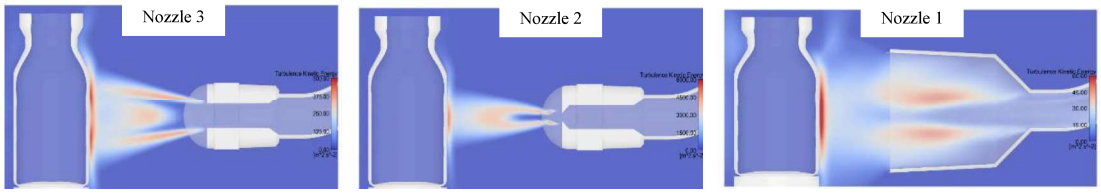


Figure 3: A slice showcasing a side view of the TKE for each nozzle to assess vertical uniformity of TKE at the vial wall

Solidification

For the freezing simulation, vial walls temperature are set equal to 220 k. Figure 4, presenting the liquid fraction of the aqueous solution inside the vial shows a bend in the film due to the ice expansion in the edges of the vial.

Figure 4: Liquid fraction of solution after 0.1 , 0.25, and 0.4 s from left to right respectively

CONCLUSION

In this study, we employed internal aerodynamic simulations to investigate the impact of different nozzle configurations on the spin freezing process. Our findings reveal that Nozzle 2 significantly enhances heat transfer in the vial's central region compared to the edges. However, it was observed that uniform cooling led to undesirable changes in the thickness of the frozen product during the spin freezing process. Specifically, the freezing simulation demonstrated that the aqueous formulation was frozen from the vial edges and results in the inhomogeneous freezed product thickness along the vial wall. Consequently, the internal aerodynamic simulation results indicate that Nozzle 2 exhibited higher heat transfer coefficients at the vial's central region compared to the other two nozzle configurations. These insights offer valuable knowledge for optimizing the spin freezing process and achieving better uniformity in solid distribution, thus enhancing the efficiency of subsequent drying processes.

REFERENCES

(1) Menter, F. R. Two-equation eddy-viscosity turbulence models for engineering applications. *AIAA Journal*,1994, *32*(8), 1598–1605. https://doi.org/10.2514/3.12149

(2) ANSYS inc. Ansys CFX-solver theory guide, 2022.

(3) Voller, V. R., & Swaminathan, C. R. General source-based method for solidification phase change. *Numerical Heat Transfer, Part B: Fundamentals*, 2019, *19*(2), 175–189. https://doi.org/10.1080/10407799108944962

(4) Mathlouthi, M., & Reiser, P. (Eds.). *Sucrose Properties and Applications*. Springer US. 1995, https://doi.org/10.1007/978-1-4615-2676-6

Demonstration of Controlled Flexible Processing for an Optimised Continuous Freeze-Drying Cycle

Zarah Schaal[1], Pieter-Jan van Bockstal[1], Joris Lammens[1], Julian Lenger[2], Adrian Funke[2], Stefan Schneid[2], Hristo Svilenov[3], Thomas De Beer[1]

[1] RheaVita, IIC UGent, Technologiepark Zwijnaarde 3, 9052 Ghent, Belgium
[2] Bayer AG, Pharmaceuticals, Friedrich-Ebert-Str. 475, 42096 Wuppertal, Germany
[3] Ghent University, Laboratory of General Biochemistry and Physical Pharmacy, Ottergemsesteenweg 460, 9000 Ghent, Belgium

INTRODUCTION

Continuous freeze-drying is an emerging manufacturing approach that allows enhanced real-time monitoring and control at the individual vial level as opposed to conventional batch lyophilisation. This study aims to investigate the impact of different critical process parameters (CPPs) during spin-freezing such as cooling rate and crystallisation rate, on the critical quality attributes (CQAs) of a model peptide formulation.

METHODS & MATERIALS

The continuous freeze-drying technology involves generating a thin layer of frozen product by rapidly spinning vials along their longitudinal axis whilst applying a cold gas flow during freezing. Subsequently, the spin-frozen samples are dried under vacuum with infrared heaters providing energy for sublimation and desorption. The assessed CQAs included monomer purity, peptide recovery, moisture content, cake appearance, and pore structure.

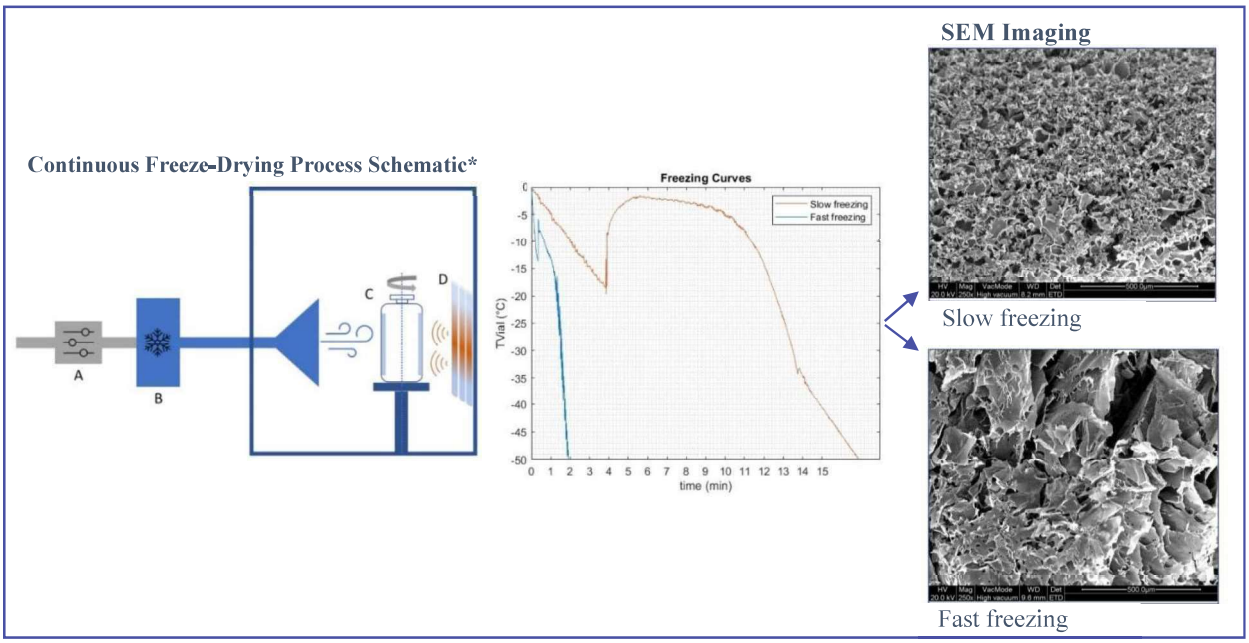
RESULTS & DISCUSSION

The findings revealed that varying the freezing parameters had no impact on monomer purity and peptide recovery, as their target specifications were met irrespective of the applied freezing conditions. However, different cooling and crystallisation rates significantly affected the cake appearance and pore structure of the final product. Lower crystallisation rates resulted in fewer cracks and less shrinkage compared to higher rates. In addition, scanning electron microscopy (SEM) imaging demonstrated clear differences in pore structure depending on the freezing conditions. Furthermore, in-line near-infrared (NIR) spectroscopy enabled real-time monitoring of residual moisture content during secondary drying, indicating variations in desorption kinetics as a function of freezing conditions.

CONCLUSION

Based on these insights, further evaluations will be conducted to determine how various process parameters impact the critical quality attributes (CQAs) of the drug product, with the aim of optimising both primary and secondary drying of the examined formulation.

The technology's high flexibility, real-time monitoring capabilities, and reduced processing times offer considerable benefits in terms of process development. Additionally, these advantages also provide opportunities for further customisation of freeze-drying cycles to meet specific product requirements and enhance the final product quality.



* Lammens, J., Goudarzi, N. M., Leys, L., Nuytten, G., Van Bockstal, P. J., Vervaet, C., Boone, M. N., & De Beer, T. Spin Freezing and Its Impact on Pore Size, Tortuosity and Solid State. Pharmaceutics, **2021**, 13(12), 2126. https://doi.org/10.3390/pharmaceutics13122126

Spin-freeze-drying of a live attenuated viral vaccine.

Frederik Laleman[1]; Frédéric Mathot[2]; Erwan Bourlès[2];Thomas De Beer[1]
[1] Ghent University, Ottergemsesteenweg 460, 9000 Gent
[2] GSK - Rue de l'Institut 89, 1330 Rixensart

INTRODUCTION

Live, attenuated viruses are used in many vaccines because of the strong immune response they generate. However, their low stability severely compromises their potency when formulated as an aqueous solution. Most live attenuated viral vaccines (LAVV) rely on lyophilization to preserve long-term stability and facilitate distribution. On the other hand, this well-established batch-drying process suffers from severe limitations, such as long processing times and batch-to-batch variations in product quality. These drawbacks have motivated the biopharmaceutical industry to explore innovative drying technologies. A continuous freeze-drying method that processes single dosages would be the most appealing option for vaccines.

MATERIAL AND METHODS

The spin-lyophilization process settings were optimized through mechanistic models and process analytical technologies (PAT). An annealing step was introduced during the freezing phase to promote the formation of larger ice crystals, thereby reducing the primary drying duration. The adverse effect of the thermal treatment on the desorption rate due to the increased specific surface area was assessed by measuring the moisture content in real time using near-infrared spectroscopy. Optimal settings were chosen to minimize the loss in viral infectivity and drying time. Finally, an accelerated stability study was conducted to ascertain whether this spin-lyophilized vaccine exhibited a comparable decline in viral infectivity when stored at 37°C for ten days as its traditional lyophilized counterparts.

RESULTS AND DISCUSSION

The spin-freeze-drying process was able to reduce the multi-day batch freeze-dry cycle by tenfold. Real-time inline near-infrared spectroscopy enabled stoppering at the target residual moisture content and monitoring of the desorption rate. This PAT approach facilitated secondary drying optimization, consuming a minimum amount of drug product. The additional annealing step during freezing reduced the primary drying duration by a factor of two, but this reduction in time was lost due to the slower desorption kinetics. A direct comparison of spin-and batch lyophilized samples during the accelerated stability study showed no significant difference in *in vitro* potency between the two drying technologies.

CONCLUSION

This study underscores the ability of innovative drying technologies, such as continuous spin-freeze drying, to preserve the long-term stability of live attenuated viral vaccines. Continuous spin-freeze-drying may have the potential to replace the time- and energy-consuming batch-freeze-drying process.

REFERENCES

(1) Hansen, L. J. J.; Daoussi, R.; Vervaet, C.; Remon, J.-P.; De Beer, T. R. M. Freeze-Drying of Live Virus Vaccines: A Review. *Vaccine* **2015**, *33* (42), 5507–5519. https://doi.org/10.1016/j.vaccine.2015.08.085.

(2) Meyer, L. De; Bockstal, P. Van; Corver, J.; Vervaet, C.; Remon, J. P.; Beer, T. De. Evaluation of Spin Freezing versus Conventional Freezing as Part of a Continuous Pharmaceutical Freeze-Drying Concept for Unit Doses. *Int. J. Pharm.* **2015**, *496* (1), 75–85. https://doi.org/10.1016/j.ijpharm.2015.05.025.

Validation of a new secondary drying model for spin-frozen formulations using in-line NIR spectroscopy

Laurens Leys[1]; Gust Nuytten[1]; Thomas De Beer[1]
[1] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University

INTRODUCTION

Using mechanistic models is an established method for process optimization in freeze-drying models. However, while primary drying models have proven to be very reliable, conventional desorption models tended to overestimate drying rates at the end of the secondary drying in several cases.[1,2] In this work, a new semi-mechanistic model was developed for a continuous spin freeze-drying process, introducing a residual moisture dependent activation energy for desorption.

METHODS

A semi-mechanistic lumped model was developed describing both heat and mass transfer phenomena for the desorption phase of the continuous spin freeze-drying process. This model assumes first order drying kinetics but was adapted by introducing a moisture dependent activation energy.[2,3] Both calibration and validation of the desorption model was performed by using an in-line NIR setup and a predictive machine learning model to monitor the residual moisture content over time during secondary drying. In addition, the effect of freezing rate on the pre-exponential kinetic desorption parameter was investigated.

RESULTS

By using a moisture dependent activation energy, a clear improvement was observed regarding the description of the desorption process in comparison with the conventional model. Validation results showed good overlap between the data and the prediction of the model for both residual moisture and product temperature. In addition, the influence of the freezing rate on the desorption kinetics was investigated showing that a higher freezing rate improved desorption kinetics.

CONCLUSION

Using the presented adapted model, a better understanding of the desorption phase during continuous lyophilization was created. In the future, this model can therefore reliably be used to optimize the secondary drying phase of the continuous spin freeze-drying process.

REFERENCES

(1) Trelea IC, Fonseca F, Passot S. Dynamic modeling of the secondary drying stage of freeze drying reveals distinct desorption kinetics for bound water. Dry Technol. 2016;34(3):335-345. doi:10.1080/07373937.2015.1054509

(2) Bobba S, Zinfollino N, Fissore D. Model-based design of secondary drying using in-line near-infrared spectroscopy data. Dry Technol. 2022;40(15):3186-3202. doi:10.1080/07373937.2021.2008423

(3) Chen X. The Basics of a Reaction Engineering Approach to Modeling Air-Drying of Small Droplets or Thin-Layer Materials. Dry Technol - DRY TECHNOL. 2008;26:627-639. doi:10.1080/07373930802045908

Improving blend potency monitoring inside the feed frame of a rotary tablet press through the combined use of NIR and Raman spectroscopy

A. De Man[1]; L. De Souter[1]; Z. Shi[2]; C.Mao[2]; T. De Beer[1]

[1] *Ghent University, Laboratory of Pharmaceutical Process Analytical Technology, Ottergemsesteenweg 460, 9000 Ghent, Belgium*

[2] *Small Molecule Pharmaceutical Sciences, Genentech, Inc., South San Francisco, California, 94080, USA*

INTRODUCTION

In the scope of achieving real-time release of pharmaceutical products through continuous manufacturing, Process Analytical Technology (PAT) is implemented at critical positions of the manufacturing line. This study presents the added value of combining both Near-Infrared (NIR) and Raman spectroscopy simultaneously inside the filling chamber of the feed frame of a continuous rotary tablet press. The main objective of this work was to evaluate the PAT performance of a multichannel "NIRaman" fiber optic probe to improve blend potency monitoring inside the feed frame.

MATERIALS AND METHODS

A 5-component platform formulation was of interest, where various blends with drug loads ranging from 0.75 % to 6.25 % (w/w) were investigated. Both steady-state and step-change experiments at fixed process conditions were conducted on a continuous rotary tablet press to obtain spectra containing information on blend potency. NIR and Raman spectra were collected in reflection mode using the NIRaman multichannel probe connected to a NIR diode array spectrometer and a Raman spectrometer. Equal numbers of both NIR and Raman spectra were extracted from the steady-state experiments to develop multiple calibration models. For every calibration model, spectra were first preprocessed and transformed into scores vectors through Principal Component Analysis (PCA) in order to combine the information present within both types of spectra. The relevant number of principal components (PCs) for both the NIR and Raman PCA models was determined based on the fractions of explained variance, resulting in equal numbers of NIR (N x K) and Raman (N x L) scores vectors. NIR and Raman scores vectors were subsequently merged in a single scores vector matrix (N x K+L) for further model development.

Partial Least Squares (PLS) regression was applied to regress PCA scores versus blend potency. Since not every PC score is ought to be equally relevant for method development, critical PCA scores were extracted first through a cross-validated Elastic Net regression step. Subsequently, optimized fused PLS calibration models (1 – 3 – 5 %) were obtained using the critical PCA scores as input features and fused models were externally validated through the step-change experiments. PLS models were evaluated through the Root Mean Square Error (RMSE) and coefficients of determination (R^2). Model performance was also assessed through prediction precision (Signal-to-Noise ratio) and accuracy (RMSEp) of the step-change experiments.

RESULTS AND DISCUSSION

Optimized fused PLS models were obtained through critical PCA scores selection based on cross-validated Elastic Net regression. For every calibration model, the critical feature selection resulted in the selection of both NIR and Raman PCA scores, suggesting that combining both spectral data proved beneficial. The model performance of the optimized fused PLS models was subsequently evaluated by predicting the independent step-change experiments. Accuracy and precision results were compared to those obtained with classic spectra-based models of the singular spectroscopy techniques. Apart from one fused calibration model, i.e. 1 % (w/w) fused PLS model, fused models showed improved Signal-to-Noise ratios and reduced prediction bias compared to the classic spectra-based models of the singular techniques.

CONCLUSION

The novelty of the current study lies in evaluating the PAT performance of a NIRaman probe for blend potency monitoring inside the filling chamber of the feed frame of a continuous rotary tablet press. Combining both NIR and Raman spectral data in scores-based PLS models proved beneficial for monitoring blend potency compared to separate models obtained through the singular spectroscopy techniques.

ACKNOWLEDGEMENTS

The authors would like to thank art photonics GmBh and Tornado Spectral Systems for the use of their equipment, as well as DFE Pharma for supplying excipients free of charge.

Non-Destructive THz-TDS Quantification of Uncontrolled Agglomeration in Pharmaceutical Tablets

A. Ryckaert[1]; K. Murphy[2]; T. Vandeputte[1], A. Anderson[3], D. Markle[2], T. De Beer[1]

[1] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Ottergemsesteenweg 460, Ghent, Belgium

[2] Strathclyde Institute of Pharmacy & Biomedical Sciences, University of Strathclyde, Glasgow G1 1XQ, UK

[3] Analytical development – Small molecules method development, Division of Janssen Pharmaceutica NV, Belgium

INTRODUCTION

Homogeneous distribution of the Active Pharmaceutical ingredient (API) in the powder blend ensures consistent content uniformity during manufacturing. However, uncontrolled API agglomeration of micronized API in the powder blend occurs frequently with the risk of content uniformity failure. Chemical imaging (CI) based both on Raman and near-infrared (NIR) has already been used to study the presence of API agglomerates in powder blends or tablets. Nevertheless, the use of NIR-CI for the analysis of agglomeration in tablets is a cumbersome technique as the sampling volume is small because the penetration depth of a NIR beam is less than 1 mm in most cases. Therefore, there is a need for a non-destructive transmission technique that offers a larger sample volume to accurately measure agglomeration in pharmaceutical compacts. Terahertz time-domain spectroscopy (THz-TDS) has emerged as a notable non-destructive technique sensitive to domain size changes but has never been evaluated for this purpose.

MATERIALS AND METHODS

Formulation and tablets

The formulation under study consisted of 13.3% (w/w) API, two fillers, a disintegrant, and a lubricant. Three batches of tablets with each a different API particle size distribution with a d50 value of 30 (batch A), 40 (batch B) and 50 µm (batch C)) were fabricated at various compaction pressures: 52, 104, 156, 208, 260, 312, and 416 MPa.

Spectroscopic techniques

THz-TDS measurements were carried out on a commercial system (TeraPulse Lx, Teraview) THz to non-destructively determine both the refractive index (RI) and loss coefficient of different tablet batches. In addition, the API homogeneity for all API batches was evaluated using a NIR-CI device.

RESULTS AND DISCUSSION

The RI of the compacts rises with increasing compaction pressure because a reduction in the sample porosity with increasing compaction is observed (Figure 1 – b). Surprisingly, the scattering contributions of the particles become less significant with increasing particle size, resulting in an overall decrease in the loss coefficient (Figure 1 – a). This contradicts the theory as a rise in particle size leads to more pronounced scattering. Since there is no noticeable change in the RI values (optical density) and the tablet assay has confirmed uniform API content throughout the batch (data not shown), this change in loss can only be attributed to a change in domain size or shape. Therefore, the higher loss coefficient values suggest that there is some form of uncontrolled agglomeration taking place with the two lowest API particle sizes.

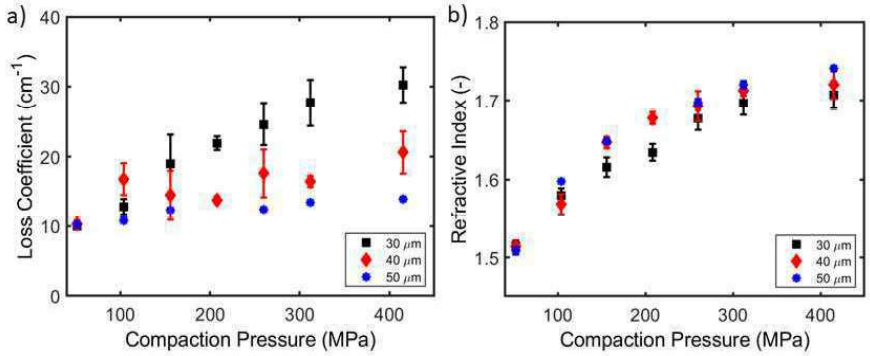


Figure 1: Loss coefficient extracted at 1 THz (a) and effective RI (b) for each of the particle size batches at various compaction pressures. The values plotted are the mean and standard deviation (n= 10).

The presence of agglomeration was subsequently evaluated by taking NIR-CI images of the tablets. For batch A, the score map of principal components 1 and 2 shows two features whereof the colour deviates from the remaining tablet surface. The loadings of these principal components were compared to the raw API spectra, which confirmed that the pixels corresponded to the API (data not shown). Although the effect was less pronounced for batch B, a smaller yellow dot in the score map of principal component 2 with a similar loading plot was observed, also demonstrating the presence of API agglomerates in these tablets. Agglomeration was not observed for the largest API particle size (i.e, batch C)

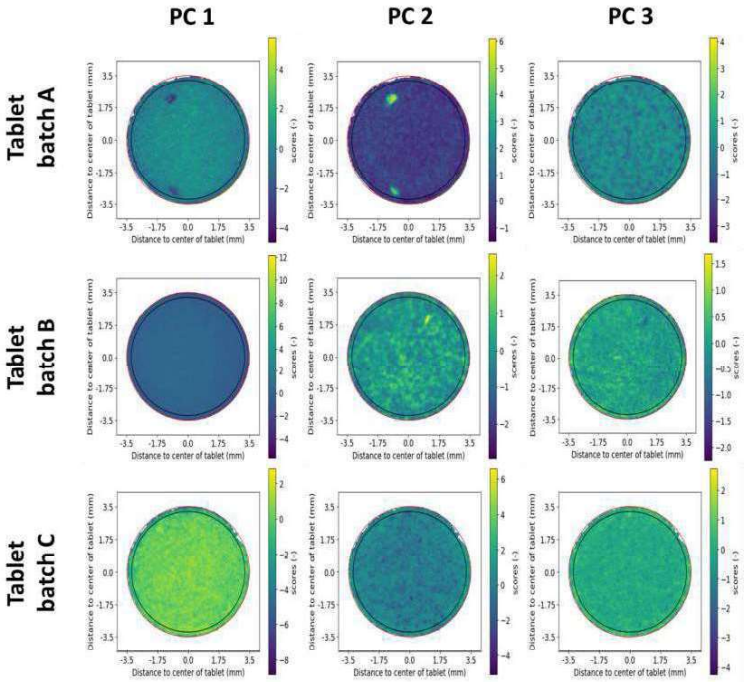


Figure 2: Score map plot for NIR-CI images recorded from the inside of a tablet manufactured at the lowest compression pressure (52 MPa) using the batch A B and C.

CONCLUSION

In this study, RI and loss coefficient of tablets manufactured at various compaction pressures ranging from 52 to 416 MPa using multiple API particle size distributions was determined using THz-TDS. API agglomeration was observed for tablet batches consisting of the two smallest API particle sizes and was subsequently confirmed using NIR-CI.

Impact of process settings on the quality attributes of low-dosed oral solid dosage forms produced via twin screw wet granulation

L. Bouckaert[1]; C.Portier[2]; V.Vanhoorne[3]; C.Vervaet[4]

[1] Department of Pharmaceutics, Ghent University, Ghent, Belgium, louis.bouckaert@ugent.be
[2] Department of Pharmaceutics, Ghent University, Ghent, Belgium, christoph.portier@ugent.be
[3] Department of Pharmaceutics, Ghent University, Ghent, Belgium, valérie.vanhoorne@ugent.be
[4] Department of Pharmaceutics, Ghent University, Ghent, Belgium, chris.vervaet@ugent.be

INTRODUCTION

Over the last decade, an increasing number of highly potent and more selective drugs have emerged from the drug development pipeline.[1] Consequently, these active pharmaceutical ingredients (APIs) need to be formulated in a low dose. The manufacturing of low-dosed oral solid dosage forms (OSDs) presents an additional challenge compared to manufacturing of OSDs with a higher drug content: ensuring the content uniformity (CU) requirements for the API.[2] The purpose of this study is to investigate which process parameters during twin screw wet granulation have an impact on the quality attributes of the low-dosed OSDs containing a freely water soluble API at a drug load of 1% w/w.

MATERIALS AND METHODS

To evaluate the impact of the process settings on the quality attributes of low-dosed OSDs, a full factorial screening design was conducted, varying the liquid-to-solid (L/S) ratio (0.21-0.28), screw speed (500-900rpm), binder addition method and screw configuration. This latter variable was implemented in the screening design as qualitative factor by changing the stagger angle (60° and 90° forward) of the penultimate kneading element in both kneading blocks. During this screening design, a freely water-soluble API was dissolved in the granulation liquid and added in a wet state to the process (i.e. wet addition method). In further research, the API will be preblended with the other excipients and fed gravimetrically in a dry state into the barrel. The CU of the tray dried granules was analyzed by separating them into seven size fractions.

RESULTS AND DISCUSSION

Among all the included variables, the L/S ratio and screw speed exhibited the most significant impact on the quality attributes. However, underdosing was observed for the smallest size fractions, a lower L/S ratio and screw speed resulted in improved CU for these fractions. In order to assess the relevance of these underdosed granules, their mass percentage was taken into account to determine the weighted average and the mean absolute deviation (MAD). A higher L/S ratio and screw speed resulted in a substantial reduction of fines, leading to the smallest MAD and improved friability. The method of binder addition and applied screw configurations had a negligible impact on the API distribution or other quality attributes.

When employing the wet API addition method, the API distribution is considered to be identical to the water distribution during the wet granulation process. The observation of underdosing in the smallest size fractions suggests that the L/S ratio is inadequate for these fractions.

CONCLUSION

A higher L/S ratio and screw speed yielded the smallest MAD, resulting in adequate quality attributes. Based on the results of this study, the wet API addition method of a freely water soluble API showed opportunities for further research in the continuous granulation process of low-dosed OSDs.

REFERENCES

(1) Janssen, M. *The Rise of HPAPI Molecules*. https://pharma.lonza.co.jp/-/media/Lonza/knowledge/Small-Molecules/Whitepapers%20and%20Executive%20Summaries/Lonza_whitepaper_Rise-of-HPAPI_SMM.pdf

(2) Bi, M.; Sun, C. C.; Alvarez, F.; Alvarez-Nunez, F. The Manufacture of Low-Dose Oral Solid Dosage Form to Support Early Clinical Studies Using an Automated Micro-Filing System. *AAPS PharmSciTech* 2011, *12* (1), 88. https://doi.org/10.1208/S12249-010-9549-Y.

The effect of filler particle size on the API homogeneity of controlled release formulations via continuous twin-screw granulation

P. Denduyver[1], C. Vervaet[1], V. Vanhoorne[1]

[1] **Ghent University**, Laboratory of Pharmaceutical Technology, Ottergemsesteenweg 460, B-9000 Ghent, Belgium, Phaedra.Denduyver@UGent.be, +32 92 64 81 18

INTRODUCTION

In previous research, hydroxypropyl methylcellulose (HPMC) was identified as suitable hydrophilic matrix former for controlled release formulations produced via twin screw granulation. However, an inhomogeneous distribution of theophylline over the sieve fractions was observed with underdosing of the API in the fines fraction (<150 µm), which could potentially result in content uniformity issues [1]. It was shown that the inhomogeneous API distribution is caused by the swelling properties of HPMC 90SH-4000SR into contact with water. Altering the process parameters did not yield a homogeneous API distribution. Therefore, the aim of current study is to investigate the effect of filler type and filler particle size on the API distribution over different sieve fractions during different stages of continuous granulation process of controlled release formulations.

MATERIALS & METHODS

Granules were produced via twin screw wet granulation. Ternary formulations consisting of theophylline/HPMC 90SH-4000SR/filler (20/20/60% w/w) were granulated, using lactose, mannitol, dicalcium phosphate (DCP) or microcrystalline cellulose (MCC) as filler. For each filler, two grades with distinct particle size distribution (PSD) were chosen. One grade had a d50 value smaller than the API, the other grade had a d50 value higher than the API. L/S-ratio for each filler grade was selected based on the granule quality (friability below 15% and less than 5% fines). Four stages of granule growth in the granulator barrel were defined, applying the compartmental approach described by Verstraeten et al [2]. Granules were collected from two stages, the wetting zone and the zone at the granulator outlet, the first and last zone respectively. Granules were divided in 7 sieve fractions and UV analysis was performed to measure theophylline content in the granule fractions.

RESULTS

The PSD of the filler has a distinct effect on the theophylline distribution over the sieve fractions throughout the different stages of the granulation process. In the wetting zone, underdosing of theophylline was observed in the 150-250 µm fraction using the filler grade with the smallest d50 values. The extent of theophylline underdosing in this size fraction was even more pronounced using the larger filler grades. In addition, theophylline underdosing was observed in the 250-500 µm fraction for all large filler grades and in the 500-710 µm fraction for the large mannitol grade. In the remaining fractions, theophylline was overdosed. These observations can be attributed to the larger primary particles present in those filler grades as these are not yet incorporated in granules in the first zone of the granulator barrel (i.e. wetting zone). At the granulator outlet, a more homogeneous API distribution is obtained for the smaller filler grades compared to larger fillers, but theophylline underdosing in the fines fraction is still present.

CONCLUSION

The impact of filler particle size on API homogeneity over different sieve fractions is highlighted for the continuous granulation of a controlled release formulation. Using a filler grade with a smaller particle size compared to the API had a positive effect on the API distribution over the various granule size fractions throughout the different compartments of the granulator barrel.

ACKNOWLEDGEMENTS

The authors would like to acknowledge ShinEtsu (Tokyo, Japan), DFE Pharma (Goch, Germany), JRS Pharma (Rosenberg, Germany), Roquette (Lestrem, France) and Merck (Darmstadt, Germany) for supplying the HPMC, lactose, dicalcium phosphate and mannitol, respectively.

REFERENCES

1. Vanhoorne V, Janssens L, Vercruysse J, De Beer T, Remon JP, Vervaet C. Continuous twin screw granulation of controlled release formulations with various HPMC grades. Int J Pharm [Internet]. 2016;511(2):1048–57. Available from: http://dx.doi.org/10.1016/j.ijpharm.2016.08.020

2. Verstraeten M, Van Hauwermeiren D, Lee K, Turnbull N, Wilsdon D, am Ende M, et al. In-depth experimental analysis of pharmaceutical twin-screw wet granulation in view of detailed process understanding. Int J Pharm [Internet]. 2017;529(1–2):678–93. Available from: http://dx.doi.org/10.1016/j.ijpharm.2017.07.045

Investigation of die filling performance during transfer from pilot to commercial scale production

L. De Souter[1], Bernardus Joseph Nitert[2], T. De Beer[1]

[1] Laboratory of Pharmaceutical Process Analytical Technology, Department of Pharmaceutical Analysis, Ghent University, Ghent, Belgium

[2] Janssen Pharmaceutica NV, Beerse, Belgium

INTRODUCTION

Throughput of a continuous manufacturing line (i.e. the amount of material that passes through the line per unit of time) is an important process parameter. When increasing the throughput (e.g. pilot to commercial scale production or to meet increased demand), there are some challenges that need to be investigated to ensure process robustness. For example, formulation characteristics which were not giving issues at low throughput, can give rise to suboptimal die filling at higher throughput due to changing powder flow. Consequently, higher tablet weight variations, capping and lamination, poor content uniformity can be observed. This study was performed to investigate and quantify the impact of throughput on tablet process performance.

METHOD

Sixteen divergent blends were characterized for their blend properties and included in a design of experiments to investigate the effect of process settings (turret speed, paddle speed (ratio), overfill and tablet diameter) and formulation properties on die filling performance. Partial least squares (PLS) regression was applied to correlate responses related to die filling performance and feed frame flow to the material property descriptors and process settings.

CONCLUSION

It could be concluded that an increase of the throughput had a major impact on die filling variability, which in its term is related to a reduced residence time and a lower fill fraction of the feed frame and dies. The impact of other investigated process settings was limited. On the other hand, a relatively higher die filling consistency was observed for dense, less porous, less compressible and better flowing powders. For each blend, the change in die filling variability as a function of throughput was quantified and used as a measure to assess the feasibility of scaling up to higher throughputs. Finally, external validation of the model predictability with 2 additional blends proved its validity and usefulness in the transfer from pilot to commercial scale production.

An in silico framework for the robust tuning of a MPC for a continuous blender in a production line for pharmaceutical oral solid dosages

Ruben Waeytens

Confidential

Model-based comparison of dissolution behavior between batch and continuous direct compression manufacturing platforms

Kensaku Matsunami[1]; Remco Mariën[2]; Valérie Vanhoorne[3]; Thomas De Beer[4]; Chris Vervaet[5]; Ashish Kumar[6]

[1] Pharmaceutical Engineering Research unit, Ghent University, Ghent, Belgium, kensaku.matsunami@ugent.be
[2] Pharmaceutical Engineering Research unit, Ghent University, Ghent, Belgium, remco.marien@ugent.be
[3] Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium, valerie.vanhoorne@ugent.be
[4] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Ghent, Belgium, thomas.debeer @ugent.be
[5] Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium, chris.vervaet@ugent.be
[6] Pharmaceutical Engineering Research unit, Ghent University, Ghent, Belgium, ashish.kumar@ugent.be

INTRODUCTION

In general, dissolution testing is considered a Critical-to-Quality Attribute for oral solid dosage forms. Along with the development of process analytical technology (PAT), real-time release testing (RTRt) of tablet dissolution has been attracting attention in the industry since it can reduce product lead-time significantly. RTRt is expected to be used in continuous manufacturing that is more beneficial than conventional batch manufacturing in terms of operation time, flexibility, process control, and cost[1]. Among possible routes of continuous manufacturing, continuous direct compression (CDC) is the most preferred route in terms of process simplicity and energy consumption.

So far, numerous studies have been performed for CDC, e.g., comparison with batch manufacturing[2], the analysis of key process parameters[3], and process analytical technology (PAT)[4]. While the application of CDC has increased in the industry, batch operation may still be needed during the research and development (R&D) phase due to the limited availability of active pharmaceutical ingredients (APIs). To shift from batch to continuous manufacturing smoothly, obtained process and product quality information during R&D should be transferable to CDC lines. For example, the applicability of CDC for commercially batch-produced tablets was analyzed[5]. However, a more detailed understanding of both processes is required toward a smooth shift from batch to continuous direct compression (DC)[5]. This study shows the model-based comparison of dissolution behavior between batch and continuous DC. Dissolution behavior is one of the most critical quality attributes (CQAs) and is therefore one of the key factors to keep similar when changing the process from batch to continuous manufacturing.

MATERIALS & METHODS

Tablets were produced in both a batch mode using a ModulTM P tablet press (GEA Pharma systems, Collette™, Wommelgem, Belgium) and continuous DC ConsiGma CDC-50 (GEA Pharma Systems, Collette™, Wommelgem, Belgium) using the same formulations to measure process performance and product quality. Ibuprofen was used as an API, whereas materials and composition ratio of excipients were varied, resulting in nine formulations. Each formulation was processed at three different hardnesses, and dissolution testing was performed with different pH values. During the operation, process performances, e.g., feed factor, main compression, and ejection forces, were monitored in addition to a near-infrared (NIR) probe placed in the feed frame to asses the blend uniformity; CQAs, e.g., dissolution, disintegration, content uniformity and hardness, were measured after the operation.

Different types of models, including statistical, empirical, and mechanistic models, have been applied to the analyses of experimental results. First, all blends were characterized by a principal component analysis (PCA) model. Then, two Partial Least Square (PLS) models were constructed to predict the blend uniformity in the feed frame prior to tableting and the content uniformity of the obtained tablets in a non-destructive manner, these models could then be linked to the dissolution behavior of the drug product. To understand the differences of dissolution behavior deeply, both empirical and mechanistic models of tablet dissolution were applied to experimental data. Finally, obtained results were further analyzed by statistical approaches.

RESULTS & DISCUSSION

Process responses were compared between batch and continuous DC lines. Higher ejection forces were observed for the CDC trials potentially due to different conditions of lubricant blending and compression. Several problems arose during the tableting process related to the blend properties, this required flexibility from the initial

experimental plan. Additional experiments with different process settings of lubricant blending and compression can identify the cause of different ejection forces.

Comparison of the dissolution profiles obtained after batch and CDC processing gave rise to identical dissolution curves, where the standard deviation of batch trials was larger compared to the ones obtained from the CDC trials. The difference can be linked to the highly controlled environment of the continuous line, where label claims were more consistent over time. Different hardnesses and pH ranges gave rise to different dissolution, as expected. The formulation compositions also had a significant impact on dissolution profiles, where more hydrophilic filler components exhibited slower release profiles in comparison to hydrophobic filler combinations. This observation could be attributed to the water competition effect. By fitting dissolution results into empirical and mechanistic models, the differences in the values of model parameters deepened the understanding of differences between batch and continuous DC lines as well as the impact of formulation properties and process settings. Through the analyses, key process parameters that need to be tuned from batch to CDC can be identified.

CONCLUSION

The model-based comparison of dissolution behavior was performed between batch and continuous DC. Comparison of the dissolution profiles obtained after batch and CDC processing gave rise to identical dissolution curves, where the standard deviation of batch trials was larger compared to the ones obtained from the CDC trials. From this work, it is concluded that the type of process, i.e. batch mode or continuous mode, did not change the dissolution dynamics of the resulting tablets significantly. Other factors, e.g., materials of fillers and disintegrant concentrations, played a more dominant role in changing dissolution kinetics. Therefore, changing from a batch process to a continuous process while keeping the formulation constant, does not lead to changes in dissolution performance.

ACKNOWLEDGMENTS

The authors would like to acknowledge, in no particular order, AstraZeneca and Janssen R&D for their financial support and fruitful collaboration in this project.

REFERENCES

(1) Ierapetritou, M.; Muzzio, F.; Reklaitis, G. Perspectives on the Continuous Manufacturing of Powder-Based Pharmaceutical Processes. *AIChE J.* **2016**, *62*, 1846–1862. https:// doi.org/10.1002/aic.15210.

(2) Karttunen, A.-P.; Wikström, H.; Tajarobi, P.; Fransson, M.; Sparén, A.; Marucci, M.; Ketolainen, J.; Folestad, S.; Korhonen, O.; Abrahmsén-Alami, S. Comparison between Integrated Continuous Direct Compression Line and Batch Processing – The Effect of Raw Material Properties. *Eur. J. Pharm. Sci.* **2019**, *133*, 40–53. https:// doi.org/10.1016/j.ejps.2019.03.001.

(3) Van Snick, B.; Holman, J.; Cunningham, C.; Kumar, A.; Vercruysse, J.; De Beer, T.; Remon, J. P.; Vervaet, C. Continuous Direct Compression as Manufacturing Platform for Sustained Release Tablets. *Int. J. Pharm.* **2017**, *519*, 390–407. https://doi.org/10.1016/j.ijpharm.2017.01.010.

(4) Bekaert, B.; Van Snick, B.; Pandelaere, K.; Dhondt, J.; Di Pretoro, G.; De Beer, T.; Vervaet, C.; Vanhoorne, V. Continuous Direct Compression: Development of an Empirical Predictive Model and Challenges Regarding PAT Implementation. *Int. J. Pharm. X* **2022**, *4*, 100110. https:// doi.org/10.1016/J.IJPX.2021.100110.

(5) Lyytikäinen, J.; Stasiak, P.; Kubelka, T.; Olenius, T.; Korhonen, O.; Ketolainen, J.; Ervasti, T. Parameter Optimization in a Continuous Direct Compression Process of Commercially Batch-Produced Bisoprolol Tablets. *Int. J. Pharm.* **2022**, *628*, 122355. https:// doi.org/10.1016/j.ijpharm.2022.122355.

Impact of glidant addition on the continuous blending of cohesive active pharmaceutical ingredients

T. Verbeek[1], A. De Man[2], B. Van Snick[3], M. Otava[3], T. De Beer[2], C. Vervaet[1] , V. Vanhoorne[1]

[1] **Ghent University**, Laboratory of Pharmaceutical Technology, Ottergemsesteenweg 460, B-9000 Ghent, Belgium, Valerie.Vanhoorne@UGent.be

[2] **Ghent University**, Laboratory of Pharmaceutical Process Analytical Technology, Ottergemsesteenweg 460, B-9000 Ghent, Belgium

[3] **Johnson & Johnson**, Pharmaceutical Research and Development, Division of Janssen Pharmaceutica, Turnhoutsesteenweg 30, B-2340 Beerse, Belgium

INTRODUCTION

In recent years, the interest in continuous direct compression (CDC) has significantly increased within the pharmaceutical industry. Good flowing, high density and poorly compressible powders showed excellent performance on loss-in-weight feeders. Nevertheless, a significant number of cohesive Active Pharmaceutical Ingredients (APIs) have been identified with severe processing issues at the feeding and refilling stages. These issues can affect the subsequent unit operations, e.g., blending unit, resulting in drug product quality issues. The main objective of this research is to evaluate the impact of the blender impeller speed, API loading, glidant type and glidant concentration on the blender hold-up mass.

MATERIALS & METHODS

Micronized acetaminophen and metoprolol tartrate, two cohesive APIs exhibiting processing issues (inconsistent feeding resulting in blend inhomogeneity) were selected to perform an in-depth feeding and blending analysis after pre-blending with three different glidants. For each API/glidant pair, a central composed faced design (CCF) was performed on the continuous GEA blender (Halle, Belgium) equipped with two loss-in-weight feeders. The compact feeder (GEA, Halle, Belgium) was used for the gravimetric feeding of the API/glidant pre-blend and the QT-20 (Coperion, Niel, Belgium) was used for the gravimetric feeding of a 2:3 pre-blend of Suptertab 11 SD and Prosolv SMCC 90. The CCF design varied the glidant concentration, API loading and impeller speed at a cumulative mass flow of 20 kg/h. First, Principal Component Analysis (PCA) was performed to group the different API/glidant pre-blends based on related properties. Second, a T-shaped Partial Least Regression (T-PLS) model was calibrated to link these blend properties to the blender-holdup mass, bulk residence time and blade passes.

RESULTS

The PCA analysis of the API/glidant pre-blends showed clustering for API, glidant type and glidant concentration. Generally, a higher glidant concentration for a cohesive API reduced the compressibility and increased the flow and density parameters. The T-PLS model revealed that the blender hold-up mass, bulk residence time and blade passes could all be linked to material characteristics and the impeller speed of the blender. A higher glidant concentration and reducing the API feed rate increased the bulk density and improved the flowability of the final blend, resulting in a higher blender hold-up mass.

CONCLUSION AND FUTURE PERSPECTIVES

This study established a direct link between the impeller speed, glidant type, glidant concentration and API loading on the one hand and the blender hold-up mass on the other hand. However, external continuous blending experiments including blend uniformity testing using spectroscopic techniques such as online near infrared monitoring should be performed for a more in-depth analysis.

ACKNOWLEDGEMENTS

VLAIO and Janssen Pharmaceutica are acknowledged for co-funding the study.

Analyzing the impact of screw-agitator rotational speed ratio on pharmaceutical powder feedability using DEM

L. Naranjo[1,3]; P. Van Liedekerke[2]; T. De Beer[3]; A. Kumar[1]

[1] PharmaEng, Department of Pharmaceutical Analysis, Ghent University, Ottergemsesteenweg 460, Ghent, 9000, Belgium, luz.naranjo@ugent.be

[2] Department of Data Analysis and Mathematical Modelling, Ghent University, Coupure Links 653, Ghent, 9000, Belgium, paul.vanliedekerke@ugent.be

[3] LPPAT, Department of Pharmaceutical Analysis, Ghent University, Ottergemsesteenweg 460, Ghent, 9000, Belgium, thomas.debeer@ugent.be

INTRODUCTION

Powder feeding is crucial in continuous pharmaceutical manufacturing. It must provide precise and consistent material discharge to the subsequent manufacturing steps. Good flowing powders pose fewer handling issues, while challenging materials that tend to stick may need density conditioning and flow facilitation with an agitator. The agitation system prevents bridging and ensures a stable and accurate mass flow rate.

Recent studies show that the agitator influences feeding behavior, affecting flow patterns (e.g., funnel flow), bulk density distribution, mass flow rate variability, and material traceability[1]. All these aspects suggest that controlling screws and agitator speed independently could be beneficial. This contribution uses a combination of experimental and predictive modeling tools-Discrete Element Method (DEM) to understand the impact of the agitator on flow and mixing behavior when changing the rotational speed ratio. The insight will enable the adequate selection of feeding operating conditions based on material characteristics.

MATERIALS & METHODS

This contribution studies the effect of screw-agitator rotational speed changes on powder feedability using a twin-screw LIW feeder. Three powders with different flowability levels are tested in a virtual emptying feeding experiment. The obtained results include mass flow rate, flow patterns, and variability of the mass flow rate from setpoint. The methodology uses a virtual replicate of the LIW feeder to perform a design of simulations (DoS) using scaled monodisperse bi-spheres and Hertz-Mindlin with JKR contact model[2]. A set of emptying experiments with a free-flowing powder is performed to validate the DEM simulation, using white and pink colored powders.

RESULTS & DISCUSSION

DEM simulation results show the flow profile development for different powders and operating conditions. Three relevant aspects are observed: non-uniform flow with agitator-induced bypass, stagnant zones, and powder back preferential extraction. Regarding the screw-agitator ratio, it is clear that it influences flow patterns and mass flow rate values. This is especially evident for poorly flowing powders, which show a cyclic variability at a high screw-agitator ratio (i.e., low agitator speed), as seen in Figure 1. In contrast, free and intermediately flowing powders show low sensitivity to changes in ratio. Lastly, the predictive capabilities of the DEM model are confirmed as a similarity in the main flow characteristics is observed between the model and the colored emptying experiments.

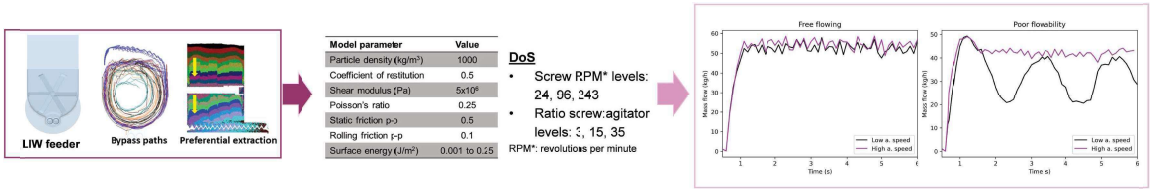


Figure 1. DEM flow pattern and mass flow rate predictions for a free-flowing and cohesive powders

CONCLUSION

The results of this contribution confirm the ability of DEM as a tool to provide detailed insight into the flow pattern development in a feeding system considering different powder characteristics and operating conditions.

The modeling and experimental results show the relevance of an adequate selection of the screw-agitator ratio in the feeding process to ensure, in some cases (e.g., cohesive powders), a system less prone to feeding challenges and reduce mass flow rate variability. Besides, these results could be considered an initial step towards determining an adequate or optimal operating window (e.g., a minimum level of agitation required to induce unhindered flow or reduce mass flow rate variability from setpoint) instead of using a fixed screw-agitator ratio.

Acknowledgements

The financial support for this research from BOF (Bijzonder Onderzoeksfonds Universiteit Gent, Research Fund Ghent University) and the experimental support from Fette Compacting (Fette Compacting Belgium, Mechelen, Belgium) are gratefully acknowledged.

REFERENCES

(1) De Souter, L.; Waeytens, R.; Van Hauwermeiren, D.; Grymonpré, W.; Bekaert, B.; Nopens, I.; De Beer, T. Elucidation of the Powder Flow Pattern in a Twin-Screw Liw-Feeder for Various Refill Regimes. International

(2) Johnson, K.; Kendall, K.; Roberts, A. Surface Energy and the Contact of Elastic Solids. *Proc. R. Soc. London. A. Math. Phys. Sci.* **1971**, *324* (1558), 301–313. https://doi.org/10.1098/rspa.1971.0141.

Implementation of a precursor transfer model within the CFD-DEM framework for a cold plasma fluidized bed coating reactor

P. Martin Salvador[1,2]; T. De Beer[2]; A. Kumar[1]
[1] Pharmaceutical Engineering Research Group (PharmaEng), Ghent University
[2] Laboratory of Pharmaceutical Process Analytical Technology (LPPAT), Ghent University

INTRODUCTION

Surface functionalization of particles is an effective approach to introduce new characteristics or new functionality, such as improved flowability[1] and hydrophobicity in otherwise hydrophilic materials[2]. This has applications in the production of pharmaceuticals and many other industries. We choose to model the fluidization and coating process with the Discrete Elements Method (DEM) framework coupled with Computational Fluid Dynamics (CFD), as it has been proven on many occasions to successfully represent the behaviors present in such processes[3]. We present here the model we use together with the CFDEM coupling software[4] capabilities to reproduce the transfer of precursor to the powder particles surface.

MODEL DESCRIPTION

The CFD-DEM equations of motion are extensively discussed by Zhou[5]. The two types of motion, translational and rotational, are governed by

$$m_i \frac{d\boldsymbol{v}_i}{dt} = \boldsymbol{f}_{pf,i} + \sum_{j=1}^{kc}\left(\boldsymbol{f}_{c,ij} + \boldsymbol{f}_{d,ij}\right) + m_i\boldsymbol{g} \qquad 1$$

and

$$I_i \frac{d\boldsymbol{\omega}_i}{dt} = \sum_{j=1}^{kc}\left(\boldsymbol{M}_{t,ij} + \boldsymbol{M}_{r,ij}\right) \qquad 2$$

Where $\boldsymbol{v}_i$ and $\boldsymbol{\omega}_i$ are the translational and angular velocity of the particle, kc is the number of particles that interact with the particle, $\boldsymbol{f}_{pf,i}$ the particle-fluid interaction force, $\boldsymbol{f}_{c,ij}$ and $\boldsymbol{f}_{d,ij}$ the elastic and viscous damping forces, and $\boldsymbol{M}_{t,ij}$ and $\boldsymbol{M}_{r,ij}$ the torque generated by tangential and rolling friction forces. Note that $\boldsymbol{f}_{pf,i}$ includes several forces, of which we use the drag, pressure gradient and viscous forces. On the fluid side, the formulation includes the mass, momentum and heat conservation equations, extensively discussed in the literature. On the particle side, the application of coating is seen as a change in particle mass m_p:

$$\frac{dm_p}{dt} = -k_i \rho_{pre} a_{p,i} cg^3 \qquad 3$$

Where k_i is the mass transfer coefficient evaluated from the correlation by Gunn[6], $a_{p,i}$ the surface area of the spherical particle, and cg the coarse graining factor. Coarse graining is an important tool to reduce the number of particles and hence the computational requirements of the simulations.

RESULTS

The simulations show that not all particles are coated the same, especially during the first few seconds after starting the process. Many particles have not yet had any coating applied after 11s, as seen in figure 1, however after 23 seconds a normal distribution starts to develop.

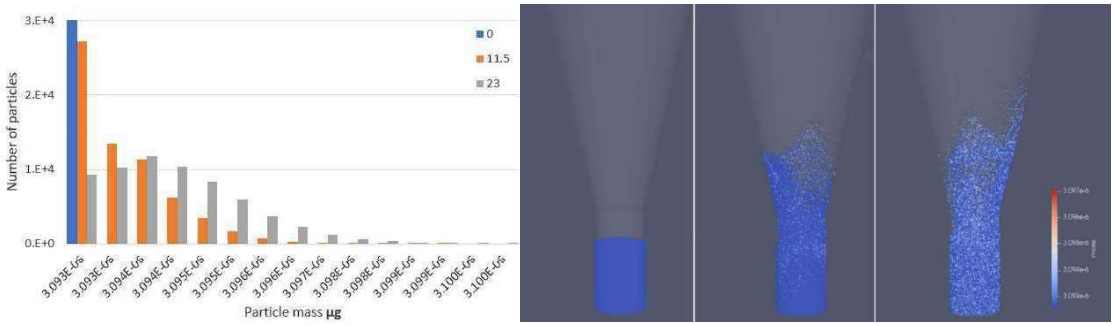


Figure 1. (a) Histogram of particle mass (b) Snapshop of the process with particles colored by mass after 0s, 11s, and 23s

CONCLUSION

The simulations results show that interparticle variability can be observed despite the average particle mass being consistent with the expected value. Further work is needed to verify this result experimentally.

REFERENCES

(1) Schmidt, J., Sachs, M., Blümel, C., Winzer, B., Toni, F., Wirth, K. E., & Peukert, W. A novel process chain for the production of spherical SLS polymer powders with good flowability. Procedia engineering, 102, 2015, 550-556. DOI 10.1016/j.proeng.2015.01.123

(2) Rendon Piedrahita, C., Baba, K., Quintana, R., Bardon, J., Borek Donten, J., Heyberger, R., & Choquet, P. (2022). Effect of crosslinker on the wettability and mechanical properties of hydrophobic coatings deposited via atmospheric pressure plasma. Plasma. Process. Polym. 2022, e2200023. DOI 10.1002/ppap.202200023

(3) Di Renzo, A.; Napolitano, E.S.; Di Maio, F.P. Coarse-Grain DEM Modelling in Fluidized Bed Simulation: A Review. Processes 2021, 9, 279. DOI /10.3390/pr9020279

(4) Goniva, C., Kloss, C., Deen, N.G., Kuipers, J.A.M. and Pirker, S. (2012): "Influence of Rolling Friction Modelling on Single Spout Fluidized Bed Simulations", Particuology, DOI 10.1016/j.partic.2012.05.002

(5) Zhou, Z. Y.; Kuang, S. B.; Chu, K. W.; Yu, A. B. Discrete Particle Simulation of Particle–Fluid Flow: Model Formulations and Their Applicability. Journal of Fluid Mechanics 2010, 661, 482–510. DOI 10.1017/s002211201000306x

(6) N. G. Deen, E.A.J.F. Peters, J. T. Padding, J.A.M. Kuipers. Review of direct numerical simulation of fluid–particle mass, momentum and heat transfer in dense gas–solid flows, Chemical Engineering Science, 2014, 116, 710–724. DOI 10.1016/j.ces.2014.05.039