Book of Abstracts

CESPE Conference 2024

The Drivers of Tomorrow's Landscape in Pharmaceutical and Biopharmaceutical Manufacturing

Thursday October 24th

RodeBol Events

Sint-Denijslaan 485

9000 Gent

GHENT UNIVERSITY

CESPE

CENTRE OF EXCELLENCE

SUSTAINABLE PHARMACEUTICAL ENGINEERING & MANUFACTURING

Conference Program

Conference Opening and Introduction

09h00 – 09h30

Registration & Welcome

Networking Breakfast

Poster Exhibition + Booths

09h30 – 09h40

Conference Opening

Prof. Dieter Deforce, *Principal Investigator, Ghent University*

09h40 – 10h00

CESPE – Reflections and Future Perspectives

Christoph Portier*, CESPE General Manager*

Theme 1: Digitalization: Exploring Big Data, Modeling, AI, and Beyond

10h00 – 10h20

GenAI in Life Science Manufacturing: Just Another Tool in the Box or the Ultimate Game-Changer?

Elisa Canzani*, Data Science Lead, Cognizant*

10h20 – 10h40

Advancing Sustainable AI Across Diverse Domains

Michaël Rademaker*, AI Solution Provider, IDLab – imec – Ghent University*

10h40 – 11h00

AI in Direct Compression: Supercharging Process and Formulation Design with Quantitative Tools

Alexander Ryckaert*, Co-Founder, Elegent*

11h00 – 11h15

Short Presentations

AI-Driven Green Chemistry: Towards More Sustainable Organic Synthesis

Maarten Dobbelaere*, PhD Researcher, Ghent University*

Smart Maintenance: Using AI to Automate and Perfect CMMS Metadata in Pharma

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***Arne Deloose**, PhD Researcher, Ghent University*

Spatial Modeling Techniques for Digital Twins of Cell Cultures

***Prof. Paul Van Liedekerke**, Principal Investigator, Ghent University*

11h15 – 11h35

Coffee Break

Poster Exhibition + Booths

Theme 2: Enabling Technologies

11h35 – 11h55

A Journey Towards Implementation of Continuous Flow Chemistry in the Pharmaceutical Industry

***Geert Schelkens**,* R&D Manager Early Phase API and Technology Development, Ajinomoto Omnichem

11h55 – 12h15

Mastering Spontaneous Nucleation of APIs from Lab Exploration to Pilot Production

***Bart Rimez**, Co-owner and Technology Lead, Secoya Technologies*

12h15 – 12h30

Short Presentations

From Assay to Impact – Creating Hardware in Life Science

***Mathieu Rabaey**, Project Leader, Comate*

Advanced Real-time Monitoring of Low-dose Formulations: Dual Spectroscopy Data Fusion as Enabling Process Analytical Technology

***Alexander De Man**, PAT Subject Matter Expert, UCB*

3D Printing of Personalized Pharmaceutical Tablets via Direct Extrusion Additive Manufacturing

***Lotte De Wever**, PhD Researcher Ghent University*

12h30 – 14h15

Networking Lunch

Poster Exhibition, Booths and Speed Networking Session

14h15 – 14h40

HighTru Lab Paving the Way for Next-Gen Innovators – Following Industry's Lead

***Prof. Chris Stevens**, Principal Investigator, Ghent University*

&

***Nico Vervoort**, Scientific Director High Throughput Experimentation,* Johnson & Johnson

Theme 3: Biomanufacturing

14h40 – 15h00

Energy, Carbon and Water Flow of a Biopharmaceutical Drug Substance Facility Including Derived Improvement Possibilities

***Alessandro Rosengart**, Head of the Sustainability Expert Group, VTU*

15h00 – 15h20

Unleashing the Potential of Plant-Based Manufacturing for Biologics – SwiftPharma Taking the Lead

***Jeroen Hofenk**, Founder & CSO, SwiftPharma*

15h20 – 15h40

The Challenges in Development of a Biological Drug for Veterinary Applications: the D in CDMO

***An Cerdobbel**, CMC Subject Matter Expert, 272Bio*

15h40 – 16h10

Coffee Break

Poster Exhibition + Booths

16h10 – 16h30

Belgium's Biomanufacturing Landscape: Key Learnings and Future Directions

***Natalia Moretti Violato**, Engagement Manager – ATMPs & Biologics, PwC*

16h30 – 17h15

Panel Discussion: Biomanufacturing in Belgium: Strengths, Unmet Needs, Roadmapping Exercises and Ongoing Initiatives

Representatives from different key stakeholder groups will engage in an open discussion about the strengths and challenges facing the biomanufacturing industry in Belgium. Gain insights from these key opinion leaders in industry, academia, and policymaking.

Moderator

Tineke Van Hooland, *Founder and CEO, Epic 10*

Panel

Samuel Speltdoorn, *Senior Business & Network Development Manager Cargo, Brussels Airport Company*

Koen Tyberghein, *Business Development Manager, VIB*

Prof. Thomas De Beer, *Director, CESPE*

Natalia Moretti Violato, *Engagement Manager – ATMPs & Biologics, PwC*

Kristof Lowyck, *Director Americas, Flanders Investment & Trade*

Closing

17h15 – 17h30

Closing Word

Sofie Bracke, *Deputy Mayor of Ghent, responsible for Economy, Port and Sports*

Networking Reception & Dinner

17h30 - …

Poster exhibition + booths

PwC Belgium: Your Partner in Health Industries Excellence

We draw from experience working with various clients on Manufacturing & Quality in the bio-pharmaceutical sector

Deals

- Fundraising, valuations & modelling
- Venture capital (VC) gap analysis
- Corporate finance
- Sell-side & buy-side support
- M&A due diligence (finance, tax, legal, …)
- Integration & carve-out value realisation

Customer

- Patient Experience Strategy & Design
- Pricing, Reimbursement & Health Economics
- Sales & Marketing Strategy
- Brand & Reputation Management
- Sales effectiveness (incl. Pharmacists & other stakeholders)

Finance

- ERP software selection & set-up design
- Budgeting and EPM support
- Carve-out and Fin Target Operating Model
- Chart of Accounts Optimisation
- (Compliance) reporting

R&D transformation

- R&D Strategy and Transformation
- Clinical Trial Design
- RWE and AI services
- Next Gen Therapies
- R&D Portfolio Management
- Digital & Data Analytics

Manufacturing & quality

- **Operational Excellence**
- **Innovative Manufacturing**
- **Quality and Regulatory Compliance**
- **GMP Ops Readiness**
- **Documentation support**
- **Backlog Reduction**

Supply chain & distribution

- Planning optimization
- Network Design
- Transport and warehousing optimization
- Control Tower
- Cost To Serve

ESG and digitization are two topics with high focus on in all offerings

Connect with PwC Belgium's Health Industry practice

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Theme 1: Digitalization: Exploring big data, modeling, AI, and beyond

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GenAI in Life Science Manufacturing: Just Another Tool in the Box or the Ultimate Game-Changer?

***Elisa Canzani**, Data Science Lead, Cognizant*

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***Prof. Paul Van Liedekerke**, Principal Investigator, Ghent University*

GenAI in Life Science Manufacturing: Just Another Tool in the Box or the Ultimate Game-Changer?

Elisa Canzani
Cognizant, Av. du Port 86C, 1000 Bruxelles

What is Generative AI? And how do we make it happen at Cognizant? An overview of our cognitive architecture to build and develop at scale responsible GenAI solutions. Strengths, caveats, and best practices to master this new technology along with emerging opportunities within life science manufacturing.

A brief demo on pharma supply chain optimization will showcase how GenAI can be a game changer when combined with other decision-making tools and already established technologies within the AI toolbox.

Advancing Sustainable AI Across Diverse Domains

Philip Leroux, Michaël Rademaker
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This presentation explores how IDLab (imec - UGent) advances sustainable AI across multiple domains, focusing on robotics, AI energy labeling, hybrid AI, data-efficient machine learning, and digital twins. By integrating these technologies, we highlight innovations that reduce energy consumption, enhance industrial efficiency, and promote sustainable practices. Our work demonstrates how AI-driven solutions can foster sustainability in both biomanufacturing and digital ecosystems, offering a path towards greener, more efficient industry operations.

AI in Direct Compression: Supercharging Process and Formulation Design with Quantitative Tools

Alexander Ryckaert; Daan Van Hauwermeiren
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Formulation development for (new) pharmaceutical drug products such as tablets manufactured via direct compression is crucial to consistently produce safe and high-quality products. However, the development is complicated for several reasons. First, the amount of pure active pharmaceutical ingredient (API) is often limited. Secondly, the price of the API can be quiet high. Lastly, the variety and concentration of potential excipients that can be combined with the API creates an immense number of possible combinations. An experimental evaluation of even a selection of options is time-consuming which makes finding the optimal formulation through traditional methods inefficient and costly. To address these challenges, a digital and data-based model was developed to powerfully support the formulation development.

The creation of this model involves developing a database to describe the behavior of the API and excipient powders, executing a well-structured experimental plan to measure tablet quality attributes, and applying a predictive model to link powder behavior to tablet quality. The developed machine learning model can predict critical quality attributes, such as tablet weight consistency and tensile strength. The former is essential for ensuring a consistent dose in the manufactured tablets, while the latter is linked to the drug release. This model allows for the rapid in silico evaluation of the most promising excipients, their concentrations, and the maximum possible API content, significantly reducing the number of experiments and the amount of API used.

AI-Driven Green Chemistry: Towards More Sustainable Organic Synthesis

Maarten R. Dobbelaere[1]; István Lengyel[1,2]; Christian V. Stevens[3]; Kevin M. Van Geem[1]

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[2] ChemInsights LLC, Dover DE 19901, United States of America

[3] SynBioC Research Group, Department of Green Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, 9000 Gent, Belgium

Machine learning (ML) can accelerate chemical tasks such as retrosynthesis, outcome prediction, property prediction, and condition recommendation. However, current databases and algorithms face challenges that hinder (experimental) experts in the field from fully utilizing ML-based tools. The first challenge is that databases are not tailored to real-world structures and applications. Second, the applications often remain confined to theoretical proofs-of-concept. In response, we present user-friendly software solutions that address these database and applicability-related issues on three levels: the molecule, the reaction, and the catalysts. In the first part, we introduce chemperium, a ready-to-use geometric deep learning tool that can achieve “chemical accuracy” for a wide range of molecules, catering to various branches of the chemical and pharmaceutical industry (1). Next, we demonstrate how we can predict potential reaction conditions based on popularity and similarity using the open-source software tool Rxn-INSIGHT (2). Finally, we showcase a human-in-the-loop active machine learning workflow that allows for the optimization of catalysts and reaction conditions in a manner that is adaptable to the applied equipment (3). These user-friendly tools address various needs in green chemistry and lay the groundwork for self-driving laboratories of the future.

References

(1) Dobbelaere, M. R.; Lengyel, I.; Stevens, C. V.; Van Geem, K. M. Geometric deep learning for molecular property predictions with chemical accuracy across chemical space. Journal of Cheminformatics 2024, 16 (1), 99. DOI: 10.1186/s13321-024-00895-0.

(2) Dobbelaere, M. R.; Lengyel, I.; Stevens, C. V.; Van Geem, K. M. Rxn-INSIGHT: fast chemical reaction analysis using bond-electron matrices. Journal of Cheminformatics 2024, 16 (1), 37. DOI: 10.1186/s13321-024-00834-z.

(3) Kuddusi, Y.; Dobbelaere, M. R.; Van Geem, K. M.; Züttel, A. Accelerated design of nickel-cobalt based catalysts for CO2 hydrogenation with human-in-the-loop active machine learning. Catalysis Science & Technology 2024, 10.1039/D4CY00873A. DOI: 10.1039/D4CY00873A.

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Smart Maintenance: Using AI to Automate and Perfect CMMS Metadata in Pharma

Deloose Arne[1]; Glenn Gysels[2]; Bernard De Baets[1]; Jan Verwaeren[1]

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Our research explores the innovative integration of Natural Language Processing (NLP) and machine learning techniques to enhance the efficiency and accuracy of Computerized Maintenance Management Systems (CMMS) in pharmaceutical production environments. CMMS, widely used for logging maintenance operations, generates extensive unstructured failure notifications enriched with structured metadata such as failure types and corrective actions. However, these metadata entries are prone to human error and inconsistencies, requiring a method for automated prediction and correction.

This research demonstrates how NLP models can analyze the free-text descriptions in failure notifications to predict and correct mislabeled or ambiguously tagged metadata fields. The complexity of technical jargon, abbreviations, and telegraphic writing in CMMS logs presents unique challenges, which this study addresses using multidimensional classification. This method exploits interdependencies between metadata components to significantly improve labeling accuracy, allowing for better maintenance decision-making and resource allocation.

Key contributions include the development of advanced NLP and classification models—such as Support Vector Machines (SVM), Random Forests (RF), and Recurrent Neural Networks (GRU)—that are optimized for processing highly technical, domain-specific text. Furthermore, transformer-based models like BERT were explored, but were found to underperform compared to custom-trained embeddings due to the highly specific vocabulary used in industrial settings. The models are trained on ten years of failure notification data from a large pharmaceutical company and evaluated based on metrics such as accuracy, F1-score, and precision.

This research holds immense potential for pharmaceutical companies seeking to improve operational efficiency by automating the correction of CMMS metadata, thus optimizing maintenance policies and minimizing operational costs.

Spatial Modeling Techniques for Digital Twins of Cell Cultures

Paul Van Liedekerke
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Modern (3D) in-vitro culturing techniques of cells, although promising, still poses challenges regarding reproducibility and cost efficiency. Mathematical and computational models can greatly help in identifying the key process parameters that have an impact on those burdens. So-called spatial agent-based models display each cell individually in the computer, considering the interactions with other cells and with the environment. We propose this approach as a dry-lab digital twin of the cell culture in which various process parameters can be modified and their effect can be predicted in advance to a real experiment. The technology further allows to serve as a 3D virtual microscopic insight tool for the cultures, creating virtual images of all cells and their physiological states.

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Theme 2: Enabling Technologies

11h35 – 11h55

A Journey Towards Implementation of Continuous Flow Chemistry in the Pharmaceutical Industry

Geert Schelkens, R&D Manager Early Phase API and Technology Development, Ajinomoto Omnichem

11h55 – 12h15

Mastering Spontaneous Nucleation of APIs from Lab Exploration to Pilot Production

***Bart Rimez**, Co-owner and Technology Lead, Secoya Technologies*

12h15 – 12h30

Short Presentations

From Assay to Impact – Creating Hardware in Life Science

***Mathieu Rabaey**, Project Leader, Comate*

Advanced Real-time Monitoring of Low-dose Formulations: Dual Spectroscopy Data Fusion as Enabling Process Analytical Technology

***Alexander De Man**, PAT Subject Matter Expert, UCB*

3D Printing of Personalized Pharmaceutical Tablets via Direct Extrusion Additive Manufacturing

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14h15 – 14h40

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&

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A Journey Towards Implementation of Continuous Flow Chemistry in the Pharmaceutical Industry

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Aji Bio-Pharma Services is the pharmaceutical fine chemicals division within the global Ajinomoto group. The company has started more than a decade ago to develop continuous flow chemistry. The traject started by learning where continuous flow chemistry can aid and where it is better to go for batch chemistry. Technology-wise, various aspects of continuous flow chemistry have been studied and were developed, from the classical tubular reactor to high pressure, high temperature, photochemistry, moving slurries around and exploring downstream processing techniques. Managing flow chemistry within the regulatory framework is not an easy task, and still requires further thinking. Opportunities were taken to scale up various technologies to Pilot and to commercial manufacturing in both the cGMP field and in the non-pharmaceutical business. Ajio Bio-Pharma's targets towards sustainable manufacturing are further supporting the need to go continuous. This journey will be sketched during the talk.

- Economics
  - More automated unit operations
    - Greatly reduced operating efforts
    - More reproducible process
  - Increased (mobile) capacity
    - Pressure reactors, cryogenic reactors
- Increased safety
  - Toxic, highly energetic compounds
- Minimizing side products
  - Increased yield
  - Better quality
- Process intensification

Mastering spontaneous nucleation of APIs from lab exploration to pilot production

Bart Rimez

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Secoya's crystallization technology is developed to overcome laborious post synthesis work-up of Active Pharmaceutical Ingredients (API) in order to reach classic critical material attributes (CMAs) for drug powders like average particle size, particle size distribution, shape of crystals, etc. Secoya's focus is on separating nucleation of materials in solution from crystal growth towards the equilibrium state[1,2]. By controlling the number of generated nuclei per mL of solution, the final particle size obtained is predicted for any combination of API inside a solution. Therefore, a direct steering of the APIs final and desired particle size for the application is generated during the crystallization step itself, rather than having to post-process the obtained crystals during a classic crystallization like grinding, milling, perform partial dissolution, and others.

Using different API examples as well as other organic molecules the basic principles of this technology will be discussed in detail at the laboratory level. At this level small quantities are injected inside capillary reactors at low temperatures to reach primary nucleation conditions. Optimizing both the thermodynamic and kinetics of the system demonstrates how to change the size of the obtained crystallized material. As an example in Table 1 the decrease in average particle size and standard deviation values are shown for the commercial molecule Brivaracetam whilst changing hydrodynamics inside the tubular reactors[1]. Depending on these conditions, the nucleation rate can be increased with two orders of magnitude from ten thousand to over the million of crystals produced per mL slurry per second.

Table 1. Crystallization Tests of Brivaracetam as taken from Rimez et al[1]. Average crystal size L_c and nucleation rate J are shown as a function of hydrodynamic perturbations in the reactor.

Number of perturbations	L_c (mean + standard deviation) / µm	J / $mL^{-1}.s^{-1}$
0	195 ± 62	2.4×10^4
1	62 ± 29	5.6×10^5
1	62 ± 20	3.0×10^5
2	46 ± 21	1.5×10^6
2	43 ± 18	1.3×10^6
3	37 ± 19	2.2×10^6
3	40 ± 19	2.0×10^6
4	35 ± 13	1.8×10^6

Once the optimal parameter set is generated at the laboratory level, all ruling parameters like solution concentration and temperature, flow rate(s), the mixing with antisolvent, reactor length, reactor temperature and crystal growth conditions, are kept constant for the translation of the process at continuous production level thanks to the plug flow conditions inside of the reactors. Therefore, whether producing samples of 20 mL of solution or several liters at a time, there is no work-up necessary to optimize the process conditions, as will be demonstrated using Lactose and Paracetamol as examples. Also, the completion of the total crystallization process step including crystal growth, filtration and drying will be demonstrated.

(2) Rimez, B., Debuysschère,R. Conté, J., Lecomte-Norrant, E., Gourdon, C., Cognet, P., Scheid, B. Continuous-Flow Tubular Crystallization To Discriminate between Two Competing Crystal Polymorphs. 1. Cooling Crystallization. *Cryst Growth Des.* **2018**, *18*, 6431-6439. https://doi.org/10.1021/acs.cgd.8b00928

(8) Rimez, B., Debuysschère, R.,Scheid, B. On the effect of flow restrictions on the nucleation behavior of molecules in tubular flow nucleators. *J. Flow Chem.* **2020**, *10*, 241-249.

From Assay to Impact – Creating Hardware in Life Science

Mathieu Rabaey

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Developing a successful and performant lab protocol or assay in a research environment is already a challenge on its own but translating this for scalable impact is still a next step. Creating hardware as an enabler to scale your life science application can be the solution, but where to start?

We as Comate are experts in high-tech hardware development and will share our learnings and case studies of the last decade in this field in how to keep focusing on your core technology and competences but leverage engineering support to go form assay to impact.

Advanced Real-time Monitoring of Low-dose Formulations: Dual Spectroscopy Data Fusion as Enabling Process Analytical Technology

Alexander De Man[1,3,§]; Lisa De Souter[1,4,§]; Zhenqi Shi[2]; Chen Mao[2]; Thomas De Beer[1,*]

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In continuous manufacturing, Process Analytical Technology (PAT) is part of the control strategy to evaluate the quality attributes of pharmaceutical products and promote Real-Time Release (RTR). For low-dose formulations, real-time monitoring of the content uniformity remains rather challenging as detection issues can occur for in-line PAT instruments. For this reason, a study was performed to investigate the potential of Near-infrared (NIR) and Raman spectroscopy data fusion as an enabling PAT strategy.[1]

This presentation briefly covers the use of a multifiber optic probe (NIRaman Combi Fiber probe, Measure Analyze Control & art Photonics GmbH) combining NIR and Raman fibers into a single instrument. This PAT instrument was used to measure the blend potency inside the feed frame of a rotary tablet press. NIR and Raman spectra were simultaneously obtained from various low-dose powder blends with acetylsalicylic acid as the Active Pharmaceutical Ingredient (API). Subsequently, the spectra were used for the development and validation of calibration models based on either preprocessed spectra or fused data. NIR and Raman data fusion proved beneficial in terms of sensitivity and accuracy if both spectroscopy techniques provide meaningful API content information. Future work should investigate the added value of combined spectroscopy for multiple APIs. In addition, further investigation regarding the achieved sampling volumes is required to facilitate practical implementation for RTR in accordance with regulatory demands.

References

(1) De Man, A.; De Souter, L.; Shi, Z.; Mao,C.; De Beer, T. Evaluating the Improvement of Blend Potency Measurements in the Feed Frame of a Rotary Tablet Press Using Combined NIR and Raman Spectroscopy. *Analytical Chemistry* ***2024*** *96 (26), 10586-10593.* https://doi.org/10.1021/acs.analchem.4c01134.

3D Printing of Personalized Pharmaceutical Tablets via Direct Extrusion Additive Manufacturing

L. De Wever[1]; C. Vervaet[1]; L. Cardon[2]; V. Vanhoorne[1]

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[2] Centre for Polymer and Material Technologies, Faculty of Engineering and Architecture, UGhent, Gieterijcentrum, Technologiepark- Zwijnaarde, 9052 Ghent

INTRODUCTION

Fused Filament Fabrication (FFF) is one of the most commonly used 3D printing techniques to prepare personalized pharmaceutical products where melted drug-polymer formulations are deposited as thin strands on a heated building bed. However, FFF presents several limitations, such as the need for filaments with appropriate mechanical and physical properties (e.g. homogeneous diameter and adequate stiffness and brittleness) resulting in a narrow formulation window[1]. To overcome these limitations, pellets produced via hot-melt extrusion (HME) could be used as feedstock material for direct extrusion additive manufacturing (DEAM). (Figure 1)[2] The purpose of the current study is to show the potential of pellets as feedstock material using a design-of-experiments approach.

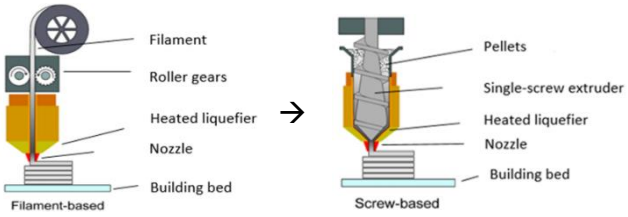

Figure 1: Schematic overview of the working principle of FFF (left) and DEAM (right)[2]

MATERIALS AND METHODS

A brittle filament containing an Active Pharmaceutical Ingredient (API) and thermoplastic polymer (60/40% ratio) was prepared via HME and cut into small pellets using a shredder. A full factorial screening design was conducted to evaluate the effects of printing parameters (extrusion multiplier, print temperature, infill and overlap) of the single-screw pellet printer on various critical quality attributes of the 3D printed tablets. These attributes include content uniformity and API degradation (UHPLC analysis), mechanical properties (texture analyzer), dissolution behaviour, dimensions and porosity.

RESULTS

The study revealed that different process settings affect the visual quality and dimensions of the 3D printed tablets, known as printlets. Weight variation met Ph.Eur. guidelines in all but 2 of the 19 runs, likely due to lower viscosity at higher print temperatures, which increased volume deposition and led to a less controlled printing process. The factors infill, extrusion multiplier and overlap had a significant impact on the weight range, which varied from 135 mg to 335 mg between the runs. The 3D printed tablets possessed an excellent content uniformity without any API degradation regardless of the printing temperature. Furthermore, they all achieved a tensile strength above the minimal diametral strength which was mainly affected by infill. The porosity was correlated with the dissolution behavior which was heavily affected by the infill and extrusion multiplier.

CONCLUSION

Pellet-based DEAM showed to be a successful method to manufacture oral solid dosage forms with diverse properties. This research confirms that the use of pellets as feedstock for DEAM has less restrictions for 3D printing compared to filaments. In the future, printer settings could easily be adapted to achieve the desired critical quality attributes for personalized dosing (e.g. certain dose/size/weight and dissolution profile). Finally, the factor extrusion multiplier can be identified as a new critical process parameter which can aid in the personalized medicine approach of DEAM.

ACKNOWLEDGEMENTS

This research is financially supported by Fonds voor Wetenschappelijk Onderzoek (FWO) (SB-Beurs 1SH2X24N).

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(1) Samaro, A.; Janssens, P.; Vanhoorne, V.; Van Renterghem, J.; Eeckhout, M.; Cardon, L.; De Beer, T.; Vervaet, C. Screening of Pharmaceutical Polymers for Extrusion-Based Additive Manufacturing of Patient-Tailored Tablets. *Int J Pharm* **2020**, *586* (March), 119591. https://doi.org/10.1016/j.ijpharm.2020.119591.

(2) Gonzalez-Gutierrez Joamin, Cano Santiago, Schuschnigg Stephan, Kukla Christian, J. S. and H. C. Additive Manufacturing of Metallic and Ceramic Components by the Material Extrusion of Highly-Filled Polymers: A Review and Future Perspectives. *MDPI* **2018**. https://doi.org/10.3390/ma11050840.

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HighTru Lab Paving the Way for Next-Gen Innovators – Following Industry's Lead.

Chris Stevens[1]; Nico Vervoort[2]

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Over the past two decades, high-throughput experimentation (HTE) has gained traction among process and medicinal chemists as a valuable tool. The implementation of HTE involves the miniaturisation, parallelisation, and automation of synthetic protocols, which requires a significant investment in specialised laboratory equipment. Therefore, adoption of HTE has primarily been by large corporations.

We introduce HighTru, the recently established open access HTE facility at Ghent University, which aims to democratise access to this technology for academic researchers and industry professionals who focus on small molecules and polymers. HighTru provides an advanced integrated platform for experimental design, execution of reactions, and analysis. The lab focusses on HTE workflows comprising of automated handling of solids and liquids, reaction platform versatility (including conventional, high-pressure, photocatalytic, and electrochemical reactions), and a state-of-the-art high-throughput analysis and data processing capability.

We also demonstrate the applicability of HTE from the perspective of Johnson&Johnson. At J&J, HTE has been well established and plays a pivotal role in shortening the design-make-test-analyse cycle. HTE facilitates the optimisation of reaction parameters, leading to scalable and robust reaction conditions with high yields. Additionally, HTE enables the exploration of novel synthetic routes, and thus expanding the accessible chemical space.

Theme 3: Biomanufacturing

14h40 – 15h00

Energy, Carbon and Water Flow of a Biopharmaceutical Drug Substance Facility Including Derived Improvement Possibilities

***Alessandro Rosengart**, Head of the Sustainability Expert Group, VTU*

15h00 – 15h20

Unleashing the Potential of Plant-Based Manufacturing for Biologics – SwiftPharma Taking the Lead

***Jeroen Hofenk**, Founder & CSO, SwiftPharma*

15h20 – 15h40

The Challenges in Development of a Biological Drug for Veterinary Applications: the D in CDMO

***Christine Labeur**, CMC Subject Matter Expert, 272Bio*

16h10 – 16h30

Belgium's Biomanufacturing Landscape: Key Learnings and Future Directions

***Natalia Moretti Violato**, Engagement Manager – ATMPs & Biologics, PwC*

16h30 – 17h15

Panel Discussion: Biomanufacturing in Belgium: Strengths, Unmet Needs, Roadmapping Exercises and Ongoing Initiatives

Energy, Carbon and Water Flow of a Biopharmaceutical Drug Substance Facility Including Derived Improvement Possibilities

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Energy improvement strategies require a holistic approach to effectively minimize carbon emissions and maximize the value of capital investments. Therefore, it is essential to understand the energy, CO2, and OPEX flows within a facility. These can be visualized easily understandable using flow diagrams, such as Sankey diagrams. However, generating and updating these diagrams often requires substantial data. To address this, modern data science tools have been developed to simplify the process, making it feasible with minimal sensor data.

Using these visualizations, improvement projects are discussed which include optimizing HVAC systems, recapturing waste steam, enhancing the efficiency of WFI loops, and optimizing CIP/SIP procedures.

Unleashing the Potential of Plant-Based Manufacturing for Biologics – SwiftPharma Taking the Lead

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The global demand for biologics, such as vaccines, antibodies, and therapeutic proteins, continues to rise, yet access to these life-saving medicines is hindered by high production costs and complex manufacturing processes. Transient expression in plants, particularly in *Nicotiana benthamiana*, offers a scalable, flexible, and cost-effective alternative to traditional mammalian and microbial cell-based platforms. This keynote will highlight how plant molecular farming, coupled with advanced glycan engineering, can democratize biologic production, ensuring that everyone, everywhere, has access to the medicines they need, when they need them.

Historically, one of the key challenges in plant-based biomanufacturing has been the issue of glycosylation, as plant-derived proteins often display plant-specific glycans that differ from those produced in human or mammalian cells, potentially affecting therapeutic efficacy. However, with cutting-edge glycan-engineering technologies, our glyco-engineered plants have been specifically designed to produce humanized glycosylation patterns, overcoming this barrier. These engineered plants can now generate complex and therapeutically relevant glycoproteins with human-like glycan structures, ensuring compatibility with the human immune system and maintaining the therapeutic functionality of the biologics.

In addition to solving the glycosylation challenge, plant-based expression systems present several advantages over conventional platforms. They bypass the need for costly cell line development and complex bioreactors, allowing for rapid, large-scale production in response to urgent public health needs. Moreover, plant systems avoid animal-derived materials, reducing contamination risks and making them safer and more sustainable.

By comparing plant-based systems to mammalian and microbial cell-based platforms in terms of production timelines, scalability, regulatory compliance, and cost-effectiveness, this keynote will showcase the unique selling points of plant molecular farming. Ultimately, we will demonstrate how this innovative approach, now free from glycosylation limitations, can play a pivotal role in reshaping the global biomanufacturing landscape, providing affordable, high-quality biologics to underserved populations and fostering equitable healthcare access worldwide.

The Challenges in Development of Biological Drug for Veterinary Applications: the D in CDMO

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For over 20 years, antibody-based therapies (or biological drugs) have been developed for use in human health and many approved antibody drugs are now commonly used for treating a variety of medical conditions and thus have improved the quality of life for many patients. Development of these antibody-based drugs in animal health (AH) is only emerging. However, many AH companies wish to enter the field of biological drugs to drive innovation and develop safer alternatives than current standards of care. Today, three block-buster monoclonal antibody-based drugs are on the market for use in companion animals, all marketed by Zoetis.

272BIO aims to bring innovative, low cost antibody solutions by leveraging the VHH technology to the AH market The current portfolio of 272BIO covers mainly products for companion animals and some niche applications in livestock.

However, these so called “biological drugs” require complex recombinant expression and production strategies that come with a relatively high cost of goods (COG) and require innovative development to allow more convenient administration routes. Although many veterinary pharmaceutical companies have significant interest in antibody therapeutics most companies do not have access to the technologies required to develop a biological drug and must rely on outsourced activities both for their discovery phases but also in selecting and bringing leads to the clinic and commercialization stage. Most of the expertise in veterinary health is based on the application of small molecule drugs; hence, the technical expert teams are not familiar with these quite different and more complex technologies. However, lead selection and early development requires very hands-on, flexible, and experienced teams that can bring the lead into preclinical and clinical testing.

A successful development trajectory for a biological drug requires an intensive collaboration between the ‘discovery teams ‘ and the development team ensuring the selection of the best development candidate. These data allow the development team to build an early quality target product profile and set the manufacturing strategy. Whereas in human health there is a step wise development of the process and the level of control when a drug transitions from phase I to phase III and commercial, the timelines and the regulatory expectations for AH studies are substantially different. Early in the development strategy the development team needs to identify a suitable host, process and scale meeting the market and regulatory requirements. Moreover most large scale manufacturers are built on the ‘human processes and regulatory requirements” and are often less familiar with the AH market.

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Belgium's Biomanufacturing Landscape: Key Learnings and Future Directions

Natalia Moretti Violato

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Belgium's biomanufacturing ecosystem stands out as a dynamic and leading landscape, excelling in research and development and ranking third in Europe for pharmaceutical exports. In 2023, the country surpassed €80 billion in exports and ascended to the top position in the European biotech industry by public market capitalization.

This success is driven by a collaborative environment supported by federal and regional initiatives, involving industry, academia, and government. Belgium's dense urban infrastructure enhances accessibility and connectivity, further boosting its competitive edge. The ecosystem includes a diverse network of companies, research institutes, universities, and academic hospitals, fostering innovation and development.

Despite its strengths, Belgium faces challenges such as digital maturity and competition for talent from neighboring countries. This study provides a comprehensive assessment of Belgium's biomanufacturing ecosystem, analyzing its strengths, weaknesses, opportunities, and threats from the perspectives of value chain, ecosystem support, and innovation and talent. The methodology includes a literature review and historical quantitative data analysis, highlighting the ecosystem's capability to facilitate innovation and talent through robust infrastructure and government-led support initiatives.

Panel discussion: Biomanufacturing in Belgium

Representatives from different key stakeholder groups will engage in an open discussion about the strengths and challenges facing the biomanufacturing industry in Belgium. Gain insights from these key opinion leaders in industry, academia, and policymaking.

Moderator

***Tineke Van Hooland**, Founder and CEO, Epic 10*

Panel

***Samuel Speltdoorn**, Senior Business & Network Development Manager Cargo, Brussels Airport Company*

***Koen Tyberghein**, Business Development Manager, VIB*

***Prof. Thomas De Beer**, Director, CESPE*

***Natalia Moretti Violato**, Engagement Manager – ATMPs & Biologics, PwC*

***Kristof Lowyck**, Director Americas, Flanders Investment & Trade*

Posters

1) Semi-continuous Pan Coating of Controlled Release Tablets: a Screening Study – Phaedra Denduyver
2) Micro-environmental Optimization as a Stabilization Technique to Inhibit Salt Disproportionation in Tablets – Charlotte Geleyn
3) Comprehensive Analysis of Semi-continuous Blending Using in-line NIR Spectroscopy for the Continuous Production of Low-dose Formulations – Louis Bouckaert
4) Investigating the Effect of Agitator Dynamics on the Twin-screw Feeder Performance for Pharmaceutical Powders – Luz Naranjo
5) CFD-DEM-Coating Model for Cold Plasma Coating – Pedro Martin Salvador
6) Thermodynamic Model as a Predictive Model for Tablet Film Coating – Behrad Aminahmadi
7) Conjugate Heat Transfer Simulation of Spin Freezing Process with Infrared Validation – Isar Charmchi
8) Upscaling of a Debenzylation Reaction in Pharmaceutical Synthesis: The Mass Transfer Paradox – Wout Callewaert
9) Ultrafast Compound Screening Using Molecular Machine Learning – Gaston Dejaeghere
10) Continuous Flow Synthesis of DMT-Analogues with Therapeutic Potential – Andreas Simoens
11) Synthesis of Biodegradable Ciprofloxacin Derivatives – Nathan Raeymackers
12) Continuous Solvent Recuperation using Zaiput Membrane Technology – Andreas Dejaegere
13) Harnessing levoglucosenone (LGO) potential for the production of biomass-derived specialty chemicals at scale – Martha C.Mayorquín-Torres

Semi-continuous Pan Coating of Controlled Release Tablets: a Screening Study

Phaedra Denduyver[1]; Quinten Speleers[1]; Leslie Van Eeckhout[2]; Fabian Penson[2]; Chris Vervaet[1]; Valérie Vanhoorne[1]

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The integration of semi-continuous pan coaters in continuous manufacturing lines has increased due to recent advancements in continuous manufacturing. Although there is a profound knowledge of semi-continuous pan coating of tablets with a non-functional coating, research on the semi-continuous pan coating process of tablets with functional coatings is limited. While a case study investigated the delayed drug release of enteric coated tablets [1], no studies have addressed the controlled release coating of tablets via a semi-continuous pan coater.

Therefore, current study investigates the coating of tablets with a controlled release film using the semi-continuous ConsiGma® coater of GEA Pharma Systems, which can be integrated into a continuous manufacturing line. In this pan coater the tablets are subjected to a cascade system that enables efficient and uniform coating within a limited time frame [2]. The tablet cores consisted of dense acetaminophen, microcrystalline cellulose and lactose. The coating dispersion was formulated as a mixture of two controlled release polymers, Eudragit RS 30 D and Eudragit RS 30 L in a ratio 9:1, triethylcitrate as plasticizer and mesoporous silica as anti-tacking agent. The influence of several coating parameters (weight gain (WG), inlet air temperature, spray rate and inlet air flow rate) on coating efficiency, inter-tablet coating variability, film coating surface and dissolution profile of the coated tablets was investigated via a fractional factorial screening design.

This screening study showed the potential of semi-continuous pan coating of tablets with a controlled release profile integrated into a continuous manufacturing line and identified the critical process parameters. Coated tablets with a controlled release profile over 24h were obtained at a coating time of 8 min (4% WG and spray rate of 75 g/min). In addition, all runs produced tablets with low inter-tablet coating variability (<1% RSD) irrespective of the process parameters. A rough coating surface was obtained for tablets coated at wet thermodynamic conditions, but did not affect the dissolution profile. Tablets coated at dry thermodynamic conditions and short coating time showed a low coating efficiency and discontinuous, porous coating surface yielding a faster drug release compared to tablets with a continuous tablet surface on similar process conditions. A controlled release profile was obtained between a WG of 4 - 8% with slower release at higher WG. However, as a WG of 4% is the tipping point to achieve controlled release, the inlet air temperature must be high enough to achieve full coalescence of the polymer particles. In future research, additional process parameters should be further investigated to gain in-depth process knowledge.

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Micro-environmental Optimization as a Stabilization Technique to Inhibit Salt Disproportionation in Tablets

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INTRODUCTION

Many newly developed Active Pharmaceutical Ingredients (APIs), show poor solubility and bioavailability.[1] Therefore, in approximately 50% of these cases, salts are employed to increase solubility and bioavailability, which emphasizes their significance.[2,3,4] However, salts can undergo salt disproportionation, a chemical reaction reverting them back to the original API. This poses a substantial concern due to its impact on the bioavailability. Research has shown that lowering the micro-environmental pH can be an effective stabilization mechanism.[4] This study explored a novel stabilization mechanism, which combines lowering the micro-environmental pH and common ion effect, as well as the impact on Critical Quality Attributes (CQAs) in two tablet formulations containing salt disproportionation inducing excipients Croscarmellose Sodium (CCS) and Magnesium Stearate (MgSt).

MATERIALS AND METHODS

Tablets consisted of 60 mg API (PioglitazoneHCl) and following excipients: formulation 1 (F1): 20% API, 59.5% microcrystalline cellulose (MCC), 15% D-mannitol, 5% CCS and 0.5% MgSt; formulation 2 (F2): 20% API, 59% MCC, 15% D-mannitol, 3% CCS and 3% Glyceryl dibehenate. Stabilizer X, which combines lowering the micro-environmental pH and the common-ion effect, was added at 10% and 15% and at two particle sizes, (d50 = 489 µm and d50 < 250 µm). Blends were prepared with a Turbula mixer at 101 rpm for 20 minutes and then compressed at 100 MPa. Tablets were subjected to accelerated stability conditions of 40°C/75% RH, open dish, for 4 weeks. Three tablets were withdrawn on a weekly basis and the degree of disproportionation was assessed with Raman spectroscopy. Besides, dissolution, appearance and tablet disintegration were closely monitored.

RESULTS

Reference formulations showed extensive disproportionation with 21.18% free base for F1 after 4 weeks and 17.49% for F2. Contrary, free base formation was inhibited completely when 15% of stabilizer X was added to the formulation and this during the entire stability test. Still, F1 + 10% X showed 1.61% of free base after 1 week, and 0% for the subsequent weeks. This initial free base formation is likely caused by inhomogeneous distribution of X within the tablet due to the large particle size used. For F2 + 10% X on the other hand, again, no free base was detected. When the particle size of X was reduced, initial free base formation was no longer detected. As for CQAs, tablets with stabilizer X showed a slightly increased disintegration time, as well as a slight delay in dissolution, attributed to pore formation due to the high solubility of the stabilizer and the disintegrant used.

CONCLUSION

Complete inhibition of disproportionation in a drug product was achieved by combining the effect of lowering the micro-environmental pH and the common ion effect. This study demonstrates that the efficacy of this inhibition is highly dependent on formulation, stabilizer concentration and particle size. Furthermore, a smaller particle size of the stabilizer will enhance its homogeneous distribution throughout the tablet matrix as well as inhibition performance, particularly at lower concentrations of the stabilizer. Additionally, a reduction of concentration and particle size of the stabilizer, improves tablet appearance and dissolution during stability testing.

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Comprehensive Analysis of Semi-continuous Blending Using in-line NIR Spectroscopy for the Continuous Production of Low-dose Formulations

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Introduction

Real-time release (RTR) and real-time release testing (RTRt) are essential in continuous manufacturing to evaluate the quality of intermediate or final products. Process analytical technology (PAT) tools, such as near-infrared spectroscopy (NIR), can be used in-line as non-destructive and non-invasive quantitative and qualitative analysis strategies to evaluate blend uniformity. However, this becomes increasingly challenging for low-dosed formulations, since sensitivity issues may occur for in-line PAT tools, and issues regarding blend homogeneity become increasingly important. Recently, a semi-continuous mini blender with a volume of 10l (GBM 10-P, Gericke AG, Regensdorf, Switzerland) was developed where a small mass of active pharmaceutical ingredients (APIs) is dosed next to excipients and blended for a few seconds or minutes.[1]. The objective of this study is to implement in-line PAT into this mini blender and to evaluate the impact of process settings on blend uniformity.

Materials & methods

A full factorial screening design was conducted, varying the impeller speed (60-140rpm), fill level (5-10l), and NIR probe location (A, B & C). During this design, a binary blend of 2% (w/w) caffeine anhydrous powder and lactose monohydrate (SuperTab 11SD) was used. An integration time of 5 milliseconds and an average number of 40 was applied on the NIR spectrophotometer for each run. During each experimental run, spectra were collected for six minutes and analyzed via the Moving Block Standard Deviation (MBSD) method (using a window size of 3 consecutive spectra) and a Partial Least Squares (PLS) model. For both methods, the raw spectral data were pre-processed by applying the Savitzky-Golay 2nd derivative method, followed by Standard Normal Variates (SNV) filtering. The powder blend was considered homogeneous as soon as the observed spectral variance was lower than the spectral variance of the last two minutes of mixing.

Results

Among the included variables, the impeller speed had the most significant impact on blending time. When operating at high speed, blend homogeneity was reached in a few seconds compared to a few minutes at lower impeller speed. Additionally, an interaction term between fill level and impeller speed was significant. At lower impeller speed, a higher fill level resulted in a longer blending time, while the effect of fill level was less pronounced at high impeller speed. Finally, position B was considered the optimal probe location, as the probe remained fully covered for a wider range of process settings during powder mixing.

Conclusions

In this study, PAT was implemented in a semi-continuous blender to monitor the blend homogeneity of a low-dosed formulation. Results showed that for this formulation, the impeller speed had the most significant impact on blending time to attain homogeneity. Moreover, blend homogeneity was rapidly reached when processing at high impeller speed.

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Investigating the Effect of Agitator Dynamics on the Twin-screw Feeder Performance for Pharmaceutical Powders

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Powder feeding is critical to process performance in the continuous manufacturing of solid dosage forms. The feeder must provide accurate and consistent material discharge to downstream manufacturing steps. When handling difficult materials that tend to stick to the hopper walls and bridge, density conditioning, flow facilitation, and consistent screw filling are required. An agitator in the feeder hopper is installed to achieve these goals, thus promoting a stable and accurate mass flow rate. However, while many difficult materials fail to be fed consistently, the role of the agitator is often overlooked..

This contribution uses a combination of experimental and predictive modeling approaches using DEM to understand and unveil the complex flow and mixing behavior induced by the agitator in a commercial-scale twin-screw feeder. The focus is on assessing the effect of changes in the screw and agitator rotational speed ratio on powders with different flowability levels. The model development steps include calibration, validation (emptying experiments), and feeding scenarios.

The experimental results and model predictions allowed the visualization of three main flow features induced by the equipment design and affected by the feeding operation and material flow characteristics: non-uniform flow with a bypass trajectory, formation of stagnant zones in the feeder corners, and preferential back drawdown powder flow. Besides, using scenario analysis, the impact of the screw-agitator ratio and screw speed is determined considering the cohesive properties of the powder. The findings suggest that powders with poor flow characteristics require restrictive operational constraints, as the screw agitator ratio is susceptible to variations in mass feed rate. This contribution, therefore, highlights the importance of properly choosing a screw-to-agitator ratio to determine an optimal operating window, achieving minimum agitation required to induce unimpeded flow and reduce variability in mass flow rate.

This work demonstrated DEM's capabilities as a decision-support tool in determining suitable operating conditions for powders with different flowabilities. This framework could, therefore, be used as a de-risking tool in feeding system design when handling powders prone to feeding challenges (e.g., cohesive powders) and selecting a feeder with the required capability.

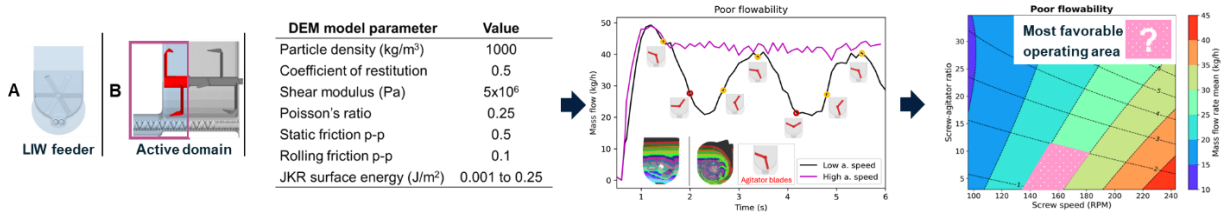

Figure 1. Stages of model development and its use

Acknowledgments

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.

CFD-DEM-Coating Model for Cold Plasma Coating

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INTRODUCTION

Cold plasma coating technology for surface functionalization and coating of pharmaceutical powder particles is a promising approach to introduce new characteristics such as controlled release layers, improved powder flow properties, and stability coatings. This is typically achieved in a fluidized bed reactor, where a jet containing the chemical precursor and plasma afterglow is introduced through a nozzle while fluidization gas is injected from the bottom plate. However, effective mixing of particles and precursor inside the plasma active zone is necessary to ensure a homogeneous coating. In this study, we investigate the effect of fluidization gas flow through simulations.

METHOD

We employ the CFD-DEM approach as implemented in the CFDEM®coupling package. This hybrid approach combines computational fluid dynamics (CFD) to model the gas flow and discrete element method (DEM) to simulate particle behavior. Furthermore, the coating kinetics are included as a mass transfer process from the surrounding gas onto the powder particles. Fluidization flow rates from 1 to 200 L/min are tested, while plasma and precursor flow rates are held constant. The simulations output detailed data on particle trajectories and precursor deposition rates. These are summarized into 3 metrics: an entropy-based mixing index which incorporates the particle movement data, the coefficient of variation (CV) of the coating mass which incorporates the coating quality, and the coating mass distributions, which provide further insight on the coating variations.

RESULTS

Figure 1-a shows how the mixing index for the 1 L/min case is always lower than for the other cases. Similarly, Figure 1-b shows how the particle distribution for the 1 L/min case presents many particles at 0 coating while this is not the case in the other simulations, suggesting some particles are not being fluidized. The same trend is seen in the CV, which is always higher for the 1 L/min case. Overall, the 1 L/min case is the worst performer, suggesting that operating the equipment with excessive lowering of the fluidization rate results in a non-uniform coating. On the flip side, no improvement can be observed from operating at flow rates above 50 L/min.

CONCLUSION

This study demonstrates how problematic operating conditions that lead to non-uniform coating can be identified, which in turn demonstrates the value of using CFD-DEM simulations in the process design of fluidized bed type plasma coating processes.

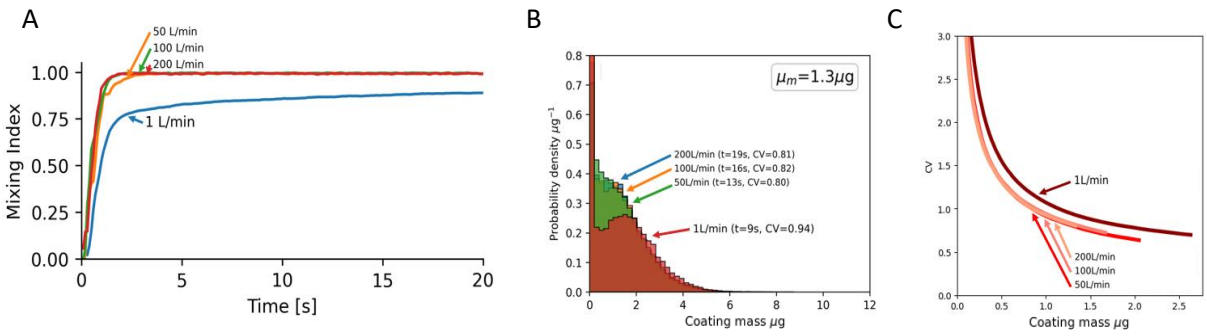

Figure 1. Metrics used to evaluate the effect of the fluidization gas on the coating performance for 4 simulations. A: Evolution of the mixing index over the coating time. B: Coating mass distribution after an average of 1.3μg of coating per powder particle has been applied. C: Evolution of the coefficient of variation as more coating is applied.

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Thermodynamic Model as a Predictive Model for Tablet Film Coating

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Introduction:

Film coating of solid pharmaceutical dosage forms is a common practice in the industry. This can be applied with non-functional, functional, and active coatings. This process improves the physicochemical stability and mechanical strength of tablets and enhances their appearance, smell, taste, and ease of swallowing.

The coating process is influenced by several critical factors, including tablet movement, spray atomization, and thermodynamic behaviour at the macro scale. On a microscopic level, key factors include droplet wetting, spreading, coalescence, and drying. These variables are intricately linked to tablet properties, coating formulations, coater type, and operating conditions[1]. This project aims to fill significant gaps in knowledge by providing a foundational understanding of the key mechanisms involved in coating development.

Method (model):

A Bohle coater, BFC50, is an elongated cylindrical drum where hot air is introduced through the tablet bed into the drum. The air is afterward drawn back through the tablet bed at the spray zone where the spraying nozzle is located. The film coating can essentially be considered as an adiabatic evaporative cooling process. Our model is a system of coupled ordinary differential equations (ODEs) to represent mass or energy balances[2]. A supplement of heat transfer and mass transfer (evaporation)[3] calculations is needed to run the model.

$$M_{Air}\frac{dY}{dt} = \dot{M}_{evap} + \dot{M}_{AirI}Y_I\ (t) \qquad Q_{AirP} = \alpha\, A_{Pbulk}\left(T_{Air} - T_p\right) \qquad M_{evap} = K_c A_{film}(C_{film} - C_{bulkAir})$$

$$M_{Air}\left\{\left[C_{pAir} + Y(t)C_{pv}\right]\frac{dT_{Air}}{dt} + C_{pv}\,T_{Air}\frac{dY}{dt}\right\} = \dot{M}_{evap}\left[\Delta\dot{h}_v + C_{pv}T_p\ (t)\right] + \dot{M}_{AirI}\left\{C_{pAir}T_{AirI}\ (t) + Y_I\left[\Delta\dot{h}_v + C_{pv}T_{AirI}(t)\right]\right\} - \dot{Q}_{AirP}$$

Result:

Spraying coating solution at the beginning of the coating stage decreases the tablet and exhaust-air temperatures in the system. This can be explained by the lower temperature of the coating solution compared to the tablets and air. Then, temperatures in the system will increase until they reach equilibrium. Furthermore, in the drying stage, spraying is stopped, which leads to an increase in the temperatures. Finally, the system is cooled down by means of cooling air.

Conclusion:

Thermodynamic parameters, including exhaust air temperature and humidity, can serve as key indicators of coating quality. If the environment is too dry, it may lead to defects like surface roughness. Conversely, an extremely humid environment can cause tablets to stick or pick. To develop innovative predictive models, it is pivotal to quantify, predict, and optimize the interplay of these mechanisms. Process Analytical Tools (PAT), such as NIR spectroscopy, can be a potential approach to couple with a thermodynamic model to measure generic predictors such as inter-tablet and intra-tablet coating variability. Another method could be studying the effect of spray characteristics and droplet size distribution on the evaporation rate.

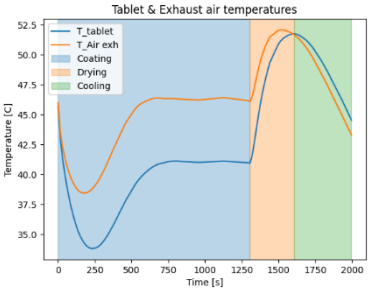

Figure 2: Tablet and exhaust air temperature of tablet film coating

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Conjugate Heat Transfer Simulation of Spin Freezing Process with Infrared Validation

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This study explores the application of Computational Fluid Dynamics (CFD) and Conjugate Heat Transfer (CHT) simulations to enhance the spin freeze-drying process, a novel technique in stabilizing temperature-sensitive biological products. Traditional freeze-drying methods face challenges such as extended processing times and non-uniform product quality. To address these disadvantages, Corver et al. proposed a continuous freeze-drying concept for unit doses [1]. This approach involves spinning the vials during the freezing stage, resulting in a thin layer of the product evenly distributed across the inner vial wall. The primary and secondary drying stages are carried out in separate process units, where individual IR heaters supply non-contact radiative energy to the spin-frozen vials. Unlike the time-based separation used in batch freeze-drying, this continuous concept relies on spatial separation of the consecutive process steps.

Our study investigates the spin freezing process using detailed 3D CFD model coupled with CHT simulation. We simulate the cooling gas dynamics and heat transfer within the vial, focusing on cooling gas flow rates and temperature effects on the cooling gas dynamic, heat transfer, and the temperature gradient within the vial. This comprehensive modeling allows us to predict temperature distribution more accurately, thus enhancing process control and product quality. Experimental validation is achieved using infrared thermography, which provides non-invasive surface temperature measurements of the vials during processing. This experimental data validates our simulations, ensuring our models accurately reflect real-world conditions. Figure 1 shows the thermal images obtained from the infrared camera and measuring points compared to simulation results.

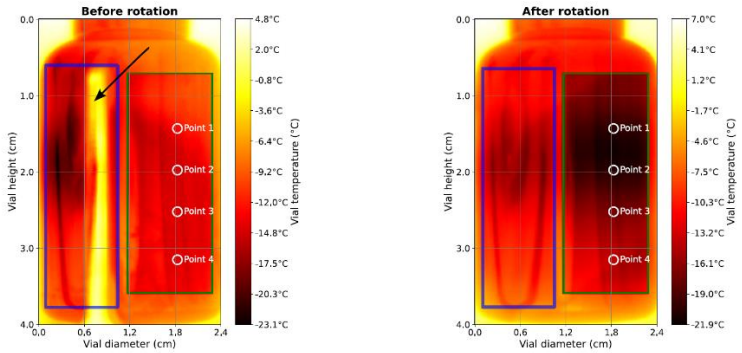

Figure 1: Thermal images of an empty stationary vial subjected to cooling gas (left) and an empty vial undergoing spin cooling after 6 minutes (right). The blue rectangular indicates the area on the vial wall affected by external reflectance. The minimum temperature is measured within the green box, and the minimum temperature at points 1, 2, 3, and 4 is monitored.

The results demonstrate that our CFD-CHT model aligns closely with the experimental outcomes. Table 1 compares the experimental and simulation data quantitatively, confirming the model's potential as a reliable tool for optimizing spin freezing process. Integrating CFD in the spin-freezing process provides insights into the thermal and fluid dynamic aspects and opens avenues for substantial improvements in the scalability and efficiency of pharmaceutical manufacturing.

Measurement Point	Experimental (°C)	Simulation (°C)
Minimum temperature	-18.78 ± 3.21	-21.4
Point 1	-17.43 ± 3.13	-20.5
Point 2	-18.28 ± 3.27	-17.1
Point 3	-14.98 ± 3.14	-14.3
Point 4	-12.38 ± 2.91	-12.8

Table 1: Comparison of experimental data with simulation results for a cooling gas at −50 ◦C (including 95% confidence intervals with 2 ◦C measurement error)

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Upscaling of a Debenzylation Reaction in Pharmaceutical Synthesis: The Mass Transfer Paradox

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The scale-up of multi-phase reactions in pharmaceutical processes often presents significant challenges due to the complex interplay between reaction kinetics and mass transfer phenomena. This work explores the upscaling of a debenzylation reaction catalyzed by a Pd/C catalyst, which removes a benzyl group from an amine-containing precursor, a common reaction in pharmaceutical synthesis. Lab-scale data were used to develop a kinetic model that predicts the intrinsic reaction behavior under various conditions. Notably, the model revealed that increasing hydrogen pressure negatively impacts the reaction rate due to competitive adsorption between hydrogen and the precursor.

By incorporating gas-liquid mass transfer into the model through the introduction of a volumetric mass transfer coefficient (k_La), accurate simulation of both pilot and industrial scales was achieved. Figure 1 shows the concentration profile of the precursor R_2N-Bn during the debenzylation reaction at the pilot scale. The profile reveals that mass transfer of hydrogen from the gas to the liquid phase initially limits the reaction. As the reaction progresses and the reactant depletes, the chemical kinetics become the rate-limiting phenomenon. Interestingly, mass transfer limitations initially enhance the observed reaction rate by rendering the inhibition by hydrogen less pronounced. This emphasizes the importance of understanding mass transfer effects during scale-up to optimize reaction conditions.

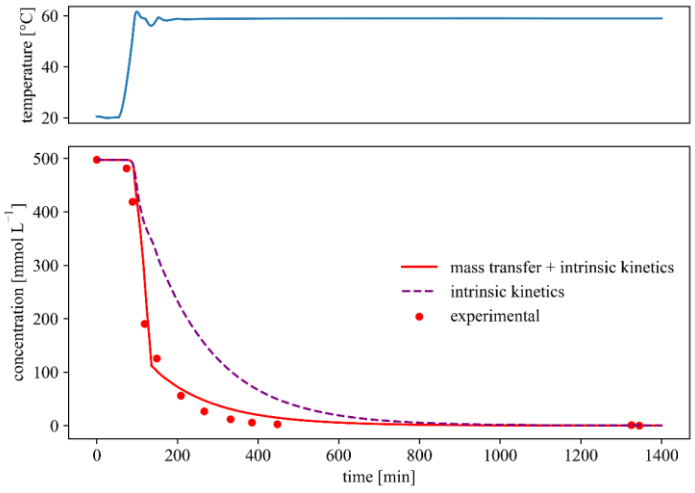

Figure 1. Concentration profile of the precursor R_2N-Bn during the debenzylation reaction for a batch conducted in the pilot-scale reactor. The temperature profile is displayed above the concentration profile. The reaction is limited by mass transfer of hydrogen between 90 and 130 minutes. The concentration profile in absence of mass transfer limitations is also shown.

The developed model enables prediction of concentration profiles and reaction endpoints at industrial scale where real-time sampling is unfeasible, supporting optimization of reactor design and operation. This work demonstrates the potential of multiscale modeling for more efficient and cost-effective pharmaceutical process engineering, offering new insights into the scale-up of complex reactions with complex kinetics and mass transfer phenomena.

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Ultrafast Compound Screening Using Molecular Machine Learning

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Chemical engineers rely on precise knowledge of physicochemical properties to design and model chemical processes. Typically, relevant properties are estimated computationally with methods such as group contribution. Despite the growing popularity of deep learning, it is rarely applied for property prediction due to data scarcity and limited accuracy for compounds in industrially-relevant areas of the chemical space. Herein, we present a geometric deep learning framework[1] for predicting gas- and liquid-phase properties based on novel quantum chemical datasets comprising 183,000 real-world molecules. Our findings reveal that including quantum chemical information in deep learning models increases the prediction accuracy of physicochemical properties. In the case study, the developed algorithm is applied to solvent selection by performing ultrafast compound screening to score the safety of solvents used in the pharmaceutical industry. The safety score of solvents can be estimated based on physicochemical properties[2]: flash point, autoignition temperature, resistivity, peroxide formation. The comparison between the results of this ultrafast screening and scores assigned based on manually gathered experimental data is shown in Figure 3. The results on the heat map are closely grouped around the main diagonal with a few outliers, illustrating the high accuracy of the screening performed.

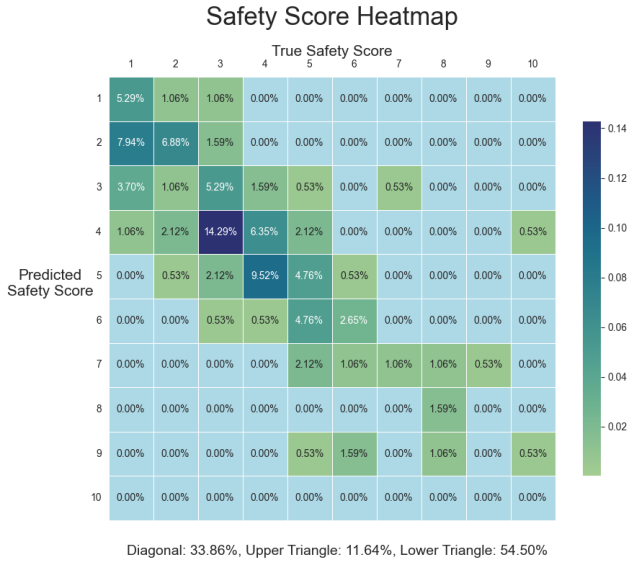

Figure 3: Heat map comparing solvent safety scores assigned based on manually gathered experimental data and score assigned based on data predicted using molecular machine learning.

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Continuous Flow Synthesis of DMT-Analogues with Therapeutic Potential

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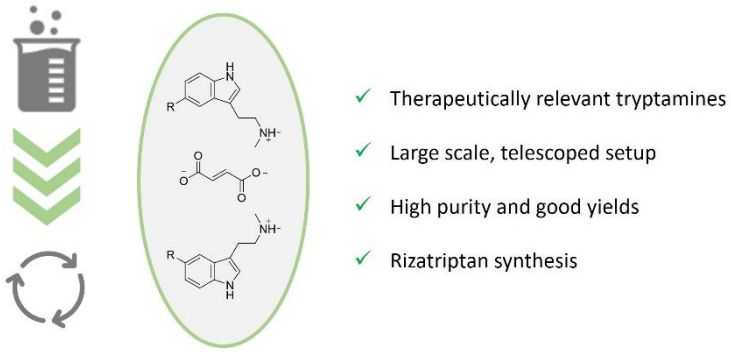
Major depressive disorder (MDD) is a debilitating neuropsychiatric disorder which comes at high cost for the patient as well as society, causing a significant health care cost, productivity decrease and unemployment burden. The World Health Organization (WHO) estimates the number of people living with depression on 322 million. This number has been further increased by the COVID-19 pandemic by a reported 27.6% compared to pre pandemic levels, making it an absolute priority to find effective and affordable treatments for patients dealing with this disorder.

Currently the majority of prescribed antidepressants act by inhibiting the synaptic uptake of serotonin (SRIs), norepinephrine (NRIs) or both (SNRIs). However, these treatments are known to only reduce symptoms in about one third of patients, with one third of patients having full remission and the last third not responding to these drugs at all, which is known as treatment-resistant depression (TRD). Therefore, there is a widely recognized urgency to finding alternatives to the commonly used, yet suboptimal first-line antidepressants.

After decades of tightened pharmaceutical regulations in the 1960s & 70s on hallucinogens such as psilocybin, DMT, LSD, ketamine and MDMA, these compounds have gained renewed interest as potential candidates for the treatment of psychiatric disorders in recent years. A standout example of this is the recent regulatory approval for intranasal administration of esketamine in conjunction with a conventional antidepressant for adults suffering from treatment resistant depression (TRD). Contrary to the earlier described conventional methods, it has been observed that a single exposure to one of these hallucinogenic agents can elicit an instantaneous and lasting improvement in symptoms for the patient. Results which last long after the drug has been metabolized and excreted from the body.



In our work we describe the continuous flow synthesis and in-line extraction of DMT and several of its analogues using a Fischer indole reaction, also including a larger gram scale synthesis (4.75 g) of the model compound. The setup itself includes inline purification through continuous extraction, which is made possible by a zaiput device. The obtained products could easily be transformed into their respective fumarate salts, making them easier to handle and stable for long time storage. The presented method employs green solvents both for the synthesis and purification of the target products.

Synthesis of Biodegradable Ciprofloxacin Derivatives

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A significant challenge with antibiotics (and APIs in general) lies in the intended design for maximum stability. The issues arising from this persistence is their resilience to flow through most wastewater treatment processes. Consequently, they find their way into the environment, giving rise to evident adverse side effects, such as the development of antibiotic resistance.

In this work, ciprofloxacin is used as case study. Ciprofloxacin is a commercially available and widely used antibiotic that belongs to the fluoroquinolone class. While the fluoroquinolones rank among the most prescribed, this class of antibiotics is known for their persistence.[1–3]

Using the benign by design approach, Leder and coworkers developed a (bio)degradable fluoroquinolone molecule called CIP-hemi.[4] Ciprofloxacin was redesigned by introducing a tetrahydrofuran group instead of a persistent cyclopropyl group on position N1, thereby creating a hemi aminal functionality (Figure 1). In silico and in vivo testing showed that the molecule retains antibiotic activity but partially degrades when excreted in the environment. Using this principle, the impact on the environment could be minimized without using advanced (and often expensive) water treatment techniques.

Within the European transpharm project, in collaboration with the group of prof. Kümmerer, a robust synthesis platform for CIP-hemi was developed. Subsequently, derivatives were synthesized with the aim of sustaining antibiotic activity while increasing environmental (bio)degradability (Figure 1).

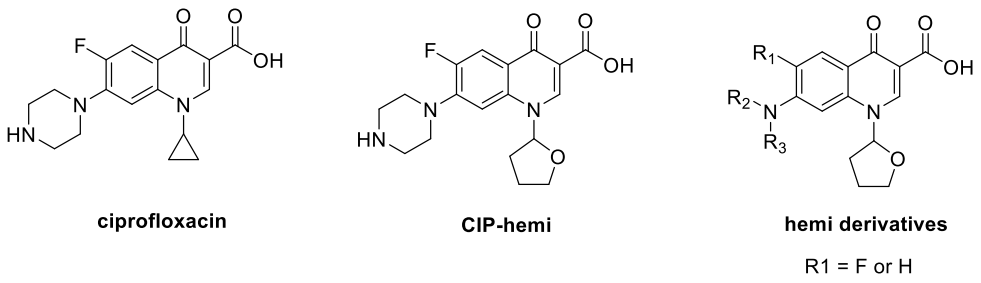

Figure 1: Structures of ciprofloxacin (antibiotic on the market), CIP-hemi and new hemi derivatives are shown.

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Continuous Solvent Recuperation using Zaiput Membrane Technology

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The extensive use of diverse solvents in pharmaceutical production processes results in substantial waste generation. This not only poses economic challenges but, more importantly, has adverse effects on both humanwell-being and the environment. Implementing strategies such as using a single solvent or solvent system for multiple steps or recovering solvents has the potential to significantly reduce this waste stream.

In the presented work, we concentrate on the continuous recuperation of Cyrene™, a renewable solvent derivedfrom non-food waste biomass[1,2]. This particular solvent is water-soluble, allowing for its removal through an aqueous workup post-reaction[3]. However, in many cases, the solvent is not recovered and instead ends up in theaqueous waste stream. To address this issue, we apply the concept of counter-current back extraction using an organic solvent, such as ethyl acetate, to recover the target solvent from the water phase. For this extraction process, we rely on the MS10 multi-stage extraction platform provided by Zaiput Flow Technologies[4].

Figure 1: MS10 multi-stage extraction platform[4]

The conducted tests have confirmed the functionality of the extraction system. Currently, efforts are underwayto optimize the system further, aiming to maximize the extraction efficiency.

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Harnessing levoglucosenone (LGO) potential for the production of biomass-derived specialty chemicals at scale

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The demand for sustainable and eco-friendly chemical processes has attracted significant interest in biomass- derived feedstocks. Levoglucosenone (LGO), a highly functionalized and chiral compound obtained from biomass, presents a promising platform for the synthesis of specialty chemicals.[1] Circa is exploring the versatile applications of LGO in developing high-value chemicals with potential uses in pharmaceuticals, agrochemicals, and materials science.[2]

Through a series of chemical transformations, LGO is converted into a variety of functional derivatives that serve as key intermediates in the synthesis of these specialty chemicals. LGO has been shown to be an excellent starting material for synthesizing biologically active compounds, including those with anti-cancer, anti-microbial, or anti- inflammatory activity.[3] The efforts also addresses the scalability of these processes, demonstrating that LGO- based reactions can be efficiently scaled from the gram to the kilogram scale without compromising yield or purity.[1]

The potential of LGO as a sustainable building block for the fine chemical industry is further reinforced by economic analyses and life cycle assessments that compare its environmental impact to traditional petrochemical routes.[4] Circa´s research not only contributes to the advancement of sustainable chemistry from non-fossil feedstocks but also underscores the viability of LGO as an innovative and differentiated development platform for bioactive ingredients . Circa is seeking partnerships for broader industrial adoption and further development with selected partners.

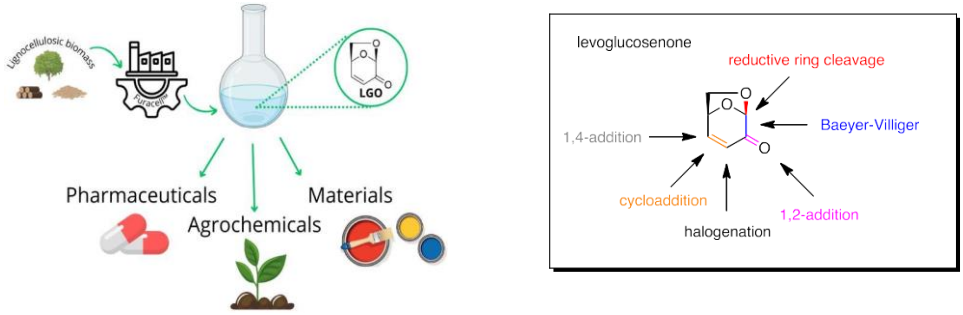

Figure 1. Production and potential uses of levoglucoseone (LGO).

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