PHARMASEL-PROSPERITY NEWSLETTER

PharmaSEL Prosperity

A bimonthly newsletter

ISSUE 5 JULY 2022

In this issue:

- Mr Hamish Mitchell, Co-Editor in Chief, Department of Chemical Engineering, Imperial College London, shares his perspective about the PharmaSEL-Prosperity Newsletter.
- Research from the Molecular Systems Engineering group on model-based solvent selection for integrated synthesis, crystallisation, and isolation processes.
- Dr Monica Tirapelle, a Research Associate working on Work Package 3 (WP3) shares her background, research interests, and her role within WP3.
- A glance at a prominent publication on the latest achievements in the screening of coformers for API cocrystallisation.
- A highlight of our most recent awards.

Co-Editor in Chief Perspective

Having now been involved with the PharmaSEL-Prosperity Partnership for two years as part of Work Package 2, it has been very exciting to witness the achievements that have been made as part of the project, as well as interesting discussions generated with both other research groups and Lilly collaborators.

I've always found the newsletter to be a great way to accentuate this reading about the achievements of other Work Packages has helped me to understand how my objectives fit within the wider goals of the project. Malak and Othman have both done a fantastic job in producing the newsletter, and I'm very excited to be taking over the role of co-editor from Malak as she focuses on finishing up her PhD.

I'm hoping to expand the newsletter over the coming months to include other topics of interest to members of the Prosperity Partnership, such as an image competition or video interviews with members of the project, to provide different aspects to the newsletter and encourage participation from researchers in every work package. If you'd like to be featured in one of these newsletter issues, or have any ideas about improvements we could make, please do email me or Othman. I hope you enjoy this issue!

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Research Feature: Model-based solvent selection for integrated synthesis, crystallisation, and isolation processes - Mohamad Muhieddine

Aim and Methodology:

Solvents are extensively used in the pharmaceutical industry for a variety of processing tasks, such as chemical reactions, separations and formulations[1,2]. The use of solvents has been identified as a main source of waste and carbon emissions in the pharmaceutical industry, contributing to the poor environmental performance of the sector relative to other chemical industries, and highlighting the need for systematic solvent selection tools to develop resource-efficient processes[3,4]. The aim of this project is to establish a process-wide systematic approach based on computer-aided mixture/blend design (CAM^{b}D)[5] to the design of solvents and reaction/separation processes, which would facilitate the development of fully integrated pharmaceutical processes that incorporate multiple reaction, separation and purification steps. Currently, our focus is on developing a mathematical formulation and solution strategy for a combined solvent and process synthesis problem, to account for the complex effects of solvent properties on process performance, and accordingly, to employ a holistic/systems view for solvent selection. More specifically, the design problem can be described as follows:

Given:

- a synthetic step in the manufacturing of a pharmaceutical compound, as shown in Figure 1
- a specified production rate, reaction conversion and selectivity, and product purity
- a list of possible solvents

Identify:

- the solvents
- mixture composition
- process conditions

that **optimise** selected key performance indicators (KPIs).

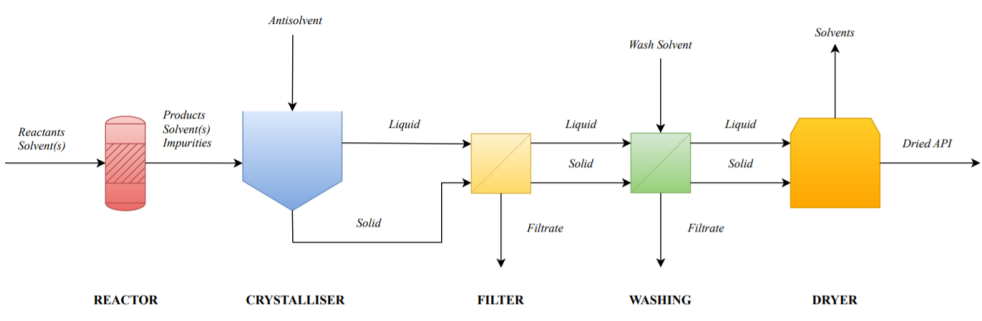
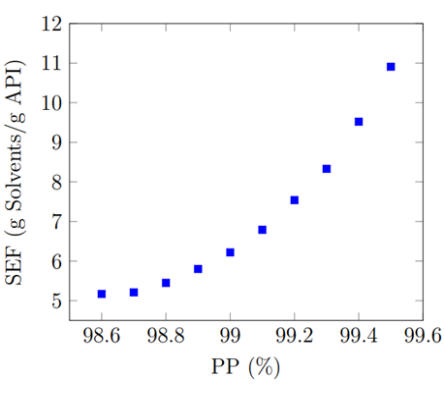


Figure 1: End-to-End Process Flow Diagram

Sample Results:

The approach has been developed to identify optimal solvent(s) and process conditions for integrated synthesis, crystallisation and isolation processes, and has been illustrated on the production of mefenamic acid from 2,3-dimethylaniline and 2-chlorobenzoic acid as a case study. For example, the Pareto front of a bi-objective optimisation problem for minimising the solvent E-factor or SEF (grams of Solvents/grams of API) and maximising product purity or PP (%) is shown in Figure 2. Each point corresponds to a different design (solvent identities, stream composition and process conditions) identified by the optimiser as a Pareto-optimal solution. It can be seen that a marginal increase in product purity beyond 98.8% requires a significant increase in the SEF. Since the Pareto curve before PP = 98.8% is relatively flat, indicating a small increase in solvent consumption with increasing purity, the solution corresponding to (SEF,PP) = (5.45,98.8) would be a good compromise solution.



Relevance to Lilly:

The CAM^{b}D tool is of interest to Lilly as it:

1. Constitutes a digital approach to solvent selection, hence eliminating the need for resource-intensive solvent screening experiments during early-stage pharmaceutical process development – only a shortlist of optimal solvent candidates identified by the proposed computational tool can then be validated experimentally.
2. Offers an integrated approach to solvent selection and process design, linking molecular-level decisions, i.e., solvent identities, to process performance, e.g., process yield or product purity, in contrast to traditional drug product development workflows where solvents are selected/fixed early on in the process with little to no consideration of solvent effects on process performance (sub-optimal design decisions).

Future Work:

The CAM^{b}D tool is currently being extended to explore multi-step routes (more than 1 reaction) and will be applied to evaluate different synthetic routes within a given reaction network based on process-wide KPIs such as process economics, environmental impact and energy consumption.

References

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Early Career Researcher Profile

Dr Monica Tirapelle

Dr Monica Tirapelle is a Post-Doctoral Research Associate at UCL. She received her bachelor's degree in Chemical and Materials Engineering in 2016 and her master's degree in Chemical and Process Engineering in 2018 from the University of Padova. In April 2022, she obtained the degree of Doctor of Philosophy from the same institution. During her studies, she collaborated with different research groups from the University of Surrey, the French Institute of Science and Technology for Transport, Development and Networks, and University College London.

During her Ph.D., Monica's research activities were primarily in the field of Particle technology. Specific research areas that she focused on include powder characterization, powder flowability, powder mixing and segregation, solid flow rheology, and transport phenomena. She also dealt with mathematical modelling, computational fluid dynamics and discrete elements method simulations. The results of her PhD work are new and original models for predicting size- and density-driven segregation mechanisms in dense granular flows, which enable a better design and scale-up of several industrial applications.

Monica joined the Department of Chemical Engineering at UCL in January 2022 as a postdoctoral researcher working with Professor Eva Sorensen, Dr Luca Mazzei and Dr Max Besenhard. She is currently contributing to Work Package 3 of the PharmaSEL-Prosperity partnership which aims to obtain new insights into industrial separation processes for peptides. The main objective of her research is to develop an in-silico framework for High-Performance Liquid Chromatography (HPLC) that is based on hybrid models and describes the adsorption of small molecules and peptides onto the stationary phase. A successful computational model will allow us to reduce the number of expensive and time-consuming experiments that are currently required for HPLC method development, and to save valuable drug products.

Monica believes that the experience of working on this project, and being a part of the PharmaSEL-Prosperity Partnership at UCL and Imperial, is an excellent opportunity to achieve her long-term career goals of working within R&D related to pharma, as well as making a contribution towards building a healthier society.

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Featured Publication

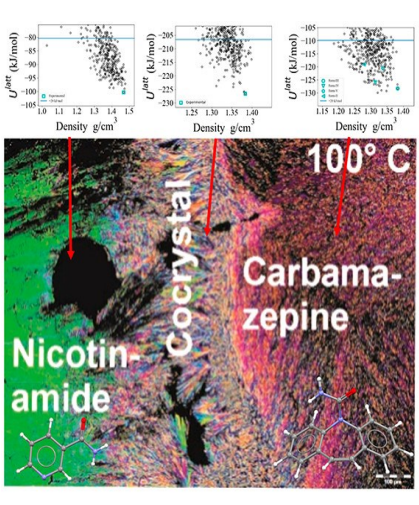
Efficient Screening of Coformers for Active Pharmaceutical Ingredient Cocrystallization

Isaac J. Sugden, Doris E. Braun, **David H. Bowskill**, **Claire S. Adjiman**, and **Constantinos C. Pantelides**

DOI: 10.1021/acs.cgd.2c00433

Abstract

Controlling the physical properties of solid forms for active pharmaceutical ingredients (APIs) through cocrystallization is an important part of drug product development. However, it is difficult to know a priori which coformers will form cocrystals with a given API, and the current state-of-the-art for cocrystal discovery involves an expensive, time-consuming, and, at the early stages of pharmaceutical development, API material-limited experimental screen. We propose a systematic, high-throughput computational approach primarily aimed at identifying API/coformer pairs that are unlikely to lead to experimentally observable cocrystals and can therefore be eliminated with only a brief experimental check, from any experimental investigation. On the basis of a well-established crystal structure prediction (CSP) methodology, the proposed approach derives its efficiency by not requiring any expensive quantum mechanical calculations beyond those already performed for the CSP investigation of the neat API itself. The approach and assumptions are tested through a computational investigation on 30 potential 1:1 multicomponent systems (cocrystals and solvate) involving 3 active pharmaceutical ingredients and 9 coformers and one solvent. This is complemented with a detailed experimental investigation of all 30 pairs, which led to the discovery of five new cocrystals (three API–coformer combinations, a polymorphic cocrystal example, and one with different stoichiometries) and a cis-aconitic acid polymorph. The computational approach indicates that, for some APIs, a significant proportion of all potential API/coformer pairs could be investigated with only a brief experimental check, thereby saving considerable experimental effort.



Awards

Dr Mingxia Guo & Dr Othman Almusaimi

Won a project under Imperial College London's Julia Higgins funding scheme to design ATR Kinase peptide-based inhibitors as novel chemotherapeutics

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