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## Advanced Pharmaceutical Materials Characterisation

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Drug Substance (Primary Processing)
Estimating Crystallisation Kinetics from Small-Scale Experiments

J. McGinty\textsuperscript{1,2}, A. Cashmore\textsuperscript{1,2}, J. Flannigan\textsuperscript{1,2}, J. Sefcik\textsuperscript{1,2}

\textsuperscript{1}CMAC Future Manufacturing Research Hub
\textsuperscript{2}Department of Chemical and Process Engineering

Introduction

- Crystallisation kinetics can be estimated from images taken during the crystallisation process.
- This can be done at the small-scale in order to allow for rapid screening and the minimisation of material use.
- There may be a trade-off in accuracy compared with more time-intensive methods but is useful for giving "order of magnitude results" in process development i.e. candidates can be more quickly ruled out.
- These techniques are being developed and used by several researchers here within CMAC.

Methods – Images to Kinetics

- Small-scale crystallisation experiments performed in 8 mL Technobis Crystalline reactors.
- Images obtained from these small-scale crystallisation experiments in order to visualise the evolution of crystal nucleation and growth.

- Experiments can be seeded or unseeded depending on the supersaturation levels being investigated.
- Performing small-scale experiments allows for rapid screening and the minimisation of material use.

Results Overview from Case Studies

- Mefenamic Acid in Diglyme/Water – CMAC Hub model compound being used to develop the microfactory. Crystallisation kinetics being estimated to inform "prediction-first" approach to process development.
- Glycine in Water – Andrew Cashmore PhD project looking to develop these methods for quickly estimating crystallisation kinetics from small-scale crystalline experiments.
- Sodium Chloride in Water – James Flannigan PhD project using these methods to inform their work. Obtaining greater understanding of crystallisation kinetics allows for easier use of "Optical Tweezing" technique.

Technobis Crystalline Reactors

- Small-scale crystallisation experiments performed in 8 mL Technobis Crystalline reactors.

Images to Kinetics

- Images are obtained from these small-scale crystallisation experiments in order to visualise the evolution of crystal nucleation and growth.

Case Studies

- Induction Times > Primary Nucleation Rates
- Particle Number Increase > Secondary Nucleation Rates
- Particle Size Increase > Growth Rates

Good agreement with more labour-intensive methods

Kinetics used by models for full-scale process design
Crystallization of Mefenamic Acid
Wei Li*, Brahim Benyahia, Chris D. Reilly
Continuous Manufacturing and Advanced Crystallization (CMAC) Future Research Hub at Loughborough University, Loughborough, LE11 3TU, UK *Email: w.li@lboro.ac.uk

1. Motivation

2. Parameter estimation and model validation

3. Model-based optimization of a batch system

4. Multistage continuous MSMPRs optimization

5. Conclusions

Acknowledgement: The authors would like to acknowledge support from EPSRC Future Continuous Manufacturing and Advanced Crystallisation Research Hub Grant EP/P006965/1
Spherical Agglomeration: Mechanistic Understanding, Modelling and Workflow

Bilal Ahmed, Omid Arjmandi-Tash, Jonathan D. Tew, Kate Pitt, Victoria R. Kitching, Rachel M. Smith, James D. Litster
Particle Technology Group, Department of Chemical & Biological Engineering, The University of Sheffield, UK

Introduction

Spherical agglomeration is a particle formation technique which improves problematic particle shapes, increases the particle size and enhances downstream powder processing.

Agglomeration in suspension (post-crystallization) is an emerging strategy in pharmaceutical manufacturing.

Aim to develop a spherical agglomeration workflow and investigate a novel population balance model for mechanistic understanding and prediction of product properties from the influence of critical process parameters.

Workflow

Stage 1: Prior Knowledge & Characterisation
Stage 2: Wetting & Nucleation
Stage 3: Select Mixed Solvent System
Stage 4: Consolidation by Layering
Stage 5: Platform Configuration
Stage 6: Parameter Sensitivity Analysis
Stage 7: Coalescence
Stage 8: Target Scale Vacuum

Population Balance Model Framework

Rate Processes
- Wetting & Nucleation
- Consolidation by Layering
- Coalescence

Key Research Outputs and Engagements

Publications

Conferences
1. Litster, J., Model driven design of particulate processes and products - applications in pharmaceutical manufacture and beyond. In International Congress on Particle Technology (PARTEX), Nuremberg, Germany, April 2019 (Plenary speaker), 2019.

CMAC Events

Conclusions
- Holistic and targeted workflow for spherical agglomeration process development
- Population balance model incorporates customized nucleation & agglomerate rate kernels for predictive approach
- Wide engagement on the emergence of spherical agglomeration as a key particle engineering tool for pharmaceutical manufacturing
Secondary Nucleation and Crystal Growth of α-Glycine

Andrew Cashmore1,2, Mei Lee3, Mark Haw2, Jan Sefcik1,2

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3. GlaxoSmithKline, Gunnels Wood Rd, Stevenage, SG1 2NY

Introduction

- Assessing nucleation and growth kinetics at small, laboratory scale can rapidly and economically enable the optimization of crystallization processes by providing the tools to make more informed decisions early in process development.
- With a good understanding of the nucleation and growth kinetics and mechanisms, secondary nucleation can be exploited to control particle size distribution and solid form.

Nucleation and Growth Kinetics Workflow

1. Induction Times
2. Growth Kinetics
3. Secondary Nucleation Kinetics
4. Delay Time
5. Growth Kinetics
6. Secondary Nucleation Kinetics

Minimum Induction Time and Crystal Growth

The minimum seed size for secondary nucleation estimated using regression analysis from minimum induction time and crystal growth. Crystal growth kinetics can also be estimated.

Assessing Secondary Nucleation Kinetics and Mechanisms

(A) Secondary nucleation rates from seeded experiments plotted on a linear scale, easy to assume that there is a threshold at $S=1.08$. (B) A different perspective can be taken if plotted on a log scale, similar trend to growth data. From the same seeded experiments, secondary nucleation rates have been plotted directly against corresponding growth rates. This reveals there is a close relationship between the secondary nucleation rate and crystal growth rate over a wide range of supersaturations.

Relationship between Secondary Nucleation and Growth

Conclusions

1. A rapid small-scale workflow enabling the assessment of secondary nucleation and crystal growth kinetics has been developed
2. New insights into secondary nucleation and growth mechanisms
3. Absence of crystal growth dead zone and secondary nucleation threshold for α-glycine crystallisation
4. Close relationship between crystal growth and secondary nucleation
**Modelling Diffusive Mixing in Antisolvent Crystallisation**

Russell Miller1,*, Jan Sefcik1,*, Leo Lue2

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2Department of Chemical and Process Engineering, University of Strathclyde, 75 Montrose St, Glasgow, G1 1XL

**Projects aims:**
- Model diffusive mixing in multicomponent antisolvent crystallisation processes
- Implement model to investigate the effect of key process parameters
- Gain insight into the role of thermodynamic activity in antisolvent crystallisation by modelling diffusion in non-ideal mixtures

**Composition profiles across channel**

- In non-ideal diffusion glycine is pushed backwards into the solution due to presence of activity gradient as shown by mass fraction profiles (dashed lines represent non-ideal composition profiles)
- Peak supersaturation is on the solution side of channel for non-ideal diffusion and is below the final supersaturation; there is no supersaturation overshoot in contrast to (non-physical) ideal diffusion model prediction

**Composition profiles in ternary phase diagram**

- Ideal and non-ideal composition profiles follow different pathways across phase diagram
- In non-ideal diffusion, the composition profile may reach the spinodal curve during mixing and localised liquid-liquid phase separation (LLPS)/oiling out is predicted
- LLPS can occur in system in which final composition (black cross) suggests otherwise
- Phase separation complicates efforts to control nucleation
- By considering non-ideality of system nucleation and oiling out can be better understood

**Conclusions**

- Ternary diffusion model was developed for ideal and non-ideal mixtures
- Role of activity gradients in non-ideal diffusive mixing is crucial in qualitatively accurate understanding of mixing in antisolvent crystallisation
- There is no supersaturation overshoot expected in real (non-ideal) system
- Intermittent oiling out can occur even if final composition suggests otherwise

**References**

Primary Nucleation of Sodium Chloride from Water and Deuterium Oxide under Isothermal Agitated Conditions

James Flannigan\(^1\), Mark Haw\(^1\) & Jan Sefcik\(^1,2\)

**Introduction**

Typically crystallisation of sodium chloride is performed using solar ponds to evaporate water. In contrast little has been done to examine nucleation from solution at constant supersaturation. Here we explore a range of parameters that can impact nucleation, including sample scale, the impact of agitation and the comparison between nucleation in water (H\(_2\)O) and deuterium oxide (D\(_2\)O). We focus on low supersaturation where previous work is lacking\(^1\). We compare 1 g scale using the Technobis Crystal16 device with 3 g scale using the Technobis Crystalline, and measure nucleation rates via induction time plots for repeat samples at a range of supersaturations.

**Solubility and Metastable Zone Width (MSZW)**

The phase behaviour in both systems (H\(_2\)O and D\(_2\)O) was examined at 1 g scale (Crystal16), exposing samples to multiple controlled heating and cooling cycles to determine cloud points (extent of metastable zone or MSZW) and clear points (solubility) (Fig 1). The solubility was found to be lower in D\(_2\)O: for example at 25 °C Van’t Hoff fitting of data gives C*= 0.3599 g\(_{\text{solute}}\)/g\(_{\text{solvent}}\) in H\(_2\)O compared with C*= 0.3071 g\(_{\text{solute}}\)/g\(_{\text{solvent}}\) in D\(_2\)O.

**Induction Times at 3 g Sample Scale (Crystalline)**

From the results gained from the 1 g scale a new S range was selected for induction times examinations at the 3 g scale, since the induction time measured in H\(_2\)O at the 1 g scale showed a large number of vials nucleating before reaching isothermal conditions. Figure 3 shows measured induction times in 3 g samples agitated by magnetic stirrer at 700RPM. We observe increased induction times in D\(_2\)O, consistent with 1 g scale.

**Impact of agitation on nucleation**

The role of agitation was examined by comparing results in samples at 3 g scale (Crystalline) agitated by magnetic stirrer bar (Figure 3) and overhead downflow propeller agitation at 1250RPM (Figure 4).

**Conclusions**

- Solubility of NaCl lower in D\(_2\)O compared to H\(_2\)O
- Primary nucleation rate of NaCl is reduced in D\(_2\)O compared to H\(_2\)O
- Nucleation rates significantly impacted by agitation conditions in both solvents H\(_2\)O and D\(_2\)O
- Impact of solvent isotopologue in other solute systems.

**References**


**Acknowledgements**

The authors would like to thank EPSRC and the Future Continuous Manufacturing and Advanced Crystallisation Research Hub (Grant Ref: EP/P006965/1 & EP/R513349/1) for funding this work.

**Future work:** Secondary nucleation of sodium chloride from
Comparing the determination of nucleation rate from induction time and microfluidic methods.

Nucleation is one of the key processes in crystallization of pharmaceutical products as it determines various crystal product quality attributes such as crystal size distribution and crystal structure. Therefore, understanding the fundamentals of nucleation is key to attaining control over these properties. Nucleation refers to the generation of a new phase of nanoscopic clusters of molecules from a supersaturated mother liquor. Nucleation rates gathered from small scale (1 ml) induction time measurements were compared with those gained from micro scale measurements in a microfluidic device. This work endeavours to present microfluidics as a tool for simple, quick acquisition of nucleation rate data.

Due to the high level of control provided by microfluidic systems it is possible to determine the nucleation rate by counting the number of crystals nucleated over time. This relies on the generation of a supersaturated solution and storage of that solution in droplets over a period of time for monitoring of nucleation. Initial experimentation used a single chamber device for droplet storage. However, droplet storage was an issue. The concave pattern used to store the droplets was ineffective and the droplets moved over the course of several hours observation making it very difficult to track an individual droplet. In addition, due to the permeability of PDMS to water, the droplets lost volume over time as solvent diffused out. This led to increased supersaturation which rendered the device unusable for nucleation rate measurements as supersaturation must be tightly controlled.

In order to overcome some of the problems presented by the single chamber device a new device was used based on a design by Schmitz et al who developed a configuration they named “dropspot”. This device consisted of a Y-junction for mixture of a saturated solution and a crystallizing agent and a T-junction for droplet formation as shown in Figure 3a. Droplets formed were captured in the “dropspot” matrix (Figure 3b). This storage array consisted of 2128 chambers for long term storage. Each chamber was 150µm in diameter and the maximum volume of each droplet stored is calculated as the volume of an ellipsoid.

In addition, to compensate for the evaporation of water from the droplet solutions the device was immersed in a solution replicating the solution composition used in the device. This significantly reduced the rate of evaporation.

The microfluidic device design is currently undergoing rigorous testing.

Results are forthcoming.

References:
Aims and Objectives
The focus of this research is around the use of mechanistic model development to allow optimal control of the continuous crystallisation of α-lactose from water via cooling.

Method and Temperature Profile
The model can be built from the small batch experiments with the resulting data set inputted within gPROMS with a corresponding flowsheet of the experimental set-up as depicted within Figure 5. The parameter estimation capabilities of gPROMS can then be utilised to define the parameter based upon the experimental results. The gathering of this kinetic data allows for the complete crystallisation system to be defined.

Results – Particle Size Distribution
• The predicted trends, shown in figure 6, adequately fall within the error of the concentration profile error. However, the predictions follow more linear trend and deviate from the exponential decay format of the measured results
• Particle size distribution comparisons in figure 7 show a consistent under-prediction of the particle size distribution from the model

Conclusion and Future Work
• Building on the current model by assessing different parameters of crystallisation experimentally as depicted in Figures 1 and 2
• Continuous parameter estimation within gPROMS – specifically focus on incorporating agglomeration within the model to improve size predictions
• Integration of the gPROMS model within PharmaMV for controller design

Model-driven Control for Continuous Crystallisation of α-Lactose Monohydrate
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1 ESPRC future manufacturing Research Hub for Continuous Manufacturing and Advanced Crystallization (CMAC), University of Strathclyde
2 Strathclyde Institute of Pharmacy & Biomedical Sciences

Theory
The basic theory of this work is to assess the individual mechanisms within the crystallisation process separately and define their unknown parameters. These individual mechanisms can then be combined to give a full mechanistic model representing the system.

Results – Concentration Profiles
In order to gauge the surface integration step within the growth process it is important to try and encapsulate the problem space in its entirety. As such, within these experiments it was determined key to alternate more than one variable to gain greater understanding of the factors affecting the surface integration step. As such, supersaturation ratio and initial concentration were all varied

Agglomeration - SEM images
• SEM images of material recovered from the growth experiments show agglomeration across all tested conditions (shown in Figure 8).
• The increase of particles size due to agglomeration has not been incorporated into the mechanistic model at this stage and therefore explains the consistent under-sizing seen in figure 7.
Controlling Crystallisation with Heterogeneous Nucleation

Samira Anker1,2, David McKechnie1,2, Paul A. Mulheran3, Jan Sefcik1,2, Karen Johnston1
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3 EPSRC Future Manufacturing Hub in Continuous Manufacturing and Advanced Crystallisation, University of Strathclyde, Glasgow, UK

Introduction
• Better control of nucleation essential for crystallisation industries
• Liquid and solid interfaces greatly influence glycine nucleation due to interfacial concentration enhancement1,2
• Urea-water model system is fast nucleating so good for simulations
• Investigate effect of surfaces on solution structure and nucleation at various concentrations

Methodology
• Molecular dynamics simulations using LAMMPS3,4
• NPT simulations for system validation
• NVT for simulations with LJ wall
• Urea force field – GAFF5
• Water force field – SPC/E6

Acknowledgements
EPSRC and the Future Manufacturing Research Hub in Continuous Manufacturing and Advanced Crystallization (Grant ref: EP/P006965/1)
ARCHIE-WeSt High Performance Computer (www.archie-west.ac.uk)

Preliminary results
• Urea concentration enhancement at Lennard-Jones wall
• Urea concentration depletion at vacuum interface

Density

Radial distribution functions

Urea diffusion coefficient

Equilibrated aqueous urea solution at LJ wall

Lennard-Jones 9-3 wall
\[ \varepsilon = 10 \text{ kcal/mol} \]
\[ \sigma = 3.4 \text{ Å} \]

Future work
• Vary interface dispersion and dipole interactions
• Seed small crystals at interfaces to test for stability and growth
• Design high-throughput experiments to complement simulations

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Interface induced concentration enhancements in molecular mixtures

R. Mackay\textsuperscript{1,2}, D. McKechnie\textsuperscript{1,2}, K. Johnston\textsuperscript{1}, K. H. A. Lau\textsuperscript{3}, J. Sefcik\textsuperscript{1,2}

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Introduction

Primary nucleation of crystals from solution typically proceeds heterogeneously at various interfaces present in crystallisation processes, yet comprehensive understanding of the underlying mechanisms and their control has not yet been achieved.

- Internal collaborators have identified that glycine nucleation is rapidly accelerated at a hydrophobic oil-solution interface, which leads to the formation of a concentrated interfacial layer of solution.\textsuperscript{1}

- Aim to explore the use of widely available surface measurement techniques, such as surface plasmon resonance (SPR) spectroscopy and optical waveguide spectroscopy (OWG), to quantify the expected changes in reflectivity and \( \theta_{\text{coupl}} \) of aqueous glycine solution.

- Multi-layer optics analysis of the interface shows that the predicted interfacial concentration enhancements are within the sensitivity range of SPR and OWG.

- Experiments are designed to “close the loop” (from property prediction using molecular simulations) and facilitate understanding of the underlying drivers of heterogeneous nucleation from solutions.

Methods

- Comparison of common angular and laser intensity measurement sensitivities in a Kretschmann setup with the shifts in SPR and OWG coupling angles expected from interfacial saturation.

- Shifts were determined using the “Winspall” program, which implements a standard transfer-matrix calculation of the light propagating through the glass/prism-metal-(waveguide)-glycine-solution “multi-layer”.

Multi Layer Optics Analysis

- SPR parameters: Thin Au layer deposited on a glass slide, with a Cr layer to adhere the two together.

- OWG parameters: Polystyrene (PS) slabs of varying thickness.

- Selected configuration leads to markedly different SPR responses.

The Need for High Sensitivity

- Position and intensity of the signal at \( \theta_{\text{coupl}} \) are used to determine the degree of interaction between surface and solution.

- Small changes in solution composition lead to shifts in these parameters.

- This is further emphasised experimentally.

Conclusions

- The expected magnitude of the concentration enhancement (~30%) appears to be possible to detect in concentrated glycine solutions.

- The sensitivity of the waveguides for determining any shift in \( \theta_{\text{coupl}} \) due to glycine saturation will be small.

- Measured change in R at an off-resonance angle \( \theta \) is possible to observe and differentiate from other measurements using SPR sensors with lock-in amplification for detection of reflected light.

Acknowledgements

- EPSRC and the Future Continuous Manufacturing and Advanced Crystallisation Research Hub (Grant Ref. EP/P006955/1) for funding this work.

References


The Influence of Vessel, Agitator Geometry and Speed on Flow Characteristics in Spherical Agglomerators
Victoria R. Kitching, Kate Pitt, Bilal Ahmed, Rachel M Smith, James O Lister 
Particle Technology Group, Department of Chemical and Biological Engineering, University of Sheffield, UK

Introduction
Spherical agglomeration is a size enlargement process in which a bridging liquid is added to suspended particles, resulting in agglomerate formation [1]. The overall aim of this project is to generate a coupled CFD-PBM for spherical agglomeration at multiple scales, with different agitator types and speeds. Initial studies presented here are designed to identify the optimum bridging liquid to solid ratio (BSR) for chosen system.

Various baffle configurations were investigated both experimentally and using CFD simulations.

Experimental Methodology
Effect of BSR
52 μm PMMA plastic beads were suspended in water at a 3% wt/wt solid loading, and agglomeration experiments were performed using the shortened baffles. Toluene was used as bridging liquid, and the BSR was varied from 0.4 to 0.7. The system was agitated at 500 rpm.

Effect of Baffle Configuration
3 different baffle configurations were tested:
- No Baffles
- Shortened Baffles
- Full Baffles

To investigate the effect of baffle configuration, 52 μm PMMA plastic beads in water were used with toluene as a bridging fixed at BSR of 0.5, and the mixture was agitated at 500 rpm for 60 minutes after toluene addition.

Computational Methodology
Effect of Baffle Configuration
Multizonal meshing with hexahedral and prism elements was used.

<table>
<thead>
<tr>
<th>Geometry Zone</th>
<th>Mesh Size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tank Wall</td>
<td>2</td>
</tr>
<tr>
<td>Outer Domain</td>
<td>2</td>
</tr>
<tr>
<td>Impeller Shaft</td>
<td>2</td>
</tr>
<tr>
<td>Impeller Blades</td>
<td>0.8</td>
</tr>
<tr>
<td>Inner Domain</td>
<td>0.8</td>
</tr>
</tbody>
</table>

The geometries of the three baffle configurations were created in CFD to investigate the impact of baffles on flow in the reactor.

CFD Experimental Validation Plan
CFD flow validation is planned. Glass Beads of a predetermined size will be suspended in water. 90% of the beads will remain clear, and 10% will be coloured red to act as tracer particles. Mixtures will be agitated at a set speed between 300-600 rpm, with images captured at 8 frames per second. The images will be analysed using MATLAB Image Toolbox and compared with CFD results.

Population Balance Methodology
PBM will be implemented in gPROMS. It is intended to develop a one-way coupled model, with CFD results, such as velocity profile, as input to the PBM. The PBM portion of this project is currently focused on identifying and developing appropriate kernels for use in the population balance model. The nucleation kernel will be based on the model developed by Arjmandi-Tash [2]. Various agglomeration kernels are being considered including the kernels developed by Maric et al [3] and Blandin [4].

Results

<table>
<thead>
<tr>
<th>Varying BSR</th>
<th>0.4 BSR</th>
<th>0.5 BSR</th>
<th>0.6 BSR</th>
<th>0.7 BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity Magnitude (m/s)</td>
<td>100</td>
<td>120</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>Particle Size Range (μm)</td>
<td>0.04</td>
<td>0.06</td>
<td>0.08</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Conclusion
The experimentally determined optimal BSR for the PMMA beads, water, and toluene system is 0.5.
- Experiments demonstrate that full length baffles narrow the particle size distribution.
- The velocity magnitude and wall shear stress in the reactor increase greatly without baffles.

Future Work
- Experimental validation of the CFD simulations.
- Development of CFD with particle tracking.
- Begin construction of the PBM with the nucleation kernel based on the Arjmandi-Tash model.

References
Towards Controlling Crystallization Using Liposomes: Manipulation of Liposome Size Through Microfluidics

Greg Chambers, PhD student, CMAC & SIPBS
Supervisors: Joop ter Horst, Yvonne Perrie

Background

Crystallization plays an important role in defining the physico-chemical characteristics of pharmaceuticals. The ubiquity of crystal nucleation reactions - as well as the strong influence on product quality - emphasises the importance of understanding and controlling the process. Within this project, we are investigating the use of liposomes to control crystallization. Due to their nanoscale size and ability to facilitate well-controlled process conditions, liposomes present an excellent vehicle for crystallization studies. It has been shown that nanocrystalline precipitates of drugs such as doxorubicin, topotecan and idarubicin can be encapsulated inside liposomes for drug delivery purposes; however, the formation of these nano-crystals has never been extensively studied. In order to control the particle size of liposomes and to establish transmembrane gradients, we have used microfluidics.

Aims

Characterise liposomes of varying size and composition on their suitability as crystallisation vehicles

Closely study nucleation rates within liposomes, eventually relating the rate of nucleation to process conditions and lipid characterisation

Control the crystallisation of a loaded pharmaceutical compound in drug delivering liposomes

Results

Flow rate ratio was shown to impact liposome size - as the ratio increased from 2:1 to 4:1, the liposomes reduced in size from 106.8 ± 4 nm to 87.4 ± 14.6 nm (Fig. 1A). However, the change in flow rate ratio did not affect the size distribution, polydispersity index (PDI) values were < 0.2 for all formulations. In the case of total flow rate, increasing the flow rate from 5 to 15 mL/min resulted in a decrease in size from 207 ± 27 nm to 73.9 ± 14.6 nm (Fig. 1B). The final lipid concentration was also tested and at concentrations of 5 mg/mL and 10 mg/mL liposomes of consistent size (≈ 75 nm) and PDI (< 0.2) were produced (Fig. 1C). Despite these differences, encapsulation efficiency was typically high (>85%), with particle size having no notable impact (Fig. 1D). We can conclude that liposomes produced via microfluidics offer in-process size control and high reproducibility, therefore providing an ideal format for studying crystal nucleation behaviour.

Ongoing Research

Before analyzing crystal nucleation within liposomes, we must first identify suitable model compounds to use. It is known that in the liposomal formulation Doxil®, doxorubicin citrate crystals form nano-rod structures almost instantaneously within the aqueous core of liposomes. The speed of the process makes studying nucleation rates challenging. Therefore, it is key that we find model compounds that crystallize slowly enough to allow us to determine nucleation rates. Some potential model compound candidates are: mefenamic acid, DL-alanine and paracetamol. Using solubility data from these model compounds, we can create supersaturated solutions inside various liposomes, calculate the rate of nucleation and eventually develop new crystal nucleation theories.
Digital Medicines Manufacturing
Developing the CMAC Digital Platform

Murray N. Robertson & Blair F. Johnston
murray.robertson@strath.ac.uk

The CMAC Digital Strategy

• Digitalising Research Data from all operations of the end to end process
• Accelerate Digital Design Research

Research Questions

• Can structured data accelerate process development by utilising artificial intelligence?
• Can Digital Workflows be developed and implemented within CMAC projects?

Central location for all CMAC researchers to record their daily findings.

Applying models to workflows developed within CMAC to help standardise protocols and data collection.

Digital Workflows:

Approach

• Centralising data throughout CMAC
• ELN templates
• Structured data
• Data driven decisions

Proof of Concept

• Mefenamic acid solvent selection for crystallisation
• Solvent selected after testing just 12 solvents
• Compared to 54 previous campaign

Central location for all CMAC researchers to record their daily findings.

ELN extracted

Data driven decisions via digital workflows

Results reported and researcher guided to next steps

Automated modelling and AI correction applied

ELN templates
SAFT-γ Mie group-contribution approach; application to lactones and mefenamic acid

Thomas Bernet  t.bernet@imperial.ac.uk
Claire S. Adjiman, Amparo Galindo, George Jackson

SAFT-γ Mie molecular modelling

- interactions between groups and parameter estimation
- group-contribution approach for pure fluids or mixtures
- current work: lactone group cCOO, i.e., cyclic ester group

Parameter estimation and prediction of thermodynamic properties

Thermodynamic properties of lactones:

- Density at 298 K:

- Mixing enthalpy at 298 K:

Other application to solubility prediction:

- SAFT-γ Mie molecular modelling of mefenamic acid:

- Solubility:

Other considered solvents: hydrocarbons, ketones, esters, aromatic compounds, water

Reference: Febra et al., Extending the SAFT-γ Mie approach to model benzoic acid, diphenylamine, and mefenamic acid: solubility prediction and experimental measurement, Fluid Phase Equilib, 540, 113002 (2021)

⇒ No solubility data used to produce these graphs; only heat of fusion and melting point of the API are needed.
Medicines Manufacturing Innovation Centre (MMIC): the use of a Digital Twin

Hikaru Jolliffe*, Carla Mendez Torrecillas, Martin Prostredny, Maria Blazejczak, Daniel Markl, John Robertson.

hikaru.jolliffe@strath.ac.uk

1. Background and motivation

Current State of Pharmaceutical Industry

• Pharma R&D costs significantly increasing.
• Increasing globalised competition from generic pharma manufacturers.
• Technological innovation required to maintain profitability & sustainability.

Current State of Pharmaceutical Industry

• Technological innovation required to maintain profitability & sustainability.
• High solvent waste: reactions + separations.
• Generic pharma manufacturers significantly increasing.
• Pharma R&D costs cons of the Advanced Manufacturing Innovation District Scotland (AMIDS)
• MMIC project lead by Centre for Process Industry (CPI), U. o. Strathclyde, AZ, GSK, UKRI, Scottish Enterprise, and the Scottish Government.
• Goal: "to become an international leader for innovation in small-molecule medicine manufacturing"
• 3-yr project (started summer 2018). 80 high-value jobs by 2023, £80m R&D attracted by 2028, further 90 jobs created during design and construction.

2. Medicines Manufacturing Innovation Centre (MMIC)

MMIC project strategic partner.
• Key objective: Digital Twin of secondary processing unit operations.
• Working with various materials commonly used by industrial partners.

3. University of Strathclyde and MMIC

Digital Twin Concept

Digital Twin Concept

What It Is
• Appropriately accurate and precise representation of the real process.
• Based on real data and measurements.
• Validated against additional data.

What It is not
• A 100% replication that can predict conditions vastly different to than what it was designed for.
• A complete replacement for experimentation.

What It can do
• Reduce the need for experimentation.
• Allow the rapid evaluation of new materials and process configurations.

4. Digital Twin: MMIC project

Digital Twin: at a glance

Linking of software packages into a workflow

Digital Twin Design and Construction

5. State-of-the-art for feeders and blenders

• Established modelling approaches largely consist of:
  – Empirical equations describing mass flow profiles
  – PCA and PLS models to relate material characteristics / equipment operation to key variables and parameters
  – RTD modelling (fitting to pulse/step change data)
  – Discrete Element Method

6. Digital Twin: MMIC project

Digital Twin: at a glance

Digital Twin Design and Construction

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What It can do
• Reduce the need for experimentation.
• Allow the rapid evaluation of new materials and process configurations.

7. CDC rapid development using Digital Twin workflow

CDC rapid development using Digital Twin workflow

INPUT: Materials and recipe development

Material property database

INPUT: Materials and equipment database

INPUT: Materials and equipment database

INPUT: Process flowsheet

Process model

OUTPUT: Optimal equipment configuration and CPPs for CDC

OUTPUT: Optimal equipment configuration and CPPs for CDC

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8. Summary & future directions

The Medicines Manufacturing Innovation Centre will be a cutting-edge R&D centre for pharmaceutical manufacturing.

University of Strathclyde are the strategic partner, providing experimental expertise and leading research in experimental model development for secondary processing unit operations.

State-of-the-art models are being evaluated and potential improvements identified.

Digital tools are being employed to increase efficiency and research productivity.

9. References

• Tossas, P et al., 2018. Int. J. Pharm., 552, 288–300.
Crystallisability

- Crystallisability: the ability of a compound to nucleate fast/medium/slow.
- Aim: To develop machine learning workflows to predict crystallisability.
- In order to predict the crystallisation propensity, experimental screening was performed by following the workflow shown in figure 1.

![Figure 1: Experimental screening workflow.](image)

To develop a classification model, the images were converted into feature vector representation using the outcome of crystallisation.

A classification model was developed using the images obtained from screening experiments to predict images.

The RF model developed for segmenting one image was used to perform automatic segmentation of time series images.

A plot of the decrease in mean background integrated intensity was used to classify datasets as fast, medium and slow nucleating.

Mean integrated density

To develop a predictive model for crystallisability, image analysis was performed on the time series images by following the sequence of steps as shown in figure 6.

![Figure 6: Sequential steps to classify time series images.](image)

The RF model developed for segmenting one image was used to perform automatic segmentation of time series images.

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![Figure 7: ML workflow to predict crystallisability.](image)

The results indicate a classification accuracy of 73%.

Results:

- The results indicate a classification accuracy of ~73%.
- Follow the experimental DSC curves the compounds are divided into three classes.
- Based on the experimental DSC curves, the compounds are divided into three classes.

Glass forming ability (GFA)

- Glass forming ability (GFA): The GFA of a material is the ease of vitrification of liquid on cooling.
- Why Amorphous from:
  1. Its is estimated that 55% of drugs and 90% of new chemical entities are poorly water soluble.
  2. Low permeability.
  4. Elimination from the body along with poor safety and tolerability.

Amorphous drugs provide an alternative route to increase the bioavailability.

The best results to predict GFA were obtained using support vector machine learning algorithm.

In SVM we are looking for optimal separating hyperplane by projecting the data points into higher space.

The use of radial kernel resulted in a model with 0.18% misclassification.

The results indicate a classification accuracy of ~99%.

![Figure 9: Confusion matrix of the data to predict crystallisability.](image)

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Conclusion

- Workflows were developed to predict crystallisation outcome, crystallisability and glass forming ability.
- Following experimental screening, the crystallisation propensity of some organic pharmaceutical compounds can be predicted with an accuracy of ~73%.
- Glass forming ability in pharmaceutical compounds can be predicted with an accuracy of ~99%.

Aim: To develop machine learning workflows to predict crystallisability.

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AI Strategy for Advanced Imaging Capabilities

Antony D Vassileiou¹, Cameron J Brown², Murray N Robertson³, Alastair J Florence⁴, Blair F Johnston¹,⁵

¹ EPSRC ARTICULAR, University of Strathclyde, Glasgow, G1 1RD, United Kingdom
² EPSRC CMAC Future Manufacturing Research Hub, University of Strathclyde, Technology and Innovation Centre, Glasgow, G1 1RD
³ National Physical Laboratory, University of Strathclyde, Glasgow, G1 1RD, United Kingdom

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**AT PRESENT**

- In-depth characterisation of individual particles is possible through instrumentation, e.g. Morphologi G3 or QICPIC
- This is achieved by physically separating particles prior to imaging
- More complex images, such as those from a standard microscope or in-line images from, e.g. PVM, cannot be characterised in the same way

**PROPOSAL**

- Previous work within CMAC used GANs to generate artificial images of individual particles, based on output from Morphologi G3
- Further previous work with G3 images used RF to classify particles by shape properties
- In combination, individual particle images with controlled size and shape properties can be generated and compiled into synthetic images
- Properties of constituent shapes are available, therefore ground truth is retained and controlled

**PROGRESS**

_Long-term goal: segmentation and characterisation of multi-particle, in-situ images_

- Preliminary images mimicking a composite Morphologi G3 output have been produced successfully, exerting control over particle selection and placement
- Preliminary CNN results working from low-res images indicate that particle size estimation is feasible
- Next steps:
  - refine CNN to work with high-res images
  - deploy GANs to generate particles with wider range of sizes/shapes/properties
  - Develop method for compilation of synthetic PVM-like images (retaining ground truth)

---

Universities:

- University of Strathclyde
- Loughborough University

Companies:

- Siemens
- Booth Welsh
- Perceptive Engineering Ltd
Research Aims

- Research problem: Crystal shape is one of the key attributes affecting the bulk particle properties of a crystalline material as well as its downstream manufacturability. However, the prediction of experimental crystal shapes remains very challenging.
- This research aims to explore the potential application of machine learning algorithms to solve this problem.

Research Methodology

Solvent Selection

Organic solvents used in this work were selected from the solvent cluster classified by Strathclyde24, which is a solvent library clustering which categorizes solvents into 24 clusters based on solvent’s molecular descriptors 3.

Solubility Test

- Solubility screening by solvent addition method: Each solvent was gradually added to a known-amount of mefenamic acid powder of which the temperature controlled at 25°C and 50°C until the clear solution was obtained.
- Using a multi-reactor crystallisation platform (Crystal16): Measure real-time turbidity of sample solutions at different concentrations and determine solubility from clear points (transmission = 100%) at specific temperatures.

Cooling crystallisation screening

- Sample solutions were prepared at different initial concentrations.
- The samples were heated on a hot plate to get clear solutions and then left in an incubator at 25°C without disturbance until crystals occur.
- The crystal were observed under an optical microscope.
- Crystal images from 261 samples were collected and classified into either polyhedral crystals, needles, or no crystals.

Preparing the dataset for machine learning

Input - 211 columns:
- 201: 2D - Molecular descriptors calculated from MOE using SMILES codes
- Additional solvent properties: boiling point, melting point, and density
- Solubility of mefenamic acid at 25°C in particular solvent
- Degree of supersaturation: 
- Crystal outcomes: Polyhedral, needle, no-crystals

Model evaluation:
- Train/test split: 75% trained (196 trained data) 25% tested (data)
- Cross-validation

Table 1. Number of observations classified into each group based on the shape of crystals

<table>
<thead>
<tr>
<th>Crystal outcomes</th>
<th>Number of experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyhedral</td>
<td>135 (51.72%)</td>
</tr>
<tr>
<td>Needle</td>
<td>83 (31.80%)</td>
</tr>
<tr>
<td>No-crystals</td>
<td>43 (16.48%)</td>
</tr>
<tr>
<td>Total</td>
<td>261</td>
</tr>
</tbody>
</table>

Results & Discussions

Model Evaluation

- Random Forest Classification

From 1,000 consecutive running the model evaluation by train/test split (randomly selected the train/test set from the whole dataset for each run), the mean accuracy of the model was 85.6% with 3.9% standard deviation (SD). The maximum and minimum accuracies were 95.5% and 72.3%, respectively.

Figure 7. The confusion matrix showing the results of the predictive model. The matrix on the left was built from the train/test set which generated maximum accuracy and the right one was built from the train/test set which generated minimum accuracy.

Note: N = needle, NC = no crystals, and P = polyhedral

Feature Selection

Set of the variables were selected from all 211 variables and were used for training the model. Then the model’s accuracy was calculated and compared.

Table 2. Mean accuracy calculated by mean of 4-fold cross validation

<table>
<thead>
<tr>
<th>Feature selection</th>
<th>Top-20 most important variables</th>
<th>Atom count and bond counts</th>
<th>Pharmacophore features</th>
<th>Physical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>49.7%</td>
<td>60.1%</td>
<td>47.1%</td>
<td>49.7%</td>
</tr>
</tbody>
</table>

In conclusion, Random forest classification model has the potential to predict the shape of mefenamic acid crystallised from organic solvents with approximately 60% accuracy. Regarding the importance score, supersaturation was the most important variable to predict the crystal shape.

Acknowledgement

Many thanks to Dr. Monika Warzecha, and Dr. Cameron Brown, EPSRC Future Manufacturing Research Hub for Continuous Manufacturing and Advanced Crystallisation (CMAC), University of Strathclyde, Technology and Innovation Centre, for their expertise and kind support along this work.
Introduction

The Cambridge Structural Database (CSD) currently holds records of over a million crystal structures. This research seeks to isolate and discuss organic crystal structures containing solvents, which account for approximately 52,249 structures in the CSD. Several different categories arise from these structures, including traditional solvates, clathrates, ionic solvates, solvate hydrates and heterosolvates. Water, methanol, ethanol, chloroform, DCM and acetone are found in the most structures within each of the aforementioned categories. Some consideration is also given to the absence of metadata in some fields associated with entries in the CSD, such as temperature and recrystallisation solvent. In addition, this work seeks to address the challenges that arise when attempting to curate negative data and the barriers to utilising the wealth of data available in the CSD for the purpose of data-driven modelling.

Crystal Structures Containing Solvents

There are several different types of crystal structures containing solvents in the CSD, which are summarised in Table 1. Hydrates are the most common type of solvate with 13,179 total structures. Water is used frequently in polymorph screening, both as a pure solvent and in solvent mixtures, which may explain the high number of hydrated structures in the CSD. Additionally, evidence suggests that water inclusion in small organic molecules is linked to the volume of void space within the crystal. Currently, methanol, dichloromethane (DCM) and chloroform are amongst the most frequently occurring solvates in the CSD (Table 2). Methanol solvates form readily due to its small size and high polarity, potentially enhancing its ability to navigate void space and encourage solvent inclusion. With regards to DCM and chloroform, the acidic C-H protons found in both solvents are potent hydrogen bond donors, which may account for their tendency to form solvates. In Figure 2, the majority of solvates form for solvents with a molecular weight of below 80. There is also an overabundance of solvates formed with both high and low dielectric constants, though the data is skewed due to the presence of water in the >50 category.

<table>
<thead>
<tr>
<th>Structure Type</th>
<th>Crystal Structure Definition</th>
<th>Number of CSD entries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvate Hydrate</td>
<td>Crystalline forms in which one unique solvent molecule, or water, is incorporated into the lattice</td>
<td>33,235</td>
</tr>
<tr>
<td>Ionic Solvate</td>
<td>Crystals containing at least one cation, one anion and one solvent molecule</td>
<td>11,223</td>
</tr>
<tr>
<td>Clathrate</td>
<td>Inclusion compounds which consist of a host and a trapped guest solvent molecule (e.g. in voids, channels)</td>
<td>3,362</td>
</tr>
<tr>
<td>Solvate Hydrate</td>
<td>Crystalline forms in which both water and solvent molecules are incorporated into the lattice</td>
<td>3,132</td>
</tr>
<tr>
<td>Heterosolvate</td>
<td>Crystalline forms in which more than one unique solvent molecule is incorporated into the lattice</td>
<td>1,297</td>
</tr>
<tr>
<td>Non-Solvate</td>
<td>Single crystal structures which have been recrystallised from a particular solvent, but do not contain any solvent molecules within the crystal lattice</td>
<td>31,000</td>
</tr>
</tbody>
</table>

Table 1 – definitions of different structure types which contain solvent molecules.

Solvates

Table 2 – the number of solvates for selected solvents in the CSD.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Number of CSD solvates containing solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>13,179</td>
</tr>
<tr>
<td>Methanol</td>
<td>2,739</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>2,717</td>
</tr>
<tr>
<td>Chloroform</td>
<td>2,721</td>
</tr>
<tr>
<td>Acetone</td>
<td>1,294</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>1,246</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1,023</td>
</tr>
<tr>
<td>N,N-dimethylethylenediamine</td>
<td>958</td>
</tr>
<tr>
<td>Acetone</td>
<td>904</td>
</tr>
<tr>
<td>Other</td>
<td>6,384</td>
</tr>
</tbody>
</table>

Table 2 – the number of solvates formed for solvents with varying molecular weight/properties.

Ionic Solvates and Clathrates

Table 2 – the number of ionic solvates and clathrates for selected solvents in the CSD.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Number of ionic solvates</th>
<th>Solvent</th>
<th>Number of clathrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>6,975</td>
<td>Water</td>
<td>765</td>
</tr>
<tr>
<td>Methanol</td>
<td>644</td>
<td>Acetone</td>
<td>228</td>
</tr>
<tr>
<td>Acetone</td>
<td>576</td>
<td>Methanol</td>
<td>187</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>484</td>
<td>Benzene</td>
<td>166</td>
</tr>
<tr>
<td>Chloroform</td>
<td>339</td>
<td>Chloroform</td>
<td>167</td>
</tr>
<tr>
<td>Ethanol</td>
<td>222</td>
<td>Acetone</td>
<td>152</td>
</tr>
<tr>
<td>Acetone</td>
<td>153</td>
<td>Ethanol</td>
<td>135</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>106</td>
<td>Benzene</td>
<td>117</td>
</tr>
<tr>
<td>Benzene</td>
<td>99</td>
<td>Dimethyl sulfoxide</td>
<td>117</td>
</tr>
<tr>
<td>Other</td>
<td>1,025</td>
<td>Other</td>
<td>1,325</td>
</tr>
</tbody>
</table>

Table 2 – the number of ionic solvates and clathrates for selected solvents in the CSD.

Multi-Solvate Forming Molecules

Molecules which solvate with more than one solvent may be thought of as ‘multi-solvate formers’. While the CSD contains over a million structures, there is an absence of data where systematic screenings are conducted. The highest number that appears in both Venn diagrams is 31 molecules which solvate with methanol and ethanol. Interestingly, no molecules solvate with all 5 solvents listed in either Venn diagram. Consequently, it is difficult to draw conclusions and characterise molecules which are multi-solvate formers. Systematic screenings are most likely to be conducted in the pharmaceutical industry during exploratory work. Such data is unlikely to be shared or published due to patent retention and confidentiality issues.

Non-Solvates/“Negative” Data

Non-solvates are relevant when utilising machine learning in solvate formation prediction, as the training data must contain examples of both solvates and non-solvates. Training data for data-driven modelling, negative data is equally as valuable as positive data. In the case of some of the solvents there is an absence of negative data, which provides a barrier to producing models for solvate formation prediction.

<table>
<thead>
<tr>
<th>Metastable</th>
<th>Number of CSD solvates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>97.942 (24.1%)</td>
</tr>
<tr>
<td>Pressure</td>
<td>405.328 (99.8%)</td>
</tr>
<tr>
<td>Recrystallisation solvent</td>
<td>324.052 (79.6%)</td>
</tr>
</tbody>
</table>

Table 3 – The number of organic CSD entries (of which there are 407,031) for which temperature, pressure and recrystallisation solvent are absent.

Conclusions

Organic crystals containing solvents account for around 2.5% of the CSD, which consists of traditional solvates, solvate hydrates, heterosolvates, clathrates and ionic solvates. In all of these subcategories, water, methanol, ethanol, chloroform, DCM and acetone are found to be the most frequently. The majority of solvates form with solvents of a molecular weight of 80 g/mol or less, and solvents with both high and low dielectric exhibit large numbers of solvates formed. Negative data is often underreported in the scientific community, whether because the data does not relate to the researcher’s objectives or because it seems to be of low significance.

This work has been prepared as a manuscript with the intent to submit to Crystal Growth & Design.
Understanding powder flow and how it affects pharmaceutical manufacturing process performance remains a significant challenge for industry, adding cost and time to the development of robust production routes. This work aims to improve decision making for manufacturing route selection in the early stages of the drug product manufacturing process development when available material are at a premium. A Machine Learning (ML) model approach is proposed to predict the flow properties, specifically the flow function coefficient (FFc) of a new material from its physical particle properties. The goal is that the model produced as an outcome can help decide whether a new material is suitable for Direct Compression (DC).

**INTRODUCTION**

**Prediction of Powder Flow from Physical Particle Properties using Machine Learning**

Laura Pereira Diaz, Cameron Brown, Alastair Florence

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Continuous Manufacturing and Advanced Crystallisation Future Research Hub at the University of Strathclyde

**MATERIALS AND METHODS**

**Materials:** 115 materials (APIs, excipients and blends) have been fully characterised.

**Experimental methods:** Particle size shape distribution have been analysed using the QIC/PIC - Sympatec. Flow function coefficient and bulk density have been measured using a shear cell test (Freeman FT4). A bin blender was used to make the binary and multicomponent systems.

**Machine Learning:** A PCA was carried out on the data as a dimensional reduction analysis. The ML algorithms selected for classification problems were Random Forest (RF), Neural Network (NN), Logistic Regression (LR), Support Vector Machine (SVM), k-Nearest Neighbor (kNN), Naïve Bayes (NB), and AdaBoost (AB). Furthermore, they were evaluated by 10-fold cross-validation and with an external data set.

**RESULTS**

**Pearson Correlation:** between variables and target (FFc).

**Experimental data:** classes assigned according FFc.

**Machine Learning:** PCA and classification algorithms.

**External validation:** 9 "unseen" materials

- 3 materials → Class 1
- 3 materials → Class 2
- 3 materials → Class 3

Particle size and shape distribution were fed into the ML algorithms

<table>
<thead>
<tr>
<th>Predicted</th>
<th>Actual Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

- Particle size distribution (D10) is highly correlated with the Flow Function Coefficient (FFc).
- In the training set, the materials were classified based on their FFc into class 1 (cohesive), class 2 (easy flowing) and class 3 (free flowing)
- PCA does not give useful classification of these data.
- Random Forest had the highest performance
  - AUC = 0.802 → there is an 80% of possibility that the algorithm distinguish between classes.
- **External validation:** 6 of 9 materials were correctly classified

**FUTURE WORK**

- Surface are and surface energy measurements.
- Adding more materials to the training set.
- Applying transfer learning.

**REFERENCES**


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Introduction

The discrete element method (DEM) is a computational modelling tool commonly used for the simulation of granular and powder processes. DEM involves the numerical computation of physical properties and interactions of particles based on inputs such as particle properties, equipment geometries, process parameters, and governing equations [1]. Tablet compression (see Fig.1) is one of the key processes in drug manufacturing, and are affected by factors such as particle size and shape, density, and compression force. Overall goal of this project is to simulate the compaction of pharmaceutical tablets and use the this tablet model to simulate the tablet disintegration considering liquid absorption and swelling of particles.

Method and Material

The tablet compaction was modelled using DEM using the open source software YADE-DEM. The Luding elasto-plastic contact model was used to model particle-particle and particle-wall interactions [1], equations are given in Eq.1-3 for normal force \( F_n \) and tangential force \( F_t \). The particle undergoes deformation during tablet compression which was modelled using Haustein et al. (2017) [2] deformation engine (Eq. 4). The original sphere of radius \( r_p \) is deformed into a larger sphere of radius \( r'_p \), reduced by a spherical cap (see Fig. 2).

Figure 1: Different stages of the compaction process: a) filling of the die, b) re-packing of powder and initial compaction, c) maximum compaction, d) unloading and e) tablet after compaction.

**Table1: Parameter for Luding contact model, the values are taken from Gao et al. (2021)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_1 )</td>
<td>1.26 \times 10^1 \text{N/m}</td>
</tr>
<tr>
<td>( k_2 )</td>
<td>12</td>
</tr>
<tr>
<td>( k_3 )</td>
<td>0.1</td>
</tr>
<tr>
<td>( \rho ) (density)</td>
<td>1050 \text{kg/m}^3</td>
</tr>
<tr>
<td>( r_p )</td>
<td>79 \mu m</td>
</tr>
</tbody>
</table>

**Future Work**

- To use this tablet model to simulate the disintegration process using DEM and coupling it with pore unit assembly model [5] to include the mechanisms: swelling of single particle, liquid penetration and break-up of the tablet.
- The swelling of single particle will be modelled using the Soundaranathan et al. (2020). We have quantified the swelling characteristics of various pharmaceutical material including MCC PH101 and PH102 and superdisintegrant (Fig. 5).

**Figure 2: Schematic illustrating the extension of the DEM with the deformation engine. The material in the overlapping area (dashed line) is redistributed in the free area (dark gray) resulting in an increased radius \( r'_p \) and overlapping-distance \( \delta' \)[2]**

**Figure 3: Left) Two particle contact with overlap \( \delta \) in normal direction. Right) Schematic graph of the piece-wise linear, hysteretic, adhesive force-displacement model in normal direction. The non-contact forces, indicated by \( F(p) \) and the line for negative \( \delta \), are neglected in this Luding model.**

**Figure 4: Illustration of the deformation engine by Haustein et al. (2017). Deformation of a sphere with a diameter of 10 mm compressed between two walls at distances of 10 mm, 5 mm and 3.3 mm. The original spheres with the radii \( r_p \) (white sphere) and deformed spheres with the radii \( r'_p \) (coloured mesh) are shown. The colour of the mesh corresponds to the degree of deformation [2]**

**Equations**

\[
F_n = \begin{cases} 
 k_1 \delta, & \text{if } k_1(\delta - \delta_0) \geq k_1 \delta \\
 k_2 (\delta - \delta_0), & \text{if } k_1 \delta \geq k_1 (\delta - \delta_0) \geq -k_2 \delta \\
 x - k_2 \delta, & \text{if } k_2 \delta \geq k_2 (\delta - \delta_0) \geq -k_2 \delta \end{cases} \\
(1)
\]

\[
k_2 = \begin{cases} 
 k_2, & \text{if } \frac{\delta_{\text{over}}}{\delta_{\text{min}}} \geq 1 \\
 k_1 + (k_2 - k_1) \frac{\delta_{\text{over}}}{\delta_{\text{min}}}, & \text{if } \delta_{\text{over}} < \delta_{\text{min}} 
\end{cases} \\
(2)
\]

\[F_t = -k_3 \delta_l \\
(3)
\]

\[\delta_l = \frac{\rho_d^2 - \frac{1}{2} \sum_{i=1}^{N} \left[ (r_p^2 - d_i^2) \left( 2r_p + d_i \right) \right]}{2 \rho_d^2} \\
(4)
\]

**Figure 5: Anisotropic swelling analysis for PH101/PH102 and three disintegrants showing the a) diffusion coefficient, \( D \), and b) maximum absorption ratio, \( Q_{\text{max}} \), CCS - Croscarmellose sodium, SSG - Sodium starch glycolate and L-HPC - Low-substituted hydroxypropyl cellulose**

**Reference**

7. Soundaranathan et al., 2020, Int. J. Pharm., 590, 119903.

Acknowledgement

The authors would like to thank National Manufacturing Institute for Scotland (NMIS) for funding this work. In addition, the authors would like to thank the Future Continuous Manufacturing and Advanced Crystallisation Research Hub and the Royal Society for funding this work.
Applying Machine Learning To The Prediction Of Crystal Morphology

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Introduction

• Morphology control of primary crystalline particles can be critical in the design and delivery of crystallisation processes, including continuous crystallisation.
• Current morphology screening relies on manually testing APIs against solvents; an approach expensive on human resources, materials and time.
• Predictive models will reduce time, costs and waste; improving existing models will benefit from use of a maximal set of descriptors and prior data.
• Data from Cambridge Structural Database (CCDC) was passed to the Mordred chemical descriptor calculator to generate the largest data set possible.
• Machine learning algorithms were implemented to develop data-driven models correlating the precursor’s chemical descriptors with morphologies.

Machine Learning Approach

Algorithm Performance

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Data Set</th>
<th>Random Accuracy (%)</th>
<th>Algorithm Accuracy (%)</th>
<th>Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random Forest Classifier</td>
<td>All Data</td>
<td>10</td>
<td>40.30</td>
<td>30.9</td>
</tr>
<tr>
<td>Multilayer Perceptron</td>
<td>All Data</td>
<td>10</td>
<td>38.19</td>
<td>28.29</td>
</tr>
<tr>
<td>Random Forest Classifier</td>
<td>Binary</td>
<td>50</td>
<td>61.63</td>
<td>11.63</td>
</tr>
<tr>
<td>Multilayer Perceptron</td>
<td>Binary</td>
<td>50</td>
<td>59.55</td>
<td>9.55</td>
</tr>
<tr>
<td>Random Forest Classifier</td>
<td>Single Solvent</td>
<td>25</td>
<td>15.89</td>
<td>-9.11</td>
</tr>
<tr>
<td>Multilayer Perceptron</td>
<td>Single Solvent</td>
<td>25</td>
<td>43.70</td>
<td>18.7</td>
</tr>
</tbody>
</table>

Data Visualisation

Using Principal Component Analysis, the dimensionality of the data can be reduced, allowing it to be visualised on a 2D plot.

There is no clear divide between cases with different morphologies. This shows why the algorithm was unable to fit a function to the data.

Key limitations:
1. Lacking key descriptors.
2. Forced to assume synthesis was carried out with the same method.
3. Data set was not sufficiently large.

Morphology Labelling With Deep Learning

When building large data sets, labelling samples with consistent class names is essential. Although sometimes challenging by eye, convolutional neural networks are well established in image processing tasks.

Even with as few as 50 labelled examples, the network was able to classify images with extremely high accuracy. For wider application a far larger data set must be used for training however, as an initial test, the results are incredibly promising.

Convolutional Neural Networks are the industry standard when it comes to image recognition tasks. These will be applied to images produced by the screening device. The network used four different layers (below) and the ReLu activation function:
1. Convolutional
2. Pooling
3. Flattening
4. Fully Connected
Digital Design Strategies for Industrial Crystallisation Development

Mitchelle Mnemo1, Dr Cameron Brown1,2, Prof Jan Sefcik2
1EPRSC Future Manufacturing Hub for Continuous Manufacturing and Advanced Crystallisation (CMAC), University of Strathclyde
2Department of Chemical and Process Engineering, University of Strathclyde

Transfer of crystallisation processes from the lab to manufacturing is complex involving several technology transfer steps. As the scale or technology changes, a change in the hydrodynamics can also occur, resulting in an impact on the underlying process mechanisms. However, there are multiple mechanisms that do not all respond in the same manner to a change in scale or technology, nor will the impact be the same for each active pharmaceutical ingredient (API) being developed. Process scale-up and/or technology transfer can only be achieved by deeply understanding the interconnection between the API properties, its crystallisation behaviour, and the vessel hydrodynamics. Machine learning predictive models provide state-of-the-art feature interpretation techniques that will save experimental time, costs and are viable.

Project Aims and Objectives
The initial aim of this project is to develop a machine learning model that screens API molecules, to identify diverse chemical and mechanical properties, targeting at building a database of diverse crystallisation behaviours.

Machine Learning Methods
A total of 34 compounds obtained from literature. Variables include, temperature, volume, supersaturation ratio, induction times and 2D molecular descriptors calculated for each compound.

Anomalies and missing data identified and replaced by most frequent/average to prevent loss of data.

Correlation between all features analysed. Data was then separated into features and targets

Algorithm performance analysed for linear (Linear regression, Lasso, Ridge Regression) and non-linear (kNN, SVM, Random Forest(RF) algorithms.

Best performing model selected and validated

Results

Feature ranking: Variables scored to assess influence on induction times.

Future work
1. Solvent fractions, solubility data and crystal growth rates of each compound are currently being generated and will be added as additional features to explore.
2. Comparison of predictive model with data set split into organic and inorganics.
3. Vessel model systems will be created using computational fluid dynamics (CFD) models to extract hydrodynamic parameters.
4. Simulated crystallisation experiments using kinetics obtained from database.
Quality by Design (QbD) has been adopted within many industries and employs forward thinking where the process is designed with the end goal as the main attribute. Due to recent advancements in technology there is a need to adapt manufacturing practices to include digital design especially within pharmaceutical development.

The aim of this work is to design a workflow for small scale crystallisation that can be adapted for use by an autonomous robotic platform. The workflow will consist of simple experimental steps and data collection to supply machine learning training and testing sets. The objectives of this work will be the determination of numerous suitable solvent and solute pairings that allows for kinetic and thermodynamic data extraction using QbDD methods. Following on from the determination of experimental parameters a machine learning model will be designed to predict crystal properties.

### MATERIALS AND METHODS

**Solvent screen:** Literature data of the solubility of lamivudine in various solvents was classified into antisolvent, good cooling crystallisers and high solubility. Validation of literature ‘good’ solvents or determination of predicted ‘good’ solvents solubility with lamivudine was conducted. Solvent addition method was used to determine solubilities and thermocycling on Crystalline (Technobis) was used to confirm.

**Solvent selection:** Confirmation of clear point and cloud point, used to determine MSZW, was done on solvents with lamivudine. Yield was determined by filtration and drying open to air, oiling out and encrustation were noted by visual observation.

**System understanding:** Simple recrystallisation was performed in Crystalline, using a heating profile consisting of isothermal calibration, metastable holding, dissolution and cloud point determination. Various parameters can be changed to explore the design space.

- Stock solution and varied hold temperature.
- Varied concentration and fixed hold temperature.
- Fixed supersaturation and varied temperature.

**Off-line analysis:** Recovered solid underwent ‘fingerprint’ analysis of XRPD and Optical Microscopy. Full ‘reference’ analysis was performed on raw material and a sample of form I and form II lamivudine, this included Morphologi, IR, DSC and Raman.

**Machine learning:** A database was created collating all collected data on lamivudine in various solvents. Simple decision trees were created using Python in Jupyter Notebook and using Orange.

### RESULTS & DISCUSSION

All results shown below were from lamivudine in methanol.

*Figure showing data and analysis*

- Increase in solubility per 20 °C increase aligned with Black’s rule.
- Primary nucleation threshold, growth rates, nucleation rates, induction times, polymorphic form and yield was determined.

### CONCLUSIONS & FUTURE WORK

**Conclusions:**
- Demonstrated a thorough workflow that can be adapted for use by a robotic component as only minor aspects were human orientated.
- Useful kinetic, thermodynamic and observational data was easily extracted to be entered into a machine learning database.
- Started to develop a model, from the workflow process, that can be used to understand, develop and apply QbDD principles. Essentially created a method by implementing QbD principles that can be built upon to explore a QbDD framework.

**Future work:**
- Design and build an autonomous crystallisation classification system (Data Factory) that can run with minimal human input following a workflow.
- Build upon initial models, experimenting with more solvents and APIs, to create a robust machine learning algorithm to predict crystal properties.

### REFERENCES

Motivation
1. Develop a digitally twin of an integrated continuous pharmaceutical processes.
2. Model based design and optimisation of an integrated continuous pharmaceutical processes.
3. Quality by digital design; ensuring high quality medicines with minimal resource expenditure.
4. Improved model based decision making and optimally operate pharmaceutical processes.

Through the use of digital twins, more economical, flexible and greener processes will be developed to advance pharmaceutical manufacturing.

Steady state optimisation in MATLAB
Finding the optimal Temperature, Residence time and Water ratio in order to grow Ibuprofen crystal in a 1L MSMPR. The crystals must be between 100-500 μm and produced at a rate of 80 to 100 kg/year (9.1 to 11.4g/hr).

Nucleation of Ibuprofen in E-W mixture
\[ B = 1.74 \times 10^{10} \times e^{-\frac{\Delta G}{R T}} \times e^{-\frac{\Delta G}{R T}} \times C \times 1000 \times \rho_w \]

Crystal Growth of Ibuprofen in E-W mixture
\[ C = 9.657 \times 10^{-5} \times e^{\frac{\Delta U}{R T}} \times 1 \times 10^5 \]

Optimal Control
- Measure the performance under disturbances.
- Measure the performance under disturbances.
- Optimise the process; Volume split, Residence time split, Temperature.

Table 1. the optimisation specifications used in MATLAB

<table>
<thead>
<tr>
<th>Variable</th>
<th>MSMPR 1</th>
<th>MSMPR 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature/K</td>
<td>313</td>
<td>313</td>
</tr>
<tr>
<td>Residence time mins</td>
<td>26.5</td>
<td>26.5</td>
</tr>
<tr>
<td>Mass fraction Water</td>
<td>0.605</td>
<td>0.605</td>
</tr>
<tr>
<td>XE</td>
<td>0.0225</td>
<td>0.0225</td>
</tr>
</tbody>
</table>

Table 2. the results of the mean diameters from the MSMPR model.

Optimal Control Variables
- Temperature
- Residence time
- Mass fraction of water

Table 2. the optimal values for the control variables of the MATLAB optimization

Optimal Control Variables
- Temperature: 313 K
- Residence time: 53 mins
- Mass fraction of water: 0.605 kg/kg

Table 3. variables and parameters used in the MSMPR model.

Conclusions and Future Work
- The gPROMs model is able to simulate the crystal growth with reasonable results. This enables further testing on the model to be performed.
- Optimise the process, Volume split, Residence time split, Temperature.
- Measure the performance under disturbances.

Want to chat more?
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LinkedIn: linkedin.com/in/timothy-campbell-9b6b09138
Want to keep up to date?
LinkedIn: linkedin.com/in/timothy-campbell-9b6b09138

References
Drug Product (Primary to Secondary)
Advances in pharmaceutical isolation

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2 Department of Chemical & Process Engineering, University of Strathclyde, Level 4, James Watt Building, 75 Montrose Street, Glasgow, G1 1QX, UK

Collaborations: Astra Zeneca, Alconbury Weston Ltd, and Prespective Engineering (as part of REMEDIES programme), Sigma Tau, Cordell Ltd, Process System Engineering

Collaborations: NPL, University of Leeds, Diamond Light Source

Collaborations: Process System Engineering
Publications: in progress

Collaborations: Imperial College London

Collaborations: Loughborough University, Process System Engineering
Publications: in progress

Flowsheet model: filtration and washing parameters estimation and strategies implementation.

- Continuous isolation and prototyping
- Isolation models
- Isolation science
- Flowsheet model
- Critical Quality Attributes
- Critical Process Parameters
- Critical Material Attributes
- ...continuous isolation strategy can be designed by a prediction first approach.

1. From batch-wise lab scale experiments...
   - Correlation porosity and driving force
   - Heel effect

2. Using parameter estimation and....driver:
   - Correlation porosity and driving force
   - Heel effect

3. ...and global sensitivity analysis...
   - Solid content vs filtration properties
   - Particle size distribution effect on filtration and washing properties
   - Diffusion coefficient on impurity removal
   - Porosity and wash ratio during washing
   - Particle sphericity impact on washing

Conclusions:
- A filtration and washing model has been developed to predict the first isolation of mefenamic acid campaign
- The model has useful predictive capabilities shown to match outcomes determined experimentally by DoE
- A global sensitivity analysis reveals how the variance of the model output depends on the uncertainty of the input factors
- The flowsheet model enables unit operation strategy design from a limited amount of experiments, allowing prediction of integrated unit system performance

References:

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Filter wash dissolution
Crystallisation
Synthesis
Filter wash drying

Biotage manual filtration and washing unit
Dissolution manual unit
AWL CFD205 continuous isolation platform

...continuous isolation strategy can be designed by a prediction first approach.

Small scale batch filtration, washing and dissolution data collection enable continuous isolation design

Flowsheet model: filtration and washing parameters estimation and strategies implementation.

A filtration and washing model has been developed to predict the first isolation of mefenamic acid campaign

The model has useful predictive capabilities shown to match outcomes determined experimentally by DoE

A global sensitivity analysis reveals how the variance of the model output depends on the uncertainty of the input factors

The flowsheet model enables unit operation strategy design from a limited amount of experiments, allowing prediction of integrated unit system performance
Microfactory for a Mefenamic acid immediate release formulation

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Introduction

Mefenamic acid (MFA) product performance is highly dependant on particle size and can lead to variable efficacy. In this study, a structured development program was applied, developing a crystalline solid dispersion (CSD) formulation, retaining API properties and improving performance consistency compared to a commercial product.

Conclusion

Rheology guided process development was successful, but also highlights the limitations of this technique. The targeted immediate release profile for the CSD of MFA in Soluplus®-Sorbitol formulation has been met, whilst the stable crystalline form (I) of MFA has been retained and the consistency of drug release has been significantly improved. A Microfactory prototype, combining Feeder, HME and 3D printer, has successfully produced MFA tablets.

References:


Acknowledgements

EPSRC (Grant ref EP/P006965/1), UKRPIF award from HEFCE (Grant ref HH13054). G. W. Halbert is funded by Cancer Research UK (C149/A20496).

HUB target product profile

<table>
<thead>
<tr>
<th>Dose form</th>
<th>Oral solid dose form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>250 mg Mefenamic acid (MFA)</td>
</tr>
<tr>
<td>Release profile</td>
<td>IR release profile, controlled via particle size</td>
</tr>
<tr>
<td>Consistent performance</td>
<td></td>
</tr>
<tr>
<td>Formulation</td>
<td>Crystalline solid dispersion (CSD)</td>
</tr>
<tr>
<td>Process</td>
<td>HME – 3D print injection mould</td>
</tr>
<tr>
<td>Predictive approach</td>
<td>Rheology screening tool to predict HME process parameters</td>
</tr>
</tbody>
</table>

Table 1: HUB acid target product profile.

Prediction:

- HME process temperature
- HME screw speed
- die swell behaviour

Limitation:

- failed with API > 20% w/w

Microfactory: Feeder – HME – 3D printing

Product characterisation

Microfactory: Feeder – HME – 3D printing

Product characterisation

Rheology screening

Figure 1: USP II dissolution test (pH 9) of 250mg MFA capsules, Pharmavit Limited (PVL), Batch 4348: red dashed line 85% drug release.

Figure 2: Complex viscosity versus angular frequency for Soluplus +15% w/w Sorbitol (SOL15) at 120°C (blue), 130°C (orange) and 140°C (black).

Figure 3: Storage (filled) and Loss (open) modulus versus angular frequency for SOL15 at 120°C (blue), 130°C (orange) and 140°C (black).

Figure 4: 50% w/w MFA in SOL15 after rheology test

Figure 5: Mechanical properties of 50MFA-SOL15 extrudate compared to polymer matrix only (SOL15): A) Flexural modulus, Strain at max stress, B) Max stress and Modulus of toughness (MoT).

Figure 6: USP II dissolution test (pH 9) of 250mg MFA capsules with 50MFA-SOL15 extrudate: red dashed line 85% drug release.

Conclusion

Rheology guided process development was successful, but also highlights the limitations of this technique. The targeted immediate release profile for the CSD of MFA in Soluplus®-Sorbitol formulation has been met, whilst the stable crystalline form (I) of MFA has been retained and the consistency of drug release has been significantly improved. A Microfactory prototype, combining Feeder, HME and 3D printer, has successfully produced MFA tablets.

References:


Acknowledgements:

EPSRC (Grant ref EP/P006965/1), UKRPIF award from HEFCE (Grant ref HH13054). G. W. Halbert is funded by Cancer Research UK (C149/A20496).
Structured workflow for accelerated multicomponent tablet property predictions

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GOAL
To develop a structured model selection workflow for multicomponent tablet property prediction using minimal numbers of experiments.

Objectives
- Select platform formulation, fix load disintegrants and compression aid, from that, select a model in terms of mixing rule etc. and use that to predict a range of API loadings.
- Can we see a rationale for model selection based on the data generated & mechanical properties of the API/system.

Hypothesis
- Can we adopt a lean experimental approach to rapidly develop an initial formulation for DC through application of models parameterised with component material properties.

Workflow Implementation

Functionality | Materials | Low API (%) | Med API (%) | High API (%)
--- | --- | --- | --- | ---
API | Ibuprofen | 5.0 | 20.0 | 40.0
Paracetamol (c) | 5.0 | 20.0 | 40.0
Paracetamol (gran) | 5.0 | 20.0 | 40.0
Mefenamic acid | 5.0 | 20.0 | 40.0
Calcium carbonate | 5.0 | 20.0 | 40.0
Filter | Lactose (fastflo 316) | 70.5 | 50.5 | 35.5
Comp aid | Avicial PH102 | 20.0 | 20.0 | 20.0
Disintegrants | Croscarmellose Na | 3.5 | 3.5 | 3.5
Lubricant | Magnesium Stearate | 1.0 | 1.0 | 1.0

- Step 1 defined platform formulation (Ibuprofen shown here as a case study). A total of Five APIs considered.

Workflow Outcomes

- Stage 6 mixing rule verification returned Power rule as the best performing mixing rule. > 0.79 regression considered good predictions.

Investigation Conclusions
- A structured workflow was developed to select appropriate mixing rules for tablet tensile strength predictions.
- 5 investigated APIs (at different PSD and densities) showed good predictions either at Stage 6 or 8 for the three API loadings.
- 7 experiments were sufficient to parameterise and validate the mixing rule/model predictions.
- Potential to accelerate formulation development (max 3 days of lab-time) and reduce material usage if the workflow structure is followed.
Process modelling and Parameter estimation for a continuous carousel filter including a custom wash model

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1. Introduction
The separation of solid particles from liquids via filtration is a key unit operation in the pharmaceutical sector which normally occurs after crystallization of an Active Pharmaceutical Ingredient (API) and could include several wash cycles. In this work we detail a mechanistic model-based workflow for the modelling and parameter estimation of a continuous carousel filter for the isolation of paracetamol (API) in ethanol (crystallization solvent) and n-heptane (wash solvent). The workflow described includes:
- A modelling and parameter estimation of cake properties.
- Introduction and specifications of a custom wash model.
- Global Systems analysis to explore the design space for a more efficient process.

2. Process Workflow
- Description of the workflow established to create the model.
- Is a loop as the model is continuously iterated to add more complexity and robustness.

3. Mechanistic Model for the AWL Continuous Carousel Filter
- Pressure filter model is used initially to estimate the specific cake resistance using the Carman and Kozeny cake resistance model equation, with dynamic cake formation. The governing equations are given below:
  \[ \frac{\partial \rho_d v}{\partial t} = \frac{1}{\epsilon} \left( -\frac{\partial P}{\partial x} + \frac{\partial}{\partial x} \left( \frac{\rho_d v^2}{\epsilon} \right) \right) \]
  Darcy: \[ q = -k \frac{\partial P}{\partial x} \]
- Custom wash models added for further complexity and constraints during optimization.
- Assumptions of the custom model:
  - No changes in solid phases
  - Diffusion-dispersion washing of mother liquor and wash solvent phases

4. Parameter estimation and updated model
- Parameter estimation conducted using performed experiments showed a good fit, and estimation for the particle sphericity.
- The confidence interval and calculated t-value suggest the experimental data is sufficient and the predictions are reliable.
- The parameters were then added back to the initial model and simulated.

5. Global Systems Analysis (GSA)
- GSA allows for exploration of the design space, allowing for a quick and efficient way to find relevant points for improvement.
- Results suggest that the first wash ratio (vol of wash/vol of slurry) can be doubled to allow for a higher recovery of paracetamol, with a lower mass fraction of impurities in the filtrate.
- This will also reduce the requirement of wash solvent, as the second wash may no longer be needed for further API recovery.

6. Conclusions
- A mechanistic-model was established within gPROMS FormulatedProducts to describe a continuous carousel filter with custom wash models.
- The model validation and GSA components were used within gPROMS FormulatedProducts to estimate relevant parameters and find the best case scenario.

Acknowledgement
This project has received funding from Innovate UK for research collaboration between CMAC at the University of Strathclyde and PSE. We would like to thank Dr. Matthew Hogan from Knowledge Transfer Network and Prof Alastair Florence from CMAC for useful discussions and contributions.
Manufacturing Tablets with Desired Specific Surface Area

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Rapid Tooling Injection Moulding (RTIM) is a novel manufacturing technique which couples stereolithography (SLA) 3D printing with hot melt extrusion (HME) and injection moulding (IM). Moulds are produced using the 3D printing technique, allowing for more complex and detailed structures to be produced at a reduced cost and lead-time. HME allows freedom to formulate pharmaceutical polymers with drugs and other excipients and is used to prepare the material for injection. IM is then used to form the material produced by HME into the geometry of the SLA printed moulds. The coupling of these techniques can be used to produce tablet geometries otherwise impossible through traditional means.

RTIM is capable of producing tablets from a digital design with surface micro-features with a high degree of accuracy and precision. The ability to produce tablets with micro-features allows fine-tuning of the SSA of the tablets amongst other applications. The polymer base of the formulation plays a critical role in determining how sensitive the drug release is to changes in the tablets SSA. We observe significant changes when increasing the SSA for PVA based tablets but no significant changes for Affinisol based tablets. It is hypothesised that the difference in drug release profiles is due to differing release mechanisms.

| Acronyms: FC – Formlabs Clear Resin, FHT – Formlabs High Temp Resin, RUHT – 3DResyns UHT Resin, RUHR – 3DResyns UHR Resin, HDT – Heat Deflection Temp | * Indicates data obtained from literature |
Understanding Drying Effects on Active Pharmaceutical Ingredient Particle Properties

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Methodology

Preliminary experiments were performed using glass beads to investigate the effect of solvent, solution concentration, particle size and solvent drop size on lump formation. These experiments determined the robustness of the lumps formed from the glass beads held together by the deposited paracetamol left behind when the solvent was evaporated. Then the effect of decreasing concentration of solute and solution drop volume on lump formation was investigated.

Characterization

The anticipated impact of the research will be to deliver strategies to mitigate undesired granule formation (lumping) and particle breakage which routinely occur during drying and to develop these into a workflow. The main objective of this work is to quantify the amount of deposited material which can cause lump formation. This has been addressed using glass spheres of different sizes and paracetamol (PCM) solutions of different concentrations.

Conclusions

This initial work was performed to quantify the amount and concentration of residual mother liquor which can cause lump formation. The transport mechanism of residual solvent and solute in particle beds during static drying was also investigated.

Future work

• After completion of experiments with glass beads implication of this methodology for actual API (Paracetamol).
  • Sieving of 250-300μm sieve fractions by microscopy to get single crystals.
  • Paracetamol wet with heptane – presume free flowing as no solubility – check is this true?
  • If true, then by using solubility data of paracetamol in ethanol or methanol heptane mixtures choose a composition which deposits similar amount of paracetamol as shown in the graph: Mass of Paracetamol per sphere against the beads size

Acknowledgement

The authors would like to Acknowledge CMAC and Alconbury Weston Ltd (AWL) for providing Experimental rig.
**Can We 3D Print Any Drug Using Fused Deposition Modelling (FDM) 3D printer?**

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**PURPOSE**

3D printing (3DP) open a new era in manufacturing and tailoring complex geometries in different industries. In the last decade researchers explored the advantages of tailoring medicine using different 3D printing technologies; mostly Fused deposition modelling (FDM) 3DP.

The ink of FDM-3DP is a thermoplastic filament that has good mechanical properties including high flexural modulus to push the liquefied formula out of the 3DP nozzle and high flexibility (strain at break) to be able to bend and fed into the printer. As a result the filament should have high modulus of toughness (total energy that the object can take).

**OBJECTIVE**

- Explore process space of 3DP printing on binary mixture polymer-drug
- Develop the formula for FDM 3D printing application applying the minimum change on the formula

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**CONCLUSION**

Polymer mechanical properties and drug-polymer miscibility.

- Drug load and Drug-Polymer Process space consideration
- Dissipated on molecular level (transmission or separation plastization effect) or heterogeneous solid dispersion (Particle size, shape, concentration, and ...)
- Additives: Plasticizer influence durability, filler improve toughness
- Inclusion of the ingredients to find the optimum formula for 3DP printing

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**RESULTS**

- **Binary system (Polymer - Drug):**

  The most significant change in the mechanical properties happened above the saturation level.

  When MFA suspended in molecular level (≤20%) increases in the flexural modulus and brittleness and decrease in the toughness were noticed.

  The changes were steeper above the saturation level (i.e. drug suspended in crystalline level, ≥30%).

- **Binary to ternary system (Polymer - Drug - Plasticizer):**

  MFA (drug) and additives, namely TEC TWIN PEG and SIA showed plastization effect. Additives reduced brittleness and flexural modulus in contrast to MFA.

  The difference behavior of matrices assigned to the difference molecular interactions between drug/additive-polymer (Fig 5).

- **Ternary to quaternary system (Polymer - Drug - Plasticizer - Filler):**

  Filler was used to increase the toughness of the ductile matrix

  Particle size surface (polymer) − surface (polymer) interaction played a role in improving the mechanical properties.

- **Design of Experiment (DoE) and 3D printing test**

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**ACKNOWLEDGMENTS, FUNDING AND GRANTS**

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Analysis of Terahertz Scattering of Granular Materials

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Objectives

1. To investigate terahertz scattering as a function of:
   - Concentration of the primary particles.
   - Particle size.
2. To utilise scattering to determine performance related properties:
   - Fragmentation in compaction and its effect on drug release.
   - Monitoring mass flow rate.
   - Monitoring granule and tablet density/porosity.

Introduction

When light is incident on an interface between two different materials a part of it is reflected while the rest is transmitted to travel through the material. As a consequence, when light travels through inhomogeneous material, it undergoes multiple reflections giving rise to scattering, and resulting in a scattering loss. If the material is also absorbing, then the total transmission loss experienced by the traversing light is the sum of absorption ($\alpha_{\text{absorption}}$) and scattering ($\alpha_{\text{scattering}}$) and is referred to as the loss coefficient ($\alpha_{\text{total}}$) at a specific frequency (Garet et al., 2014):

$$\alpha_{\text{total}} = \alpha_{\text{absorption}} + \alpha_{\text{scattering}}$$

There are two main types of light scattering:
- Rayleigh scattering occurs when the scattering particles are significantly smaller than the wavelength.
- Mie scattering occurs when particle size is comparable to the wavelength.
Each type of scattering has its characteristic spectral profile depending on particle size and shape as can be seen in Figure 1.

Methods and Materials

- Simulation samples were created by compacting a mixture of glass beads and PTFE at various pressures.
- The materials were mixed using a mortar and pestle addition based method to ensure homogenous mixing.
- After which the samples were analysed using a terahertz time-domain spectroscopy (THz-TDS) system utilising a photoconductive based generation and detection system.

Preliminary Results

Before modelling can be done on the properties proposed validation of the sample fabrication method is required. To this end the optimal compaction pressure for the pellets must be determined. Finding this pressure ensures minimal porosity of the samples, thus simplifying data analysis.

In order to accomplish this 10% w/w glass beads and PTFE as well as pure PTFE pellets were created utilising various compaction pressures. These pellets were analysed utilising THz-TDS with the obtained refractive index being plotted against compaction pressure (Figure 2).

Discussion

- It is evident that the optimal compaction pressure for this mixture is 392 MPa.
  - This is due to refractive index reaching its maximum suggesting minimal porosity.
  - Further more at 392 MPa the mixtures reach the predicted refractive index suggesting that the mixing technique utilised is suitable to obtain a homogenous mixture.
  - While other compaction pressures reach the predicted refractive index the standard deviation is significant suggesting significant porosity or cracking at the higher compaction pressures.

Future Work

- Creation and analysis of simulation samples.
  - Multiple Particle size distributions.
  - Multiple concentration levels of each particle size distribution.
  - Isolating the terahertz scattering profiles from absorption of the samples utilising various Mathematical models.
  - Modelling the effects of increasing concentration and particle size distribution on terahertz scattering.
  - Investigating the effects of concentration and particle size distribution on refractive index.

Acknowledgements

EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation

References

Analysis of Novel Spherical Agglomerates: Compaction Behaviour and Impact on Tablet Properties

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Introduction

Oral solid dosage (OSD) forms are the most common formulations for marketed pharmaceuticals (Savjani et al., 2012), while tablets are the most common form of OSD produced (Wu et al., 2005). The properties of the materials used will directly influence the tabletting process; both the former and latter will determine the mechanical properties of the final product. A bespoke compaction simulator was used to compact tablets containing either novel spherical agglomerates, or the non agglomerated form of the active pharmaceutical ingredient (API). Pore structure will be quantified post compaction, as will particle deformation and fragmentation. These processes will be studied in relation to particle size and individual material properties. Finally, breaking force, disintegration, and dissolution tests will be conducted on the tablets produced to assess the impact of material properties on the tabletting process.

Objectives

- To produce tablets from single crystal, batch made spherical agglomerate, and continuous made spherical agglomerates.
- To analyse differences between agglomerated and non agglomerated tablets based on compressibility, compactability and tabletability analysis.
- To understand the impact of agglomerated materials on dissolution outcomes.

Materials & Experimental Plan

- Position control mode used to produce 540 tablets (270 AGC, 270 PC) across 10 groups.
- AGC results indicate good weight uniformity.
- PC results show larger variance between samples, indicating inhomogeneity to be confirmed with terahertz time-domain spectroscopy (THz-TDS).
- Ejection shear stress slightly higher for PC at lower compaction pressure (Figure 2).
- Ejection shear stress increases with increasing compression pressure, where tablets with an ejection shear stress > 3 MPa likely to have defects (Pitt et al., 2013).
- Larger immediate axial recovery evident in AGC batch (Figure 3) which yields a ↑ porosity recovery – supported by Figure 4b.
- PC demonstrated higher degrees of compactibility, compressibility, and tabletability (Figure 4).
- AGC results indicate more predictable compaction behaviour – PC demonstrates significant changes in tensile strength and solid fraction.

Results

- THz analysis, to validate content uniformity and porosity calculations. Will begin ex-situ, with plans to integrate the technology with the compaction simulator, allowing in-situ.
- Impact of agglomeration and porosity on tablet performance will be assessed via dissolution tests.

Next Steps

- THz-TDS analysis of tablets
- (Figure 5) THz-TDS analysis of tablets
- (Figure 6) Tablet dissolution
- (Figure 4) (above): Batches AGC and PC assessed for (a) compactibility, (b) compressibility, and (c) tabletability.

References


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https://doi.org/10.1016/j.powtec.2005.01.010
https://doi.org/10.1016/j.powtec.2012.10.001
Measuring and Modelling Agglomeration and Breakage during Agitated Vacuum Thermal Drying

William Eales, Supervisors: Prof. Chris Price, Dr. Paul Mulheran

Introduction

Agglomeration is where particles join together during isolation to form clusters, known as agglomerates. These agglomerates then cause issues for further processing, due to varying sizes, strengths and potentially containing impurities, which often results in the material having to be reprocessed or discarded.

Aims and Objectives

The initial aim of this project is to produce a model that can simulate the packing of spherical particles in both 2D and 3D. This model will then be used to investigate the properties of the packed bed, such as the strengths of the contact points, impurity transport throughout the bed and how clusters form when the bed breaks apart.

Model Procedure

1. An initial particle location is determined randomly.
2. The possible points of rest along its path are determined.
3. The particle iterates through them until it finds a particle in a depression.

Multiple Sizes

The model is also capable of producing a bed with particles of different sizes present, allowing us to investigate how particles of different sizes interact within the bed.

3D

Producing a 3D bed has been briefly attempted however was put to the side in order to fully complete the 2D counterpart, which can then be translated into 3D.

Future Plan

Once the initial model has been completed, different areas will be investigated for it to be applied to. We also aim to update the model so that it can use non-spherical particles such as crystal structures to allow for specific beds to be analysed.
Advanced Pharmaceutical Materials Characterisation
A Structured Approach to Implementation of Loading Space Standardisation for Temperature Correction of Spectra

Case Study: Ultraviolet (UV) spectra of ibuprofen (IBU) in EtOH/H₂O

**Stage 1: Construct global model**

**Stage 2: Review model requirements**

- Required model performance
  - Prediction of IBU concentration to an error margin of 10 gIBU kg⁻¹ solvent (equivalent to 1% over the 700 to 1650 cm⁻¹ operating range).
  - For the global model (Table 1), this is almost achieved by the calibration RMSE but the validation RMSE is more than double.

**Stage 3: Evaluate temperature effects**

- Decision 2: The requirements are not met by the global model constructed (Stage 1) and further exploration will be undertaken to investigate factors that may affect the UV spectra.

- Decision 3: Temperature effects are evident on the raw spectra and the local model performance indicates an improvement may be achieved with removal of temperature effects on the spectra.

**Stage 4: Construct LSS model**

- Sample selection
  - The samples used to construct the LSS model cannot include all of the samples (concentration and temperature) within the design space.

- Spectral region
  - The global model (Figure 2, Table 1) is constructed from the spectral region of 215-280 nm, which includes IBU absorption bands.

- Prior preprocessing of spectra
  - As there are no significant baseline effects evident, preprocessing is not required prior to LSS.

- Number of components in LSS model
  - Evaluated from a combination of the singular value decomposition results and loadings. Inclusion of superfluous components leads to potential overfitting and introduction of noisy features.

**Stage 5: Apply LSS model**

- Decision 5: A PLS model with improved accuracy and precision can be constructed from the spectra that have been transformed via LSS. The workflow explores factors associated with the process of constructing a calibration model for prediction of solute concentration, which is particularly applicable to cooling crystallisation owing to a change in temperature being inherent to the process.

**References**

Advanced Characterisation of pharmaceuticals: Methods for nucleation studies and particle surface properties

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Case study: Multi-scale understanding of Lovastatin crystallisation

X-ray Phase Contrast Imaging (XPCI)

Time-resolved molecular, mesoscopic and macroscopic information during continuous anti-solvent crystallisation of Lovastatin using a concentric tube crystallizer helps understand the nucleation and growth mechanism.

Sub-second visualization of complex multiphase and multiscale processes

X-ray pair Distribution Function (XPDF) Analysis

A Leeds-Astra Zeneca-Diamond Collaboration

Local structure and inter-molecular interactions of Lovastatin in acetone-water binary systems to validate nucleation mechanisms, phase behavior and molecular dynamics; contributing to model libraries

CMAC Lovastatin campaign

SEM images of continuous flow anti-solvent crystallisation product

ATR-FITR spectra shows surface water in AS2

XPCI tomogram of continuous flow anti-solvent crystallisation product

Evolved gas analysis using IR spectroscopy of continuous flow anti-solvent crystallisation product

X-ray Photoelectron spectroscopy

Reduction in surface impurity presence on Lovastatin drug substance crystallized from acetone-water continuous flow system is observed

This research was supported by the EPSRC Future Manufacturing CMAC Research Hub. We are grateful to Diamond Light Source for the Single crystal, XPDF and XPDF beamtime awards at beamlines 11-3, 11-3-2 and 115-1. Thanks to G.Das (UoL), T.Kathyola (UoL), J. McGinty (UoS), R.Miller (UoS), J.Sefcik (UoS), B.Evans (UoL), A.Pugejs (UoL), K.Wanislek (DLS), J.Lang (UoL), D.Keeble (DLS), E.Bordos (UoS), J.Robertson (UoS), O.Tash (Sheffield), C.Brown (UoS), W.Li (Bath), S.Ottoboni (UoS), S.Y. Chang (DLS), L.A.H. Al-Madhagi (UoL), M.Shahid (UoS), A.Britton (VSXF, UoL) and E.Willneff (VSXF, UoL)
1 – Motivation

Particle size and shape are an important quality control measure in the pharmaceutical industry – they can affect downstream processes (e.g. granulation, drying) or even the final product.

In-line PAT have many advantages for controlling size and shape; (representative measurement, fast/time) but also disadvantages (analysis can require tuning to system/lighting, or requires knowledge of shape a-priori).

To overcome these issues and to better enable process control and particle model development, this project seeks to combine in-line inputs to achieve an overall better measurement of particle size and shape characteristics.

2 – Models and Inputs

Models form the basis of MDPC. Combining models is main goal. Machine learning (ML) provides dynamic and flexible framework – can be set up to take input from different sources to create more accurate output.

Models and Inputs considered:

- PVM – image analysis (traditional, ML)
- FBRM – CLD Inversion (deterministic, ML)
- Crystalline – Crystalline algorithm

Focused mainly on PVM image analysis of polystyrene standard spheres (right) so far.

This large dataset covers a wide range of sizes (90μm up to 500μm) and concentrations (1wt% to 10wt%).

Other, more realistic, datasets are available and will be considered next:

3 – Previous Work

Previous work on obtaining particle size and shape from in-line measures:

- image analysis (‘ImagingApp’)
- CLD inversion to PSD

4 – Machine Learning

Neural networks (NNs) have ability to learn complex tasks - such as recognising shapes. Used here as bedrock to improve image analysis by training the algorithm on a variety of datasets – thereby teaching the model the generic process of particle detection – not just detection of a specific particle.

5 – Case Study: Model Validation

- Dataset of standard silicon cuboids
- Stirred in IPA for >13 hours
- Start with known size and shape
- Kinetics involved: pure breakage, no agglomeration, growth or nucleation

Unique dataset presents opportunity to validate breakage models.

Size quantiles (D10, D50, D90) obtained via in-line image analysis used to estimate parameters for 6 models in gPROMS. Parameter estimation performed using one quantile (D50) and three (D10, D50, D90).

More models is better, but not enough

Some models is not able to capture system behaviour at all

Detailed representative size information crucial for accurate model validation

6 – Next Steps

- Develop case study
- Use PSD in breakage model parameter estimation
- Improve ML image analysis
- Expand to more realistic datasets
- Develop ML model to invert CLD
- Fusion of techniques (image analysis and CLD) to improve accuracy of resulting PSD
- Incorporate further models
  - other imaging
  - turbidity sensors

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**Multi-Dimensional Particle Characterisation from *In-Situ* Sensors**

Christopher Boyle, Javier Cardona, Jan Sefcik, Cameron Brown
A Holistic Approach to Physical Stability of Amorphous Solid Dispersions

Ecatlera Bordos, Gunjan Das, Eleonora Paladino, Michael Devlin, Sven Schroeder, Gavin W. Halden & John Robertson

The author thanks the EPSRC Future Manufacturing Research Hub, University of Strathclyde, CMAC, Glasgow, UK.

Introduction
Amorphous solid dispersions (ASDs) are a promising formulation strategy designed to enhance the oral bioavailability of poorly water-soluble drugs. However, concerns with physical stability have limited their integration into appropriate dosage forms. Thus, the manufacture of stable ASD systems remains quite challenging and often requires optimization of formulation, manufacturing route and processing parameters to attain reliable drug product quality.

Project aims:
Identify, develop and apply tools to develop further understanding of ASD stability and establish structure-process-property interactions for a rational predictive design of stable ASDs.

API-POLYMER SOLUBILITY DETERMINATION – LOW-FREQUENCY RAMAN

- Novel empirical approach combining low-frequency Raman and hot melt extrusion (HME)
  - Provides more accurate reflection of the likely solubility equilibria for optimum HME processing.
  - Demonstrates promising potential to predict solid-state solubility and physical stability of ASDs.

ASD 3D MICROSTRUCTURE – X-RAY PHASE CONTRAST TOMOGRAPHY

- Effect of saturation on the degree of ASD structural complexity
  - Multiple structural defects identified: crystalline API clusters, pores, impurities and PRHs.
  - Total porosity, pore network and pore morphology vary according to the HME processing temperature.
  - The overall degree of structural complexity varies across the temperature-composition space.

Impact of processing temperature on the polymer phase homogeneity

- Incomplete polymer softening at all drug loadings processed at T > Tm
- Indicates heterogeneous molecular mixing with different local drug loadings.
- Suggests need for process and formulation optimisation (e.g. plasticisers).

CONCLUSIONS

- Low-frequency Raman has been successfully coupled to HME to determine API-polymer solubility. This approach enables construction of solubility phase diagrams and displays promising potential to predict solid-state ASD stability.
- X-ray phase contrast imaging identified multiple structural domains and indicated the presence of different degrees of structural heterogeneity across the temperature-composition space.
- ToF SIMS enabled detection of early signs of surface instability, showing the existence of drug-rich clusters that act as precursors for surface-mediated recrystallisation.
- PDF analysis allowed insights into the complex nature of the local structure in formulated amorphous systems and showed that drug-loading and processing history have a strong impact on the short range order.
- The unique knowledge gained from this multi-disciplinary approach provides further understanding of the dynamics of API-polymer solubility and the subsequent structure and homogeneity of the ASD drug product. This can be used to optimise the HME operational window and develop predictive capabilities for the targeted manufacture of stable ASD systems with desired structural and functional features.

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Impact of drug loading on surface API recrystallisation upon ageing

- Undersaturated
- Cc
- Supersaturated

Quantification of API Surface Coverage

- Drug loadings > Cc (20wt%) display surface API enrichment with consequent recrystallisation phenomena.
- Drug loadings < Cc (20wt%) constitute single phase ASDs that do not recrystallise or undergo API.
- ToF SIMS detected early signs of surface instability (within less than 24h after HME).
- Traditional analytical methods such as DSC and XRD detected crystallinity as late as 150 days after HME.

Impact of HME processing temperature on surface distribution homogeneity

- Sub micron API-rich domains observed at all processing temperatures at drug loadings > Cc.
- The drug-rich domains act as nucleation points for surface recrystallisation upon ageing.
- Highlights the supersaturated character of drug loadings ≤ Cc and/or HME mixing inefficiencies.

Impact of processing temperature on local structure

- Processing temperatures > Tm have minimal impact on local structure (despite viscosity variations).
- Synchrontron XRD confirmed residual crystallinity of supersaturated samples processed ≤ Tm.
- Results corroborate low-frequency Raman solubility determination.

Local structure evolution upon cooling and ageing

- Structural changes observed upon cooling of the extrudates (potential phase separation).
- Major structural differences between undersaturated and saturated systems found upon ageing.
- Mechanical stress (MS) showed potential for accelerated stability prediction.
**Introduction to THz Raman**

- THz-Raman spectroscopy extends the range of Raman spectroscopy from the fingerprint region into the terahertz regime (<200 cm⁻¹ or < 6 THz)
- The THz-Raman region provides structural information while the Raman region provides chemical information

**Powder Blending**

- Active pharmaceutical ingredient (API) content in powder blends is commonly measured using NIR or Raman spectrometry
- However, there are issues with the detection limit of these techniques for measurement of API content in low dose, high potency formulations
- The THz Raman region exhibits enhanced sensitivity compared to the Raman region
- Therefore, the research aim is to explore the sensitivity gain of THz-Raman for in situ monitoring of powder blending

**Results**

- The blends were analysed at 5 different positions and the aspirin signal intensities in the THz Raman (69 cm⁻¹) and Raman (1606 cm⁻¹) regions were compared

**Discussion**

- The aspirin peak intensity in the THz Raman region is approx. 5x greater compared to that in the Raman region
- Avicel has no significant peaks in the THz Raman region
- The sensitivity of response is greater for the THz Raman region compared to the Raman region
- The % RSD is larger for lower concentrations of aspirin
- The % RSD is larger for replicate measurements made at 5 different positions compared to a single position owing to sample heterogeneity

**Experimental**

- Blends of aspirin (0 – 40 g) and Avicel PH-101 (75 g) were prepared in a 500 mL blender
- The blends were then analysed at-line using THz Raman and Raman with a laser spot diameter of approx. 100 um.

**Increasing the sampling area**

- Sample heterogeneity causes scatter in the plots. Therefore, spectra were acquired at 50 different positions to increase the sampling area and hence, obtain a more representative sample

**Future work**

- Use of THz Raman for the monitoring of static and dynamic low dose formulations
- Investigating the possibility of wide area illumination THz Raman spectrometry
Analysing the Physical Stability of Amorphous Solid Dispersions via Laboratory X-Ray Technique

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Introduction

A growing concern in the pharmaceutical industry is the poor solubility that many new chemical entities (NCE) suffer from. Estimates put the amount of NCE in biopharmaceutics bioavailability issues associated with low solubility. As such it is paramount that formulation scientists utilise all available tools to allow more of these compounds to make it to market. Amorphous solid dispersions (ASDs), consisting of the amorphous drug molecularly dispersed within a polymer, are one such tool currently used as a formulation strategy to combat this instability. However, ASDs suffer from poor physical stability and have a tendency to recrystallise, this negates the solubility and bioavailability advantages gained in using them. It is vital that research is conducted to begin understanding the root mechanisms of the instability. The aim of this project is to utilise a novel X-Ray setup to monitor the recrystallisation of ASDs during dissolution, the process will be investigated to understand the underlying mechanisms of the process. The main objectives are to:

- Produce truly amorphous samples of paracetamol and affinosil using hot melt extrusion (HME).
- Develop a novel in-situ X-Ray dissolution technique to allow for real time crystallisation monitoring.
- Understand the thermodynamic stability of differing paracetamol affinosil ASD compositions through the crystallisation behaviour of various compositions.

Experimental Setup

ASD Preparation

![Fig. 1 Area detector X-Ray setup](image1)

![Fig. 2 3D printed sample stage loaded with sample](image2)

![Fig. 3 Phase behaviour as a function of paracetamol concentration and HME processing temperature](image3)

![Table. 1 Compositions and processing temperatures of samples prepared](image4)

Results

![Fig. 4 XRPD of ASD samples prepared via HME](image5)

![Fig. 5 XRPD of ASD samples prepared via HME](image6)

The X-Ray dissolution setup has shown that paracetamol and affinosil dispersions remain stable at 20wt% paracetamol and lower, while above this crystallisation peaks are evident. A difference is also observed in the degree of crystallisation between the 25 and 27.5wt% results, the higher drug loading has yielded a greater degree of crystallinity.

Conclusions

Utilising an area detector has given the advantage of being able to take multiple quick images allowing for the crystallisation process to be monitored. Samples of 20% and below appear to remain stable and in the amorphous form throughout the experiment, while samples containing 25 and 27.5% paracetamol have crystallised during the experiment. Increased crystallinity and quicker crystallisation times were also observed for higher drug loaded samples.

Future Work

- Utilising a flow cell type experimental setup to allow for a more dissolution like setup to be mimicked.
- Attach a UV spectrometer at the outlet of a flow cell to enable monitoring of the drug release kinetics alongside the crystallisation tendencies.
- Repeat experiments using SAXS to monitor structural changes occurring during the crystallisation event.

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Determination of the solubility of a crystalline active pharmaceutical ingredient in a polymer during hot melt extrusion (HME) using terahertz (THz) - Raman spectroscopy

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Objectives
To investigate the solubility limit and changes in polymorphic form of mefenamic acid (MFA) in a matrix of sorbitol and Soluplus® with THz-Raman spectroscopy

Introduction

Material and methods

- MFA
- Sorbitol (Parteck® SI 150)
- Polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol graft copolymer (Soluplus®)

Extruding from high to low processing temperatures (PTs)
Continuously collecting spectra from the melt mixture

Blending 10 – 40% MFA with Soluplus® and sorbitol (85:15)

Results and discussion

- Fig 3A depicts that PM spectra are correlated to those of pure form I MFA powder1 consisting of a strong peak at 34, a shoulder at 48, and a triplet 85, 97, and 110 cm⁻¹. Spectral shapes of PM and the melt are not comparable which indicates the formation of solid dispersions with new intermolecular bonds.

- Spectra of the melt mixture at individual temperatures are inconsistent. These changes imply the molecular re-arrangement. Fig 3B and 4A show the changes in, respectively, raw spectra and pre-processing spectra of the 40% MFA melt mixture. The existence and intensity of peak at 28 cm⁻¹, respectively, indicate the presence and level of crystalline MFA. The lowest PTs (125 °C) contains the highest amount of crystalline content while 3 highest PTs (170 – 180 °C) illustrate the formation of amorphous MFA.

- Fig 4B depicts that the lowest PT to achieve ASDs is a function of mixture concentration. For example, the formation of amorphous solid dispersions (ASDs) of 10 and 40% MFA mixture could be initially found at 125 and 170 °C, respectively. However, MFA could be degraded at certain PTs during formation of ASDs.

Future work
- Investigate the remaining mixture compositions (15, 25, 35, 45% MFA)
- Quantitative analysis of MFA crystalline content in the melt

Bibliography


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From crystal to tablet – linking structure to function through compression studies

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INTRODUCTION
• The PhD project aims to develop a predictive tool for performance-controlling bulk properties of relevant pharmaceutical materials.
  - Compressibility
  - Compactibility
  - Tabletability
• This will be achieved by studying the impact of moderate pressures (≤ 3 kbar = 0.3 GPa) at a molecular and macroscopic scale.
  - X-ray diffraction
  - Compaction simulation
  - THz imaging

EQUIPMENT
• Pressure studies to follow the changes in the internal structures of single crystals and powders will be carried out using a diamond anvil cell (DAC).
• A sample is placed in a metal gasket between two diamond cutlets.
• A pressure transmitting medium provides a hydrostatic environment (e.g., silicone oil).
• Diacell© One20DAC by Almaz EasyLab Ltd. is the DAC of choice.
• In comparison to a traditional DAC, it:
  1. Has a larger aperture (120° vs 80°) – X-rays can approach the diamond cutlets at wider angles, allowing access to larger reciprocal space during diffraction.
  2. Has a larger gasket hole (1 mm vs 0.25 mm) – larger or more crystals can be loaded into the DAC.
  3. Achieves smaller pressure jumps (Cu vs W gasket, larger diamond cutlets) – softer gasket material, pressure is applied to a wider surface; more measurements can be taken at low pressures.

EQUIPMENT SET-UP
• Ruby is widely used to determine the pressure inside a DAC.
• The R1 fluorescence line of ruby is sensitive to the pressure environment.
• Equations such as Ruby2020 [2] relate the shift in the ruby R1 wavelength with the pressure experienced.
• The low sensitivity of ruby at lower pressures (< 10 kbar = 1 GPa) provides inaccurate pressure readings.
• This interferes with our pressure range of interest (0 – 10 kbar).
• We have tested hexamethylenetetramine (i.e., hexamine) as a more suitable gauge of pressure.
• Raman spectra of hexamine displays sharp peaks that can be easily fitted and tracked. Additionally, McMonagle et al [3] determined the unit cell parameters of hexamine when compressed in 1 kbar steps up to 10 kbar.

RESULTS
• A hexamine crystal and multiple ruby chips were loaded into the DAC.
• The pressure in the cell was increased in small steps until ~ 10 kbar were reached, three times (i.e., 3 runs).

CONCLUSIONS
• Small variability (i.e., standard deviation) within the ruby R1 wavelength readings.
• Linear increase in the Raman shift of the hexamine peaks studied at increasing pressure.
• Both ruby chips and hexamine crystals can be used as pressure gauges for the Diacell© One20DAC.
• Multiple ruby chips may be required to achieve a more accurate reading. These, however, can interfere with the diffraction data collected, so a minimal amount should be loaded (i.e., two ruby chips).

FUTURE WORK
• Use hexamine and ruby as pressure markers for future collections of data on relevant pharmaceutical materials.
• For hexamine to fully substitute ruby, compare Raman shifts measured to the unit cell parameters of hexamine obtained through diffraction. The unit cell parameters can be linked to the pressure experienced through the equation of state determined by McMonagle et al [3].

REFERENCES
Real-Time In-situ Imaging and Structural Characterisation of Continuous Crystallisation in a Concentric-Flow Antisolvent Crystalliser

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Summary

• Synchronous X-ray imaging has been applied to study in-situ crystallization processes in real-time and -space.
• Time-resolved synchronous-based X-ray Phase Contrast Imaging (XPCI) has the potential to visualise the sequence of events taking place in the mixing zone of an antisolvent flow crystalliser.
• Image processing techniques have been applied to reveal even more detail, as we extended this work to imaging filtration processes and extrusion products.

Technique

• X-ray Phase-Contrast Imaging (XPCI)
• Real-time visualisation was achieved with ~1 µm resolution
• Phase shift (Δφ) of incoming x-rays generated by the materials having different refractive indices (Medium 1 and Medium 2)

Method

• A concentric device with an outer Kapton tube (for X-ray transparency) was placed in the beam.
• Continuous antisolvent crystallisation of Glycine and Lovastatin was studied
• Various solvent:antisolvent ratios and flow rates were studied.
• XPCI on I13-2 Diamond, pink beam at 23 keV

Results

2D XPCI In-situ of Anti-solvent Crystallisation

3D XPCI of Anti-solvent Crystallisation Products

Ongoing work

• Developing a GUI-driven software, Crystal Growth Tracker (CGT)
• CGT analyses crystal size as a function of time
• Provides crucial mass transport information
• In collaboration with J. Leng & J. Pickering

Future Work

• Continue lovastatin studies with XPCI
• Interested to find out the molecular structure of these phases (highlighted in orange)
• Explore different synchrotron-based imaging modalities:
  • Diffraction imaging
  • Pair-distribution function imaging

Conclusions

XPCI is a promising and versatile tool for early stage process development, predictive design and control.

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技术

• X-ray Phase-Contrast Imaging (XPCI)
• 实时可视化实现了~1 µm的分辨率
• 不同折射率材料（介质1和介质2）生成的入射x射线的相位移（Δφ）

方法

• 筒形设备，外层是透明的Kapton管
• 连续抗溶剂结晶化实验
• 各种溶剂：抗溶剂比和流速都进行了研究
• XPCI在I13-2 Diamond中，粉色光束，23 keV

结果

2D XPCI原地反溶剂结晶化

3D XPCI反溶剂结晶化产品

正在进行的工作

• 开发GUI驱动的软件，Crystal Growth Tracker (CGT)
• CGT分析了晶体的尺寸随时间的变化
• 提供了至关重要的质量转移信息
• 与J. Leng和J. Pickering合作

未来工作

• 继续Lovastatin的研究
• 感兴趣找出这些相的分子结构（橙色高亮）
• 探索不同同步加速器成像

结论

XPCI是一个有前途和多功能工具，用于早期阶段过程开发，预测性设计和控制。

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