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Developing an autonomous DataFactory workflow for small-scale batch cooling crystallisation with the antiviral lamivudine

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Introduction

Lamivudine: Lamivudine is an antiviral medication used to treat and prevent human immunodeficiency virus (HIV)[1]. Past studies have well characterised the two polymorphs, form I as needles and form II as bipyramidal but the literature is sparse for solubility and kinetic parameter estimations[2].

DataFactory: The DataFactory project will be an autonomous data collection platform focusing on active pharmaceutical ingredient (API) solubility and kinetic parameters. Therefore, this work aims to design a consistent method that can be adapted by robotics to be carried out without supervision.

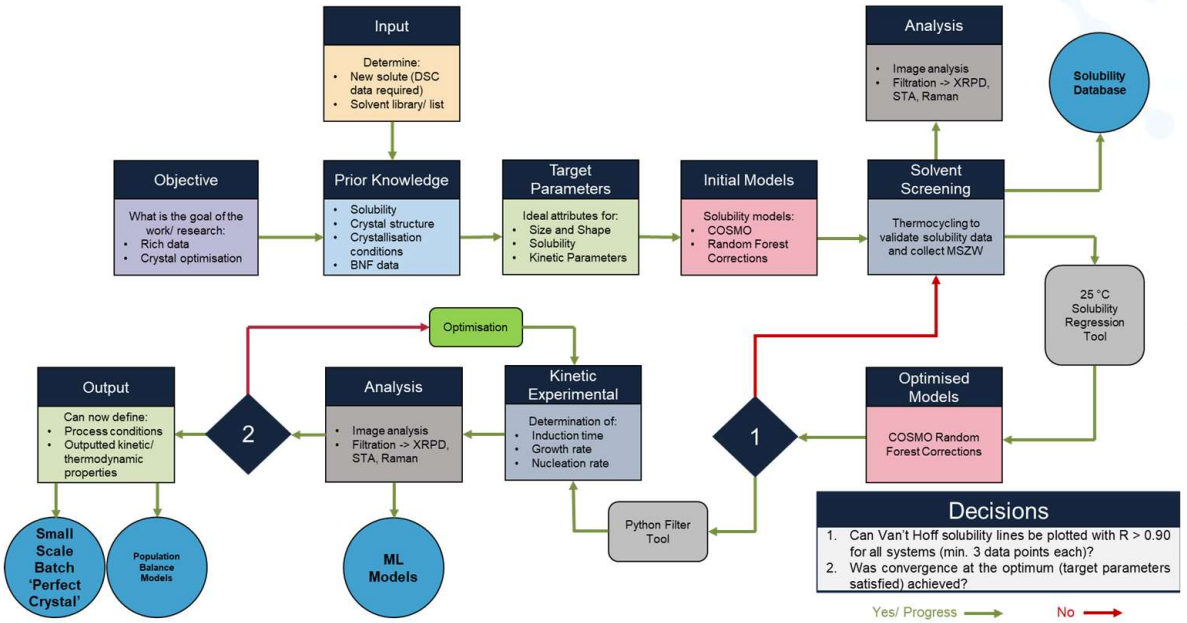
Aims and Objectives:

- Establish a workflow that guides decision making for the automated data collection of the DataFactory
- Establish a crystallisation parameter database to be used towards a crystallisation classification system (CCS)
- Integration of a solid/ solvent dosing station with the Crystalline (Technobis) platform

1 D. T. Y. Lau and D. Lau, *Hepatology* : 2000, *32*, 828-834. 2 R. K. Harris, R. R. Yeung, R. B. Lamont, R. W. Lancaster, S. M. Lynn and S. E. Staniforth, *Perkin transactions. 2* 1997, 2653-2660.

Why autonomous?

- 'Out of hours' operation of research equipment
- Enables researchers to reallocate time previously spent performing routine experiments
- Consistent, reliable and reproducible results across many API/solvent systems
- Hands-off nature enables pharmaceutical development during pandemics



Materials and Methods

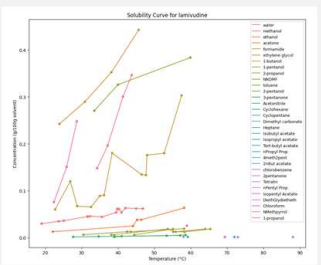
Solvent screening: Thermocycling (x3) of ~2 - 7 mL of API and solvent to determine clear and cloud points. Data collected at 0.5 °C/min, 600 rpm.

Kinetic parameter estimation: Dissolution followed by crash cooling to an isothermal hold (x3) of ~2 mL of API and solvent.

Results

Solvent screening:

- Methanol, ethanol and ethylene glycol fell within the optimum region set out by the target parameters
- Solubility decreased with increasing alcohol size
- Solubility decreased when shifting the alcohol functional group along the chain
- Ethanol was chosen as the solvent as target solubility and shape were achieved in this system



Kinetic parameter estimation:

- Full factorial DoE screening gave an initial indication of induction times and growth rates for lamivudine in ethanol
- Process parameters were optimised to be 19.5 °C, 600 rpm and 1.74 SS using multiple linear regression (Modde 12.1 software)

Conclusions

This work used the proposed workflow to identify the following experimental conditions as appropriate for small-scale batch cooling crystallisation of lamivudine: crystallisation from ethanol at 19.5 °C, 600 rpm and supersaturation of 1.74. Crystalline imagery and XRPD data confirmed the presence of form II, the most stable polymorph with desired downstream processing properties. The solubility data and kinetic parameters here contribute to a consistent reliable database of API/solvent systems as part of the DataFactory goals. The workflow used to collect this data will guide decision making for identifying industrial relevant systems for the crystallisation of future APIs.

Future Work

The next stage of development includes smarter experimental planning guided by predictive tools trained on this work. These tools will improve efficiency by decreasing time and material usage. Additionally, this workflow will be incorporated with automated hardware thereby enabling autonomous decision making in small-scale cooling crystallisation of future APIs.

SCAN ME

The Process