POSTER 65

Towards an Autonomous DataFactory for the Small-Batch Cooling Crystallisation of Active Pharmaceutical Ingredients

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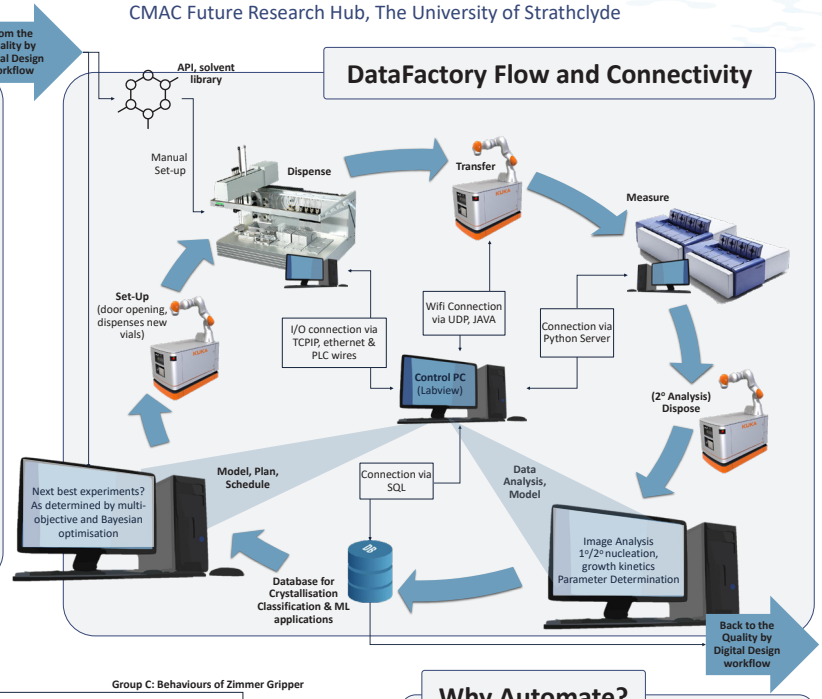
An Autonomous DataFactory

As a method of forming and purifying the pharmaceutically relevant polymorph[1], crystallisation of an active pharmaceutical ingredient (API) is a key step in pharmaceutical manufacturing. Determining an industrial-relevant approach for API crystallisation can be resource-intensive as a candidate crystallisation process is constrained by and assessed against industrial relevant solubilities, downstream processing practicalities, and regulator-determined Critical Quality Attributes (CQA) of the API[2-4].

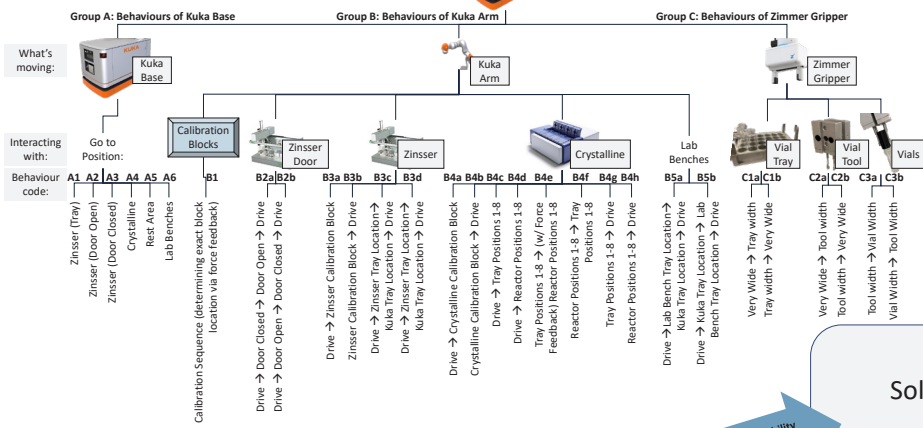
The DataFactory at the CMAC aims to use high throughput small-batch cooling crystallisation experiments coupled with machine learning to reduce the time and material costs associated with this process. Alongside the development of automated data collection, we are incorporating an autonomous decision-making system to optimize the small-batch cooling crystallisation of APIs and calculate relevant kinetic parameters to inform larger-scale experiments.

Here we present the steps we're taking to integrate and automate different platforms via a cobot and a central control PC, in addition to the beginnings of the database that will be the foundation of a crystallisation classification system.

DataFactory Flow and Connectivity



Introducing the Cobot



Why Automate?

- '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 of the system enables pharmaceutical development during pandemics

A Database for a Crystallisation Classification System

This work is establishing a consistent and reliable database for dozens of API-solvent systems. While current data collection still requires manual loading, unloading, and human-made decisions, integrating the cobot with programming logic and autonomous decision-making will accelerate this data collection. The resulting dataset will be used with machine learning to predict industrial relevant experimental approaches for the crystallisation of future APIs.

AS	**Antisolvent***
N	**Not run yet**
PM	**Phobic Material**
Y-G	**Yes - Good** (in desired solubility range**, no needles)
Y-A	**Yes - Acceptable** (near desired solubility*** range limits)
WS	in OR near solubility range**/*** but **Wrong Shape** (i.e. needles)
DNN	in OR near solubility range**/*** but **Did Not Nucleate**
OO	in OR near solubility range**/*** but **Oiled Out**
TS	**Too Soluble**

Solvent screening: thermocycling (x3) of ~2 - 7 mL of API and solvent to determine clear and cloud points. Data below.
Kinetic parameter estimation (results not shown here): dissolution followed by crash cooling to an isothermal hold (x3) of ~2 mL of API and solvent.

All solubility and kinetic experiments done by Thomas Pickles

T_1 > ~50 °C and T_2 < T_1 - 50 °C
* Solubility < 5 g/L at T_1
** In desired solubility range: at temp T_1, solubility is 50-250 g/L AND at temp T_2 solubility is > 5 g/L
*** Near desired solubility range: at temp T_1, solubility is 5-50 g/L OR 250-500 g/L AND at temp T_2 solubility is > 5 g/L

The Solubility Database to date...

Solvent\ Solute

Solvent\ Solute	Lamivudine	Aspirin	Ibuprofen	Ascorbic Acid	Salicylic Acid	Mannitol	Benzoic Acid	Sodium Benzoate
Butan-1-ol	Y-A	Y-G	TS	Y-A	TS	AS	N	N
Pentan-2-ol	AS	Y-G	TS	Y-A	TS	AS	N	N
Pentan-2-one	AS	N	TS	AS	TS	AS	N	N
IPA [Propan-2-ol]	DNN	DNN	TS	Y-A	TS	AS	N	N
Pentan-3-one	AS	Y-G	TS	AS	TS	AS	N	N
Acetonitrile	AS	Y-G	TS	Y-A	Y-A	AS	N	N
Cyclohexane	PM	OO	Y-A	OO	AS	AS	N	N
Cyclopentane	PM	DNN	Y-A	AS	PM	AS	N	N
Dimethyl Carbonate	AS	Y-G	TS	AS	Y-A	AS	N	N
Ethanol	Y-G	N	TS	DNN	TS	AS	N	N
n-Heptane	AS	Y-A	Y-A	AS	OO	AS	N	N
iso-Butyl Acetate	AS	Y-G	TS	AS	Y-A	AS	N	N
iso-Propyl Acetate	AS	Y-G	TS	AS	Y-A	AS	N	N
tert-Butyl Acetate	AS	Y-G	TS	AS	Y-A	AS	N	N
Methanol	WS	N	TS	N	TS	AS	N	N
Ethylene Glycol [1,2-Ethanediol]	DNN	DNN	Y-G	N	DNN	WS	N	N
Formamide	TS	N	Y-A	N	DNN	DNN	N	N
Water	WS	N	AS	TS	WS	WS	N	N
n-Propyl Propionate	AS	N	TS	N	N	AS	N	N
n-Pentyl Propionate	AS	N	TS	N	N	AS	N	N
MIBK [Methyl iso-Butyl Ketone or 4-Methyl-2-pentanone]	AS	N	TS	N	N	AS	N	N
Isopentyl Acetate [Isoamyl acetate]	AS	N	TS	N	N	AS	N	N
Butyl Cellosolve Acetate (2-n-Butoxyethyl acetate)	AS	N	TS	N	N	AS	N	N
Diethyleneglycol diethyl ether	AS	N	TS	N	N	AS	N	N
NMP [N-Methylpyrrolidone]	DNN	N	TS	N	N	WS	N	N
DMF [N,N-Dimethylformamide]	DNN	N	TS	N	N	WS	N	N
Tetralin	AS	N	TS	N	N	AS	N	N
Toluene	AS	Y-A	TS	N	N	AS	N	N
Chlorobenzene	AS	N	TS	N	N	AS	N	N
Chloroform	AS	N	TS	N	N	AS	N	N
Propan-1-ol (extra solvents)	Y-A	N	N	N	N	N	N	N
Pentan-1-ol (extra solvents)	WS	Y-G	TS	N	N	N	N	N

Total No. Systems **256**
Approximate # of Data Points to date 1024

References

1 Lee EH. A practical guide to pharmaceutical polymorph screening & selection. Asian Journal of Pharmaceutical Sciences. 2014 Aug 1;9(4):163-75.
2 Chen J, Sarma B, Evans JM, Myerson AS. Pharmaceutical crystallization. Crystal growth & design. 2011 Apr 6;11(4):887-95.
3 Kesisoglou F, Wu Y. Understanding the effect of API properties on bioavailability through absorption modeling. The AAPS Journal. 2008 Dec;10(4):516-25.
4 Brown CJ, McGlone T, Yerdelen S, Srirambhatla V, Mabbott F, Gurung R, Briuglia ML, Ahmed B, Polyzois H, McGinty J, Perciballi F. Enabling precision manufacturing of active pharmaceutical ingredients: workflow for seeded cooling continuous crystallisations. Molecular Systems Design & Engineering. 2018;3(3):518-49.