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Autonomous DataFactory: High-throughput screening for large-scale data collection to inform medicine manufacture

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SUMMARY

Using small-scale crystallisation to inform downstream processes, we can reduce time and material costs in medicine manufacturing. This work introduces a preliminary workflow for information-rich data collection of crystallisation parameters including solubility, induction time, growth rate, secondary nucleation rate, particle shape and size. Large-scale data collection was achieved for 6 active pharmaceutical ingredients (APIs) in 31 solvents in less than 9 months with the results for aspirin presented here. Highlights include the identification of 24 potential alternative crystallisation solvents for manufacturing aspirin, all of which yield the biorelevant polymorph. Automation of this workflow will enable the use of robotics to further reduce time and material usage when conducting crystallisation experiments for future APIs.

INTRODUCTION

Crystallisation is an integral part of the synthesis and manufacturing processes of APIs. Information-rich, high-throughput data collection for small-scale crystallisation experiments can rapidly guide medicine manufacturing by informing digital models. The DataFactory at the CMAC Future Manufacturing Research Hub is establishing an automated crystallisation parameter collection platform that incorporates the following data to inform medicine manufacture. To enable this automation of crystallisation experiments, we present a workflow that guides consistent crystallisation data collection for a range of APIs and solvents under various process conditions. The data collected for aspirin is presented here.

Existing patents for the crystallisation of aspirin in manufacturing (Hamer, Phillips *et al.*, 1957) use acetone and other organic solvents such as benzene. However, the use of benzene comes with significant health risks. In this study, we identified greener, safer and more sustainable crystallisation solvents for aspirin with industrially-relevant solubilities while also introducing a preliminary workflow to guide future autonomous data collection.

MATERIALS AND METHODS

Aspirin was purchased from Alfa Aesar. Solvents were purchased from Sigma Aldrich, Fisher Scientific, VWR and Alfa Aesar. For solubility screening, vials of known concentrations of aspirin and solvent were thermocycled between 5 °C and 90 °C (or 10 °C below solvent boiling point if the boiling point of the solvent used was below 100 °C), with a heating rate of 0.5 °C/min and a stirring rate of 600 rpm in the Crystalline (Technobis). For kinetics estimation, vials of known concentration were heated to dissolution and then crash-cooled (5 °C/min) to an isothermal hold with a stirring rate of 600 rpm.

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Crystalline images, collected at a frequency of 5s, were analysed using a machine learning algorithm.

RESULTS AND DISCUSSION

The preliminary workflow used in this study (Figure 1) guides experimental work using existing knowledge and model predictions followed by the integration of experimental analysis into a parameter database that guides future experiments.

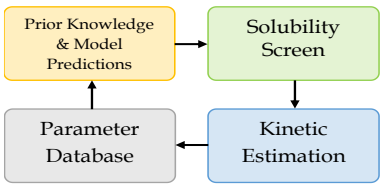

Fig. 1. *Workflow for crystallisation data collection.*

This workflow guided the small-scale crystallisation experiments for 6 APIs in 31 solvents in just under 9 months with the results for aspirin presented here. A representative group of solvents was chosen using principal component analysis of laboratory-grade solvents (Diorazio, Hose *et al.*, 2016).

The solubility profiles (Figure 2) of aspirin showed that 24 of the solvents investigated have a suitable solubility range for cooling crystallisation in a manufacturing process (Muller, Fielding *et al.*, 2009).

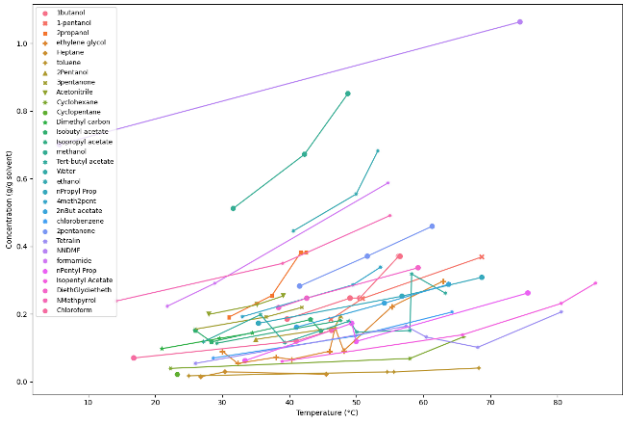

Fig. 2. *Solubility profiles for aspirin in 31 solvents.*

Isolation and subsequent analysis of crystals by XRPD confirmed all successful crystallisations yielded only the biorelevant polymorph. Isopentyl acetate was then used for kinetics estimation due to its favourable aspirin solubility and relative safety. In isopentyl acetate, a supersaturation of 1.22 and a temperature of 28.9 °C gave an optimal crystallisation process with target values of induction time of 1 h, growth rate of 1 µm/min and secondary nucleation rate of 1 count/sec.

These small-scale experiments (2-8 mL) can be compared to a study by Maia *et al.*, where samples were circa 50 – 75 mL and heated at 0.01 °C/min. Aspirin solubility in ethanol in the literature (Maia and Giulietti 2008) and aspirin solubility collected by the methodology here yielded a value difference of only 1.4% (Table 1). This comparison suggests the reliability of the method used here despite each data point being collected 50 times quicker and with a 10-fold reduction in material. Similar comparisons were observed for other APIs when data was available.

Table 1. *Comparison of solubility collection methods at 30 °C for aspirin in ethanol.*

Solvent	Small-scale[a] (g/g solvent)	Mid-scale[b] (g/g solvent)	Difference[c] (%)
Ethanol	0.295	0.299	1.36

[a] values are extracted by linear regression using the Van't Hoff relationship, [b] (Maia and Giulietti 2008), [c] the difference was calculated in respect to small scale

CONCLUSIONS

Solubility data for aspirin in 31 solvents was collected rapidly (~ 3 weeks) using only 62 g of API. The method was found to be reliable and on par with a method previously described in the literature. Kinetic parameter estimations were also achieved using only 9 g of API. These values will allow for the parameterisation of digital twin models which will, in turn, inform larger-scale medicine manufacturing. The workflow used here will guide autonomous robotic data collection for a range of APIs and solvents as part of the CMAC DataFactory.

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