Electronic Supplementary Material (ESI) for CrystEngComm.

ESI: Developing a model-driven workflow for the digital design of small-scale batch cooling crystallisation with the antiviral lamivudine.

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Table 1. Details of each key task and decision in the workflow, listing all outputs and equipment or tools required to carry out the step.

Stage	Description	Output	Equipment/ Tools
1. Define the Aim of the Study	Determine the goal/ basis for undertaking the research i.e., full quantitative/ fast qualitative dataset.	A clear aim for the work to be carried out	User
2. Review Prior Knowledge	Collate any past experimental or calculated data or prior knowledge	An understanding of previous studies and what analytical methods are available	Lab notebooks, published work
Decision A	*Are initial experiments required?*	YES – progress to 'Experimental Input' NO – progress to 'Review Workflow Specific Target Parameters'	Manual user check
3. Characterise Raw Material	Execute experiments to select analytical methods, analyse raw materials and generate reference data for further characterisation and phase ID	Polymorph, physical properties, molecular analysis of raw material	XRPD, STA, Raman, UV-Vis, IR
4. Define Workflow-Specific Target Parameters	Set objective based on crystallisation process screening objectives	Target particle (size, shape) and process (solubility, kinetics, yield) attributes for operable crystallisation process outcomes	Literature, Quality Target Product Profile (QTPP)
5. Solubility and Solvent Effects Study (Polythermal Global Search)	Conduct polythermal experiments (3 cycles) of the API at varying concentrations in a wide range of solvents	Solubility profiles, solvent effects, indications of fouling, kinetic estimates (MSZW), yield estimates	Crystalline (Technobis), 8 mL vials, stirrers, Zinsser Crissy Platform (Zinsser Analytics)
6. & 9. Off-Line Analysis	Conduct experiments with other analytical techniques	Solid form determination, thermodynamic data	XRPD, STA, Raman, Microscopy, Solubility
Decision B	*Can solubility-temperature profiles be plotted with the Van't Hoff relationship (R2 > 0.81) for solvents?**	YES – progress to next step NO – loop back to secure more data points	Manual user inspection, R-Value filters (coded)
7. Solvent Ranking & Selection	Rank solvents based on target parameters and top solvent progressed to next stage. Collect extra solubility points to give a more accurate temperature-solubility profile.	Solvent choice with a solubility-temperature profile of 6-8 experimental data points	Crystalline (Technobis), 8 mL vials, stirrers, Zinsser Crissy Platform (Zinsser Analytics)
8. Kinetic Parameter Study (Isothermal Local Search)	Conduct isothermal kinetic parameter estimation experiments (3-5 cycles).	Nucleation rate, growth rate, induction time, aspect ratio	Crystalline (Technobis), 8 mL vials, stir bars, Zinsser Crissy Platform (Zinsser Analytics), Image analysis
Decision C	*Were the experiments free from fouling?*	YES – progress to next step NO – change solvent and loop back	User visual checks
Decision D	*Were target parameters or algorithm convergence achieved?*	YES – progress to next step NO – loop back via optimisation	Manual user check
10. Optimisation	Run optimisation algorithms (Multiple Linear Regression/ Partial Least Squares).**	Experimental plan for next best 8-16 experiments	Modde 12.1 software
Decision E	*Are additional experiments needed?*	YES – call out to additional workflows where seeding, antisolvent and larger scale can be explored*** NO – progress to next step	Manual user check
11. Optimum Process Conditions for Small-Scale Crystallisation	Record and pass along conditions from this workflow to complete API process development.	Optimum process conditions for small-scale batch crystallisation	Manual user documentation

Update Crystallisation Parameter Database****	Ensure data is stored in crystallisation parameter database with all conditions, associated responses and outputs from the workflow.	Structured data storage: solute, solvent, concentration (all), dissolution temperature (solubility), induction time, aspect ratio, nucleation rate, growth rate (kinetics)	SQL, Knowledge graph, ontology

**Minimum of 3-4 data points must be used for reliable estimates of R^2 values. Some solvent systems this may not be achievable as qualitative solubility can be used.*

***In current software implementation allows only 2 simultaneous optimisation objectives, sufficient for this study.*

****Although not explicitly discussed in the case study of this paper, if the target parameters for the study are not met then further study can be done to explore seeded, antisolvent and larger-scale crystallisation.*

*****Although not represented in the graphical workflow diagram, it is important to note that all data from the experimental sections and the offline analysis is stored in a standardised data format.*

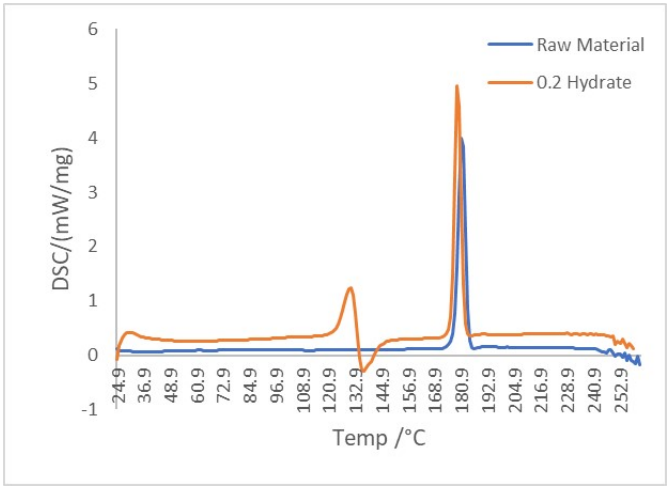

Figure 1. DSC data for raw material (Form II) and the 0.2 hydrate (Form I).

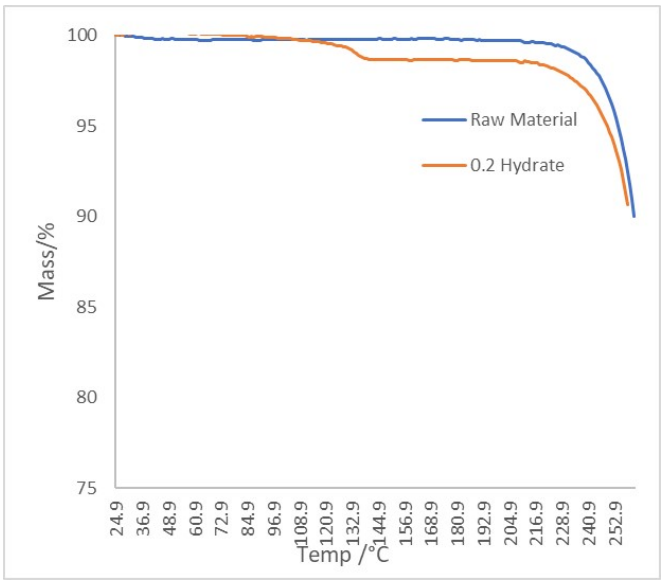

Figure 2. TGA data for raw material (Form II) and the 0.2 hydrate (Form I).

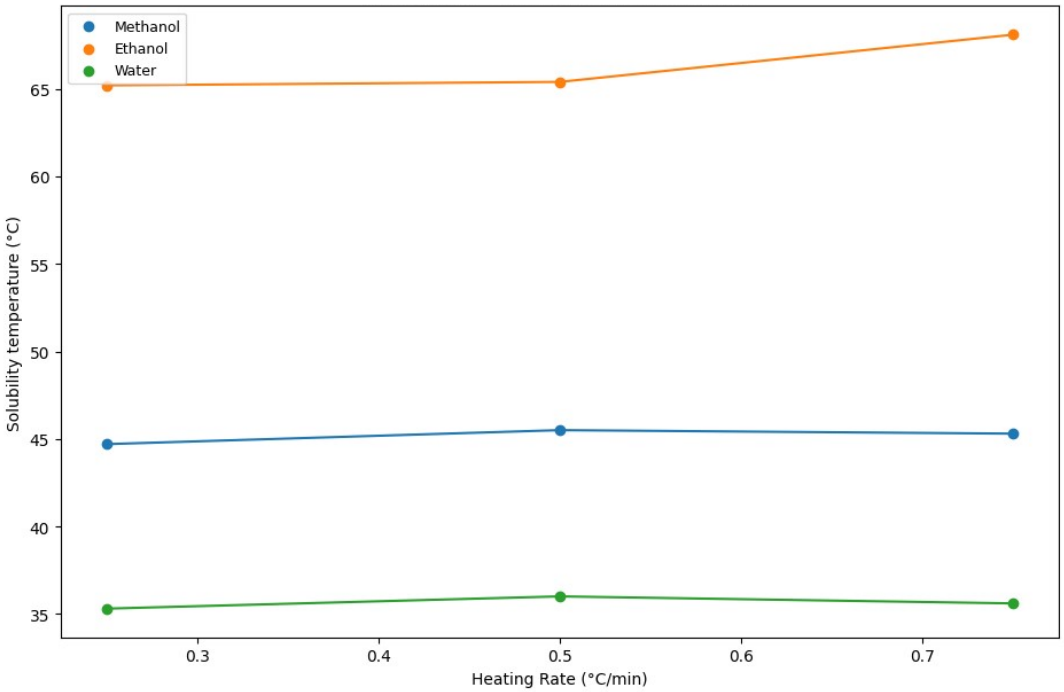

Figure 3. Dissolution temperature measurement of lamivudine in 3 chosen solvents (methanol, ethanol and water) at different heating rates. The figure shows a large stepwise change for ethanol at the fastest heating rate and minimal differences across all other systems and heating rates. Therefore, for efficiency, whilst still maintaining accurate measurements, a heating rate of 0.5 °C/min was used for all experiments.

Table 2. Solubility parameter coefficients (m, c) for lamivudine across all solvents in which quantitative data was collected. Van't Hoff relationship was applied where concentration was expressed as lnX (g/g solvent) and temperature expressed as 1/T (K^{-1}) and linear regression applied.

Solvent	m	c	R^2
1-butanol	-4520.92	9.510173	0.811304
1-pentanol	-5465.74	12.25163	0.729647
1-propanol	-2190.75	3.480024	1*
2-pentanol	-5420.37	11.1428	0.821315
2-propanol	-3951.18	8.04683	0.950545
N,N-dimethylformamide	-1244.04	2.792469	0.90898
N-methylpyrrolidone	-16807.2	54.29446	0.999524
acetonitrile	-3291.86	4.602571	0.976261
ethanol	-3428.49	7.130674	0.992587
ethylene glycol	-4334.9	11.63974	0.920213
formamide	-2612.22	7.363137	0.996196
methanol	-2657.61	5.603299	0.928051
water	-8918.68	27.11113	0.993517

*Only two data points were collected due to the low solubility of lamivudine.

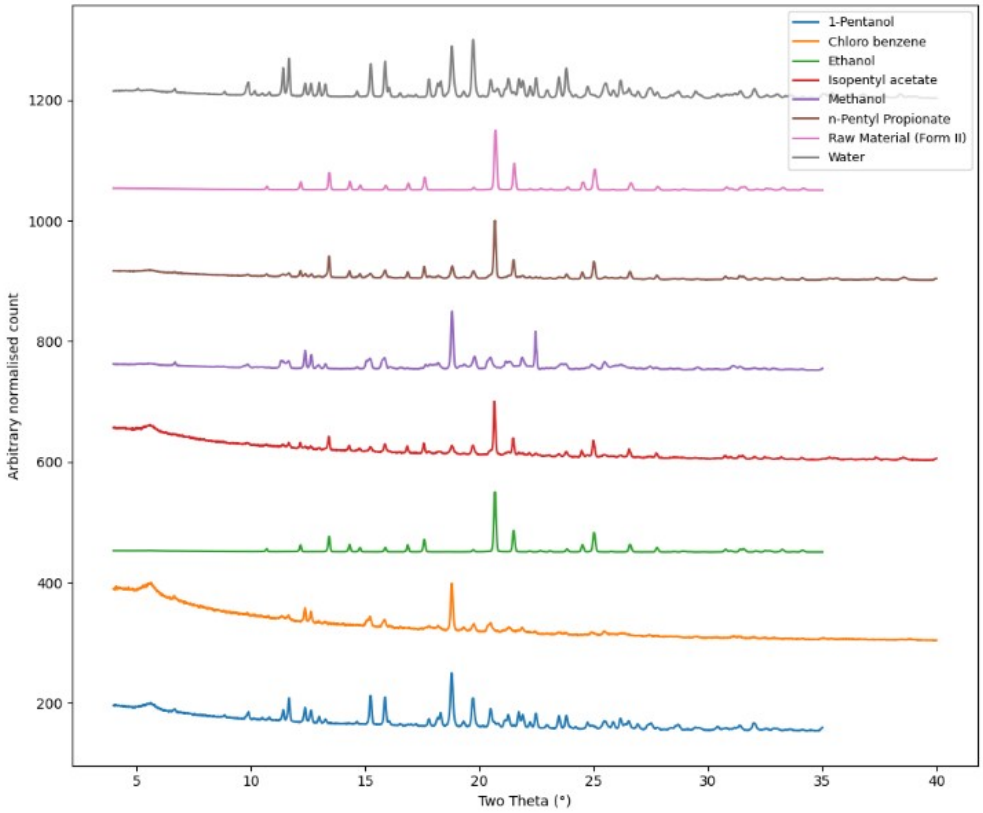

Figure 4. X-ray powder diffraction patterns of lamivudine from various solvents, offset to allow for polymorph comparison.

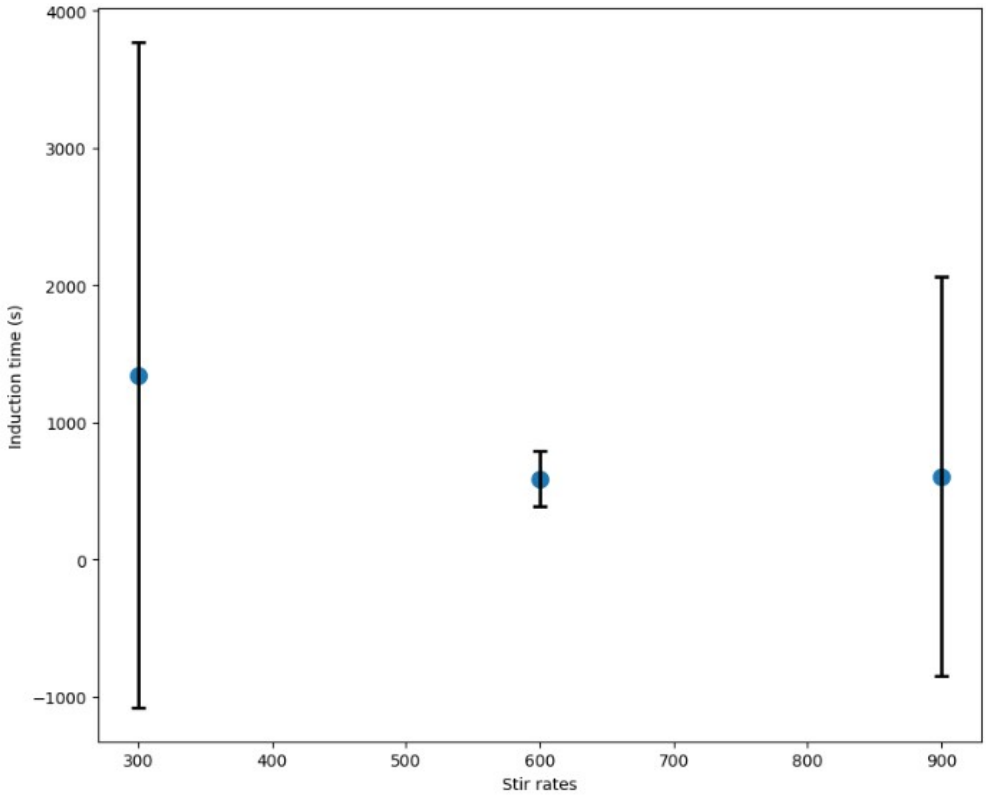

Figure 5. Induction time measurement (8 replicates) of lamivudine in ethanol at different stir rates. The figure shows large statistical differences in induction time for 300 and 900 RPM likely due to slow mixing and magnetic stir bar bumping respectively. Therefore, a fixed stir rate of 600 RPM was used for all experiments in this study.

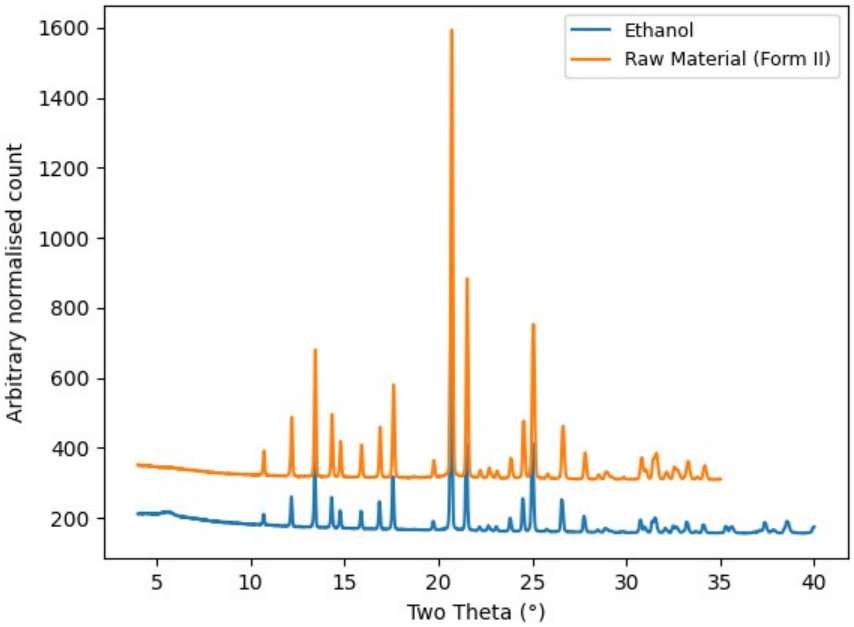

Figure 6. X-ray powder diffraction patterns of lamivudine from ethanol (taken from the kinetic parameter estimation experimental) showing that the recovered solid form was form II