Supplementary Information (SI) for CrystEngComm.

Integration of a Model-Driven Workflow into an Industrial Pharmaceutical Facility: Supporting Process Development of API Crystallisation

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Supporting Information

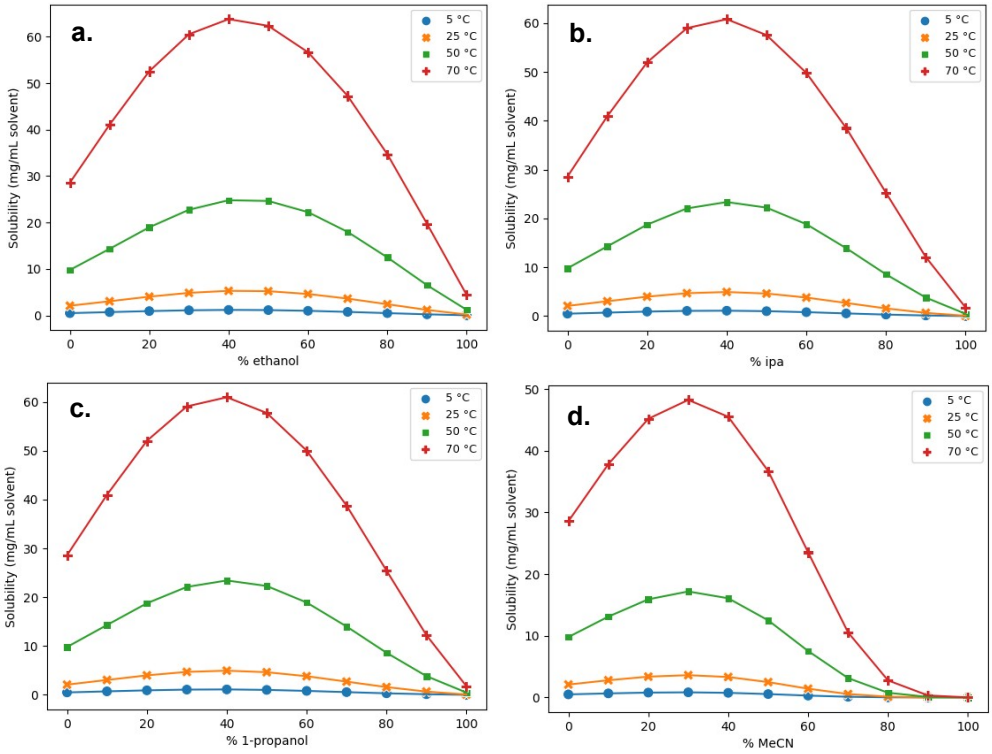


Figure 1. Predicted solubility profiles of varying mass compositions of binary solvent mixtures at 5, 25, 50 and 70 °C of ethanol/ water (a), IPA/ water (b), 1-propanol/ water (c) and acetonitrile/ water (d).

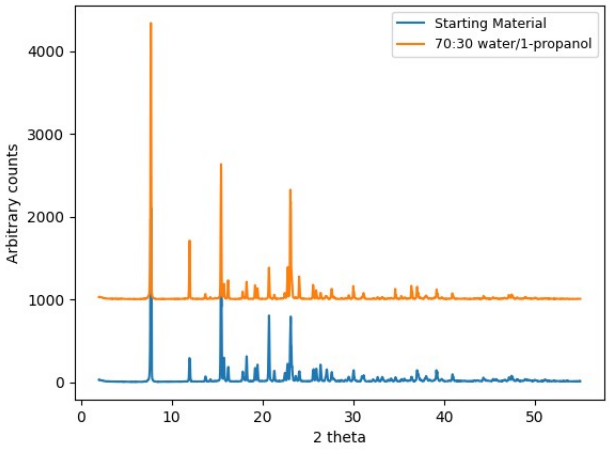


Figure 2. X-ray powder diffraction patterns for PD-299685 recrystallised from 70:30 (v/v) water/ 1-propanol overlayed against reference Form A/ starting material.

Table 1. Design of Experiment (DoE) plans for the kinetic parameter study.

Vial	Isothermal temperature (°C)	SS
1	36	1.84
2	16	3.2
3	35	2.26
4	24	3.1
5	21	3.2
6	31	2.64
7	28	2.91

Table 2. Design of Experiment (DoE) plans for the seeded kinetic parameter study. Note: supersaturation for each vial increases for the seeded experiments due to the addition of seed from the previous cycle changing the starting compositions.

Cycle	Vial	Isothermal temperature (°C)	SS
1	1	36	1.2
	2	16	1.4
	3	35	1.41
	4	24	1.08
	5	21	1.45
	6	31	1.28
	7	28	1.33
2	1	36	1.25
	2	16	1.45

	3	35	1.51
	4	24	1.23
	5	21	1.62
	6	31	1.35
	7	28	1.41
3	1	36	1.3
	2	16	1.63
	3	35	1.6
	4	24	1.31
	5	21	1.64
	6	31	1.43
	7	28	1.55

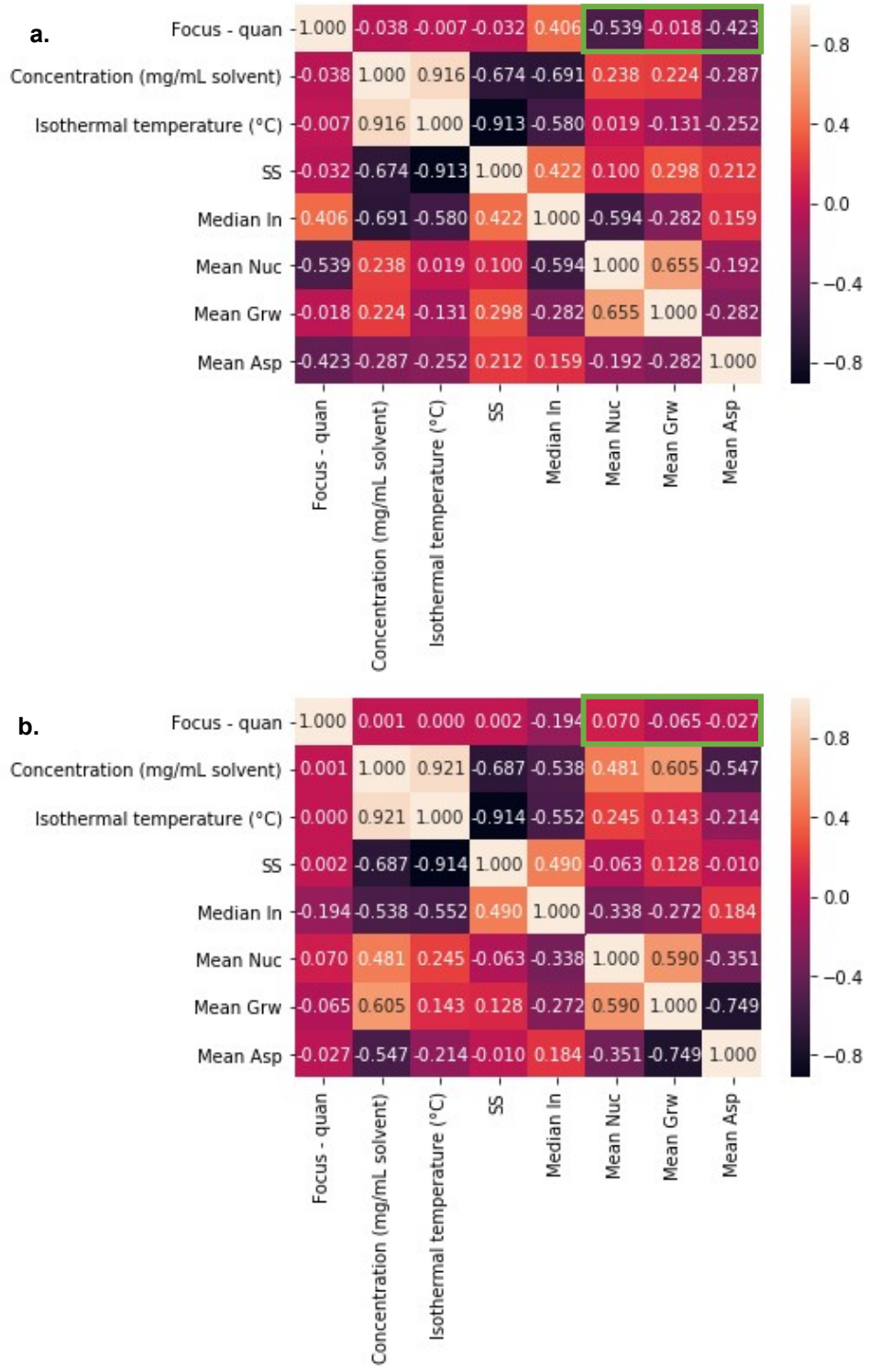
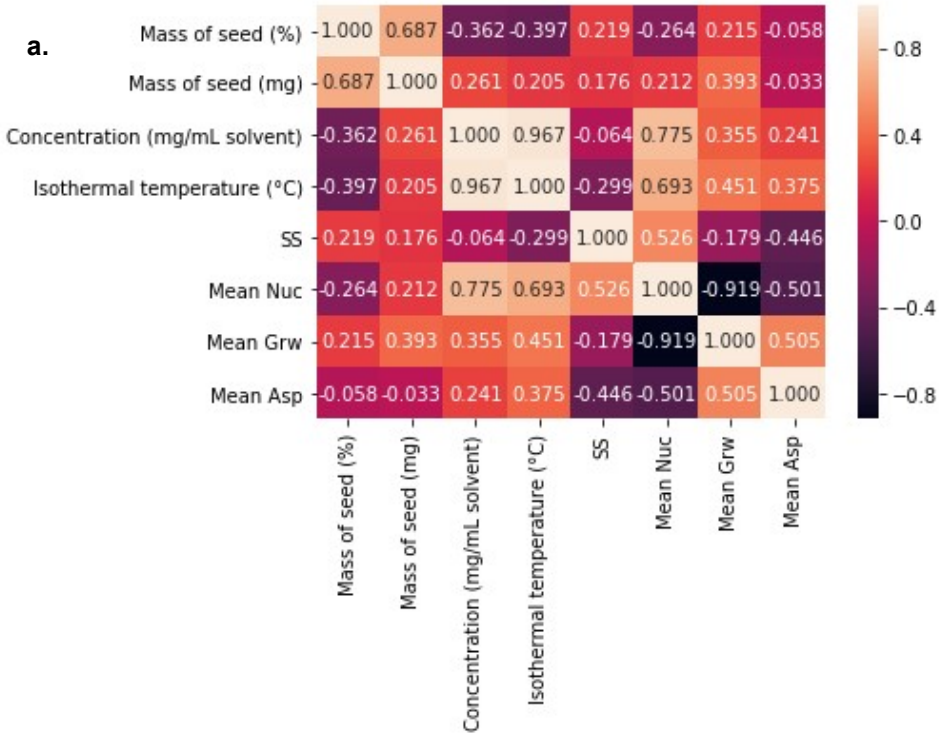


Figure 3. The covariance matrices of input and output variables across the kinetic parameter study for two different agitation methods, magnetic flea (assigned as 0) and the 3-blade pitched impellor (assigned as 1) (a) and for the 3-blade pitched impellor (assigned as 3), 3-blade double pitched impellor (assigned as 6) and the hook stirrer (assigned as 2)** (b). The green box resembles the main point of interest.*

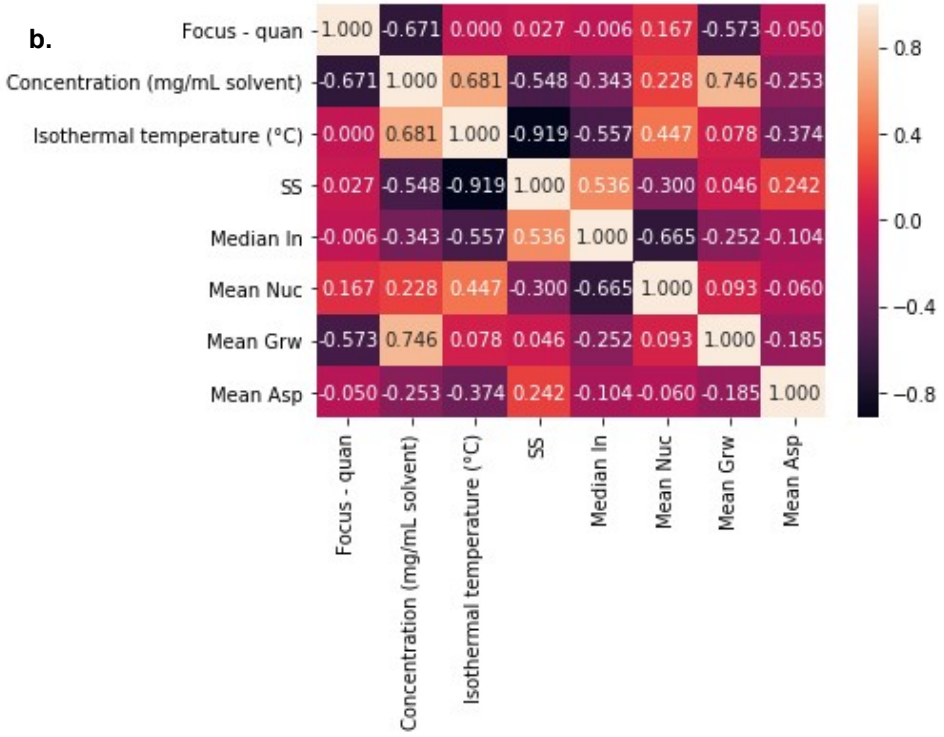
*Abbreviations in the legend are as follows: Focus – quan refers to a quantitative assignment of the qualitative focus of the analysis (see the comment on eigenvalues below), SS is supersaturation, In is induction time, Nuc is nucleation rate, Grw is growth rate and Asp is aspect ratio.

**As the focus of the covariance analysis was looking at differences between stirrer types, these categoric variables needed a quantitative value eigen value which was assigned to reflect the number of corners/ blades in the stirrer.

a.


Mass of seed (%) 1.000 0.687 -0.362 -0.397 0.219 -0.264 0.215 -0.058
Mass of seed (mg) 0.687 1.000 0.261 0.205 0.176 0.212 0.393 -0.033
Concentration (mg/mL solvent) -0.362 0.261 1.000 0.967 -0.064 0.775 0.355 0.241
Isothermal temperature (°C) -0.397 0.205 0.967 1.000 -0.299 0.693 0.451 0.375
SS 0.219 0.176 -0.064 -0.299 1.000 0.526 -0.179 -0.446
Mean Nuc -0.264 0.212 0.775 0.693 0.526 1.000 -0.919 -0.501
Mean Grw 0.215 0.393 0.355 0.451 -0.179 -0.919 1.000 0.505
Mean Asp -0.058 -0.033 0.241 0.375 -0.446 -0.501 0.505 1.000
Mass of seed (%)
Mass of seed (mg)
Concentration (mg/mL solvent)
Isothermal temperature (°C)
SS
Mean Nuc
Mean Grw
Mean Asp
0.8
0.4
0.0
−0.4
−0.8

b.


Focus - quan 1.000 -0.671 0.000 0.027 -0.006 0.167 -0.573 -0.050
Concentration (mg/mL solvent) -0.671 1.000 0.681 -0.548 -0.343 0.228 0.746 -0.253
Isothermal temperature (°C) 0.000 0.681 1.000 -0.919 -0.557 0.447 0.078 -0.374
SS 0.027 -0.548 -0.919 1.000 0.536 -0.300 0.046 0.242
Median ln -0.006 -0.343 -0.557 0.536 1.000 -0.665 -0.252 -0.104
Mean Nuc 0.167 0.228 0.447 -0.300 -0.665 1.000 0.093 -0.060
Mean Grw -0.573 0.746 0.078 0.046 -0.252 0.093 1.000 -0.185
Mean Asp -0.050 -0.253 -0.374 0.242 -0.104 -0.060 -0.185 1.000
Focus - quan
Concentration (mg/mL solvent)
Isothermal temperature (°C)
SS
Median ln
Mean Nuc
Mean Grw
Mean Asp
0.8
0.4
0.0
−0.4
−0.8

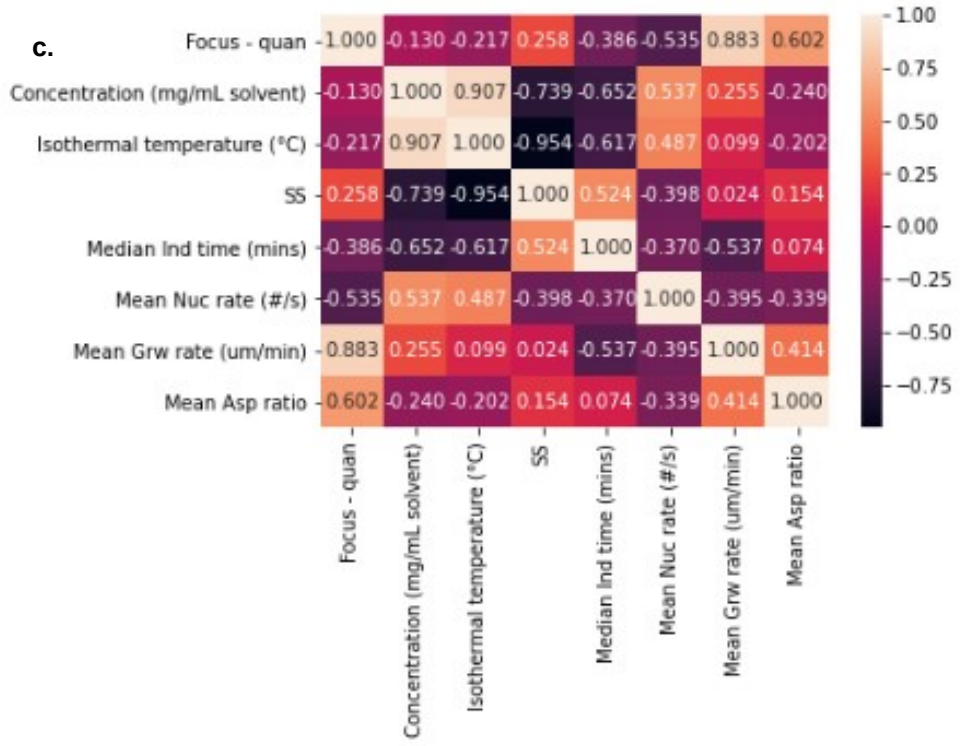


Figure 4. The covariance matrixes of varied and measured variables across the kinetic parameter study for seeded isothermal experiments (a) for three different antisolvent compositions, initial (assigned as 0), halfway (assigned as 0.25) and final (assigned as 0.5) (b) and study for Crystalline and EasyMax isothermal experiments (c).*

*Eigenvalues were assigned according to the part of antisolvent added relative to the initial starting volume.

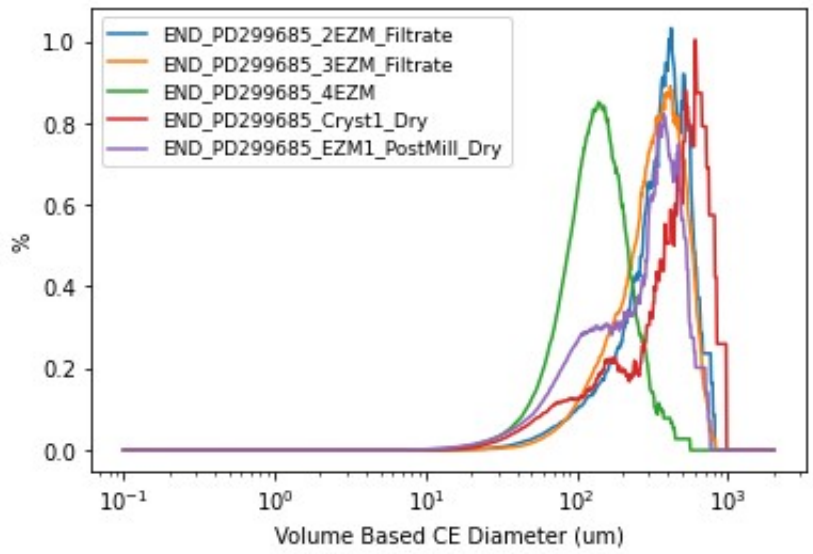


Figure 5. Volume-based PSD of the various end process crystallisation of PD-299685 from the Crystalline and EasyMax.