Electronic Supplementary Material (ESI) for Molecular Systems Design & Engineering.

In situ non-invasive Raman spectroscopic characterisation of succinic acid polymorphism during segmented flow crystallisation

Anuradha R. Pallipurath,[1†] Pierre-Baptiste Flandrin,[1] Lois E. Wayment,[1, 2, 3] Chick C. Wilson[1,2] and Karen Robertson[1‡*]

1. Department of Chemistry, University of Bath, Claverton Down, BA2 7AY, UK
2. CMAC Future Manufacturing Hub, University of Bath, Claverton Down, Bath BA2 7AY, UK
3. Diamond Light Source, Harwell Campus, Didcot, Oxfordshire OX11 0DE, UK

* Email: Karen.Robertson@nottingham.ac.uk

† Present Address: Department Chemistry, CMAC Future Manufacturing Hub, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT

‡ Present Address: Department of Chemical and Environmental Engineering, University of Nottingham, University Park, Nottingham NG7 2RD

Supporting information

Contents

1. Scale_all algorithm

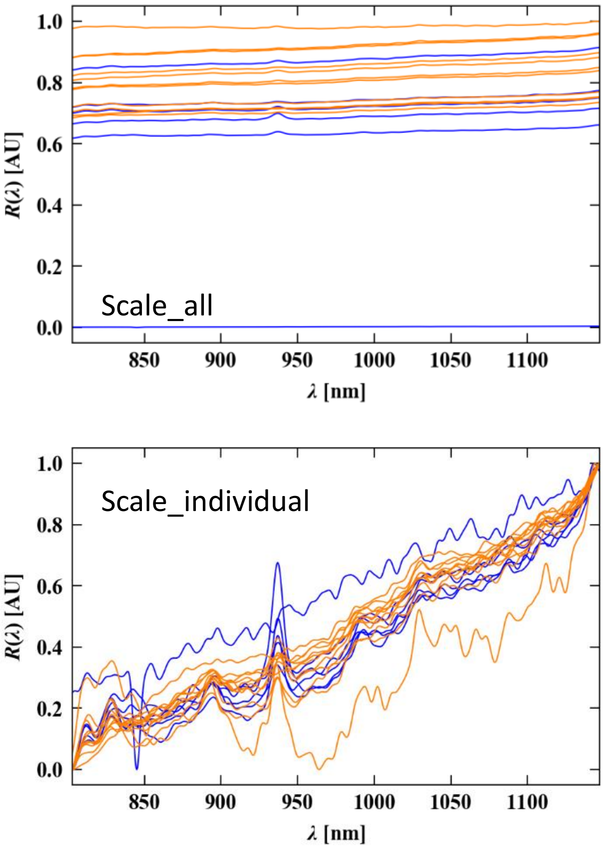

Figure S1: Time-resolved Raman spectra of succinic acid form β high density slurry collected after segmentation in the KRAIC set-up. The ‘scale_all’ algorithm exaggerates the effect of the background thereby enabling distinction between regions of high and low Raman density from solids. The ‘scale_individual’ algorithm improves the S/N ratio of the features from the solids against the background.

‘Scale_all’: Each spectra in the time-dependent data collection is treated simultaneously. Every data point (intensity) in a spectrum is subtracted by the lowest intensity across all of the spectra and divide by the difference in the maximum and minimum intensity across all of the spectra.

$$I_{Sa} = \frac{I - I_{\min\_all}}{I_{\max\_all} - I_{\min\_all}} \qquad \text{eq (1)}$$

2. 2D plots of Raman spectra for slurry of β-SA

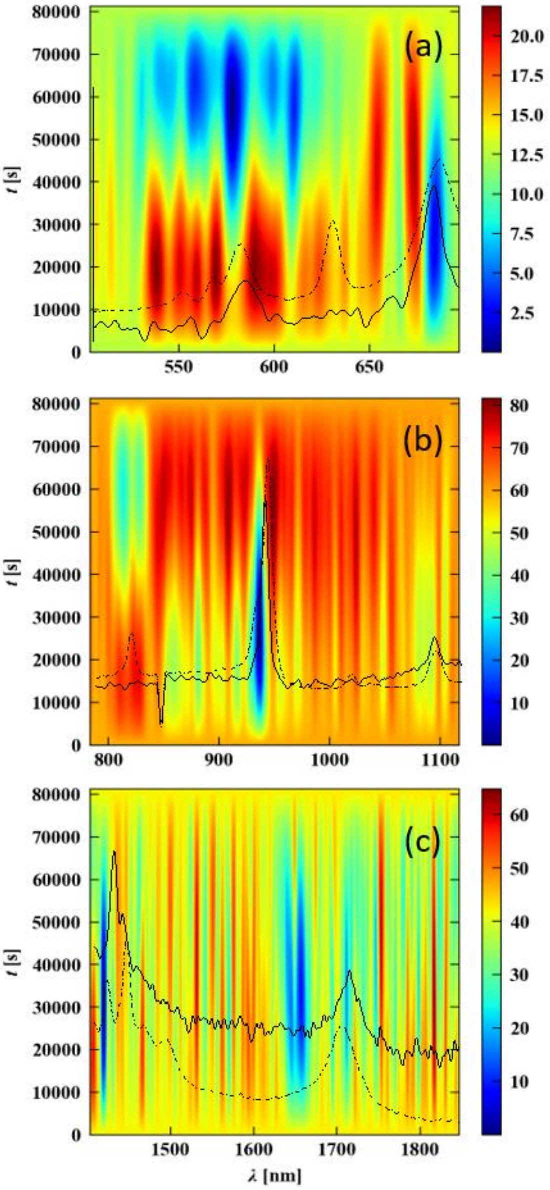

Figure S2: Time-dependent Raman spectra collected from pre-prepared high density slurry of succinic acid form β. In the region of (a) 500 – 700 cm^{-1} (b) 780 – 1120 cm^{-1} (c) 1400 – 1850 cm^{-1}. The regions of interest were scaled individually, to enhance the Raman peaks from the solids flowing through. Overlayed spectra are β-SA (red) and α-SA (grey).

3. Offline analysis of SA produced in the KRAIC

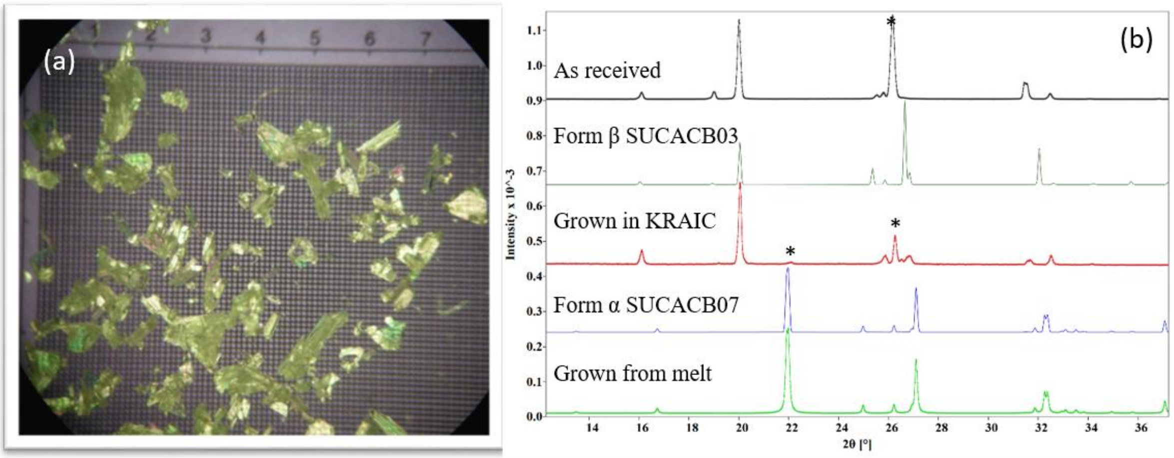

Figure S3: (a) Microscope image of succinic acid (SA) crystallised from KRAIC, (b) Powder X-ray diffraction of the polymorphic forms of SA as received (form β), grown from KRAIC (form β, with small α impurities), form α grown from melt and simulated patterns of both forms from crystal structures deposited in the Cambridge Structural Database (CSD) – REF code: SUCACB03 and SUCACB07.

4. 1D plots of Raman data

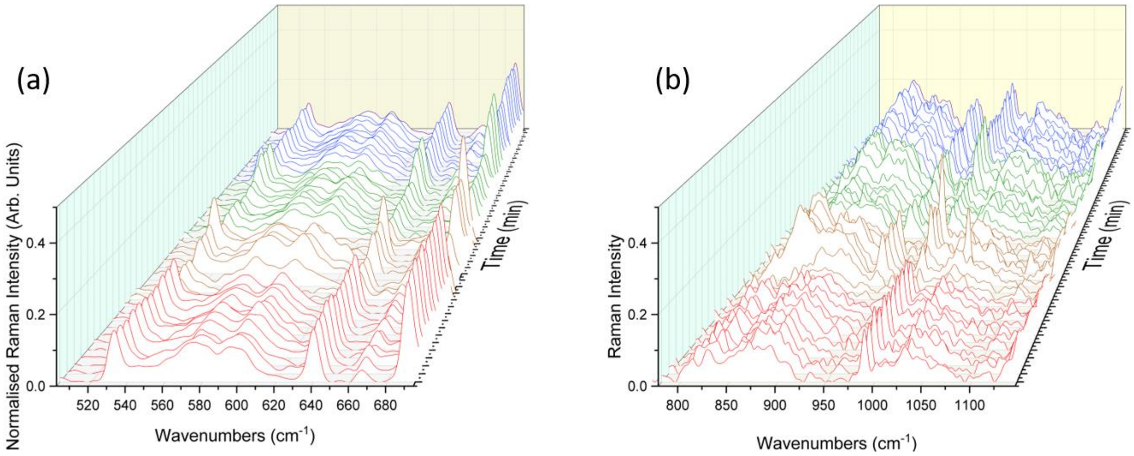

Figure S4: 1d plots of PCM FI and FII slurry before background subtraction. The major intensities are from the FEP tubing.

5. Tentative assignments of Raman peaks

Table S1: Tentative assignments for fluro ethylene propylene reactor and reactor with cyclohexane.

FEP	**FEP+solvent**	**Tentative analysis**
208.4961		C-C stretches
239.2048		
295.2031	293.3967156	
387.3293	387.3292999	C-C deformations
19.8444	418.0380294	
580.6137		
602.2904		
643.8375		
	692.6101988	C-F deformation
734.1573	734.1573034	
752.2213	750.414866	
940.0864		C-C-C-C Symmetric vibrations
1109.888		
1164.08	1151.434745	C-C-C stretches
	1191.175454	
1218.271		C-F stretching
1247.174		
1299.559	1299.559205	CH_2-CH_2 twisting
	1326.655143	
1348.332	1351.944685	
1382.653	1382.653414	
	1435.038894	
1545.229	1543.422645	CH_2F deformation
	1604.840104	
	1850.509939	
	2052.826275	
	2060.051858	
	2164.822818	
	2240.691443	
	2331.011236	
	2370.751945	
2601.971		C-H stretching
2876.543	2880.155575	
	2986.73293	

Table S2: Tentative assignments for succinic acid polymorphs

α-SA	β-SA	Tentative analysis
	83.8548	Phonon modes
94.69317	94.69317	
	125.4019	
130.8211	136.2403	
148.885		
175.981	161.5298	
212.1089		C-C stretches
	266.3008	
	304.2351	
320.4927	320.4927	
392.7485	387.3293	C-C deformation in aliphatic carbons
	457.7787	
549.9049		
569.7753		C-O out-of-pane deformation
582.4201	582.4201	
631.1927		out-of-plane bending of H-bonded OH
	663.7079	
687.191	685.3846	
	703.4486	
	714.2869	
817.2515		
900.3457	887.701	Out-of-plane C-O deformations
940.0864	940.0864	
	963.5696	
	983.4399	
1012.342		monomeric C-O stretching
1032.213	1035.825	
1088.211	1086.404	
1165.886	1160.467	C-H deformations
	1198.401	
1216.465		
1238.142	1232.723	
	1247.174	
	1265.238	
	1277.882	
1297.753	1295.946	

1382.653	1323.042 1371.815	
1400.717 1413.362 1435.039	1400.717 1420.588	C-O …OH combination band
1449.49 1472.973 1548.842		CH_2 deformation
1650	1655.419 1687.934 1725.869	C=O stretching
1816.188 1848.704 1875.799 1908.315 1931.798	1763.803 1799.931	
2329.205 2553.198 2591.132	2576.681 2645.324 2782.61	H-bonded COOH stretches
2851.253 2865.704	2865.704 2885.575 2910.864	Aliphatic C-H stretching
2934.347 2946.992 2966.863 3008.41	2928.928 2948.799 2968.669	Aromatic C-H stretching
3089.697		O-H vibrations

Table S3: Tentative assignments for paracetamol polymorphs

PCM FI	PCM FII	Tentative analysis
89.7		Phonon modes
128.0355	118.774	
	137.2969	
158.9069		
217.5628	205.2142	
328.7001	331.7873	C-C stretching
	365.7459	
393.5303	396.6174	
415.1403	421.3146	
467.6219	452.1861	
501.5805	510.8419	
603.4564	606.5436	out-of-plane bending H-bonded OH
631.2408	628.1536	
652.8508	649.7637	
686.8095		
711.5066	711.5066	out-of-plane N-H deformation in H-bonded secondary amides
739.291		
797.9468	801.034	N-H wagging in secondary amines and C-H out of plane deformation in ortho substituted aromatics
834.9926	838.0798	
858.3	862.777	out-of-plane C=O deformation
967.74	970.8272	
1023.309	1023.309	
	1041.832	C-C-C stretches
1100.487	1109.749	
1168.8	1171.492	
	1220.886	CH_2 deformations + Amide III band
1237.5	1248.671	
1261.019		Amide III band
1279.542	1282.629	
1324.5	1332.024	C-N stretching amide III
1372.157	1378.331	C-O O-H combination bands
	1430.812	
1449.335	1455.51	N-H bonding
1507.991		N-H deformation and C-N stretching amide II
1514.165	1511.078	
1560.473	1560.473	C=C stretches
	1578.996	

1610.7	1612.954	
1618.5	1628.39	C=O stretches amide I
1648.8	1650	
	2733.589	carboxylic acid dimer
	2841.64	aliphatic C-H stretches
	2884.86	
2931.9	2937.341	
	2983.648	
3014.52	3014.52	
3055.2	3060.827	
3066.3	3079.35	aromatic C-H stretches
3110.222	3104.047	
	3178.139	O-H stretches
	3205.923	