Supplementary Material

Controlling the Polymorphic Outcome of 2,6-Dimethoxybenzoic Acid Crystallization Using Additives

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Table S1. List of additives used in the study.

Additive	Purity/Characteristics	Supplier
Microcrystalline cellulose (MCC)	Avicel PH-101	Sigma
Sodium carboxymethyl cellulose (Na CMC)	M.W. 250,000 (DS = 1.2)	Acros
Polyvinyl chloride (PVC)	M.W. 43,000	Sigma-Aldrich
Polycaprolactone (PCL)	M.W. 14,000	Sigma
Glycine	99%	Acros
2,2-Bis(hydroxymethyl)-2,2',2''-nitrilotriethanol (BIS-TRIS)	99%	Fluorochem
4-carboxybenzeneboronic acid (4-COOHPhBorA)	98%	Fluorochem
Phenylboronic acid (PhBorA)	98%	Fluorochem
NH_4Cl	99%	Acros
Polysorbate 80	≤4.0% H_2O	Alfa
Tween 20 (polysorbate 20)	≤3.0% H_2O	Sigma
Sorbitan monolaurate (Span 20)	≤1.0% H_2O	Merck
n-octyl-β-D-glucopyranoside (OGP)	>99%	Fluorochem
Poly(acrylic acid) (PAS)	25 wt% soln. in water	Alfa
Poly(acrylic amide) (PAA)	M.W. 5 to 6,000,000	Acros
4-iodphenylboronic acid (4-IPhBorA)	98%	Fluorochem
Cellulose acetate (CA)	M.W. 100,000	Acros
Hydroxypropylmethyl cellulose	n.a.	Pharmacoat 606

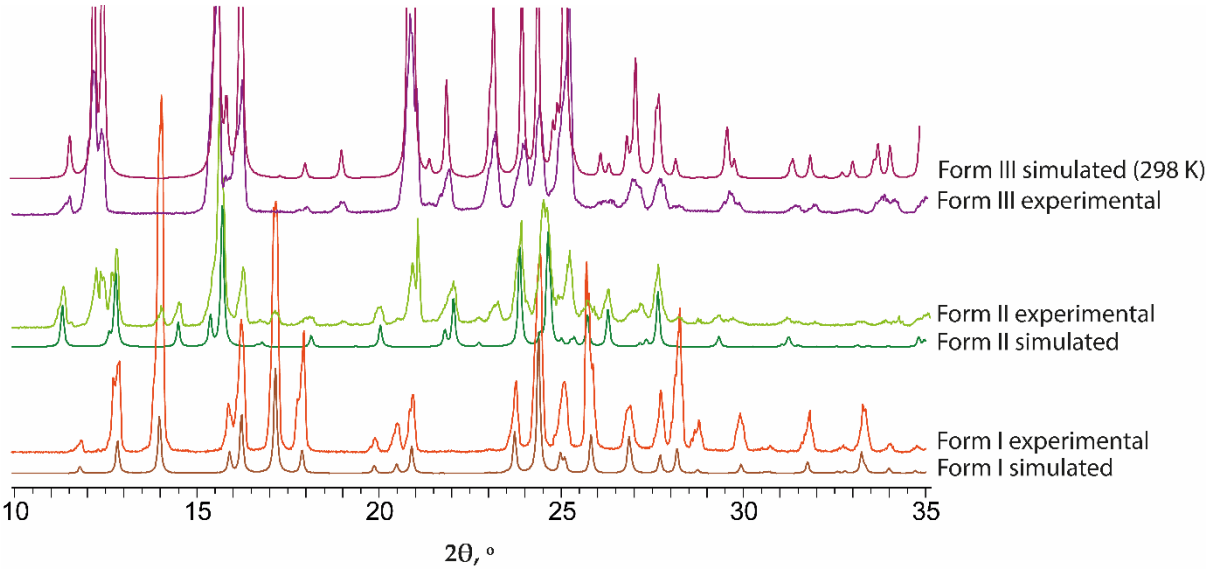

Figure S1. Phase identification of 2,6MeOBA polymorphs using PXRD patterns simulated from crystal structures deposited in the CSD.The experimental PXRD pattern of form II has form I and III impurities.

Table S2. Experimental solubility data for form I in water and coefficients a and b found in the fitting using the least-squares approach.

T_{exp}, ℃	S_{exp}, mg mL^{-1}	lnS_{exp}	1/T_{exp}
18.8	3.0	1.11	0.00343
30.8	4.4	1.48	0.00329
34.7	6.3	1.83	0.00325
46.7	8.9	2.18	0.00313
53.6	9.9	2.30	0.00306
60.3	14.2	2.65	0.00300
64.5	18.0	2.89	0.00296
69.4	22.1	3.10	0.00292
74.7	23.5	3.16	0.00288
76.6	27.3	3.31	0.00286
81.8	31.0	3.43	0.00282
83.5	35.7	3.57	0.00281
		a	−3960 ± 130
		b	15 ± 0.4
		R^2	0.9894
		SE_{lnS}	0.09

Table S3. Experimental solubility data for form III in water and coefficients a and b of Equation (1) found in the fitting using the least-squares approach.

T_{exp}, ℃	S_{exp}, mg mL^{-1}	$\ln S_{exp}$	$1/T_{exp}$
11.6	3.1	1.13	0.00351
21.1	4.3	1.46	0.00340
33.0	6.3	1.84	0.00327
43.1	8.0	2.08	0.00316
56.0	14.0	2.64	0.00304
61.3	17.9	2.89	0.00299
66.7	22.1	3.10	0.00294
72.7	23.5	3.16	0.00289
75.3	27.8	3.33	0.00287
82.4	29.2	3.37	0.00281
85.0	33.6	3.51	0.00279
		a	−3400 ± 110
		b	13 ± 0.3
		R^2	0.9909
		SE_{lnS}	0.08

Table S4. Detailed results from the crystallization of pure solvents and quantification results of mixtures from the Rietveld refinement. The Rietveld refinements here and in further experiments were performed on PXRD patterns of unground samples measured without any optimization for quantitative phase analysis, therefore, the Rwp values are rather high because of the preferred orientation or presence of additive peaks in the PXRD patterns (in preliminary crystallization with additives).

Solvent	Cooling	Evaporation		
		5 °C	25 °C	50 °C
1,4-Dioxane	I + III↓ 95:5 (Rwp 12.14%)	III	III / I + III 58:42 (Rwp 12.47%)	III
Methanol	I + III↓ 98:2 (Rwp 20.09%)	I	I / III + I↓ + II 50:1:49 (Rwp 11.33%)	I
Acetone	I	I + III 72:28 (Rwp 19.05%)	I	III
Tetrahydrofuran	I	I + III 77:23 (Rwp 14.19%)	I + III 77:23 (Rwp 14.12%)	I↓ + III 10:90 (Rwp 11.66%)
Isopropanol	I	I	I / I + III↓ 98:2 (Rwp 12.79%)	III
Acetonitrile	I	I + III↓ 94:6 (Rwp 7.03%)	III / I + III 67:33 (Rwp 12.63%)	I / III
Butan-2-one	I + III↓ 97:3 (Rwp 12.40%)	III	III	I
4-Methyl-2-pentanone	I	I	I + III↓ 96:4 (Rwp 11.67%)	I + III 25:75 (Rwp 10.07%)
Methyl acetate	I	I + III↓ 91:9 (Rwp 7.60%)	I + III 14:86 (Rwp 10.70%)	I↓ + III 6:94 (Rwp 15.45%)
Tert-butyl methyl ether	I	I	I	I + III 59:41 (Rwp 7.07%)
Water	I	I	I	I
Toluene	I	N/A	I + III 67:33 (Rwp 21.07%) *	N/A
Chloroform	I	N/A	I + III↓ 92:8 (Rwp 38.47%) *	N/A

Dichloromethane	I + III↓ 93:7 (Rwp 30.67%) *	N/A	I + III↓ 96:4 (Rwp 22.25%) *	N/A
Ethyl acetate	I	N/A	I	N/A
Formic acid	I	N/A	I	N/A
Nitromethane	I	N/A	I	N/A

↓—low concentration, N/A—crystallization was not performed. *—high Rwp values due to low crystallization outcome and rough PXRD patterns.

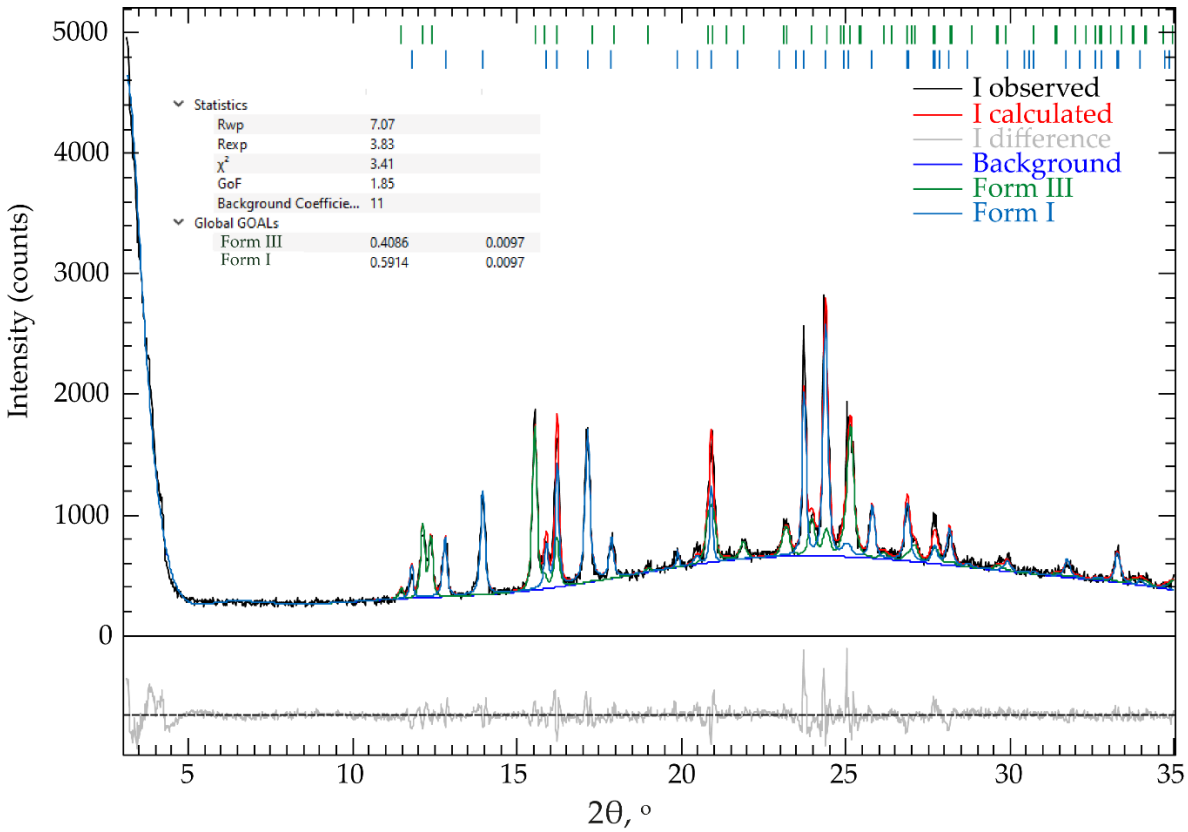

Figure S2. Example of Rietveld refinement from Profex 4.3.6. with the obtained Rietveld R-factors and phase composition. The refinement was carried out on the sample obtained in crystallization from tert-butyl methyl ether with evaporation at 50 °C.

Table S5. Detailed results from the crystallization with additive presence and quantification results of mixtures from the Rietveld refinement.

Solvent	**Additive**	**Number of Vial**		
		1.	**2.**	**3.**
THF	**Blank**	I + III 36:64 (Rwp 10.29%)	I + III 30:70 (Rwp 15.15%)	I + III 53:47 (Rwp 14.36%)
	PVC	I + III 85:15 (Rwp 7.31%)	I + III 25:75 (Rwp 5.41%)	I + III 41:59 (Rwp 6.53%)
	Poly 80	I + III 15:85 (Rwp 20.71%)	III	III
	Span 20	I + III 44:56 (Rwp 35.90%)	I + III 53:47 (Rwp 43.82%)	I
	OGP	I + III 88:12 (Rwp 17.82%)	I + III 6:94 (Rwp 21.77%)	III
	Tween 20	I	I	I
	PCL	I + III 84:16 (Rwp 23.30%)	I + III 67:33 (Rwp 30.95%)	I

	PEG	I + III 77:23 (Rwp 36.67%)	III	III
MeCN	**Blank**	III	III	III
	PVC	I + III 20:80 (Rwp 17.97%)	I	I
	Poly 80	III	III	I + III 27:73 (Rwp 12.81%)
	Span 20	III	III	I
	OGP	I + III 18:82 (Rwp 14.34%)	I + III 31:69 (Rwp 16.50%)	I + III 34:66 (Rwp 20.50%)
	Tween 20	I + III 80:20 (Rwp 10.30%)	I + III 55:45 (Rwp 15.47%)	I
	PCL	III	III	I + III 36:64 (Rwp 22.70%)
	PEG	I + III 93:7 (Rwp 34.64%)	I + III 3:97 (Rwp 19.96%)	I + III 84:16 (Rwp 29.39%)
Water	**Blank**	I + III 83:17 (Rwp 9.07%)	I + III 94:6 (Rwp 13.88%)	I + III 37:63 (Rwp 10.84%)
	Poly 80	I + III 88:12 (Rwp 14.07%)	I	I
	PheBorA	I + III 97:3 (Rwp 9.57%)	I + III 92:8 (Rwp 8.67%)	I + III 90:10 (Rwp 12.24%)
	2,6MeOPheBorA	I + III 13:87 (Rwp 6.97%)	I + III 3:97 (Rwp 8.49%)	I + III 19:81 (Rwp 7.61%)
	OGP	I	I	I + II + III 20:14:66 (Rwp 32.18%)
	PEG	III	III	I + II + III 81:9:10 (Rwp 8.14%)
	HPC	III	III	III
	PAA	I	I	I + III 39:61 (Rwp 15.97%)
	4IPheBorA	I	I	I + III 95:5 (Rwp 23.48%)
	NH_4Cl	I + III 94:6 (Rwp 15.71%)	I + III 54:46 (Rwp 13.84%)	I + III 87:13 (Rwp 15.76%)
	Glycine	I	I	I + III 99:1 (Rwp 17.77%)
	BIS-TRIS	I	I	I + II + III 6:14:80 (Rwp 8.83%)
	CA	I + III 5:95 (Rwp 19.59%)	I + III 14:86 (Rwp 13.35%)	I + III 90:10 (Rwp 16.96%)
	PAS	I + III 50:50 (Rwp 10.05%)	I + III 28:72 (Rwp 8.54%)	I + II + III 6:63:31 (Rwp 10.34%)
Water	**MCC**	I + III 10:90 (Rwp 26.32%)	I + III 82:18 (Rwp 15.44%)	I + III 89:11 (Rwp 20.19%)
	4COOHPheBorA	I + III 94:6 (Rwp 12.86%)	I + III 92:8 (Rwp 12.84%)	I + III 94:6 (Rwp 14.01%)
	Na CMC	I	I	I + III 97:3 (Rwp 9.75%)
	HPMC	I + III 10:90 (Rwp 6.44%)	I + III 36:64 (Rwp 8.36%)	I + II + III 5:61:34 (Rwp 15.92%)

The high Rwp values are due to the additive presence or dominant orientation in the PXRD patterns.

Table S6. Detailed results from the crystallization experiments from highly concentrated water solutions using different additives and cooling rates with quantification results of mixtures from the Rietveld refinement.

Additive	Cooling Rate, °C min^{-1}	Number of Vial			
		1.	2.	3.	4.
Blank (A)	20	I + II + III 30:40:30 (Rwp 8.98%)	I + II + III 41:14:45 (Rwp 8.65%)	I + II + III 35:14:51 (Rwp 10.57%)	I + II + III 5:51:44 (Rwp 13.73%)
	10	I + III 11:89 (Rwp 10.46%)	I + III 5:95 (Rwp 12.58%)	I + II 5:95 (Rwp 6.74%)	II + III 21:79 (Rwp 10.24%)
	1	I + III 17:83 (Rwp 8.70%)	I + III 16:84 (Rwp 19.55%)	I + III 83:17 (Rwp 6.86%)	I
	0.1	III	III	III	III
1% PEG (B)	20	I + III 17:83 (Rwp 11.42%)	I + III 12:83 (Rwp 12.70%)	I + III 15:85 (Rwp 14.43%)	III
	10	I + III 9:91 (Rwp 16.63%)	I + III 27:73 (Rwp 8.55%)	I + III 86:14 (Rwp 9.16%)	I
	1	I + III 93:7 (Rwp 23.86%)	I + III 5:95 (Rwp 14.98%)	III	III
	0.1	I + III 6:94 (Rwp 13.99%)	I	I	I
0.5% 2,6Me-OPheBA (C)	20	I + III 35:65 (Rwp 11.55%)	I + III 5:95 (Rwp 15.61%)	I + III 29:71 (Rwp 46.76%)	I + III 6:94 (Rwp 15.00%)
	10	I + III 15:85 (Rwp 7.13%)	I + III 15:85 (Rwp 7.27%)	I + III 17:83 (Rwp 11.39%)	I + III 8:92 (Rwp 12.51%)
	1	I + III 42:58 (Rwp 6.90%)	I + III 12:88 (Rwp 11.42%)	I + III 13:87 (Rwp 37.00%)	I + III 65:35 (Rwp 10.95%)
	0.1	I + III 22:78 (Rwp 13.18%)	I + III 3:97 (Rwp 8.16%)	I + III 45:55 (Rwp 13.77%)	I
0.1% HPC (D)	20	III	III	III	I + II + III 26:12:62 (Rwp 55.32%)
	10	I + III 4:96 (Rwp 21.34%)	I + III 21:79 (Rwp 9.21%)	III	III
	1	I + III 2:98 (Rwp 11.08%)	I + III 5:95 (Rwp 18.10%)	I	I + II + III 1:90:9 (Rwp 12.88%)
	0.1	I + III 3:96 (Rwp 8.84%)	I + III 42:58 (Rwp 8.68%)	I	III
0.5% HPC (E)	20	III	III	I	I
	10	III	III	III	III
	1	III	III	III	III
	0.1	III	III	III	I

The high Rwp values are due to the dominant orientation in the PXRD patterns.

Table S7. Detailed results from the crystallization experiments with different amounts and cooling rates with quantification results of mixtures from the Rietveld refinement.

Cooling Rate, °C min^{-1}	Additive	Number of Vial			
		1.	**2.**	**3.**	**4.**
20	Blank	I + III 68:32 (Rwp 48.69%)	I + III 48:52 (Rwp 43.14%)	I + III 57:43 (Rwp 51.42%)	I
	0.5% PEG	I + III 6:94 (Rwp 25.14%)	III	III	I
	0.7% PEG	III	III	III	III
	1% PEG	III	III	I	I
	1.5% PEG	III	III	I	I
	2% PEG	I + III 3:97 (Rwp 12.70%)	I + III 54:46 (Rwp 23.85%)	III	III
1	Blank	I	I	I	I
	0.5% PEG	I + III 4:96 (Rwp 11.91%)	I + III 60:40 (Rwp 10.79%)	I	I
	0.7% PEG	I + III 95:5 (Rwp 12.19%)	I + III 99:1 (Rwp 11.26%)	I	I
	1% PEG	I + III 1:99 (Rwp 12.31%)	I + III 3:97 (Rwp 11.86%)	I	III
	1.5% PEG	I + III 97:3 (Rwp 16.10%)	I + III 96:4 (Rwp 10.26%)	I	I
	2% PEG	I	I	I	I + III 90:10 (Rwp 11.14%)
20	Blank	I + III 36:64 (Rwp 44.89%)	I + III 88:12 (Rwp 15.55%)	I	I
	0.5% HPC	I	I	III	III
	0.7% HPC	III	III	I + III 32:68 (Rwp 54.17%)	I + III 78:22 (Rwp 25.34%)
	1% HPC	III	III	III	I + III 20:80 (Rwp 7.95%)
	1.5% HPC	I	I	I + III 97:3 (Rwp 12.82%)	III
	2% HPC	III	III	III	I + III 40:60 (Rwp 26.75%)
10	Blank	I	I	I	I
	0.5% HPC	III	III	III	III
	0.7% HPC	I	I	I + III 6:94 (Rwp 6.80%)	III
	1% HPC	I	I	I	III
	1.5% HPC	III	III	I	I + III 74:26 (Rwp 5.84%)
	2% HPC	I	I	I + III 7:93 (Rwp 10.94%)	III

The high Rwp values are due to the dominant orientation in the PXRD patterns.

Table S8. Experimental solubility data for form I in 1% PEG water solution and coefficients a and b from Equation 1 found in the fitting using the least-squares approach.

T_{exp}	S_{exp}	lnS_{exp}	$1/T_{exp}$
20.3	3.3	1.19	0.00341
27.3	4.0	1.37	0.00333
377	5.9	1.78	0.00322
37.5	6.3	1.84	0.00322
48.6	8.3	2.11	0.00311
52.4	10.2	2.33	0.00307
60.0	14.0	2.64	0.00300
65.6	18.2	2.90	0.00295
69.5	22.1	3.10	0.00292
73.6	23.6	3.16	0.00289
		a	−3910 ± 150
		b	14 ± 0.5
		R^2	0.9885
		SE_{lnS}	0.08

Table S9. Experimental solubility data for form III in 1% PEG water solution and coefficients a and b from Equation 1 found in the fitting using the least-squares approach.

T_{exp}	S_{exp}	lnS_{exp}	$1/T_{exp}$
17.8	4.3	1.45	0.00344
27.0	6.1	1.80	0.00333
32.0	6.3	1.84	0.00328
44.2	7.8	2.06	0.00315
50.8	10.3	2.33	0.00309
58.2	14.3	2.66	0.00302
67.2	18.2	2.90	0.00294
70.1	21.4	3.06	0.00291
72.3	23.3	3.15	0.00290
74.9	26.9	3.29	0.00287
		a	−3180 ± 200
		b	12 ± 0.6
		R^2	0.9698
		SE_{lnS}	0.11