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Supplementary Materials

Impact of Impurities on Crystallization and Product Quality: A Case Study with Paracetamol

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1. Crystallization

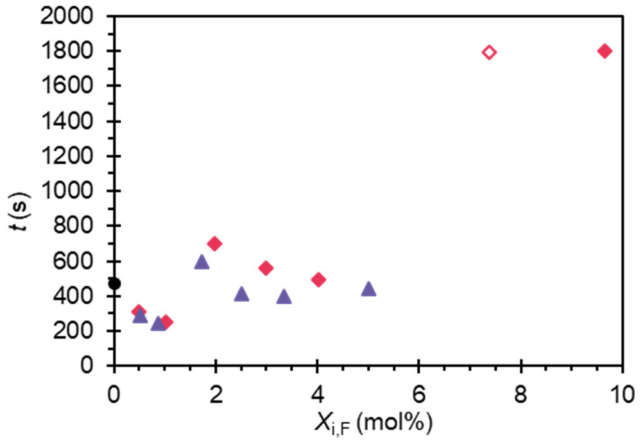

Figure S1. Induction time (t) as a function of initial impurity concentration ($X_{i,F}$). (●) Pure component paracetamol, (▲) paracetamol with acetanilide added and (◆) or (◇) paracetamol with metacetamol added.

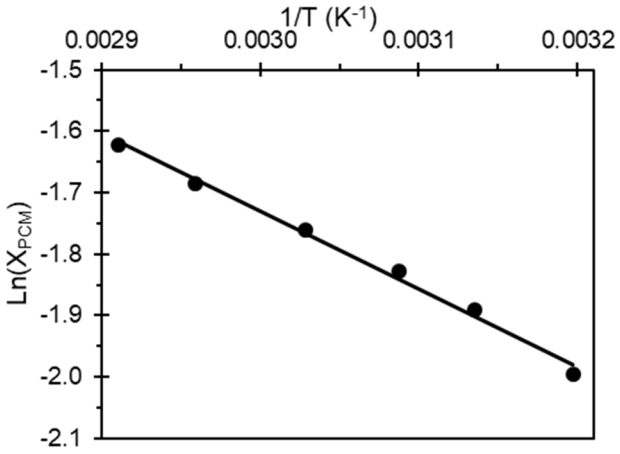

Figure S2. Van't Hoff solubility plot of paracetamol in 2-propanol. Linear regression $\ln(X_{PCM}) = -1261.9\ T^{-1} + 2.0429$, $R^2 = 0.993$.

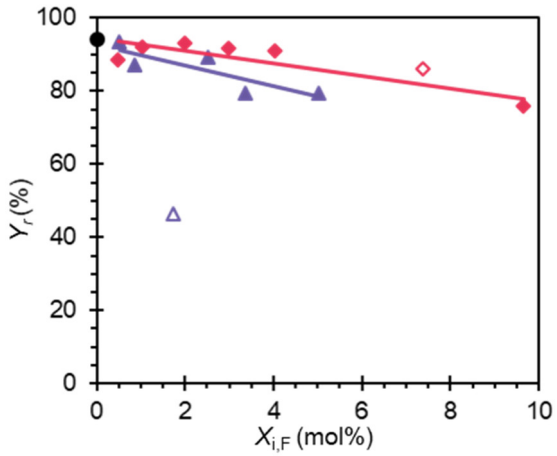

Figure S3. Product recovery as a function of initial impurity concentration, from crystallizations nucleated at $\sigma = 2.10$. (●) Pure paracetamol from 2-propanol. (◆) In the presence of metacetamol. Linear regression $Y_r = -1.6971X_{i,F} + 94.359$, $R^2 = 0.7618$. (▲) In the presence of acetanilide, and (△) was identified as an outlier and removed from fitted line. Linear regression $Y_r = -2.8573X_{i,F} + 92.789$, $R^2 = 0.7036$.

2. Product Purity

Table S1. Summary of paracetamol cooling crystallizations from 2-propanol in the presence of metacetamol or acetanilide

	Impurity	Initial Suspension		Crystallized Solid		Mother Liquor	
		X_{PCM}	X_{IMP}	X_{PCM}	X_{IMP}	X_{PCM}	X_{IMP}
1	Metacetamol	0.995	0.005	0.999	0.001	0.982	0.018
2		0.990	0.010	0.995	0.005	0.964	0.036
3		0.980	0.020	0.990	0.010	0.937	0.063
4		0.970	0.030	0.984	0.016	0.920	0.080
5		0.960	0.040	0.975	0.025	0.907	0.093
6		0.904	0.096	0.932	0.068	0.848	0.152
7	*(Form II)*	0.931	0.069	0.987	0.014	0.828	0.172
8	Acetanilide	0.991	0.009	0.998	0.002	0.979	0.021
9		0.995	0.005	0.998	0.002	0.986	0.014
10		0.983	0.017	0.997	0.003	0.955	0.045
11		0.975	0.025	0.996	0.004	0.936	0.064
12		0.967	0.033	0.994	0.006	0.920	0.080
13		0.950	0.050	0.992	0.008	0.885	0.115

3. Polymorphic Form

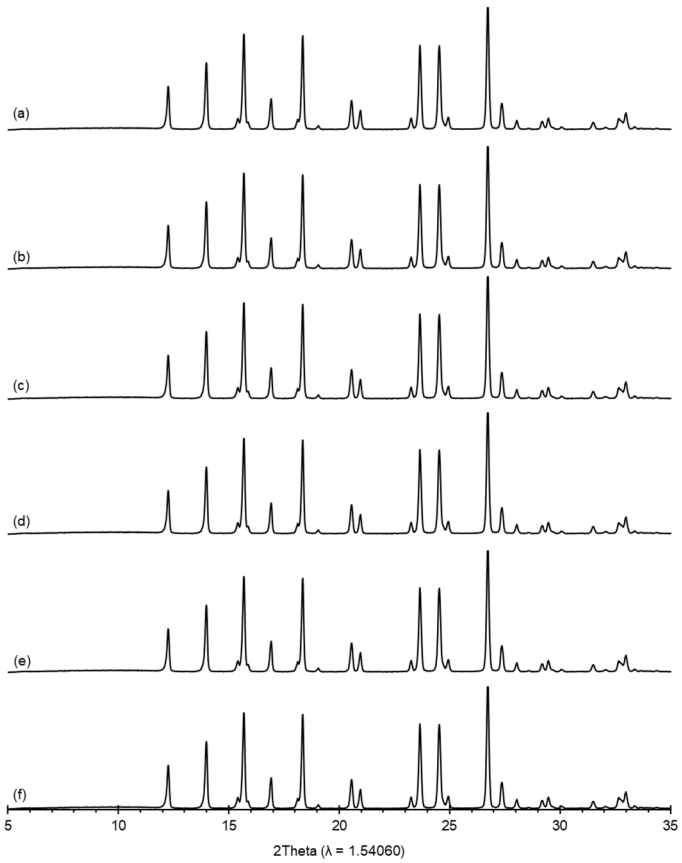

Figure S4. XRPD of crystallized paracetamol from 2-propanol in the presence of metacetamol (**a**) $X_{i,p}$ = 0.09 mol%. (**b**) $X_{i,p}$ = 0.46 mol%. (**c**) $X_{i,p}$ = 1.01 mol%. (**d**) $X_{i,p}$ = 1.62 mol%. (**e**) $X_{i,p}$ = 2.51 mol%. (**f**) $X_{i,p}$ = 6.78 mol%.

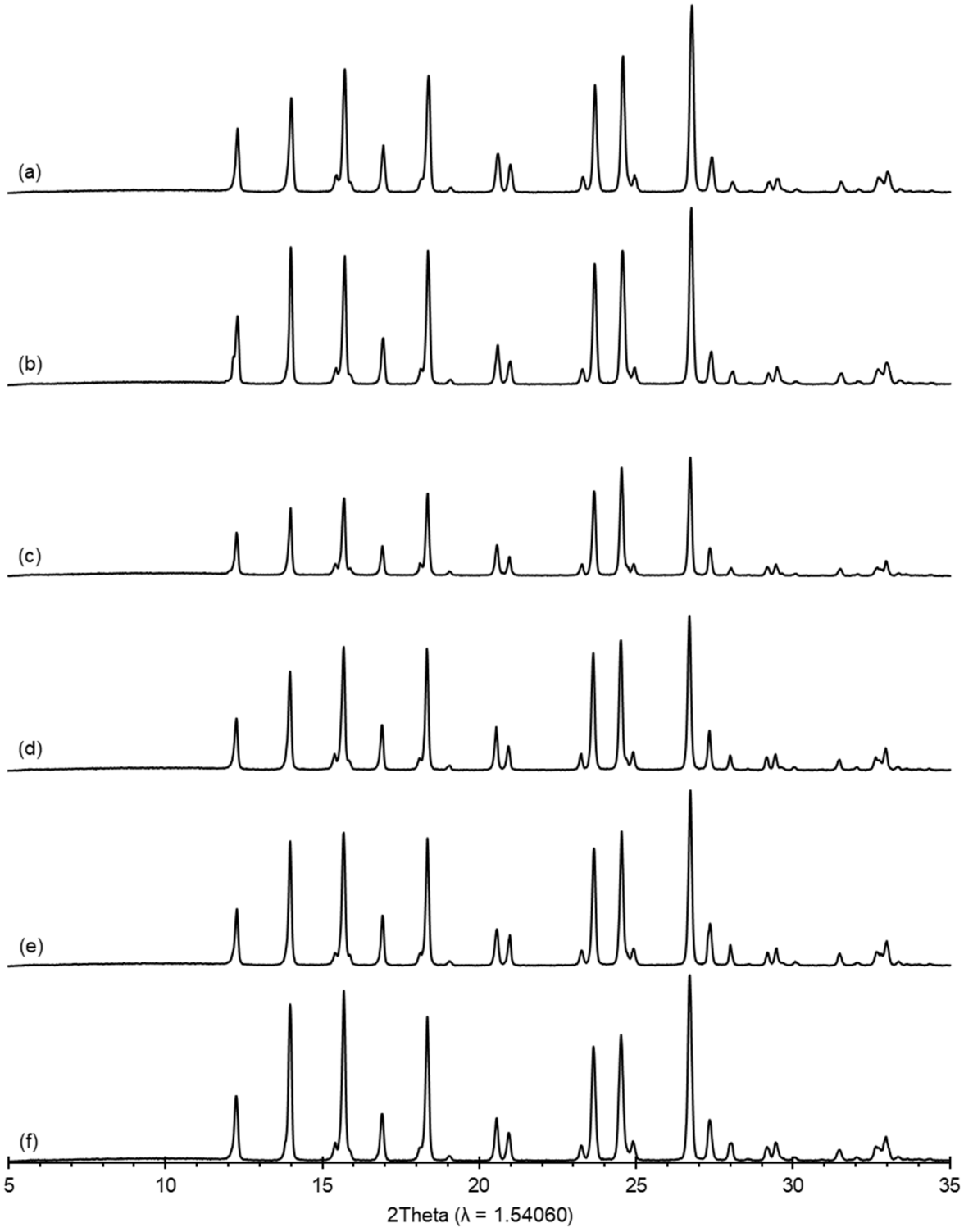

Figure S5. XRPD of crystallized paracetamol from 2-propanol in the presence of acetanilide (**a**) $X_{i,p}$ = 0.17 mol%. (**b**) $X_{i,p}$ = 0.18 mol%. (**c**) $X_{i,p}$ = 0.31 mol%. (**d**) $X_{i,p}$ = 0.43 mol%. (**e**) $X_{i,p}$ = 0.56 mol%. (**f**) $X_{i,p}$ = 0.79 mol%.

Table S2. Comparative 2Theta peak position at the maximum of the 7 most intense peaks in the XRPD patterns of paracetamol crystallized from 2-propanol in the presence of either metacetamol or acetanilide.

	Impurity	$X_{i,p}$ (mol%)	1	2	3	4	5	6	7
1	Metacetamol	0.09	26.715	24.525	20.946	20.552	18.343	13.983	12.267
2		0.46	26.741	24.556	20.969	20.571	18.362	13.996	12.277
3		1.01	26.723	24.529	20.957	20.558	18.349	13.989	12.266
4		1.62	26.735	24.544	20.971	20.561	18.361	13.989	12.274
5		2.51	26.747	24.546	20.979	20.567	18.365	14.015	12.278
6		6.78	26.783	24.554	21.025	20.566	18.398	14.061	12.278
7	Acetanilide	0.18	26.767	24.574	20.987	20.59	18.379	14.005	12.291
8		0.17	26.75	24.564	20.972	20.58	18.368	13.996	12.289
9		0.31	26.719	24.534	20.953	20.56	18.349	13.981	12.268
10		0.43	26.692	24.506	20.925	20.539	18.331	13.964	12.254
11		0.56	26.721	24.534	20.964	20.553	18.348	13.972	12.269
12		0.79	26.704	24.514	20.937	20.547	18.344	13.972	12.255

Table S3. Unit cell dimensions determined from Pawley refinements of XRPD patterns of paracetamol crystallized from 2-propanol in the presence of either metacetamol or acetanilde

	Impurity	$X_{i,p}$	a (Å)		b (Å)		c (Å)	
		(mol%)	Value	Error	Value	Error	Value	Error
1	Metacetamol	0.09	7.100114	0.000188	9.380845	0.000272	11.70634	0.00056
2		0.46	7.0923586	0.000165	9.370624	0.000242	11.69675	0.000508
3		1.01	7.0955971	0.000159	9.380633	0.000233	11.70395	0.000491
4		1.62	7.0912404	0.000224	9.375168	0.000339	11.70059	0.000731
5		2.51	7.0836917	0.000153	9.376393	0.000228	11.69263	0.000545
6		6.78	7.0596954	0.000189	9.379106	0.000279	11.67919	0.000617
7	Acetanilide	0.18	7.0870446	0.000181	9.364603	0.000261	11.68297	0.000548
8		0.17	7.0915409	0.000205	9.369529	0.000293	11.68878	0.000623
9		0.31	7.0991053	0.000175	9.378311	0.000248	11.70708	0.000523
10		0.43	7.1053511	0.000153	9.389834	0.00022	11.71763	0.000465
11		0.56	7.1010517	0.000178	9.379492	0.000271	11.705	0.000554
12		0.79	7.0998663	0.000184	9.384272	0.000281	11.7137	0.000587

4. Particle Size

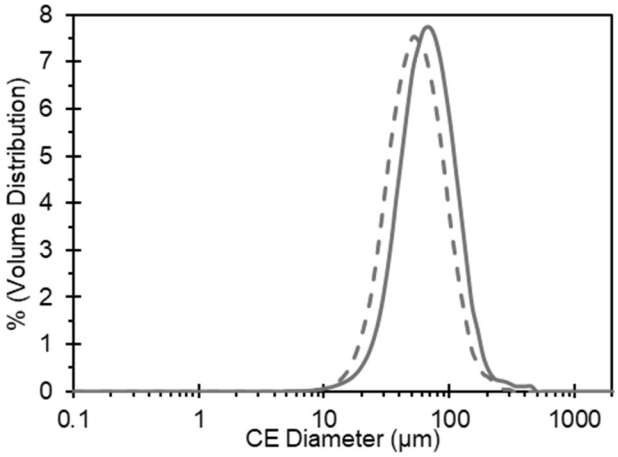

Figure S6. CE Diameter measurements of paracetamol crystals grown under the same conditions without added impurity (solid line), and the same crystals after slurry (dashed line).

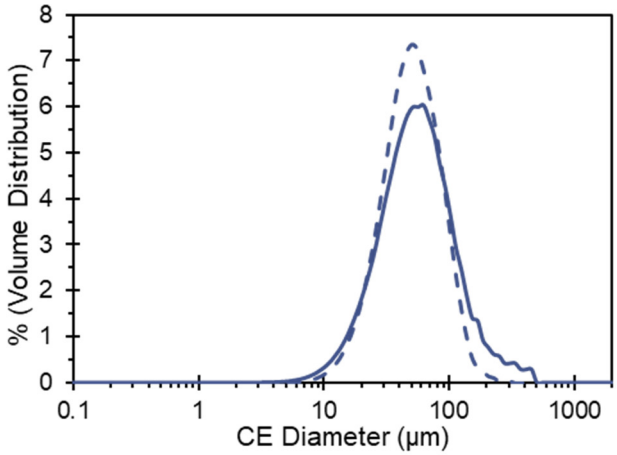

Figure S7. CE Diameter measurements of paracetamol form II crystals contaminated with 1.35 mol% metacetamol (solid line) and the stable form I product formed after slurry, contaminated with 0.81 mol% metacetamol (dashed line).

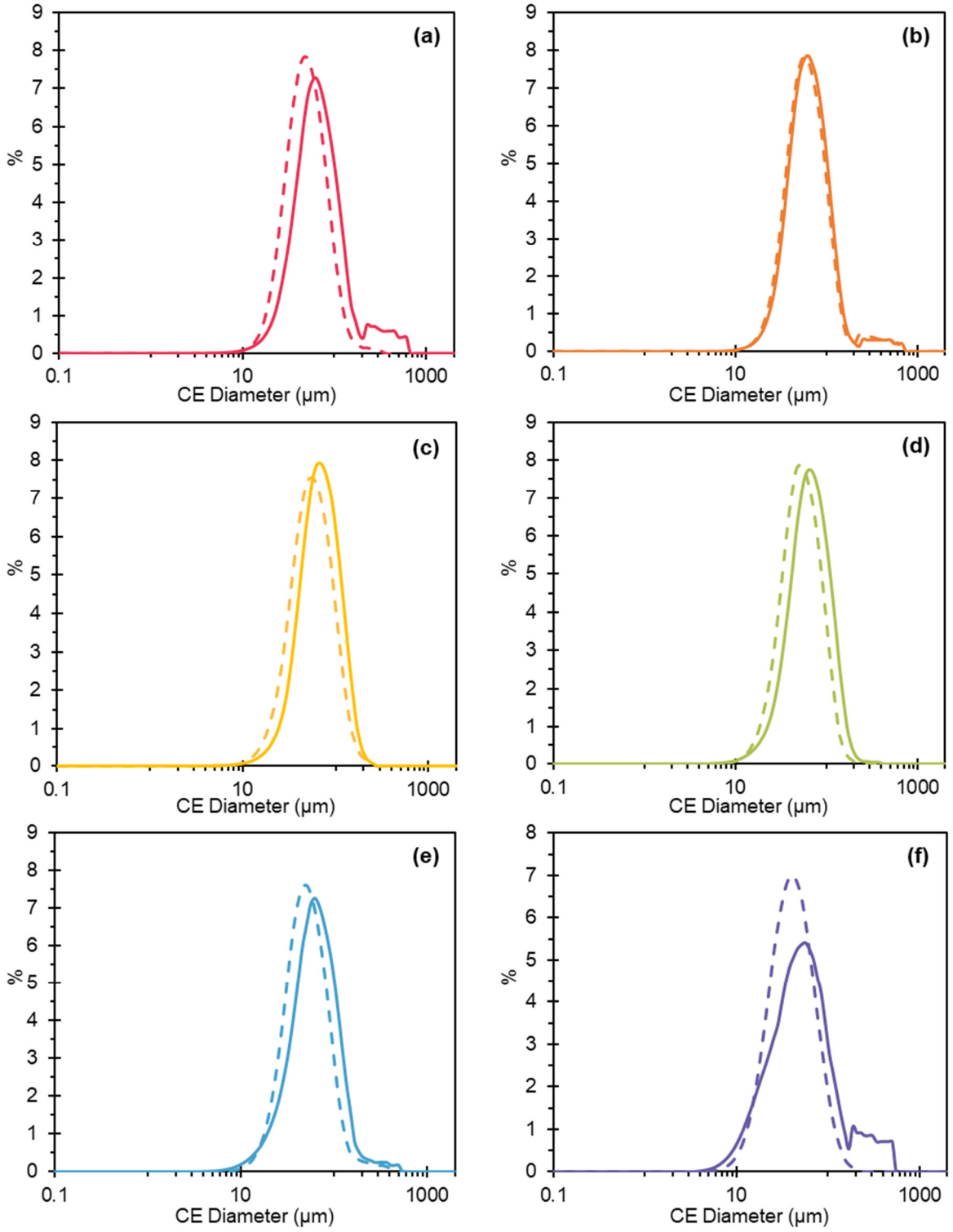

Figure S8. CE Diameter (Volume) measurements of PCM contaminated with MET after crystallizations (solid line), then after re-slurry (dashed line). (**a**) $X_{i,p}$ = 0.09 mol%; $X_{p,s}$ = 0.61 mol%. (**b**) $X_{i,p}$ = 0.46 mol%; $X_{p,s}$ = 0.96 mol%. (**c**) $X_{i,p}$ = 1.01 mol%; $X_{p,s}$ = 0.63 mol%. (**d**) $X_{i,p}$ = 1.62 mol%; $X_{p,s}$ = 0.72 mol%. (**e**) $X_{i,p}$ = 2.51 mol%; $X_{p,s}$ = 1.17 mol%. (**f**) $X_{i,p}$ = 6.78 mol%; $X_{p,s}$ = 1.54 mol%.

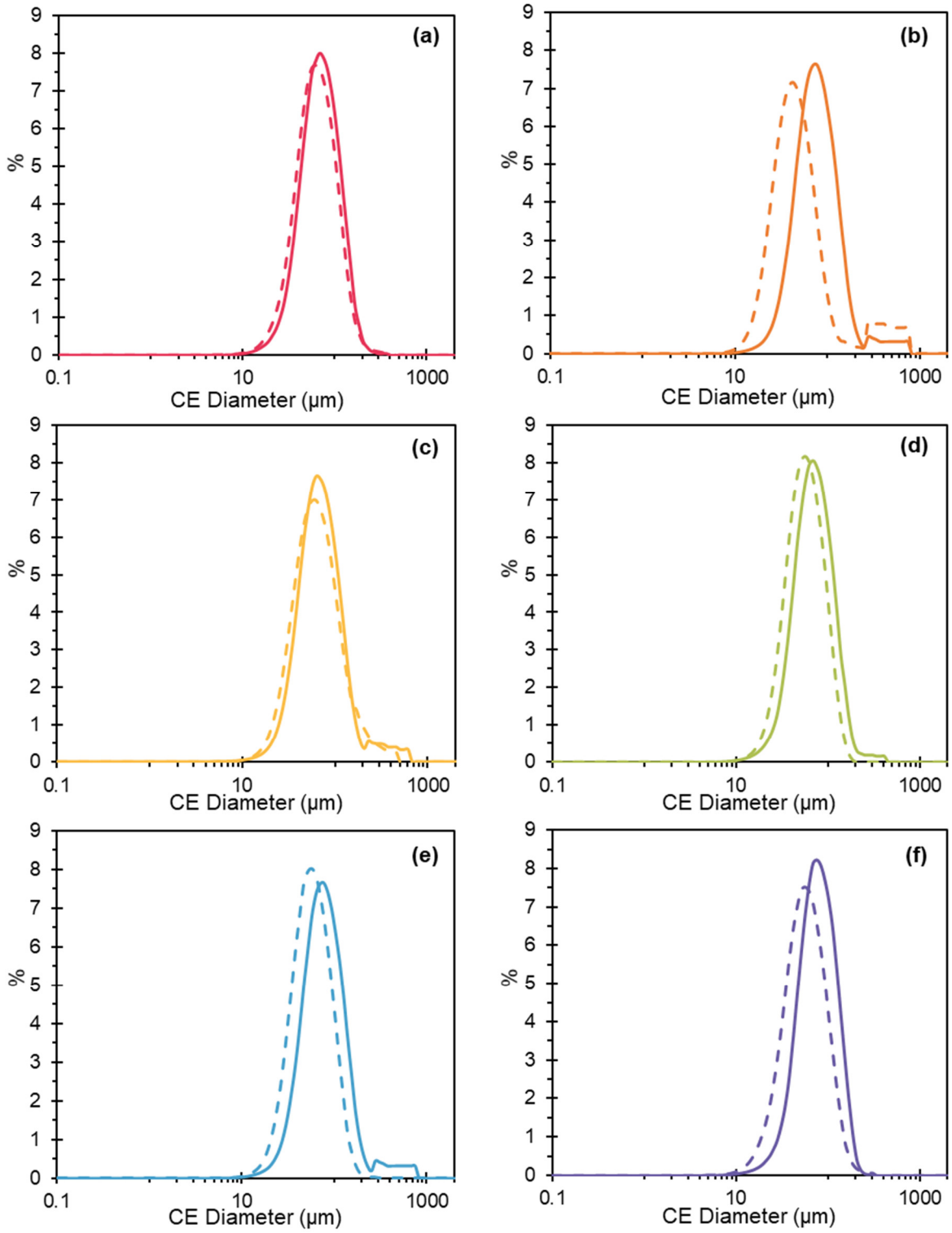

Figure S9. CE Diameter (Volume) measurements of PCM contaminated with ACE after crystallizations (solid line), then after re-slurry (dashed line) (**a**) $X_{i,p}$ = 0.17 mol%; $X_{p,s}$ = 0.09 mol%. (**b**) $X_{i,p}$ = 0.18 mol%; $X_{p,s}$ = 0.10 mol%. (**c**) $X_{i,p}$ = 0.31 mol%; $X_{p,s}$ = 0.17 mol%. (**d**) $X_{i,p}$ = 0.43 mol%; $X_{p,s}$ = 0.21 mol%. (**e**) $X_{i,p}$ = 0.56 mol%; $X_{p,s}$ = 0.23 mol%. (**f**) $X_{i,p}$ = 0.79 mol%; $X_{p,s}$ = 0.27 mol%.

Table S4. Comparative span measurements from PSD distributions of crystallization and slurry product. Span = $(D_{90}-D_{10})/D_{50}$

	Impurity	Crystallization Product					Slurry Product				
		C_{imp} (mol%)	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)	Span (µm)	Cimp (mol%)	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)	Span (µm)
1	Metacetamol	0.09	34.81	62.42	105.20	1.13	0.61	28.44	46.79	72.91	0.95
2		0.46	36.98	60.32	91.95	0.91	0.96	34.98	57.16	87.84	0.92
3		1.01	37.82	34.78	95.27	0.89	0.63	29.84	53.11	83.04	1.00
4		1.62	35.17	63.51	93.75	0.92	0.72	29.36	50.86	75.05	0.90
5		2.51	29.81	61.43	94.35	1.05	1.17	28.54	48.9	76.35	0.98
6		6.78	18.53	49.95	128.0	2.19	1.57	20.82	37.97	67.35	1.23
7	Acetanilide	0.18	43.26	72.22	113.90	0.98	0.10	25.39	42.12	94.84	1.65
8		0.17	40.50	67.29	99.83	0.88	0.09	35.00	60.68	92.21	0.94
9		0.31	38.85	64.68	101.6	0.97	0.17	33.19	57.95	112.3	1.37
10		0.43	40.94	66.89	97.91	0.85	0.21	33.23	54.05	79.32	0.85
11		0.56	40.18	69.32	99.52	0.86	0.23	32.70	53.79	80.21	0.88
12		0.79	45.17	73.87	105.4	0.82	0.27	29.89	54.21	83.66	0.99

5. Morphology

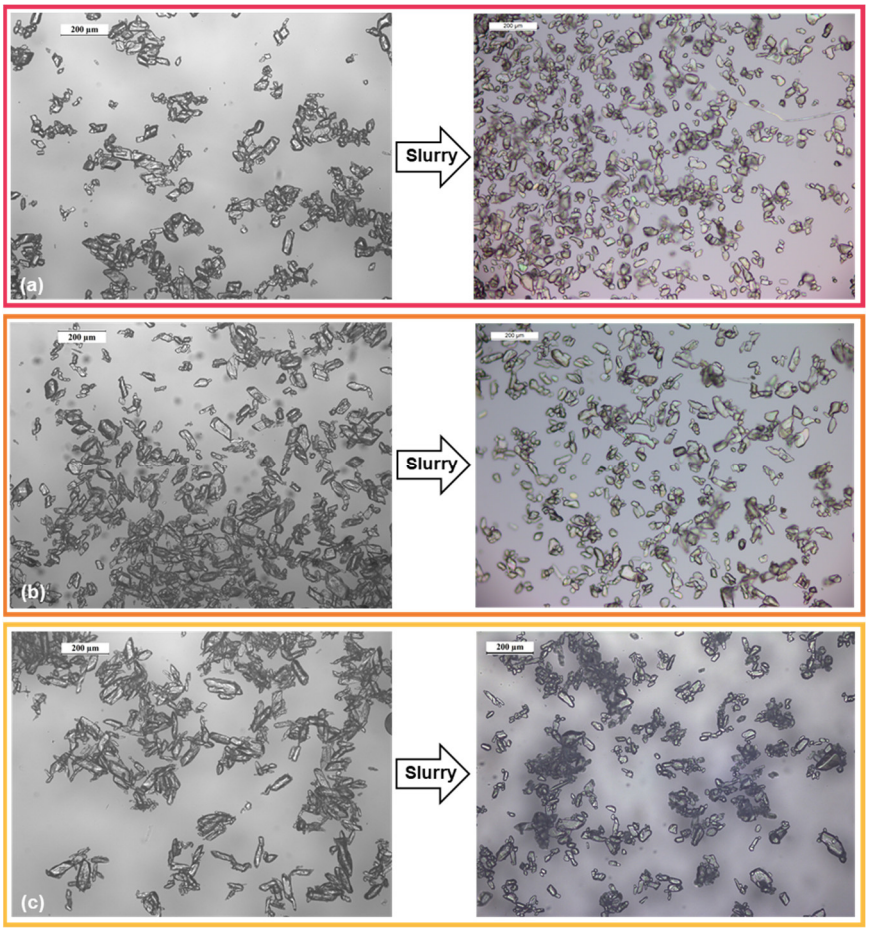

Figure S10. Microscopy images of PCM contaminated with MET after crystallizations, then after re-slurry. (**a**) $X_{i,p}$ = 0.09 mol%; $X_{p,s}$ = 0.61 mol%. (**b**) $X_{i,p}$ = 0.46 mol%; $X_{p,s}$ = 0.96 mol%. (**c**) $X_{i,p}$ = 1.01 mol%; $X_{p,s}$ = 0.63 mol%.

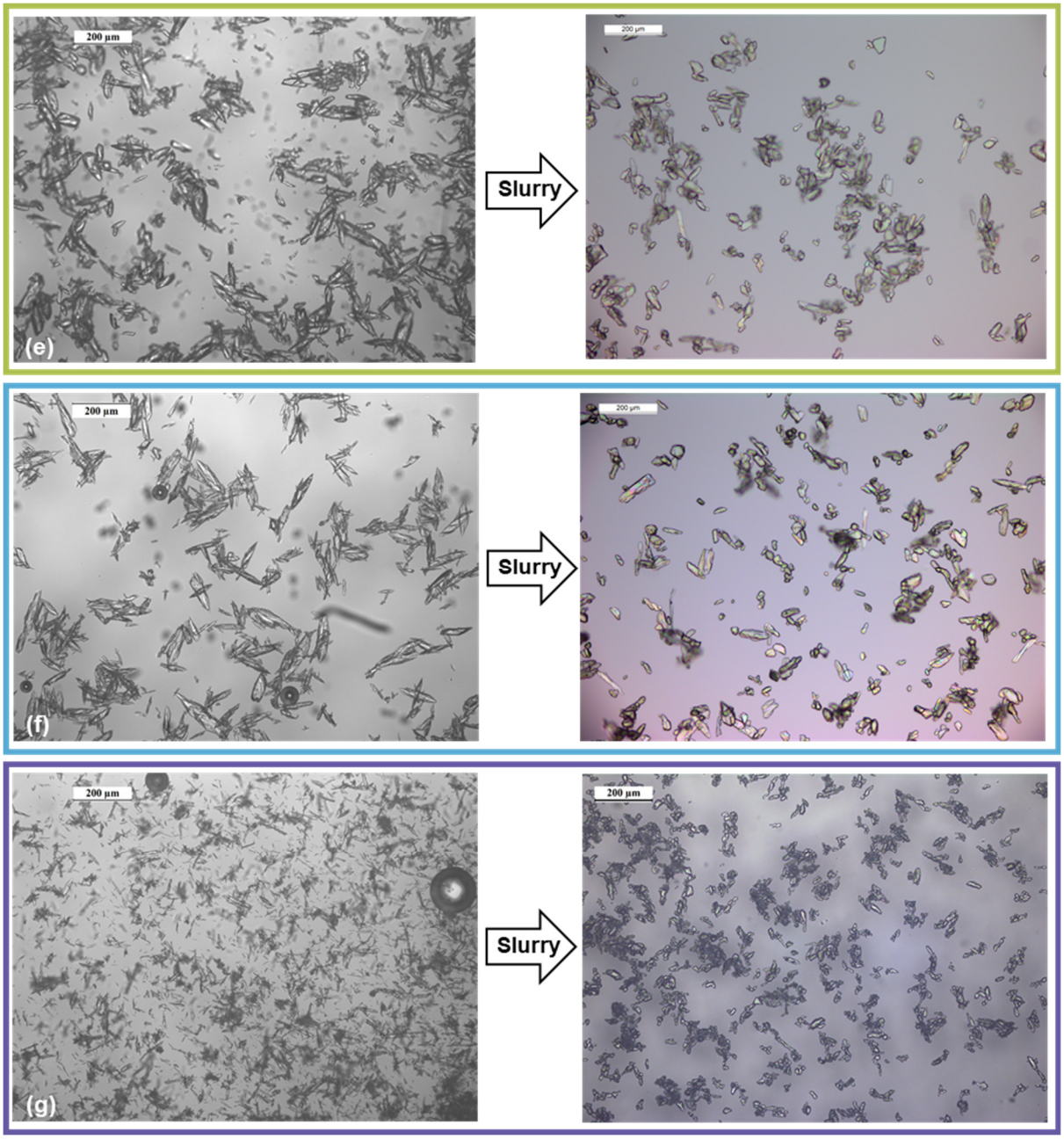

Figure S11. Microscopy images of PCM contaminated with MET after crystallizations, then after re-slurry. (**a**) $X_{i,p}$ = 1.62 mol%; $X_{p,s}$ = 0.72 mol%. (**b**) $X_{i,p}$ = 2.51 mol%; $X_{p,s}$ = 1.17 mol%. (**c**) $X_{i,p}$ = 6.78 mol%; $X_{p,s}$ = 1.54 mol%.

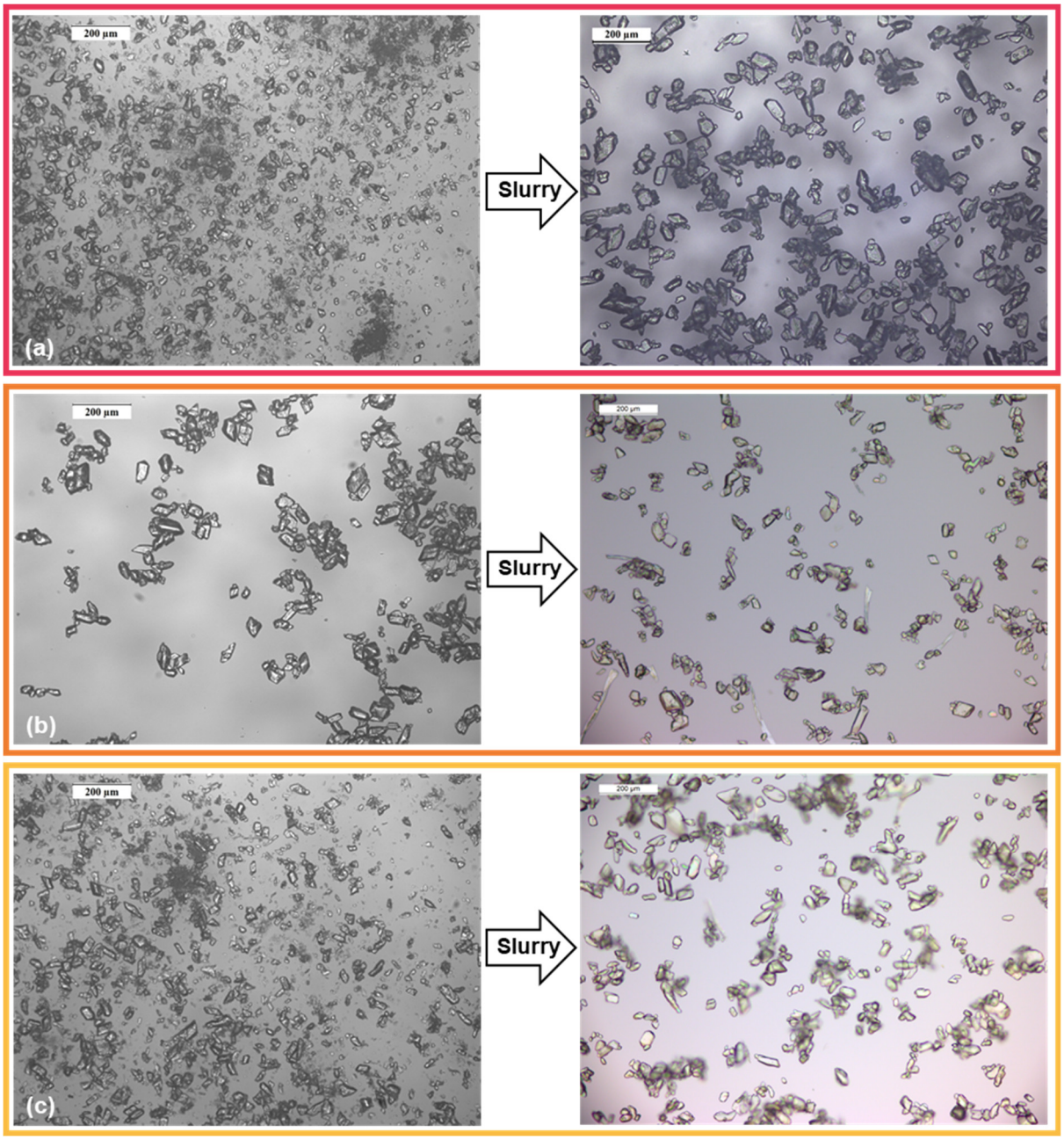

Figure S12. Microscopy images of PCM contaminated with ACE after crystallizations, then after re-slurry. (**a**) $X_{i,p}$ = 0.17 mol%; $X_{p,s}$ = 0.09 mol%. (**b**) $X_{i,p}$ = 0.18 mol%; $X_{p,s}$ = 0.10 mol%. (**c**) $X_{i,p}$ = 0.31 mol%; $X_{p,s}$ = 0.17 mol%.

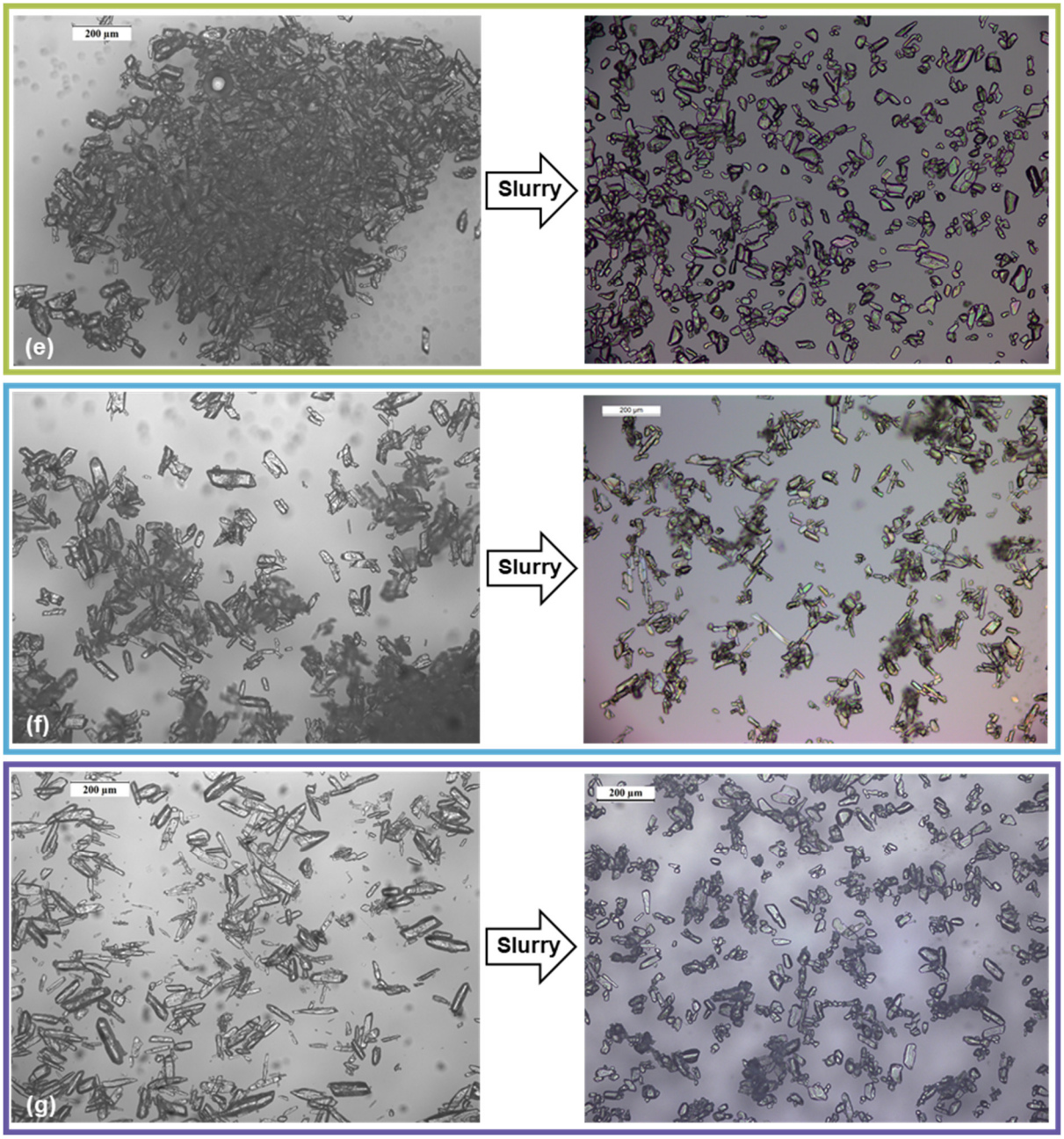

Figure S13. Microscopy images of PCM contaminated with ACE after crystallizations, then after re-slurry. (**a**) $X_{i,p}$ = 0.43 mol%; $X_{p,s}$ slurry = 0.21 mol%. (**b**) $X_{i,p}$ = 0.56 mol%; $X_{p,s}$ = 0.23 mol%. (**c**) $X_{i,p}$ = 0.79 mol%; $X_{p,s}$ = 0.27 mol%.

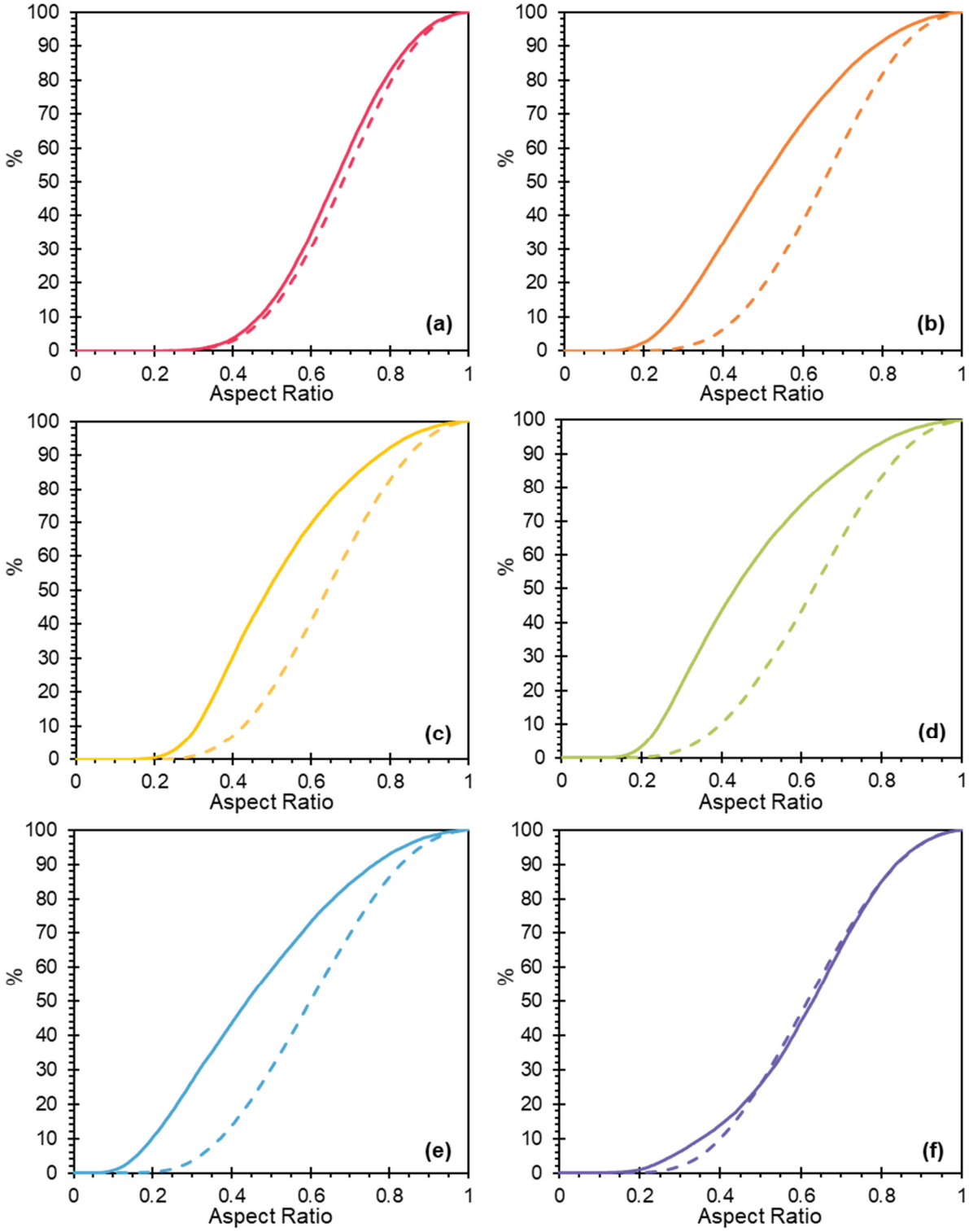

Figure S14. Elongation measurements (Malvern Morphologi G3) of PCM contaminated with MET after crystallizations (solid line), then after re-slurry (dashed line). (**a**) $X_{i,p}$ = 0.09 mol%; $X_{p,s}$ = 0.61 mol%. (**b**) $X_{i,p}$ = 0.46 mol%; $X_{p,s}$ = 0.96 mol%. (**c**) $X_{i,p}$ = 1.01 mol%; $X_{p,s}$ = 0.63 mol%. (**d**) $X_{i,p}$ = 1.62 mol%; $X_{p,s}$ = 0.72 mol%. (**e**) $X_{i,p}$ = 2.51 mol%; $X_{p,s}$ = 1.17 mol%. (**f**) $X_{i,p}$ = 6.78 mol%; $X_{p,s}$ = 1.54 mol%.

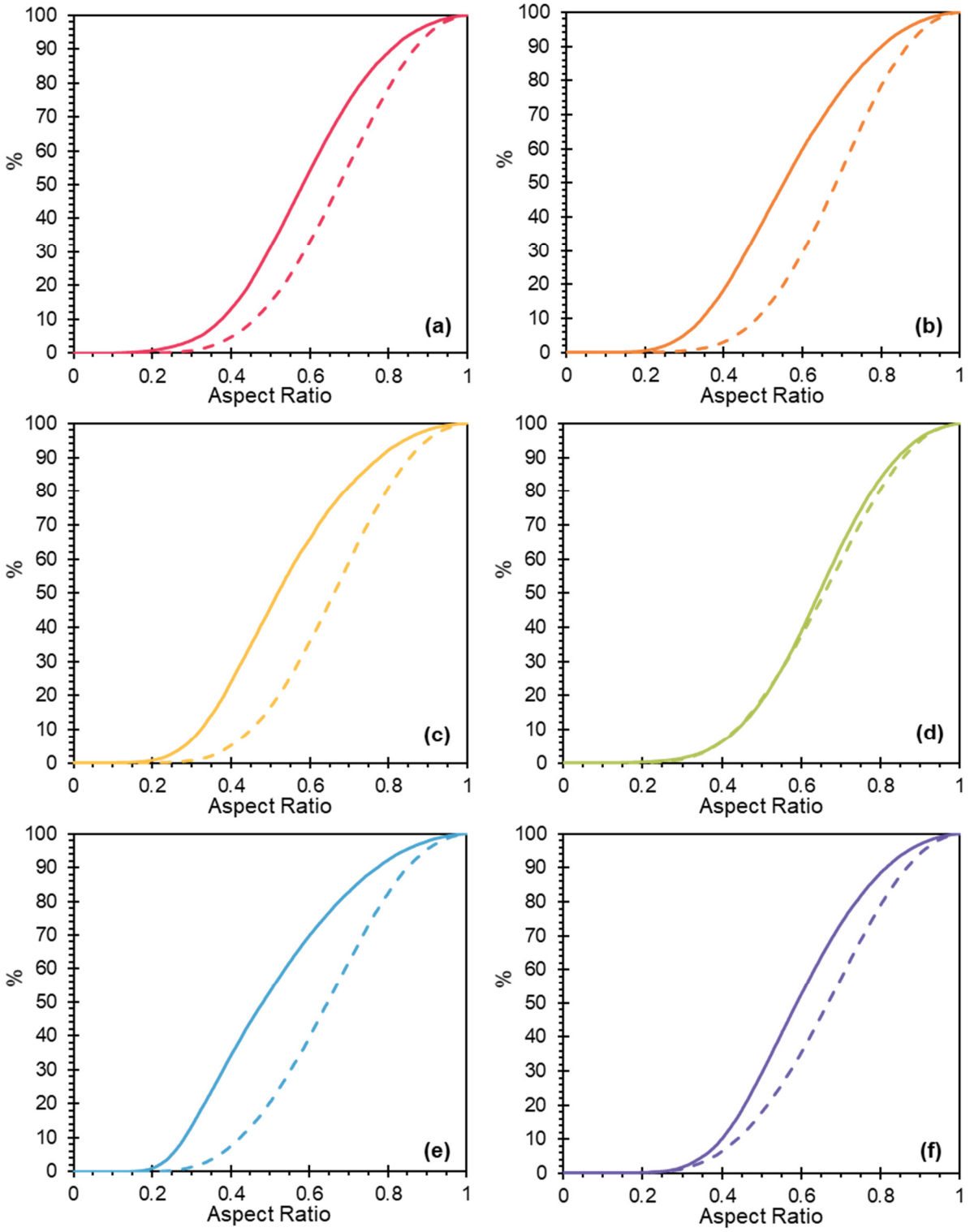

Figure S15. Elongation measurements (Malvern Morphologi G3) of PCM contaminated with ACE after crystallizations (solid line), then after re-slurry (dashed line). (**a**) $X_{i,p}$ = 0.17 mol%; $X_{p,s}$ = 0.09 mol%. (**b**) $X_{i,p}$ = 0.18 mol%; $X_{p,s}$ = 0.10 mol%. (**c**) $X_{i,p}$ = 0.31 mol%; $X_{p,s}$ = 0.17 mol%. (**d**) $X_{i,p}$ = 0.43 mol%; $X_{p,s}$ = 0.21 mol%. (**e**) $X_{i,p}$ = 0.56 mol%; $X_{p,s}$ = 0.23 mol%. (**f**) $X_{i,p}$ = 0.79 mol%; $X_{p,s}$ = 0.27 mol%.