Determination of composition distributions of multi-particle crystalline samples by sequential dissolution with concomitant particle sizing and solution analysis

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SUPPLEMENTARY INFORMATION

Contents

Synthesis of *N*-(2-nitro-4-trifluoromethylphenyl)pivalamide 4

N-(2-nitro-4-trifluoromethylphenyl)pivalamide **4** was prepared by heating a mixture of 2-nitro-4-trifluoromethylaniline (1.0 g, 4.852 mmol), trimethylacetic anhydride (1.5 mL, 7.390 mmol), and two drops of sulphuric acid to 80 °C for 3 hours. The resulting solution was allowed to cool to room temperature with the formation of yellow plate-like crystals. Water (10 mL) was added to the reaction mixture, and with manual stirring further solid precipitated out of solution. The crude product was isolated by vacuum filtration, washed with two 10 mL portions of water and air dried. The crude product was purified by recrystallization with 20 mL of ethanol, isolated by vacuum filtration, washed with a further 10 mL of ice-cold ethanol and air dried. Yield 0.462 g (33 %) of a yellow crystalline solid. M.p. 92 - 94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.89 (1H, s, N*H*), 9.05 (1H, d, $^{3}J_{HH}$ = 9 Hz, H6), 8.52 (1H, d, $^{4}J_{HH}$ = 2 Hz, H3), 7.87 (1H, dd, $^{3}J_{HH}$ = 9, $^{4}J_{HH}$ = 2 Hz, H5), 1.37 (s, 9H, 3 × CH_3) ppm; ^{13}C{^{1}H} NMR (DEPTQ-135) (75 MHz, $CDCl_3$): δ 178.17 (s, *C*=O), 138.37 (s, C1), 135.54 (s, C2), 132.43 (q, $^{3}J_{CF}$ = 3.3 Hz, C5), 124.86 (q, $^{2}J_{CF}$ = 34.6 Hz, C4), 123.77 (q, $^{1}J_{CF}$ = 272.1 Hz, *C*F_3), 123.51 (q, $^{3}J_{CF}$ = 4.1 Hz, C3), 122.67 (s, C6), 40.91 (s, *C*$(CH_3)_3$), 27.43 (s, 3 × *C*H_3) ppm; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ -62.65 (s, C*F*$_3$) ppm. ESI-MS (CH_3CN): 291.2 positive mode [M + H^+, calc. 291.10 for $C_{12}H_{14}N_2F_3O_3$]; 292.2 positive mode [M + H^+ + 1, calc. 292.10 for $C_{12}H_{14}N_2F_3O_3$]; 289.2 negative mode [M - H, calc. 289.08 for $C_{12}H_{12}N_2F_3O_3$]; 290.3 negative mode [M - H + 1, calc. 290.09 for $C_{12}H_{12}N_2F_3O_3$] R_f (1:7 ethyl acetate:hexane on silica gel) = 0.55.

[^{1}H (300 MHz), ^{13}C{^{1}H} (75 MHz), and ^{19}F{^{1}H} NMR (282 MHz) spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were prepared in acetonitrile.]

NMR

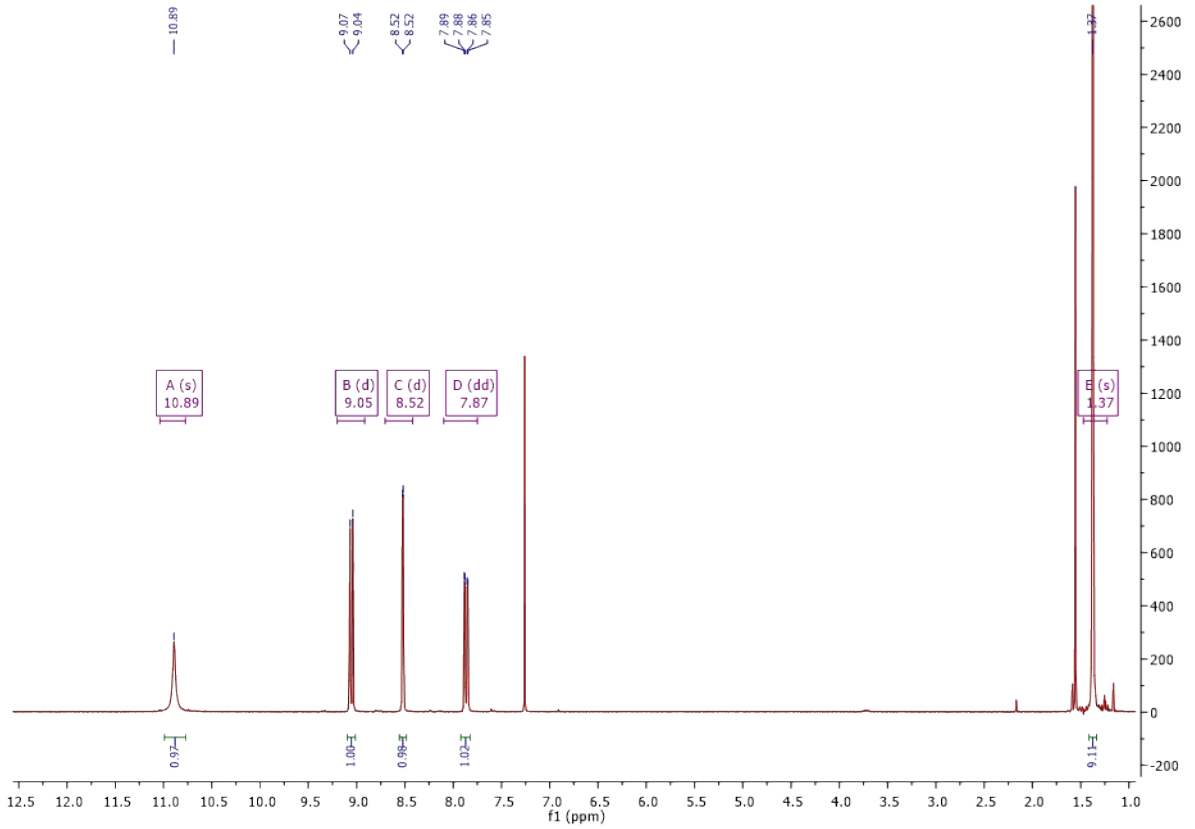

Figure S1. ^{1}H NMR spectrum of **4** in $CDCl_3$.

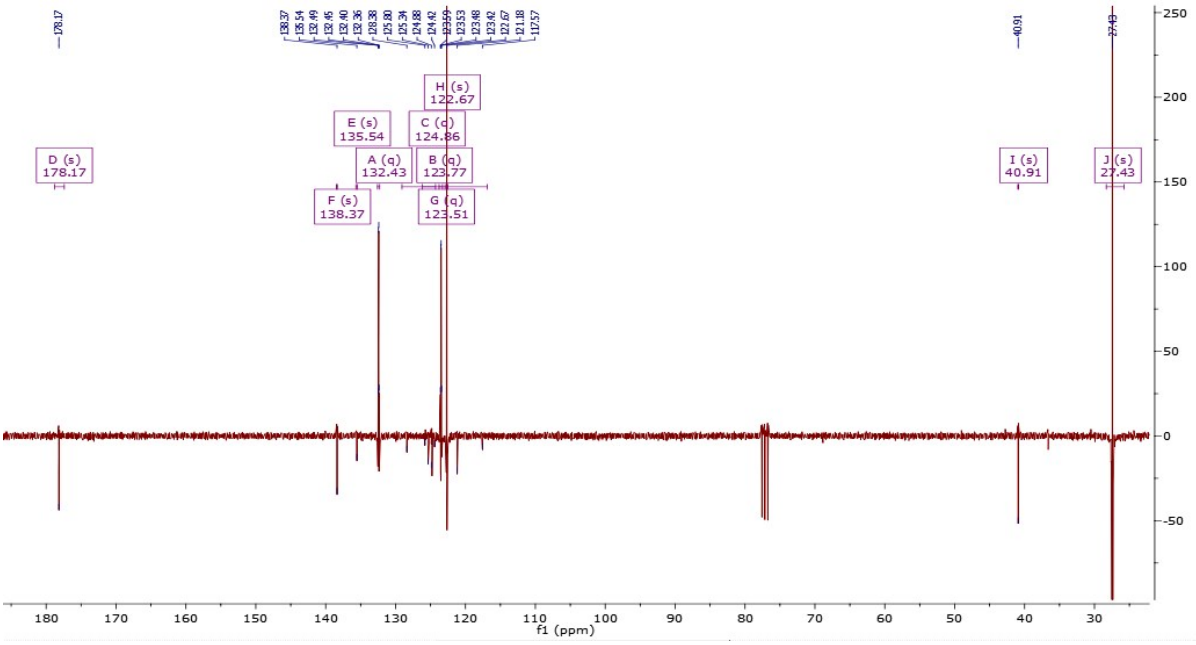

Figure S2. ^{13}C NMR $\{^{1}H\}$ (DEPTQ-135) spectrum of **4** in $CDCl_3$. CH and CH_3 signals are positive, all other signals are negative.

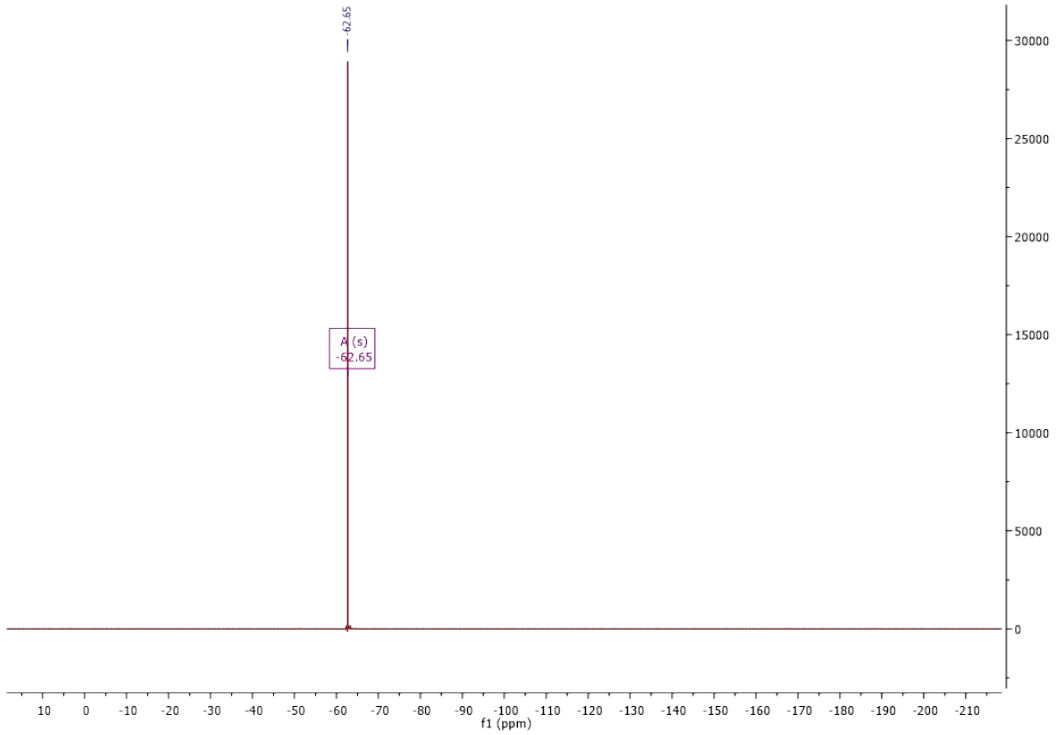

Figure S3. ^{19}F NMR $\{^{1}H\}$ spectrum of **4** in $CDCl_3$.

HPLC Calibration Data

General Calibration Setting

Calib. Data Modified : 21-Jun-17 12:24:13 PM
Signals calculated separately : No
Rel. Reference Window : 5.000 %
Abs. Reference Window : 0.000 min
Rel. Non-ref. Window : 5.000 %

Abs. Non-ref. Window : 0.000 min
Uncalibrated Peaks : not reported
Partial Calibration : Yes, identified peaks are recalibrated
Correct All Ret. Times: No, only for identified peaks
Curve Type : Linear
Origin : Forced
Weight : Equal
Recalibration Settings:
Average Response : Average all calibrations
Average Retention Time: Floating Average New 75%

Signal Details

Signal 1: DAD1 A, Sig=234,4 Ref=360,100

Overview Table

RT	Sig	Lvl	Amount [ng/ul]	Area	Rsp.Factor	Ref	ISTD	#	Compound
5.059	1	1	1.03000	47.69269	2.15966e-2	No	No	**2**	
		2	2.57500	120.68970	2.13357e-2				
		3	5.15000	246.91501	2.08574e-2				
		4	10.30000	497.15610	2.07178e-2				
		5	25.75000	1238.43115	2.07924e-2				
		6	51.50000	2416.96289	2.13077e-2				
		7	103.00000	4937.32324	2.08615e-2				
6.990	1	1	9.80000e-1	50.16642	1.95350e-2	No	No	**3**	
		2	2.45000	125.26588	1.95584e-2				
		3	4.90000	257.21909	1.90499e-2				
		4	9.80000	518.87018	1.88872e-2				
		5	24.50000	1292.15259	1.89606e-2				
		6	49.00000	2516.06958	1.94748e-2				
		7	98.00000	5164.98242	1.89739e-2				
12.732	1	1	1.02000	48.12077	2.11967e-2	No	No	**1**	
		2	2.55000	113.33391	2.24999e-2				
		3	5.10000	230.78233	2.20987e-2				
		4	10.20000	465.83960	2.18959e-2				
		5	25.50000	1158.93127	2.20030e-2				
		6	51.00000	2261.68774	2.25495e-2				
		7	102.00000	4634.19922	2.20103e-2				
23.282	1	1	1.02000	34.24325	2.97869e-2	No	No	**4**	
		2	2.55000	86.07143	2.96266e-2				
		3	5.10000	175.30609	2.90920e-2				
		4	10.20000	354.45395	2.87767e-2				
		5	25.50000	883.34070	2.88677e-2				

6	51.00000	1717.42346	2.96956e-2
7	102.00000	3517.49609	2.89979e-2

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Calibration Curves

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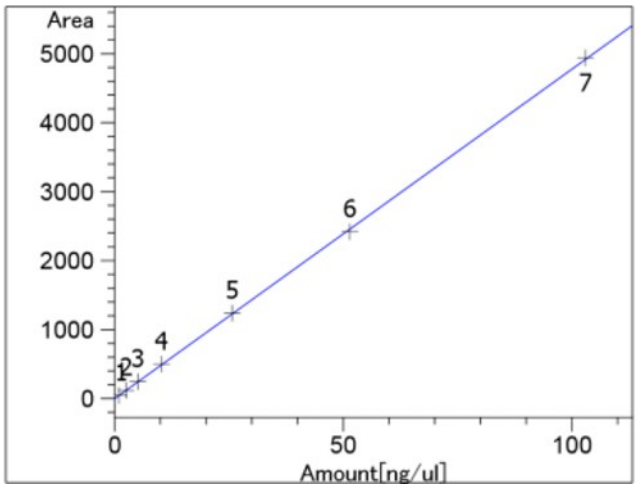

2 at exp. RT: 5.070
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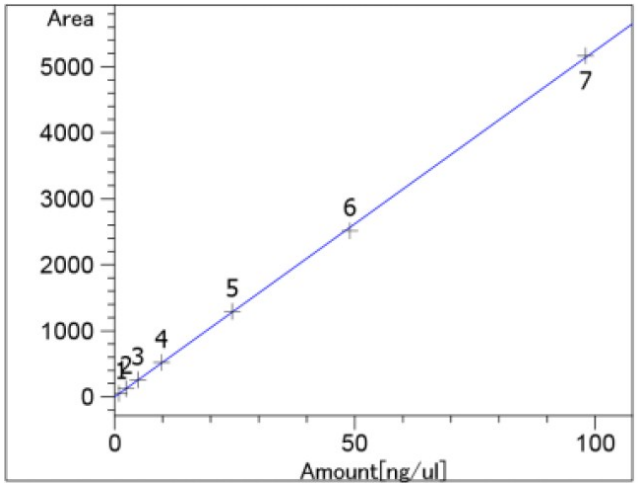
Correlation: 0.99996
Residual Std. Dev.: 19.39276
Formula: y = mx
m: 47.75528
x: Amount[ng/ul]
y: Area



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Residual Std. Dev.: 24.56110
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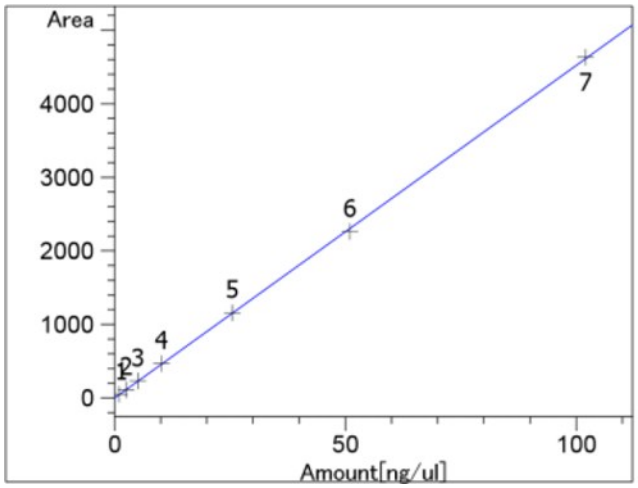
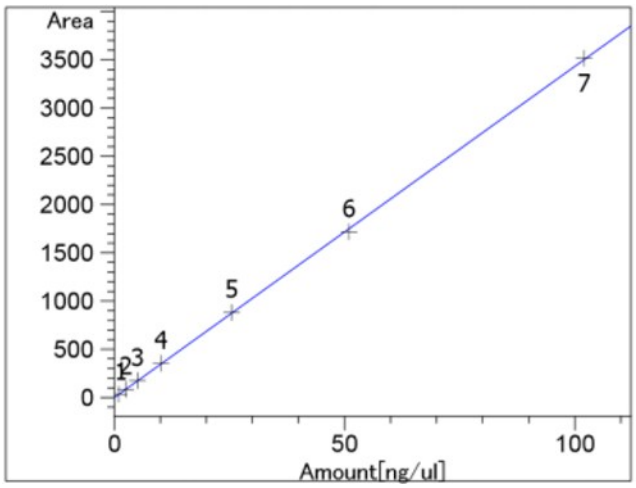
y: Area



1 at exp. RT: 12.745
DAD1 A, Sig=234,4 Ref=360,100
Correlation: 0.99996
Residual Std. Dev.: 20.48602
Formula: y = mx
m: 45.23025
x: Amount[ng/ul]
y: Area



4 at exp. RT: 23.275
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Correlation: 0.99996
Residual Std. Dev.: 15.54065
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x: Amount[ng/ul]
y: Area

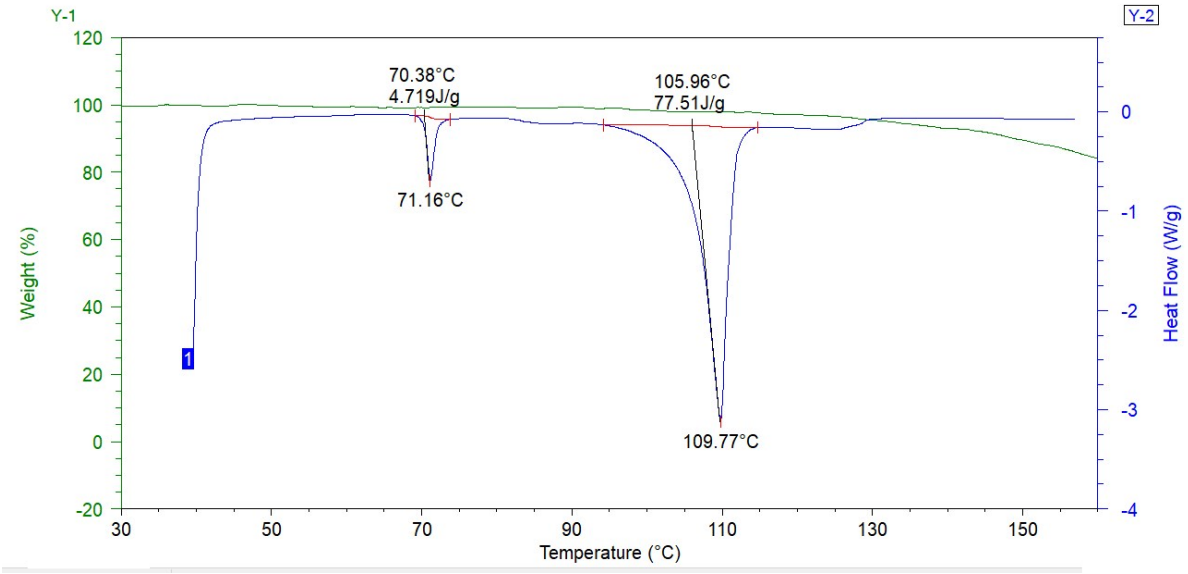

Figure S4. TGA curve overlaid the DSC curve for **1** doped with 8 mol % of **4**.

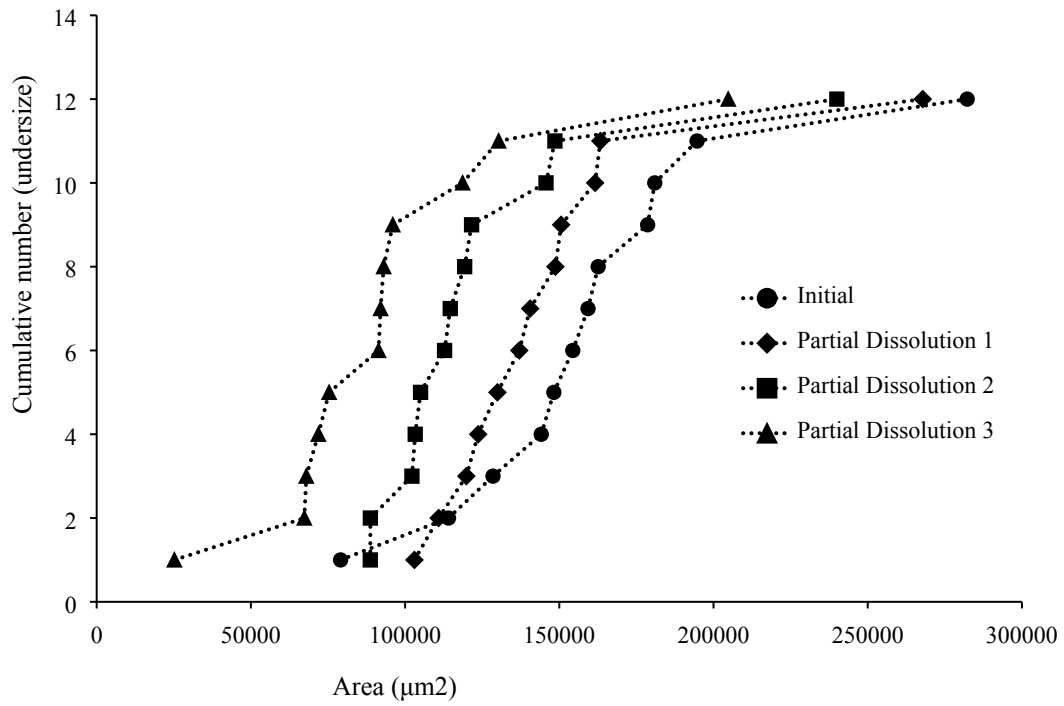

Figure S5. Chart comparing particle area versus the ranking of each particle in a partial dissolution series of **1** doped with 0.5 mol % of **2**.

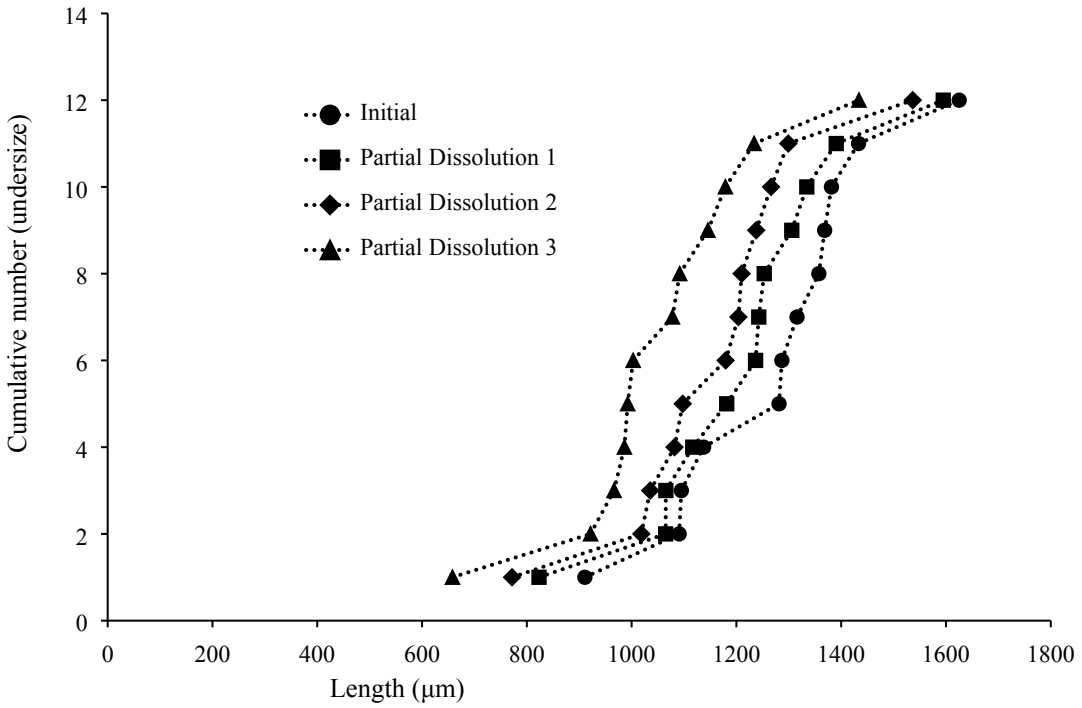

Figure S6. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 0.5 mol % of **2**.

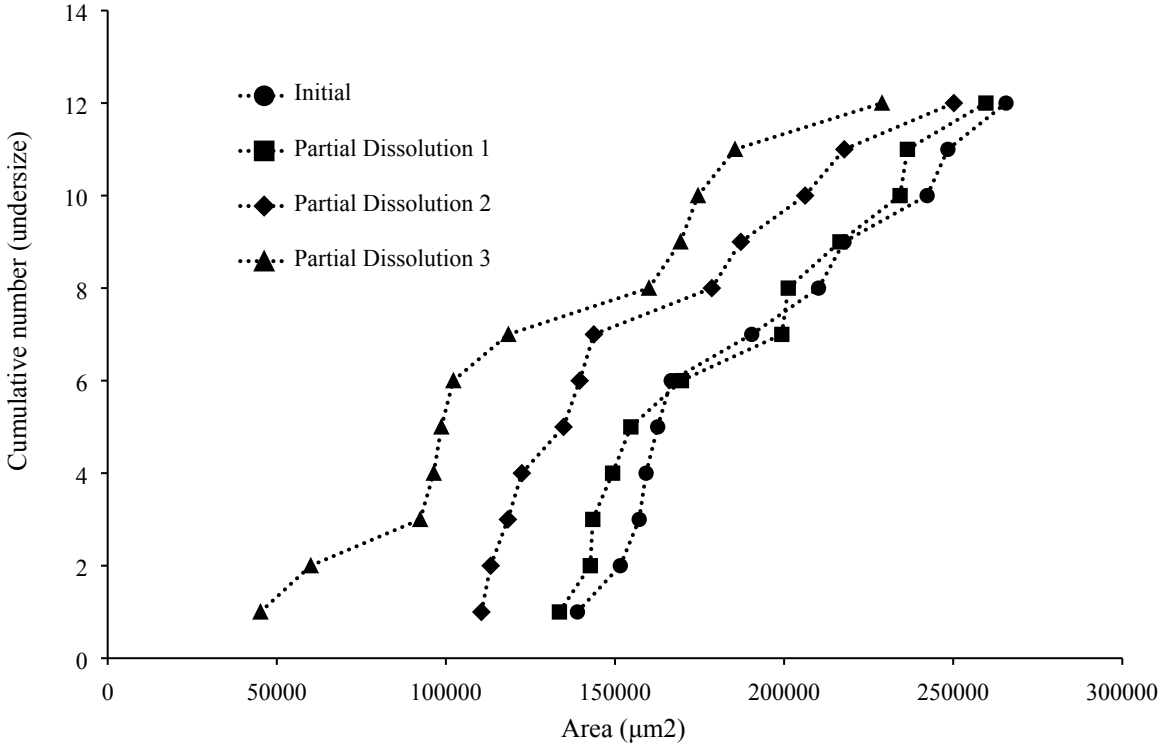

Figure S7. Chart comparing particle area versus the ranking of each particle in a partial dissolution series of **1** doped with 1.0 mol % of **2**.

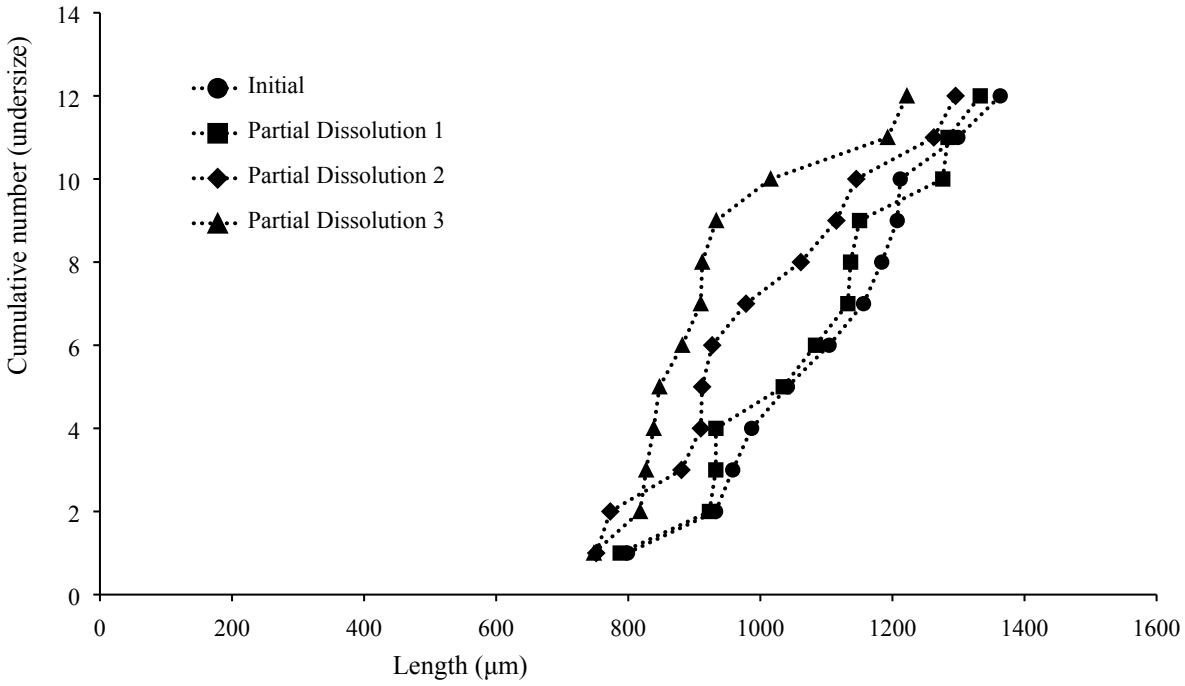

Figure S8. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 1.0 mol % of **2**.

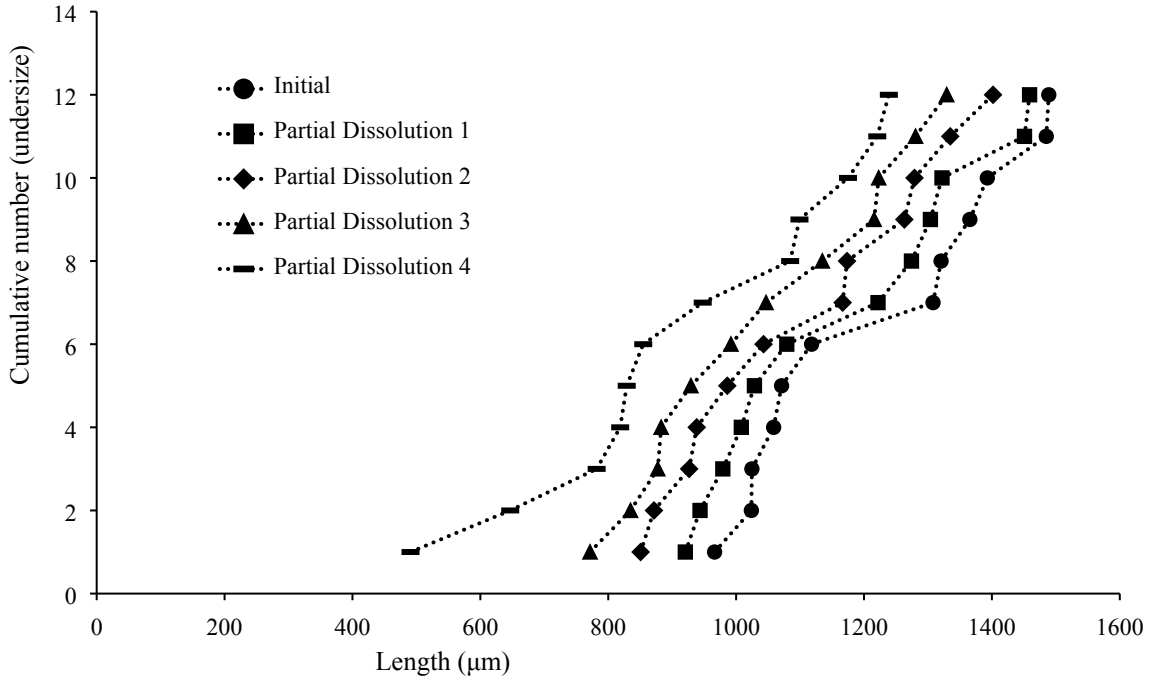

Figure S9. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 1.5 mol % of **2**.

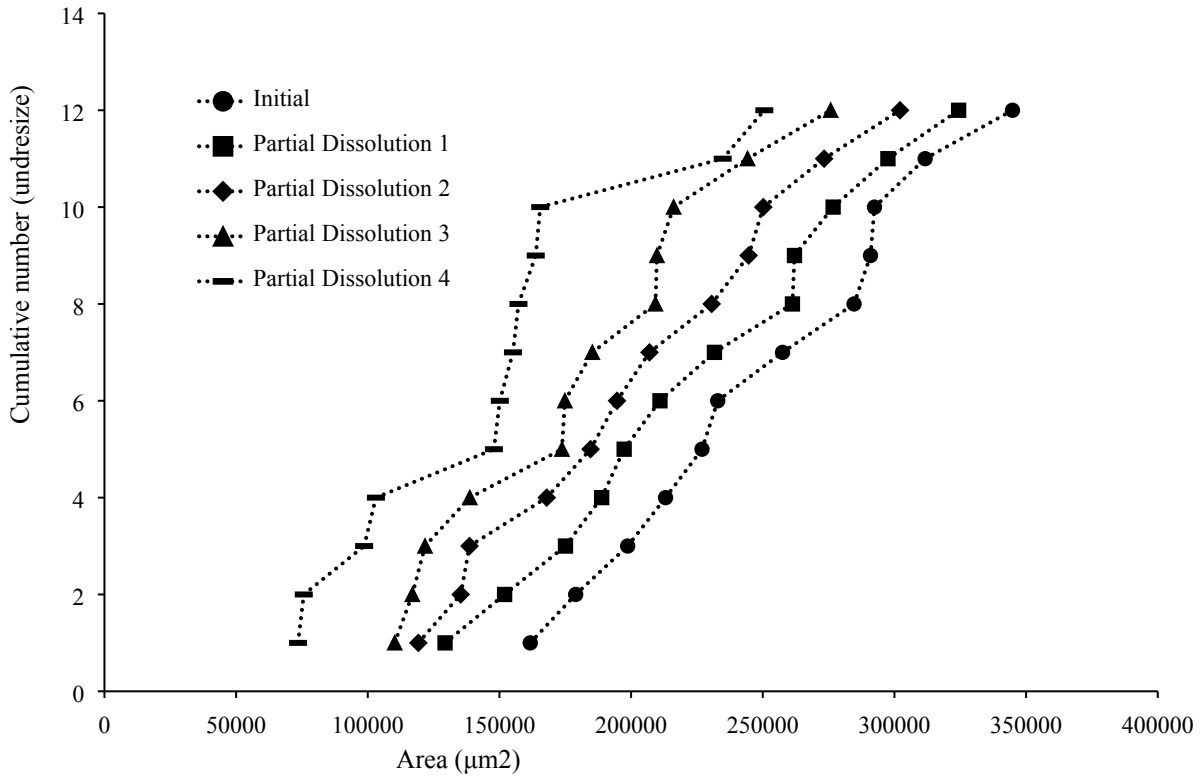

Figure S10. Chart comparing particle area versus the ranking of each particle in a partial dissolution series of **1** doped with 2.0 mol % of **2**.

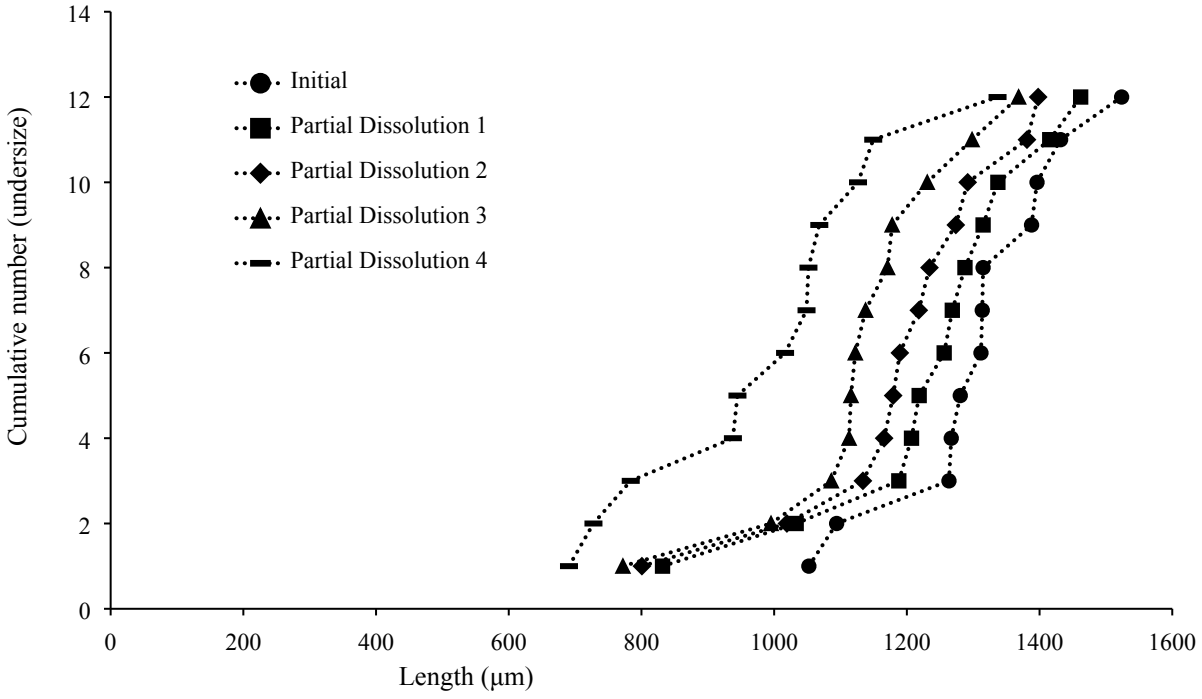

Figure S11. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 2.0 mol % of **2**.

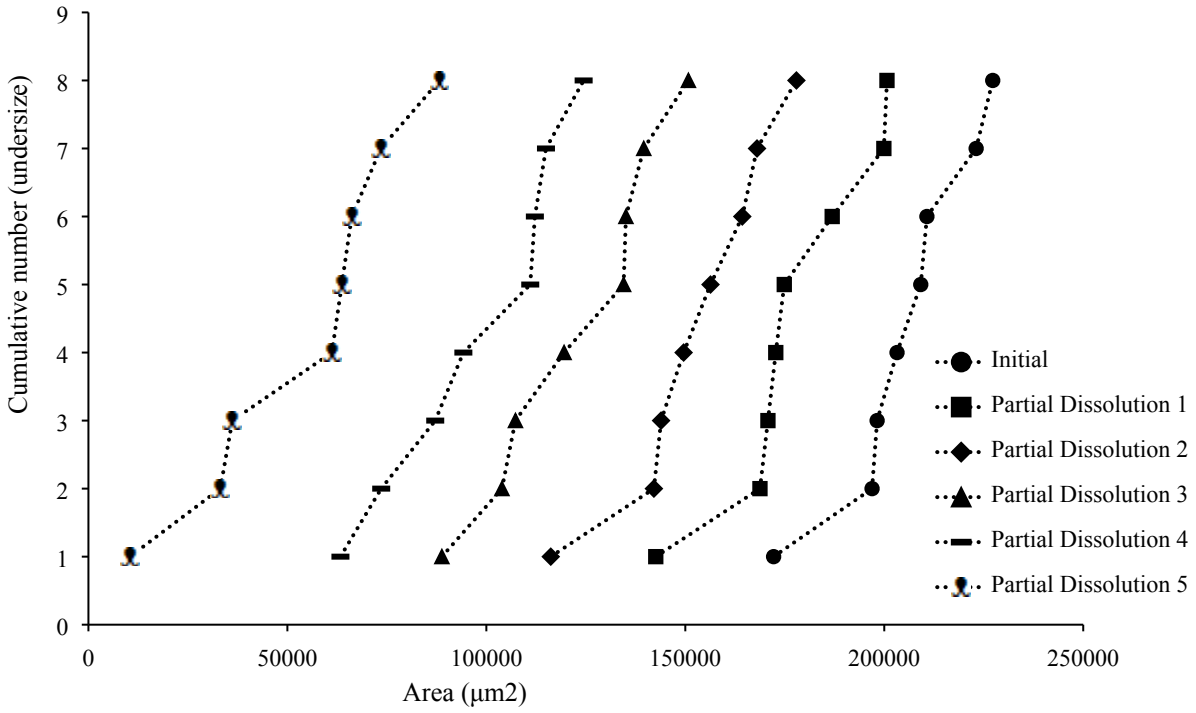

Figure S12. Chart comparing particle area versus the ranking of each particle in a partial dissolution series of **1** doped with 2.5 mol % of **2**.

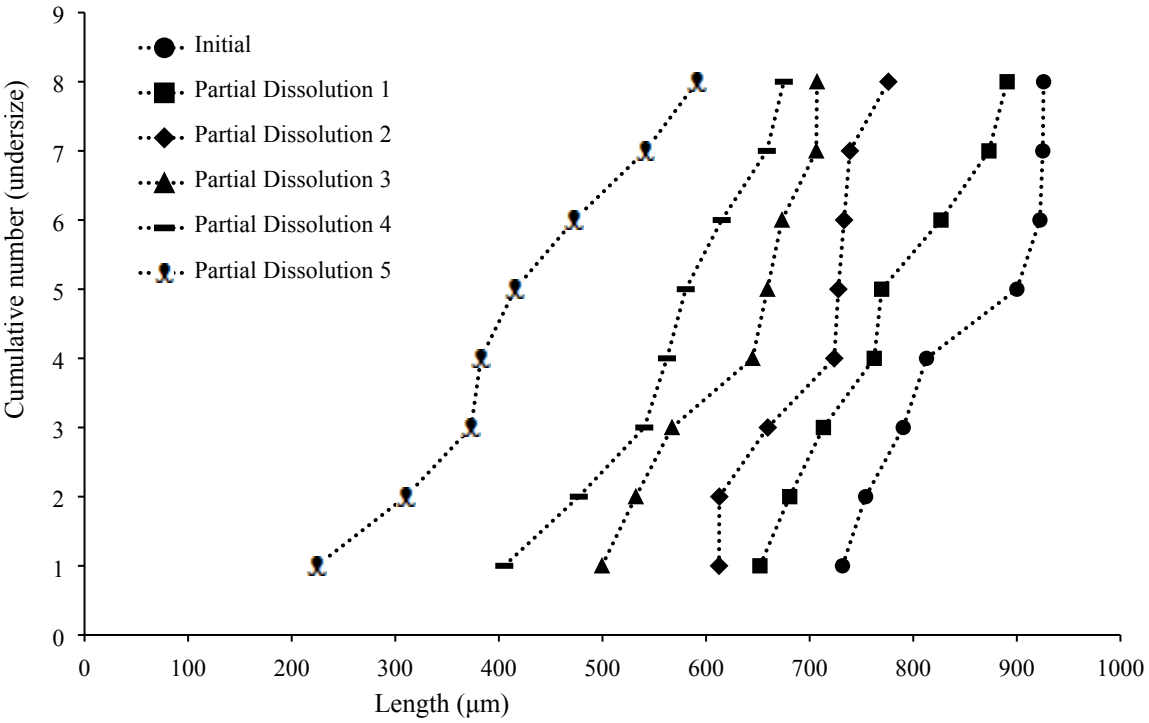

Figure S13. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 2.5 mol % of **2**.

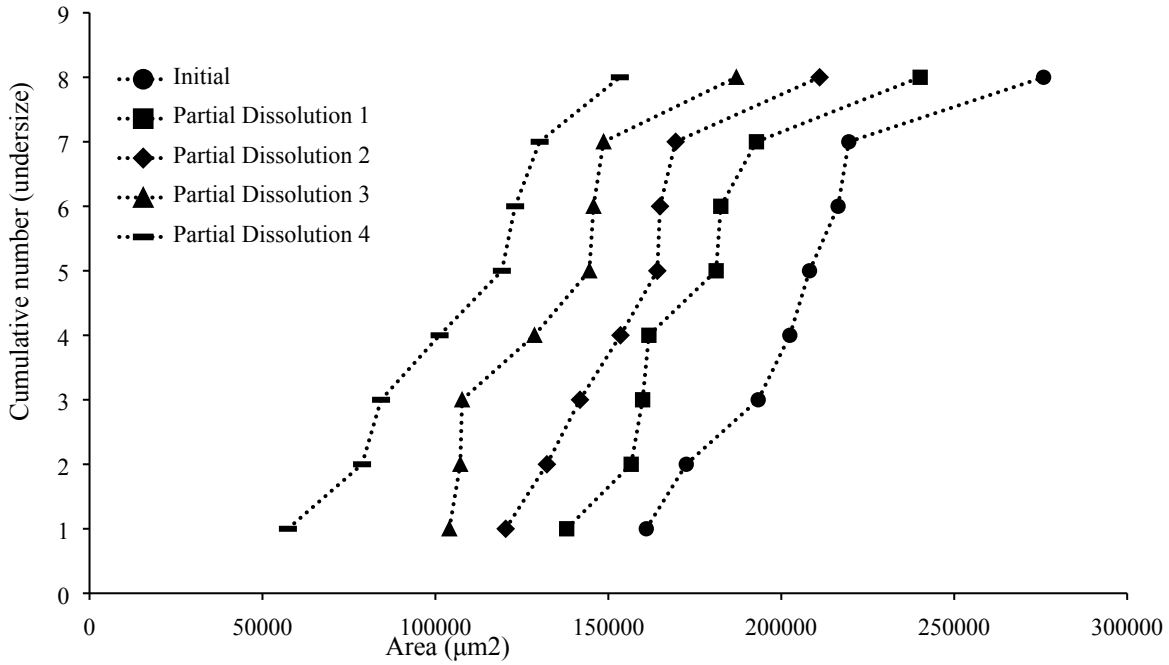

Figure S14. Chart comparing particle area versus the ranking of each particle in a partial dissolution series of **1** doped with 3.0 mol % of **2**.

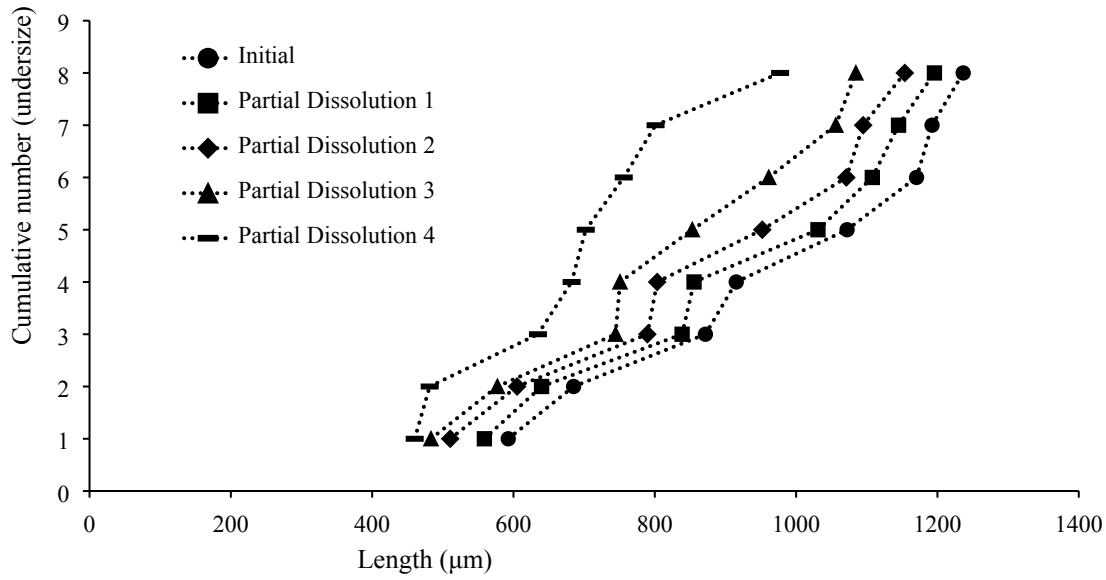

Figure S15. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 3.0 mol % of **2**.

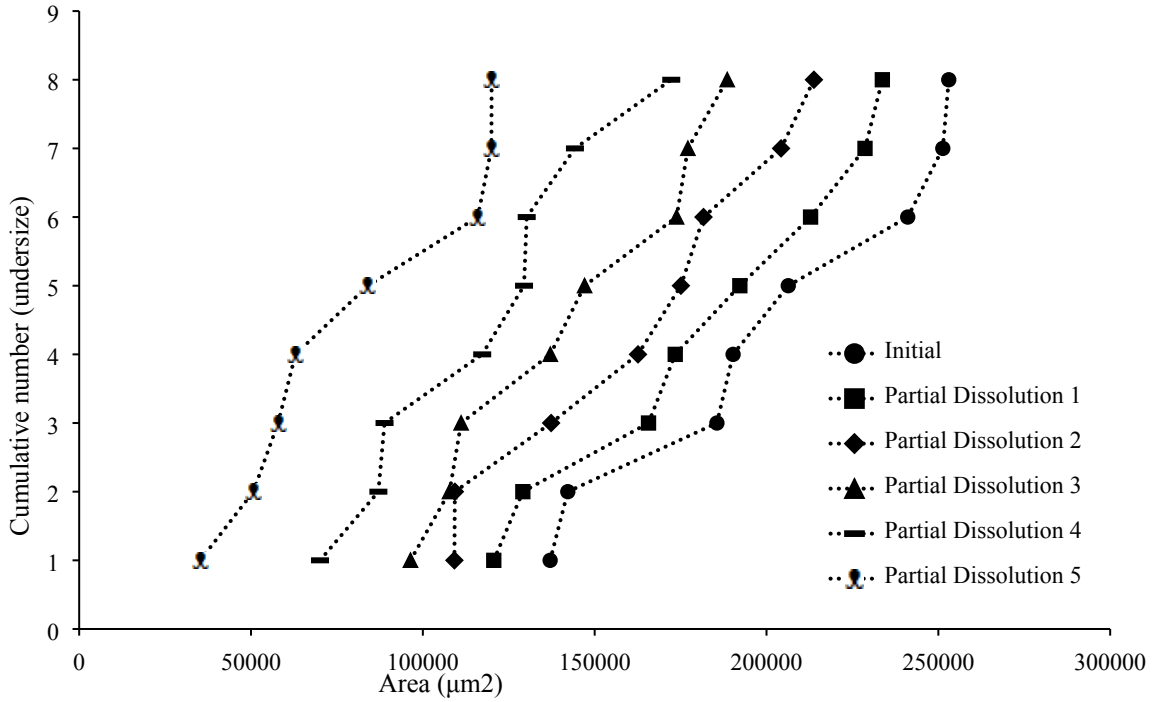

Figure S16. Chart comparing particle area versus the ranking of each particle in a partial dissolution series of **1** doped with 0.5 mol % of **3**.

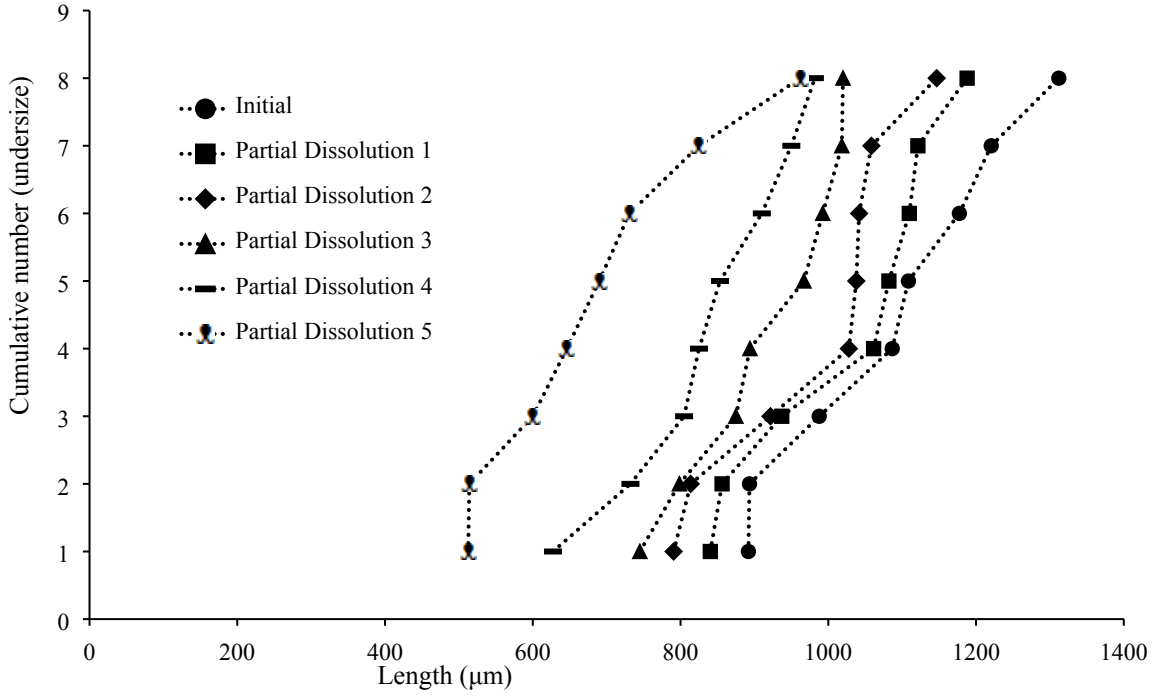

Figure S17. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 0.5 mol % of **3**.

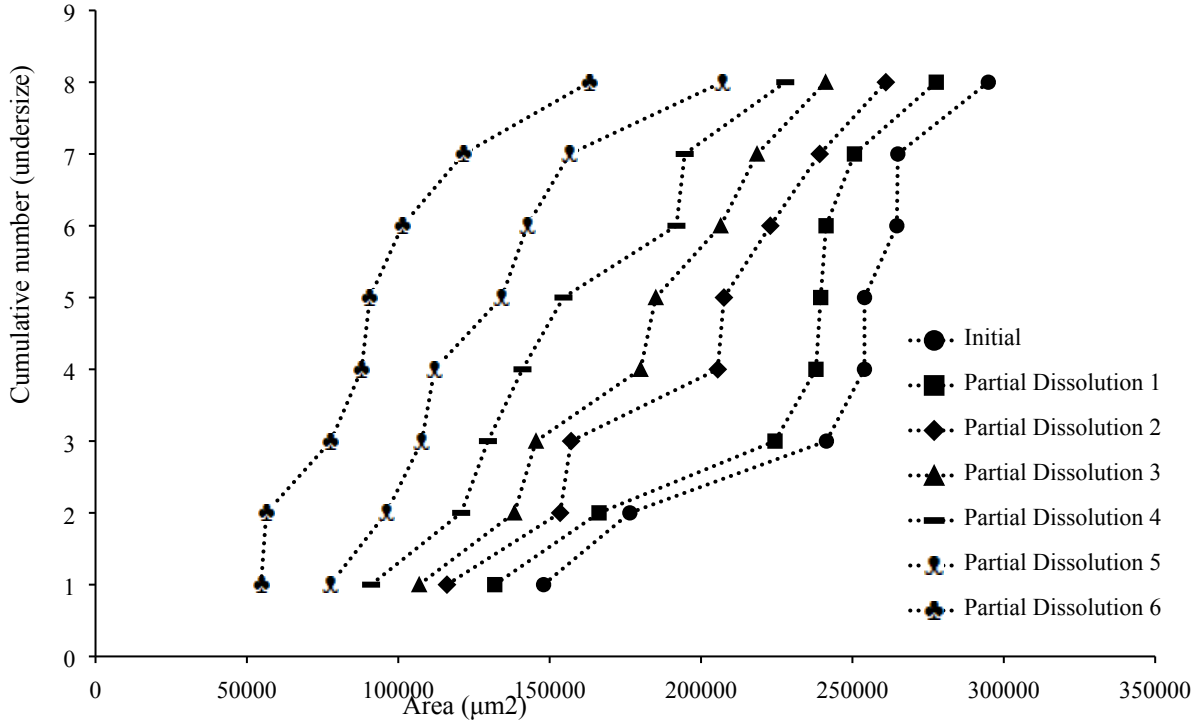

Figure S18. Chart comparing particle area versus the ranking of each particle in a partial dissolution series of **1** doped with 1.0 mol % of **3**.

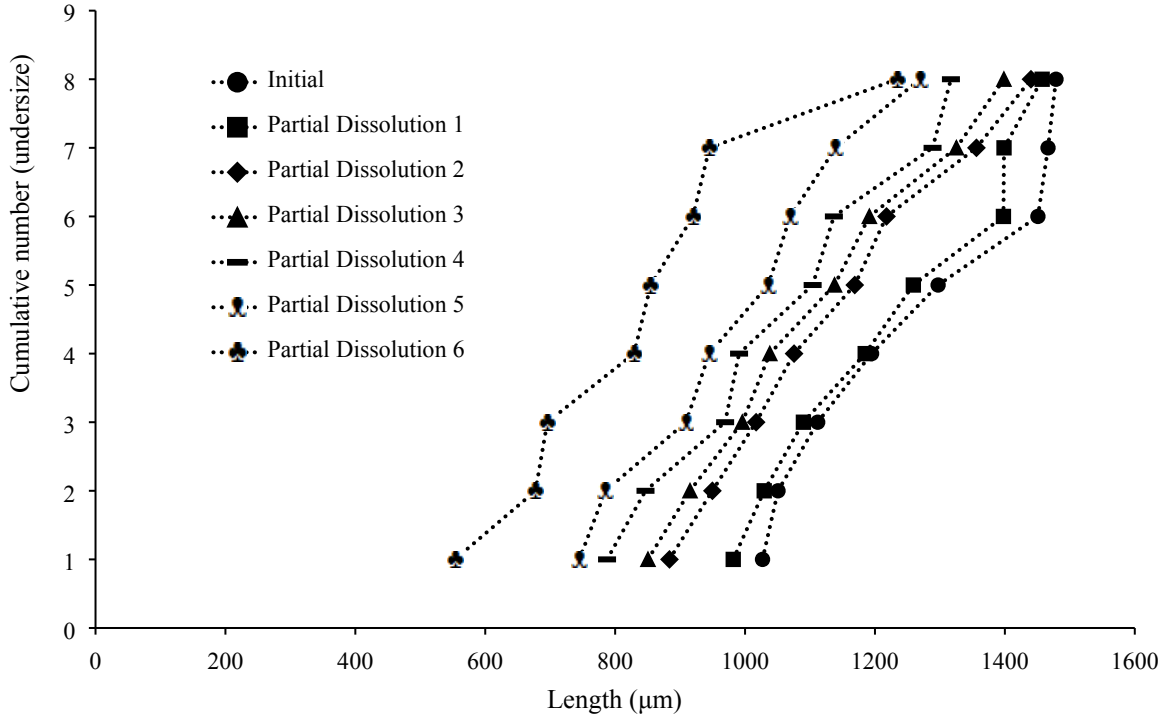

Figure S19. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 1.0 mol % of **3**.

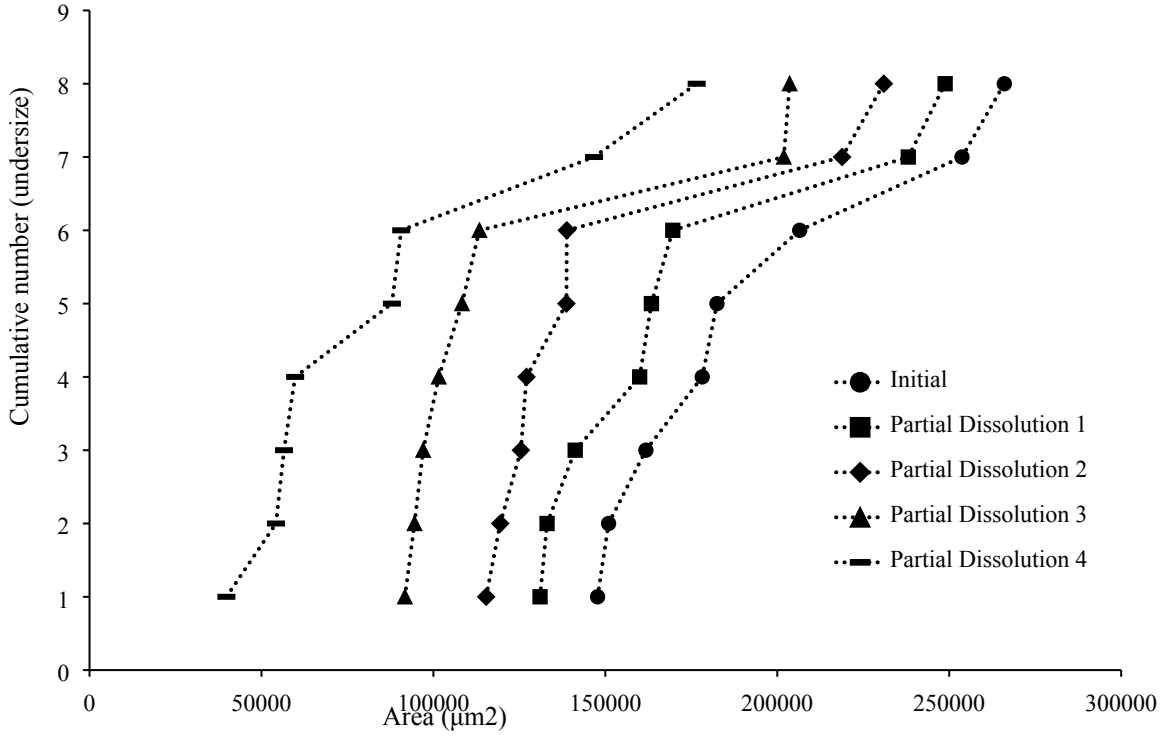

Figure S20. Chart comparing particle area versus the ranking of each particle in a partial dissolution series of **1** doped with 1.5 mol % of **3**.

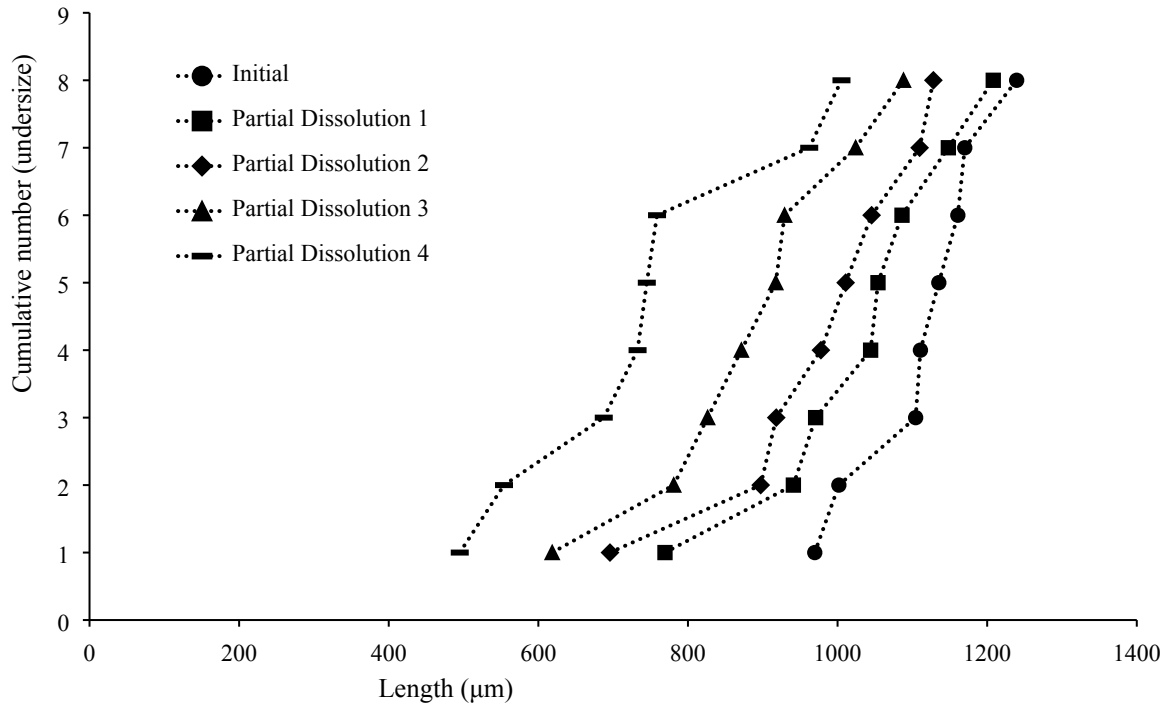

Figure S21. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 1.5 mol % of **3**.

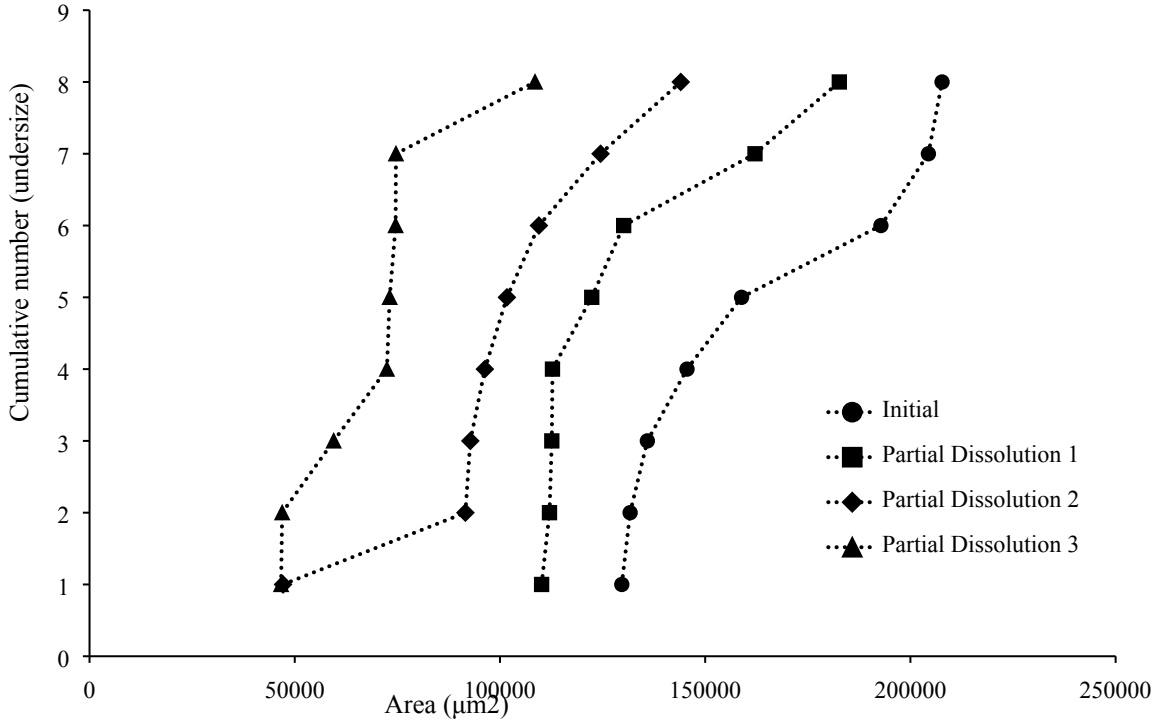

Figure S22. Chart comparing particle area versus the ranking of each particle in a partial dissolution series of **1** doped with 2.0 mol % of **3**.

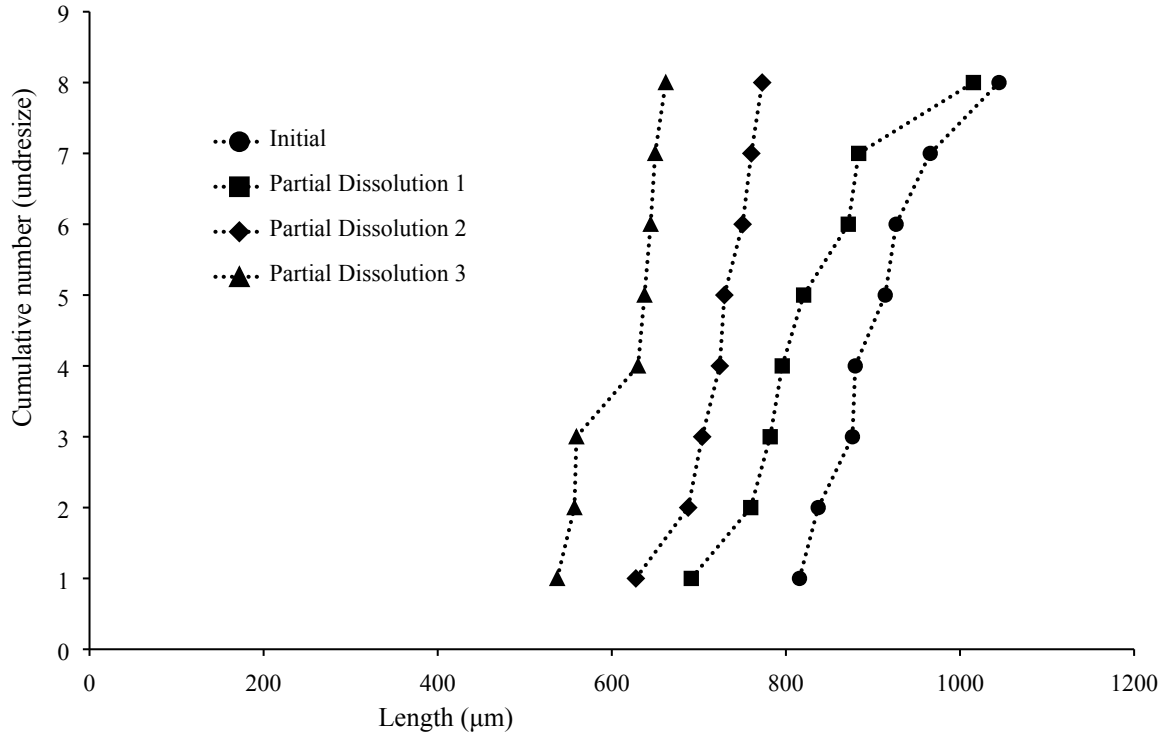

Figure S23. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 2.0 mol % of **3**.

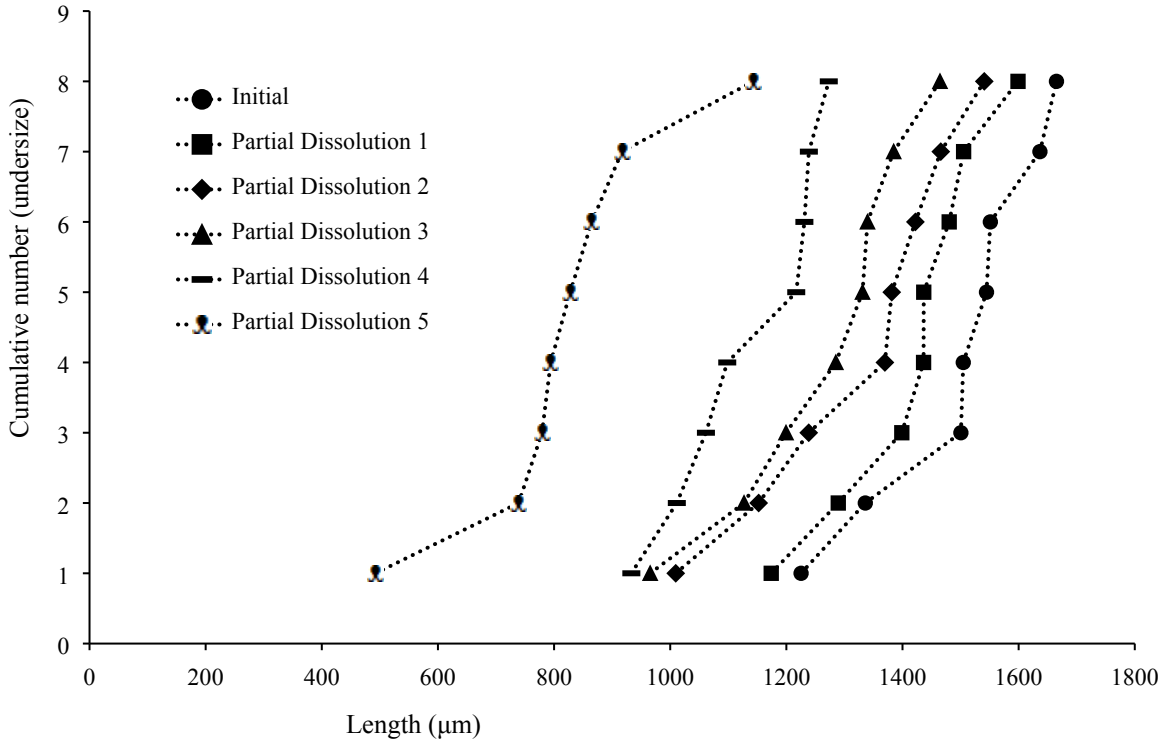

Figure S24. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 2.5 mol % of **3**.

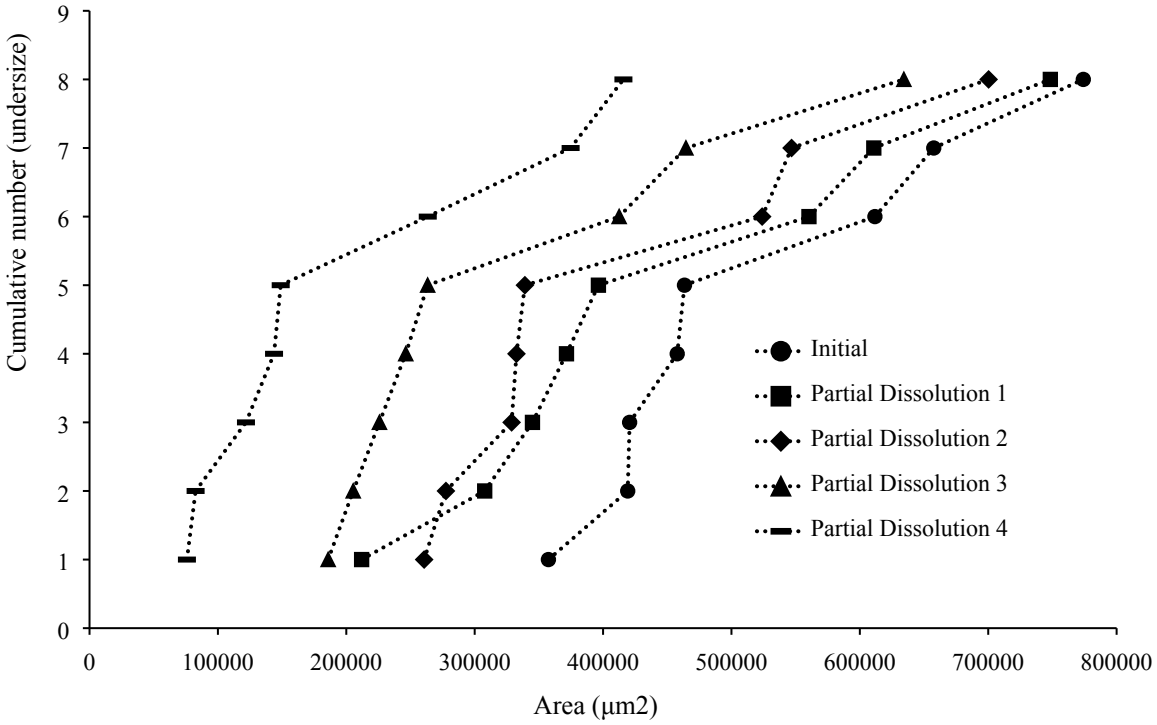

Figure S25. Chart comparing particle area versus the ranking of each particle in a partial dissolution series of **1** doped with 3.0 mol % of **3**.

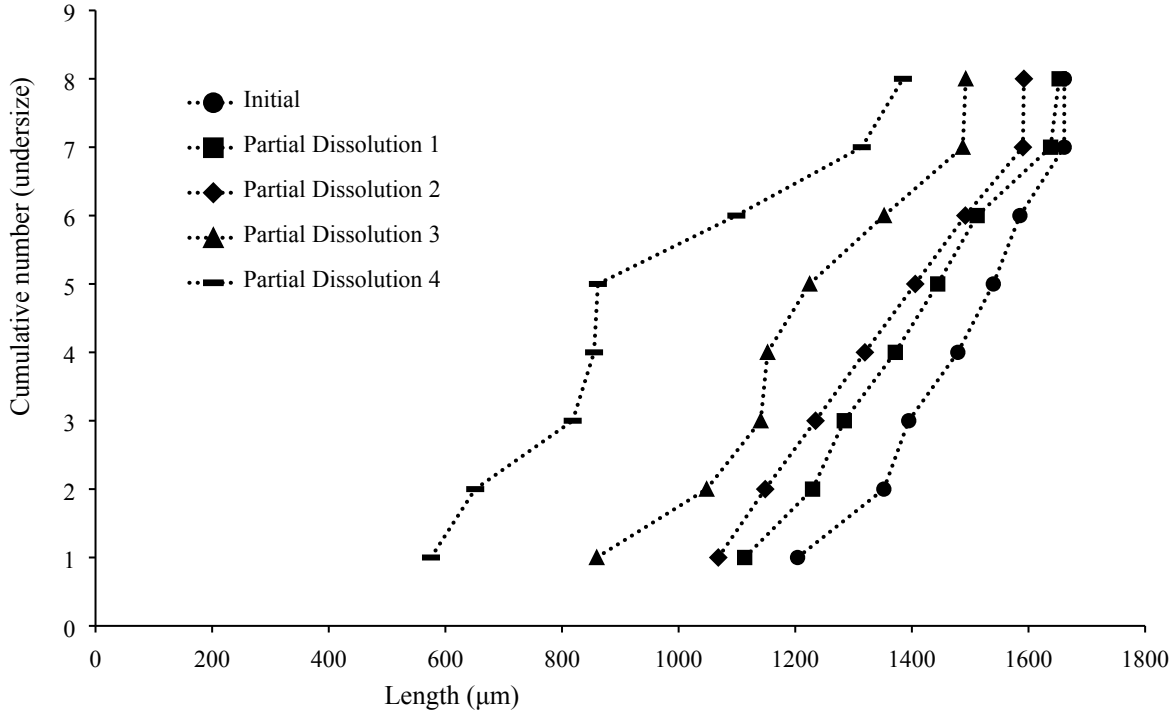

Figure S26. Chart comparing particle length versus the ranking of each particle in a partial dissolution series of **1** doped with 3.0 mol % of **3**.

%Impurity vs Dissolution mid-points% for the above

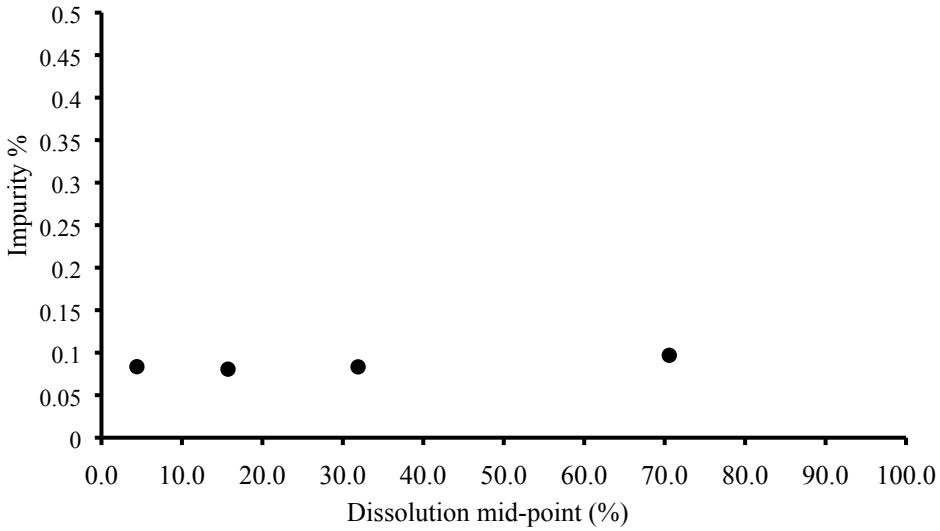

Figure S27. Plot of percentage by HPLC of added impurity in crystals of compound **1** *vs.* the dissolution mid-point for the sample of crystals grown from solutions containing 0.5 mol % of additive **2**.

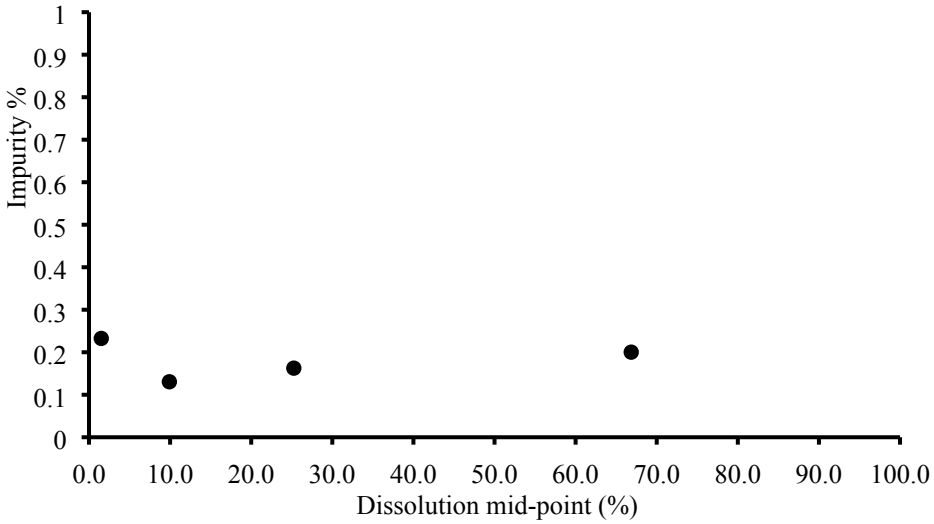

Figure S28. Plot of percentage by HPLC of added impurity in crystals of compound **1** *vs.* the dissolution mid-point for the sample of crystals grown from solutions containing 1.0 mol % of additive **2**.

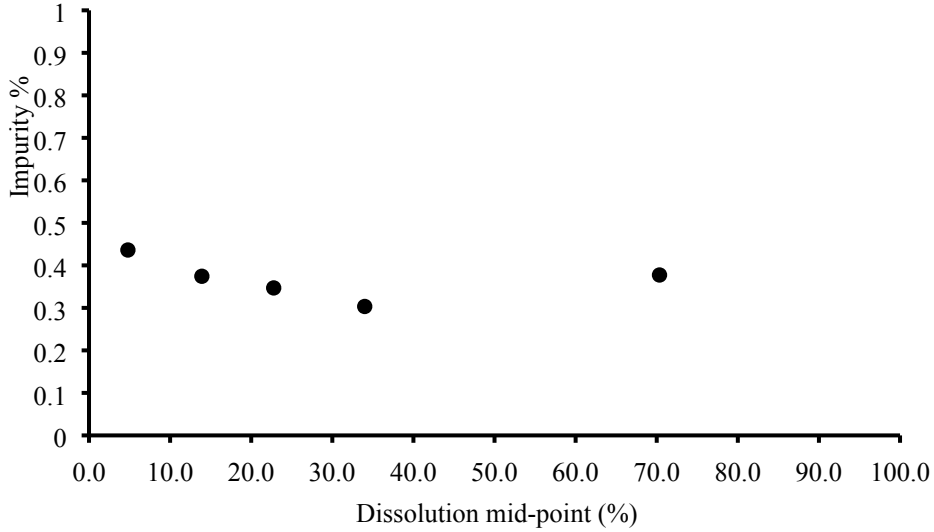

Figure S29. Plot of percentage by HPLC of added impurity in crystals of compound **1** *vs.* the dissolution mid-point for the sample of crystals grown from solutions containing 2.0 mol % of additive **2**.

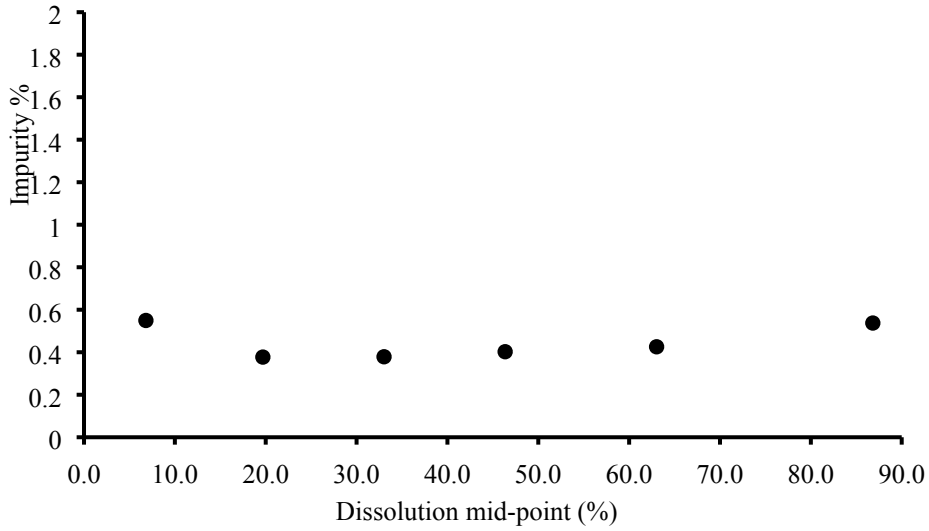

Figure S30. Plot of percentage by HPLC of added impurity in crystals of compound **1** *vs.* the dissolution mid-point for the sample of crystals grown from solutions containing 2.5 mol % of additive **2**.

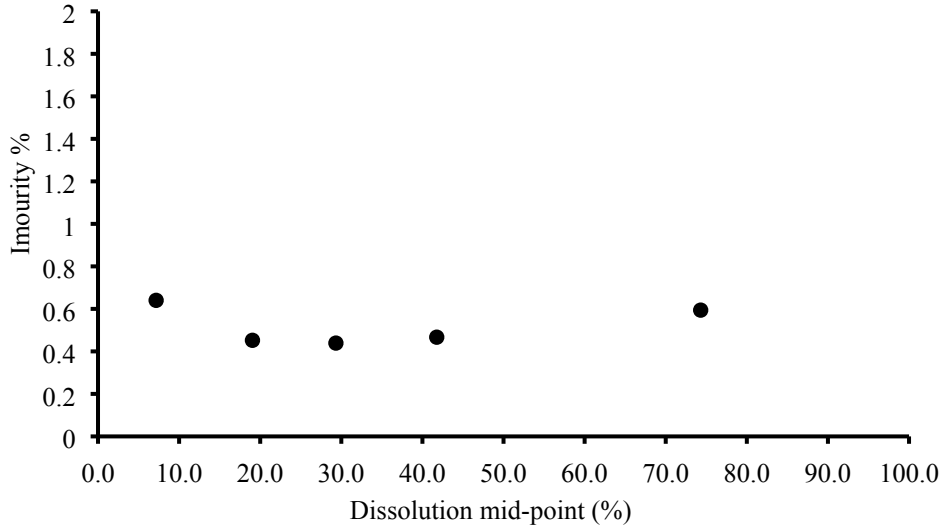

Figure S31. Plot of percentage by HPLC of added impurity in crystals of compound **1** *vs.* the dissolution mid-point for the sample of crystals grown from solutions containing 3.0 mol % of additive **2**.

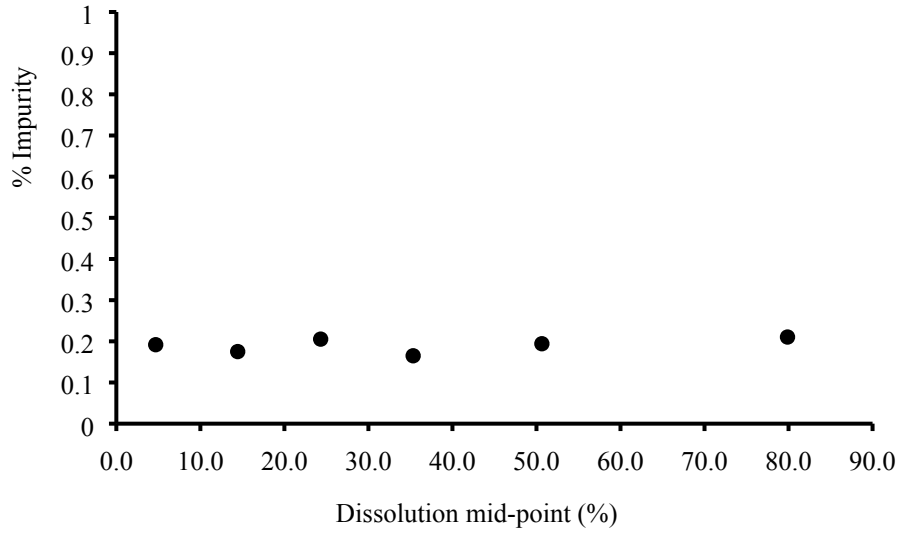

Figure S32. Plot of percentage by HPLC of added impurity in crystals of compound **1** *vs.* the dissolution mid-point for the sample of crystals grown from solutions containing 0.5 mol % of additive **3**.

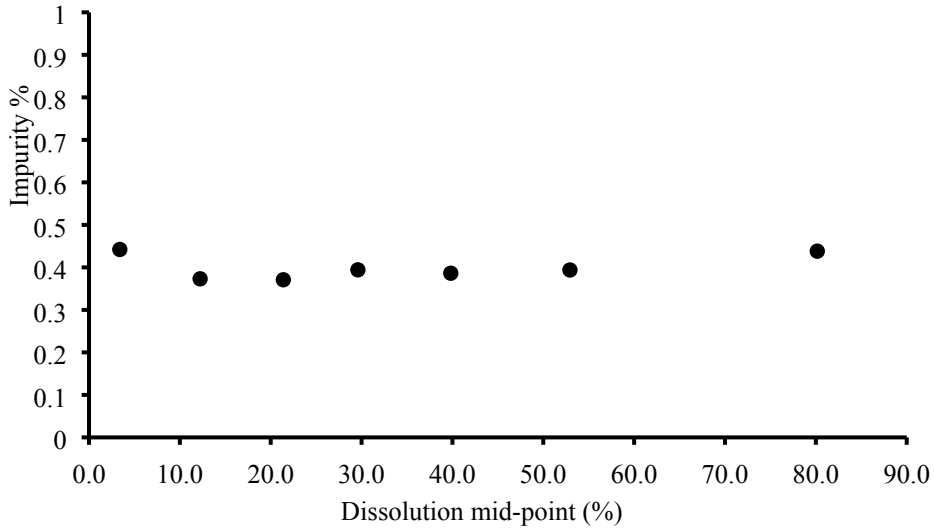

Figure S33. Plot of percentage by HPLC of added impurity in crystals of compound **1** *vs.* the dissolution mid-point for the sample of crystals grown from solutions containing 1.0 mol % of additive **3**.

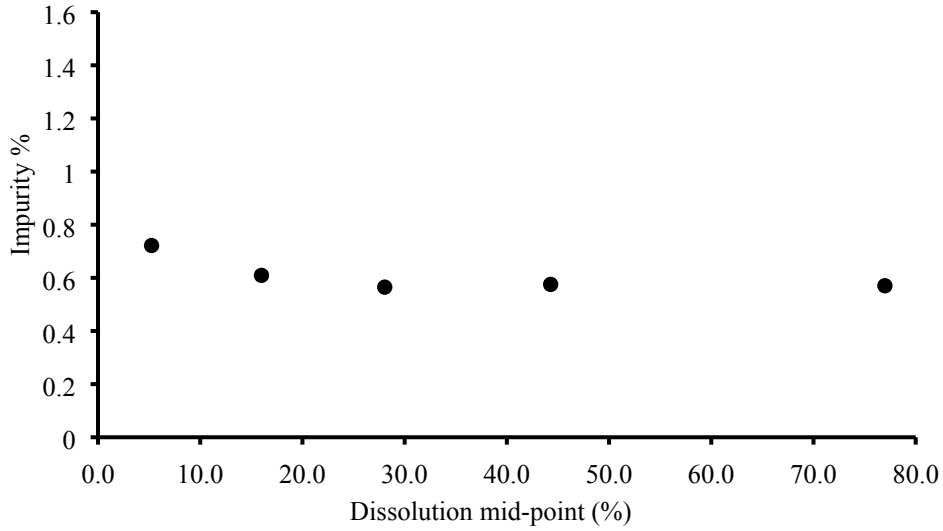

Figure S34. Plot of percentage by HPLC of added impurity in crystals of compound **1** *vs.* the dissolution mid-point for the sample of crystals grown from solutions containing 1.5 mol % of additive **3**.

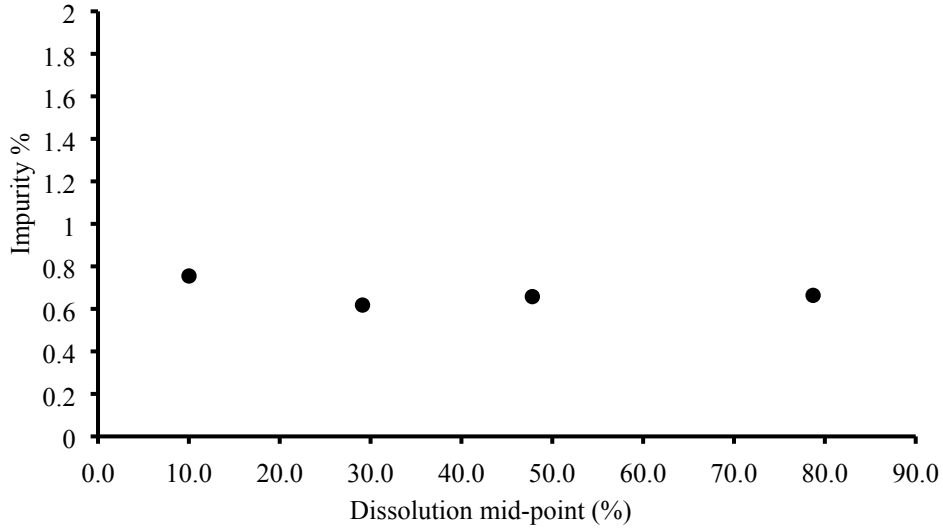

Figure S35. Plot of percentage by HPLC of added impurity in crystals of compound **1** *vs.* the dissolution mid-point for the sample of crystals grown from solutions containing 2.0 mol % of additive **3**.

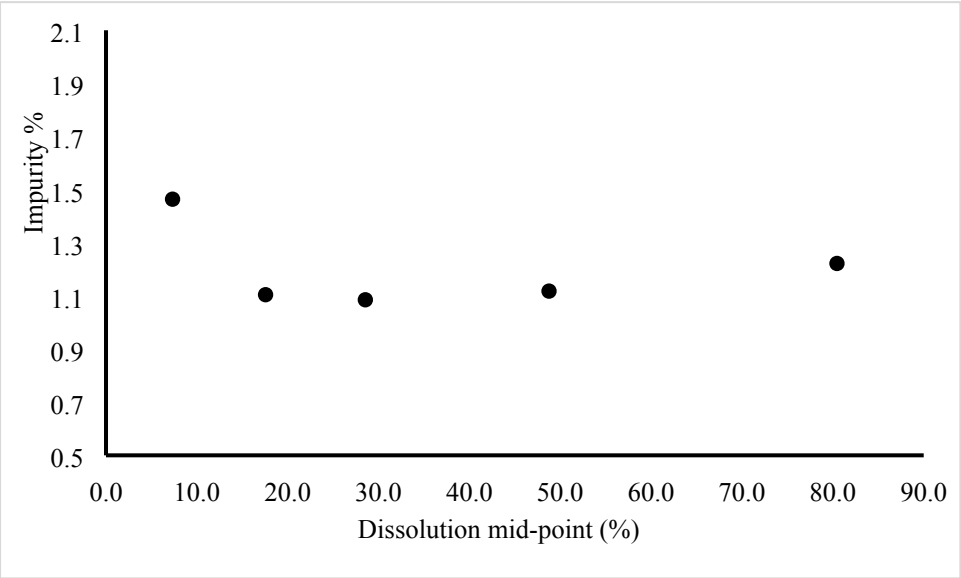

Figure S36. Plot of percentage by HPLC of added impurity in crystals of compound **1** *vs.* the dissolution mid-point for the sample of crystals grown from solutions containing 3.0 mol % of additive **3**.

Data from dissolution of single crystal grown from solution containing 3.0 mol % **3**.

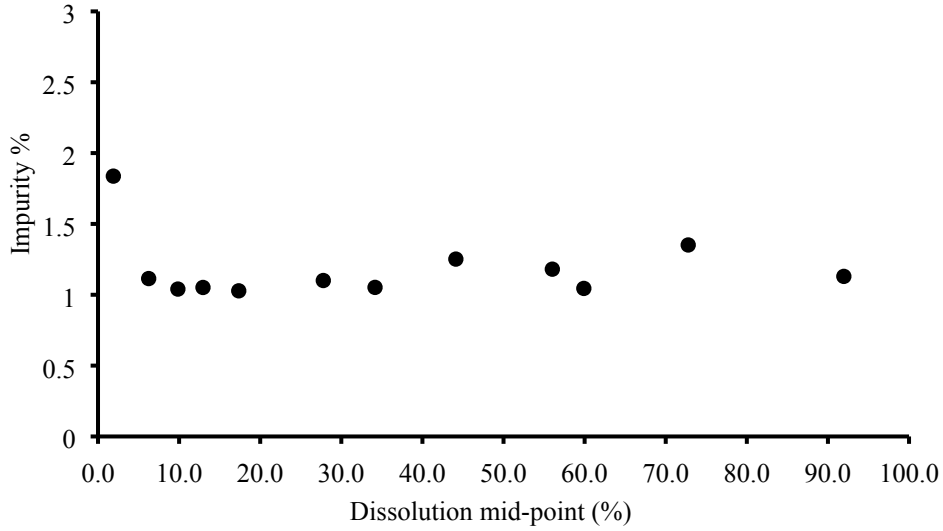

Figure S37. Plot of percentage by HPLC of added impurity in a single crystal of compound **1**, grown from solutions containing 3.0 mol % of additive **3**, *vs.* the dissolution mid-point for the crystal.