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Supplementary Information

Solvent-Mediated Polymorphic Transformation of Famoxadone from Form II to Form I in Several Mixed Solvent Systems

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Content

1 Experimental details

1.1 Solubility measurement for famoxadone polymorphs

An excess amount of famoxadone polymorphs was added to 15 mL of the corresponding mixed solvent system and was left to stir overnight at 30 ± 1 °C. The saturated solution was filtered through a 0.22-μm syringe filter, and then, 10.0 mL of the clear solution were transferred to a preweighed vial. The solution was left to evaporate at room temperature and weighed, and famoxadone solubility was calculated. The XRPD patterns of the filtrate were recorded to ensure that the solubility of the desired polymorph was determined. To determine the solubility of Form II, a certain amount of solvent was introduced to the vessel previously, and then, preweighed solute was added. The solution was stirred continuously at 200 rpm under 30 °C. The solute was added repeatedly until it could not be dissolved completely within 30 min. Finally, the solution was regarded as a saturated one. The total addition was recorded, and the range of the solubility could be determined. Two parallel experiments of solubility measurements were performed.

1.2 Slurry Experiment for famoxadone transformation

The slurry experiment was investigated in the corresponding mixed solvent system. For each experiment, about 60 mL of saturated solution of Form I, prepared under set temperatures, was added to the vessel, and then, preweighed Form II was added. The agitation speed was set at 200 rpm, and the system temperature was investigated by a detector. In addition, it was assumed that the insertion of PAT analyzers had no influence on the nature of the polymorphic transformation mechanism.

1.3 Quantitative phase analysis

The calibration curve of the famoxadone Form I and Form II mixture is given in Figure S10. The homogenous composition of the analyzed mixtures and the

equivalent extinction effects for both polymorphs could ensure that the diffraction peak intensity of each phase depends linearly on the phase weight fractions in the sample. Nevertheless, experimental data can be described by the linear equation y = 1.00785x–0.16369 with an R^2 value of 0.9991.

2 Tables

Table S1

Data of peaks in the PXRD patterns of famoxadone Form I.

Form I	
2	***I* (Height)%**
4.998	6.5
5.321	2.2
6.179	99.5
8.079	22.4
9.758	57.6
10.42	32
12.16	31.5
12.6	9.9
14.981	43.9
15.4	10.6
15.979	8.2
16.719	2.8
17.499	16.4
18.178	1.9
18.64	68.4
19.36	80
19.98	100
20.379	21.2
20.72	53.7
21.378	2.3
21.859	3.4
22.52	3.2
23.361	9.9
23.601	20.7
24.021	12.7

Table S2

Data of peaks in the PXRD patterns of famoxadone Form II.

Form II	
2	***I*** **(Height)%**
5.219	25.2
5.72	5.1
8.54	7
10.219	79.4
13.058	7.8
14.62	7.7
15.22	16.3
16.84	100
18.26	7.9
18.8	10.4
20.338	4
20.979	6.5
21.36	8.6
22.32	36.5
22.799	5.1
23.272	0.9
24.439	4.9
25.401	7.7
25.98	4.9
28.12	5
28.639	19.9

Table S3

Data of peaks in the PXRD patterns of famoxadone Form III.

Form III	
2	***I*** **(Height)%**
4.9	59.7
5.643	4.5
9.18	69.3
11.119	19.1
13.358	25.3
13.957	5.4
14.841	8.3
15.88	11.2
18.04	100
19.58	91.2
20.501	24.9
21.179	27.8
22.32	52.9
23.144	4.2
25.181	4.2
26.099	9.6
27.399	17.8
29.44	11.9

Table S4

Data of peaks in the PXRD patterns of famoxadone Form IV.

Form IV	
2	***I*** **(Height)%**
7.021	18.6
9.523	35.6
10.358	47.2
10.819	16.1
14.079	1
15.177	1.2
16.259	4.3
18.461	11.6
19.118	13.6
19.72	100
21.182	45.1
21.757	5.2
22.901	9.5
23.117	6
23.74	0.7
24.78	11.6
25.281	2.4
26.119	5.5
26.519	2.8
27.48	3
27.838	4.1
28.397	2.7
28.82	12.1

Table S5

Data of peaks in the PXRD patterns of famoxadone Form V.

Form V	
2	***I* (Height)%**
5.18	100
10.1	57.1
11.461	81.5
14.76	27.1
15.92	26.9
16.959	16.9
17.479	14.2
18.6	91.9
20.038	24
20.922	54.9
22.9	9.9
23.501	19
25.701	21.1
26.999	16.9

Table S6

Data of peaks in the PXRD patterns of famoxadone Form VI.

Form VI	
2	***I* (Height)%**
4.539	6.1
5.821	16.7
6.34	31.5
8.68	42.4
9.101	52.7
10.299	1.5
11.441	9.2
12.501	46.2
15.282	6.4
15.841	9.1
16.591	10.4
17.198	22
18.081	100
18.641	47
19.182	3.6
20.34	23
20.881	44.8
21.418	7.4
21.68	4.9
22.181	6.4
22.759	5.6
23.259	5.5
23.899	9.4
24.88	4.8
25.821	14
27.02	6.4
27.44	5.8
28.7	7.1

Table S7

The correlation of the experimental data with the theoretical model in each solvent.

Mixed solvent systems	**Fitting equation**	**Correlation with the P2 model, R^2**
nitromethane/toluene (1:1)	$\alpha = 35.760\ t^2$	0.99
nitromethane/isopropylbenzene (1:1)	$\alpha = 10.628\ t^2$	0.96
acetone/*m*-xylene (1:1)	$\alpha = 7.728\ t^2$	0.98
acetone/toluene (1:1)	$\alpha = 2.993\ t^2$	0.95
acetone/*o*-xylene (1:1)	$\alpha = 0.303\ t^2$	0.99
acetone/*p*-xylene (1:1)	$\alpha = 0.212\ t^2$	0.97
acetone/mesitylene (1:1)	$\alpha = 0.096\ t^2$	0.98

3 Figures

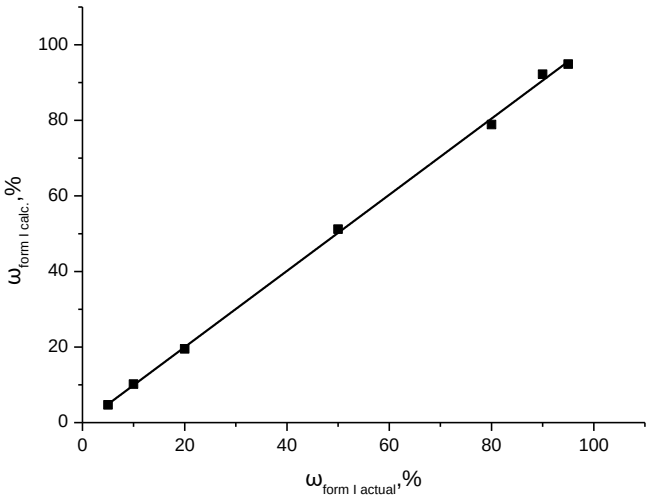

Figure S1. Dependence of the calculated Form I weight fraction (ω form I calc.) on the actual Form I content in the sample (ω form I actual).

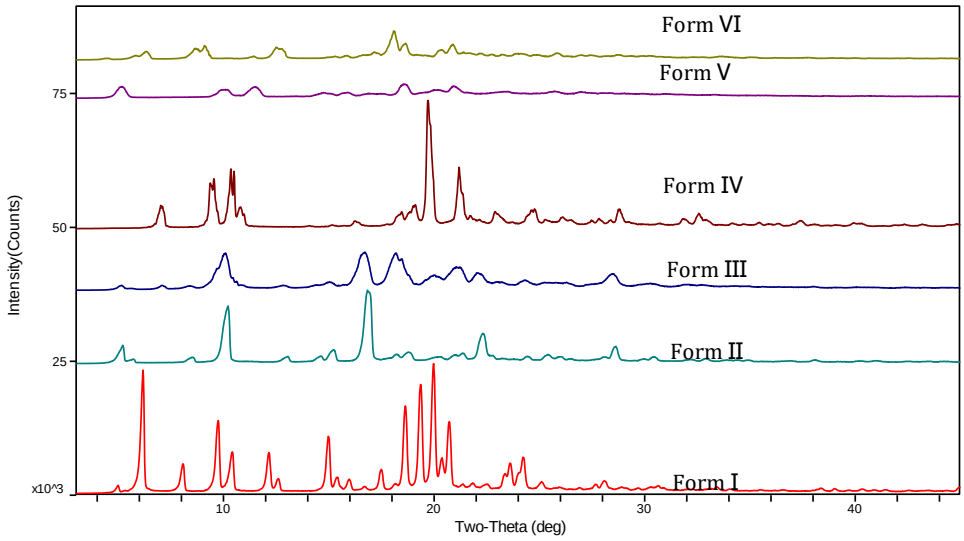

Figure S2. Stability experiments of high temperature for the six famoxadone polymorphs.

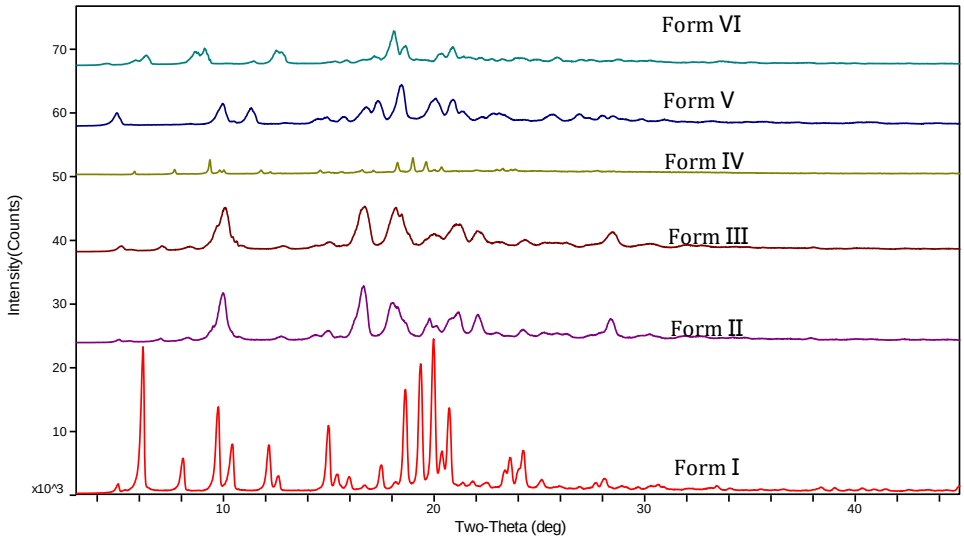

Figure S3. Stability experiments of high humidity for the six famoxadone polymorphs.

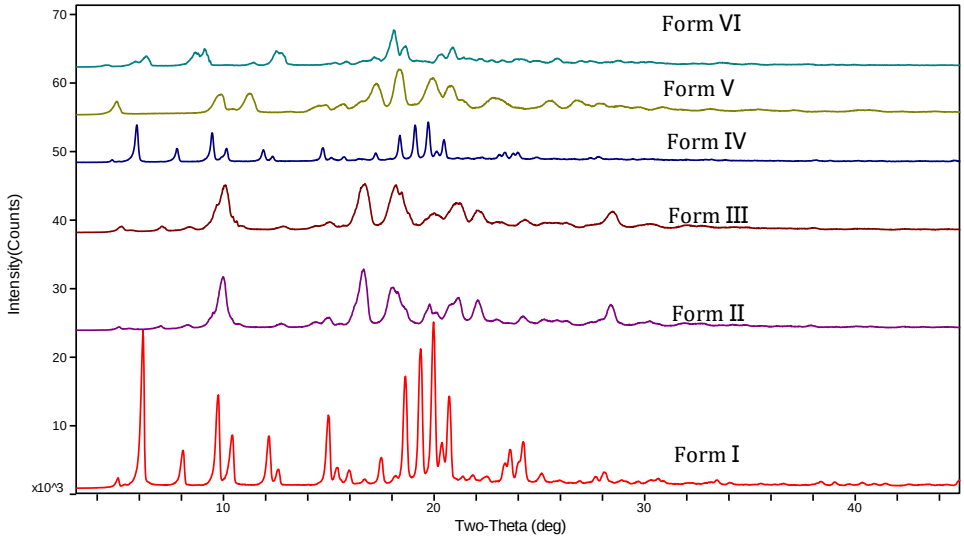

Figure S4. Stability experiments of strong light for the six famoxadone polymorphs.

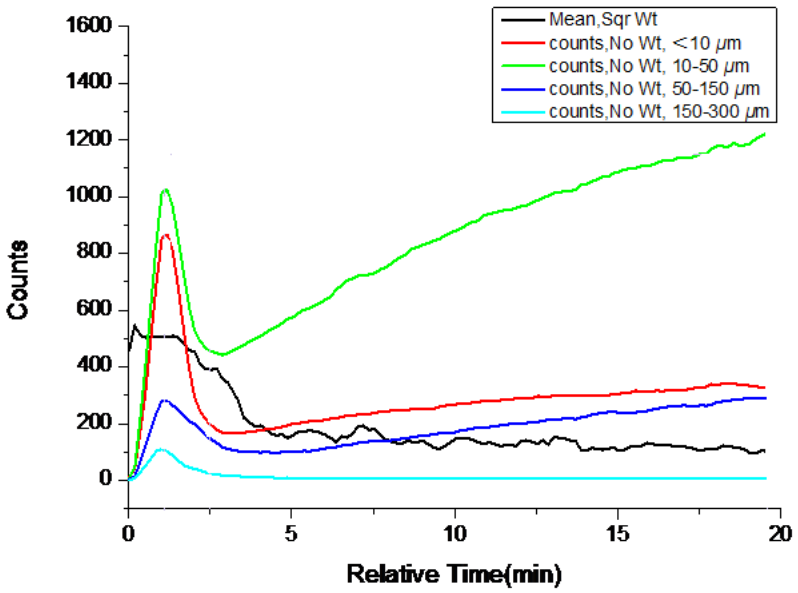

Figure S5. Variation curve of particle counts and the mean of the chord length in Experiment #1.

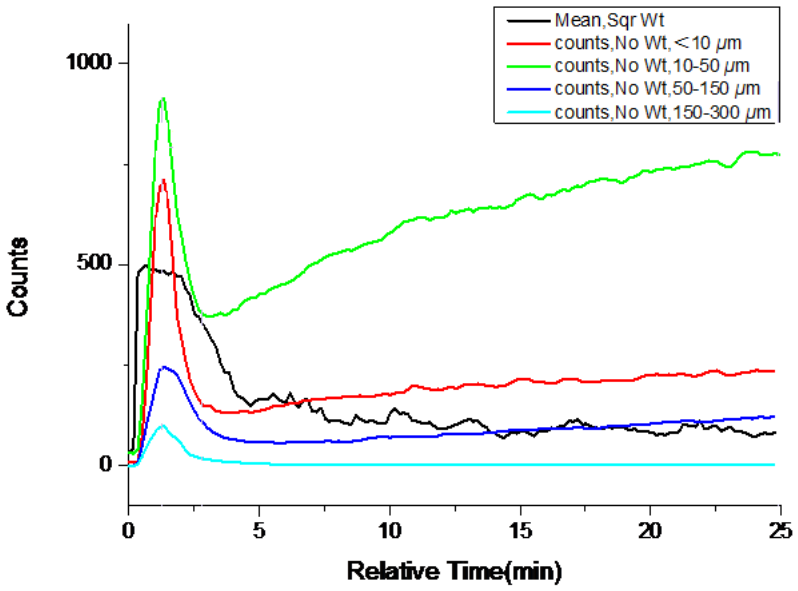

Figure S6. Variation curve of particle counts and the mean of the chord length in Experiment #2.

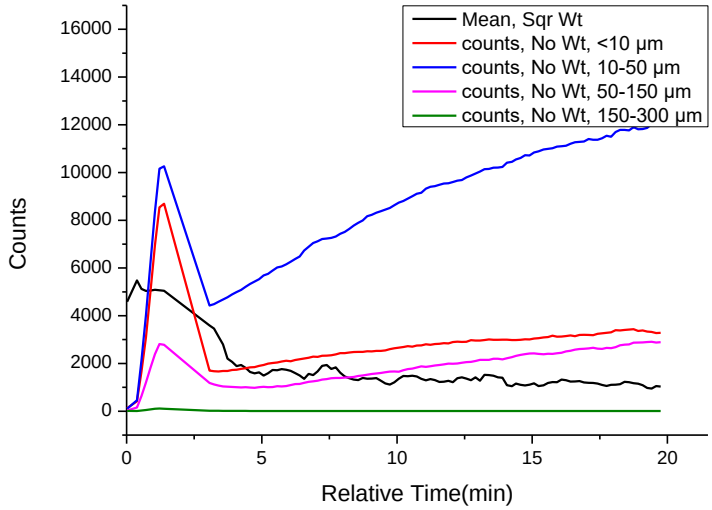

Figure S7. Variation curve of particle counts and the mean of the chord length in Experiment #3.

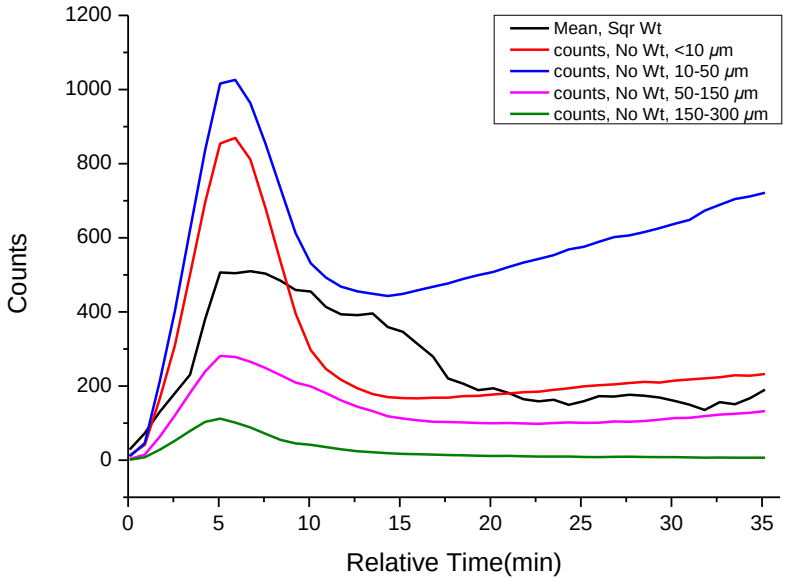

Figure S8. Variation curve of particle counts and the mean of the chord length in Experiment #5.

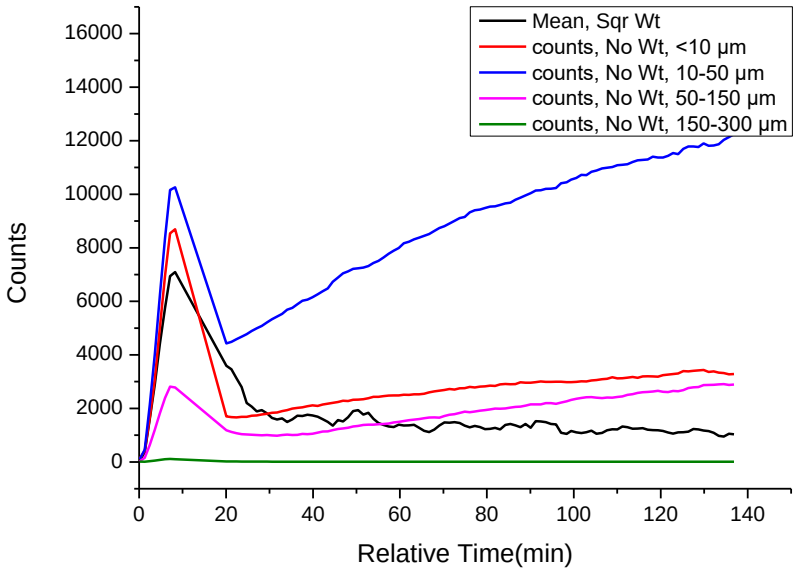

Figure S9. Variation curve of particle counts and the mean of the chord length in Experiment #6.

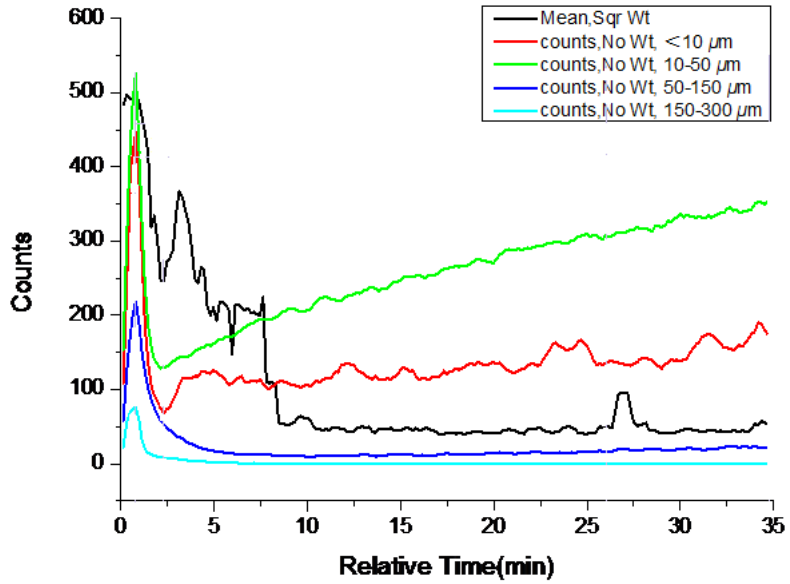

Figure S10. Variation curve of particle counts and the mean of the chord length in Experiment #7.

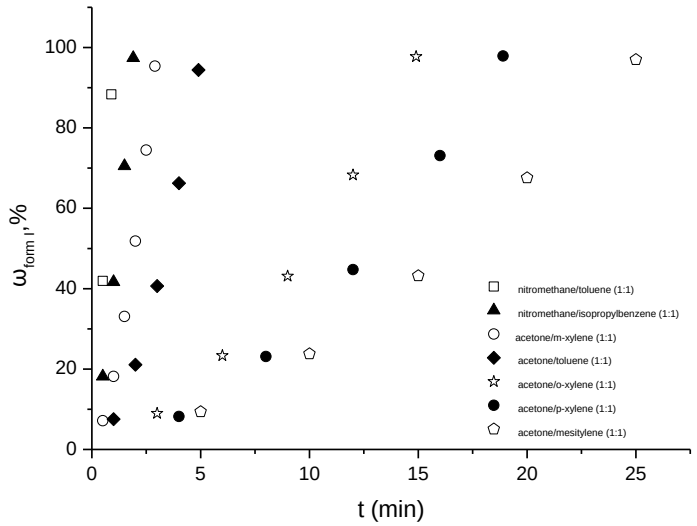

Figure S11. Weight fraction of Form I during the solvent-mediated polymorphic transformation (SMPT) from Form II to Form I in nitromethane/toluene (1:1), nitromethane/isopropyl benzene (1:1), acetone/*m*-xylene (1:1), acetone/toluene (1:1), acetone/*o*-xylene (1:1), acetone/*p*-xylene (1:1), and acetone/mesitylene (1:1) at 30 °C, normalized to a state where the transition to Form I is complete.