Selective Formation of Form II Paracetamol through the Assistance of Paracetamol Co-crystals as Templates in Solution

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Supporting Information

1. Experimental procedures

1.1 Cooling crystallization of paracetamol (PCA) without co-former addition.

100 mg of PCA was dissolved in 1.7 mL water in a 7 mL scintillation vial at a constant temperature of 75ºC maintained by a water bath. The vial with a clear PCA solution was immersed in the other 10ºC water bath for 5 min for cooling. The temperature of the solution was decreased from 75ºC to 10ºC in 2 min. The solution was gently shaken intermittently until the crystals appeared, and then the resulted suspension was placed in a water bath for 5 min to produce more crystals. The resulted crystals were collected by vacuum filtration and oven dried at 40ºC overnight.

1.2 Cooling crystallization of PCA with oxalic acid dihydrate (OXADH).

100 mg of paracetamol and 167 mg of OXADH were dissolved in 1.7 mL water in a 7 mL scintillation vial at a constant temperature of 75ºC maintained by a water bath. The vial with a clear solution was immersed in the other 10ºC water bath for 5 min for cooling. The temperature of the solution was decreased from 75ºC to 10ºC in 2 min. The solution was gently shaken intermittently until the crystals appeared, and then the resulted crystals were collected by vacuum filtration after 5 min of crystallization, and oven dried at 40ºC overnight.

1.3 Cooling crystallization of PCA with maleic acid (MAL).

200 mg of paracetamol and 153 mg MAL were dissolved in 1.36 mL water in a 7 mL scintillation vial at a constant temperature of 75ºC maintained by a water bath for 8 h. The vial containing a clear solution was immersed in the other 10ºC water bath for 5 min for cooling. The temperature of the solution was decreased from 75ºC to 10ºC in 2 min. The solution was kept cooled at 10ºC for 8 h, and then the

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resulted crystals were collected by vacuum filtration, and oven dried at 40 ºC overnight.

1.4 Solubility measurement of the physical mixtures of PCA, OXADH, and MAL.

The solubility values of the physical mixture of commercial PCA (Form I PCA) with commercial OXADH and MAL in water were all measured at 10ºC, 25ºC, 40ºC and 70ºC. PCA powders were blended by OXADH and MAL powders into a 7 mL scintillation vial with the molar ratios of PCA-to-OXADH of 1:2, and PCA-to-MAL of 1:1. The temperature of solutions were maintained at a constant temperature which was controlled by a water bath. Water was added dropwise into the vials until all solids were totally dissolved as determined by eyes. The total volume of water used was recorded and the solubility of PCA was calculated in terms of the weight of PCA (mg) over the volume of water added (mL).

1.5 Solubility measurement of PCA in OXADH and MAL aqueous solution with different concentrations.

Commercial PCA powders were weighed into a 7 mL scintillation vial. The aqueous solutions of OXADH with the concentrations of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 and 0.7 M, were added into each vial dropwise at 10ºC until all PCA solids were dissolved. The solubility of PCA in the OXADH aqueous solution was calculated in terms of PCA (M)/OXADH (M). The solubility of PCA in MAL solution was measured by the same procedure, but the concentrations of MAL aqueous solution used were 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7 and 0.8 M. The temperature of the PCA solution was controlled by the water bath.

1.6 Preparing slurry of Form I PCA with OXADH for isothermal conversion.

0.5 g of PCA and 0.83 g of OXADH were weighed into a 20 mL scintillation vial, then 8.5 mL of water were introduced into the vial to make a slurry under agitation by a spin bar at 10ºC. The slurry was sampled at 10 min, 30 min, 1 h and 2 h. The slurry samples were filtered and oven dried at 40ºC overnight.

1.7 Preparing slurry of Form I PCA with MAL for isothermal conversion.

0.6 g of PCA and 0.46 g of MAL were weighed into a 20 mL scintillation vial, then 4 mL of water were introduced into the vial to make a slurry under agitation by a spin bar at 10ºC. The slurry was sampled at 10 min, 30 min, 1 h and 2 h. The slurry samples were filtered and oven dried at 40ºC overnight.

1.8 Cooling crystallization of PCA with or without co-former in a 500 mL vessel.

In the case of PCA crystallization without co-former, 10 g of PCA and 170 mL of water were added into a 500 mL vessel, and heated to 75ºC to dissolve all solids under the agitation of 300 rpm. The agitator was turned off, and the clear solution was swiftly cooled by switching the water bath at 75ºC to the other water bath at

10ºC. The agitator was turned on again and the cold solution was stirred at 300 rpm for 1 min to induced crystallization near 10ºC. The resulting crystals were withdrawn at 5, 10, 15, 30, 45 and 60 min and observed by optical microscopy.

In the PCA-OXA system, 10 g of PCA, ad 16.69 g of OXADH were dissolved in 170 mL of water at 75ºC with stirring at 300 rpm. The agitator was turned off, and the solution was swiftly cooled by switching water bath at 75ºC to the other water bath at 10ºC. The temperature profile was shown in Fig. S2. The agitator was turned on again and the cold solution was stirred at 300 rpm for 1 min to induce crystallization near 10ºC. The resulting crystals were withdrawn at 5, 10, 15, 30, 45 and 60 min and observed by optical microscopy.

As to the case of PCA-MAL system, 30 g of PCA, ad 23 g of MAL were dissolved in 200 mL of water at 75ºC with stirring at 300 rpm. The agitator was turned off, and the solution was swiftly cooled by switching the water bath at 75ºC to the other water bath at 10ºC. The temperature profile was also shown in Fig. S2. The agitator was turned on again and the cold solution was stirred at 300 rpm for 1 min to induce crystallization near 10ºC. The resulting crystals was withdrawn at 20, 30, 40, 50 and 60 min and observed by optical microscopy. All resulting crystals were filtered after crystallization for 1 h, and the filter cakes were oven dried at 40ºC overnight.

2 Instrumental analyses

2.1 Optical microscopy (OM).

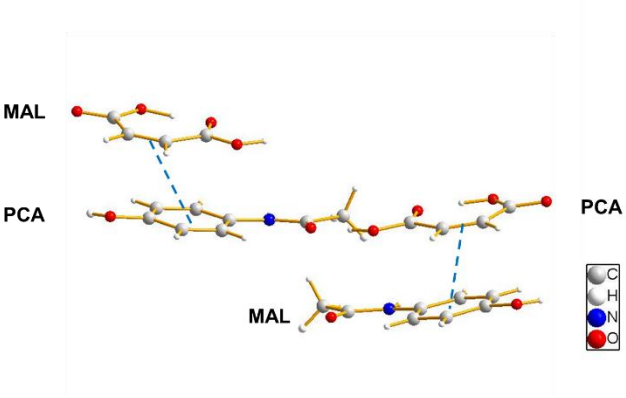
The crystal morphology of obtained PCA solids was determined by Olympus BX-51 (Tokyo, Japan) equipped with an industrial digital camera XCAM1080PHB.

2.2 Powder X-ray diffraction (PXRD).

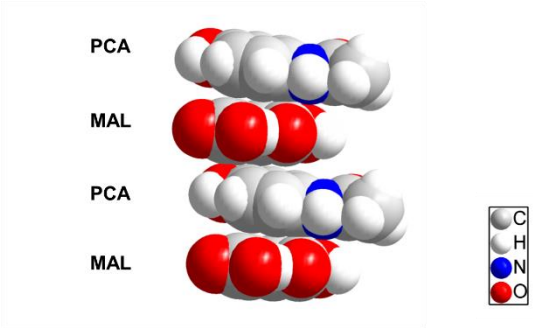
PXRD patterns of PCA crystals were characterized by Bruker D8 Advance (Karlsruhe, Germany). The source of PXRD was Cu K_α (λ = 1.5418 Å), and the diffractometer was operated at 40 keV and 25 mA passing through a nickel filter. Crystals were subjected to PXRD analysis with a constant scanning rate of 0.05°/step, and a scanning speed of 1 s/step over an angular range from 2θ = 5 to 35º.

2.3 Fourier-transform infrared (FTIR) spectroscopy.

FT-IR spectroscopy was conducted on Perkin Elmer Spectrum One (Norwalk, CT, USA.) to identify functional groups and polymorphs. Every sample was ground with potassium bromide powders with a weight ratio of 1 to 100, and then compressed into a disk through the hydraulic press. Each tablet was scanned 8 times with a resolution of 2 cm^{-1} in the wavenumber range of 4000 to 400 cm^{-1}.

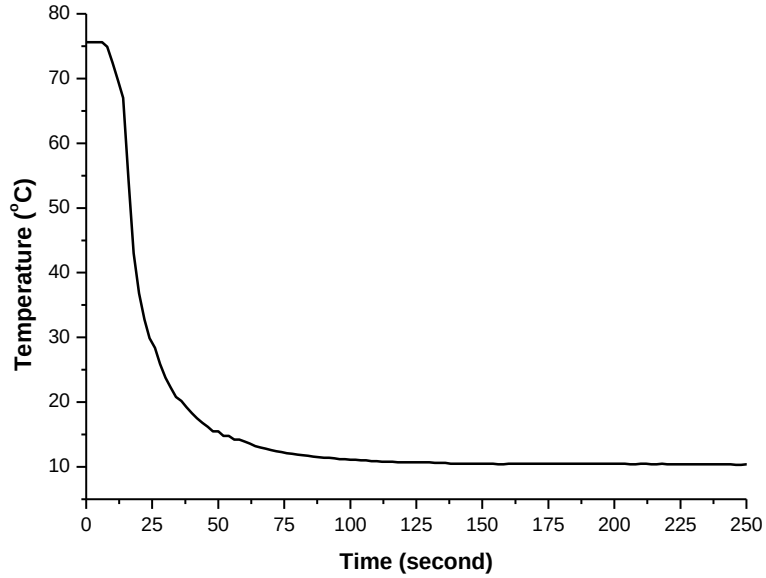


(a)

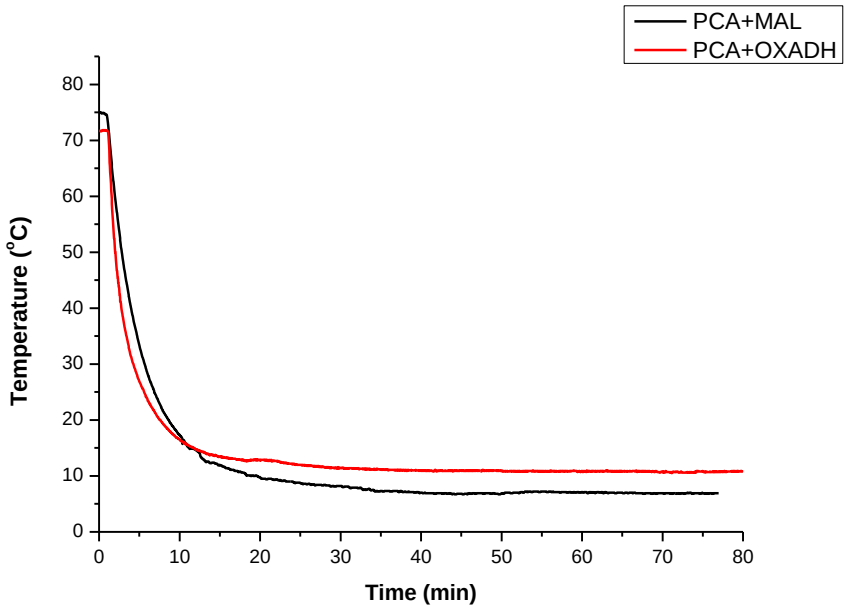


(b)

Fig S1. Illustration of (a) π—π interactions (depicted by blue dash lines) and (b) the alternate stacking arrangement between PCA and MAL in the PCA-MAL co-crystal[1] as depicted by a software (Diamond 3.1).



(a)



(b)

Fig. S2 Temperature profiles of solution upon cooling in (a) 7 mL scintillation vial and (b) 500 mL vessel.

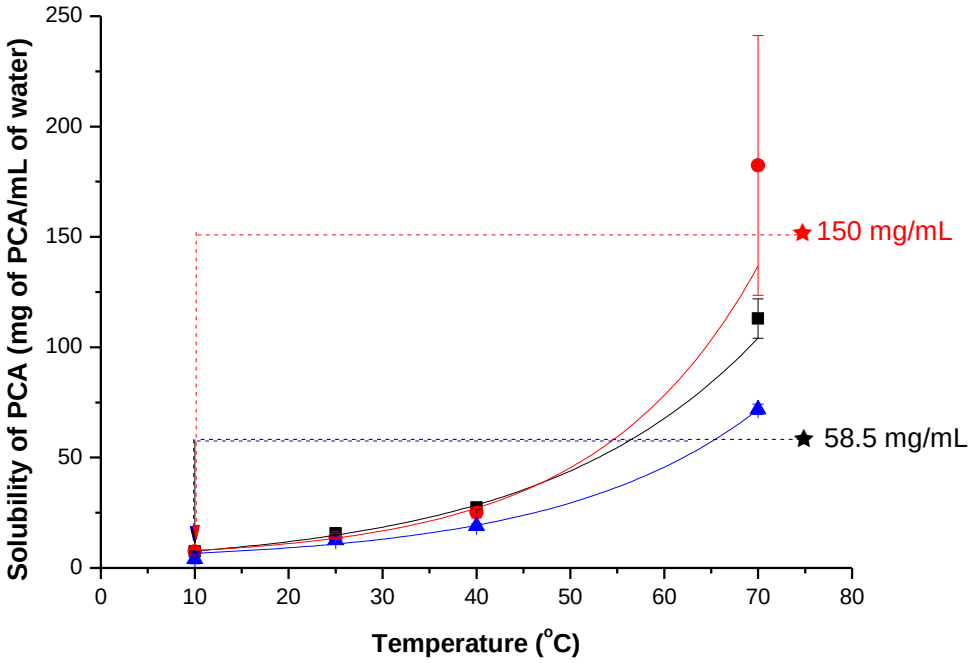


Fig. S3 Solubility curves of Form I PCA (blue triangle), physical mixture of Form I PCA and two equivalents of commercial OXADH (black square), a physical mixture of Form I PCA and an equivalent of commercial MAL (red circle) in water at various temperatures. The solubility of PCA was referred to the data in Ref. 1. The solubility curves were fitted by the solubility values at 10°, 25°, 40° and 70°C using the exponential formula. The star symbols stand for the concentration of PCA before cooling. The arrows indicated the degrees of supersaturation resulted from cooling.

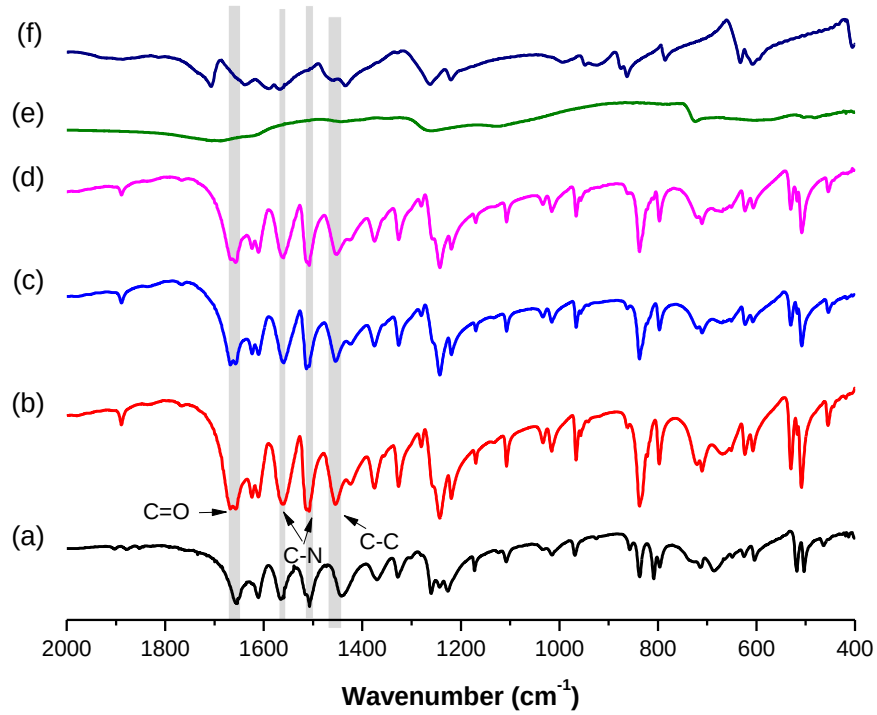
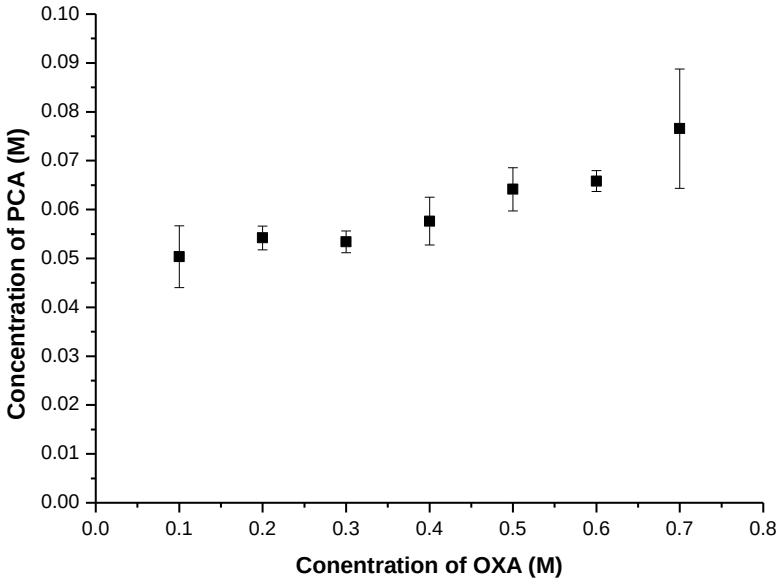


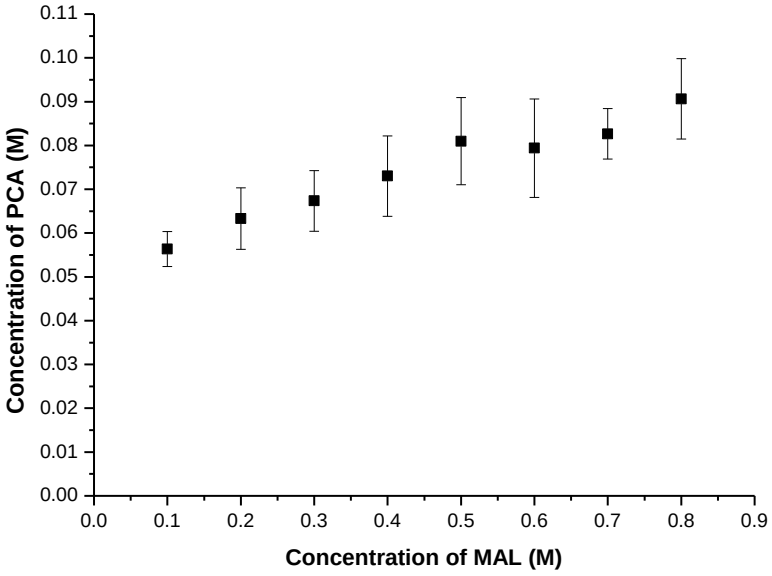
Fig. S4 FTIR spectra of PCA re-crystallized (a) without co-former, (b) with OXA, (c) with MAL, and (d) obtained by reaction coupling,[2] and (e) commercial OXADH, and (f) commercial MAL.

Table S1. Characteristic bands of IR spectra of Form I and Form II PCA.[3,4]

Functional Group	Form I PCA	Form II PCA
C=O amide stretching (cm^{-1})	1653	1667
C-N amide stretching (cm^{-1})	1564,1516	1560,1513
C-C aromatic stretching (cm^{-1})	1610,1507,1440	1623,1507,1454

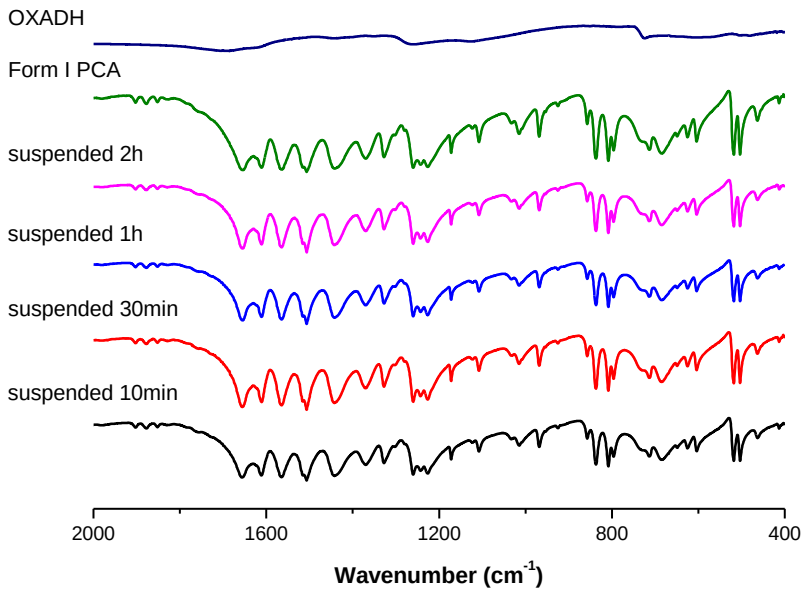


(a)

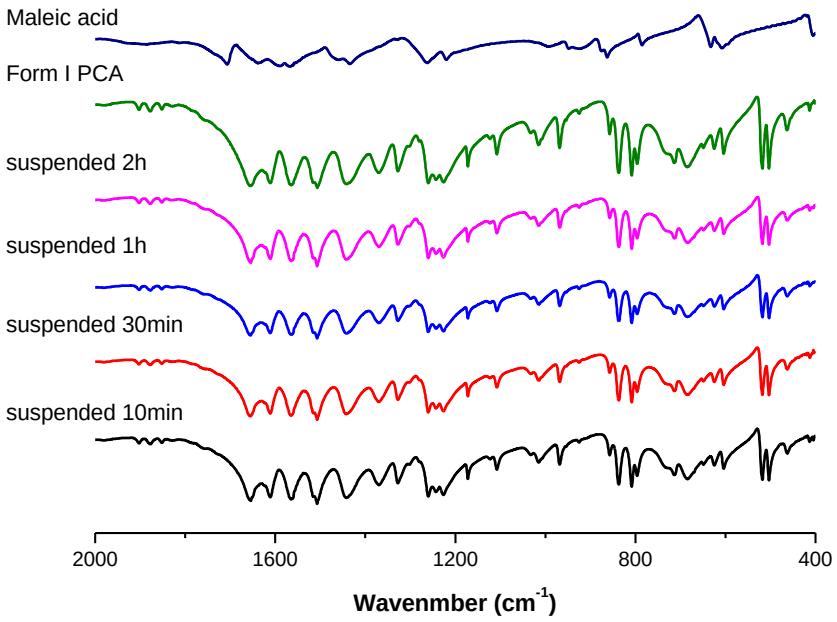


(b)

Fig. S5. Solubility diagrams of Form I PCA in the aqueous solution of different concentrations of (a) OXADH, and (b) MAL, at 10 ºC.

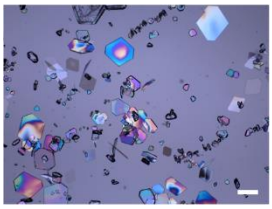
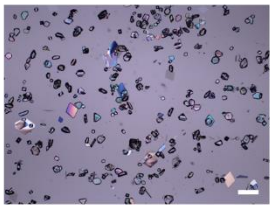
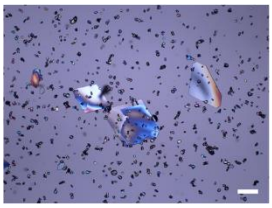
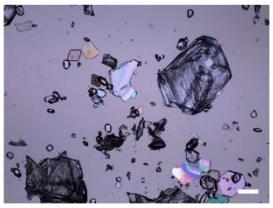
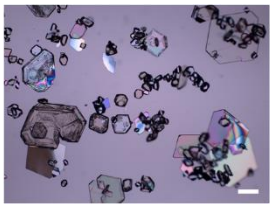


(a)

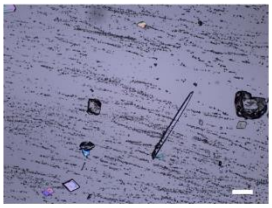
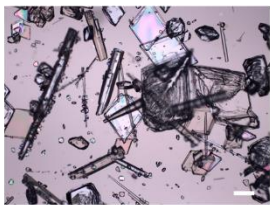
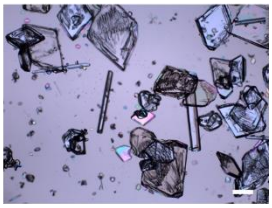
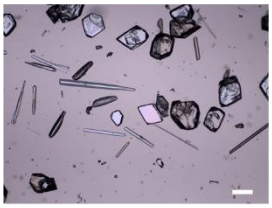
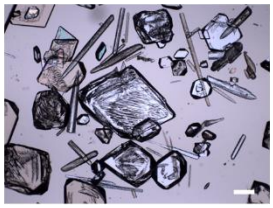
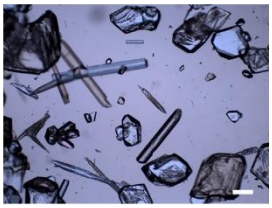


(b)

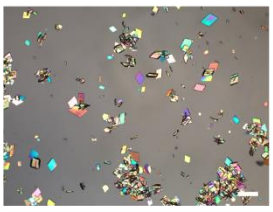
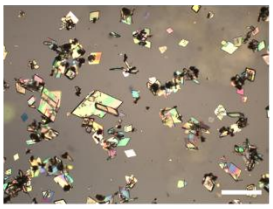
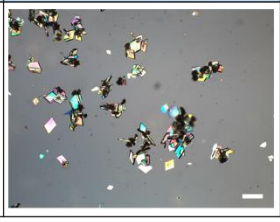
Fig. S6 FTIR spectra of PCA suspended in the aqueous solution containing (a) OXA, and (b) MAL, at room temperature for 10 min, 30 min, 1 h and 2 h.

Time for crystallization	5 min	10 min	15 min
Crystal morphology			
Time for crystallization	30 min	45 min	60 min
Crystal morphology			

(a)

Time for crystallization	5 min	10 min	15 min
Crystal morphology			
Time for crystallization	30 min	45 min	60 min
Crystal morphology			

(b)

Time for crystallization	20 min	30 min	40 min
Crystal morphology			
Time for crystallization	50 min	60 min	
Crystal morphology			

(c)

Fig S7. Crystal habits of PCA re-crystallized (a) without co-former, (b) with OXADH, and (c) with MAL, in water in a 500 mL vessel, sampled at various time points during crystallization (scale bar: 200 μm).

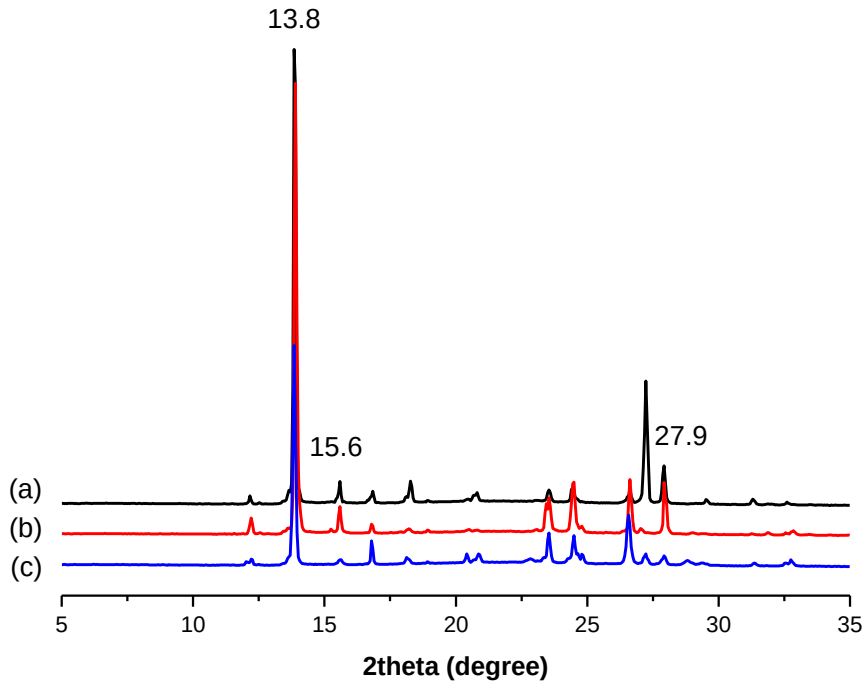


Fig. S8 PXRD patterns of PCA recrystallized (a) without co-former, (b) with OXADH, and (c) with MAL, in water in a 500 mL vessel. All PXRD patterns matched with the one of Form I PCA. The peaks labeled by their 2 θ values were the characteristic diffraction peaks of Form I PCA.

References

[1] C. Wales, Doctoral dissertation, University of Glasgow, Glasgow, Scotland, 2013.
[2] H. L. Lee, H. Y. Lin, and T. Lee, *Org. Process Res. Dev.,* 2014. **18**, 539-545.
[3] P. D. Martino, P. Conflant, M. Drache, J.-P. Huvenne, A.-M. Guyot-Hermann, *J. Thermal Anal.* 1997, **48**, 447-458.
[4] H. Takahashi, R. Chen, H. Okamoto, and K. Danjo. *Chem. Pharm. Bull*. 2005, **53**, 37-41.