

Investigation of co-crystallization using carbamazepine

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Experiment

Crystal 16 was used to study the formation of co-crystals with Carbamazepine as a sample compound. When the mixing ratio of Carbamazepine and co-former was changed (by changing the mole fraction), and the possibility of co-crystallization was investigated by observing how the saturation temperature (Ts) changed, a stable region (where Ts increased) appeared, inferring the formation of co-crystals.

*Information on sample compounds

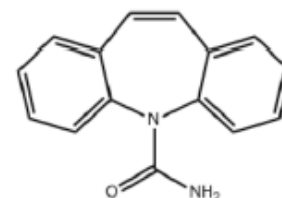
Carbamazepine (CBZ)

CAS No.: 298-46-4

Chemical formula : C₁₅H₁₂N₂O

Molecular weight: 236.27

Solubility: 25 mg/mL (25° C) in EtOH Value on solubility curve



Co-formers

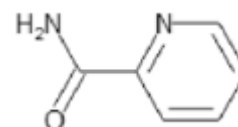
Picolinamide (PA)

CAS Number : 1452-77-3

Chemical formula : C₆H₆N₂O

Molecular weight: 122.13

Solubility: 150 mg/mL (25° C) in EtOH Value on solubility curve



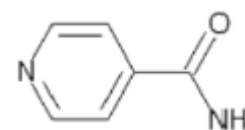
Isonicotinamide (INA)

CAS Number : 98-92-0

Chemical formula : C₆H₆N₂O

Molecular weight: 122.13

Solubility: 70 mg/mL (25° C) in EtOH Value on solubility curve



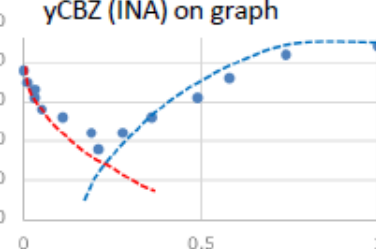
1. Preparation of measurement sample

Fourteen different EtOH solutions were prepared in conformance with the red portions of the table below.

In the case of CBZ-INA

		$\chi_{CBZ} / \chi_{CBZ}^*(T) + \chi_{INA} / \chi_{INA}^*(T) = 1$				$y_{CBZ} = \chi_{CBZ} / (\chi_{CBZ} + \chi_{INA})$			
CBZ and INA									
	Ts	$\chi_{CBZ}^*(T)$	χ_{CBZ}	$\chi_{INA}^*(T)$	χ_{INA}	yCBZ	CBZ(mg)	INA(mg)	
1	44	0.050/236	0.050/236	-	0	1	50	0	
2	42	0.048/236	0.045/236	0.120/122	0.008/122	0.74	45	8	
3	36	0.040/236	0.035/236	0.10/122	0.013/122	0.58	35	13	
4	31	0.038/236	0.031/236	0.09/122	0.017/122	0.49	31	17	
5	26	0.031/236	0.023/236	0.08/122	0.021/122	0.36	23	21	
6	22	0.025/236	0.017/236	0.07/122	0.022/122	0.28	17	22	
7	18	0.022/236	0.013/236	0.06/122	0.025/122	0.21	13	25	
8	22	0.025/236	0.014/236	0.07/122	0.031/122	0.19	14	31	
9	26	0.031/236	0.011/236	0.08/122	0.052/122	0.11	11	52	
10	28	0.035/236	0.009/236	0.08/122	0.059/122	0.05	9	59	
11	31	0.038/236	0.007/236	0.09/122	0.073/122	0.03	7	73	
12	33	0.039/236	0.005/236	0.10/122	0.087/122	0.03	5	87	
13	35	0.040/236	0.003/236	0.11/122	0.102/122	0.01	3	102	
14	38	0.042/236	0	0.12/122	0.120/122	0	0	120	

Relation between Ts and yCBZ (INA) on graph



A graph of Ts and yCBZ was generated using the values in the table. If no co-crystallization occurs, the dissolution temperature of each yCBZ sample should be similar to the above curve.

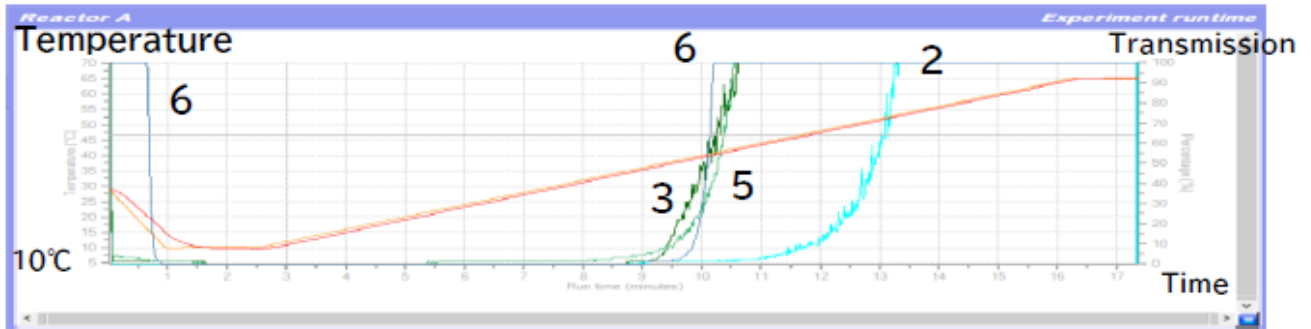
* : The saturation mole fraction of each component at the indicated temperature. Ts values are read from the graph of the solubility curve of each component.

2. Selection of measurement conditions

A total of 10 to 12 different sample solutions were used for each combination and measurement started from 10 C. The temperature was raised to 65 C at 4 C/min and the experiment was terminated after waiting for 1 minute.

3. Measurement results

C16 Example of measurement screenshot for CBZ-INA (sample numbers: 2, 3, 5, 6)

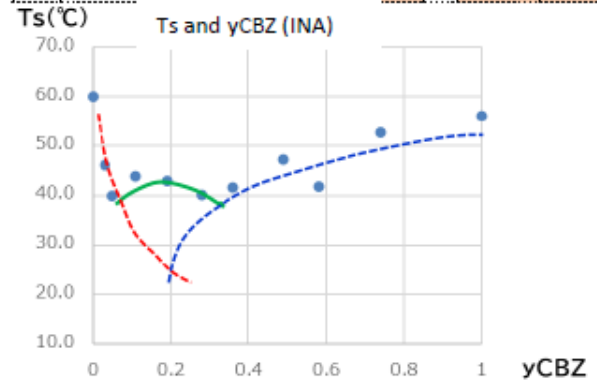
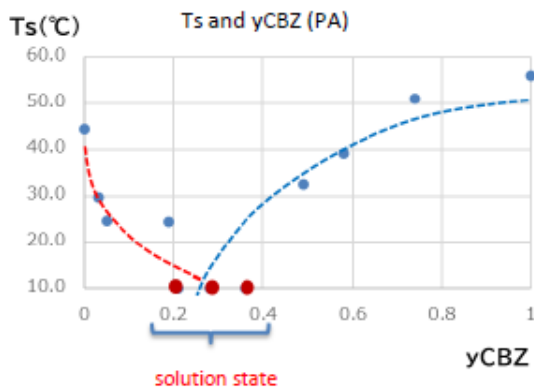


CrystalClear Analysis Example (CBZ-INA Sample No. 6)



	Ts (predicted value)	Ts (actual measured value)	yCBZ	CBZ(mg)	PA(mg)
1	44	56.0	1	50	0
2	42	51.0	0.64	45	13
3	36	39.1	0.44	35	23
4	31	32.6	0.31	30	34
5	26	10.0	0.26	24	34
6	22	10.0	0.18	18	42
7	18	10.0	0.12	14	51
8	22	24.5	0.10	14	62
9	26	28.8	0.06	11	103
11	31	29.7	0.03	7	131
14	38	44.4	0	0	210

	Ts (predicted value)	Ts (actual measured value)	yCBZ	CBZ(mg)	INA(mg)
1	44	56.0	1	50	0
2	42	52.7	0.74	45	8
3	36	41.9	0.58	35	13
4	31	47.3	0.49	31	17
5	26	41.6	0.36	23	21
6	22	40.1	0.28	17	22
8	22	42.9	0.19	14	31
9	26	43.8	0.11	11	52
10	28	39.9	0.05	9	59
11	31	46.2	0.03	7	73
14	38	60.1	0	0	120



Investigation of co-crystallization using Carbamazepine

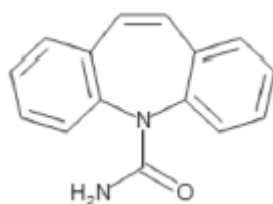
Result:

In the case of CBZ and INA, for a sample with a y_{CBZ} of approximately 0.2, a solution was obtained after mixing and stirring for a while, and new crystals were then precipitated. The crystals dissolved at approximately 45°C. Co-crystal formation was therefore considered to have occurred. Under the same conditions no crystal precipitation was observed for CBZ and PA near y_{CBZ} 0.2.

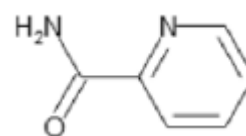
Next steps

We plan to compare the respective Raman spectra of CBZ, INA, and precipitated crystals.

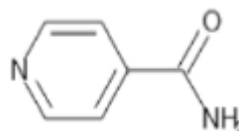
Reference data (manufacturer's announcement)



CBZ (carbamazepine)



PA (picolinamide)



INA (isonicotinamide)

$$Y_{CBZ} = X_{CBZ} / (X_{CBZ} + X_{co-former})$$

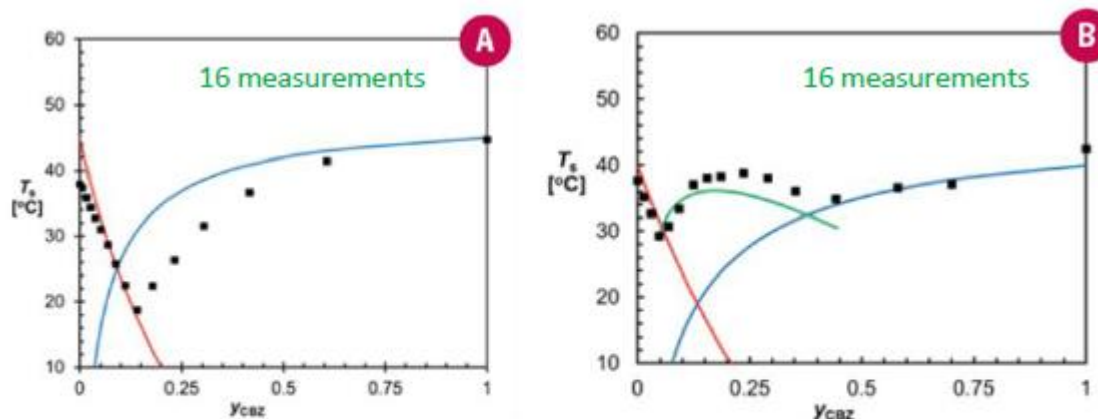


Figure 5: The saturation temperature T_s [°C] as a function of the solvent-excluded mole fraction Y_{CBZ} of CBZ with co-former PA (a) and INA (b). The saturation temperatures of the single-component API and co-former and the co-crystal predicted using the van't Hoff parameters are shown as solid lines from the pure-component axes.