

## **Preparation and optimization of Nano-sized cocrystals using quality by design approach**

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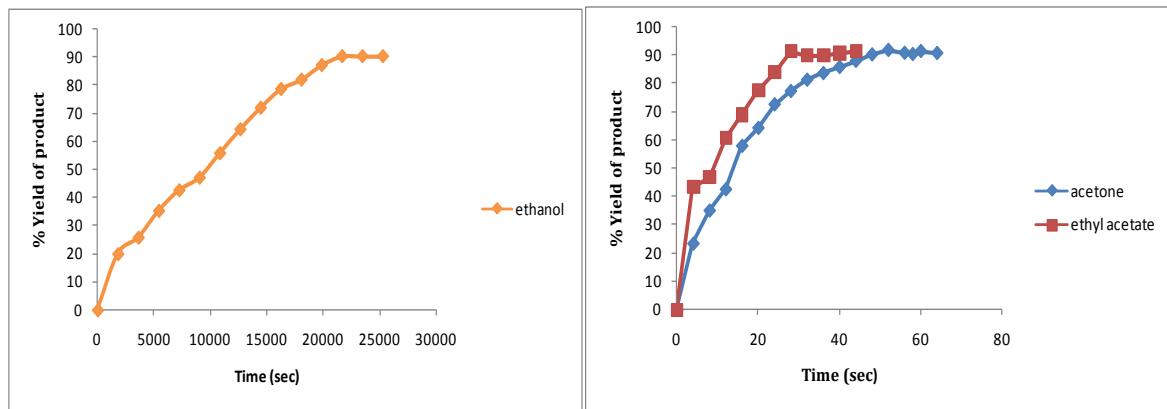
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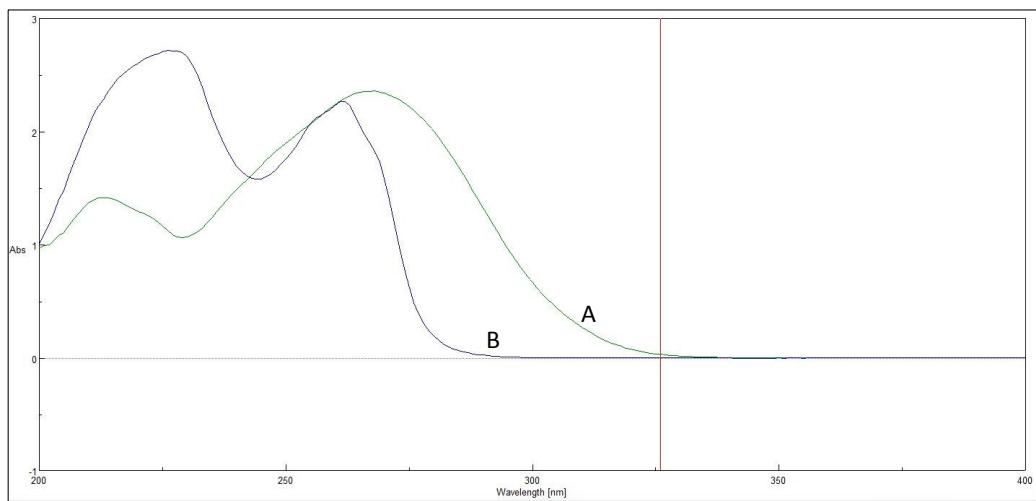
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## Supplementary Information

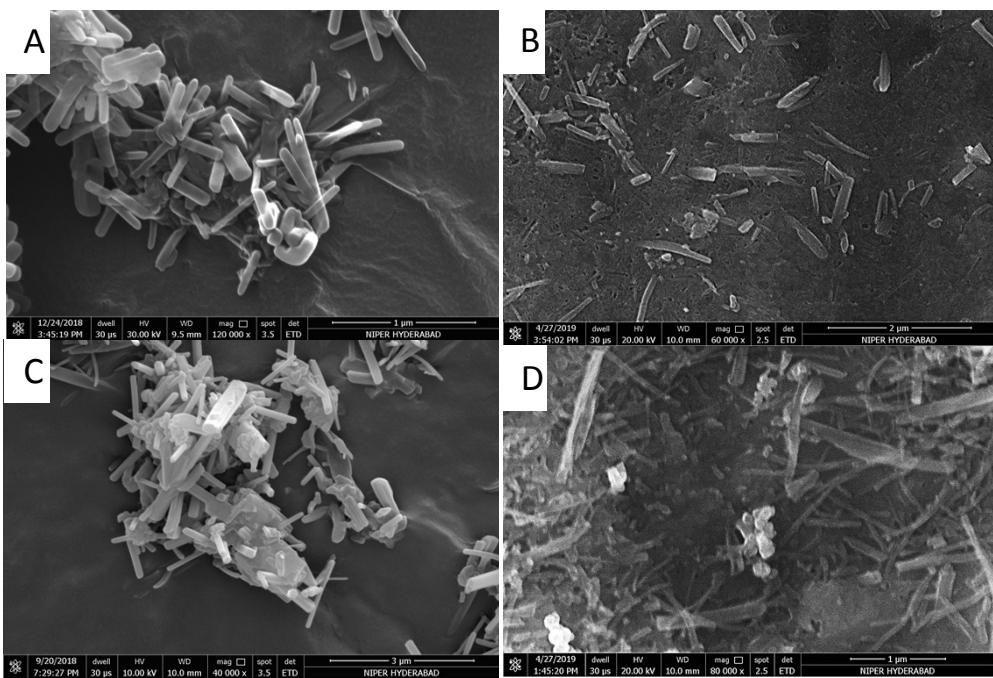
### Figures



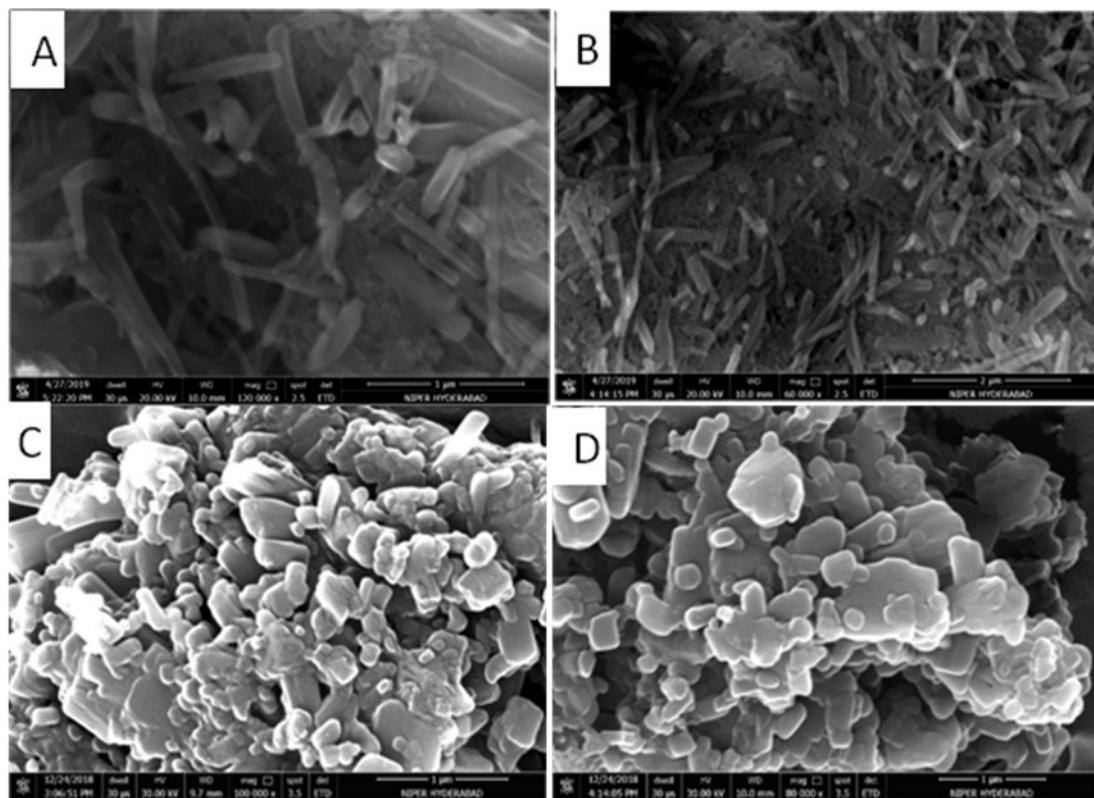
**Figure S1:** Precipitation time determination for Damkohler number with different solvents and n-hexane as antisolvent.



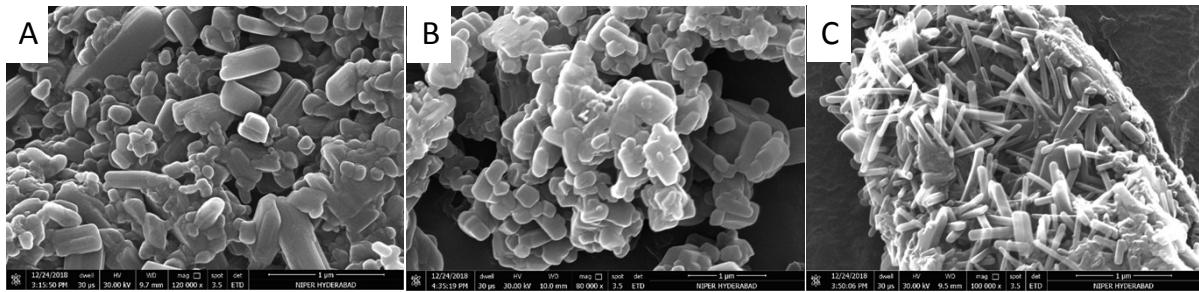
**Figure S2:** UV spectra overlay of (A) carbamazepine (B) nicotinamide



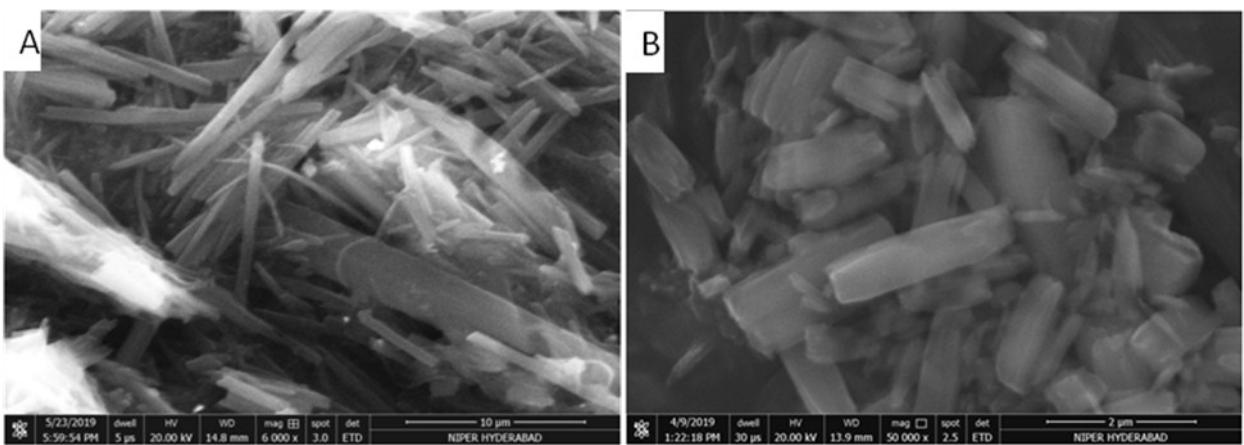
**Figure S3:** SEM images of nanocrystals prepared using solvent to antisolvent ratio (A) 33:67 (scale = 1  $\mu$ m) (B) 40:60 (scale = 2  $\mu$ m) (C) 45:55 (scale = 3  $\mu$ m) (D) 50:50 (scale = 1  $\mu$ m)



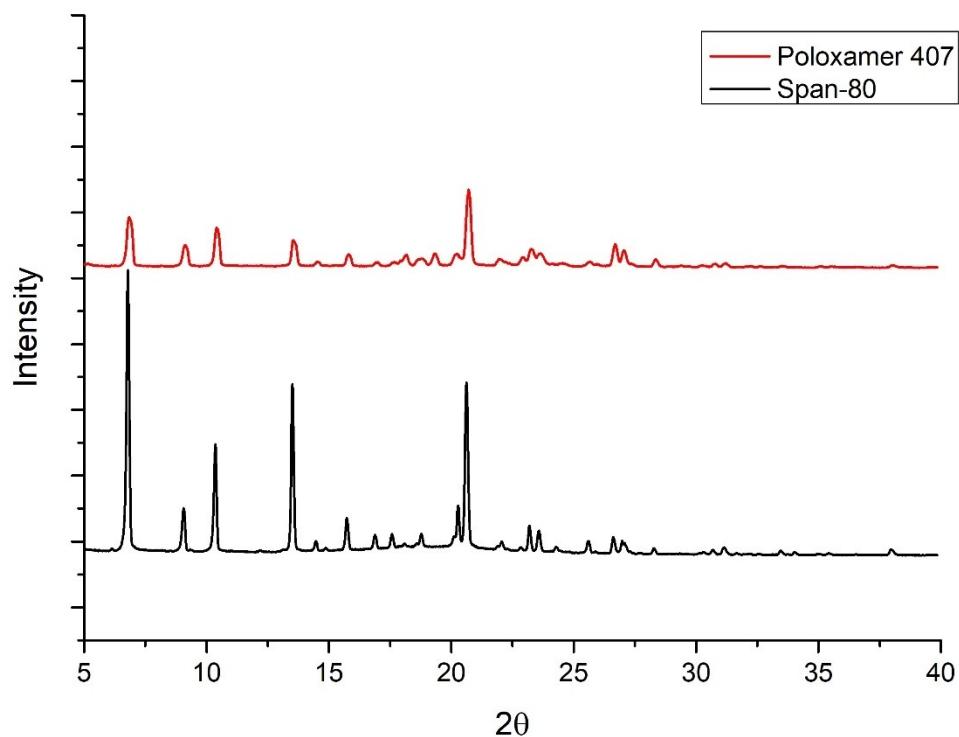
**Figure S4:** SEM images of nanocrystal prepared using (A) 0.1 % (B) 0.2 % (C) 0.3 % (D) 0.4 % concentration of stabilizers. Scale represent 1 $\mu$  scale except B (2 $\mu$  scale)



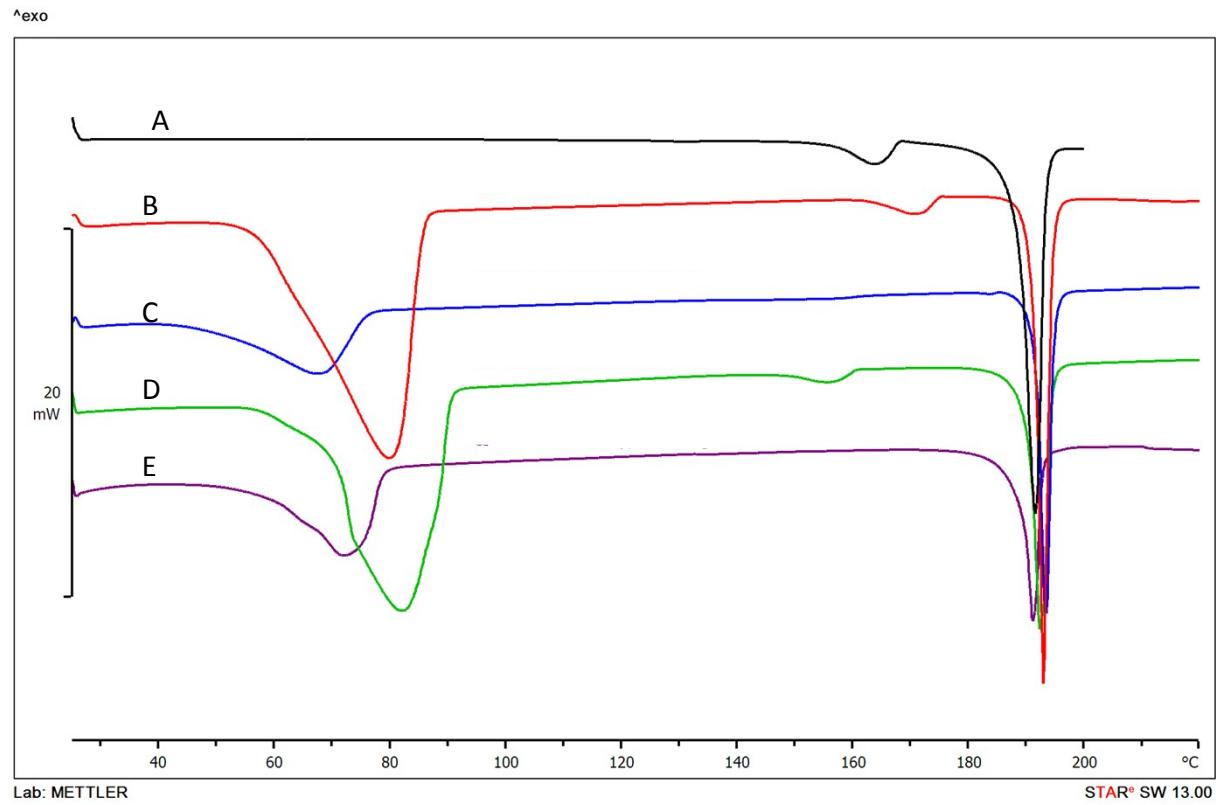
**Figure S5:** SEM images of nanocrystals prepared at (A) 250 rpm (B) 500 rpm (C) 750 rpm. (1 $\mu$  scale)



**Figure S6:** SEM images of nanocrystals prepared at (A) 40 °C (B) 60 °C. Scale 10  $\mu$  for A and 2  $\mu$  for B.



**Figure S7:** PXRD pattern of carbamazepine-nicotinamide nano-cocrystal with poloxamer-407 and span-80



**Figure S8:** DSC thermograph of (A) plain drug , solid residue of solubility samples of (B) drug (C) physical mixture (D) cocrystal (E) nano-cocrystal in 1 % w/v aqueous SLS solution.

### Tables

**Table S1:** Analysis of variance of S/N ratio

Sr no	Variation	DF	Sum of squares	F ratio (F)	P-value (P)
1	Stabilizers	2	1578.08	0.08	0.002
2	Stabilizer concentration % w/v	2	575.63	12.9	0.036
3	Sonication	1	63.27	1.03	0.333
4	Temperature (°C)	1	28.87	0.47	0.508
5	Stirring speed (rpm)	1	4.91	4.71	0.783
6	Error	10	611.46	-	-
7	Total	17	2883.97	-	-

**Table S2:** Response of S/N ratio

Coded level	Factors				
	A	B	C	D	E
1	68.40	71.79	66.76	66.37	63.36
2	51.69	63.99	62.41	63.69	65.80
3	73.65	57.97	-	-	-
Delta	21.96	13.81	4.35	2.69	2.43
Rank	1	2	3	4	5

**Table S3:** Dissolution parameters

Parameters	Drug	Cocrystal	Nano-cocrystals	Physical mixture
Q <sub>15</sub>	62.5	64.78	97.95	61.96
DE <sub>15</sub>	0.47	0.46	0.71	0.43
F <sub>2</sub>	-	84.29	25.19	67.56