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Ethinyl estradiol cocrystals assembled by chains structures: improvement in stability and solubility

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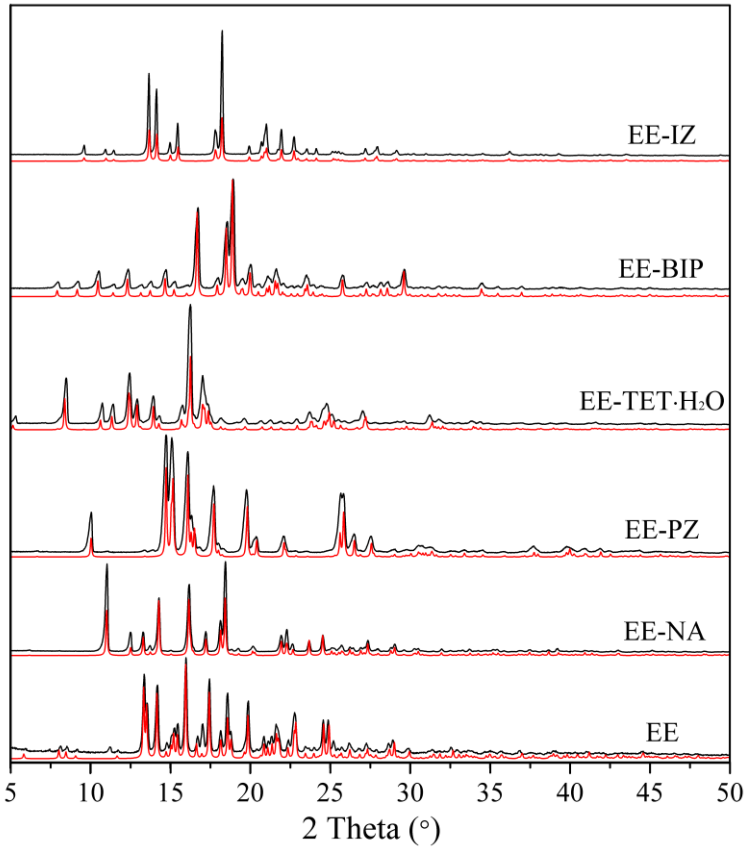

Fig. S1 Overlay of experimental (black) and the simulated (red) PXRD patterns generated from the single crystal diffraction data.

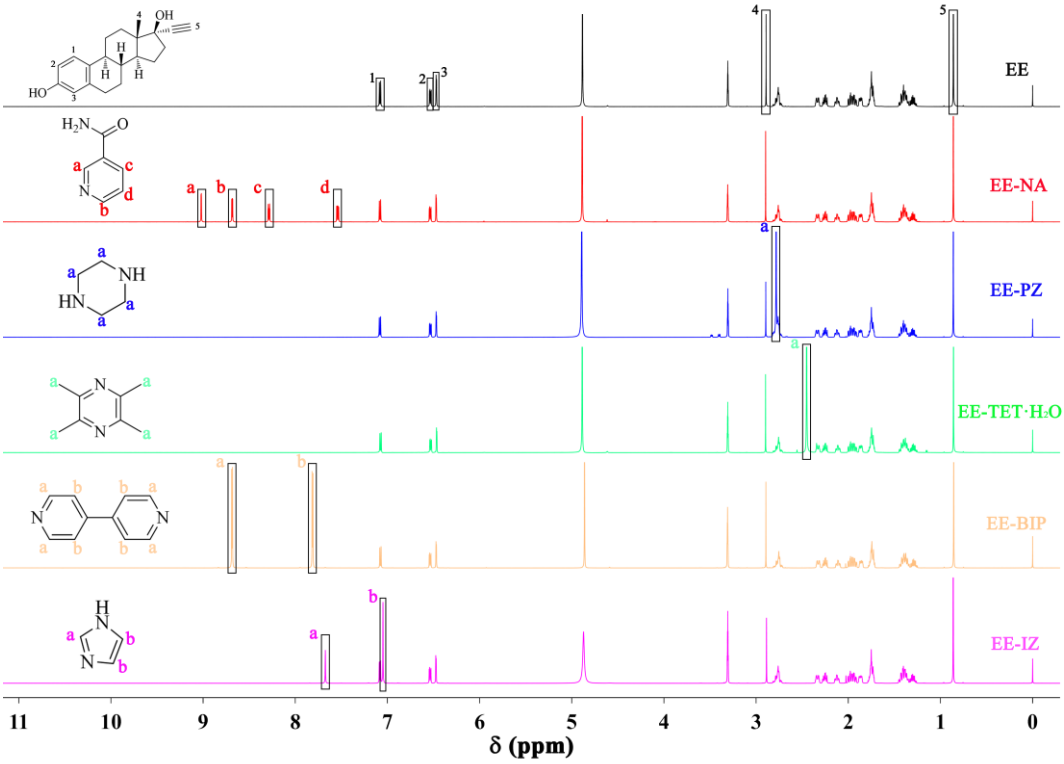

Fig. S2 ^{1}H NMR spectra of EE and its cocrystals.

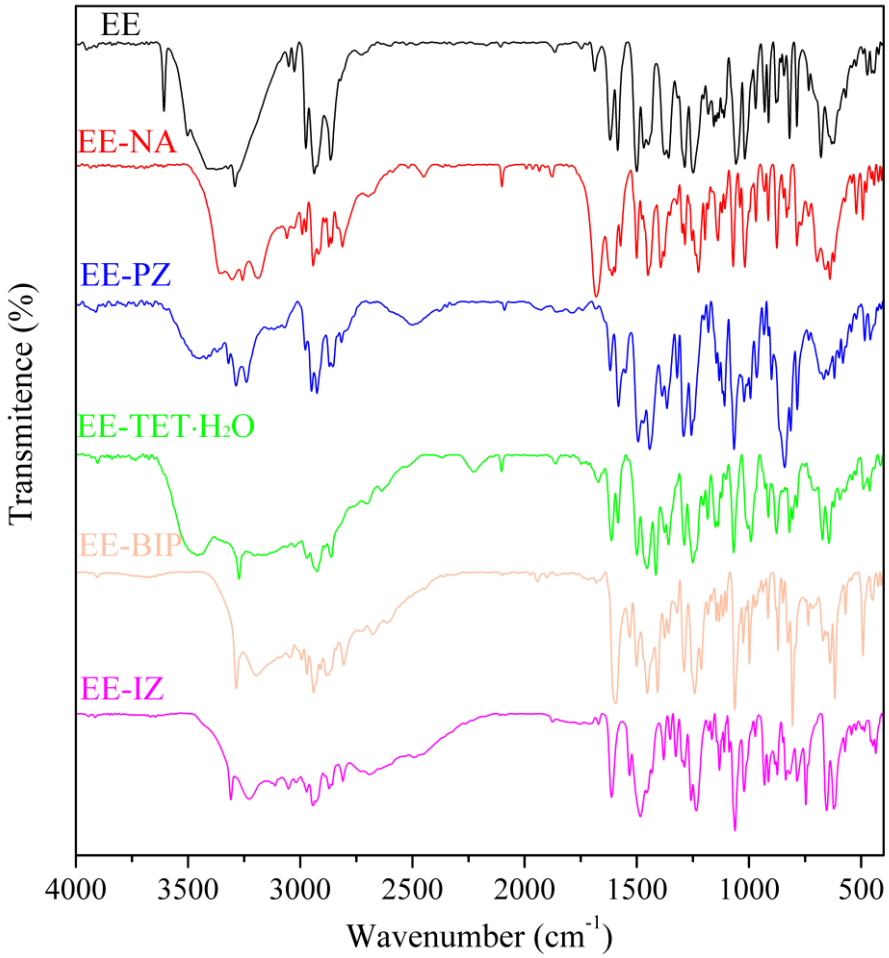

Fig. S3 FTIR spectra of EE and its cocrystals.

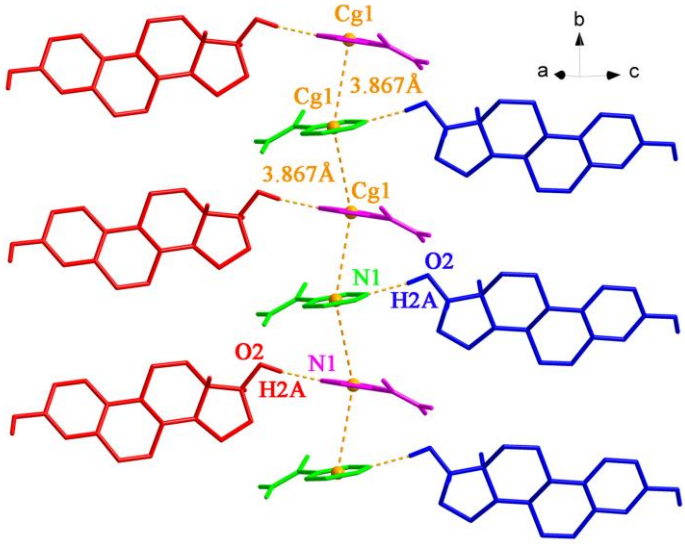

Fig. S4 The “hub” observed in the EE-NA crystal.

The dehydrated product of EE-TET·H_2O is a new anhydrous cocrystal, because its unique PXRD pattern is different from that of EE-TET·H_2O. The dissolution performance of EE-TET is similar to EE-TET·H_2O. The results of stability and hygroscopicity experiments suggest EE-TET can turn into EE-TET·H_2O in humidity environment.

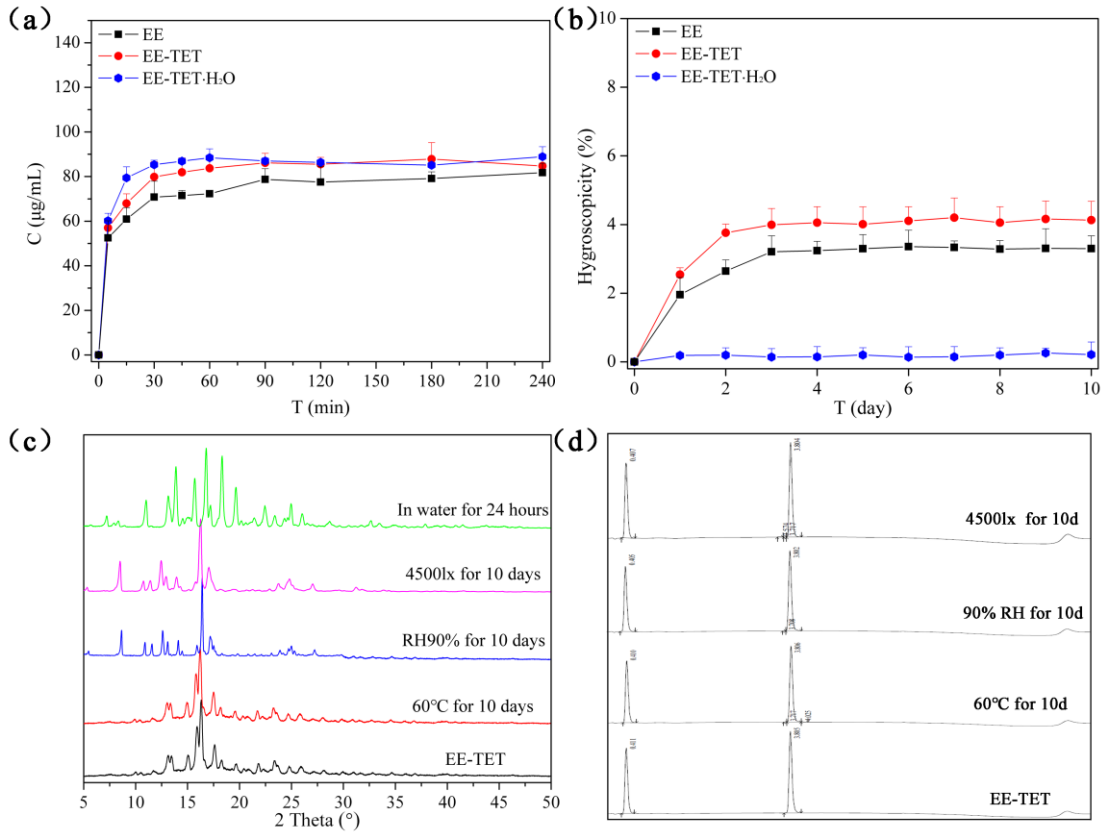

Fig. S5 The stability and dissolution performance of EE-TET·H_2O. (a) dissolution performance, (b) hygroscopicity, (c) stability and (d) the impurity analysis of stability experiments of EE-TET.

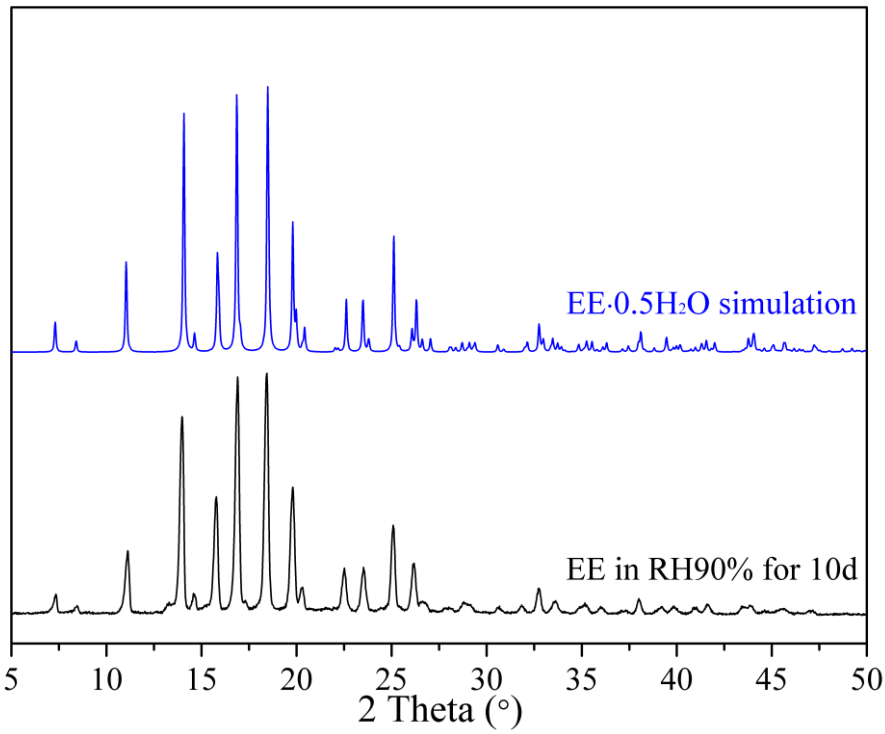

Fig. S6 The comparison of high humidity stability samples of EE and EE hemihydrate simulation by PXRD[1].

Injection Volume	0.3 μL
Column	XBRIDGE 3.5um 2.1*50mm
Mobile phase	H_2O(0.05%TFA)-ACN(0.05%TFA), ACN from 10% to 100% over 7minutes hold 1 min.
Oven temperature	60 °C
Flow rate	0.8 mL/min
Instrument	SHIMADZU LC-2010A
Detector	214 nm

A: Original sample

B: 60℃ for 10 days

C: 90% RH for 10 days

D: 4500 lx for 10 days

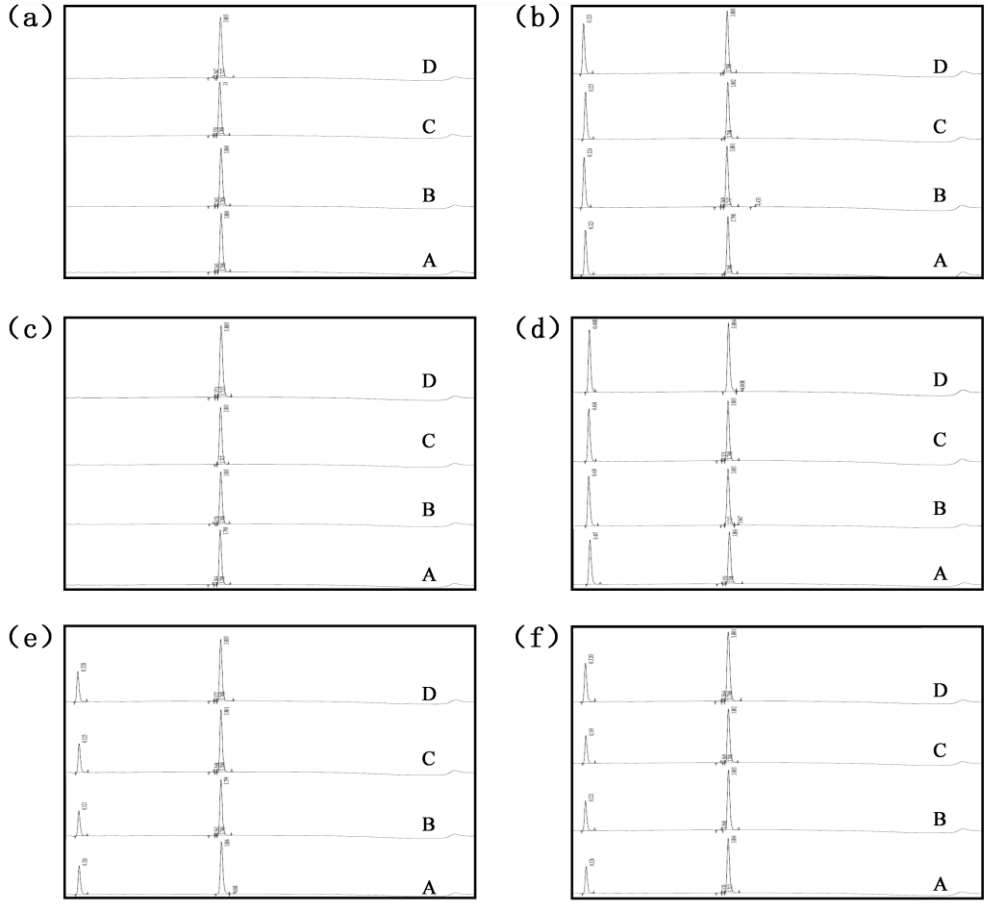

Fig. S7 Impurity analysis of stability experiments for all cocrystals. (a) EE, (b) EE-NA, (c) EE-PZ, (d) EE-TET·H_2O, (e) EE-BIP and (f) EE-IZ.

References:

1. C. Guguta, I. Eeuwijk, J. M. M. Smits and R. de Gelder, *Cryst. Growth Des.*, 2008, **8**, 823-831