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Electronic Supplementary Information

Taming photo-induced oxidation degradation of dihydropyridine drugs through cocrystallization

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Experimental Section.

Materials. The sample of **NFD** (form A, the most stable polymorph) used in the present work was purchased from Adamas Reagent, Ltd. with purity greater than 98%. All analytical grade solvents were purchased from Sinopharm Chemical Reagent Company, Ltd. and used without further purification.

Preparation of NFD·INA form I. Bulk powder sample of **NFD·INA** form I was synthesized by reaction crystallization. I**NA** was added to 4 mL methyl isobutyl ketone solvent to give a saturated solution and filtered. Then, an excess amount of **NFD** was added to the saturated solution. The resulting suspension was allowed to react in 48 hours at room temperature and was subjected to centrifugation. The cocrystal powder was obtained and dried in vacuum overnight. Yield, 85.3%. Anal. Calcd for $C_{23}H_{24}N_4O_7$: C, 58.97%; H, 5.16%; N, 11.96%. Found: C, 59.03%; H, 4.99%; N, 12.06%. Single crystal of **NFD·INA** form I was lucky to harvest by slow evaporation the unsaturated isopropyl acetate solution, which was dissolving the cocrystal powder. In addition, liquid-assisted grinding method can also successfully obtain the **NFD·INA** form I powder. **NFD** and **INA** in a 1:1 molar ratio were ground with drops of methanol or methyl isobutyl ketone after a few minutes.

Preparation of NFD·INA form II. During the preparation of **NFD·INA** form I, particularly used methyl isobutyl ketone as solvent, a polymorph was occasionally discovered. Yield, 78.5%. Anal. Calcd for $C_{23}H_{24}N_4O_7$: C, 58.97%; H, 5.16%; N, 11.96%. Found: C, 58.54%; H, 5.26%; N, 11.53%. Single crystal with good quality for single crystal structure determination of form II was collected by slow evaporation

the final filtrate.

Preparation of NFD·PCM. Bulk powder of **NFD·PCM** was synthesized by a similar method to **NFD·INA** form I except using the isopropyl acetate as the crystallization solvent. Yield, 79.5%. Anal. Calcd for $C_{23}H_{24}N_4O_7$: C, 58.97%; H, 5.16%; N, 11.96%. Found: C, 58.99%; H, 5.18%; N, 11.82%. Single crystal was obtained by slow evaporation of the final filtrate.

Powder X-ray Diffraction (PXRD). PXRD patterns were obtained using a Bruker D8 Advance X-ray diffractometer (Cu Kα radiation). Voltage and current of the generator was set to 40 kV and 40 mA, respectively. Data over the range 3−40° 2θ were collected with a scan rate of 5°/min at ambient temperature. The data were imaged and integrated with RINT Rapid and peaks were analyzed with Jade 6.0 from Rigaku. Calibration of the instrument was performed using a corindon standard (Bruker AXS Korund-probe).

Single-Crystal X-ray Diffraction (SCXRD). X-ray diffractions of all single crystals were carried out at 170(2) K on a Bruker Apex II CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å). Integration and scaling of intensity data was performed using the SAINT program. Data were corrected for the effects of absorption using SADABS. The structures were solved by direct method and refined with full-matrix least-squares technique using SHELX-2014 software. Non-hydrogen atoms were refined with anisotropic displacement parameters, and hydrogen atoms were placed in calculated positions and refined with a riding model. Crystallographic data in cif format have been deposited in the Cambridge Crystallographic Data Center,

CCDC No. 1560784, 1560787, 1560785 for **NFD·INA** form I, **NFD·INA** form II, **NFD·PCM**, respectively. Crystallographic data and refinement details are summarized in Table S1.

Thermogravimetric Analysis (TGA). Thermogravimetric analysis was carried out on Netzsch TG 209F3 equipment. Samples were placed in open aluminum oxide pans and heated at 10 °C min^{-1} to 400 °C. Nitrogen was used as purge gas at 20 mL min^{-1}.

Differential Scanning Calorimetry (DSC). DSC experiments were performed on a DSC TA Q2000 instrument under a nitrogen gas flow of 50 mL·min^{-1} purge. Ground samples weighing 1−3 mg were heated in sealed aluminum pans from 25 to 210 °C at a heating rate 10 °C·min^{-1}. Two-point calibration using indium and tin was carried out to check the temperature axis and heat flow of the equipment.

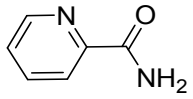
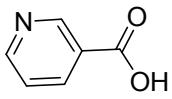
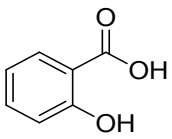
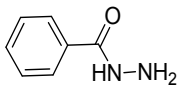
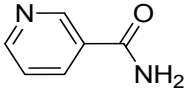
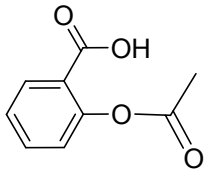
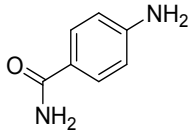
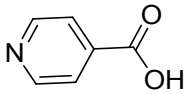
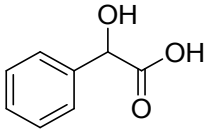
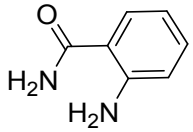
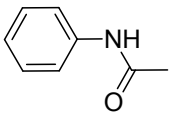
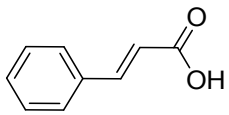
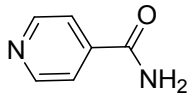
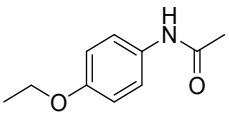
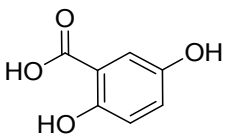
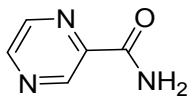
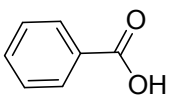
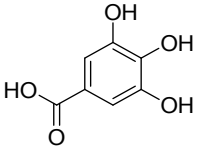
Fourier Transform Infrared (FT-IR) Spectroscopy. Fourier transform-infrared (FT-IR) spectra were collected by a Nicolet-Magna FT-IR 750 spectrometer in the range from 4000 to 350 cm^{-1}, with a resolution of 4 cm^{-1} at ambient conditions.

Hot-Stage Microscopy (HSM). All HSM examinations were performed on a XPV-400E polarizing microscope and a XPH-300 hot stage coupled with a JVC TK-C9201 EC digital video recorder (Shanghai Changfang Optical Instrument Company Ltd.). Crystals of **NFD·INA** form I, **NFD·INA** form II and **NFD·PCM** were focused under the microscope (5*10 times).

Photostability Experiment. It was carried out for **NFD·INA** form I, **NFD·INA** form II, **NFD·PCM** and **NFD** using a stability chamber (SHH-GD, China) at 25 °C with an illuminance of 4000 lx. Prior to conducted, samples were sieved through 100-

mesh sieves and spread across glass plates so as to minimize the effect on powder size. 10 mg of samples were taken out after exposure at the following time intervals: 2, 4, 6, 8 and 10 h. **NFD** content at each time point was determined by high performance liquid chromatography.

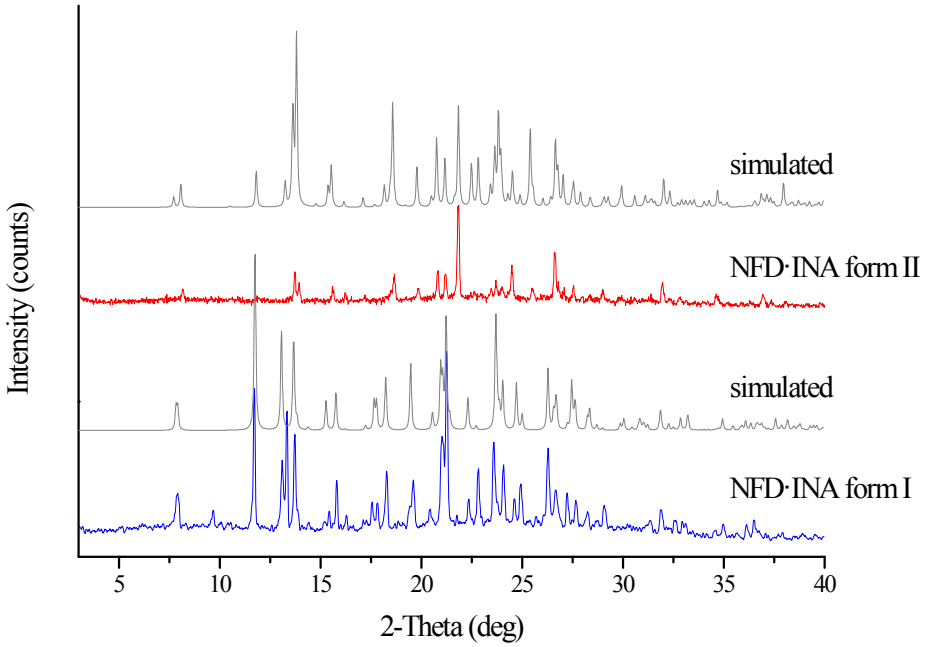
High Performance Liquid Chromatography (HPLC) Analysis. The content of **NFD** was determined by an Agilent 1260 series HPLC (Agilent Technologies) equipped with a quaternary pump (G1311C), diode-array detector (G1315D) set at 236 nm, and a 4.6 × 150 mm, 5 μm Agilent Eclipse plus C18 column. A binary mobile phase composed of 0.1% (v/v) trifluoroacetic acid in water (eluent A) and acetonitrile (eluent B) was delivered at 1 $mL \cdot min^{-1}$. The gradient elution program started with 30% B and kept at 30% B for 2 min, then linearly increased to 90% B in 12 min, and returned to the initial composition in 2 min. The column temperature was set at 35 °C, and the injection volume was 20 μL.

Coformers		Coformers		Coformers	
Picolinamide	✓	Nicotinic acid	✘	Salicylic acid	✘
					
Isoniazide	✘	Nicotinamide	✘	Aspirin	✘
					
4-aminobenzamide	✘	Isonicotinic acid	✘	Mandelic acid	✘
					
Anthranilamide	✘	N-phenylacetamide	✘	Cinnamic acid	✘
					
Isonicotinamide	✓	p-acetophenetidide	✘	2,5-dihydroxybenzoic acid	✘
					
Pyrazinamide	✘	Benzoic acid	✘	Gallic acid	✘
					

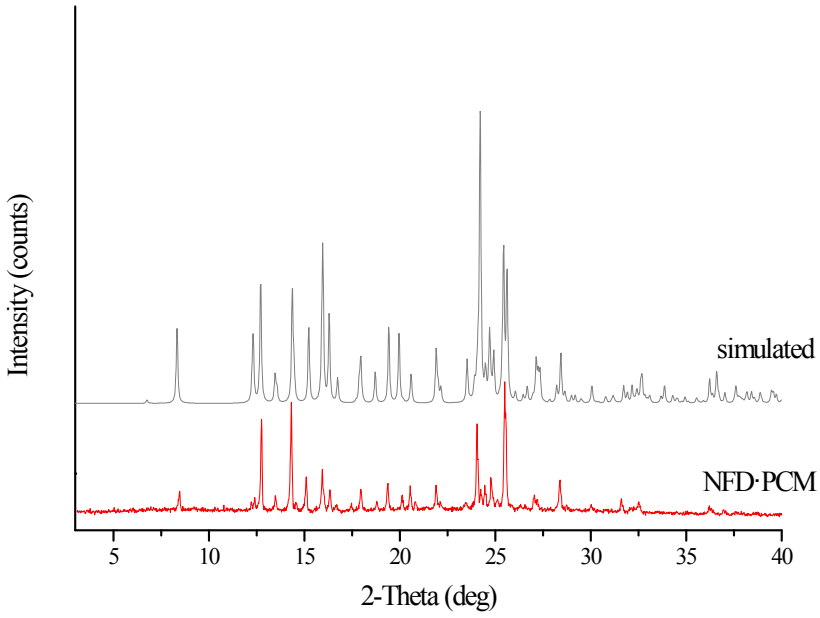
Scheme S1 List of selected coformers.

Table S1 Crystallographic data for **NFD** cocrystals

	NFD·INA form I	**NFD·INA** form II	**NFD·PCM**
formula	$C_{23}H_{24}N_4O_7$	$C_{23}H_{24}N_4O_7$	$C_{23}H_{24}N_4O_7$
crystal system	monoclinic	orthorhombic	triclinic
Space group	$P2_1/n$	$P2_12_12_1$	P-1
Temperature(K)	170	170	170
a (Å)	7.9427(16)	7.8608(9)	7.5743(2)
b (Å)	12.732(3)	12.3313(14)	11.4918(4)
c (Å)	22.382(4)	22.699(3)	13.8653(4)
α (deg)	90	90	106.089(2)
β (deg)	90.080(5)	90	97.442(2)
γ (deg)	90	90	103.739(2)
Cell volume (Å^3)	2263.4(8)	2200.3(4)	1101.47(6)
ρ_{cal} g/cm^3	1.375	1.414	1.412
Z	4	4	2
λ(Mo-Kα)	0.71073	0.71073	0.71073
Independent reflns	5263	5183	5039
S	0.994	1.011	1.052
R_1	0.0570	0.0399	0.0574
R_{int}	0.0516	0.0435	0
wR_2	0.2000	0.1026	0.1360
CCDC	1560784	1560787	1560785



(a)



(b)

Fig. S1 PXRD patterns comparison of experimental and simulated of three cocrystals, (a) **NFD·INA** form I and form II (b) **NFD·PCM**.

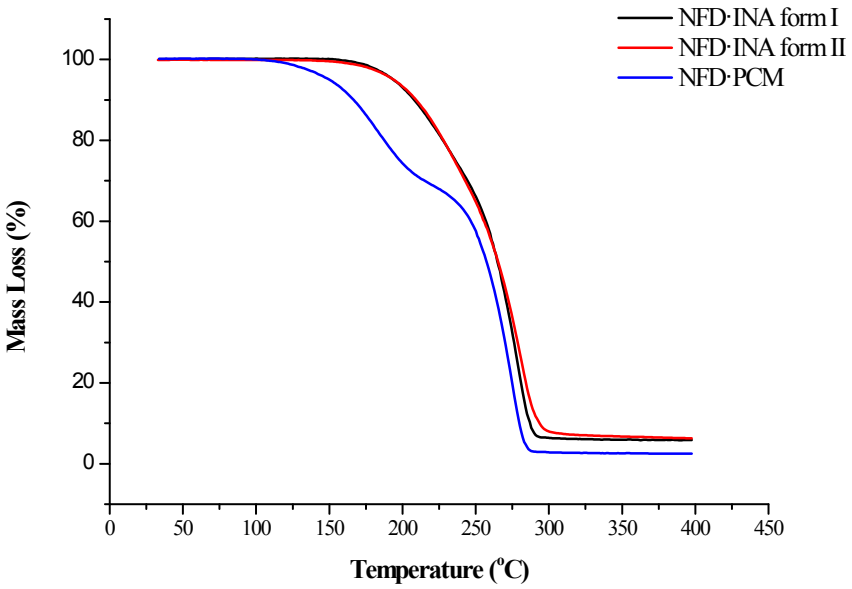


Fig. S2 The TG overlay graphs of three cocrystals.

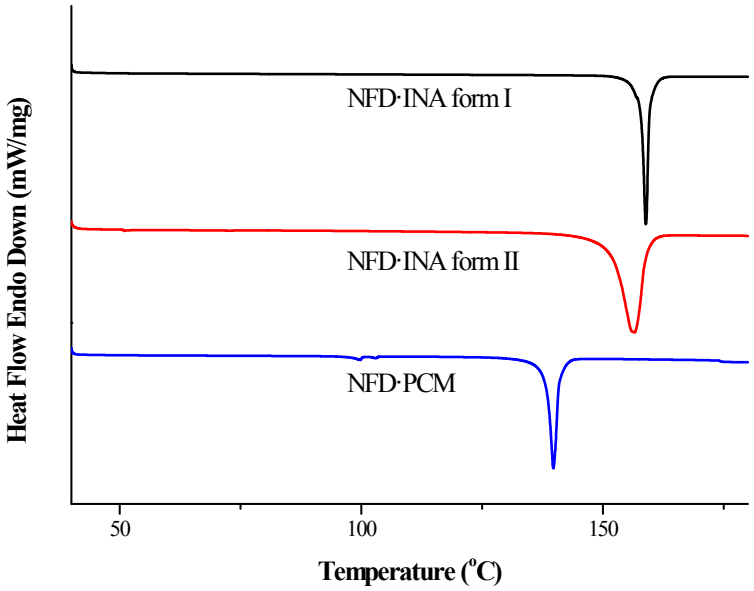


Fig. S3 The DSC overlay graphs of three cocrystals.

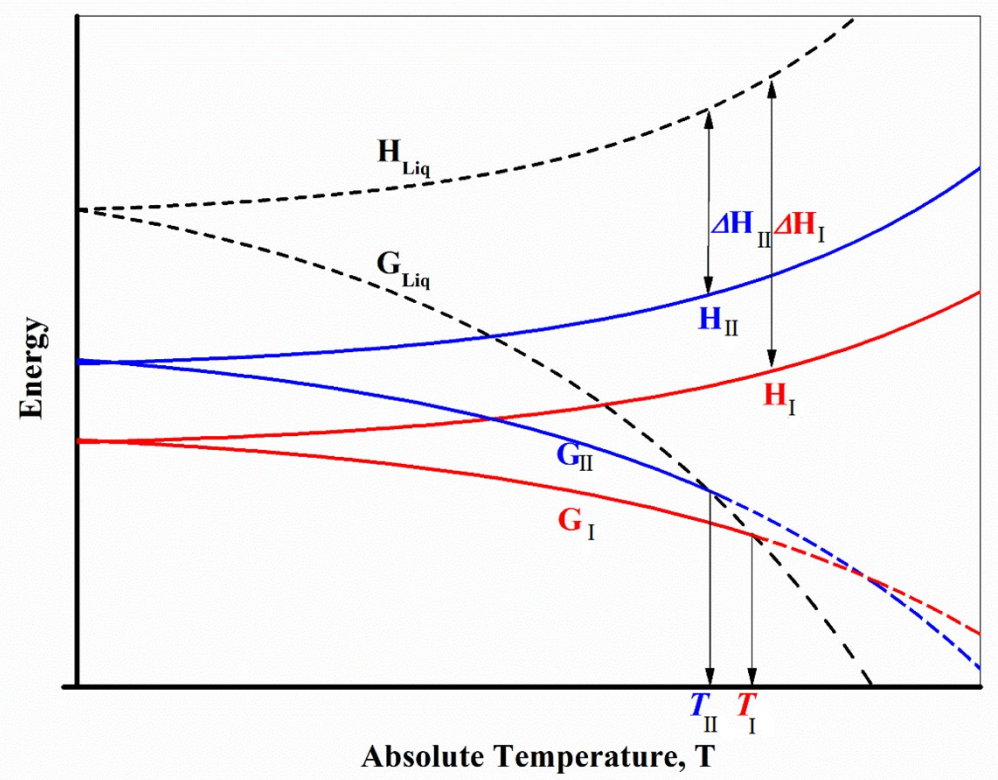
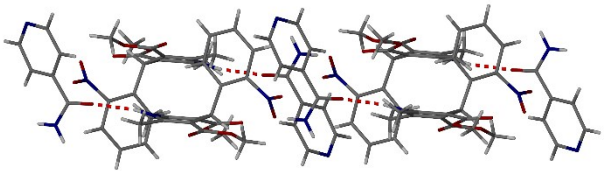
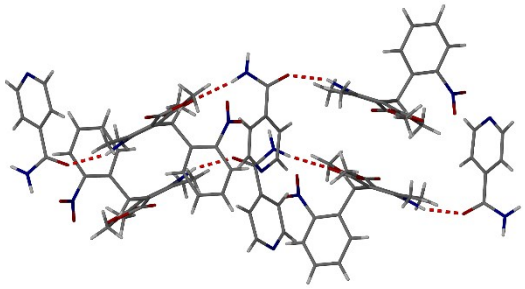


Fig. S4 Energy-temperature diagram of **NFD·INA** form I and **NFD·INA** form II.



(a)



(b)

Fig. S5 (a) Molecule arrangement along the b axis in form I. (b) Packing mode viewed along the b axis in form II.

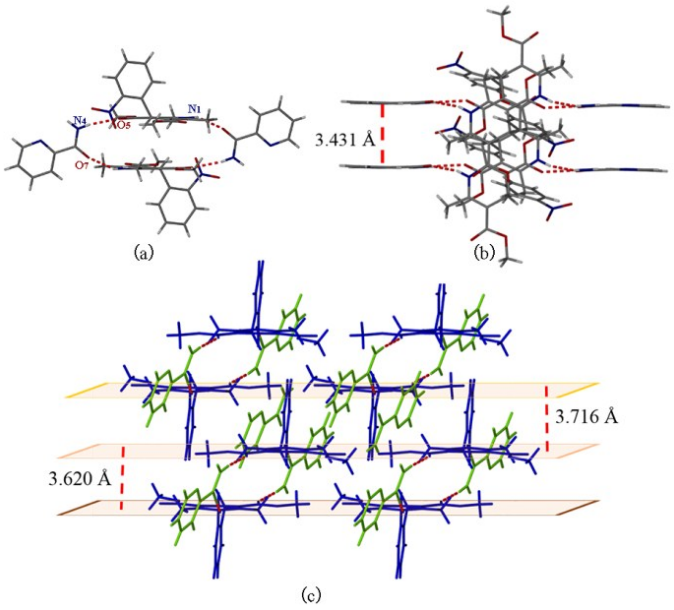


Fig. S6 Single crystal structure of **NFD·PCM**. (a) Hydrogen bonds connection of **NFD** and **PCM** molecules in each tetramer. (b) The distance of pyridine ring centroids in **PCM** molecules and the packing mode in the each adjacent tetramer. (c) The distance of interplanar and neighbouring tetramers.

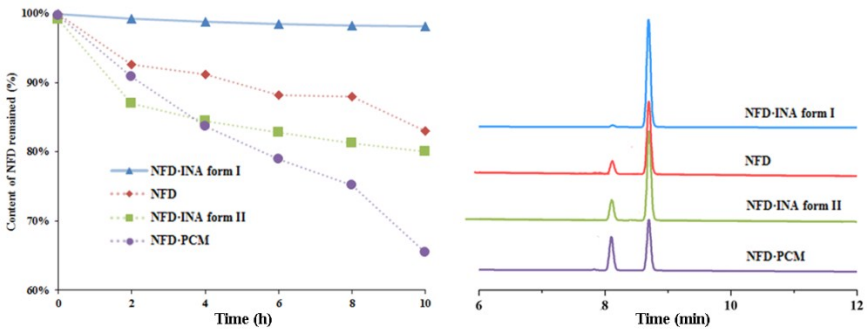
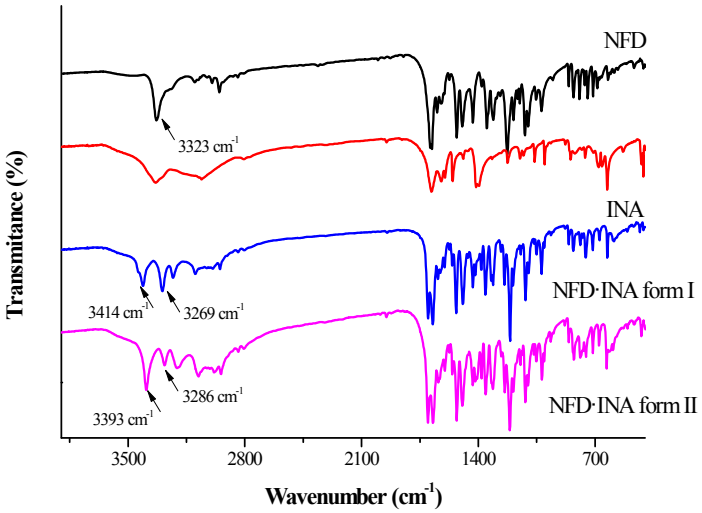
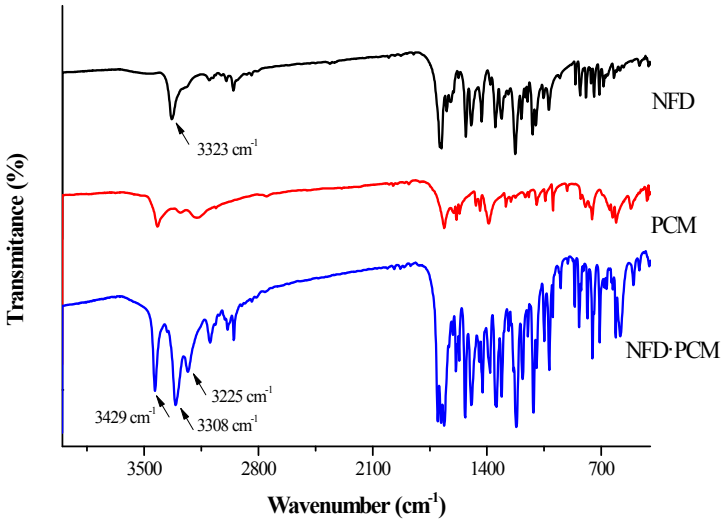


Fig. S7 The remaining content of **NFD** and three cocrystals under 10 h illuminance of 4000 lx.

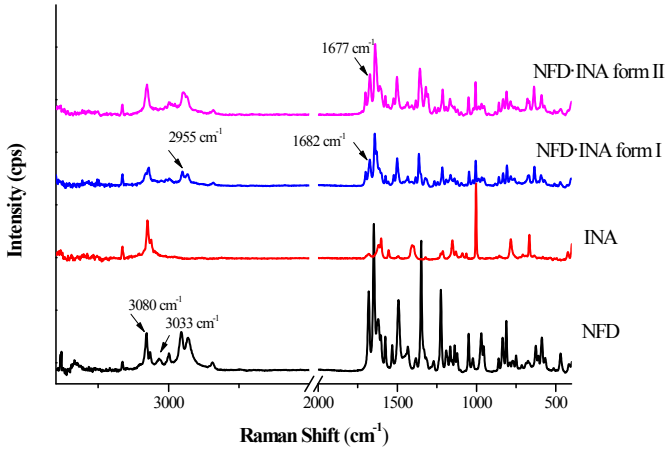


(a)



(b)

Fig. S8 FT-IR spectra of **NFD**, (a) **NFD·INA** form I and **NFD·INA** form II (b) **NFD·PCM.**



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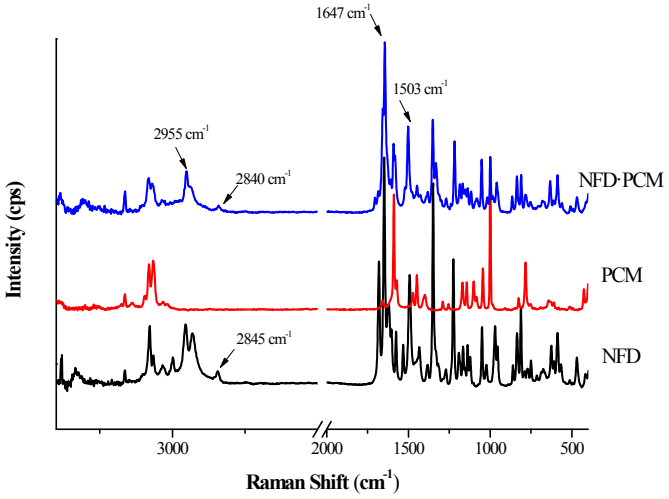

(b)

Fig. S9 Raman spectra of **NFD**, (a) **NFD·INA** form I and **NFD·INA** form II (b) **NFD·PCM.**

In the IR and Raman spectra of three cocrystals, which concludes the **NFD**, coformers and cocrystals, significant differences between **NFD** and three cocrystals can be clearly observed. Different packing mode leads to the distinction bonds vibration of **NFD·INA** form I, **NFD·INA** form II and **NFD·PCM** (black arrows showed).