Electronic Supplementary Information

Drug-drug co-crystallization presents a new opportunity for the development of stable vitamins

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EXPERIMENTAL SECTION

Materials. Vitamins D_2 and D_3 were obtained from J&K Chemical Ltd, with greater than 99% purity. All analytical grade solvents were purchased from Sinopharm Chemical Reagent Co., Ltd and used without further purification.

Preparation of form A. A mixture of VD_2 (3.96 g, 0.01 mol) and VD_3 (3.84 g, 0.01 mol) was dissolved in 0.5 L of acetonitrile in a beaker and evaporated slowly at room temperature. After about 2 days, colorless prism-shaped crystals of form A were harvested and dried under vacuum (7.75 g, 99.4% yield).

Preparation of form B. A mixture of VD_2 (3.96 g, 0.01 mol) and VD_3 (3.84 g, 0.01 mol) was dissolved in 80 mL of acetonitrile in a sealed bottle at 50 °C and fast cooling to room temperature. After about 3 hours, crystalline powder of form B were harvested and dried under vacuum (6.85 g, 87.8% yield).

Thermogravimetric analysis (TGA). Thermogravimetric analysis was carried out in Netzsch TG 209 F3 equipment, using dry air with a nitrogen gas flow of 20 mL/min and a scan rate of 10 °C/min.

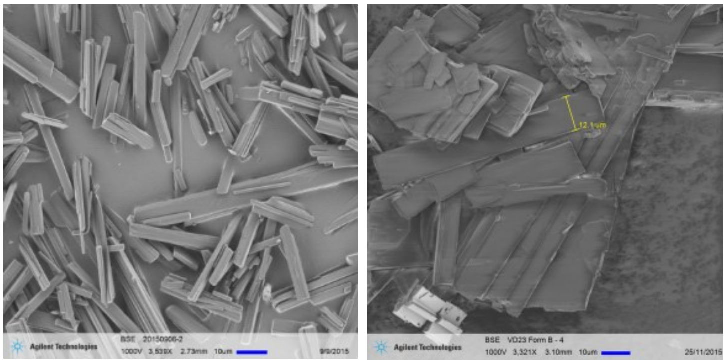
Differential scanning calorimetry (DSC). Differential scanning calorimetry (DSC) was performed with a PerkinElmer DSC 8500 instrument under nitrogen gas flow of 20 mL/min purge. Samples weighting 3−5 mg were heated in standard aluminium pans at scan rates from 5 to 10 °C/min. Two-point calibration using indium and tin was carried out to check the temperature axis and heat flow of the equipment.

Powder X-ray diffraction (PXRD). PXRD patterns were obtained using a Bruker D8 Advance X-ray diffractometer (Cu Kα radiation). The voltage and current applied were 40 kV and 40 mA respectively. Samples were measured in reflection mode in the 2θ range 3–40° with a scan speed of 1.2 °/min (step size 0.025°, step time 1.0 s) using a LynxEye detector. Data were imaged and integrated with RINT Rapid, and the peaks are analysed with Jade 6.0 software from Rigaku. Calibration of the instrument was performed using Corindon (Bruker AXS Korundprobe) standard.

Single crystal X-ray diffraction. Single crystal X-ray diffraction of forms A (0.15 × 0.12 × 0.10 mm^3) and B (0.12 × 0.08 × 0.08 mm^3) was performed on a Bruker Apex II CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å) at 100(2) K. The structures were solved by direct methods and refined with full-matrix least-squares difference Fourier analysis using SHELX-97 software. All non-hydrogen atoms were refined with anisotropic displacement parameters, and all hydrogen atoms were placed in calculated positions and refined with a riding model. Data were corrected for the effects of absorption using SADABS.

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

Raman Spectroscopy. Raman spectra were recorded with the Thermo Scientific DXR Raman microscope equipped with a 532 nm laser. Raman scans range from 3500 to 50 cm^{-1}. Samples were analyzed directly in a glass sheet using 10 mW laser power and 50 μm pinhole spectrograph aperture. Calibration of the instrument was performed using polystyrene film standard.



(1) (b)

Fig. S1 Optical micrographs of (a) form A and (b) form B

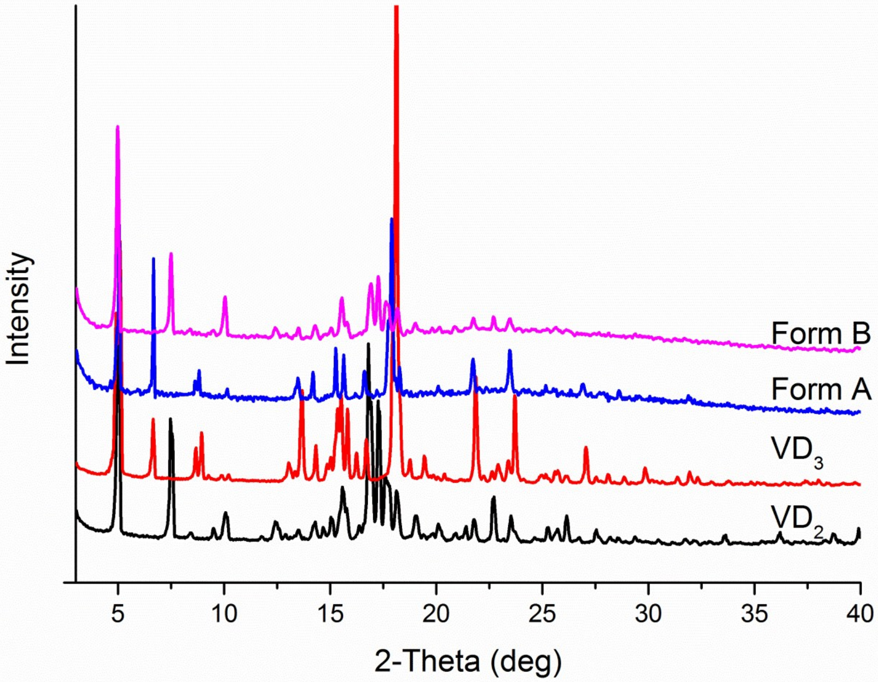


Fig. S2 Comparison of XRPD patterns of VD_2, VD_3, form A, and form B

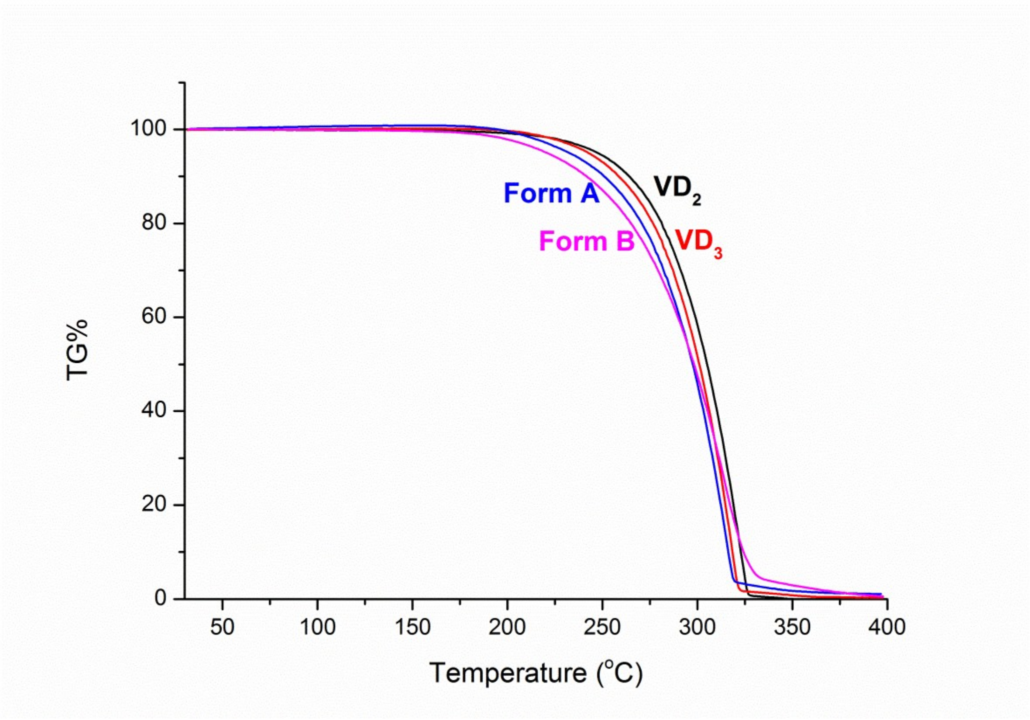


Fig. S3 Comparison of TGA diagrams of VD_2, VD_3, form A, and form B

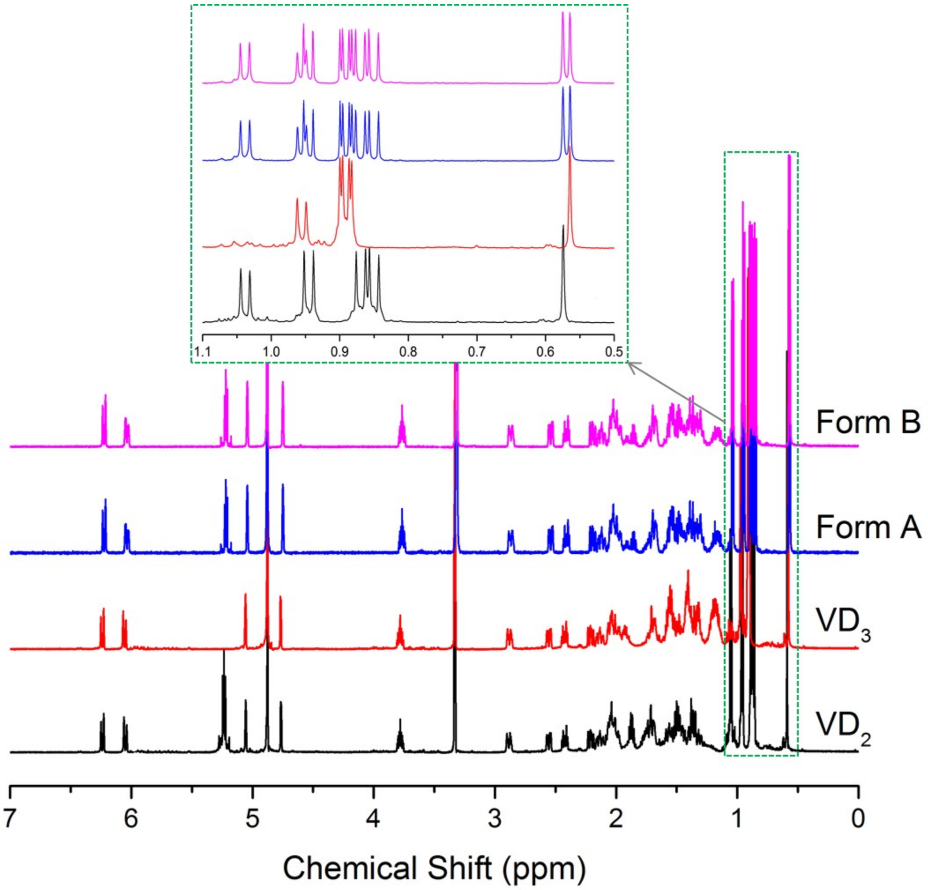
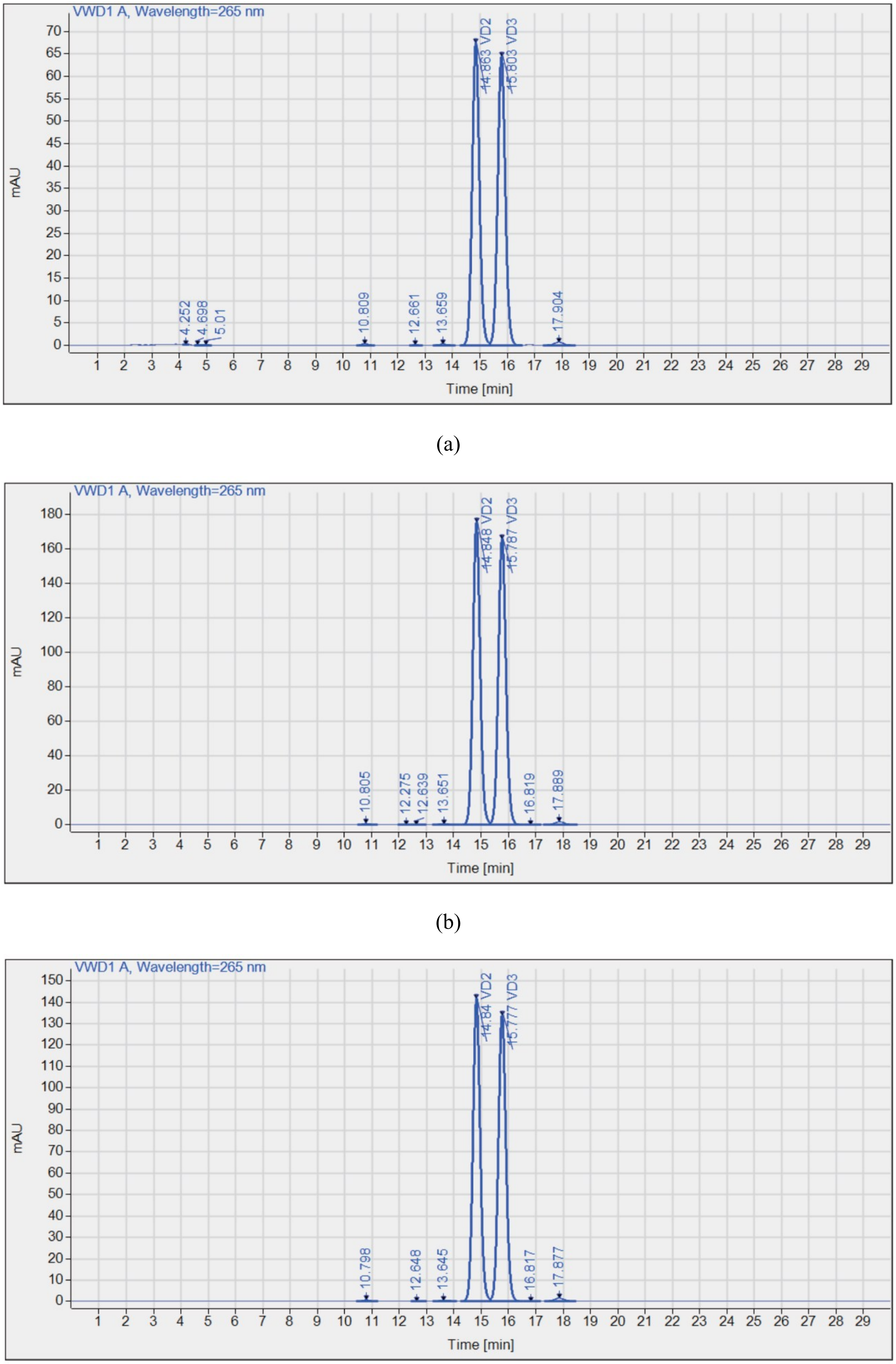


Fig. S4 Comparison of ^1H NMR spectra of VD_2, VD_3, form A, and form B (500 MHz, CD_3OD)



(a)

(b)

(c)

Fig. S5 HPLC chromatograms of (a) 1:1 mixture of VD_2 and VD_3, (b) form A, and (c) form B

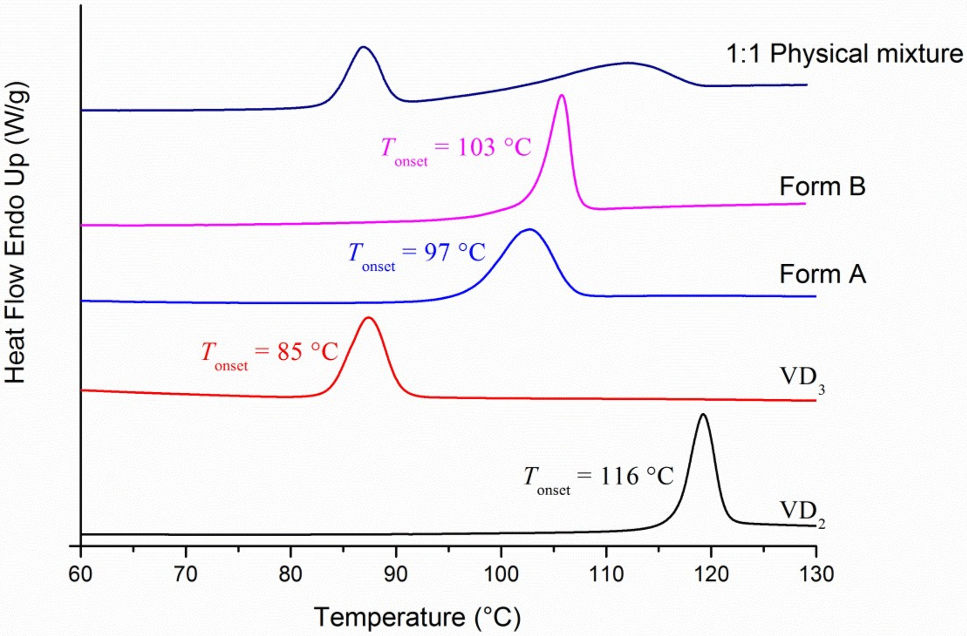


Fig. S6 Comparison of DSC diagrams of $VD_{2,}$ VD_3, form A, and form B

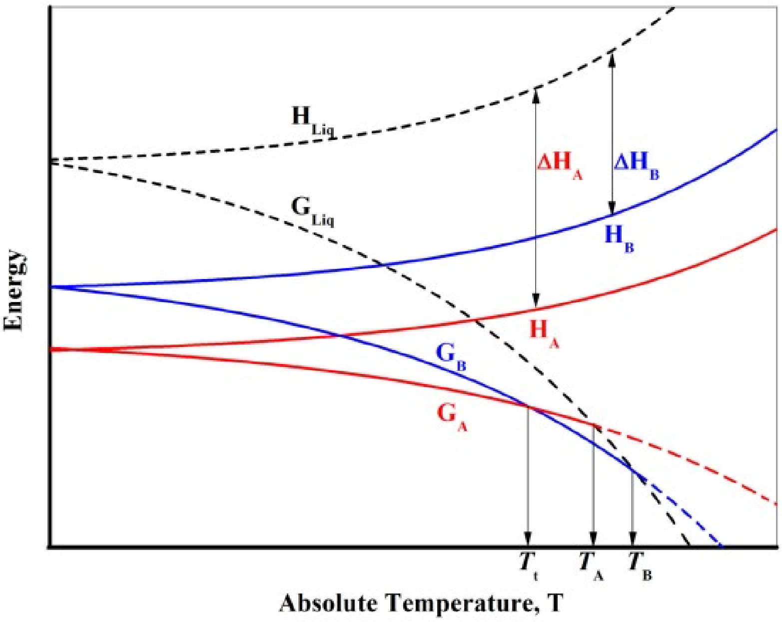


Fig. S7 Energy vs temperature diagram for form A and form B

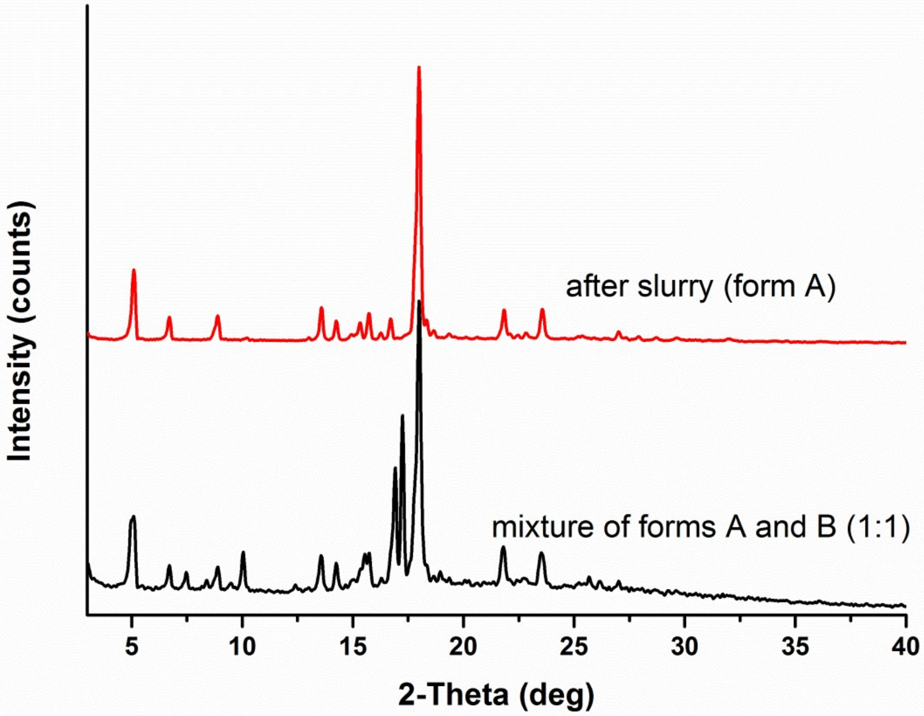


Fig. S8 Solvent-mediated transformation experiment conducted in acetonitrile at room temperature

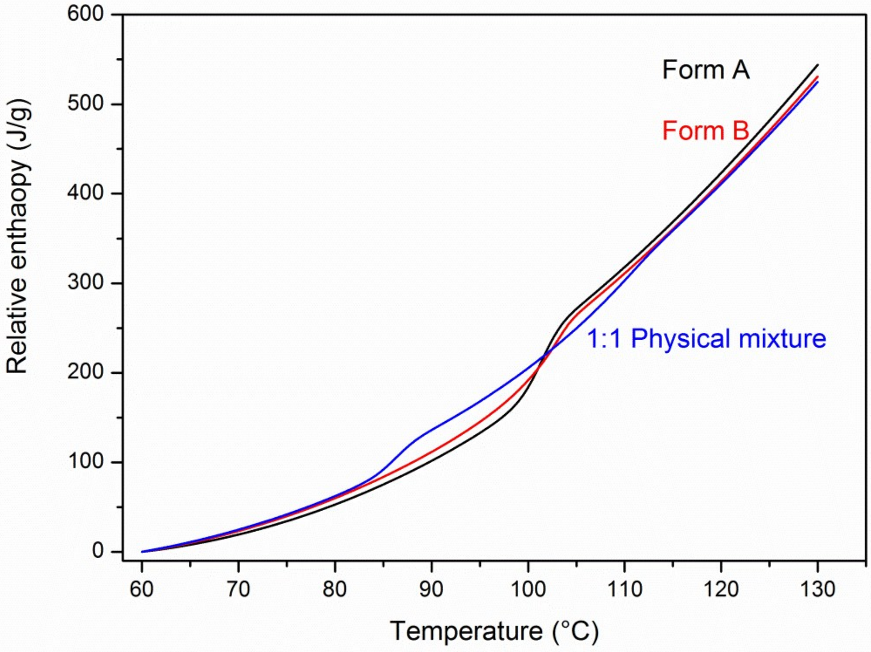


Fig. S9 Relative enthalpies of co-crystal forms A, B, and 1 : 1 VD_2/VD_3 physical mixture.

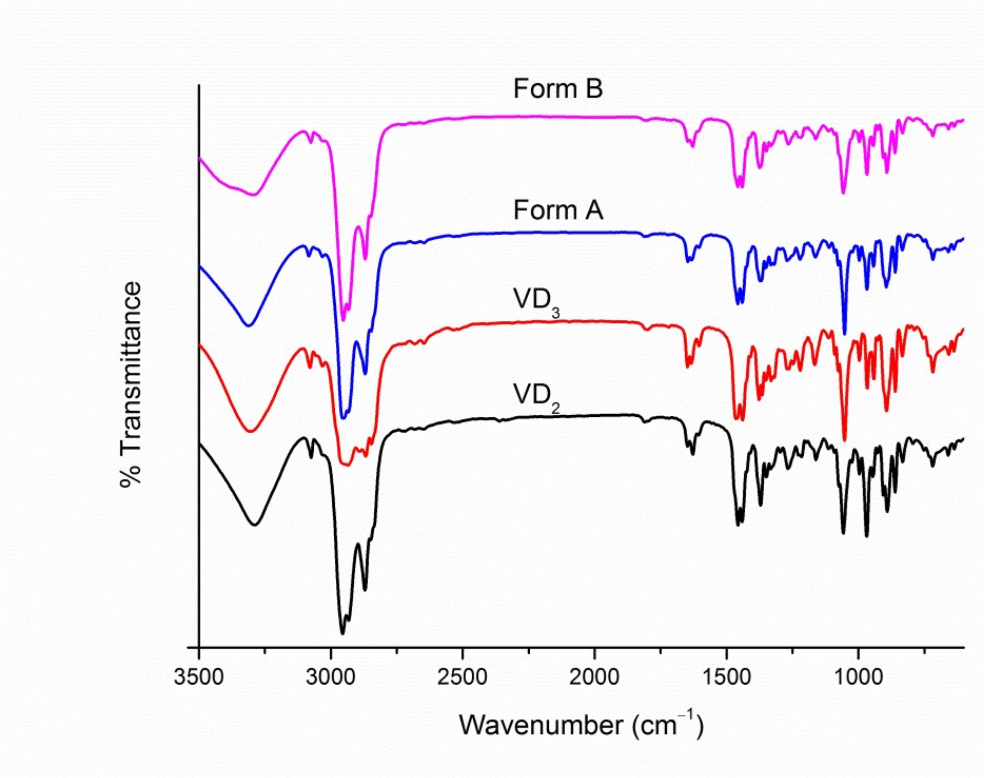


Fig. S10 Comparison of FT-IR spectra of VD_2, VD_3, form A, and form B

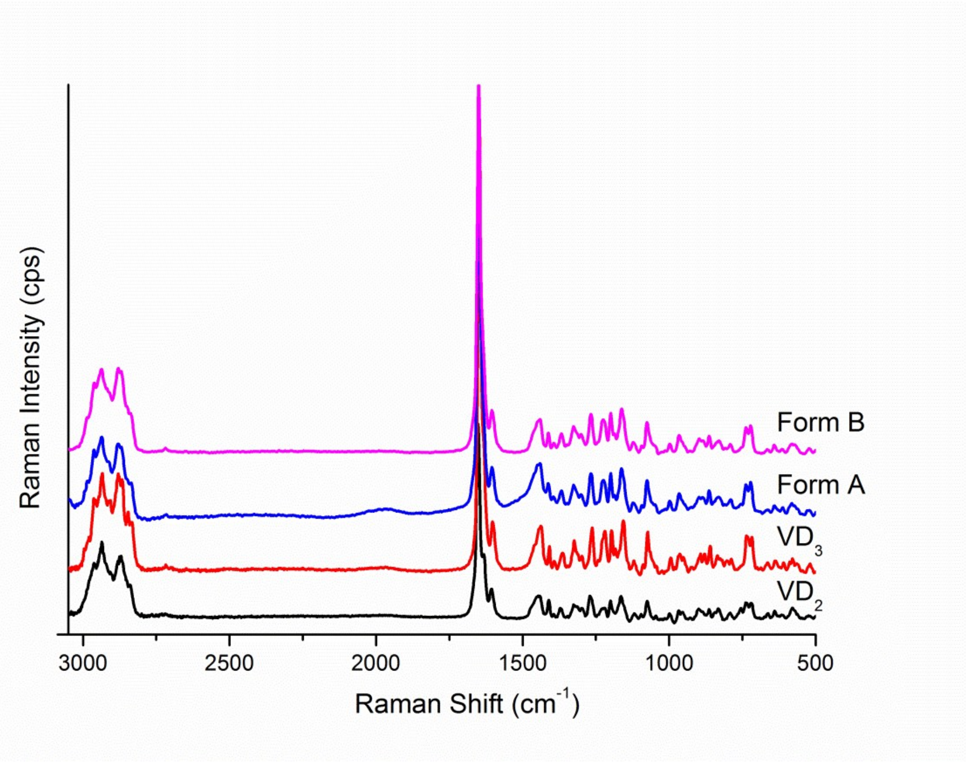


Fig. S11 Comparison of Raman spectra of VD_2, VD_3, form A, and form B

Table S1 Crystallographic Data for forms A and B.

	Co-crystal form A	Co-crystal form B
formula	$C_{55}H_{88}O_2$	$C_{110}H_{176}O_4$
Mr.	781.25	1562.50
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$
Temperature (K)	100(2)	100(2)
a (Å)	7.3985(9)	20.6101(6)
b (Å)	19.856(2)	7.2054(3)
c (Å)	35.447(4)	35.4080(10)
α (°)	90	90
β (°)	90	105.513(2)
γ (°)	90	90
Cell volume ($Å^3$)	5207.3(11)	5066.7(3)
Calc. density (g/cm^3)	0.997	1.024
Z	4	2
Z'	1	2
λ	0.71073	0.71073
S	1.064	1.190
R_1	0.067	0.097
R_{int}	0.064	0.043
wR_2	0.165	0.258

Table S2 Compared parameters of VD_2, VD_3, and co-crystals

	Co-crystal form A	Co-crystal form B	VD_2	VD_3
Hydrogen bond (Å)	2.73, 2.74	2.68, 2.69, 2.69, 2.70	2.70, 2.72	2.71, 2.73
d (C_7–C_{19}) for α (Å)	3.23 (VD_2)	3.16, 3.22	3.16	3.15
d (C_7–C_{19}) for β (Å)	3.23 (VD_3)	3.21, 3.27	3.19	3.21
Calc. density (g/cm^3)	1.00	1.024	1.00	0.99
MW	780	780	792	768
V of molecules (α + β)	855	855	866	844
V of cell	5207	5066	5254	5172
C_k	65.7%	67.5%	65.9%	65.3%

Table S3 Thermophysical data for VD_2, VD_3, form A, and form B

	T_{fus} °C (onset)	ΔH_{fus} J g^{-1}
VD_2	116	97.9
VD_3	85	54.0
Co-crystal form A	97	62.0
Co-crystal Form B	103	50.9