Electronic Supplementary Material (ESI) for CrystEngComm.

Polymorphs, cocrystal and hydrate of nilutamide

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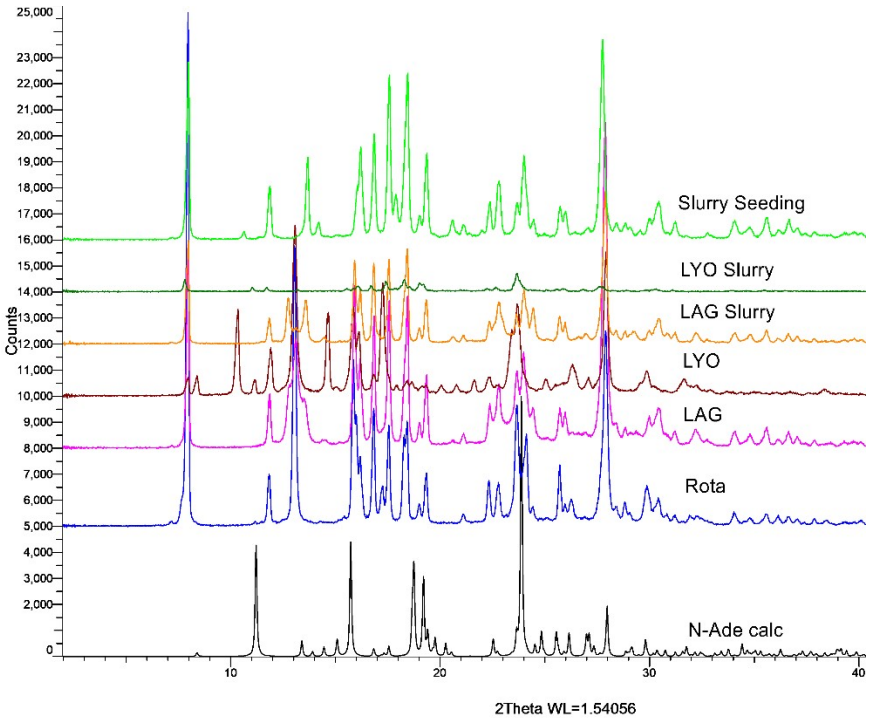

Figure S1. PXRD overlay of [Nil+Adn] (1:1) calc (obtained from SCRD data), various single step [rota evaporator (Rota), LAG, LYO] and multi-step [LAG followed by slurry (LAG Slurry), LYO followed by slurry (LYO Slurry)] and slurry seeding (phase pure cocrystal seeds were added to slurry which has initial components) experimental techniques.

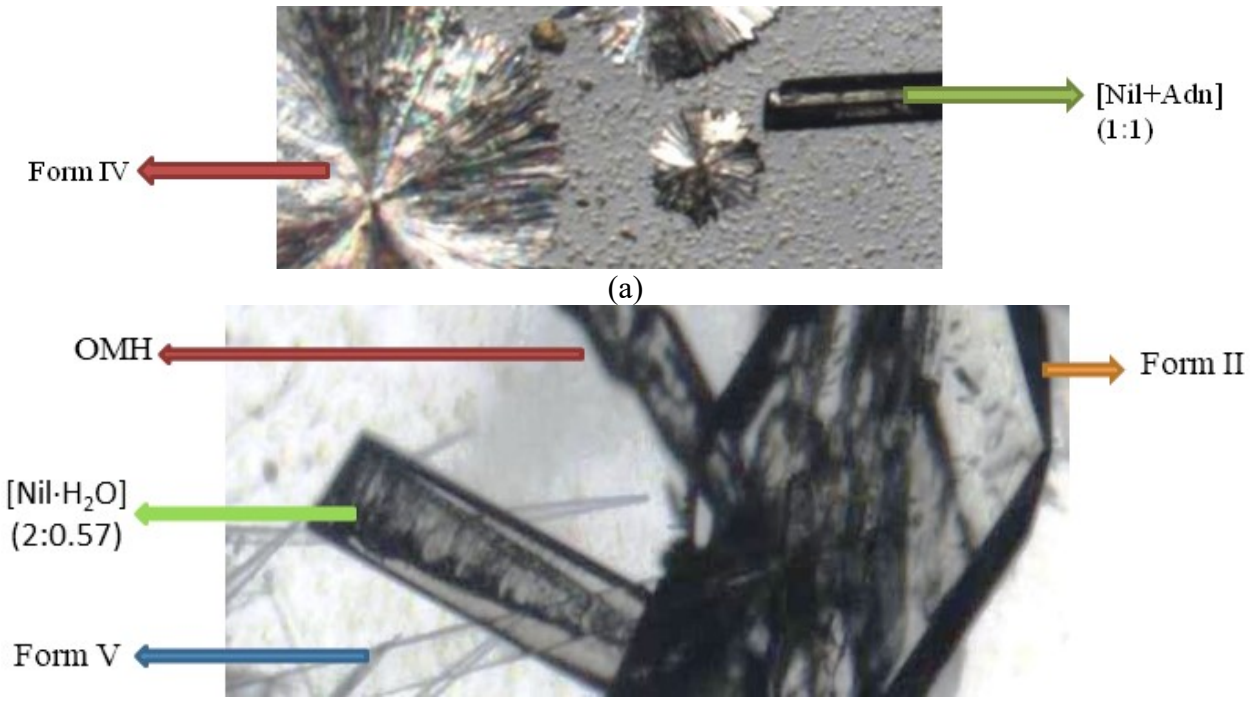

Figure S2. Microscopic image of (a) Nil Form IV and [Nil+Adn] (1:1) crystals and (b) Nil Form V, [Nil·H_2O] (2:0.57), Nil Form II and OMH crystals.

S1. Thermal analysis

The DSC thermogram of the [Nil+Adn] (1:1) cocrystal shows a sharp endotherm with a onset melting point of 203.2±0.2°C and ΔH_{fus} = 38.9±0.5 $J \cdot g^{-1}$ (Fig. S3), which falls in between Nil Form I (153.3°C)[1] and Adn (360°C)[2]. The results of HSM show a melting range of around 202°C to 212°C (Fig. S4), which is also in line with DSC data. DSC cannot be performed for Nil Forms IV and V and [Nil·H_2O] (2:0.57) due to the lack of phase-pure material. However, HSM was performed (Fig. S4), in which Form IV and Form V crystals melted around 138°C to 140°C. HSM of [Nil·H_2O] (2:0.57) (Fig. S4) shows dehydration (desolvation) at 95°C–100°C and completely melts at 158°C. After dehydration, the crystal was subjected to unit cell determination using SCXRD, which confirmed the conversion of [Nil·H_2O] (2:0.57) into Nil Form II. The present observation of desolvation followed by melting of [Nil·H_2O] (2:0.57) is in line with the unstable nilutamide hydrate as discussed by Trasi and Taylor.[3]

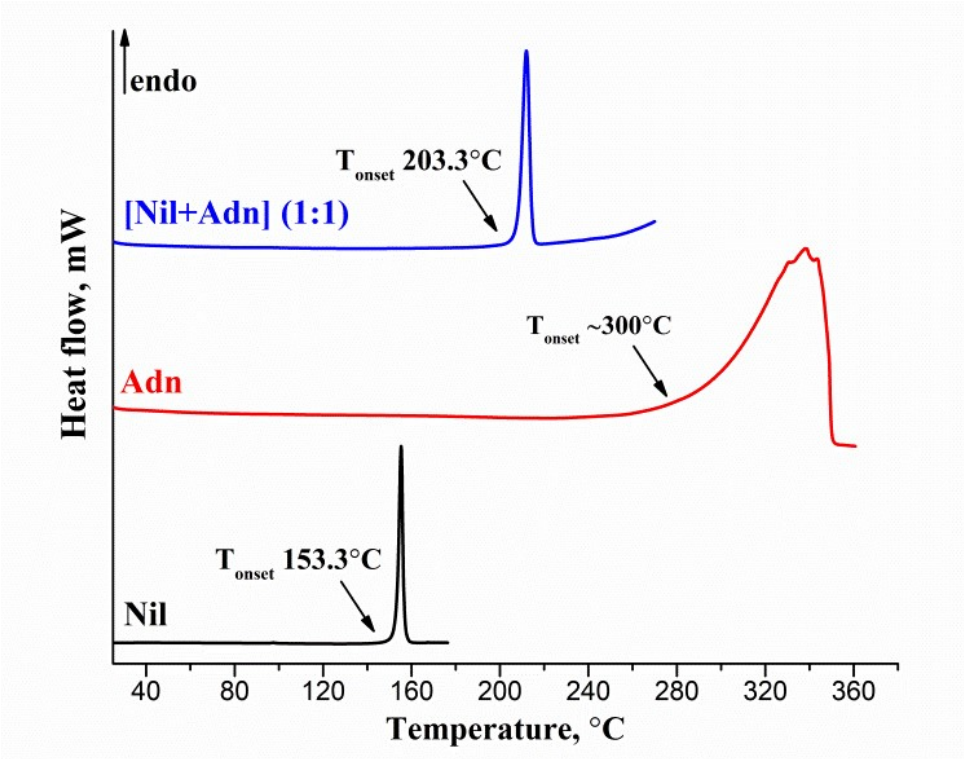

Figure S3. DSC thermograms of the parent compounds and [Nil+Adn] (1:1) cocrystal.

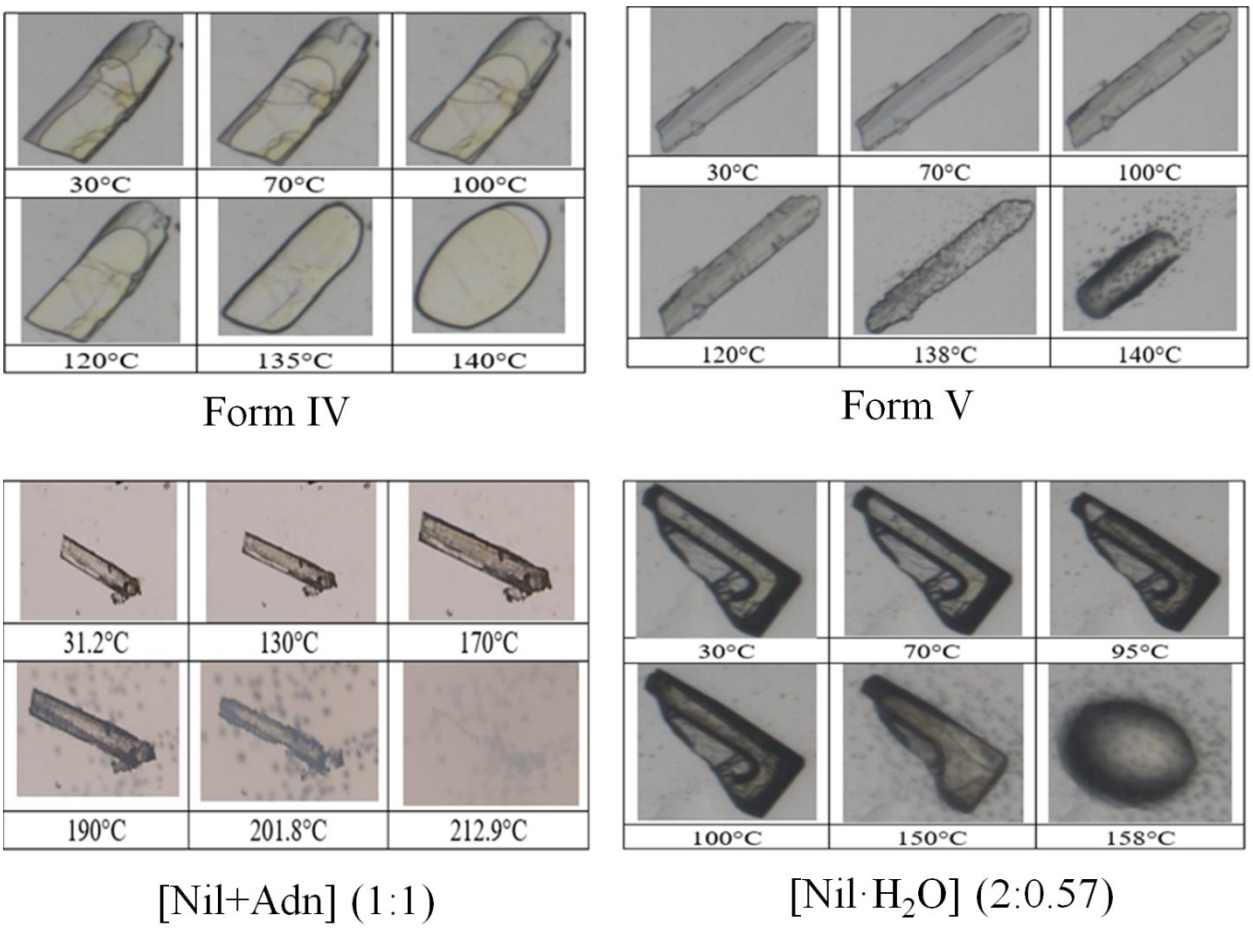

Figure S4. HSM images of Form IV, Form V, [Nil+Adn] (1:1) and [Nil·H_2O] (2:0.57).

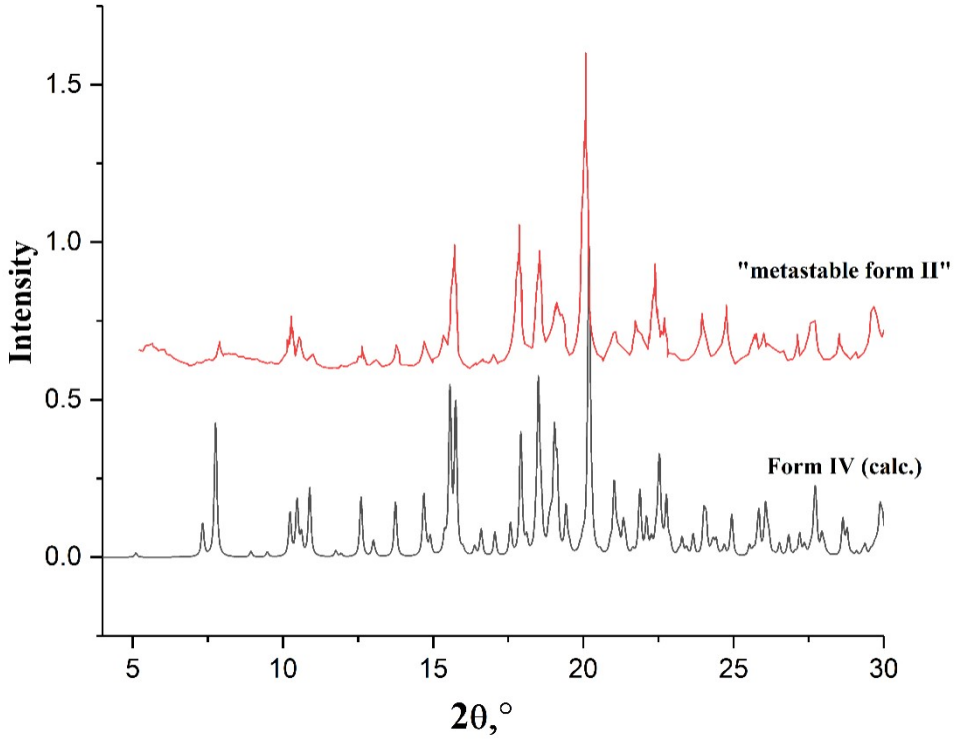

Figure S5. Calculated PXRD patterns of Nil Form IV and experimental PXRD patterns of "metastable form II" reproduced from Fig. 8 of the Trasi & Taylor paper (Trasi, N.S. and L.S. Taylor, *Nucleation and crystal growth of amorphous nilutamide – unusual low temperature behavior*. CrystEngComm, 2014. **16**(31): p. 7186-7195).

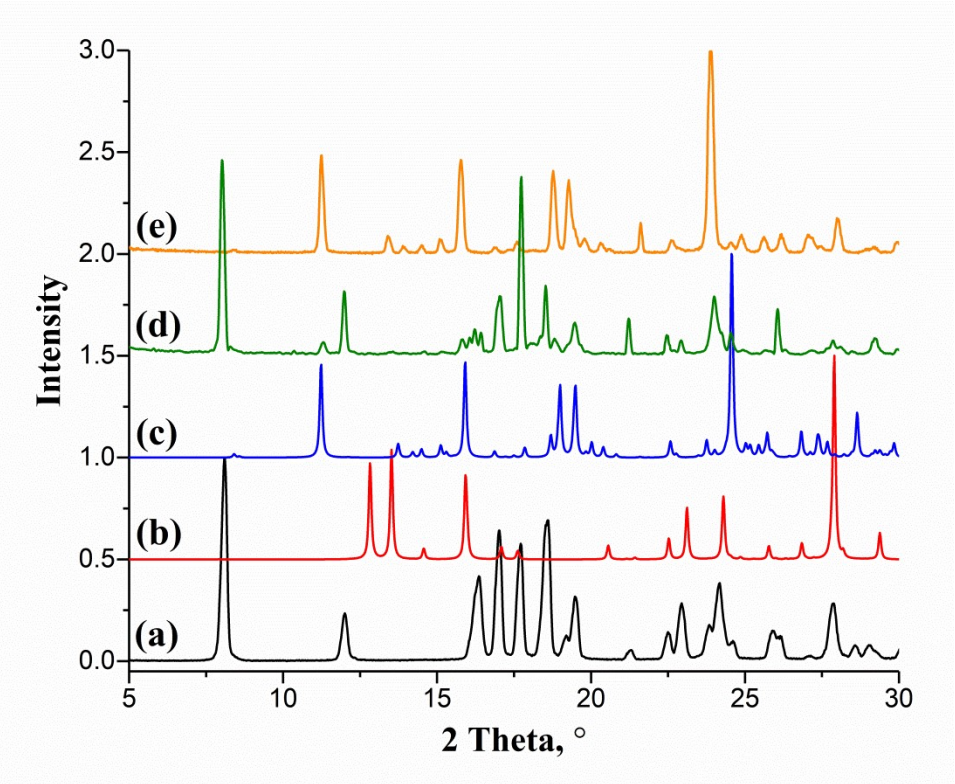

Figure S6. Experimental PXRD patterns of the solid phases after dissolution experiments in the blank pH 6.8 buffer solution (d) and pre-dissolved HPMC (e), compared with the parent compounds ((a) Nil, (b) Adn) and cocrystal (c).

Table S1. Crystallographic data and structure refinement parameters of the Nil solid forms

	Nil Form IV	Nil Form V	[Nil·H_2O] (2:0.57)	[Nil+Adn] (1:1)
Crystal data				
Chemical formula	$C_{12}H_{10}F_3N_3O_4$	$C_{12}H_{10}F_3N_3O_4$	$C_{12}H_{10}F_3N_3O_4$·0.285(H_2O)	C12H10F3N3O4·C5H5N5
M_r	317.23	317.23	322.37	452.37
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/n$	Triclinic, $P\bar{1}$	Monoclinic, $P2_1/c$
Temperature (K)	100	100	100	100
a, b, c (Å)	12.2681(13), 34.536(4), 9.8498(13)	7.1966(5), 16.2038(12), 22.6209(15)	10.2797(10), 11.1802(11), 13.2382(13)	7.3886 (5), 12.2118 (8), 20.8355 (13)
α, β, γ (°)	90, 100.837(5), 90	90, 94.633(2), 90	86.915(3), 73.762(3), 68.854(3)	98.845 (3)
V (Å^3)	4098.9(8)	2629.3(3)	1360.5(2)	1857.6 (2)
Z	12	8	4	4
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo Kα
μ (mm^{-1})	0.14	0.15	0.15	0.14
Crystal size (mm)	0.26×0.22×0.16	0.18×0.12×0.09	0.20×0.19×0.18	0.18 × 0.12 × 0.08
Data collection				
Diffractometer	Bruker D8 QUEST PHOTON-III			Bruker D8 QUEST PHOTON-100
Absorption correction	Multi-scan *SADABS* 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. &Stalke D., J. Appl. Cryst. 48 (2015) 3-10			Multi-scan *SADABS*, Bruker, 2016
T_{min}, T_{max}	0.589, 0.746	0.635, 0.746	0.665, 0.746	0.686, 0.746
No. of measured, independent and observed [I> 2σ(I)] reflections	51343, 8236, 3765	26240, 5290, 3029	31137, 8307, 5999	16255, 4256, 3867
R_{int}	0.140	0.072	0.046	0.032
(sin θ/λ)$_{max}$ (Å^{-1})	0.622	0.622	0.715	0.650
Refinement				
$R[F^2> 2\sigma(F^2)]$, $wR(F^2)$, S	0.073, 0.175, 1.03	0.044, 0.107, 1.00	0.040, 0.102, 1.02	0.070, 0.169, 1.17
No. of reflections	8236	5290	8307	4256
No. of parameters	659	409	419	344
No. of restraints	10	0	2	18
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement			
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.29, −0.30	0.25, −0.32	0.41, −0.27	0.52, −0.40

Table S2. Hydrogen bond geometries for the Nil solid forms

D–H···*A*	*D*–H, Å	H···*A*, Å	*D*···*A*, Å	*D*–H···*A*, °
Nil Form IV				
N3A–H3*NA*···O4C^{i}	0.83(5)	2.05(5)	2.861(5)	167(5)
N3B–H3NB···O3A	0.87(4)	2.04(4)	2.788(4)	143(4)
N3C–H3NC···O3B	0.84(4)	2.02(4)	2.846(5)	169(4)
C2A–H2A···O4B^{ii}	0.95	2.41	3.180(5)	139
C2A–H2A···O1C^{i}	0.95	2.33	2.959(9)	123
C6A–H6A···O4A^{iii}	0.95	2.43	3.258(5)	146
C11A–H11B···O1A^{i}	0.98	2.45	3.332(5)	150
C2B–H2B···O1C^{iv}	0.95	2.48	3.087(8)	122
C11B–H11D···F1C^{i}	0.98	2.47	3.286(10)	141
C11B–H11F···O3A	0.98	2.60	3.316(5)	130
C3C–H3C···O4B^{v}	0.95	2.60	3.528(5)	166
C11C–H11I···O2C^{i}	0.98	2.53	3.372(6)	144
Symmetry codes: (i) *x*+1, *y*, *z*; (ii) *x*, *y*, *z*–1; (iii) *x*, –*y*+3/2, *z*+1/2; (iv) *x*+1, *y*, *z*+1; (v) *x*–1, *y*, *z*–1				
Nil Form V				
N3A–H3AA···O4B	0.85(3)	2.07(3)	2.911(3)	173(2)
N3B–H3BA···O4A	0.81(3)	2.17(3)	2.967(3)	168(2)
C12A–H12B···F3A^{i}	0.98	2.35	3.169(3)	141
C11B–H11D···F3B^{ii}	0.98	2.40	3.253(3)	145
Symmetry codes: (i) –*x*+3/2, *y*+1/2, –*z*+3/2; (ii) –*x*+5/2, *y*–1/2, –*z*+3/2				
[Nil·H_2O] (2:0.57)				
N3A–H3AA···O3B	0.88	2.14	2.9839 (13)	161
N3B–H3BA···O3B^{i}	0.88	2.24	2.9759 (14)	141
N3B–H3BA···O1B^{ii}	0.88	2.43	3.1406 (14)	138
O1W–H1W···O4A^{iii}	0.90(1)	1.89(1)	2.780(2)	172(3)
O1W–H2W···O4A	0.90(2)	1.93(3)	2.826(2)	173(4)
C11A–H11B···O1A^{iv}	0.98	2.59	3.2520(18)	125
C11A–H11C···O1B^{ii}	0.98	2.58	3.5280(17)	162
C3B–H3B···O1W^{v}	0.95	2.21	3.147(2)	167
C12B–H12D···O1W^{i}	0.98	2.49	3.410(2)	157
Symmetry codes: (i) –*x*, –*y*+2, –*z*; (ii) *x*, *y*+1, *z*; (iii) –*x*+1, –*y*+1, –*z*; (iv) *x*–1, *y*+1, *z*; (v) –*x*, –*y*+1, –*z*				
[Nil+Adn] (1:1)				
N3–H1N···N8	0.85(4)	2.08(4)	2.915(3)	171(4)
N4–H2N···N6^{i}	0.86(4)	2.24(5)	3.099(4)	175(4)
N4–H3N···O3	0.90(4)	2.06(4)	2.917(3)	158(4)
N7–H4N···N5^{ii}	1.00(5)	1.85(5)	2.829(3)	167(4)
C2–H2···O1^{iii}	0.95	2.40	3.321(4)	163
C3–H3···O4^{iv}	0.95	2.50	3.300(4)	142
C11–H11C···O3^{v}	0.98	2.45	3.343(4)	152
C12–H12C···F2^{vi}	0.98	2.35	3.039(8)	126
Symmetry codes: (i) –*x*+1, *y*–1/2, –*z*+3/2; (ii) –*x*+1, *y*+1/2, –*z*+3/2; (iii) –*x*, *y*+1/2, –*z*+1/2; (iv) –*x*, *y*–1/2, –*z*+1/2; (v) –*x*, –*y*+1, –*z*+1; (vi) –*x*+1, –*y*+1, –*z*+1				

Table S3. Details of solvents and results obtained using different techniques for getting phase pure compound through single step process.

Initial phase	Experiment type	Solvents*	Time	Result
Physical mixture of Nil (20 mg) and Adn (17.03 mg) in 1:2 molar ratio	LAG	2.2 ml of ACN/H_2O mixture (1:10, v:v)	1 h	Physical mixture of Nil and Adn
	LYO	4 ml of ACN/H_2O mixture (1:1, v:v)	3 h	[Nil+Adn] (1:1), Form I, Form II
	Rotary evaporation	4 ml of ACN/H_2O mixture (1:1, v:v)	30 min	Form I, [Nil+Adn] (1:1)
Nil(120mg) and Adn(51.1mg) in 1:1 ratio	Slurry	0.4 ml of ACN/H_2O mixture (1:1, v:v)	4-6 days	[Nil+Adn] (1:1)

*ACN - acetonitrile

Table S4. Details of experiments, solvents and results obtained using two step techniques for getting phase pure compound

Initial phase	Primary experiment			Secondary experiment			Result
	Type	Solvents	Time	Type	Solvents	Time	
Physical mixture of Nil (20 mg) and Adn (17.03 mg) in 1:2 molar ratio	Rotary evaporation	4 ml of ACN/H_2O mixture (1:1, v:v)	30 min	Slurry	0.4 ml of ACN/H_2O mixture (1:1, v:v)	1 week	[Nil+Adn] (1:1)
	LAG	0.4 ml of ACN/H_2O mixture (1:1, v:v)	1h				Physical mixture of Nil and Adn
	LYO	4 ml of ACN/H_2O mixture (1:1, v:v)	4 h				[Nil+Adn] (1:1), Adn
Physical mixture of Nil (50 mg) and Adn (42.5 mg) in 1:2 molar ratio	Slurry	8 ml of ACN/H_2O mixture (1:2, v:v)	1h	Seeding*	-	1day	Physical mixture of Nil and Adn

*(Phase pure [Nil+Adn] (1:1) seeds were added to the slurry having physical mixtures of Nil (50mg) and Adn (42.59mg) with 8 ml of acetonitrile/water mixture (1:2, v/v))

Table S5. Details of solvents used and crystals obtained using slow evaporation technique

Initial phase	Solvents*	Result
[Nil+Adn] (1:1) (20mg)	6 ml of 2-butanone/ethanol/H_2O mixture (1:1:1, v:v:v)	Nil Form IV, [Nil+Adn] (1:1)
[Nil+Adn] (1:1) (20mg)	6 ml of DCE/ethanol/H_2O mixture (1:1:1, v:v:v)	Nil Form IV, [Nil+Adn] (1:1)
Nil(20mg)+ OMH (10.97mg) (1:1)	6 ml of ACN/H_2O (1:1, v:v)	Nil Form V, Nil Form II, OMH, [Nil·H_2O] (2:0.57)
[Nil+Adn] (1:1) (20mg)	4 ml of methanol/H_2O (1:1, v:v)	Nil Form V, Nil Form I, [Nil+Adn] (1:1)
[Nil+Adn] (1:1) (20mg)	4 ml of ATN/H_2O (1:1, v:v)	Nil Form I, [Nil+Adn] (1:1)
[Nil+Adn] (1:1) (20mg)	5 ml of DMF	Nil Form I
[Nil+Adn] (1:1) (20mg)	4 ml of isopropanol/H_2O (1:1, v:v)	Nil Form I
[Nil+Adn] (1:1) (20mg)	4 ml of Dox/H_2O (1:1, v:v)	Nil Form II,[Nil+Adn] (1:1)

*DCE-1,2 dichloroethane, ATN-Acetone, Dox-1,4-dioxane

Table S6. Details of experiments, solvents used and results obtained using different techniques for getting phase pure compounds of polymorphs and hydrate

Initial phase	Solvents	Experiment type	Result
Physical mixture of Nil (20 mg) and OMH (10.97mg) in 1:1 molar ratio	5.5 ml of ACN/H_2O mixture (1:10, v:v)	Anti-solvent addition	Nil Form I, OMH
	5.5 ml of ACN/H_2O mixture (1:10, v:v)	Slurry (3days)	Nil Form I, OMH
	5.5 ml of ACN/H_2O mixture (1:10, v:v)	Rotary evaporation (1 h)	Nil Form I
[Nil+Adn] (1:1) (20mg)	2.5 ml of 2-butanone/H_2O mixture (1:4, v:v)	Slurry (3 days)	Nil Form I, [Nil+Adn] (1:1)
	2.5 ml of 2-butanone/H_2O mixture (1:4, v:v)	Rotary evaporation (1 h)	Nil Form I, [Nil+Adn] (1:1)
Nil (20mg)	1 ml H_2O	Slurry (3days)	Nil Form I
	1.5 ml of ACN/H_2O mixture (2:1, v:v)	Rotary evaporation (1 h)	Nil Form I

Table S7. Selected torsion angles of the reported Nil forms

Structure	Molecule	C6–C1–N2–C10 (τ1)	C6-C1-N2-C8(τ2)
Nil Form I		-130.60(15) - ac	54.39(19) - sc
Nil Form II		143.52(10) - ac	-36.23(15) - sc
Nil Form III		31.48(15) - sc	-150.80(10) - ap
Nil Form IV	A	-80.0(5) - sc	105.1(4) - ac
	B	138.6(4) - ac	-47.2(5)- sc
	C	-131.7(4) - ac	47.2(5) - sc
Nil Form V	A	145.1(2) - ac	-23.1(3) -sp
	B	-140.9(2) - ac	25.4(3) - sp
[Nil·Hyd] (2:0.57)	A	129.47(12) - ac	-47.71(16) - sc
	B	-148.78(12) - ac	44.00(16) - sc
[Nil+Adn] (1:1)		160.3(3) - ap	-18.6(4) - sp

ac: anti-clinal; sc – syn-clinal; ap: anti-periplanar;sp- syn-periplanar

References

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2. L. J. Thompson, N. Elias, L. Male and M. Tremayne, *Cryst. Growth Des.*, 2013, **13**, 1464-1472.
3. N. S. Trasi and L. S. Taylor, *CrystEngComm*, 2014, **16**, 7186-7195.