

ESI MATERIAL

Manuscript: Co-crystals of the antiretroviral nevirapine: crystal structures, thermal analysis and dissolution behaviour

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Co-crystal screening - experimental details

Table A : Results of co-crystal complex experiments (first series) using various methods (continuous table).

Table B: Results of co-crystal complex experiments (second series) using various methods (series of tables).

Stoichiometry determination

(NVSC, NVTTA, NVMLE, NVGLT, NVSLI)

Experimental and calculated PXRD patterns

(NVSC, NVTTA, NVMLE, NVGLT, NVSLI)

Co-crystal screening - experimental details

Table A : Results of co-crystal complex experiments (first series) using various methods.

Key to abbreviations in footnote.

Method 1 ^a : Slow evaporation (192 solvent combinations with varying ratios)						
1 ^o drug	Co-former	Solvent	Molar ratio NV:co-former	Result		
NV	SC	Acetonitrile	1:1	NV		
		Methanol	1:1	Co-crystal NVSC ('CC1')		
		Diethyl ether	1:1	CC1		
		Ethyl acetate	1:1	NV ethyl acetate solvate		
		Acetic acid	1:1	CC1		
		Cyclohexane	1:1	CC1		
		Dioxane	1:1	CC1		
		n-Heptane	1:1	CC1		
		n-Hexane	1:1	CC1		
		Methanol	1:1	CC1		
		Diethyl ether	1:1	CC1		
		Chloroform	1:1	Mixture of SC and CC		
		Propan-1-ol	1:1	Sticky mass		
		Acetone	1:1	CC1		
		Dioxane	1:1	CC1		
		Toluene	1:1	Mixture of NV toluene solvate and CC1		
				Pyridine	1:1	NV pyridine solvate
				Amyl alcohol	1:1	CC1
		ISNC	n-hexane	1:1	No crystal	
			n-heptane	1:1	Mixture	
			Chloroform	1:1	NV	
				1:2	Mixture	
			Diethyl ether	1:1	NV	
			Dioxane	1:1	NV	
			Cyclohexane	1:1	NV	
			Acetone	1:1	NV	
			Propan-2-ol	1:1	NV hydrate	
			Acetonitrile	1:1	NV	
			Methanol	1:1	NV	
			Dichloromethane	1:2	ISNC	
		THF	1:2	ISNC		
		Hexane	1:1	Degraded mass		
		Carbon tetrachloride	1:1	NV carbon tetrachloride solvate		
	NC	Methanol	1:1	NV		
		Acetonitrile	1:1	NV		
		Propan-2-ol	1:1	NV hydrate		
		Acetone	1:1	NV		

	Chloroform	1:1	NV
	Diethyl ether	1:1	NV
	Ethyl acetate	1:1	NV ethyl acetate solvate
	Acetic acid	1:1	NV
	Dioxane	1:1	NV
	Cyclohexane	1:1	NV
	n-Heptane	1:1	Mixture
	n-Hexane	1:1	NV
	Acetic acid	1:1	NV
	benzene	1:1	NV
	Carbon tet	1:1	NV carbon tetrachloride solvate
SUC	Ethyl acetate	1:1	NV
	Methanol	1:1	NV methanol solvate
	Acetonitrile	1:1	NV hydrate
	Diethyl ether	1:1	Mixture NV and NV diethyl ether solvate
	n-Hexane	1:1	Mixture
	n-Heptane	1:1	Mixture
	Cyclohexane	1:1	Mixture
	Dioxane	1:1	Mixture
	Propanol	1:1	NV
	Acetic acid	1:1	No crystal
	Ethyl acetate	1:1	NV ethyl acetate solvate
	Ethanol	1:1	NV hydrate
	Toluene	1:1	NV toluene solvate
	Amyl alcohol	1;1	NV hydrate
	Benzene	1:1	NV
	Carbon tet	1:1	NV carbon tetrachloride solvate
TTA-(DL)	Diethyl ether	1:1	NV diethyl ether solvate
	Chloroform	1:1	NV
	Acetone	1:1	NV
	Ethyl acetate	1:1	NV ethyl acetate solvate
	Acetone	1:1	NV hydrate
	Methanol	1:1	NV
	Acetonitrile	1:1	Mixture of NV hydrate and NV acetonitrile
	Water	1:1	NV hydrate
	Glycerol	1:1	TTA (DL)
	Acetic acid	1:1	No crystal
	Toluene	1:1	NV toluene solvate
	Amyl alcohol	1:1	Co-crystal NVTTA ('CC 2')
	benzene	1:1	NV
TTA-L	Diethyl ether	1:1	No crystal
	Propan-2-ol	1:1	NV
	Acetonitrile	1:1	Mixture of NV and NV hydrate
	Ethyl acetate	1:1	NV ethyl acetate solvate
	Acetic acid	1:1	Mixture
	Ethanol	1:1	No crystals
	Methanol	1:1	NV methanol solvate
	MEK	1:1	Degraded
	chloroform	1:1	NV chloroform solvate

TTA-D	Propan-2-ol	1:1	NV	
	Acetonitrile	1:1	NV hydrate	
	Ethanol	1:1	No crystals	
	Acetone	1:1	NV	
	MEK	1:1	Degraded	
CAM	Benzene	1;1	NV	
	Chloroform	1:1	NV	
	Propan-2-ol	1:1	NV	
	Methanol	1:1	NV methanol solvate	
	Acetonitrile	1:1	NV hydrate	
	Amyl alcohol	1:1	NV	
	MEK	1:1	Degraded	
	ethanol	1:1	Degraded	
	Carbon tet	1;1	NV carbon tetrachloride solvate	
	THF	1:1	No crystal	
	Diethyl ether	1:1	No crystal	
	Propan-2-ol	1:1	NV	
	Acetonitrile	1:1	Mixture of NV and NV hydrate	
	Ethyl acetate	1:1	NV ethyl acetate solvate	
	Acetic acid	1:1	Mixture	
	Ethanol	1:1	No crystals	
	Methanol	1:1	NV methanol solvate	
	MEK	1:1	Degraded	
	chloroform	1:1	NV chloroform solvate	
	Stearic acid	Amyl alcohol	1:1	NV amyl alcohol solvate
MEK		1:1	No crystal	
Carbon tet		1;1	NV carbon tetrachloride solvate	
Diethyl ether		1:1	No crystal	
Propan-2-ol		1:1	NV	
Acetonitrile		1:1	Mixture of NV and NV hydrate	
Ethyl acetate		1:1	NV ethyl acetate solvate	
Acetic acid		1:1	Mixture	
Ethanol		1:1	No crystals	
Methanol		1:1	NV methanol solvate	
MEK		1:1	Degraded	
chloroform		1:1	NV chloroform solvate	
Oxalic acid		Amyl alcohol	1:1	NV
		MEK	1:1	Degraded
		Carbon tet	1;1	NV carbon tetrachloride solvate
	Diethyl ether	1:1	No crystal	
	Propan-2-ol	1:1	NV	
	Acetonitrile	1:1	Mixture of NV and NV hydrate	
	Ethyl acetate	1:1	NV ethyl acetate solvate	
	Acetic acid	1:1	Mixture	
	Ethanol	1:1	No crystals	
	Methanol	1:1	NV methanol solvate	
	MEK	1:1	Degraded	
	chloroform	1:1	NV chloroform solvate	
	Maleic acid	Amyl alcohol	1:1	NV
		MEK	1:1	Degraded
		Carbon tet	1;1	NV carbon tetrachloride solvate

	Diethyl ether	1:1	No crystal
	Propan-2-ol	1:1	NV
	Acetonitrile	1:1	Mixture of NV and NV hydrate
	Ethyl acetate	1:1	NV ethyl acetate solvate
	Acetic acid	1:1	Mixture
	Ethanol	1:1	No crystals
	Methanol	1:1	NV methanol solvate
	MEK	1:1	Degraded
	chloroform	1:1	NV chloroform solvate
Aspartic acid	Benzene	1:1	NV benzene solvate
	Amyl alcohol	1:1	NV
	Diethyl ether	1:1	No crystal
	Propan-2-ol	1:1	NV
	Acetonitrile	1:1	Mixture of NV and NV hydrate
	Ethyl acetate	1:1	NV ethyl acetate solvate
	Acetic acid	1:1	Mixture
	Ethanol	1:1	No crystals
	Methanol	1:1	NV methanol solvate
	MEK	1:1	Degraded
	chloroform	1:1	NV chloroform solvate

Method 2^b: Neat grinding (manual grinding with varying ratios)

1° drug	Co-former	Molar ratio NV:co-former	Result
NV	STA	1:1	NV
	SC	1:1	Mixture
		2:1	NV
	NC	1:1	NV
	ISNC	1:1	NV
	SUC	1:1	NV
	MA	1:1	Mixture
	D- & L TTA	1:1	Mixture
	D- TTA	1:1	Mixture
	L- TTA	1:1	Mixture
	OA	1:1	Mixture

Method 3^b: Solvent-drop grinding (manual grinding with varying ratios)

1° drug	Co-former	Molar ratio NV:co-former	Solvent	Result
NV	SC	1:2	Ethanol	Mixture
	ASP	1:2	Ethanol	Mixture
	NC	1:2	Ethanol	Mixture
	SC	1:1	Acetonitrile	NV
		1:1	Methanol	Mixture
		1:1	Diethyl ether	CC1
		1:1	Ethyl acetate	Mixture
		1:1	Acetic acid	CC1
		1:1	Cyclohexane	CC1
		1:1	Dioxane	CC1
		1:1	n-Heptane	CC1

	1:1	n-Hexane	CC1
	1:1	Methanol	CC1
	1:1	Diethyl ether	CC1
	1:1	Chloroform	Mixture of SC and CC
	1:1	Propan-1-ol	Sticky mass
	1:1	Acetone	CC1
	1:1	Dioxane	CC1
	1:1	Toluene	Mixture
	1:1	Pyridine	Mixture
ISNC	1:1	Amyl alcohol	CC1
	1:1	n-hexane	No crystal
	1:1	n-heptane	Mixture
	1:1	Chloroform	NV
	1:2		Mixture
	1:1	Diethyl ether	NV
	1:1	Dioxane	NV
	1:1	Cyclohexane	NV
	1:1	Acetone	NV
	1:1	Propan-2-ol	Mixture
	1:1	Acetonitrile	NV
	1:1	Methanol	NV
	1:2	Dichloromethane	ISNC
	1:2	THF	ISNC
	1:1	Hexane	Degraded mass
	1:1	Carbon tetrachloride	Mixture
NC	1:1	Methanol	NV
	1:1	Acetonitrile	NV
	1:1	Propan-2-ol	NV hydrate
	1:1	Acetone	NV
	1:1	Chloroform	NV
	1:1	Diethyl ether	NV
	1:1	Ethyl acetate	NV ethyl acetate solvate
	1:1	Acetic acid	NV
	1:1	Dioxane	NV
	1:1	Cyclohexane	NV
	1:1	n-Heptane	Mixture
	1:1	n-Hexane	NV
	1:1	Acetic acid	NV
	1:1	benzene	NV
SUC	1:1	Carbon tet	NV carbon tetrachloride solvate
	1:1	Ethyl acetate	NV
	1:1	Methanol	Mixture
	1:1	Acetonitrile	NV hydrate
	1:1	Diethyl ether	Mixture NV and NV diethyl ether solvate
	1:1	n-Hexane	Mixture
	1:1	n-Heptane	Mixture
	1:1	Cyclohexane	Mixture
	1:1	Dioxane	Mixture

	1:1	Propanol	NV
	1:1	Acetic acid	No crystal
	1:1	Ethyl acetate	NV ethyl acetate solvate
	1:1	Ethanol	NV hydrate
	1:1	Toluene	NV toluene solvate
	1;1	Amyl alcohol	NV hydrate
	1:1	Benzene	NV
	1:1	Carbon tet	NV carbon tetrachloride solvate
TTA-(DL)	1:1	Diethyl ether	NV diethyl ether solvate
	1:1	Chloroform	NV
	1:1	Acetone	NV
	1:1	Ethyl acetate	NV ethyl acetate solvate
	1:1	Acetone	NV hydrate
	1:1	Methanol	NV
	1:1	Acetonitrile	Mixture of NV hydrate and NV acetonitrile
	1:1	Water	NV hydrate
	1:1	Glycerol	TTA (DL)
	1:1	Acetic acid	No crystal
	1:1	Toluene	NV toluene solvate
	1:1	Amyl alcohol	Mixture
	1:1	benzene	NV
TTA-L	1:1	Diethyl ether	No crystal
	1:1	Propan-2-ol	NV
	1:1	Acetonitrile	Mixture of NV and NV hydrate
	1:1	Ethyl acetate	NV ethyl acetate solvate
	1:1	Acetic acid	Mixture
	1:1	Ethanol	No crystals
	1:1	Methanol	NV methanol solvate
	1:1	MEK	Degraded
	1:1	chloroform	NV chloroform solvate
TTA-D	1:1	Propan-2-ol	NV
	1:1	Acetonitrile	NV hydrate
	1:1	Ethanol	No crystals
	1:1	Acetone	NV
	1:1	MEK	Degraded
	1;1	Benzene	NV
CAM	1:1	Chloroform	NV
	1:1	Propan-2-ol	NV
	1:1	Methanol	NV methanol solvate
	1:1	Acetonitrile	NV hydrate
	1:1	Amyl alcohol	NV
	1:1	MEK	Degraded
	1:1	ethanol	Degraded
	1;1	Carbon tet	NV carbon tetrachloride solvate
	1:1	THF	No crystal
	1:1	Diethyl ether	No crystal
	1:1	Propan-2-ol	NV
	1:1	Acetonitrile	Mixture of NV and NV hydrate
	1:1	Ethyl acetate	NV ethyl acetate solvate
	1:1	Acetic acid	Mixture

	1:1	Ethanol	No crystals
	1:1	Methanol	NV methanol solvate
	1:1	MEK	Degraded
	1:1	chloroform	NV chloroform solvate
Stearic acid	1:1	Amyl alcohol	NV amyl alcohol solvate
	1:1	MEK	No crystal
	1;1	Carbon tet	NV carbon tetrachloride solvate
	1:1	Diethyl ether	No crystal
	1:1	Propan-2-ol	NV
	1:1	Acetonitrile	Mixture of NV and NV hydrate
	1:1	Ethyl acetate	NV ethyl acetate solvate
	1:1	Acetic acid	Mixture
	1:1	Ethanol	No crystals
	1:1	Methanol	NV methanol solvate
	1:1	MEK	Degraded
	1:1	chloroform	NV chloroform solvate
Oxalic acid	1:1	Amyl alcohol	NV
	1:1	MEK	Degraded
	1;1	Carbon tet	NV carbon tetrachloride solvate
	1:1	Diethyl ether	No crystal
	1:1	Propan-2-ol	NV
	1:1	Acetonitrile	Mixture of NV and NV hydrate
	1:1	Ethyl acetate	NV ethyl acetate solvate
	1:1	Acetic acid	Mixture
	1:1	Ethanol	No crystals
	1:1	Methanol	NV methanol solvate
	1:1	MEK	Degraded
	1:1	chloroform	NV chloroform solvate
Maleic acid	1:1	Amyl alcohol	NV
	1:1	MEK	Degraded
	1;1	Carbon tet	NV carbon tetrachloride solvate
	1:1	Diethyl ether	No crystal
	1:1	Propan-2-ol	NV
	1:1	Acetonitrile	Mixture of NV and NV hydrate
	1:1	Ethyl acetate	NV ethyl acetate solvate
	1:1	Acetic acid	Mixture
	1:1	Ethanol	No crystals
	1:1	Methanol	NV methanol solvate
	1:1	MEK	Degraded
	1:1	chloroform	NV chloroform solvate
Aspartic acid	1:1	Benzene	NV benzene solvate
	1:1	Amyl alcohol	NV
	1:1	Diethyl ether	No crystal
	1:1	Propan-2-ol	NV
	1:1	Acetonitrile	Mixture of NV and NV hydrate
	1:1	Ethyl acetate	NV ethyl acetate solvate
	1:1	Acetic acid	Mixture
	1:1	Ethanol	No crystals
	1:1	Methanol	NV methanol solvate

1:1	MEK	Degraded
1:1	chloroform	NV chloroform solvate

^aProducts obtained by method 1 were analysed by HSM, single crystal X-ray diffraction and PXRD to determine bulk consistency. ^b Products obtained by methods 2 and 3 were analysed by PXRD.

NOTE: Vapor diffusion was employed when crystals from slow evaporation were too small for diffraction purposes.

NOTE: In the table, the following abbreviations are used for simplicity: nevirapine (NV), saccharin (SC), oxalic acid (OA), tartaric acid (TTA-D, TTA-L and TTA-DL), maleic acid (MA), citric acid (CA), nicotinamide (NC), isonicotinamide (ISNC), succinic acid (SUC), L-aspartic acid (ASP) and stearic acid (STA).

TABLE B: Results of co-crystal complex experiments (second series) using various methods

Dry co-grinding

Table 1: Nevirapine dry co-grinding.

Co-former	Molar ratio	Method	Result
Fumaric acid	1:1	10 min	Physical mixture
Glutamic acid (L)	1:1	10 min	Physical mixture
Glutaric acid	1:1	10 min	Physical mixture
Malic acid (L)	1:1	10 min	Physical mixture
Nicotinamide	1:1	10 min	Physical mixture
Sorbic acid	1:1	10 min	Hit

Liquid-assisted Grinding

Table 2: Nevirapine liquid-assisted grinding.

Co-former	Solvent	Molar ratio	Method	Result
Adipic acid	Chloroform	1:1	10 min	Hit
Adipic acid	Chloroform	2:1	10 min	Hit
Arginine (L)	Chloroform	1:1	5 min	Physical mixture
Ascorbic acid (L)	Chloroform	1:1	10 min	Physical mixture
Benzamide	Chloroform	1:1	5 min	Physical mixture
Cinnamamide	Chloroform	1:1	5 min	Physical mixture
Fumaric acid	Chloroform	2:1	10 min	Hit (excess nevirapine)
Fumaric acid	Methanol	1:1	10 min	Hit
Fumaric acid	Chloroform	1:1	10 min	Hit
Fumaric acid	Chloroform	1:1	10 min	Hit
Glutamic acid (L)	Chloroform	1:1	10 min	Hit
Glutaric acid	Chloroform	1:1	10 min	Hit (co-crystal)
Glutaric acid	Chloroform	2:1	10 min	Hit (excess nevirapine)
Glutaric acid	Methanol	1:1	10 min	Hit (partial conversion)
Glycine	Chloroform	1:1	5 min	Physical mixture
Hippuric acid	Methanol	1:1	10 min	Physical mixture
Hippuric acid	Chloroform	1:1	10 min	Physical

				mixture
Isonicotinamide	Chloroform	1:1	10 min	Physical mixture
Maleic acid	Chloroform	1:1	10 min	Hit (co-crystal)
Maleic acid	Chloroform	1:3	15 min	Hit
Malic acid (L)	Chloroform	1:1	5 min	Physical mixture
Malonic acid	Chloroform	1:1	10 min	Hit
Malonic acid	Chloroform	2:1	10 min	Hit
Nicotinamide	Chloroform	1:1	10 min	Physical mixture
Nicotinic acid	Chloroform	1:1	10 min	Physical mixture
Orotic acid	Methanol	1:1	10 min	Physical mixture
Orotic acid	Chloroform	1:1	10 min	Physical mixture
Oxalic acid dihydrate	Chloroform	1:1	10 min	Hit
Piperazine	Chloroform	1:1	5 min	Physical mixture
Proline (L)	Chloroform	1:1	5 min	Hit
Propionamide	Chloroform	1:1	5 min	Hit
Saccharin	Chloroform	1:1	10 min	Hit
Salicylic acid	Chloroform	1:1	10 min	Hit
Salicylic acid	Chloroform	2:1	10 min	Hit
Sorbic acid	Methanol	1:1	5 min	Hit
Sorbic acid	Methanol	1:1	20 min	Hit
Sorbic acid	Methanol	2:1	15 min	Hit
Sorbic acid	Chloroform	1:1	10 min	Hit
Suberic acid	Chloroform	1:1	10 min	Physical mixture
Succinic acid	Chloroform	1:1	10 min	Physical mixture
Succinic acid	Chloroform	2:1	10 min	Physical mixture
Succinic acid	Acetonitrile	1:1	10 min	Physical mixture
Succinic acid	Acetone	1:1	10 min	Physical mixture
Tartaric acid (D)	Chloroform	1:1	5 min	Physical mixture
Tartaric acid (L)	Chloroform	1:1	5 min	Physical mixture
Uracil	Chloroform	1:1	10 min	Hit
Valine (L)	Chloroform	1:1	10 min	Physical mixture

STOICHIOMETRY DETERMINATION

NVSC and NVTTA:

Microanalysis for NVSC [$2(C_{15}H_{14}N_4O) \cdot C_7H_5NO_3S$] and NVTTA [$C_{15}H_{14}N_4O \cdot C_4H_6O_6$]

Co-crystal	Experimental averages (n=3)				Calculated			
	%C	%H	%N	%S	%C	%H	%N	%S
NVSC	61.73	4.77	17.88	4.62	62.08	4.65	17.61	4.48
NVTTA	54.59	5.02	13.39	-	54.80	4.84	13.46	-

For **NVMLE**, **NVGLT** and **NVSLI**, stoichiometry was determined by thermogravimetric analysis which presented distinct mass losses due to the release of the respective co-formers on heating the co-crystals to their melting points. Confirmation of the stoichiometries of **NVGLT** and **NVSLI** were obtained using 1H NMR spectroscopy. The co-crystals were dissolved in deuterated solvents and their 1H NMR spectra were recorded on 400 MHz instruments [Varian-Unity 400 and Bruker AMX 400 spectrometers]. Proton integration for diagnostic signals from each co-crystal component yielded the co-crystal stoichiometries.

NVMLE: $C_{15}H_{14}N_4O \cdot C_4H_4O_4$

TGA showed the decomposition of maleic acid at the co-crystal melting point. The experimentally determined mass loss of 32.6 ± 1.0 % (n = 2) is in reasonable agreement with the calculated value of 30.4 % expected for 1:1 co-crystal stoichiometry.

NVGLT: $C_{15}H_{14}N_4O \cdot C_5H_8O_4$

The TGA profile showed mass loss of 31.2 ± 1.5 % (n = 2) at 110-195 °C, corresponding to the degradation of glutaric acid for a 1:1 co-crystal (theoretical value: 33.2 %), while the remaining mass (nevirapine) degrades directly thereafter.

Selected proton NMR signals used for the confirmation of the NVPGLT co-crystal stoichiometry.

Assignment	δ (ppm)	Integral	Normalised integral
CH (aromatic, nevirapine)	8.57	1.0*	1
CH (aromatic, nevirapine)	8.23	1.1	1
CH ₂ (glutaric acid)	2.01	2.2	1

*Reference integral

NVSLI:

The TGA profile showed a mass loss of 20.55 ± 0.05 % (n = 2), corresponding with the loss of one molar equivalent of salicylic acid in a co-crystal of stoichiometric ratio 2:1. This experimental value is the same as the calculated result (20.6%).

Selected signals from the proton NMR spectrum of NVPSLI confirming 2:1 stoichiometry.

Assignment	δ (ppm)	Integral	Normalised integral
CH (aromatic, nevirapine)	8.49	2.1	2
CH (aromatic, salicylic acid)	7.88	1.0*	1
CH (aromatic, salicylic acid)	7.42	1.0	1
CH (cyclopropyl, nevirapine)	3.71	2.1	2

*Reference integral

EXPERIMENTAL AND CALCULATED PXRD PATTERNS



