Electronic Supplementary Information

Cocrystallization of an Antiretroviral Drug Nevirapine: An Eutectic, A Cocrystal Solvate, and A Cocrystal Hydrate

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I. SUPPLEMENTARY FIGURES

II. SUPPLEMENTARY TABLES

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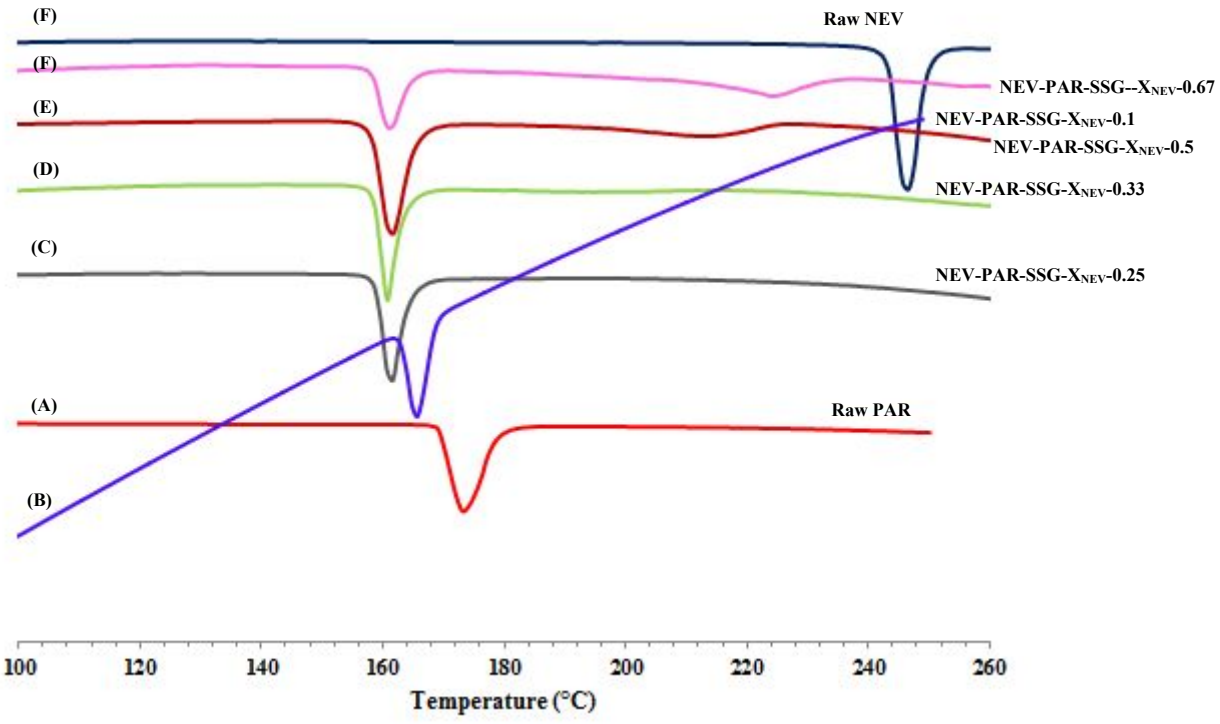

Figure S1. Overlay of DSC thermograms of various NEV-PAR-SSG mixtures (A) Raw PAR (X_{NEV}-0), (B) NEV-PAR-SSG-X_{NEV}-0.1, (C) NEV-PAR-SSG-X_{NEV}-0.25, (D) NEV-PAR-SSG-X_{NEV}-0.33, (E) NEV-PAR-SSG-X_{NEV}-0.5, (F) NEV-PAR-SSG-X_{NEV}-0.67 and (G) Raw NEV(X_{NEV}-1).

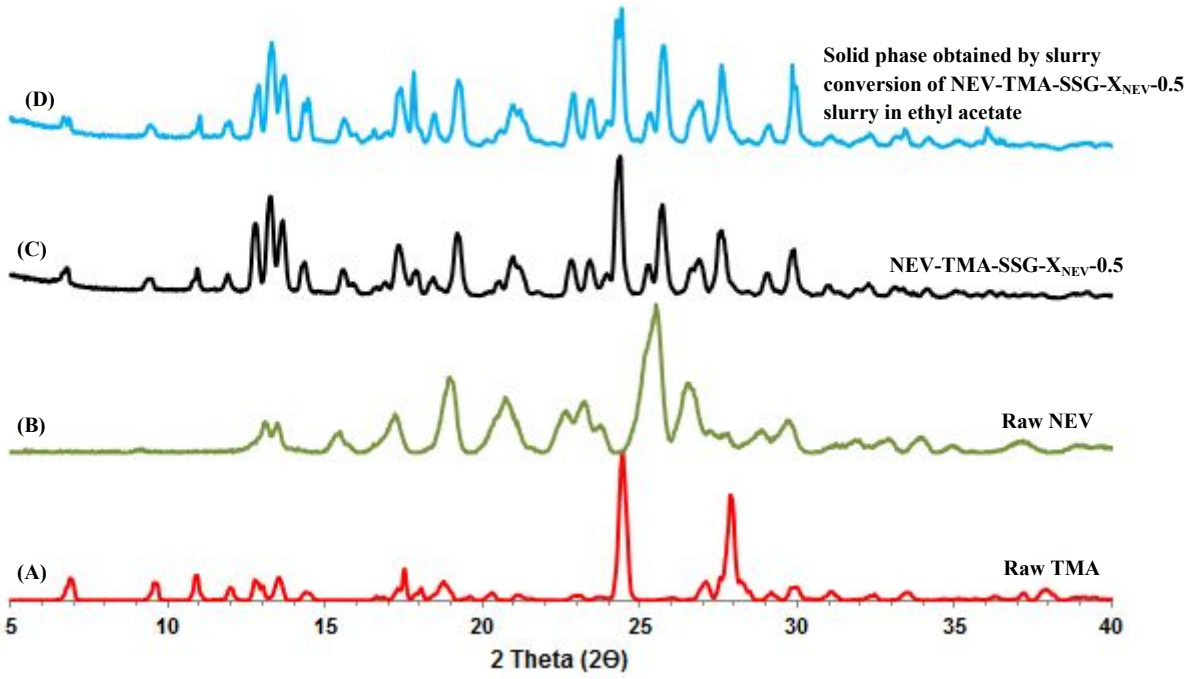

Figure S2. Overlay of PXRD patterns of (A) Raw TMA, (B) Raw NEV, (C) NEV-TMA-SSG-X_{NEV}-0.5 and (D) NEV solid phase obtained by slurry conversion of NEV-TMA-SSG-X_{NEV}-0.5 in ethyl acetate.

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Alert level B
PLAT230_ALERT_2_B Hirshfeld Test Diff for    O002     --C1       .       12.0 s.u.
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Response: The shape of the carbon atom in acetate functionality of NEV-TMEA methyl ester (1:1) cocrystal hydrate was not ideally shaped. However, it does not indicate incorrect atom assignment.

Figure S3. A snapshot of Alert level B observed in the CheckCIF report of NEV-TMEA methyl ester (1:1) cocrystal hydrate.

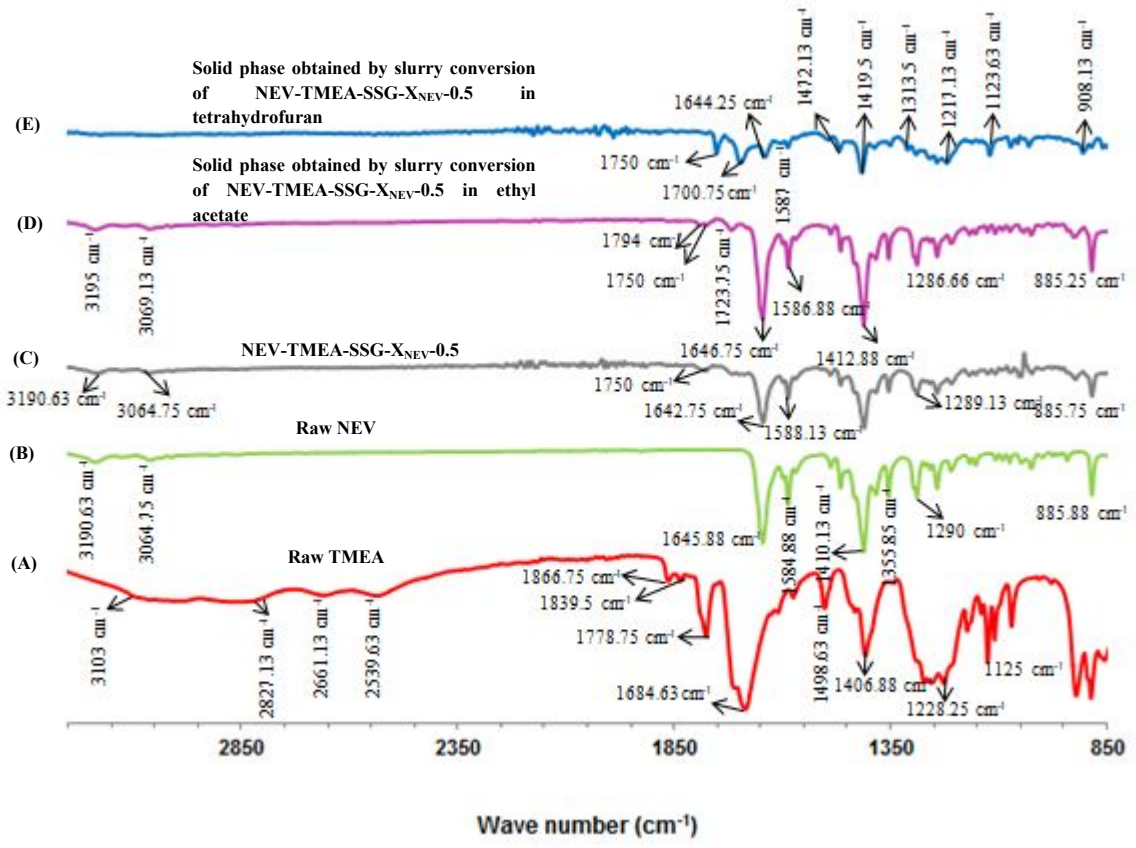

Figure S4. Overlay of FT-IR spectra of (A) Raw TMEA, (B) Raw NEV, (C) NEV-TMEA-SSG-X$_{NEV}$-0.5, (D) Solid phase obtained by slurry conversion of NEV-TMEA-

SSG-X_{NEV}-0.5 in ethyl acetate and (E) Solid phase obtained by slurry conversion of NEV-TMEA-SSG-X_{NEV}-0.5 in tetrahydrofuran.

II. SUPPLEMENTARY TABLES

Table S1. Summary of literature reports available on NEV cocrystals/eutectics and its dissolution/solubility enhancement.

S.No	Coformer	Cocrystal Stoichiometry	Cocrystallization method	Comments on dissolution/solubility Enhancement/anti-viral activity	Crystal structure reported	Reference(s)
01.	Saccharin	2:1	Neat co-grinding, liquid-assisted (solvent-drop) grinding and co-precipitation in solvents	Nevirapine-saccharin (2:1) cocrystal showed 20-25% enhanced dissolution than raw nevirapine. Also, the cocrystal exhibited 1.4 times higher solubility than raw nevirapine	Yes	1
02.	Saccharin	2:1	Reaction crystallization in 1-pentanol	Influence of pH on solubility of the cocrystal phase was investigated	No	2
03.	Saccharin	1: 1 and 2:1	Liquid assisted grinding in grinding jar with stainless steel balls and slow evaporation	Not reported	No	3
03.	*rac*-tartaric acid	1:1	Neat co-grinding, liquid-assisted (solvent-drop) grinding and co-precipitation in solvents	Nevirapine-saccharin (2:1) cocrystal showed 10-15% enhanced dissolution than raw nevirapine. The cocrystal	Yes	1

				exhibited 1.2 times higher solubility than raw nevirapine		
04.	Maleic acid	1:1	Neat co-grinding, liquid-assisted (solvent-drop) grinding and co-precipitation in solvents	Nevirapine-maleic acid cocrystal exhibited five-fold increase in the aqueous solubility of nevirapine. Also, the cocrystal exhibited 5.3 times higher solubility than raw nevirapine	Yes	1
05.	Maleic acid	1:1	Reaction crystallization in chloroform	Effect of pH on solubility of the cocrystal phase was studied	No	2
06.	Glutaric acid	1:1	Neat co-grinding, liquid-assisted (solvent-drop) grinding and co-precipitation in solvents	The cocrystal exhibited 1.2 times higher solubility than raw nevirapine	Yes	1
07.	Salicylic acid	2:1	Neat co-grinding, liquid-assisted (solvent-drop) grinding and co-precipitation in solvents	The cocrystal exhibited 1.1 times higher solubility than raw nevirapine	Yes	1
08.	Salicylic acid	2:1	Reaction crystallization in chloroform	Influence of pH on solubility of the cocrystal phase was studied	No	2
09.	Salicylic acid		Liquid assisted grinding in grinding jar with stainless steel balls and slow evaporation	Not reported	No	3
09.	1,2,4,5-	1:1	Slow evaporation	Not reported	Yes	4

	tetrafluoro-3,6-diiodobenzene					
10.	1,3-diiodobenzene	2:1	Slow evaporation	Not reported	Yes	4
11.	3-hydroxybenzoic acid	1:1 and 2:1	Liquid assisted grinding in grinding jar with stainless steel balls and slow evaporation	Not reported	No	3
12.	4-hydroxybenzoic acid	1:1 and 2:1	Liquid assisted grinding in grinding jar with stainless steel balls and slow evaporation	Not reported	Yes	3
13.	Theophylline	1:1 and 2:1	Liquid assisted grinding in grinding jar with stainless steel balls and slow evaporation	Intrinsic dissolution profile shows that the cocrystal exhibits 5 times higher dissolution than raw NEV in 0.1 N Hcl and water as dissolution medium	No	3
14.	Caffeine	1:1 and 2:1	Liquid assisted grinding in grinding jar with stainless steel balls and slow evaporation	Intrinsic dissolution profile shows that the cocrystal exhibits 10 times higher dissolution than raw NEV in 0.1 N Hcl and water as dissolution medium	No	3
15.	Urea	1:1 and 2:1	Liquid assisted grinding in grinding jar with stainless steel balls and slow evaporation	Not reported	An eutectic phase	3
16.	Saccharin, rac-	1:1	Hot-Stage microscopy was used	The dissolution of nevirapine cocrystals	No	5

	tartaric acid, maleic acid, salicylic acid and glutaric acid	for determining the purity of the cocrystal. The fourier transform - infra red spectroscopy was used as an analytical method to identify cocrystal formation.	was increased in presence of coformers in the cocrystal as well as in the physical mixture. The nevirapine-glutaric acid (1:1) cocrystal was the only cocrystal that yielded better dissolution than the physical mixture. The nevirapine cocrystals prepared with saccharin, salicylic acid, maleic acid and glutaric acid exhibited improved anti-viral activity than raw nevirapine.		
17.	Series of 30 - coformers	Two different structure-informatics methods namely Hydrogen-bond propensity (HBP) and hydrogen-bond coordination (HBC), and one approach based on hydrogen-bond interaction energies	Not reported	No	6

Table S2. Summary of different NEV solid forms obtained by evaporative crystallization of NEV-TMA-SSG-X_{NEV}-0.5 in different solvent systems.

Cocrystallization method	Product other than cocrystal	Cocrystal form (solid powders/crystal)	Confirmation technique adopted
Methanol	1:1 cocrystal methanol solvate	plate-like transparent crystals	PXRD and SCXRD
Acetone-Toluene (1:1 volume ratio)	NEV	rod-like transparent crystals	SCXRD
Ethyl acetate-Toleuene (1:1 volume ratio)	NEV and NEV hemihydrate	plate like and rod-like crystals	SCXRD
Ethyl acetate	NEV hemihydrate	aggregates of rod-like crystals	SCXRD
Tetrahydrofuran	NEV	rod-like transparent crystals	PXRD
Acetonitrile-Methanol (1:1 volume ratio)	NEV hemihydrate	plate-like transparent crystals	SCXRD
Ethyl acetate-Methanol (1:1 volume ratio)	NEV and NEV hemihydrate	rod-like and plate-like transparent crystals	SCXRD
Methanol-Toluene (1:1 volume ratio)	NEV	rod-like transparent crystals	SCXRD

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