Solubility enhancement of ezetimibe by cocrystal engineering technique

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Table S1. Preliminary screening of coformers

Sl. No.	Coformer (mp(°C))	Quantity of drug and coformer	Solvent used	Crystal mp (°C)	Remarks
Solution crystallization method					
F1.	Benzoic acid (125)	0.1 mmol each	25 mL chloroform	165.9	No interaction
F2.	Salicylic acid (161.8)	0.1 mmol each	25 mL chloroform	165.2	No interaction
F3.	Benzoic acid (125)	1 mmol each	20 mL methanol	166.2	No interaction
F4.	Salicylic acid (161.8)	1 mmol each	20 mL methanol	165.7	No interaction
F5.	Methyl paraben (130.1)	0.5 mmol each	10 mL methanol	109.2	**Interaction occurred**
F6.	Sachharin-sodium dehydrate (226)	0.5 mmol each	10 mL methanol	165.2	No interaction
Slurry technique					
F7.	L-Proline[1] (215.5)	0.25 mmol each	1 mL ethyl acetate &2 mL heptane	173.1	**Interaction occurred.**
F8.	Glycine (233) decomposed	0.25 mmol each	1 mL ethyl acetate & 2 mL heptane	163.1	No interaction
F9.	Valine (298)	0.25 mmol each	1 mL ethyl acetate & 2 mL heptane	Abrupt melting curve.	No interaction

Table S2 FTIR spectral band assignment of ezetimibe, methyl paraben and their cocrystal products

Ezetimibe	Methyl paraben	Cocrystal I	Cocrystal II	Cocrystal III	Assignment[2,3]
3261.74s	3292s	**3275.24s**	**3308.03s**	**3279.10s**	υ(O-H)
			3195.19m		
3022.55m	3034.13m	3022.55m	**3035.09w**	**3016.77w**	υ(= (C-H))
2962.76m	2964.69m	2964.69m	2965.65m	2964.69w	υ(C-H) aliphatic
1716.70s		1716.70s	1716.70w	**1729.24s**	υ(C=O) lactam
	1678.13s	1681.98m	1679.09s	1683.91s	υ(C=O)
	1591.33m	1591.33m	1589.40m	1589.40m	υ(CC)aromatic chain vibrations
1516.10m	1514.17m	**1510.31s**	1514.17m	**1511.28m**	υ(C=C)
		1473.73w	1471.74w	1471.74s	
1444.73m		1448.73m		1448.59m	υ (C-N)
	1435.09s		1435.09s		υ (C-O) enolic
	1379.15s		**1397.47w**	**1398.44m**	δ(CH3)
1354.07w		1354.07w	**1361.79w**	1355.04m	β(O-H)
1222.91s		1222.91m	**1235.45m**	1225.80s	υ (C-F)
1066.67m		1066.67m	1065.71w	1060.88w	υ (C-O) (2°OH)

s ,strong; m, medium; w, weak; υ, stretching; β, in plane deformation; δ, bending.

Table S3. Stoichiometric calculation from Area under the peak of different cocrystal

	$AUC_{2\theta=19.24}$	$AUC_{2\theta=25.08}$	Ratio[$AUC_{2\theta=19.24}$/ $AUC_{2\theta=25.08}$]
Cocrystal I	3699	2740	1.35
Cocrystal II	3484	1278	2.7
Cocrystal III	461	458	1.0

Table S4. Dissolution efficiency percent and similarity factor of CI, CII,CIII and pure ezetimibe

Parameters	Ezetimibe	Cocrystal I	Cocrystal II	Cocrystal III
$\%CDR_{15}$[a]	42.55 ± 1.66	60.50 ± 1.65[b]	69.47 ± 1.66[b]	51.53 ± 1.66[b]
$\%CDR_{45}$[a]	61.64 ± 3.35	64.93 ± 0.59	73.89 ± 0.60[b]	61.64 ± 3.34
$\%CDR_{120}$[a]	68.55 ± 3.25	76.59 ± 2.98	85.56 ± 2.98[b]	68.82 ± 3.41
$\%DE_{15}$[a]	21.28 ± 0.83	30.25 ± 0.83[b]	34.73 ± 0.83[b]	25.76 ± 0.83[b]
$\%DE_{45}$[a]	41.88 ± 1.96	51.89 ± 1.02[b]	58.91 ± 1.04[b]	46.31 ± 1.94[b]
$\%DE_{120}$[a]	56.40 ± 2.79	63.69 ± 1.38[b]	72.10 ± 1.39[b]	58.14 ± 2.81
f_2	-	48.40 ± 14.56	49.47 ± 13.74	47.92 ± 14.97

[a] Indicates ± S.D., (n=3); S.D.: standard deviation; $\%CDR_{15,}$ $\%CDR_{45\ ,}$ $\%CDR_{120}$: percentage cumulative drug released in 15 min, 45 min and 120 min; [b] Significant difference compared to pure ezetimibe i.e. significant ($p<0.05$).

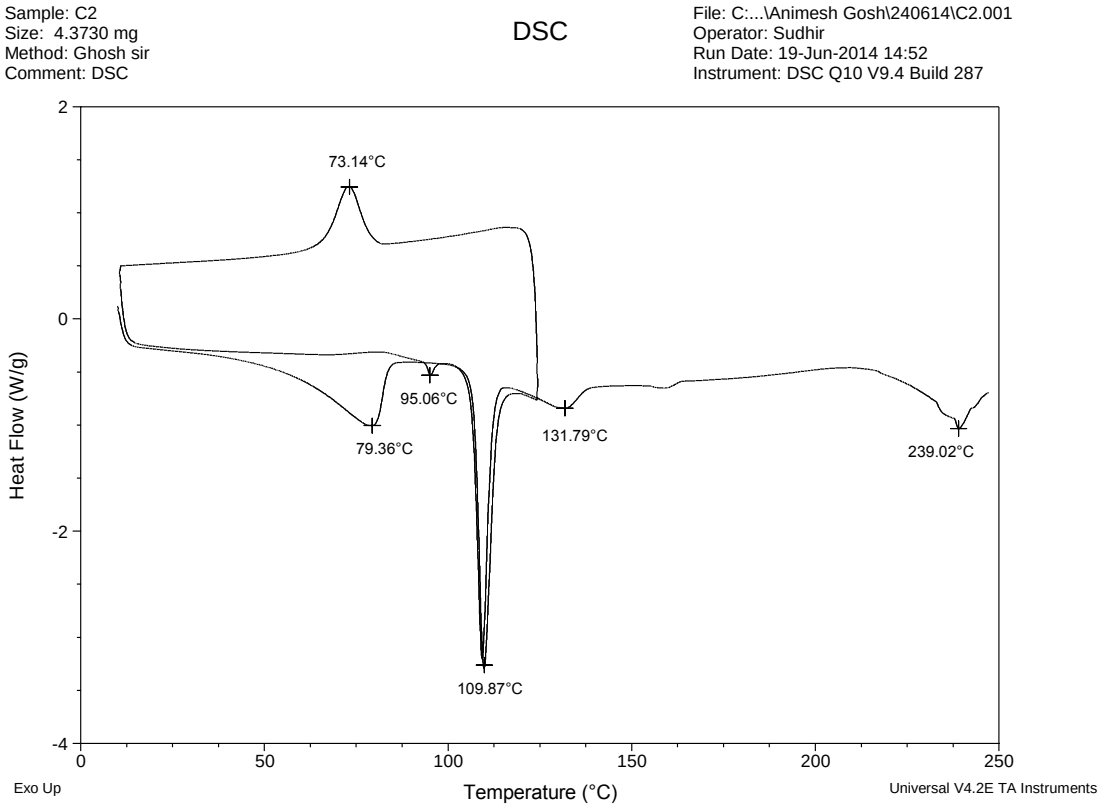

Figure S1. Differential scanning calorimetry of cocrystal II (heating up to 125 °C, then cooling up to ambient temperature and again heating up to 250 °C)

Reference:

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