Preparation, Characterization, and Evaluation of the Co-amorphous System of Dasatinib to Improve its Pharmaceutical Attributes

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Supporting document

Tables

Table S1 Gradient details

Time	Mobile Phase A: 0.1 % Trifluoro acetic acid in water	Mobile Phase B: Acetonitrile
0	5	95
1	5	95
6	100	0
8	100	0
10	5	95
12	5	95

Table S2 Outcome of coformers screening study by PXRD study

Sr. No.	Co-Former Name	PXRD results
1	Cinnamic Acid	Amorphous
2	Sebacic Acid	Amorphous
3	Ferulic Acid	Amorphous
4	Nicotinic Acid	Partially crystalline
5	Malic Acid	Amorphous
6	Succinic Acid	Amorphous
7	Citric Acid	Amorphous
8	Fumaric Acid	Amorphous
9	Gentisic Acid	Amorphous
10	Vanillic Acid	Amorphous
11	Phenanthrene	Partially crystalline

Table S3 The pKa values of the coformers used.

Entry	Name of the co-formers	pKa_1 (at 25 °C)	pKa_2 (at 25 °C)	pKa_3 (at 25 °C)	pKa (total) (at 25 °C)
1	Sebacic Acid	4.40	5.22	—	9.62
2	Citric Acid	2.63	4.11	5.34	12.08
3	Fumaric Acid	3.03	4.54	—	7.57
4	Malic Acid	2.77	4.44	—	7.21
5	Succinic Acid	3.98	5.2	—	9.18
6	Cinnamic Acid	4.45	—	—	4.45
7	Gentisic Acid	2.95	—	—	2.95
8	Ferulic Acid	4.58	9.39	—	13.97
9	Vanillic Acid	4.47	9.39	—	13.86

Table S4 pH of solubility samples

Coformer	pH of solubility samples
Sebacic Acid	2.5
Citric Acid	2.1
Fumaric Acid	2.2
Malic Acid	2.0
Succinic Acid	2.2
Cinnamic Acid	2.9
Gentisic Acid	3.0
Ferulic Acid	2.8
Vanillic Acid	2.8

Table S5 Dissolution parameters

Dissolution parameter	DAS	DAS:SU	DAS:MAL	DAS:SU PM	DAS:MAL PM
DE_{15} (%)	3.48	38.6	23.55	2.46	3.87
F_2	-	18.41	20.24	80.98	79.34

Figures

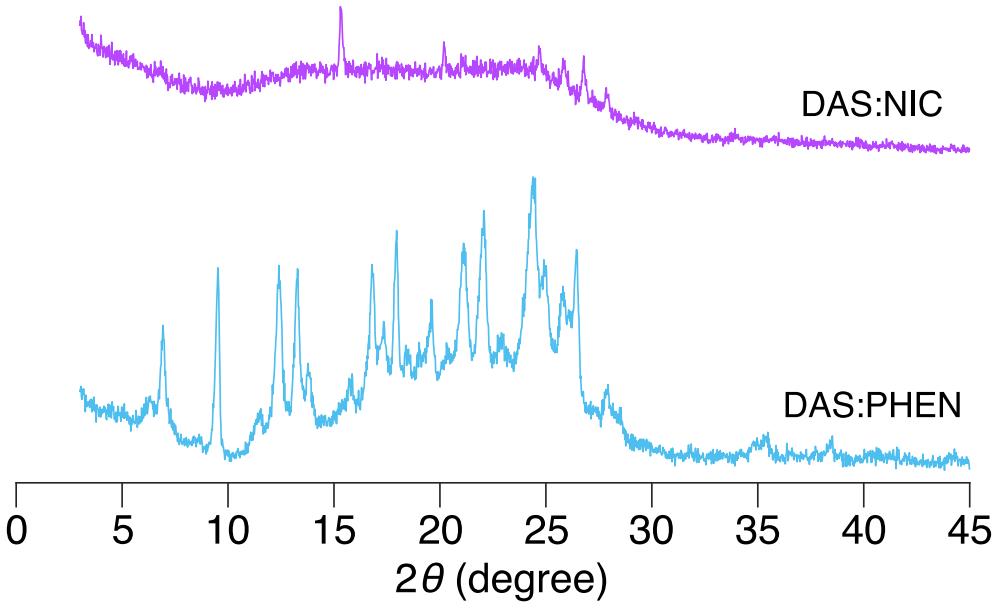

Figure S1. PXRD patterns of DAS:PHEN and DAS:NIC showing manifestation of their crystallinity in co-amorphous system.

Figure S2 shows the FTIR spectra of DAS, succinic acid (SU), malic acid (MAL), co-amorphous systems DAS: MAL and DAS: SU. The FTIR spectrum of DAS, SU and MAL shows prominent vibration bands at 3458 cm^{-1} (N-H stretch), 3205 cm^{-1} (O-H stretch), 2956 cm^{-1} (methyl C-H stretch), and 1681 (low intensity) and 1610 (high intensity) cm^{-1} (C=O stretch). Further moving to DAS: SU or DAS:MAL co-amorphous system, both the fingerprint region and functional group region appears to be broader. Consequently, it becomes very hard to track the shifts in those characteristic peaks, if present. Therefore, FTIR does not provide any conclusive idea of molecular interactions. As a result, advanced solid state NMR experiments were employed to investigate the inter- as well as intra-molecular interactions.

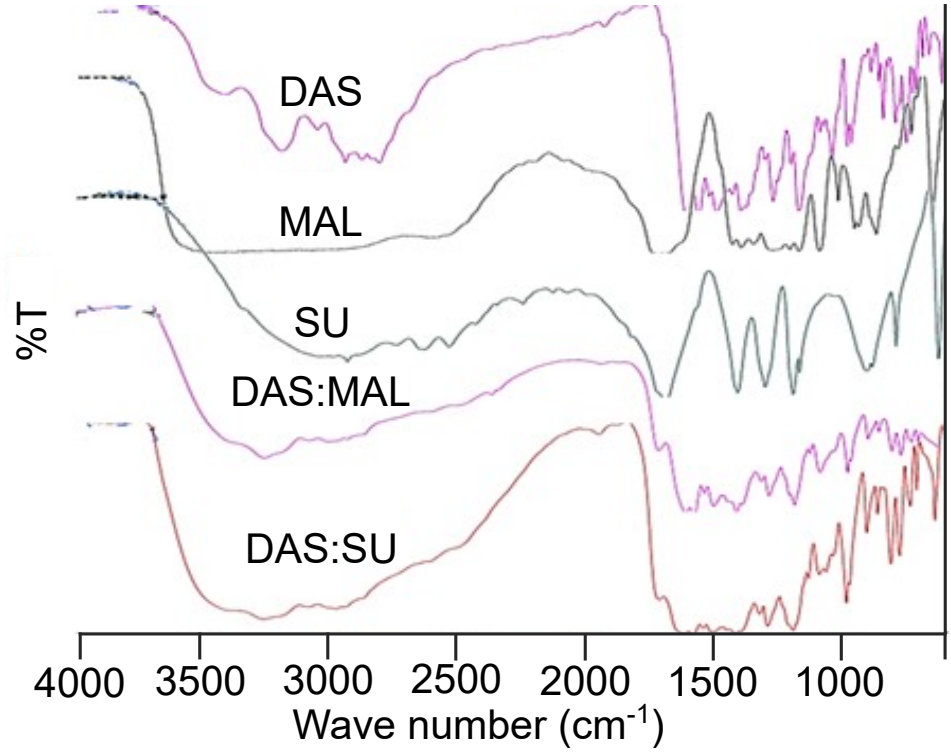

Figure S2. FTIR data of DAS, MAL and SU along with the co-amorphous system of DAS:MAL and DAS:SU.

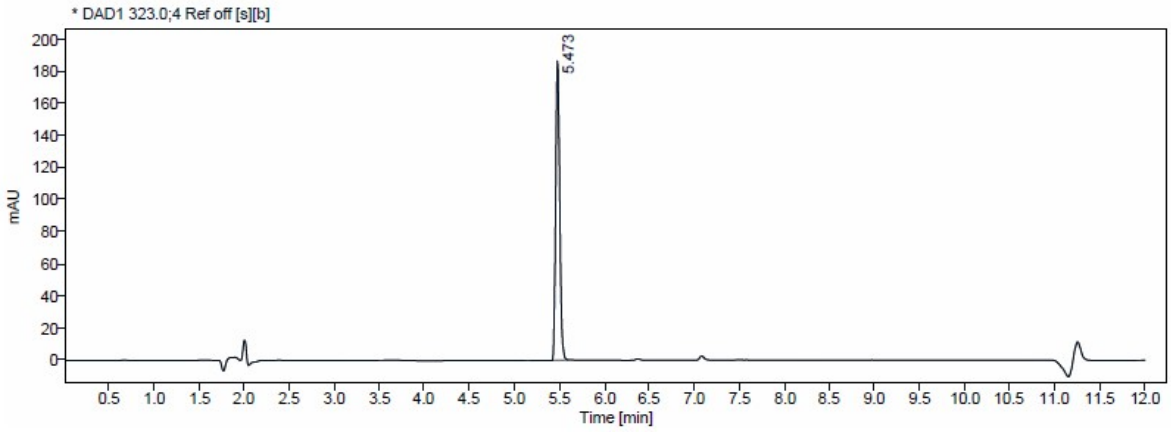

Figure S3 Representative chromatograms of Dasatinib

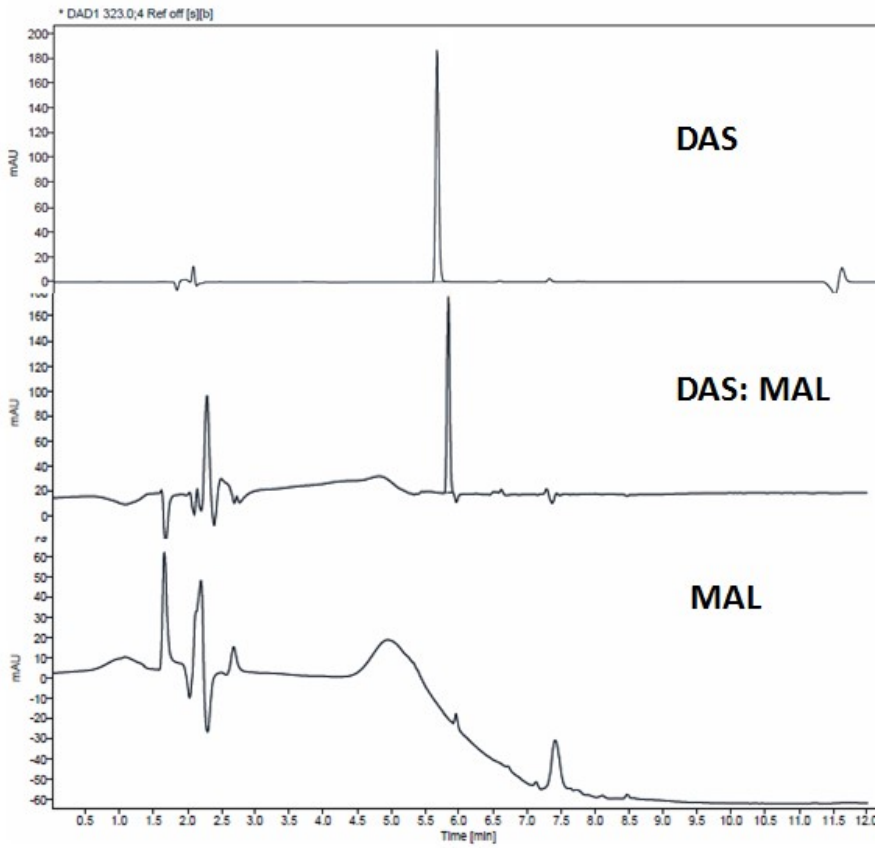

Figure S4 Overlay of chromatogram of DAS, MAL & DAS:MAL

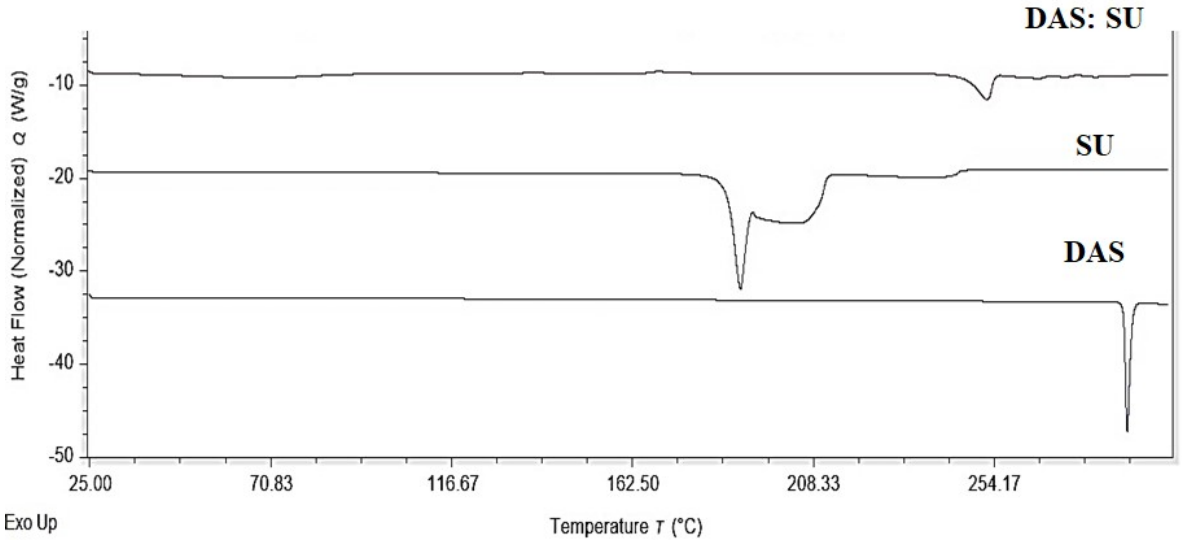

Figure S5 DSC overlay of DAS, SU and DAS:SU coamorphous system

Qualitative solubility study

To find the suitable solvent for the liquid-assisted grinding method, the qualitative solubility of API and coformers in various solvents (methanol, ethanol, acetonitrile, and iso-propyl

alcohol) were performed. One mg of API or coformers were added in centrifuge tube followed by addition of 10 µL of the solvent. If the API or coformers were not dissolved again, add 10 mL of liquids to each centrifugal tube until API or coformer dissolved completely. Calculate the amount of solvent required to dissolve 1 mg of API or coformer. Among selected solvents, solubility of API and coformers follow the order from highly solubilizing to poorly solubilizing solvents methanol > ethanol > iso-propyl alcohol > acetonitrile). Based on qualitative solubility study, methanol selected for coformer screening study.