# Supporting information

## Tuning of Solubility and Stability of Hydrochlorothiazide Co-crystals

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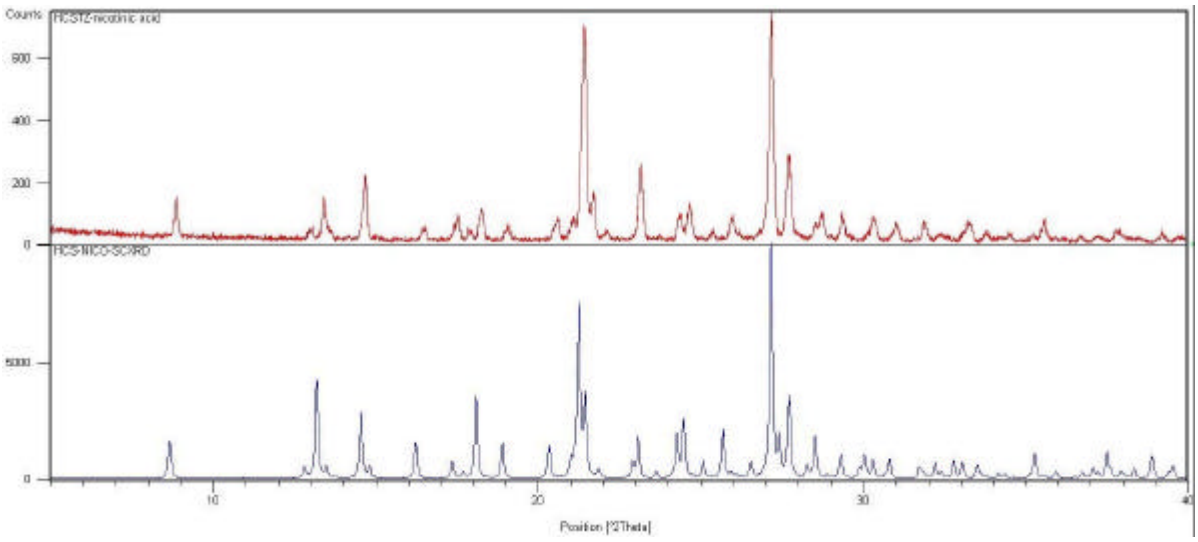
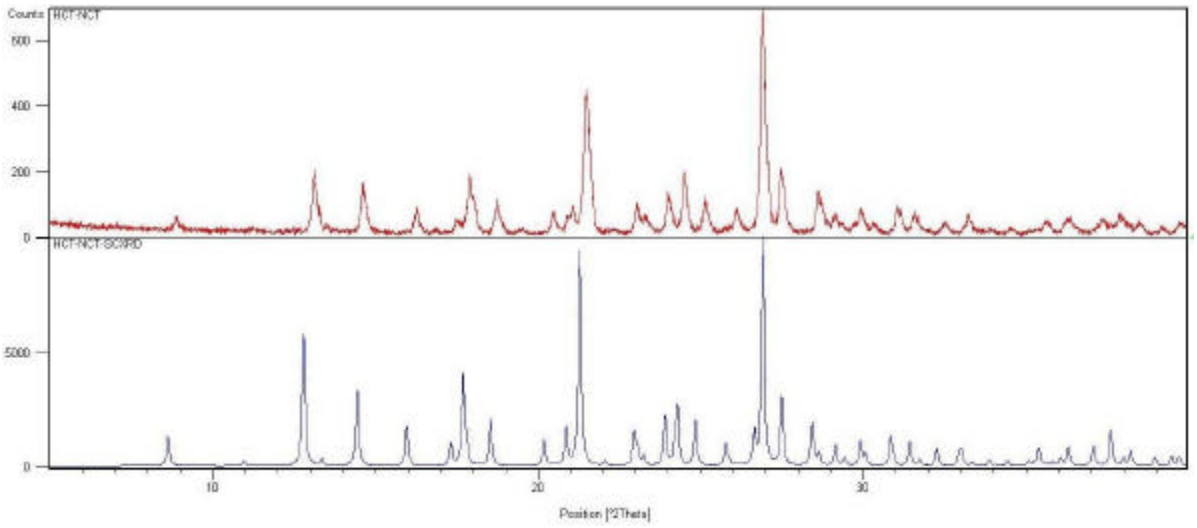
**Table S1** Co-formers attempted to obtain HCT co-crystals

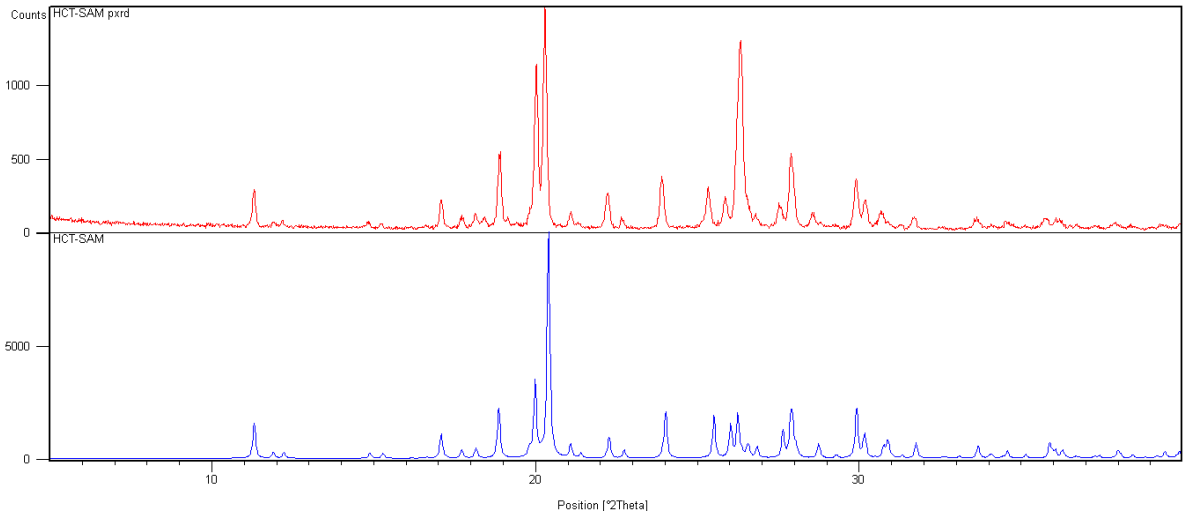
| API | Co-former | Final solid form (or co-crystal) |
|---|---|---|
| HCT | Nicotinic acid | HCT–nicotinic acid (1:1) |
| | Nicotinamide | HCT–nicotinamide (1:1) |
| | Isonicotinic acid (grind or rotor) | Physical mixture |
| | P-aminobenzoic acid | HCT–PABA (1:2) |
| | P-hydroxybenzoic acid | Physical mixture |
| | Saccharin | Physical mixture |
| | Benzoic acid | Physical mixture |
| | Salicylic acid | Physical mixture |
| | Benzamide | Physical mixture |
| | Oxamide | Physical mixture |
| | Succinamide | HCT–succinamide (2:1) |
| | Adipamide | Physical mixture |
| | Aspirin | Physical mixture |
| | Cytosine | Physical mixture |
| | Thymine | Physical mixture |
| | Caffeine | Physical mixture |
| | Urea (MeOH) | Physical mixture |
| | Resorcinol | New X-ray patterns (PXRD) |
| | Pyrogallol | New X-ray patterns (PXRD) |
| | L-glycine | Physical mixture |
| | L-Arginine | Physical mixture |
| | L-Alanine | Physical mixture |
| | ?-Aminobutryic acid | Physical mixture |



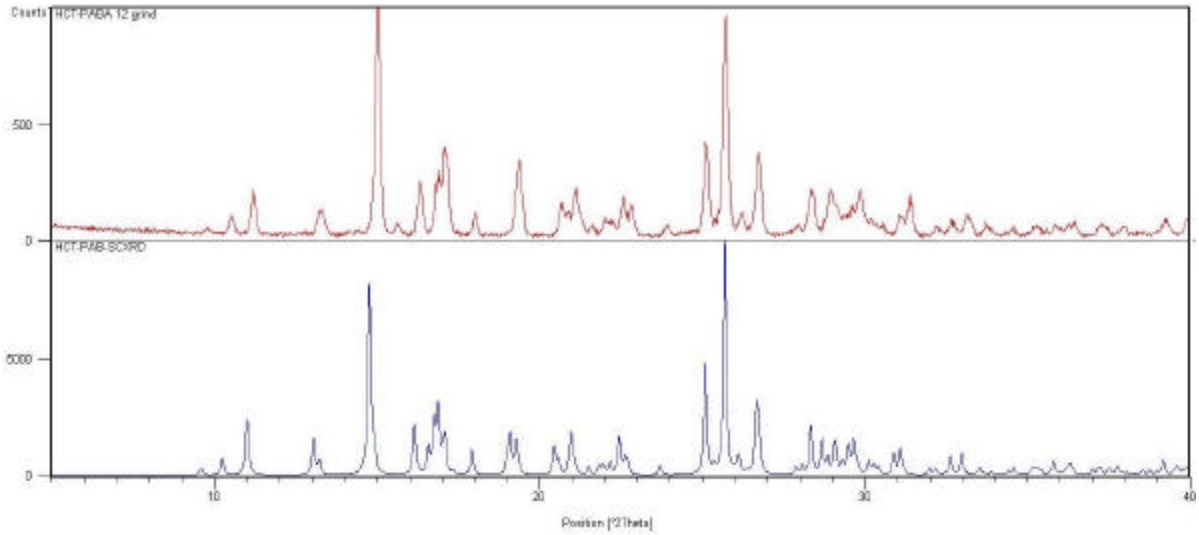

(a) HCT–NIC (1:1)



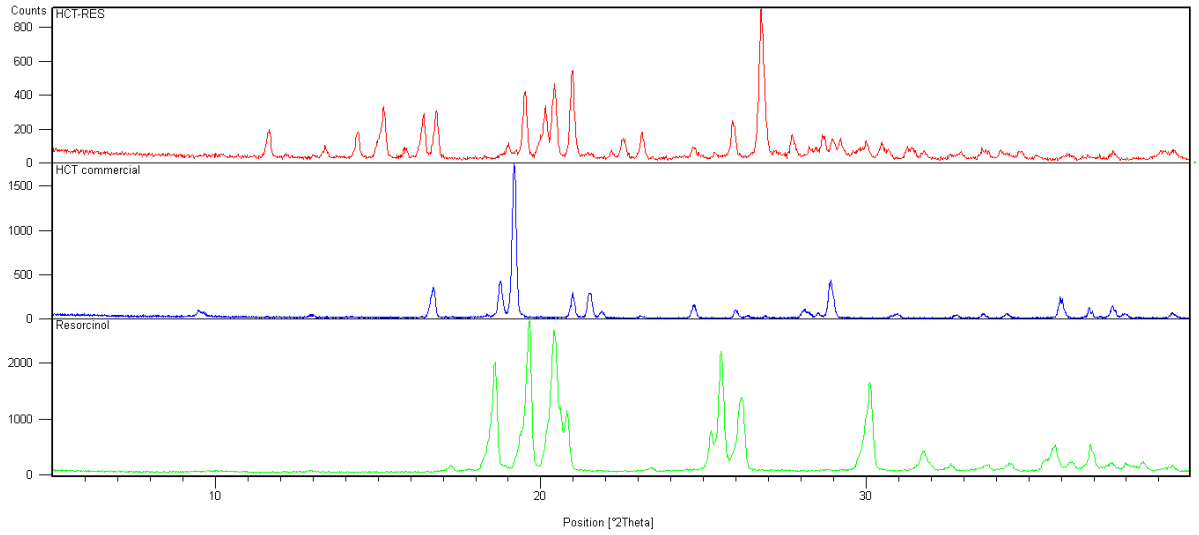

(b) HCT–NCT (1:1)



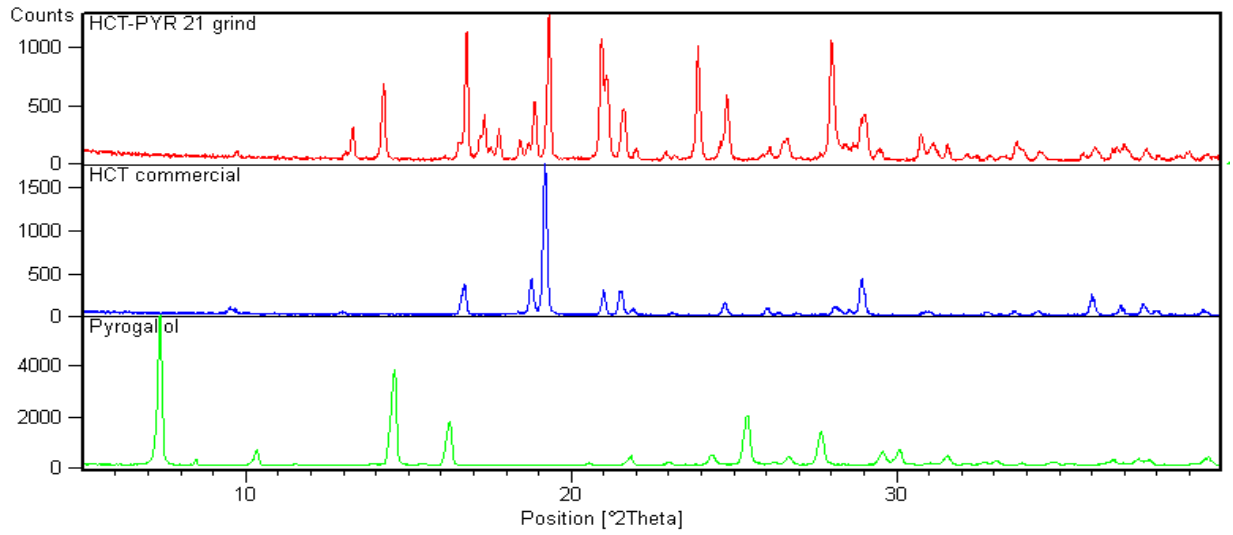

(c) HCT–SAM (2:1)




(d) HCT–PABA (1:2)

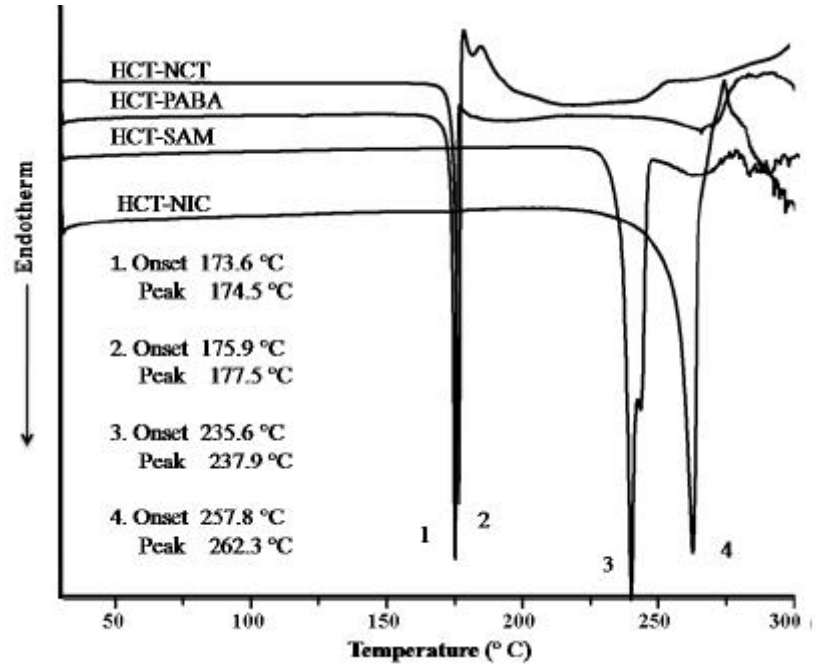



(e) HCT–RES (1:1)

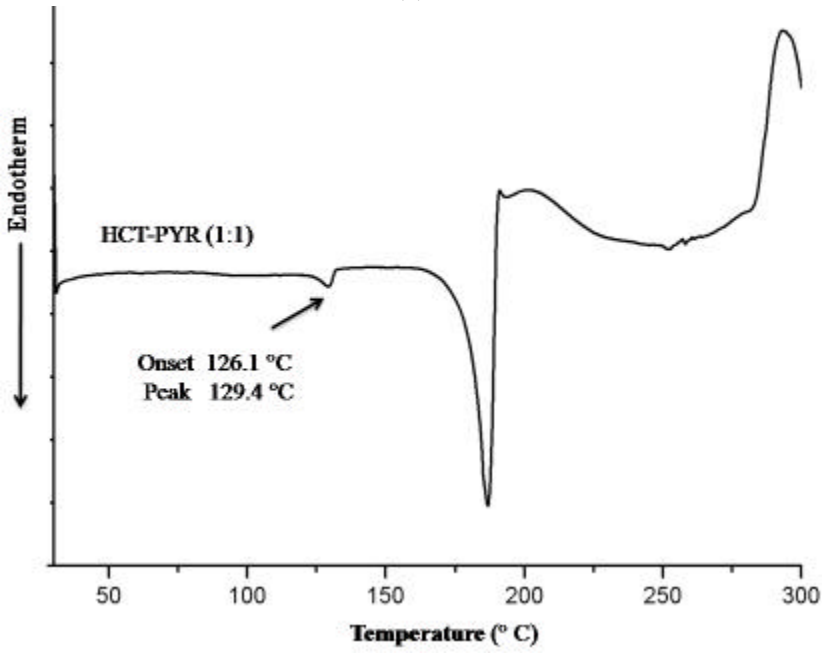



(f) HCT–PYR (2:1)

**Figure S1** PXRD comparison of HCT co-crystals (a-f) indicates bulk phase purity.

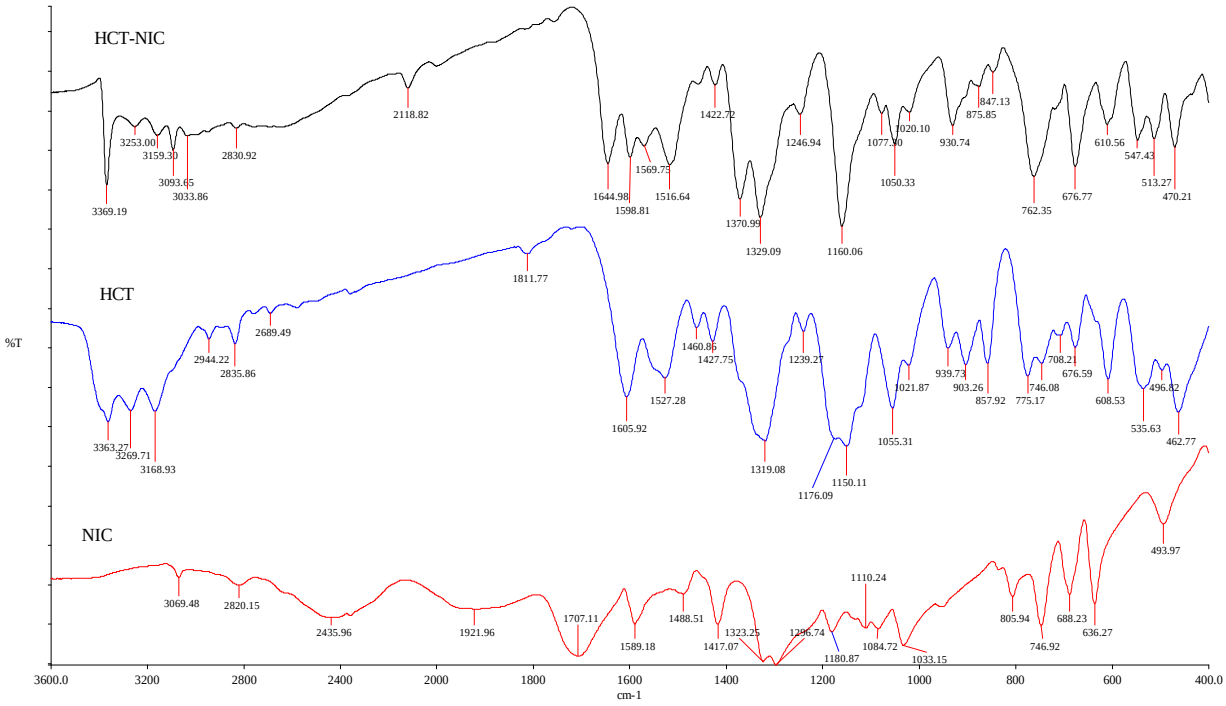



(a)

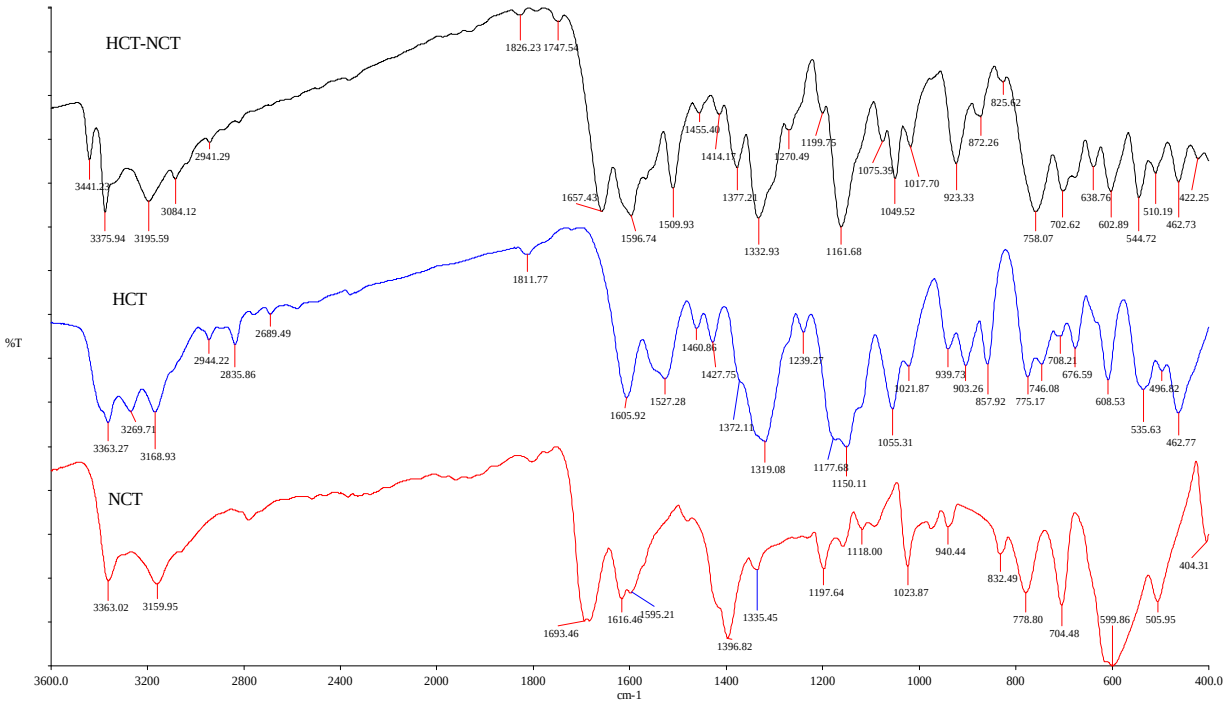



(b)

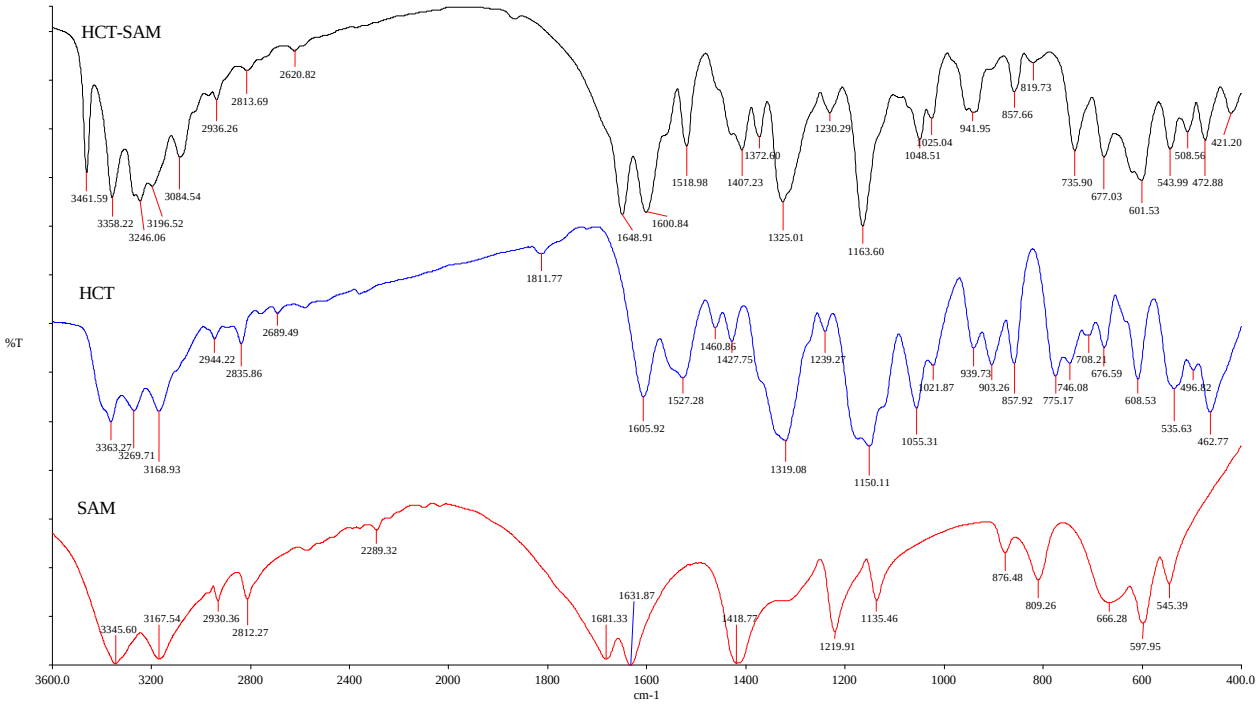
**Figure S2** DSC endotherms of (a) HCT cocrystals indicating single melting endotherms confirm homogeneity of the solid phases. (b) DSC plot of HCT–PYR (1:1) shows extra endotherm at onset 126 °C which corresponds to excess pyrogallol.


HCT-NIC
3369.19
3253.00
3159.30
3093.65
3033.86
2830.92
2118.82
1644.98
1598.81
1569.75
1516.64
1422.72
1370.99
1329.09
1246.94
1160.06
1077.70
1050.33
1020.10
930.74
847.13
875.85
762.35
676.77
610.56
547.43
513.27
470.21
HCT
%T
3363.27
3269.71
3168.93
2944.22
2835.86
2689.49
1811.77
1605.92
1527.28
1460.86
1427.75
1319.08
1239.27
1176.09
1150.11
1055.31
1021.87
939.73
903.26
857.92
775.17
746.08
708.21
676.59
608.53
535.63
496.82
462.77
NIC
3069.48
2820.15
2435.96
1921.96
1707.11
1589.18
1488.51
1417.07
1323.25
1296.74
1180.87
1110.24
1084.72
1033.15
805.94
746.92
688.23
636.27
493.97
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
cm-1

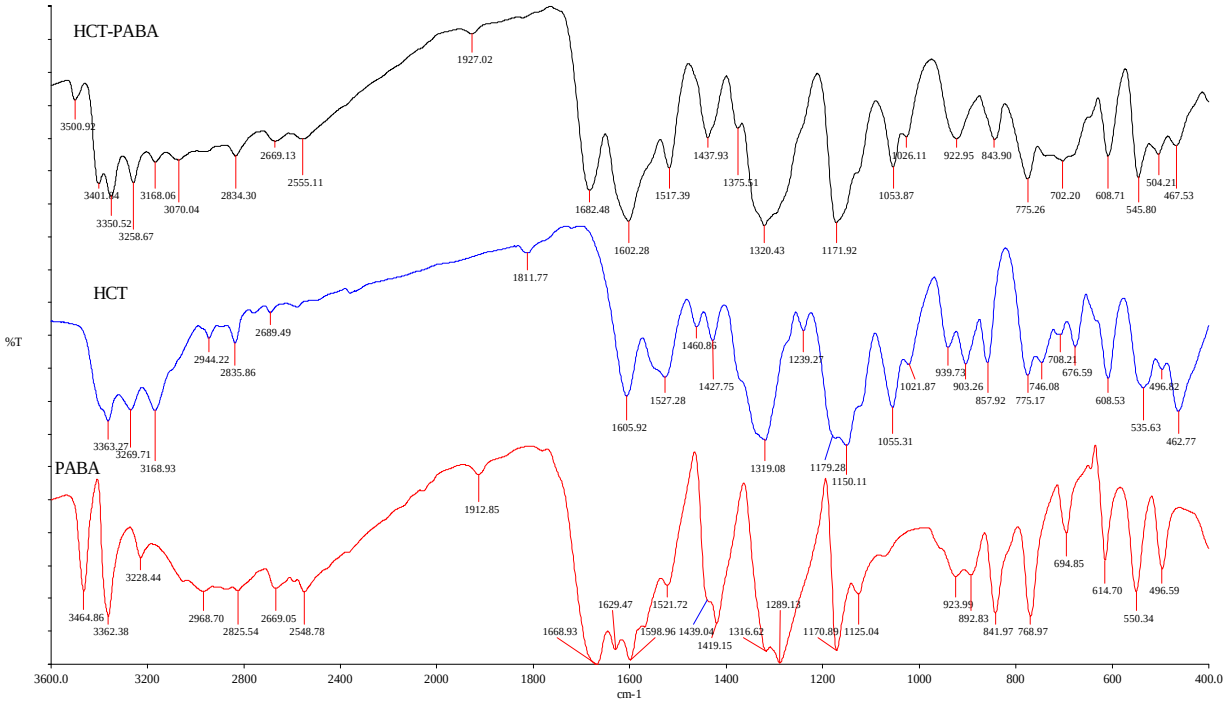
(a)


HCT-NCT
3441.23
3375.94
3195.59
3084.12
2941.29
1826.23
1747.54
1657.43
1596.74
1509.93
1455.40
1414.17
1377.28
1332.93
1270.49
1199.75
1161.68
1075.39
1049.52
1017.70
923.33
872.26
825.62
758.07
702.62
638.76
602.89
544.72
510.19
462.73
422.25
HCT
%T
3363.27
3269.71
3168.93
2944.22
2835.86
2689.49
1811.77
1605.92
1527.28
1460.86
1427.75
1372.11
1319.08
1239.27
1177.68
1150.11
1055.31
1021.87
939.73
903.26
857.92
775.17
746.08
708.21
676.59
608.53
535.63
496.82
462.77
NCT
3363.02
3159.95
1693.46
1616.46
1595.21
1396.82
1335.45
1197.64
1118.00
1023.87
940.44
832.49
778.80
704.48
599.86
505.95
404.31
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
cm-1

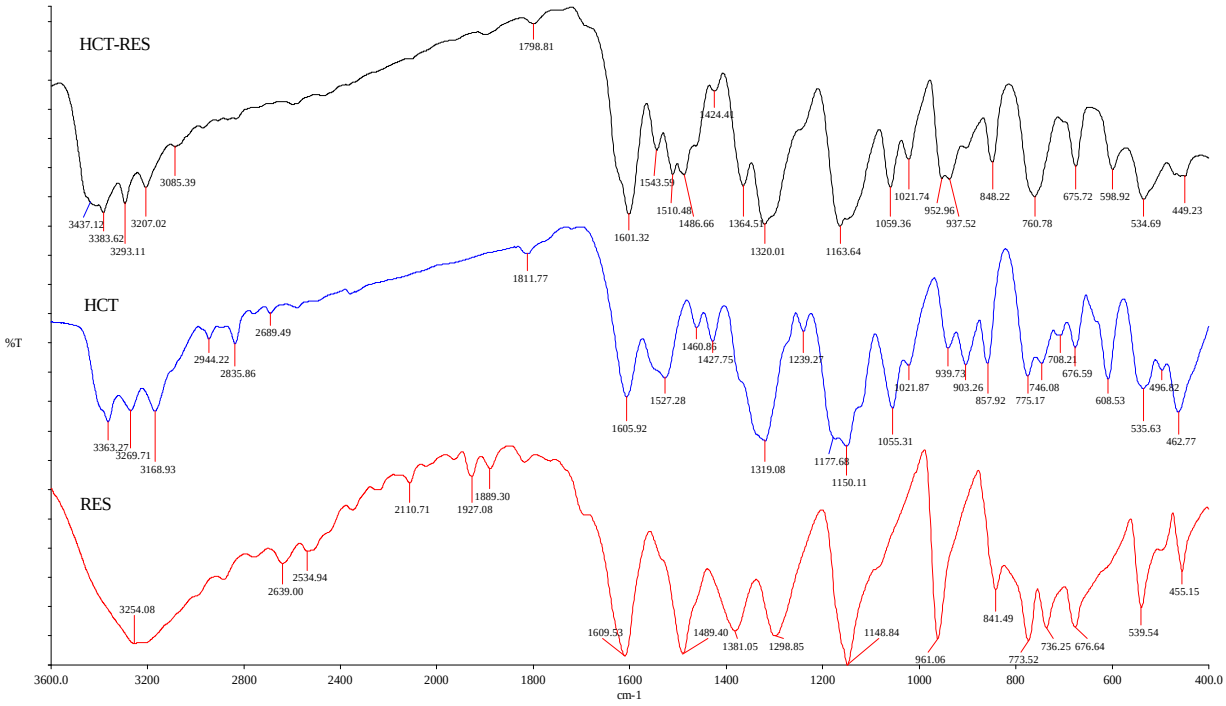
(b)


HCT-SAM
HCT
SAM
%T
cm-1
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
3461.59
3358.22
3246.06
3196.52
3084.54
2936.26
2813.69
2620.82
1648.91
1600.84
1518.98
1407.23
1372.60
1325.01
1230.29
1163.60
1048.51
1025.04
941.95
857.66
819.73
735.90
677.03
601.53
543.99
508.56
472.88
421.20
3363.27
3269.71
3168.93
2944.22
2835.86
2689.49
1811.77
1605.92
1527.28
1460.86
1427.75
1319.08
1239.27
1150.11
1055.31
1021.87
939.73
903.26
857.92
775.17
746.08
708.21
676.59
608.53
535.63
496.82
462.77
3345.60
3167.54
2930.36
2812.27
2289.32
1681.33
1631.87
1418.77
1219.91
1135.46
876.48
809.26
666.28
597.95
545.39

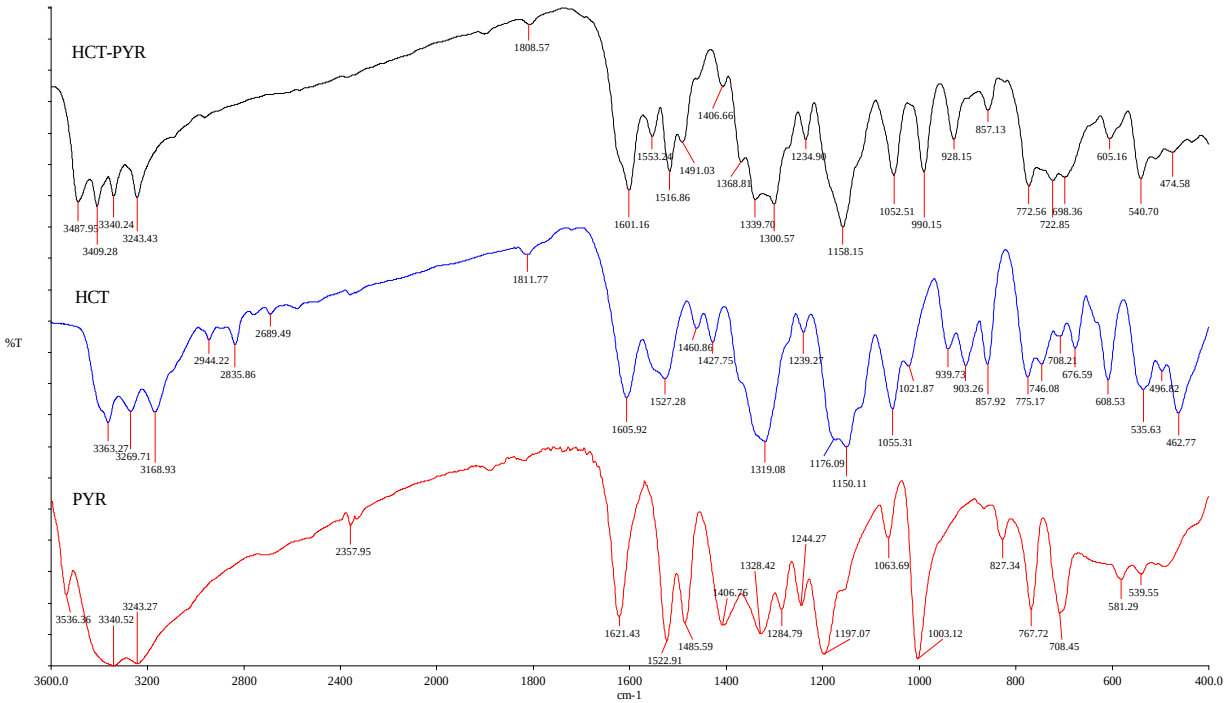
(c)


HCT-PABA
HCT
PABA
%T
cm-1
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
3500.92
3401.94
3350.52
3258.67
3168.06
3070.04
2834.30
2669.13
2555.11
1927.02
1682.48
1602.28
1517.39
1437.93
1375.51
1320.43
1171.92
1053.87
1026.11
922.95
843.90
775.26
702.20
608.71
545.80
504.21
467.53
3363.27
3269.71
3168.93
2944.22
2835.86
2689.49
1811.77
1605.92
1527.28
1460.86
1427.75
1319.08
1239.27
1179.28
1150.11
1055.31
1021.87
939.73
903.26
857.92
775.17
746.08
708.21
676.59
608.53
535.63
496.82
462.77
3464.86
3362.38
3228.44
2968.70
2825.54
2669.05
2548.78
1912.85
1668.93
1629.47
1598.96
1521.72
1439.04
1419.15
1316.62
1289.13
1170.89
1125.04
923.99
892.83
841.97
768.97
694.85
614.70
550.34
496.59

(d)

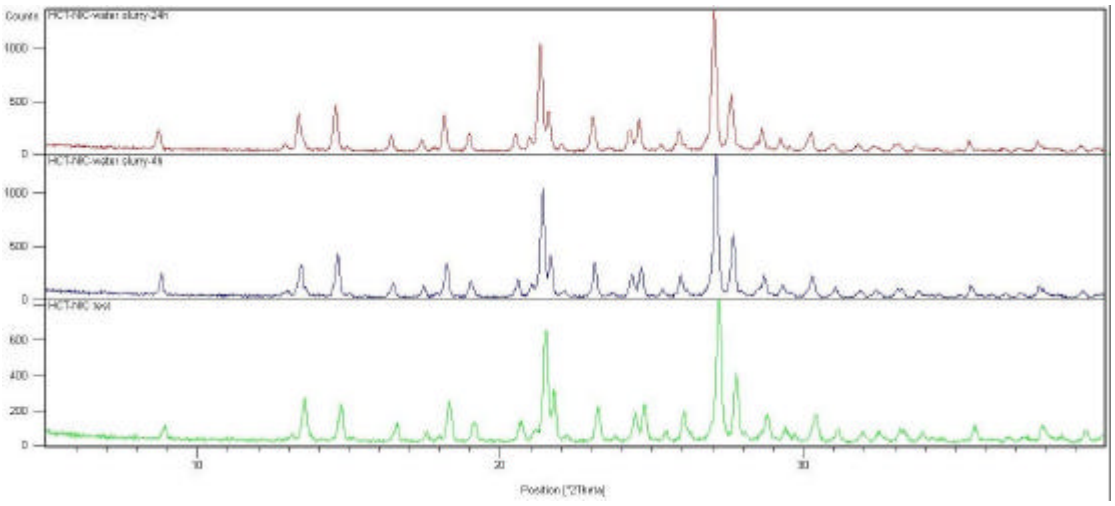



(e)

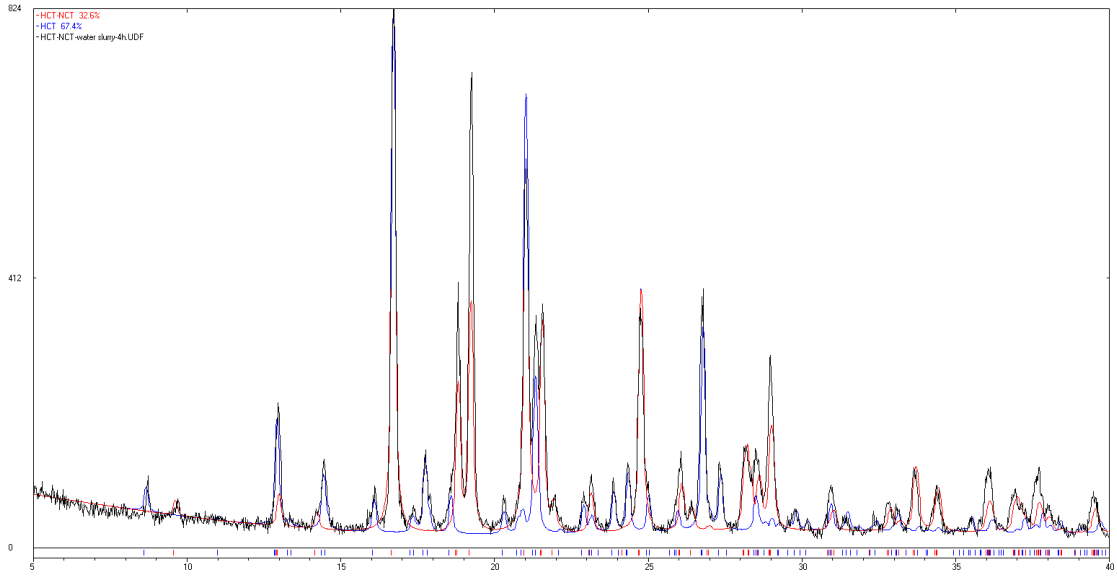



(f)

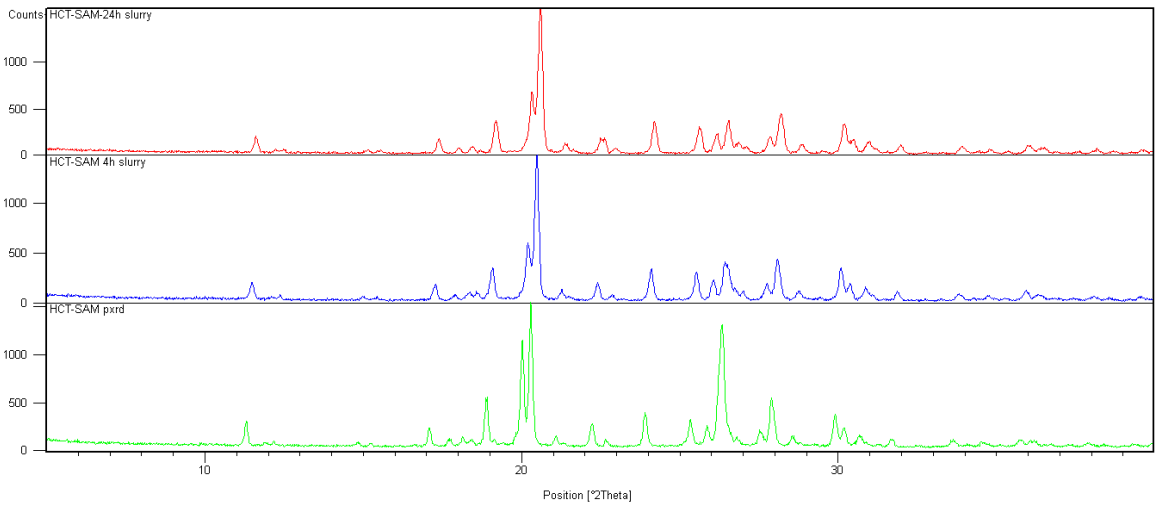
**Figure S3** FT-IR spectra comparison of (a) HCT–NIC, (b) HCT–NCT, (c) HCT–SAM, (d) HCT–PABA, (e) HCT–RES, (f) HCT–PYR cocrystals with the API and coformers.


Counts
HCT-NIC-water slurry-24h
HCT-NIC-water slurry-4h
HCT-NIC pxrd
Position [°2Theta]

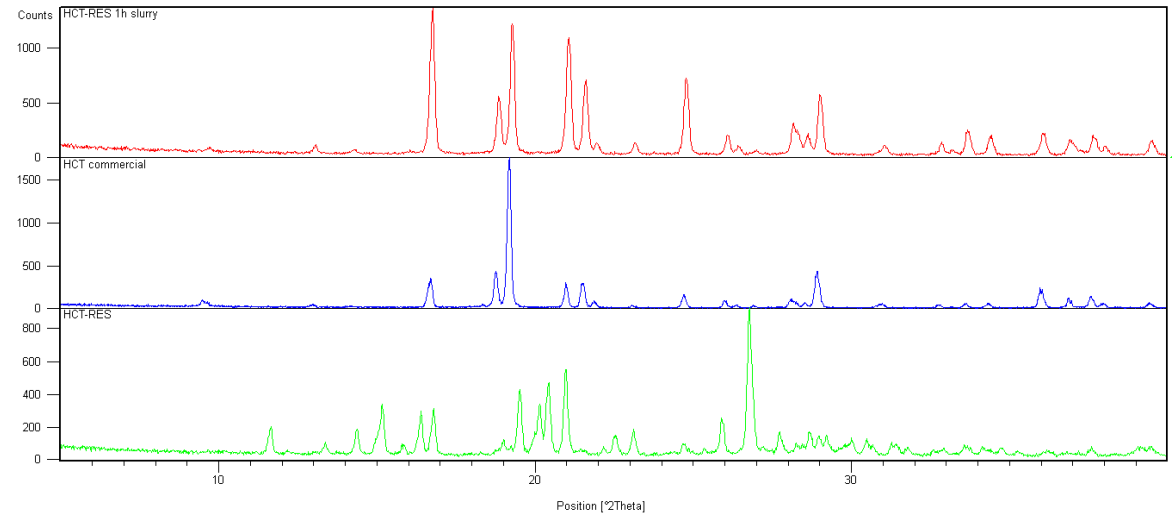
(a)


824
412
0
HCT-NCT 32.6%
HCT 67.4%
HCT-NCT-water slurry-4h.UDF

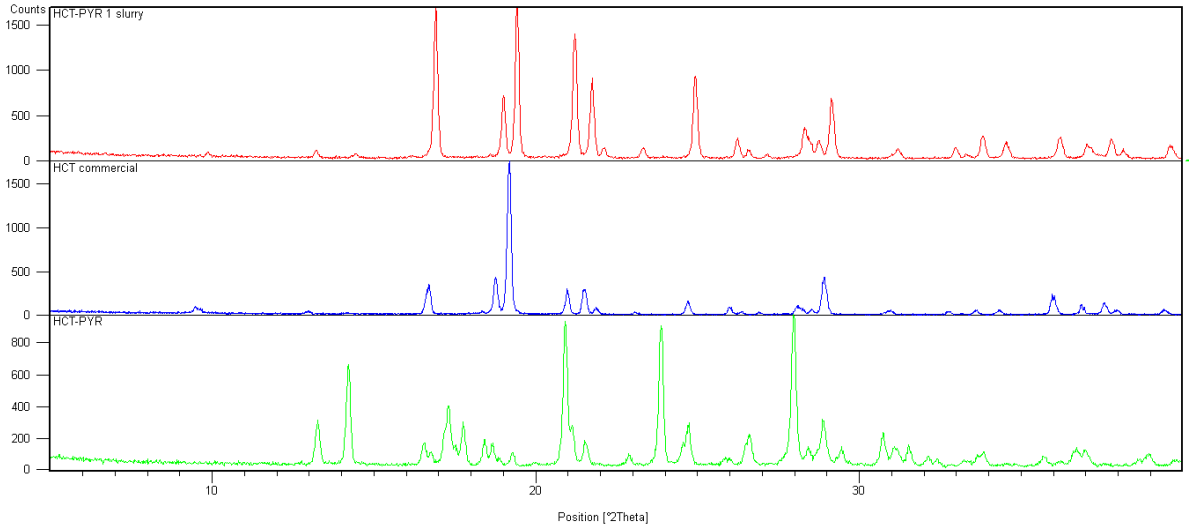
(b)


Counts
HCT-SAM-24h slurry
HCT-SAM 4h slurry
HCT-SAM pxrd
Position [°2Theta]

(c)

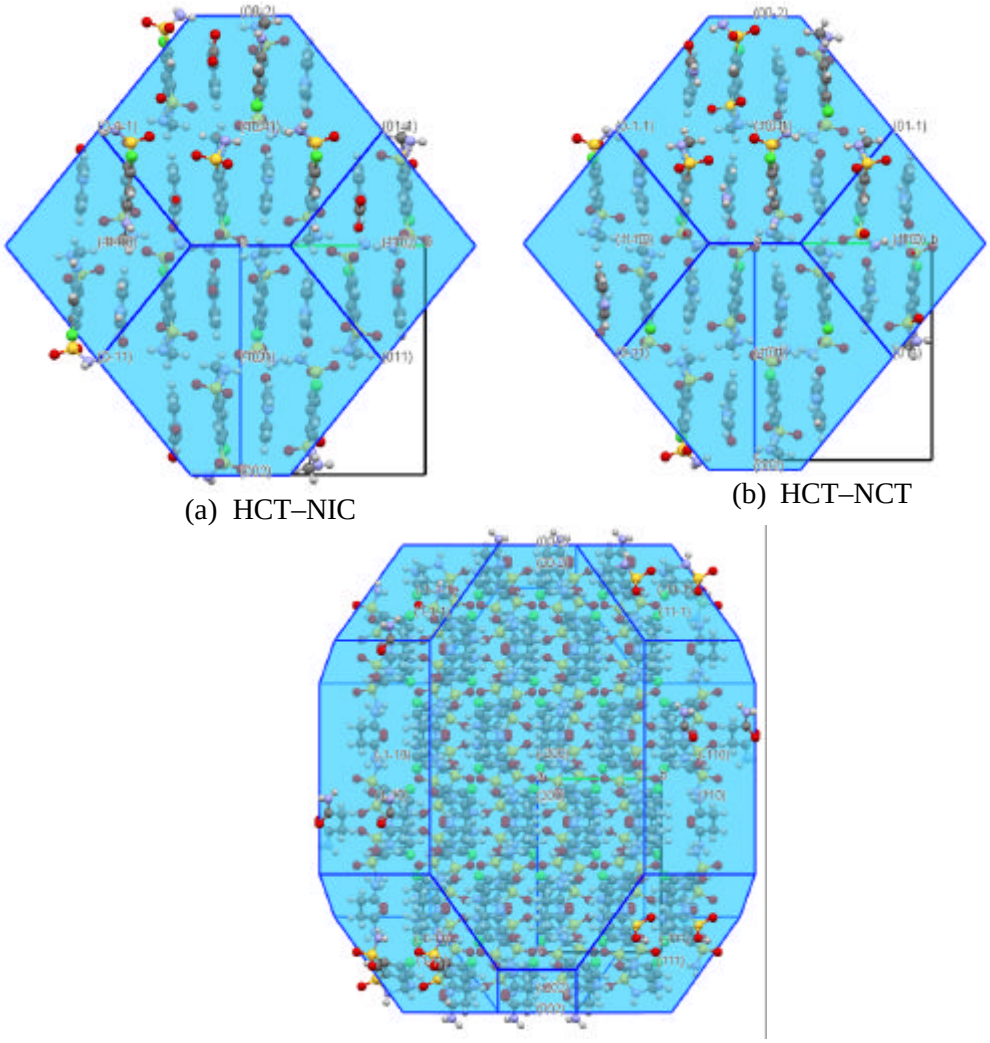



(d)




(e)

**Figure S4** PXRD comparisons of hydrochlorothiazide co-crystals (a) HCT–NIC, (b) HCT–NCT, (c) HCT–SAM, (d) HCT–RES and (e) HCT–PYR after 1, 4 and 24h slurry in water. HCT–NIC and HCT–SAM co-crystals are stable upto 24 h slurry experiments. But two third of the HCT–NCT co-crystals transformed to the API within 4h of dissolution experiments. HCT–RES and HCT–PYR co-crystals transformed completely to the API within 1 h of slurry experiments.



(a) HCT–NIC (b) HCT–NCT

(c) HCT–SAM

**Figure S5** BFDH predicted morphology of the co-crystals (a-c) showing the molecular packing and indexing of selected crystal faces. The packing diagrams are viewed down the *a* axis.